CLINICO-LABORATORY CHARACTERISTICS AND SHORT-TERM OUTCOMES OF HOSPITALISED COVID-19 PATIENTS WITH DIABETES MELLITUS AT KNH

A dissertation submitted in partial fulfilment of the requirements for the Master of Medicine Degree (MMed) in Internal Medicine of the University of Nairobi.

By

Karbolo S. Joseph

H58/37187/2020

Department of Clinical Medicine and Therapeutics

University of Nairobi

STUDENTS DECLARATION

I hereby confirm that this dissertation is my original work and has not been presented elsewhere for examination or approval for another degree or any other award.

Signature _____ Date: 06-11-2023

Karbolo S. Joseph (MBChB)

Resident, Internal Medicine

SUPERVISORS' APPROVAL

This dissertation has been submitted with our approval as the supervisors from the Department of Clinical Medicine and Therapeutics, Faculty of Health Sciences, University of Nairobi.

Prof. Seth O. McLigeyo

Professor, Consultant Physician, and Nephrologist, Department of Clinical Medicine, and Therapeutics

Signed: .....

Date: 6/11/23

Prof. C.F Otieno

Associate Professor, Consultant Physician and Endocrinologist, Department of Clinical Medicine, and Therapeutics

Signed: .....

Date: 7/11/2023

CHAIRMAN OF THE DEPARTMENT APPROVAL

Prof. E. O. Amayo

Chairman of the Department of Clinical Medicine and Therapeutics,

Professor, Consultant Physician and Neurologist, University of Nairobi

Signed.....

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
DEPARTMENT OF CLINICAL MEDICINE & THERAPEUTICS
P.O. Box 19676-00202 NAIROBI

Date.....9/11/2022

ACKNOWLEDGEMENT:
To the Almighty God to whom I am eternally bound.

I would like to extend my gratitude to my family, friends, the faculty members at the Department of Clinical Medicine and Therapeutics and my supervisors, Prof McLigeyo and Prof C.F Otieno for their immense support and guidance, my statistician and research assistant for their roles in the study. Sincere appreciation to the Kenyatta National Hospital records department staff for assistance with the retrieval of the files.

Thank You.

LIST OF ABBREVIATIONS

AKI	Acute Kidney Injury
AOR	Adjusted odds ratio
ARDS	Acute respiratory distress syndrome
COR	Crude Odds Ratio
COVID-19	Corona virus disease 19
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive protein
CVD	Cardiovascular disease
CKD	Chronic kidney disease
DM	Diabetes mellitus
DPP4-i	Dipeptidyl 4 inhibitors
DKA	Diabetes ketoacidosis
FBS	Fasting blood sugar
GLP-1	Glucagon like peptide-1
HBA1C	Glycated hemoglobin
HHS	Hyperosmolar hyperglycaemic state
HR	Hazard ratio
ICD	International code of disease
ICU	Intensive care unit
IDU	Infectious disease unit
KNH-UON	Kenyatta National Hospital- University of Nairobi
LDH	Lactate dehydrogenase
LOS	Length of stay
MERS	Middle East Respiratory Syndrome

NDDM	Newly diagnosed diabetes mellitus
OGLA	Oral Glucose Lowering Agents
OR	Odds ratio
PCR	Polymerase chain reaction
POC	Point of care
RAT	Rapid Antigen Test
RBS	Random blood sugar
ROS	Reactive oxygen species
SARSCOV2	Severe acute respiratory coronavirus 2
SGLT2-i	Sodium glucose transporter 2 inhibitors
TDD	Total daily dose
WHO	World Health Organization

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

Figures:

Tables:

ABSTRACT

Background: Since its emergence in 2019, patients with pre-existing comorbidities such as diabetes mellitus (DM) have been reported to experience severe Covid-19 disease. It has been associated with poorer outcomes among DM patients.

Objectives: This retrospective cross-sectional study aimed to determine the clinico-laboratory characteristics, short-term outcomes, glycaemic events, and management, as well as the predictors of adverse outcomes among hospitalised patients with Covid-19 and DM.

Methodology: 244 medical records of patients with Covid-19 and DM admitted to Kenyatta National Hospital between March 2020- March 2022 were reviewed. The patients' demographics, clinico-laboratory features, DM-related events and management, and outcomes were extracted. Continuous variables were expressed as mean/standard deviation and categorical variables as numbers or percentages. Logistic regression analysis was used to compute the odds ratio (OR) for predictors of adverse outcome.

Results: The study participants had a median age of 58 years, with males comprising 53% of the participants. Hypertension was the most common comorbidity, affecting 61% of all cases. Majority (78%) had Pre-existing DM while 54 (22%) had newly diagnosed diabetes (NDDM). Long term glycaemic control was poor in majority (82%) with mean glycated haemoglobin of 9 % and admission hyperglycaemia in (65%). The most frequent symptoms were Dyspnoea (60%) and cough (62%) while the average admission SPO2 was 84%. Elevated C-reactive protein (90%) and D-dimers (70%) with lymphopenia (32%) were among the laboratory observations. Diabetic ketoacidosis (DKA) occurred in 26% of patients, and 11% experienced hypoglycaemia. The mean length of stay was 10 days, and 60% were discharged within 14 days. The mortality proportion was 23%, with hypertension, NDDM, dyspnoea, and DKA/ (hyperosmolar hyperglycaemic state) HHS identified as independent predictors of mortality.

Conclusion: Hospitalised Covid-19 patients with DM had elevated RBS at admission with poor overall glycaemic control and elevated inflammatory markers. Glycaemic events, including DKA/HHS, were common during hospitalisation, and DKA/HHS was identified as an independent predictor of mortality. Our findings underscore the importance of closely monitoring and managing glycaemic control in patients with COVID-19 and diabetes.

CHAPTER ONE

1.0 INTRODUCTION:

Coronavirus disease 2019 (Covid-19) is a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly emergent coronavirus, that was first recognized in Wuhan, China, in December 2019 (1). Principally transmitted from person to person through respiratory droplets and aerosols (2,3). As at 21st February 2023, an estimated 757 million people had been infected globally with a death toll of 6.9 million (4). In Africa, the cumulative number of confirmed cases stands at 9.5 million (4). The pandemic has remained a global concern due to the numerous new strains and mutations with variable degrees of virulence and severity, resulting in repeated surges in the global number of cases and fatalities. (5). However, the introduction of vaccination has seen a dip in the number of severe cases and mortality globally (6).

Severe Covid-19 disease was associated with ICU admission and mortality in those with pre-existing comorbidities such as diabetes and hypertension. New-onset hyperglycaemia was found to be an independent predictor of severe covid-19 and death in hospitalized Covid-19 patients (7). Furthermore, patients presenting with acute metabolic dysfunctions on admission including hyperglycaemia, were more likely to receive intensive care services (8).

According to studies, the necessity for critical care admission, longer hospital stays, and mortality were significantly increased in severe Covid-19 patients with diabetes (9).

Locally, there is paucity of data on the clinical course and outcomes of patients with diabetes including those with newly diagnosed hyperglycaemia in Covid-19. Similarly, data on the putative prevalence of hyperglycaemia in Covid-19 patients and their clinical characteristics are also unavailable despite the country registering over 342,874 cases of Covid-19 and over 5000 deaths (4).

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Hyperglycaemia and Glycaemic events in Covid-19

Accruing evidence shows a bidirectional association between Covid-19 and diabetes (10). New-onset diabetes has emerged as a complication of Covid-19 among patients diagnosed and admitted with Covid-19 pneumonia and it has been observed to occur in 16-21% of cases (11). The potential mechanism for hyperglycaemia in Covid-19 includes reduced insulin secretion and increased resistance to insulin(12). This diabetogenic effects of SARsCOV-2 can be summarized as follows (13);

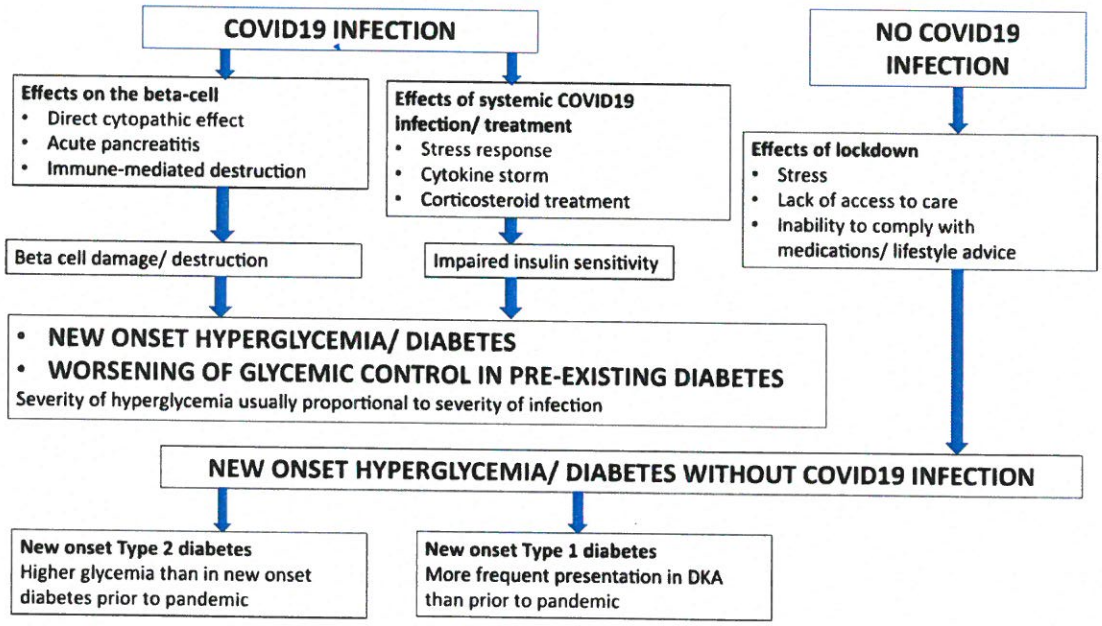


Figure 1: **Hyperglycaemia state in Covid-19 copied from**(13).

Infection with SARsCov-2 virus is known to trigger diabetic ketoacidosis (DKA) in some patients (14). This occurs both in people with established DM and in people who do not have DM (15). In the study of 658 patients hospitalized with Covid-19, the incidence of diabetic ketoacidosis (DKA) was found to be 6.4%. Among these patients, 35.7% had pre-existing diabetes. On the other hand, 64.3% of the patients had no history of DM prior to contracting covid-19 (16). Similarly, Misra *et al.* conducted a study that investigated emergency admissions in the United Kingdom coded with DKA during the first two waves of the Covid-19 pandemic. They compared these admissions to the equivalent time period three years before the outbreak. The study revealed that during the first wave of the pandemic, the number of DKA admissions was 6% higher compared to the corresponding time period three

years prior, with a (95% CI 4-9 p0.0001). Additionally, in the post-first wave period, the number of DKA admissions remained 6% higher, and during the second wave, there was a 7% increase in DKA admissions compared to the equivalent pre-pandemic period. These results suggest that there was a notable increase in DKA admissions during the Covid-19 pandemic compared to previous years (17). Therefore, healthcare professionals should be aware of the potential for DKA in Covid-19 patients, regardless of their DM status (18). Because of a decrease in insulin requirements, hospitalized Covid-19 patients were at risk of developing hypoglycaemia, especially during the resolution stage of the infection (19). Additionally, a decrease in caloric intake during illness can contribute to a higher risk of hypoglycemia. Certain antidiabetic medications, such as insulin and sulfonylureas, can also increase the risk of hypoglycemia as well as a diminished ability to recognize signs and symptoms of low blood glucose (19).

2.2 Demographics and Clinical Characteristics

A World Health Organization (WHO) analysis of 14 African nations with data on Covid-19 and related comorbidities underscored the risk of severe disease or death among diabetics with Covid-19, particularly those over the age of 60years (20). Carrao *et al.* observed a substantial association between hyperglycaemia and Covid-19 in the elderly population with type 2 DM (21). Diabetes mellitus on the other hand, does not increase the likelihood of contracting SARS-COV-2 infection as compared to the general population (22).

A retrospective investigation involving 85 patients with admission hyperglycaemia by Iacobellis *et al.* demonstrated that the average age of study participants was 65 years, with the majority of them being male; in the study, 58 patients who presented with hyperglycaemia in Covid-19 infection had no pre-existing diabetes(23).

