ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF NURSING AND MIDWIFERY
DEPARTMENT OF NURSING

LONG-TERM CARDIOVASCULAR ADVERSE OUTCOMES OF COVID-19 AMONG PATIENTS ADMITTED TO PUBLIC HOSPITALS IN ADDIS ABABA, ETHIOPIA: A RETROSPECTIVE COHORT STUDY

Hiwot Desyalew (BSC)

A THESIS SUBMITTED TO ADDIS ABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCES, SCHOOL OF NURSING AND MIDWIFERY, IN PARTIAL FULFILLMENT OF THE REQUIREMENT OF A MASTER OF SCIENCE DEGREE IN CARDIOVASCULAR NURSING

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LONG-TERM CARDIOVASCULAR ADVERSE OUTCOMES OF COVID-19 AMONG PATIENTS ADMITTED TO PUBLIC HOSPITALS IN ADDIS ABABA, ETHIOPIA

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I, the undersigned MSc student, declare that I have submitted my original work on "Long-term Cardiovascular Adverse Outcomes of COVID-19 Among Patients Admitted to Public Hospitals in Addis Ababa, Ethiopia: A Retrospective Cohort Study" prepared by Hiwot Desyalew satisfies the university's regulations and adheres to the accepted standards of originality and quality required for the Degree of Master of Sciences in Cardiovascular Nursing.

This thesis is submitted in partial fulfillment of the requirement for a graduate degree from the Addis Ababa University at College of Health Sciences, School of Nursing and Midwifery department of Nursing. The thesis is deposited in the Addis Ababa University Digital Library and is made available to local, national and international scientific community. I solemnly declare that this thesis has not been submitted to any other institution anywhere for the award of any academic degree, diploma or certificate.

Submitted by:

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APPROVAL BY THE BOARD OF EXAMINATION

This thesis by **Mrs. Hiwot Desyalew** is accepted in its present form by the board of examiners as satisfying thesis requirement for the degree of masters of Science in Cardiovascular Nursing.

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ABBREVIATIONS AND ACRONYMS

ACE2	Angiotensin-converting Enzyme 2
BMI	Body Mass Index
CRP	C-reactive Protein
HR	Hazard Ratio
HDL	High-density Lipoprotein
IHD	Ischemic Heart Disease
LDL	Low-density Lipoprotein
MACEs	Major Adverse Cardiac Events
MERS	Middle East Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
TASH	Tikur Anbessa Specialized Hospital
TIA	Transient Ischemic Attack
SPHMMC	St. Paul Hospital Millennium Medical College
WHO	World Health Organization

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ABSTRACT

Background: COVID-19 posed a serious threat to the world and presented more than 200 governments with difficult decisions. A significant percentage of hospitalized COVID-19 patients had a lower left ventricular ejection fraction. The focus of disease reporting has shifted primarily to the number of cases and deaths associated with the COVID-19 pandemic.

Objective: This study aimed to identify long-term cardiovascular outcomes of COVID-19 among patients who were admitted to COVID-19 Centers of public hospitals in Addis Ababa, Ethiopia.

Materials and Methods: A retrospective cohort study design was employed by reviewing records of adult patients with confirmed COVID-19 (cases) and pneumonia (controls) admitted in COVID-19 centers of Tikur Anbessa Specialized Hospital (TASH) and St. Paul Hospital Millennium Medical College (SPHMMC), from 01 June 2020, up to 01 June 2022. To lessen the impact of confounding variables, the study matched the two groups at a 1:1 ratio using greedy nearest neighbor matching for age at index, sex, lifestyle-related proxy variables (such as BMI and smoking), and comorbidities.

Results: The study findings revealed that COVID-19 patients exhibit heightened risks across a spectrum of cardiovascular conditions. The incidence of stroke was notably higher in the non-COVID-19 group (37.93%) compared to the COVID-19 group (23.38%), with a hazard ratio (HR) of 1.28 (95% CI: 1.66-2.43), indicating a significantly increased risk of stroke among non-COVID-19 patients. Similarly, transient ischemic attack (TIA) was observed in 3.90% of the COVID-19 group and 4.60% of the non-COVID-19 group, with a hazard ratio of 1.11 (95% CI: 1.44-3.21, p = 0.001), showing a significant association with non-COVID-19.