According to studies from China, the most often reported classic Covid-19 symptoms were fever (89%), cough (69%), dyspnoea (59%), myalgia (6%), and fatigue (9,24). Headache, nausea, anorexia, and diarrhoea were also reported (24). DM patients had various biochemical derangements including elevated levels of random blood sugar (RBS), glycated haemoglobin (HBA1C), C-reactive protein (CRP), D-dimers, leucocytosis and lactate dehydrogenase (9). Similarly, newly diagnosed diabetic (NDDM) patients reported more severe symptoms and higher levels of inflammatory markers (25).

2.3 Prevalence of DM in Covid-19

Several studies have highlighted the prevalence of DM among Covid-19 patients (26). Worldwide, more than 463 million people over the age of 20 were estimated to have diabetes in 2019, with the number expected to climb in the coming years (27). This global prevalence reflects the significant impact of diabetes on public health. According to a study conducted by Ombajo *et al.* in Kenya, which involved a cohort of 787 hospitalized Covid-19 patients, the prevalence of DM among these patients was found to be 15%. This finding highlights the significant proportion of Covid-19 patients in Kenya who also had a pre-existing diagnosis of diabetes (28). The overall prevalence of DM in the country as estimated by IDF in 2015 was 2.4% (29), and it is predicted to rise to approximately 4.5% by the year 2025 (30). Additionally, the ongoing Covid-19 pandemic has generated concerns regarding a possible link between the virus and new-onset diabetic mellitus. Emerging research suggests that Covid-19 infection can lead to the development of new instances of diabetes or exacerbate pre-existing diabetes.

The prevalence of diabetes in Covid-19 is estimated to be 10.04% based on pooled statistics, and it varies across populations (31). Yang *et al.* found an 8% prevalence in a meta-analysis involving 8 trials (32). Similarly, data from the United States involving 7162 Covid-19 patients found an 11% frequency (33). On the contrary, an Italian study found DM in approximately 36% of Covid-19 patients (34). The difference can be explained by the varied prevalence of diabetes in certain populations (31).

In Spain, the prevalence of diabetes was 30.05% among Covid-19-related deaths (35). The CORONADO study, conducted in France, focused on hospitalized Covid-19 patients with DM. The study revealed that approximately 85% of the Covid-19 patients in the study had type 2 diabetes, indicating a higher prevalence of this type of diabetes among the affected population. Interestingly, 3.1% of the patients were diagnosed with DM upon their admission to the hospital, suggesting that Covid-19 may contribute to the onset of diabetes in some individuals (36). In a comparable manner, a survey of 23,804 hospital mortalities among Covid-19 patients in the United Kingdom revealed that a considerable number of individuals had underlying DM. 32% of the patients had type 2 DM while 1.5 % had type 1 diabetes (37). This finding highlights the substantial burden of diabetes among Covid-19 patients in the United Kingdom.

New-onset diabetes among Covid-19 patients is indeed a significant and relatively frequent phenomenon, as highlighted by multiple studies (38). A systematic review and meta-analysis

conducted by Sathish *et al.* consolidated data from eight separate studies involving over 3,700 individuals. The analysis reported a pooled proportion of 14.4% for NDDM among patients with Covid-19 (39). These findings highlight the possible impact of Covid-19 on glucose metabolism and the development of diabetes. Other meta-analyses have found a 2-4 fold greater chance of developing diabetes in severe Covid-19 vs non-severe disease (40,41).

2.4 Outcome and risk factors for mortality

A meta-analysis and systematic evaluation of the mortality among Covid-19 individuals with DM found an overall mortality rate of 20%. According to the review, death rates differed by population, with Europe having a greater percentage of 28% when compared to other regions(42). In a similar vein, in the ACCREDIT study, that looked at the biochemical parameters associated with mortality, the fatality rate among the studied population was reported to be 24%. The findings of the study indicated a significant risk of mortality in individuals with DM. Two key factors associated with this higher fatality rate were increased levels of C-reactive protein (CRP) and advanced age (26).

The association between diabetes and a longer hospital stay is indeed notable. Studies have consistently shown that individuals with diabetes tend to have a prolonged duration of hospitalization compared to those without diabetes (43). The reported median duration of hospital stay was 12 (9-16) days for individuals with DM compared to 10 (8-13) days for those without DM.

The CORONADO study investigated the occurrence of unfavourable outcomes within 7 days of hospitalization for COVID-19 patients. Among the findings, 410 patients required admission to the intensive care unit (ICU), and out of those, 267 patients required intubation. The overall mortality rate observed in the study was 10.6%. In the study, male gender and a body mass index greater than 29.1Kg/m^2 were risk factors for mortality (36). Locally, the risk for mortality in all admitted patients included age >60 years, male gender, leucocytosis and elevated liver enzymes(28).

Current literature describes DM as a key determinant of mortality with Covid-19 worsening glycaemic regulation in these patients (44). When compared to those without diabetes, DM patients with Covid-19 had a greater likelihood of poor outcomes including severe acute respiratory distress syndrome (ARDS), intensive care unit admission, mechanical ventilation, and death (13). Similarly, during the Middle East respiratory syndrome (MERS) epidemic,

Jose *et al.* revealed in an observational study that diabetes was a strong predictor of mortality among the critically ill MERS patients (45).

Admission hyperglycaemia impairs the prognosis of Covid-19 patients (36). However, it is unclear how hyperglycaemia affects outcomes considering that persons with diabetes may have other established risk factors such as advanced age, obesity, and cardiovascular disease (13). Despite this, studies have linked the poorer prognosis to respiratory dysfunction, primarily due to decreased lung capacities and insufficient gas diffusion capacity (46). Generally, elevated HBA1C levels (>10% in type 1 DM) and (>6.7% in type 2 DM) significantly increased the risk of Covid-19 related fatality (47). Furthermore, DM patients are more susceptible to infections due to increased inflammatory response and lymphopenia.

Patients with new-onset diabetes had a higher likelihood of critical care admission than those with established DM (7). Bode *et al.* conducted a retrospective analysis on the glycaemic and clinical outcomes of covid-19 patients with and without diabetes. According to the findings of the study, non-diabetic acute hyperglycaemia was associated with poor clinical outcomes (48). Acute hyperglycaemia has been shown to increase the inflammatory response by generating reactive oxygen species (ROS). These ROS can lead to endothelial damage and promote thrombus formation (49). Additionally, it has been observed that acute hyperglycemia is associated with the development and progression of radiographic findings indicative of acute respiratory distress syndrome (ARDS) in patients with Covid-19 (23).

According to some sources, factors contributing to mortality included male gender, pre-existing comorbidities, advanced age, elevated C-reactive protein(CRP) and obesity(26,50,51). Likewise, the poorly controlled metabolic status among DM patients put them at the heart of serious complications and death (52). The risk of mortality was twice higher in Covid-19 patients with new-onset DM compared to known diabetics (53) while hyperglycaemia was associated with higher mortality in all patients (9). Other risk factors included pre-existing conditions like hypertension, cancer, chronic kidney disease (CKD) and obesity (3,54).

More studies have provided evidence on the association between DM and poor outcomes in Covid-19 patients. A study by Aisha *et al.* observed a higher fatality rate among critically ill Covid-19 patients with hyperglycaemia compared to normoglycemic patients(55). Additionally, hyperglycaemia and age above 60 years were identified as significant predictors of in-hospital mortality in that study. Another retrospective audit in the United States found

that diabetic patients with Covid-19 had a higher risk of ICU admission, mechanical ventilation, and mortality, even after adjusting for various factors (56). Furthermore, complications related to DM, such as diabetic ketoacidosis, retinopathy, chronic kidney failure, poor glycaemic control, and multiple antidiabetic medications, were associated with poor outcomes in Covid-19 patients (57).

2.5 Glucose control

The treatment of hyperglycaemia in patients with Covid-19 infection is the same, and it is managed in accordance with the established standards (58). Titrated insulin infusion is the most effective method of meeting blood sugar targets and enhancing patient outcomes (59). The use of insulin has been associated with increased likelihood of hypoglycaemia and thus requiring frequent point of care glucose measurements (60). Strategies that allowed patients to self-monitor their glucose during admission via use of home based glucometers were adopted to ease the monitoring of hospital glucose and protect the hospital staff from contracting and transmitting the virus (61).

Escalation of anti-glycaemic therapy was necessary and more so to intravenous insulin infusion (26). In severely ill DM patients with Covid-19, insulin requirements were high, with daily average doses reaching 201 units (2.2u/kg/day) and longer time was required to achieve glucose targets during the acute phase of the disease (62). Moreover, according to the ACCREDIT study, the percentage of patients requiring insulin infusion increased to about 10% during the Covid-19 pandemic. This was a considerable increase over the 2017 National Diabetes Inpatient Audit, which was a lower by 2 percentage (26). In the context of COVID-19, the management of DKA can present unique challenges due to infection control measures and the need to protect healthcare workers. To address these challenges, protocols have been developed that included the use of subcutaneous insulin to manage mild to moderate DKA in COVID-19 patients(63). Additionally, oral anti-glycaemic agents (OGLA) were still considered in the management of mild DM in hospital settings but generally avoided in severe illness (64).

Literature suggests that tighter blood sugar goals in hospitalized patients can have potential benefits (65). Most hospitalized patients tend to benefit from maintaining an ideal glucose range of 7.8-10 mmol/l (66). However, it is important to exercise caution as larger fluctuations in blood sugar levels and episodes of hypoglycemia may occur, which could have be detrimental effects (67).

Patients who maintain well-controlled blood glucose levels below 10 mmol/l have shown better outcomes compared to those with higher levels, with a significantly lower overall in-hospital mortality rate of 1.1% versus 11% (68). Therefore, glucose control serves as a significant predictor of mortality within the first 10 days of hospitalization.

It is worth noting that no ideal glucose targets have been established specifically for hospitalized patients with Covid-19 pneumonia (69). Thus, the management of blood glucose levels in these patients requires careful consideration and individualized approaches based on clinical judgment and monitoring.

The RECOVERY trial, a large-scale clinical trial conducted in the United Kingdom, demonstrated that the use of dexamethasone at a dosage of 6mg per day for 10 days could improve survival outcomes in individuals with moderate Covid-19 disease (70). The trial has had profound effects on the management of Covid-19 patients across the world. Dexamethasone is now considered standard therapy for people with severe COVID-19 disease who require respiratory support. However, despite the utility of steroids in the management of several respiratory illnesses, exposure to glucocorticoids is known to cause hyperglycaemia particularly in the presence of diabetes (71) and may contribute to insulin resistance (65). Thus, optimal glucose control proved to be more challenging during the management of Covid-19 due to the wide use of dexamethasone in hospitalized patients with severe disease (65,72).

2.6 Justification of the Study:

Throughout the pandemic, it is evident that patients with severe Covid-19 and diabetes were disproportionally affected with increased risk of hospitalization and mortality.

There have been reports of new-onset diabetes in Covid-19 infection, particularly following the addition of dexamethasone to the standard of care for hospitalized Covid-19 patients and its effect on worsening glycaemic control cannot be underscored.

This study highlights how patients with DM performed in our local set-up and provide insight into their clinical characteristics, demonstrate clinical experience with in-hospital metabolic control, and provide learning avenues for improving outcome.

It will provide us with information regarding the influence of Covid-19 on individuals with diabetes in our population. Consequently, this will contribute data to the already existing body of knowledge.

2.7 Research Question:

What are the clinical and laboratory characteristics and outcomes of hospitalised patients with Covid-19 infection and DM?

2.7.1 Broad Objective:

To determine the clinical characteristics and laboratory parameters, glycaemic events and their management, and short-term outcomes in hospitalised patients with Covid-19 and DM.

2.7.2 Primary Objectives:

1. To determine the clinico-laboratory characteristics of hospitalized patients with Covid-19 and diabetes mellitus at Kenyatta National Hospital.
2. To determine glycaemic events in patients with Covid-19 and diabetes mellitus during hospitalisation at Kenyatta National Hospital.
3. To determine the management of glycaemic events in hospitalised patients with Covid-19 and diabetes mellitus at Kenyatta National Hospital.
4. To determine the short-term outcomes of hospitalised patients with Covid-19 and diabetes mellitus at Kenyatta national hospital.