Conclusion: In conclusion, this retrospective cohort study reveals significant cardiovascular adverse outcomes among non-COVID-19 patients compared to a matched cohort of non-COVID-19 patients in public hospitals in Addis Ababa, Ethiopia. Therefore, there should be regular and comprehensive cardiovascular assessments for COVID-19 survivors, focusing on the early detection and management of adverse cardiovascular outcomes like arrhythmias, inflammatory heart diseases, and ischemic heart diseases

KEYWORDS: COVID-19, Cardiovascular Outcomes, TASH, SPHMMC, Ethiopia

CHAPTER ONE

1. INTRODUCTION

1.1 Background

Throughout the world, millions of people have been impacted by the coronavirus disease (COVID-19), which is brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). Initially discovered at the end of December 2019 in Wuhan, China (2), which has been declared a global public health emergency by the World Health Organization (WHO) on March 11, 2020 (3). Countries all around the world have been implementing various steps to stop the corona virus from spreading quickly, including public education, social distance, face mask use, hand washing, and avoiding crowded areas (4,5). In several countries, these actions helped to flatten the pandemic curve; but, when these limits are loosened, there have been reports of a COVID-19 comeback and an increase in the new COVID-19 subtype (4).

Common manifestations of COVID-19 are respiratory and can extend from mild symptoms to severe acute respiratory distress. The most typical symptoms include joint discomfort, exhaustion, coughing, headaches, sleeplessness, and dyspnea (6). The severity of the illness can also extend from mild disease to life-threatening acute respiratory distress syndrome (ARDS). SARS-CoV-2 infection can also affect the gastrointestinal tract, liver and pancreatic functions, leading to gastrointestinal symptoms. Moreover, SARS-CoV-2 can cause central and peripheral neurological manifestations, affect the cardiovascular system and promote renal dysfunction (7). Clinical signs can also include multi-organ failure necessitating hospitalization, acute respiratory distress syndrome, fever, exhaustion, myalgia's, and mild upper respiratory tract sickness, as well as the absence of typical symptoms (8). The conditions include hepatocellular injury, gastrointestinal symptoms, neurological disorders, ophthalmic symptoms, thrombotic consequences, cardiac dysfunction and arrhythmia, acute coronary syndromes, acute kidney injury (AKI), and issues related to dermatology (9).

It is known that COVID-19 is a hyper-inflammatory condition that causes multiple organ dysfunction, including detrimental effects on the heart, by aberrant immune activation and fulminant cytokine production (10). In addition to viral pneumonia, COVID-19 frequently results in extra pulmonary problems such as heart disease or brain damage (11). An infection with SARS-CoV2 can affect the structure and function of every organ. Patients recuperating from coronavirus illness (COVID-19) may experience persistent symptoms (6).

In addition to causing an inflammatory cytokine storm and hyper-coagulopathy, it can over stimulate the sympathetic nervous system (12). These pathways have the potential to cause permanent harm to the respiratory or cardiovascular systems even after COVID-19 recovery (12). The long-term consequences of COVID-19, such as reduced lung function or congestive heart failure, are expected to lead to a greater frequency of cardiovascular or cerebrovascular disease in the future (13). Given the well-established involvement of the circulatory system in COVID-19, including small, moderate, and large-sized veins and arteries, along with strong immune responses that produced local and systemic inflammation, one would anticipate a protracted recovery period and possibly long-term cardiovascular effects (14).

Even in individuals without a prior history of cardiovascular disease, COVID-19 has also been connected to cardiovascular problems like myocardial damage or infarction, myocarditis, heart failure, arrhythmias, and stroke. As a result, individuals who already have cardiovascular disease may be more vulnerable to negative COVID-19-related in-hospital outcomes, such as death and cardiovascular problems (15).

Serial cardiac troponin can be used to identify myocardial injury in patients with COVID-19 who have hypoxia, hypotension, and distributive shock. Furthermore, non-ischemic micro- and macro myocardial damage can be brought on by COVID-19-associated coagulopathy and hyper-inflammatory syndrome (14). The importance of this study lies in its potential to shed light on the lasting impact of the virus on cardiovascular health, thereby informing clinical management and public health strategies for individuals affected by COVID-19 (16).