2.7.3 Secondary Objective:

1. To determine the predictors of adverse outcomes in patients with Covid-19 and DM.

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Study Design:

A retrospective cross-sectional study that entailed review of charts (files) of patients admitted at Kenyatta national hospital-Mbagathi infectious disease unit (KNH-Mbagathi IDU) with Covid-19 and DM.

3.2 Study Site

The study was conducted at the Kenyatta National Hospital, a public level six hospital located in Nairobi city and serves as the training hospital for the University of Nairobi. It has a capacity of approximately 1800 beds and provides both medical and surgical services at general and advanced (specialised) levels. During the Covid-19 pandemic, KNH was designated as a covid-19 treatment centre. The annex ward was located at Mbagathi hospital is named KNH-Mbagathi infectious disease unit (KNH-Mbagathi IDU).

The patient files are kept in the records department, situated on the ground floor of Kenyatta National Hospital (KNH). For the specific purpose of this study, the files were obtained from the records department and examined there.

3.3 Study population:

Medical records of patients with Covid-19 and DM admitted at the KNH-Mbagathi IDU between the periods of 13th March 2020 to 13th March 2022.

3.4 Case definition

Covid-19 – positive patients: medical records of patient with a positive documentation of SARsCOV-2 virus infection either by polymerase chain reaction (PCR) or Rapid antigen test or disease code B34.2 (disease code for Covid-19 at KNH) and admitted at the KNH-Mbagathi IDU.

Pre-existing DM was defined by history of known DM as evidenced by the use of anti-diabetic medication before hospitalization.

Newly diagnosed Diabetes Mellitus was qualified based on a negative history of prior DM but meeting the criteria for diagnosis of diabetes (HBA1C>6.5%, random blood sugar (RBS) >11.1mmol/l or fasting blood sugar (FBS) >7.0mmol/l) (73).

3.5. Eligibility

3.5.1 Inclusion criteria:

i. Evidence of SARsCOV-2 infection.
ii. Diagnosis of Diabetes mellitus (pre-existing or newly diagnosed).
iii. Above the age of 18 years and
iv. Admitted at KNH –Mbagathi IDU

3.5.2 Exclusion criteria:

i. Patient hospitalised for more than 3 days in another facility
ii. Contracted Covid-19 while in hospital (*The laboratory parameters and glycemic events were to be documented at admission and within 72 hours of hospitalization*)
iii. Incomplete files- missing PCR reports, Incomplete documentation of DM status and temporary files.

3.5.3 Ethical consideration

The study was approved by the Department of Clinical Medicine and Therapeutics, Faculty of Health Sciences, University of Nairobi and the KNH/UON ERC. The study was registered with the KNH Medical Research and Programs department. Access to medical records was granted by the Health Record and Information department. Patient identifiers were not recorded in the data extraction forms.

3.5.4 Sample size calculation

The sample size was calculated using Cochran's formula (Cochran, 1977). We utilized a mortality proportion of 20% based on a study by Sash *et al.* (42).

$$n_0 = \frac{Z^2 pq}{e^2}$$

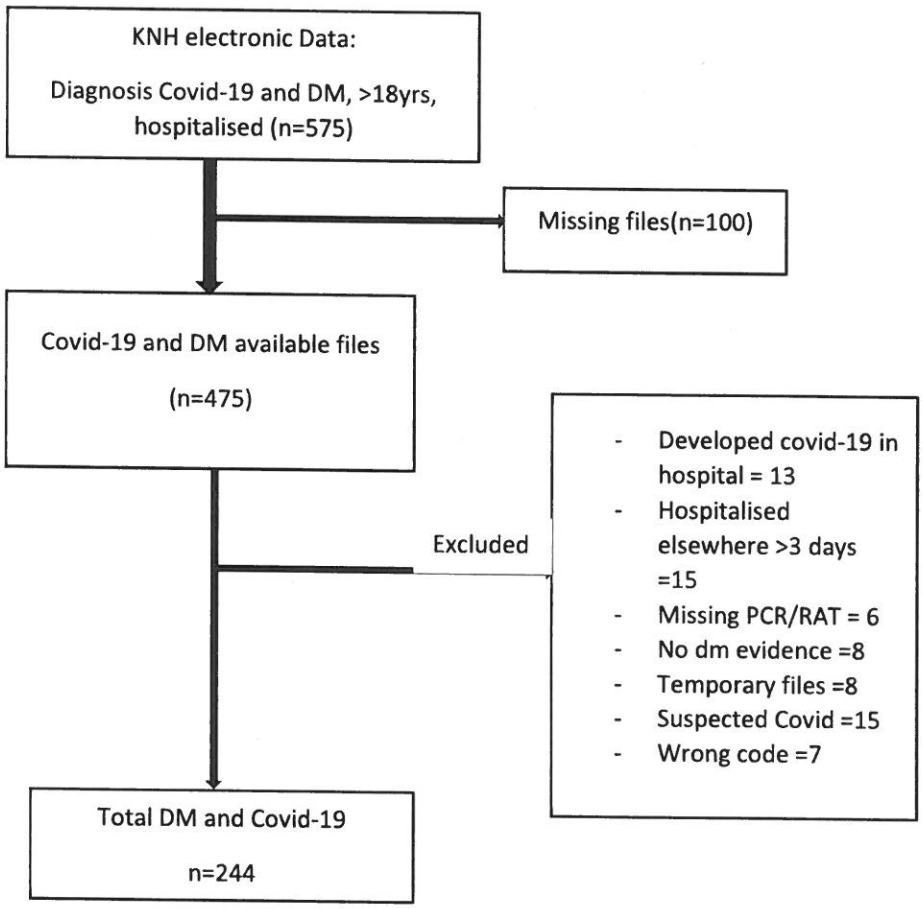
Where:

- Z–value for selected alpha level (1.96)
- p – Mortality proportion in DM was 20%
- q – 1-p
- e - acceptable error margin – 5%
- n_0= 244

Thus, a minimum of 244 files was required for the study.

A pooled mortality proportion among DM patients was selected since mortality as an outcome of interest, was deemed measurable hence its adoption from the above study for sample size calculation.

3.5.5 Sampling procedure:



3.5.6 Sampling method:

Systematic random sampling was employed. From the database with the aid of excel application, we generated the first random number from sampling frame described below:

The population size in our study was 475, and the required sample size was 244. As a result, the sampling interval was estimated as:

Population size / required sample size = sampling interval

Interval of sampling = 475 / 244

=1.9467 thus every 2nd file was chosen.

Then, while analyzing for eligibility, we chose every second file from the population, i.e. every 1, 3, 5, 7, and so on, until we reached the desired 244 files.

3.6 Data management and Analysis:

3.6.1 Data collection procedure

The files of Covid-19 patients with DM meeting our inclusion criteria were reviewed by the principal researcher together with two research assistants. We extracted data with aid of a standardized data extraction proforma created using KOBO tools. The principal investigator rechecked at least 10% of the files to ensure accuracy of the collected data.

The study collected demographic data including age, gender; cigarette smoking; presence of documented comorbidities (hypertension, chronic kidney disease, chronic obstructive pulmonary disease (COPD), asthma, human immunodeficiency virus (HIV)); the presenting complains (cough, fever, difficulty in breathing), initial SPO_2, and initial/index laboratory results (lymphocytes, admission RBS and HBA1c). The index laboratory results were accepted/collected and documented if done within 24 hours of admission. Further, HBA1c recorded during the course of hospitalisation was also recorded if not done at time of admission. The laboratory values were categorized as normal, high or low where applicable.

Information on point of care glucose (POC) readings in the in-patient was collected for the first 3 days (72 hours) of hospitalisation and where more than 1 reading was available; the average value for each day was calculated. Data on the total daily dose (T.D.D) of insulin was extracted for the initial 72 hours of hospitalisation. The first three days are considered the best reflection of a patient's glucose load and thus the overall representation of the patient's physiology at hospitalisation. Additionally, data on glycaemic events was obtained from charts as blood glucose readings to evaluate for hypoglycaemia (<3.9mmol/l) or hyperglycaemia (>10.0 mmol/l), arterial blood gas report to look at anion gap and, or urinalysis report to look for presence of ketones to diagnose DKA (Ketonuria +++) and serum osmolality (serum sodium levels) in the case of hyperosmolar hyperglycaemic state (HHS). The reference time for glycaemic events was the first 72 hours following hospitalisation. Management of glycaemic events was assessed by examination of data on glycaemic treatment strategies during hospitalisation (insulin, oral glycaemic agents (OGLA), dosing trends, mode of administration and discharge prescription). Finally, data on administered co-treatment (steroids, oxygen) and outcome (discharge, ICU admission, continued hospitalisation and death) within 14 days of hospitalisation was also extracted.

3.6.2 Study variables

Patient variable: documented age on the chart, documented gender, documented comorbidities (hypertension, HIV/AIDS, Asthma, COPD and others) as well as the recorded smoking history.

Laboratory variables: recorded data on laboratory parameters collected within the first 24 hours of hospitalization. The reference laboratory values included admission random blood sugar, markers of inflammation (CRP, D-dimers, lymphocytes count and lactate dehydrogenase (LDH)) as well as HBA1c.

Clinical variables- documented presenting symptoms at the time of admission to include presence of dyspnoea, cough, fever chest pain etc. the measured levels of oxygen saturation (SPO2) as recorded.

Glycaemic events were defined as the occurrence of DKA/HHS as documented on the charts while hypoglycaemia was defined by a single blood glucose level of <3.9mmol/l, and hyperglycaemia by levels greater than 10mmol/l during the first 72 hrs of hospitalisation.

Management variables the treatment approach employed for managing glycemic events during hospitalization. This included the use of insulin, which encompassed the mode of administration and the total daily dose (T.D.D). Additionally, the use of oral glucose-lowering agents and the treatment plan upon discharge were also taken into consideration.

Outcome variables:

- ✓ **The short-term outcome** - were events occurring within 14 days of hospitalisation. These included; discharge, admission to the ICU, continued hospitalization, or death.
- ✓ **Adverse outcome:** defined as hospitalization beyond 14 days, death or admission to the critical care unit

Predictors of adverse outcome: The examined determinants included age, gender, comorbidities, DM status (pre-existing vs NDDM), glycaemic events, inflammatory markers (CRP, D-dimers, lymphocytes count), steroid use, admission RBS and HbA1c.

3.6.3 Statistical Analysis

Data was extracted from each file by the extraction tool, assigned a study code and scrutinized. It was then keyed into a protected database by the principal investigator for subsequent data cleaning and analysis performed on Statistical Package for Social Sciences (SPSS) version 26 with the help of a statistician.

The clinico-laboratory characteristics of hospitalized patients with Covid-19 and diabetes mellitus at Kenyatta National Hospital.

Categorical clinical and laboratory characteristics were analysed using frequencies (n) and percentages (%) while continuous clinical and laboratory characteristics were analysed using Mean and standard deviation (Mean ± SD).

Glycaemic events in patients with Covid-19 and diabetes mellitus during hospitalisation at Kenyatta National Hospital

The glycaemic events were categorical in nature and thus they were analysed and summarized using frequencies (n) and percentages (%).

The management of glycaemic events in hospitalised patients with Covid-19 and diabetes mellitus at Kenyatta National Hospital

Management of glycaemic events in hospitalised patients with Covid-19 and diabetes mellitus were analysed using frequencies (n) and percentages (%).

The short-term outcomes of hospitalised patients with Covid-19 and diabetes mellitus at Kenyatta national hospital.

The short-term outcomes (discharge, admission to the ICU, continued hospitalization, or death) were analysed descriptively using frequencies (n) and percentages (%).

The predictors of adverse outcomes in patients with Covid-19 pneumonia and DM.

The adverse outcomes of interest included hospitalization beyond 14 days, death or admission to the critical care unit. Bivariable analysis was conducted using binary logistic regression. Crude odds ratio (COR) were calculated to determine the extent of association. Multivariable analysis was conducted to determine independent predictors of adverse outcomes. Adjusted odds ratio (AOR) were calculated to determine the extent of association. The findings were presented in tables and pie charts. The level of significance was set at a p value of less than 0.05.

CHAPTER FOUR

4.0 RESULTS

575 Covid-19 patients with Diabetes mellitus were hospitalized at the KNH between the periods of 13th March 2020 to 13th March 2022. A total of 244 patients records were analysed as shown in figure 2 below.