1.2 Statement of the problem

COVID-19 posed a serious threat to the world and presented more than 200 governments with difficult decisions (17). According to early reports of 2021, significant percentage of hospitalized COVID-19 patients had a lower left ventricular ejection fraction, (18). In fact, several patients in one series displayed characteristics of stress-induced cardiomyopathy, and 35% of patients had an ejection fraction of less than 50% (19,20). After being released from the hospital, patients with myocardial damage linked to COVID-19 are probably still at risk for cardiovascular events (21). Myocardial injury is a concerning complication of SARS-CoV-2 infection, which can eventually lead to a wide range of myocardial pathologies (e.g., myocarditis, myocardial infarction, Takotsubo syndrome) via the virus's interaction with myocardial and endothelial cells, mediated by direct viral invasion or indirect mechanisms such as ACE_2 receptor down regulation (22).

The number of cases and deaths related with the COVID-19 pandemic has gotten the most emphasis in disease reporting. While statistics are useful, the long-term health consequences are more relevant (23).

There is still a dearth of information regarding the true incidence and relative risk of cardiovascular disease (CVD) following COVID-19 infection.(13) The short-term cardiovascular outcomes of COVID-19 survivors have been documented in a few trials (24). When considering co-morbid variables and features for SARS-CoV-2 infection susceptibility, requirement for hospitalization, degree of care, and their combined impact on the severity of sickness, a morbidity index of COVID-19 survivors is very pertinent (13).

Various studies have shown that, like what was previously seen during the SARS outbreak, doctors were seeing unexpected, significant organ and lingering symptoms in a growing number of recovered SARS-CoV-2 patients (9). Since COVID-19 is a relatively novel illness, there is still some concern about its potential long-term health effects. This is especially important for patients with severe symptoms, such as those who needed mechanical ventilation during their hospital stay, as they are more likely to experience long-term issues and inadequate recovery

following their release. Regretfully, there aren't many studies on the clinical picture of COVID-19's aftermath (25).

There is growing evidence that alterations in patient behavior and healthcare delivery can have direct effects on several organ systems as well as indirect effects on other organ systems and disease processes, including cancer and cardiovascular illnesses (26). Research on many organ systems is required, even though the long-term impacts of COVID-19 on people and health systems are starting to become apparent. Up until now, most of the research has concentrated on post-COVID syndrome symptoms rather than organ failure (27).

Important concerns regarding possible long-term cardiovascular effects are raised by the frequency of cardiac injury, vascular dysfunction, and thrombosis in COVID-19 patients, including those who experienced no or few symptoms during their initial infection(14). These effects could include heart failure, potentially fatal arrhythmias, sudden cardiac death, impaired myocardial flow reserve from microvascular injury, the formation of coronary artery and aortic aneurysms, hypertension, labile blood pressure and heart rate responses to activity, accelerated atherosclerosis, and both venous and arterial thromboembolic disease (14). Recurrence risk is in fact increased by events that occur during the acute phase of disease, including those that are clinically unexpected and untreated (14,28).

Various previous cohort studies reported CVS sequels like arrhythmias and RV dysfunction (29), ischemic myocardial injuries and microvascular disease (30), myocarditis (31), and pericarditis (32) in developed countries. However, studies are scarce from Africa, specifically Ethiopia are scarce on reporting long-term cardiovascular events. Therefore, the current study aims to assess long-term cardiovascular adverse outcomes of COVID-19 among patients who were admitted to public hospitals in Addis Ababa, Ethiopia.

1.3 Significance of the study

The long-term effects of the illness are still mostly unknown, despite thorough descriptions of the pathophysiology, epidemiological and clinical features, and complications of COVID-19 patients during the acute phase. There is growing evidence that a variety of post-acute sequelae, including cardiovascular problems, may occur in many COVID-19 patients.

Research has shown that COVID-19's effects go far beyond hospital stays. Research is required to identify the long-term pathophysiology of many organ systems. To identify the long-term effects of COVID-19 and to identify risk variables linked to the symptoms of long-term COVID-19, this study examined patients who were hospitalized with the virus.

The significance of the study is multi-faceted and has implications for various stakeholders:

1. **Government and Policy Makers:** The study's findings can inform public health policies and resource allocation for managing the long-term cardiovascular consequences of COVID-19. It can help governments in Ethiopia and other countries to develop targeted interventions and support systems for individuals who have recovered from COVID-19 and are at risk of cardiovascular complications.