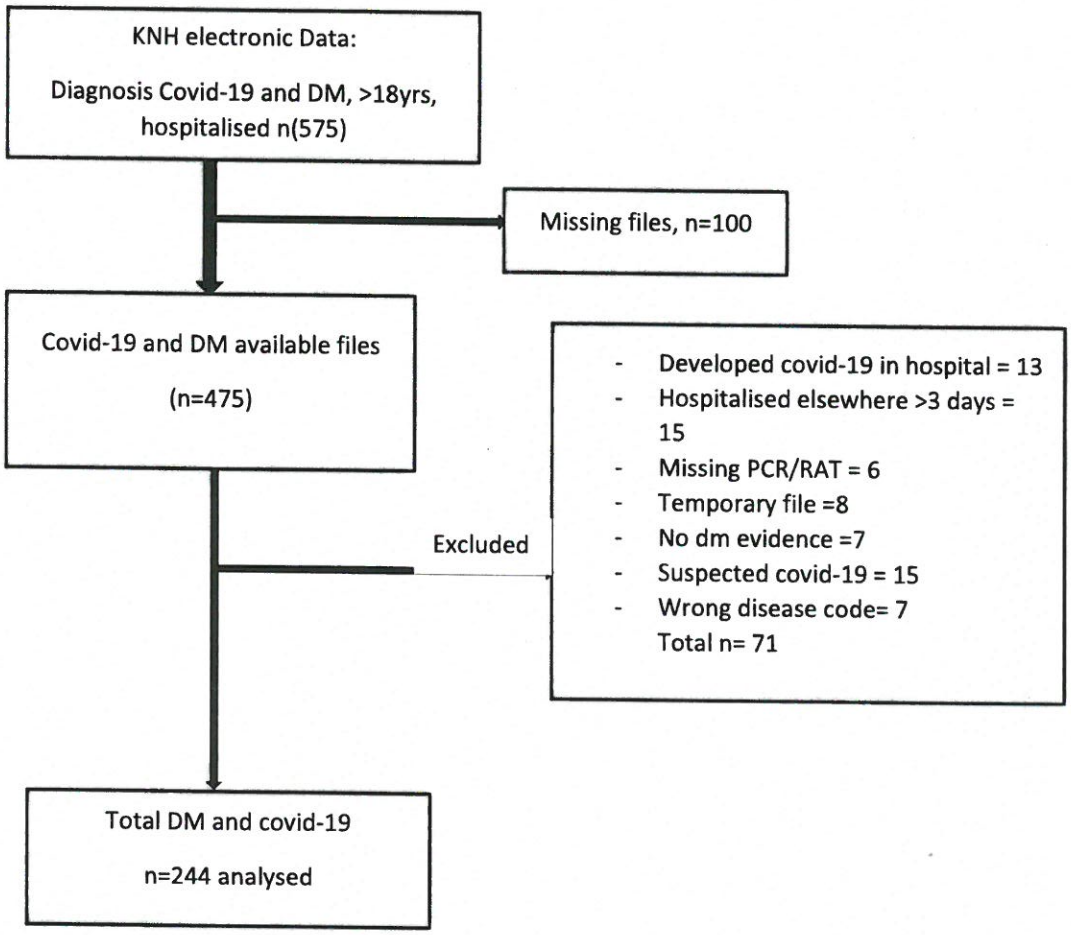


Figure 2: Recruitment flow

4.1 Demographic characteristics of Covid-19 patients with DM at Kenyatta National hospital

Male patients made up 129 (52.9%) of the study population. The majority of study participants were slightly young, with those aged 45 to 59 years making up 44.7% (109) of the patients. The median age was 58.5 years. The vast majority of study participants, 169 (69.3%), had a comorbidity. As highlighted in Table 1, the most prevalent comorbidities were hypertension 148(60.7%) and HIV/AIDS 14(5.7%). Others at combined proportion of 51.6% included Acute

kidney injury, pulmonary embolism, chronic kidney disease, hyperthyroidism, dementia and osteoarthritis.

Table 1: Demographic characteristics of Covid-19 patients with DM at Kenyatta National hospital

	Frequency (n)	Percent(%)
Age group (Median, IQR) years	58.5(48 – 61.25)	
Age		
<30 years	15	6.1
30 - 44 years	35	14.3
45 - 59 years	109	44.7
≥60 years	85	34.8
Gender		
Male	129	52.9
Female	115	47.1
Cigarette smoking	10	4.1
Presence of comorbidity	169	69.3
Hypertension	148	60.7
HIV/AIDS	14	5.7
COPD	3	1.2
Asthma	9	3.7
Cancer	10	4.1
Others*	126	51.6

**AKI, Hyperthyroidism, Pulmonary embolism, CKD, Osteoarthritis, Dementia, epilepsy*

4.2 Clinical characteristics of Covid-19 patients with DM hospitalised at Kenyatta National hospital

Cough 151(61.9%) was the most common covid-19 symptom, followed by dyspnoea 147(60.2%), chest pain 30.7%, and fever 60(24.6%). Table 2 shows that other symptoms were headache, sore throat, and broad body malaise.

Table 2: Clinical characteristics of Covid-19 patients with DM hospitalised at Kenyatta National Hospital

	Frequencies	Percent
Recorded Presenting symptoms		
Dyspnoea	147	60.2
Fever	60	24.6
Cough	151	61.9
Chest pain	75	30.7
Others*	173	70.9

**Generalized body malaise, Sore throat, headache, dizziness, loose stool, diarrhoea, joint pain, vomiting, Abdominal distention*

4.3 Baseline laboratory values of study participants at admission or hospitalisation

The median, Interquartile range (IQR) SP02 on admission was 85.5(IQR: 70.75 – 90.0)%. The Median random blood sugar level at hospitalization was 13.8(IQR: 8.38 – 18.28)mmol/l, with nearly two-thirds (64.8%) presenting with acute hyperglycaemia of greater than 11.1mmol/l. HBA1c was 8.9(SD3.4) % on average. The median D-dimer level was 1.46(IQR: 0.36 – 2.44)ug/l. The median lymphocyte cell count was 1.22(IQR: 0.88 – 1.38)109/l, with only 32.4% of the records showing lymphopenia. The median CRP was 55.9(IQR:27.3 – 59.68) mg/l. A large proportion of the patients showed increased LDH, with a median of 486(IQR: 430.3 – 577.5)U/I compared to the normal reference range (as indicated in Table 3).

4.4 Glycaemic events occurring in the first 72hrs in Covid-19 patients with diabetes mellitus during hospitalisation at Kenyatta National Hospital

Within the first 72 hours of hospitalization, 26 patients (10.7%) experienced hypoglycaemia, 216 (88.5%) developed hyperglycaemia, and 63 (25.8%) got DKA/HHS. These events occurred in both NDDM and pre-existing DM patients. The events were recorded from the time of admission to first 72 hours after hospitalisation, as seen in Table 4 below.

4.5 Management of glycaemic events in hospitalised Covid-19 patients diabetes mellitus at Kenyatta national hospital.

Subcutaneous insulin was the primary technique of insulin delivery for the management of glycaemic events 199(81.6%). Oral glucose lowering agents (OGLA) utilized were metformin (98.2%), sulphonylureas (SU) (13%) and dipeptidyl 4 (DPP4) inhibitor (9.7%). Insulin doses were gradually increased during the first three days, from a mean dose of 28.7 iu on day one to a higher level of 34.6 iu on day three. At discharge, 120 (49.2%) were on insulin and 87 (64.0%) were discharged on metformin. The management of glycaemic events is summarized in Table 5.

Table 3: Lab parameters at admission of Covid-19 patients with DM at Kenyatta National hospital enrolled in the study

Lab parameters at admission	Frequency or (Median, IQR)	Percent
SPO2 (Median, IQR) % (n = 223)	85.5(70.75 – 90.0)	
Normal >90%	95	38.9
Low	128	52.5
Missing	21	8.6
Admission RBS (Median, IQR) mmol/l (n=231)	13.8(8.38 – 18.28)	
Normal (<11.1 mmol/l)	73	29.9
High	158	64.8
Missing	13	5.3
HBA1c (Median, IQR) % (n =234)	8.3(6.0 – 11.65)	
Normal (5.5-6.5%)	33	13.5
High	201	82.4
Missing	10	4.1
D-dimers (Median, IQR) ug/l (n =217)	1.46(0.36 – 2.44)	
Normal (0.0-0.50 ug/l)	47	19.3
High	170	69.7
Missing	27	11.1
Lymphocytes (Median, IQR) 10^9/l (n =233)	1.22(0.88 – 1.38)	
Low	79	32.4
Normal (1.0-3.7 *10^9/l)	154	63.1
High	4	1.6
Missing	7	2.9
CRP (Median, IQR) mg/l (n =235)	55.9(27.3 – 59.68)	
Normal (0.0-5.0 mg/l)	15	6.1
High	220	90.2
Missing	9	3.7
LDH (Median, IQR) U/l (n =225)	486(430.3 – 577.5)	
Normal (109-254 U/l)	13	5.3
High	212	86.9
Missing	19	7.8

Table 4: Glycaemic events in the first 72 hrs in hospitalised Covid-19 patients with DM at KNH

		DM status	
Glycemic events	**Total n(%)**	**Pre-existing diabetes n(%)**	**Newly diagnosed diabetes n(%)**
Hypoglycemia			
Yes (<3.9mmol/l	26(10.7)	22(11.6)	4(7.4)
No (>=3.9mmol/l)	218(89.3)	168(88.4)	50(92.6)
Hyperglycaemia			
>10.0mmol/l	216(88.5)	169(88.9)	47(87.0)
No (<=10.0mmol/l)	28(11.5)	21(11.1)	7(13.0)
DKA/HHS			
Yes	63(25.8)	48(25.3)	15(27.8)
No	181(74.2)	142(74.7)	39(72.2)

Table 5: Management of glycaemic events in hospitalized study patients with Covid-19 and diabetes mellitus at Kenyatta national hospital

Treatment	**Frequency(n) or Mean ±SD of parameter**	**Percent**
Mode of insulin administration		
Subcutaneous	199	81.6
Infusion	23	9.4
Total daily dose of insulin(units)		
Average insulin day 1 (Mean ±SD)	28.7±15.6	
Average insulin day 2 (Mean ±SD)	31.9±16.5	
Average insulin day 3 (Mean ±SD)	34.6±16.8	
Oral anti-diabetic agents administered		
Metformin	98	40.2
Sulphonylureas (gliclazide, glibenclamide, etc)	13	5.3
DPP4 inhibitor;(sitagliptin, vildagliptin)	9	3.7
Discharge treatment		
Insulin	120	63.5
Metformin	87	46.0
DPP4 inhibitor	9	4.8
SGLT2 inhibitor	6	3.2
Sulphonylureas	17	9.0

4.6 General management approaches among hospitalized Covid-19 patients diabetes mellitus at Kenyatta national hospital

According to the records, 47.1% of the patients were given steroids, with the average dose being 6.4(SD3.8) mg for an average duration of 6.4(SD3.8) days. As seen in Table 6, 146 (59.8%) patients required oxygen supplementation.

Table 6: General management approaches of the hospitalized study patients with Covid-19 and diabetes mellitus at Kenyatta national hospital

Treatment	Frequency or Mean ±SD	Percent
Co-treatment		
Total no of patients on Steroids	115	47.1
Mean dose mg/day (Mean ±SD)	6.3±1.1	
Mean duration (Mean ±SD) days	6.4±3.8	
Total no of patients on Oxygen	146	59.8
Mean O_2flow rate per min (Mean ±SD)	11±4.6	

4.7 The short-term outcomes of the study patients with Covid-19 and diabetes mellitus at Kenyatta national hospital

The average length of hospital stay was 10.37 (SD6.4) days, with 139 (57%) of patients remaining in the hospital for 10 days or less. As shown in Table 7, discharged patients accounted for 146 (59.8%) of the study population, whereas 55 (22.5%) died and 32 (13.1%) were hospitalized for more than 14 days, with only 11 (4.5%) admitted to critical care.

Table 7: The short-term outcomes of hospitalised patients with Covid-19 and diabetes mellitus at Kenyatta national hospital

	Frequency(n)	Percent (%)
Outcome		
Hospitalized for more than 14 days	32	13.1
Death	55	22.5
Discharge within 14 days	146	59.8
Transfer to critical care	11	4.5
Length of hospital (Mean ±SD) days	10.37±6.4	
<=10 days	139	57.0
>10 days	105	43.0

4.8 The predictors of adverse outcomes in Covid-19 patients with DM

4.8.1 Predictors of mortality among Covid-19 patients with diabetes mellitus

The findings from a bi-variable analysis using binary logistic regression revealed that DM patients who had a comorbidity were 5 times more likely to die compared to the DM patients

without any comorbidity, crude odds ratio (COR) =5.46, 95%CI:2.08 – 14.38, p=0.001. Furthermore, DM patients who had hypertension were 11 times likely to die compared to non-hypertensive diabetics, COR = 10.5, 95%CI:4.03 – 27.61, p<0.001. Those who presented with dyspnoea were 3 times more likely to die compared to those who presented without dyspnoea, COR =2.72, 95%CI:1.35 – 5.51, p =0.004. Findings also revealed that those with newly diagnosed diabetes were twice more likely to die compared to those with pre-existing diabetes, COR = 2.06, 95%CI:1.06 -4.04, p =0.042. Patients who had DKA/HHS were 2 times likely to die compared to those without DKA, COR =1.94, 95%CI:1.02 – 3.70, p =0.044.

Multivariable analysis was conducted including significant variables (p<0.05) under bivariable analysis using binary logistic regression. The findings showed that hypertensive diabetic patients were six times more likely to die compared to diabetics' patients with no pre-existing hypertension, adjusted odds ratio (AOR)=6.12, 95%CI:1.78 – 21.05, p=0.004. Patients who presented with dyspnoea were 2.5 times more likely to die compared to those who presented without dyspnoea, AOR =2.51, 95%CI:1.10 -5.74, p =0.029. Patients who had DKA/HHS were 3.8 times more likely to die compared to those without, AOR =3.83, 95%CI:1.68 – 8.15, p=0.001 as shown in Table 8.

4.8.2 Distribution of mortality based on age

The study findings indicate that a significant proportion of deaths were observed among patients aged 40 years and above. Notably, out of the total number of patients who died, 20% (n = 11) were aged above 60 years as illustrated in Figure 3 below. These results emphasize the increased vulnerability of older individuals.

4.8.3 Predictors of prolonged hospitalization among Covid-19 patients with diabetes mellitus

Individuals with dyspnoea were twice as likely to stay longer in the hospital than those without dyspnoea, OR =2.02, 95% CI:1.02 - 4.01, p =0.033. As indicated in Table 9, those who presented with cough were 2.5 times more likely to remain in the hospital, OR =2.50, 95% CI:1.25 - 4.99, p =0.001. similarly, age was a significant predictor of prolonged hospitalisation.

Table 8: Predictors of mortality among hospitalised Covid-19 patients with DM

	Mortality					
Factors	**Yes n(%)**	No n(%)	**COR(95%CI)**	**P-value**	**AOR(95%CI)**	**P-value**
Demographic factors						
Age	56.1±14	55.1±14	0.99(0.97 - 1.02)	0.576		
Gender						
Male	32(58.2)	97(51.3)	0.76(0.41 - 1.39)	0.443		
Female	23(41.8)	92(48.7)	Ref			
Cigarette smoking	2(3.8)	8(4.7)	1.24(0.26 - 6.05)	0.787		
Clinical factors						
Presence of comorbidity	50(90.9)	119(64.7)	5.46(2.08 - 14.38)	**0.001**	3.22(0.69 - 15.11)	0.139
Hypertension	50(90.9)	92(48.7)	10.5(4.03 - 27.61)	**<0.001**	6.12(1.78 - 21.05)	**0.004**
HIV/AIDS	4(7.3)	10(5.3)	1.40(0.42 - 4.66)	0.525		
Asthma	2(3.6)	7(3.7)	0.98(0.20 - 4.86)	0.981		
Cancer	2(3.6)	8(4.2)	0.85(0.18 - 4.14)	0.844		
Dyspnoea	43(78.2)	104(56.8)	2.72(1.35 - 5.51)	**0.004**	2.51(1.10 - 5.74)	**0.029**
Fever	13(23.6)	47(25.7)	0.90(0.44 - 1.81)	0.86		
Cough	32(58.2)	119(65)	0.75(0.40 - 1.39)	0.425		
Chest pain	17(30.9)	58(31.7)	0.96(0.50 - 1.85)	0.527		
DM status						
Pre-existing diabetes	37(67.3)	153(81)	Ref			
Newly diagnosed diabetes	18(32.7)	36(19)	2.06(1.06 - 4.04)	**0.042**	2.96(1.21 - 7.24)	**0.017**
Glycaemic events						
Hypoglycaemia	7(12.7)	19(10.1)	0.77(0.30 - 1.93)	0.62		
Hyperglycaemia	48(87.3)	168(88.9)	1.17(0.47 - 2.91)	0.81		
DKA/HHS	20(36.4)	43(22.8)	1.94(1.02 – 3.70)	**0.044**	3.83(1.68 - 8.15)	**0.001**
Laboratory factors						
Admission RBS (Mean ±SD)	15.5±7.4	15.4±7.36)	1.02(0.79 - 1.33)	0.883		
HBA1c (Mean ±SD)	9.3(4.2	8.9±3.3	0.22(0.04 - 1.39)	0.107		
D-dimers (Mean ±SD)	1.8±1.5	1.7±1.5	0.09(0.01 - 1.24)	0.071		
Lymphocytes (Mean ±SD)	1.2±0.9	1.4±0.7	0.14(0.00 - 18.91)	0.594		
CRP (Mean ±SD)	63.0±38.7	47.2±29.2	0.88(0.74 - 1.03)	0.108		
LDH (Mean ±SD)	545.0±184.5	439.5±147.1	1.04(0.99 - 1.08)	0.106		
Management approaches						
Steroid (n, %)	23(53.5)	92(68.1)	0.54(0.27 - 1.08)	0.082		
Oxygen (n, %)	38(88.4)	108(80)	1.90(0.68 - 5.29)	0.219		

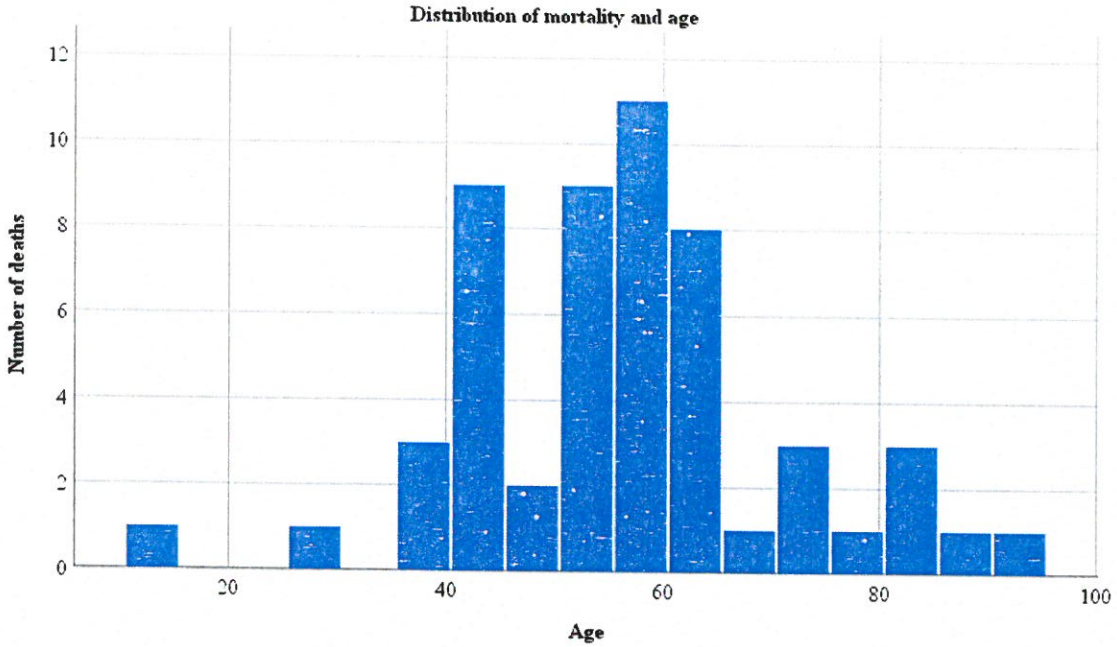


Figure 3: Distribution of mortality by age

Table 9: Predictors of prolonged hospitalization among Covid-19 patients with diabetes mellitus

Factors	Continued hospitalization Yes n(%)	No n(%)	OR(95%CI)	P-value
Demographic factors				
Age (Mean, SD)	55.4±10	49.1±12	2.31(1.51 - 4.51)	**0.024**
Gender				
Male	24(55.8)	105(52.2)	1.16(0.60 - 2.24)	0.738
Female	19(44.2)	96(47.8)	Ref	
Cigarette smoking (Yes)	6(15.4)	4(2.2)	8.27(2.21 - 30.92)	0.002
Clinical factors				
Presence of comorbidity (Yes)	28(65.1)	141(71.9)	0.73(0.36 - 1.47)	0.363
Hypertension (Yes)	21(48.8)	81(40.3)	1.41(0.73 - 2.74)	0.312
HIV/AIDS (Yes)	4(9.3)	10(5.0)	0.51(0.15 - 1.71)	0.279
Asthma (Yes)	1(2.3)	8(4.0)	1.74(0.21 - 14.30)	0.508
Cancer (Yes)	4(9.3)	6(3.0)	0.30(0.08 - 1.11)	0.079
Dyspnoea (Yes)	21(52.5)	70(35.4)	2.02(1.02 - 4.01)	**0.033**
Fever (Yes)	31(77.5)	147(74.2)	1.20(0.53 - 2.68)	0.842
Cough (Yes)	22(55.0)	65(32.8)	2.50(1.25 - 4.99)	**0.001**
Chest pain (Yes)	28(70.0)	135(68.2)	1.09(0.52 - 2.28)	0.491
DM status				
Pre-existing diabetes	32(74.4)	158(78.6)	0.79(0.37 - 1.70)	0.548
Newly diagnosed diabetes	11(25.6)	43(21.4)	Ref	
Glycaemic events				
Hypoglycaemia (Yes)	7(16.3)	19(9.5)	1.86(0.73 - 4.76)	0.183
Hyperglycaemia (Yes)	39(90.7)	177(88.1)	1.32(0.43 - 4.03)	0.794
DKA (Yes)	14(35.9)	49(27.5)	1.47(0.71 - 3.07)	0.332
Laboratory parameters				
RBS (Mean ±SD)	17.03±8.9	15.02±7.0	1.03(0.88 - 1.21)	0.713
HBA1C (Mean ±SD)	9.59±4.0	8.79±3.3	1.18(0.87 - 1.61)	0.290
D-Dimers (Mean ±SD)	1.85±1.5	1.71±1.53	1.17(0.67 - 2.04	0.587
Lymphocytes (Mean ±SD)	1.4±0.7	1.40±0.7	1.12(0.14 - 9.27)	0.917
CRP (Mean ±SD)	55.2±34.5	55.2±34.5	1.01(0.97 - 1.05)	0.703
LDH (Mean ±SD)	427.3±167.7	470.5±162.1	0.67(0.21 - 1.31)	0.469
Management approaches				
Steroid use (Yes)	17(54.8)	98(66.7)	0.61(0.28 - 1.33)	0.221
Oxygen use (Yes)	28(70)	118(72.4)	0.89(0.42 - 1.90)	0.451

5.0 CHAPTER FIVE

5.1 DISCUSION

The impact of COVID-19 on patients with diabetes mellitus (DM) has been well-documented in previous research, indicating a higher risk of severe disease and mortality (74). In this retrospective cross sectional, single centre study, we sought to highlight the clinico-laboratory characteristics and short-term outcomes of hospitalised Covid-19 patients with DM at KNH in Kenya between the periods from 13th March 2020 to 13th March 2022.

In our study, the median age was 58.5 years, with the majority (52.9%) of the participants being male. The study found that the most common comorbidity was hypertension (60.7%). Majority (78%) had Pre-existing DM while 54 (22%) had NDDM. The average RBS at admission was 15.7mmol/l with about 2/3 of the participants presenting with hyperglycaemia and poorly controlled glycemia was observed in (82.4%) of the patients, with an average HBA1c of 8.9 %. Cough (61.9%) and dyspnoea (60.2%) were the most common presenting symptoms with the mean SPO_2 at hospitalisation of 84%. Within the first 72 hours of admission, 26.5% of patients experienced DKA, while 10.7% experienced hypoglycaemia. The main laboratory findings included elevated CRP (90.2%), elevated D-dimers (69.7%), elevated LDH (86.9%) while mean lymphocyte count was of 1.36 $*10^9$/l. The average hospital stay was 10 days, with an overall mortality proportion of 22.5% and close to 60% of the participants were discharged within 14 days. Approximately 5% were admitted into the critical care unit.

The study population was relatively younger, with the majority (44.7%) aged between 45-59 years, which is consistent with an earlier study in Kenya by Ombajo et al (28). This finding is likely due to the location of KNH in the country's capital, which attracts people on transit who could be younger. On univariable analysis, an increasing risk of mortality was observed with advancing age, with patients over 60 having a 9% higher chance of dying than those under 60, supporting previous reports (20,75). The study further observed a higher prevalence of male gender among individuals who contracted and were admitted with Covid-19, which aligns with findings reported globally (23,75,76). This difference in prevalence could be attributed to various factors, including biological variations in immune systems between males and females (77). Additionally, hazardous habits or behaviors, as well as potential non-compliance with Covid-19 containment measures, may contribute to the higher incidence among men.

The study highlighted the presence of comorbidities such as hypertension, which was observed in 60.7% of the study patients as an independent risk for mortality with AOR 6.12(1.78-21.05). DM often coexists with other chronic conditions particularly hypertension (43,78). A meta-analysis conducted on hospitalized patients in the United States revealed a prevalence of 55% for hypertension among individuals with DM (79). This finding suggests a significant association between DM and hypertension in the hospitalized population. Therefore, patients Covid-19 patients who have DM, especially those with pre-existing hypertension, should receive careful and diligent monitoring. The coexistence of DM and hypertension can potentially worsen the clinical course and outcomes of Covid-19, emphasizing the need for close attention and management for this specific patient population.

At the time of presentation, cough and dyspnea were identified as the most commonly reported symptoms among the patients. Surprisingly, fever was only reported in 24.6% of the cases. While these symptoms align with findings from previous studies, the proportions of each symptom varied in comparison (24,76,80). Dawei Wang *et al.* found that the most common symptoms at onset of illness were fever 98.6%, fatigue 69.6%, dry cough 59.4%, myalgia 34.8%, and dyspnoea 31.2% (76). Hu *et al.* in a systematic review and metanalysis found the commonest symptoms to be fever 85 % and cough 65.7% while 21.4% of patients presented with dyspnoea (80). Similarly, Wei-jie Guan in a retrospective study involving 1099 patients with Covid-19 found the commonest symptoms were fever and cough at 43.7% and 67.8% respectively (24). Likewise, in the CORONADO study, the most common symptoms and signs were fever (77.9%), cough (68.7%), fatigue (62.4%), dyspnoea (61.8%). The variation in symptomatology at presentation could be attributed to documentation and the reporting of presenting complains at the time hospitalisation was done. In our study, breathlessness was found to be a significant predictor of mortality. This finding is consistent with previous research that has demonstrated DM increased the susceptibility to severe disease (79). Moreover, the presence of dyspnoea at admission serves as an indicator of the severity of the condition. In a prior study, Cariou *et al.* found that among covid-19 patients with DM, dyspnoea OR 2.17 (1.34, 3.50) on admission was positively linked with death (36). Therefore, it is important to recognize and monitor breathlessness in DM patients with Covid-19 as a potential marker for adverse outcomes.

The current study revealed that a majority of the hospitalized patients exhibited abnormalities in their inflammatory markers. On bivariate analysis, the observed laboratory parameters

were not significantly associated with mortality. The elevated makers of inflammation points to an enduring insult as well as acute nature of the disease and the resultant hyperinflammatory state(9,26). We noted from our study a prevalence of lymphocytopenia to be 32.4% which contrasts other studies that observed a higher proportion of patients with lymphocytopenia ranging from 60.1% to 83.2% (24,75,81). Lymphopenia in Covid-19 patients is thought to result from either myelosuppression, infection or destruction or from functional exhaustion of the antiviral lymphocytes (82). Low lymphocyte count is commonly recognised as an indicator of inflammation in Covid-19 (81). Elevated D-dimers in our study could be a result of increased thrombosis due to hyperglycaemia (83) or as a marker of inflammation following infection with SARSCOV-2 (84).

In our study, the proportion of NDDM was found to be 22%. The rate was similar to the 20.8% recorded in Vietnam (85). The prevalence of DM in a north India study with 401 patients was reported as 47.1% for pre-existing DM and 5.2% for new-onset DM (86). However, in a retrospective study by Li et al , the incidence of NDDM was documented as 28.4 % (7). In Wuhan China, the incidence of NDDM was 20.8 % in hospitalised patients (7). In a meta-analysis by Sathish et.al, the incidence of NDDM was found to be 14 % (39). Stress hyperglycaemia related to acute inflammation, as well as the use of corticosteroids, could contribute to the observed upsurge in NDDM cases (39,87). In our cohort, we found that 47.5% of patients were given steroids for an average of 6 days. However, the diabetogenic effect of the Sars-cov-2 virus should be considered when trying to figure out why there are so many NDDM cases in the Covid-19 pandemic (88). Some of the cases of NDDM could be a result of previously unrecognized DM (89). We did not continue to monitor the patients after they were discharged to see if the hyperglycaemia continued beyond the hospital stay. An American examination of the burden after 6 months of hospitalization revealed an 8% increase in the risk of DM, although the long-term risk of DM with Covid-19 is still unclear (90). After recovering from Covid-19, people were more likely to develop type 2 diabetes, according to the primary care study (91).

Our present study highlights the significance of glycemic control in patients with DM, particularly during Covid-19 infection, as it can impact disease outcomes. The majority of patients in this study exhibited poorly controlled long-term glucose control. Additionally, a significant proportion of patients experienced DKA within the first 72 hours of admission, while hypoglycemia and in-hospital hyperglycemia also prevalent. Notably, a small

percentage (5.3%) of DM patients continued to use SU during hospitalization. This observation raises concerns about the implications of SU use on glycemic control and treatment decisions in the context of Covid-19 infection. SU have been linked with increased cases of hypoglycaemia among hospitalised patients (92). Furthermore, Covid-19 induced anorexia leads to diminished oral intake which could result in hypoglycaemia (36). These findings emphasize the critical importance of close monitoring and effective management of blood glucose levels in DM patients with Covid-19.

Our analysis was conducted over a 2-year period and encompassed patients through all the peaks of the pandemic, including the time when dexamethasone was introduced to the treatment protocol. The inclusion of patients treated with dexamethasone might have contributed to the increased frequency of hyperglycaemia observed in the study. Elevated blood glucose is a known potential side effect of steroid use. Diabetic ketoacidosis, a life threatening acute metabolic complication of DM has been observed following infection with SARsCov-2 virus (16). In a New York study (93), the prevalence of DKA was greater during pandemic 3.14% vs pre-pandemic period 0.72%. Previous studies have established the prevalence of DKA in Covid-19 to range between 2.4 % and 13.2% (16,26,94). Viral infections have been noted to induce acute hyperglycaemia and ketosis due to their effect on the pancreas(95). Beta cell injury and reduced insulin secretion following infection with SARsCOV-2 virus have been hypothesised to trigger hyperglycaemia and subsequently DKA in Covid-19 disease (96). Other mechanisms leading to increased DKA included use of steroids and severity of covid-19 disease (94). DKA independently enhanced the risks of mortality in our current investigation. Diabetic ketoacidosis can be severe even in the absence of Covid-19, although it is manageable if detected and treated promptly. Control of acute metabolic states must therefore be a focus for persons with Dm and Covid-19

DM is closely related to worse outcomes for individuals who are hospitalized. These include all-cause mortality, the requirement for ICU treatment and mechanical breathing, as well as extended hospital stays (13,36,43). The average hospital stay in our study was 10 days, with an overall mortality rate of 22.5%. This mortality rate is higher than the reported rates in other studies (42), which could be attributed to several factors, including differences in study populations and healthcare systems. Although the design of the current study prevented us from comparing the covid-19 cohort to those without diabetes, our findings are consistent with previous research that revealed diabetic patients had higher mortality and a greater need

for intensive care unit treatment (97). There is a strong link between mortality and long-term glucose control (47,51). However, from our study, HBA1c and admission RBS were not significantly linked with mortality. These findings are similar to what was reported in ACCREDIT and CORONADO studies (26,36).

Further, factors that predicted adverse outcome among DM patients with Covid-19 included, advanced age, male gender, obesity and pre-existing comorbidities(50,51). Similarly, in our study, several factors were found to have a significant impact on mortality. They included hypertension, dyspnoea, NDDM, and the presence of DKA/HHS. Patients with these factors are at a higher risk of experiencing adverse outcomes. Uncontrolled metabolic states in DM patients increases the odds of serious complications and death (52). Across the literature, a weighty determinant of mortality in Covid-19 is presence of comorbidities with DM emerging as an important cog (98,99). Notably, DM often coexists with hypertension which can adversely impact on outcome (100). With regard to hospitalization beyond 14 days, our study inferred that smoking, age greater than 55.4 years, cough and dyspnoea were significant determinants of prolonged hospitalization. The findings emphasize the importance of closely monitoring and managing these factors in order to improve patient outcomes.

5.2 LIMITATIONS AND STRENGTHS

The use of discharge diagnosis code and discharge summary ensured that most if not all DM patients were captured hence eligible for sampling. Nonetheless, our study has several limitations, considering we centred on hospitalized Covid-19 cases, our findings cannot be applied to all Covid-19 and diabetic subjects, primarily those with a less severe form of the illness and having not compared DM vs Non-DM patients with Covid-19. Secondly, because the study was retrospective in nature, we were unable to determine a causal relationship. Some lab values contained missing data and thus could have impacted the analysis of our secondary objectives. However, these discoveries will both bridge the current knowledge gap and add to the existing island of knowledge, particularly with relation to Sub-Saharan (SSA) data.

5.3 RECOMMENDATIONS

1. Emphasis should be given to the management of pre-existing comorbidities, particularly hypertension, in Covid-19 patients with DM to prevent adverse outcomes.

2. Health care providers should consider DKA/HHS as a predictor of mortality in Covid-19 patients with DM, and timely interventions should be taken to prevent its occurrence.
3. Post hoc follow up of the newly diagnosed patients to establish the DM status post hospitalization. It remains unresolved whether the NDDM in Covid-19 was temporary or whether it persist to chronic DM.

5.4 CONCLUSION

Hospitalised Covid-19 patients with DM had elevated RBS at admission with poor overall glycaemic control and elevated levels inflammatory markers. Glycaemic events, including DKA/HHS, were common during hospitalisation, and DKA/HHS was identified as an independent predictor of mortality. Our findings underscore the importance of closely monitoring and managing glycaemic control in patients with COVID-19 and diabetes.

6. Reference:

1. Background paper on Covid-19 disease and vaccines: prepared by the Strategic Advisory Group of Experts (SAGE) on immunization working group on COVID-19 vaccines, 22 December 2020 [Internet]. Available from: https://apps.who.int/iris/handle/10665/338095

2. Liu J, Liao X, Qian S, Yuan J, Wang F, Liu Y, et al. Community Transmission of Severe Acute Respiratory Syndrome Coronavirus 2, Shenzhen, China, 2020. Emerg Infect Dis [Internet]. 2020;26(6):1320–3. Available from: http://wwwnc.cdc.gov/eid/article/26/6/20-0239_article.htm

3. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. N Engl J Med [Internet]. 2020;382(13):1199–207. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7121484

4. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data. World Health Organization. 2022. p. 1–5.

5. WHO. Tracking SARS-CoV-2 variants. Who. 2021. p. https://www.who.int/en/activities/tracking-SARS-Co.

6. CDC. COVID-19 Vaccines Work | CDC. CDC. 2021.

7. Li H, Tian S, Chen T, Cui Z, Shi N, Zhong X, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with <scp>COVID</scp> -19. Diabetes, Obes Metab [Internet]. 2020;22(10):1897–906. Available from: https://onlinelibrary.wiley.com/doi/10.1111/dom.14099

8. Alguwaihes AM, Al-Sofiani ME, Megdad M, Albader SS, Alsari MH, Alelayan A, et al. Diabetes and Covid-19 among hospitalized patients in Saudi Arabia: a single-centre retrospective study. Cardiovasc Diabetol [Internet]. 2020;19(1):205. Available from: https://cardiab.biomedcentral.com/articles/10.1186/s12933-020-01184-4

9. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Res Care [Internet]. 2020;8(1):e001343. Available from: https://drc.bmj.com/lookup/doi/10.1136/bmjdrc-2020-001343

10. Muniangi-Muhitu H, Akalestou E, Salem V, Misra S, Oliver NS, Rutter GA. Covid-19 and Diabetes: A Complex Bidirectional Relationship. Front Endocrinol (Lausanne) [Internet]. 2020;11:758–9. Available from: https://www.frontiersin.org/article/10.3389/fendo.2020.582936/full

11. Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. Diabetes Res Clin Pract [Internet]. 2020;164:108166. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168822720304162

12. Ceriello A, De Nigris V, Prattichizzo F. Why is hyperglycaemia worsening <scp>COVID</scp> -19 and its prognosis? Diabetes, Obes Metab [Internet]. 2020;22(10):1951–2. Available from:

https://onlinelibrary.wiley.com/doi/10.1111/dom.14098

13. Unnikrishnan R, Misra A. Diabetes and COVID19: a bidirectional relationship. Nutr Diabetes [Internet]. 2021;11(1):21. Available from: https://www.nature.com/articles/s41387-021-00163-2

14. Chamorro-Pareja N, Parthasarathy S, Annam J, Hoffman J, Coyle C, Kishore P. Letter to the editor: Unexpected high mortality in COVID-19 and diabetic ketoacidosis. Metabolism [Internet]. 2020;110(5):154301. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0026049520301657

15. Lim S, Bae JH, Kwon H-S, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol [Internet]. 2021;17(1):11–30. Available from: https://www.nature.com/articles/s41574-020-00435-4

16. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. <scp>COVID</scp> -19 infection may cause ketosis and ketoacidosis. Diabetes, Obes Metab [Internet]. 2020 Oct 18;22(10):1935–41. Available from: https://onlinelibrary.wiley.com/doi/10.1111/dom.14057

17. Misra S, Barron E, Vamos E, Thomas S, Dhatariya K, Kar P, et al. Temporal trends in emergency admissions for diabetic ketoacidosis in people with diabetes in England before and during the COVID-19 pandemic: a population-based study. Lancet Diabetes Endocrinol. 2021;9(10):671–80.

18. de Sá-Ferreira CO, da Costa CHM, Guimarães JCW, Sampaio NS, Silva L de ML, de Mascarenhas LP, et al. Diabetic ketoacidosis and COVID-19: what have we learned so far? Am J Physiol Metab [Internet]. 2022;322(1):E44–53. Available from: https://journals.physiology.org/doi/10.1152/ajpendo.00244.2021

19. Deborah J Wexler, Irl B Hirsch, Jean E Mulder. COVID-19: Issues related to diabetes mellitus in adults. UpToDate, Post TW (Ed), UpToDate, Waltham, MA. 2021;

20. World Health Organisation. Nearly 1 in 5 COVID-19 deaths in the African region linked to diabetes [Internet]. 2020. Available from: https://www.afro.who.int

21. Corrao S, Pinelli K, Vacca M, Raspanti M, Argano C. Type 2 Diabetes Mellitus and COVID-19: A Narrative Review. Front Endocrinol (Lausanne) [Internet]. 2021;12:267. Available from: https://www.frontiersin.org/articles/10.3389/fendo.2021.609470/full

22. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest [Internet]. 2020;43(6):867–9. Available from: http://link.springer.com/10.1007/s40618-020-01236-2

23. Iacobellis G, Penaherrera CA, Bermudez LE, Bernal Mizrachi E. Admission hyperglycemia and radiological findings of SARS-CoV2 in patients with and without diabetes. Diabetes Res Clin Pract. 2020;164:1081–5.

24. Guan W, Ni Z, Hu Y, Liang W-H, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med [Internet]. 2020;382(18):1708–20. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7092819

25. Farag AA, Hassanin HM, Soliman HH, Sallam A, Sediq AM, Abd elbaser ES, et al. Newly Diagnosed Diabetes in Patients with COVID-19: Different Types and Short-Term Outcomes. Trop Med Infect Dis [Internet]. 2021;6(3):142. Available from: https://www.mdpi.com/2414-6366/6/3/142

26. Llanera DK, Wilmington R, Shoo H, Lisboa P, Jarman I, Wong S, et al. Clinical Characteristics of COVID-19 Patients in a Regional Population with Diabetes Mellitus: The ACCREDIT Study. SSRN Electron J [Internet]. 2021;21:e777130. Available from: https://www.ssrn.com/abstract=3785999

27. International Diabetes Federation. IDF Diabetes Atlas, 9th ed (internet). IDF Diabetes Atlas, 9th edition. 2019. p. 1–764.

28. Ombajo LA, Mutono N, Sudi P, Mutua M, Sood M, Loo AM, et al. Epidemiological and clinical characteristics of patients hospitalised with COVID-19 in Kenya: a multicentre cohort study. BMJ Open [Internet]. 2022;12(5):e049949. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2021-049949

29. Webber S. Five questions on the IDF Diabetes Atlas. Diabetes Res Clin Pract [Internet]. 2013 Nov;102(2):147–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0168822713003550

30. McFerran L. Obstacles To Diabetes Care in Kenya. Med J Ther Africa. 2008;2(2):127–30.

31. Pinedo-Torres I, Flores-Fernández M, Yovera-Aldana M, Gutierrez-Ortiz C, Zegarra-Lizana P, Intimayta-Escalante C, et al. Prevalence of Diabetes Mellitus and Its Associated Unfavorable Outcomes in Patients With Acute Respiratory Syndromes Due to Coronaviruses Infection: A Systematic Review and Meta-Analysis. Clin Med Insights Endocrinol Diabetes [Internet]. 2020;13:117955142096249. Available from: http://journals.sagepub.com/doi/10.1177/1179551420962495

32. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis [Internet]. 2020;94:91–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1201971220301363

33. Chow N, Fleming-Dutra K, Gierke R, Hall A, Hughes M, Pilishvili T, et al. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 — United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2020;69(13):382–6. Available from: http://www.cdc.gov/mmwr/volumes/69/wr/mm6913e2.htm?s_cid=mm6913e2_w

34. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA [Internet]. 2020;323(18):1775–6. Available from: https://jamanetwork.com/journals/jama/fullarticle/2763667

35. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Bordell A, et al. Patient characteristics, clinical course and factors associated to ICU mortality in critically ill patients infected with SARS-CoV-2 in Spain: A prospective, cohort, multicentre study. Rev Española Anestesiol y Reanim (English Ed [Internet]. 2020;67(8):425–37. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2341192920300986

36. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia [Internet]. 2020 Aug;63(8):1500–15. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7256180

37. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Type 1 and Type 2 Diabetes and COVID-19 Related Mortality in England: A Whole Population Study. SSRN Electron J [Internet]. 2020; Available from: https://www.ssrn.com/abstract=3605225

38. Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. New-Onset Diabetes in Covid-19. N Engl J Med [Internet]. 2020;383(8):789–90. Available from: http://www.nejm.org/doi/10.1056/NEJMc2018688

39. Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmet P. Proportion of newly diagnosed diabetes in <scp>COVID</scp> -19 patients: A systematic review and meta-analysis. Diabetes, Obes Metab [Internet]. 2021;23(3):870–4. Available from: https://onlinelibrary.wiley.com/doi/10.1111/dom.14269

40. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes Metab Syndr Clin Res Rev [Internet]. 2020;14(4):535–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1871402120301090

41. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect [Internet]. 2020;81(2):e16–25. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0163445320302346

42. Saha S, Al-Rifai RH, Saha S. Diabetes prevalence and mortality in COVID-19 patients: a systematic review, meta-analysis, and meta-regression. J Diabetes Metab Disord [Internet]. 2021;20(1):939–50. Available from: https://link.springer.com/10.1007/s40200-021-00779-2

43. Kantroo V, Kanwar MS, Goyal P, Rosha D, Modi N, Bansal A, et al. Mortality and Clinical Outcomes among Patients with COVID-19 and Diabetes. Med Sci [Internet]. 2021;9(4):65. Available from: https://www.mdpi.com/2076-3271/9/4/65

44. Schoen K, Horvat N, Guerreiro NFC, de Castro I, de Giassi KS. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. BMC Infect Dis [Internet]. 2019;19(1):964. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC6852716

45. Jose J, Al-Dorzi HM, Al-Omari A, Mandourah Y, Al-Hameed F, Sadat M, et al. Critically ill patients with diabetes and Middle East respiratory syndrome: a multi-center observational study. BMC Infect Dis [Internet]. 2021;21(1):1–9. Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-021-05771-y

46. Fuso L, Pitocco D, Antonelli-Incalzi R. Diabetic lung, an underrated complication from restrictive functional pattern to pulmonary hypertension. Diabetes Metab Res Rev [Internet]. 2019;35(6):e3159.

Available from: https://onlinelibrary.wiley.com/doi/10.1002/dmrr.3159

47. Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. lancet Diabetes Endocrinol [Internet]. 2020;8(10):823–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32798471

48. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. J Diabetes Sci Technol [Internet]. 2020;14(4):813–21. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7673150

49. Ceriello A. Acute hyperglycaemia: a 'new' risk factor during myocardial infarction. Eur Heart J [Internet]. 2005;26(4):328–31. Available from: http://academic.oup.com/eurheartj/article/26/4/328/439243/Acute-hyperglycaemia-a-new-risk-factor-during

50. Li C, Islam N, Gutierrez JP, Lacey B, Moolenaar RL, Richter P. Diabetes, obesity, hypertension and risk of severe COVID-19: a protocol for systematic review and meta-analysis. BMJ Open [Internet]. 2021 [cited 2021 Dec 4];11(11):e051711. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2021-051711

51. Collaborative TO, Williamson E, Walker AJ, Bhaskaran K, Bacon S, Bates C, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv. 2020;2009–999.

52. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical Characteristics of Covid-19 in New York City. N Engl J Med [Internet]. 2020;382(24):2372–4. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7182018

53. Fadini GP, Morieri ML, Boscari F, Fioretto P, Maran A, Busetto L, et al. Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by aggravating respiratory deterioration. Diabetes Res Clin Pract [Internet]. 2020;168:108374. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7428425

54. Guan W-J, Liang W-H, Zhao Y, Liang H-R, Chen Z-S, Li Y-M, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J [Internet]. 2020;55(5):640. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7098485

55. Saand AR, Flores M, Kewan T, Alqaisi S, Alwakeel M, Griffiths L, et al. Does inpatient hyperglycemia predict a worse outcome in COVID-19 intensive care unit patients? J Diabetes [Internet]. 2021;13(3):253–60. Available from: https://onlinelibrary.wiley.com/doi/10.1111/1753-0407.13137

56. Seiglie J, Platt J, Cromer SJ, Bunda B, Foulkes AS, Bassett I V., et al. Diabetes as a Risk Factor for Poor Early Outcomes in Patients Hospitalized With COVID-19. Diabetes Care [Internet]. 2020;43(12):2938–44. Available from:

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7770271

57. McGurnaghan SJ, Weir A, Bishop J, Kennedy S, Blackbourn LAK, McAllister DA, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. lancet Diabetes Endocrinol [Internet]. 2021;9(2):82–93. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7832778

58. Ceriello A. Hyperglycemia and the worse prognosis of COVID-19. Why a fast blood glucose control should be mandatory. Diabetes Res Clin Pract [Internet]. 2020;163:108–86. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7188620

59. Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, et al. Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? Diabetes Care [Internet]. 2020;43(7):1408–15. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7305003

60. American Diabetes Association. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2020. Diabetes Care [Internet]. 2020;43(Suppl 1):S193–202. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31862758

61. Fda T. FAQs on Home-use Blood Glucose Meters Utilized Within Hospitals During the COVID-19 Pandemic. :1–5.

62. Wu L, Girgis CM, Cheung NW. COVID-19 and diabetes: Insulin requirements parallel illness severity in critically unwell patients. Clin Endocrinol (Oxf) [Internet]. 2020;93(4):390–3. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7404426

63. Umpierrez GE, Cuervo R, Karabell A, Latif K, Freire AX, Kitabchi AE. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care [Internet]. 2004;27(8):1873–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15277410

64. DeCarlo K, Wallia A. Inpatient Management of T2DM and Hyperglycemia in Older Adults. Curr Diab Rep [Internet]. 2019;19(10):104. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31520325

65. Lesniak C, Ong R, Akula MS, Douedi S, Akoluk A, Soomro R, et al. Inpatient glycemic control and outcome of COVID-19 patients: A retrospective cohort. SAGE Open Med [Internet]. 2021;9:205031212110391. Available from: http://journals.sagepub.com/doi/10.1177/20503121211039105

66. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control. Diabetes Care [Internet]. 2009;32(6):1119–31. Available from: https://diabetesjournals.org/care/article/32/6/1119/28263/American-Association-of-Clinical-Endocrinologists

67. Krinsley JS. Glycemic control in the critically ill - 3 domains and diabetic status means one size does

not fit all! Crit Care [Internet]. 2013;17(2):131. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3672498

68. Zhu L, She Z-G, Cheng X, Qin J-J, Zhang X-J, Cai J, et al. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. Cell Metab [Internet]. 2020;31(6):1068-1077.e3. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7252168

69. Langouche L, Van den Berghe G, Gunst J. Hyperglycemia and insulin resistance in COVID-19 versus non-COVID critical illness: Are they really different? Crit Care [Internet]. 2021;25(1):437. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8680062

70. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med [Internet]. 2021;384(8):693–704. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2021436

71. Kim SY, Yoo CG, Lee CT, Chung HS, Kim YW, Han SK, et al. Incidence and risk factors of steroid-induced diabetes in patients with respiratory disease. J Korean Med Sci [Internet]. 2011;26(2):264–7. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3031012

72. Ceriello A, Standl E, Catrinoiu D, Itzhak B, Lalic NM, Rahelic D, et al. Issues for the management of people with diabetes and COVID-19 in ICU. Cardiovasc Diabetol [Internet]. 2020;19(1):114. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7370631

73. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care [Internet]. 2010 Jan;33 Suppl 1(Suppl 1):S62-9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2797383

74. Abdi A, Jalilian M, Sarbarzeh PA, Vlaisavljevic Z. Diabetes and COVID-19: A systematic review on the current evidences. Diabetes Res Clin Pract [Internet]. 2020;166:108347. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7375314

75. Lu R, Qin J, Wu Y, Wang J, Huang S, Tian L, et al. Epidemiological and clinical characteristics of COVID-19 patients in Nantong, China. J Infect Dev Ctries [Internet]. 2020;14(05):440–6. Available from: https://jidc.org/index.php/journal/article/view/12678

76. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA [Internet]. 2020;323(11):1061–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7042881

77. Bwire GM. Coronavirus: Why Men are More Vulnerable to Covid-19 Than Women? SN Compr Clin Med [Internet]. 2020;2(7):874–6. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7271824

78. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people

with diabetes: understanding the reasons for worse outcomes. lancet Diabetes Endocrinol [Internet]. 2020;8(9):782–92. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7367664

79. Hentsch L, Cocetta S, Allali G, Santana I, Eason R, Adam E, et al. Breathlessness and COVID-19: A Call for Research. Respiration [Internet]. 2021;100(10):1016–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34333497

80. Hu Y, Sun J, Dai Z, Deng H, Li X, Huang Q, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Virol [Internet]. 2020;127:104371. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7195434

81. Ghizlane EA, Manal M, Abderrahim EK, Abdelilah E, Mohammed M, Rajae A, et al. Lymphopenia in Covid-19: A single center retrospective study of 589 cases. Ann Med Surg [Internet]. 2021;69:102816. Available from: https://journals.lww.com/10.1016/j.amsu.2021.102816

82. Grey. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information. Psychiatry Res. 2020;14(4):293.

83. Stegenga ME, van der Crabben SN, Levi M, de Vos AF, Tanck MW, Sauerwein HP, et al. Hyperglycemia stimulates coagulation, whereas hyperinsulinemia impairs fibrinolysis in healthy humans. Diabetes [Internet]. 2006;55(6):1807–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16731846

84. Poudel A, Poudel Y, Adhikari A, Aryal BB, Dangol D, Bajracharya T, et al. D-dimer as a biomarker for assessment of COVID-19 prognosis: D-dimer levels on admission and its role in predicting disease outcome in hospitalized patients with COVID-19. PLoS One [Internet]. 2021;16(8):e0256744. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8389366

85. Le VT, Ha QH, Tran MT, Le NT, Le VT, Le MK. Hyperglycemia in Severe and Critical COVID-19 Patients: Risk Factors and Outcomes. Cureus [Internet]. 2022;14(8):e27611. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC9356651

86. Mithal A, Jevalikar G, Sharma R, Singh A, Farooqui KJ, Mahendru S, et al. High prevalence of diabetes and other comorbidities in hospitalized patients with COVID-19 in Delhi, India, and their association with outcomes. Diabetes Metab Syndr [Internet]. 2021;15(1):169–75. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7833169

87. Fong AC, Cheung NW. The high incidence of steroid-induced hyperglycaemia in hospital. Diabetes Res Clin Pract [Internet]. 2013;99(3):277–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23298665

88. Sathish T, Tapp RJ, Cooper ME, Zimmet P. Potential metabolic and inflammatory pathways between COVID-19 and new-onset diabetes. Diabetes Metab [Internet]. 2021;47(2):101204. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7591867

89. Cromer SJ, Colling C, Schatoff D, Leary M, Stamou MI, Selen DJ, et al. Newly diagnosed diabetes vs. pre-existing diabetes upon admission for COVID-19: Associated factors, short-term outcomes, and long-term glycemic phenotypes. J Diabetes Complications [Internet]. 2022;36(4):108145. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8813764

90. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature [Internet]. 2021;594(7862):259–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33887749

91. Harrell FE. Regression Modeling Strategies With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis Second Edition Springer Series in Statistics. 2001.

92. Deusenberry CM, Coley KC, Korytkowski MT, Donihi AC. Hypoglycemia in hospitalized patients treated with sulfonylureas. Pharmacotherapy [Internet]. 2012;32(7):613–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22570146

93. Khan F, Paladino L, Sinert R. The impact of COVID-19 on Diabetic Ketoacidosis patients. Diabetes Metab Syndr [Internet]. 2022;16(1):102389. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8736268

94. Mondal S, DasGupta R, Lodh M, Gorai R, Choudhury B, Hazra AK, et al. Predictors of new-onset diabetic ketoacidosis in patients with moderate to severe COVID-19 receiving parenteral glucocorticoids: A prospective single-centre study among Indian type 2 diabetes patients. Diabetes Metab Syndr [Internet]. 2021;15(3):795–801. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8004476

95. Khunti K, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, Hyperglycemia, and New-Onset Diabetes. Diabetes Care [Internet]. 2021;44(12):2645–55. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8669536

96. Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol [Internet]. 2010;47(3):193–9. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7088164

97. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England) [Internet]. 2020;395(10229):1054–62. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7270627

98. Kaminska H, Szarpak L, Kosior D, Wieczorek W, Szarpak A, Al-Jeabory M, et al. Impact of diabetes mellitus on in-hospital mortality in adult patients with COVID-19: a systematic review and meta-analysis. Acta Diabetol [Internet]. 2021;58(8):1101–10. Available from: https://link.springer.com/10.1007/s00592-021-01701-1

99. Shi C, Wang L, Ye J, Gu Z, Wang S, Xia J, et al. Predictors of mortality in patients with coronavirus disease 2019: a systematic review and meta-analysis. BMC Infect Dis [Internet]. 2021;21(1):663.

Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8264491

100. Magdy Beshbishy A, Oti VB, Hussein DE, Rehan IF, Adeyemi OS, Rivero-Perez N, et al. Factors Behind the Higher COVID-19 Risk in Diabetes: A Critical Review. Front public Heal [Internet]. 2021;9:591982. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC8292635

7. Appendix

7.1 Data collection tool

Code..... Extractor ID.....

Part A: Demographic data.

A1: Age (Years) ..... DOB.....

A2: Gender (1) Male (2) Female

A3: Smoking (1) Yes (2) No

A4: Comorbidities (documented)

a. Hypertension (1) Yes (2) No
b. HIV/AIDs (1) Yes (2) No
c. COPD (1) Yes (2) No
d. Asthma (1) Yes (2) No
e. SLE (1) Yes (2) No
f. Cancer (1) Yes (2) No
g. Other specify.....

Part B: Clinical Data

B1: Presenting symptoms: (documented in clinical notes)

a. Dyspnoea (1) Yes (2) No
b. Fever (1) Yes (2) No
c. Cough (1) Yes (2) No
d. Chest pain (1) Yes (2) No.
e. Other specify.....

B2: Admission SPO2.....

B3: laboratory characteristics (at admission)/index

a. Random blood sugar.....
b. HBA1c.....
c. D-Dimers.....

d. Lymphocytes……..

e. CRP ……

f. Other specify……..

Part C: Glucose Control and Glycaemic events:

C1: Daily glucose levels/average:

Day	1	2	3
Mmol/l			

C2: Daily insulin dose:

Day	1	2	3
Units			

C3: DM status (1) NDDM (2) Pre-existing DM

C4: Hypoglycaemia (<3.9mmol/l) (1) Yes (2) No

C5: Hyperglycaemia (>10.0mmol/l) (1) Yes (2) No

C6: DKA/HHS (1) Yes (2) No

Ketones	Serum Na	Anion Gap

C7: Method of insulin administration

a. Subcutaneous (1) Yes (2) No

b. Infusion (1) Yes (2) No

C8: Oral anti-diabetic agents administered in the ward

a. Metformin (1) Yes (2) No

b. Sulphonylureas (1) Yes (2) No

c. SGLT2 inhibitor (1) Yes (2) No

d. DPP4 inhibitor (1) Yes (2) No

e. Other specify ……

C9: Discharge treatment……

Part D: Co-treatment given during hospital stay:

D1: Steroid (1) Yes (2) No

Dose..... Duration.....

D2: Oxygen (1) Yes (2) No l/min.....

D3: Other specify.....

Part E: Outcome after 14th day:

E1: Discharge (1) Yes (2) No

E2: Continued hospitalisation (1) Yes (2) No

E3: Transfer to critical care (1) Yes (2) No

E4: Death (1) Yes (2) No

CLINICO-LABORATORY CHARACTERISTICS AND SHORT-TERM OUTCOMES OF HOSPITALISED COVID-19 PATIENTS WITH DIABETES MELLITUS AT KNH

ORIGINALITY REPORT

13%	7%	10%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"SAEM22 Abstracts", Academic Emergency Medicine, 2022 Publication	1%
2	link.springer.com Internet Source	1%
3	erepository.uonbi.ac.ke Internet Source	1%
4	Lihua Zhu, Zhi-Gang She, Xu Cheng, Juan-Juan Qin et al. "Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes", Cell Metabolism, 2020 Publication	1%
5	"Abstracts 2007", Diabetologia, 2007 Publication	1%
6	Evangelia Tzeravini, Eleftherios Stratigakos, Chris Siafarikas, Anastasios Tentolouris, Nikolaos Tentolouris. "The Role of Diabetes	1%

Lead Supervisor and Chairman of Department Approval

Lead Supervisor:

Prof. Seth O. McLigeyo

Professor, Consultant Physician, and Nephrologist, Department of Clinical Medicine, and Therapeutics

Signed: .....

Date: 6/11/23

Chairman of the Department:

Prof. E. O. Amayo

Chairman of the Department of Clinical Medicine and Therapeutics,

Professor, Consultant Physician and Neurologist, Department of Clinical Medicine, and Therapeutics

Signed.....

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
DEPARTMENT OF CLINICAL MEDICINE & THERAPEUTICS
P.O. Box [illegible] NAIROBI

Date..... 9/11/2023