2. **Clinicians:** The study provides valuable insights into the potential long-term cardiovascular effects of COVID-19, aiding clinicians in recognizing and addressing these complications in patients who have recovered from the virus. This information can guide post-COVID-19 care protocols and help healthcare providers in Ethiopia and beyond to better manage the cardiovascular health of recovered patients.

3. **Stakeholders and Researchers:** The study's findings are significant for stakeholders such as public health organizations, non-governmental organizations, and researchers, as they shed light on the need for continued research into the long-term health outcomes of COVID-19. This can drive further investigation into the mechanisms underlying COVID-19-related cardiovascular complications and the development of targeted interventions to mitigate these effects.

In summary, the study's significance lies in its potential to influence public health policies, clinical practice, and future research efforts related to the long-term cardiovascular adverse outcomes of COVID-19, particularly in the context of public hospitals in Addis Ababa, Ethiopia.

CHAPTER TWO

2. LITERATURE REVIEW

2.1 Theoretical review

2.1.1 COVID-19 virus

Coronaviruses affect humans and animals and cause serious illnesses (33). By the end of 2019, a novel coronavirus was identified as the cause of several pneumonia cases in Wuhan, a city in the Hubei Province of China. It spread swiftly, starting an outbreak in China and eventually igniting a global pandemic (34). In February 2020, the World Health Organization designated the sickness as COVID-19, or coronavirus disease 2019. The virus that causes COVID-19 is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was formerly known as 2019-nCoV.(35).

2.1.2 Coronavirus virology

Coronaviruses are enveloped, positive-stranded RNA viruses. Full-genome sequencing and phylogenic analysis have shown that the coronavirus that causes COVID-19 is a beta coronavirus that is in a different clade while sharing a subgenus with the SARS virus and several bat coronaviruses (36). The International Committee on Taxonomy of Viruses' Coronavirus Study Group has suggested that this virus be known as SARS-CoV-2, or severe acute respiratory syndrome coronavirus (37). Somewhat more distantly related is the beta coronavirus known as the Middle East respiratory sickness (MERS) virus. The two bat coronaviruses have the closest RNA sequence similarity, suggesting that bats are the main source. It is unknown, however, whether the COVID-19 virus spreads directly from bats or via another method (such as an intermediary host) (37).

The angiotensin-converting enzyme 2 (ACE2) host receptor for SARS-CoV-2 cell entrance is the same as that of SARS-CoV. Through its spike protein's receptor-binding domain, SARS-CoV-2 interacts to ACE2. Additionally, it seems that TMPRSS2 the cellular protease is crucial for SARS-CoV-2 cell entrance (38).

2.1.3 Route of person-to-person transmission

The main way that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spread is through direct respiratory transmission between individuals. It is believed to mostly spread by close contact (i.e., within six feet or two meters) with respiratory particles; the virus that is discharged into respiratory secretions during an infected person's cough, sneeze, or speaking can infect another person if it is inhaled or encounters mucous membranes. A person's eyes, nose, or mouth could also become infected if their hands come into contact with these fluids or if they come into contact with contaminated surfaces, though this is not believed to be the main way that infection spreads (39).

2.1.4 Acute cardiovascular complications of COVID-19

Numerous direct and indirect mechanisms have been put forth to explain the possible correlation between COVID-19 and cardiovascular issues. A complex interaction between the virus, host defenses, and underlying cardiovascular disorders characterizes the link. Damage to the heart is caused by the virus's contact with the host cells (40).

Autopsy studies have also revealed viral fragments in the endothelium of cardiac arteries, along with macrophage and lymphocyte infiltration; viral replication was not observed, though. Additionally, it has been documented that cytokine storms and host immune response dysregulation cause significant inflammatory alterations. A mismatch between the supply and demand of oxygen as a result of hypoxia from COVID-19-related respiratory failure has increased the risk of myocardial infarction (40,41).

Additionally, an imbalance between the pro- and anti-inflammatory systems may exist, leading to unpredictable activation of the inflammatory response (production of catecholamines and IL-6), and an incapacity of the host to control inflammation. This exacerbates the already severe inflammation. Catecholamine release raises oxygen demand and heart rate, which is bad for heart health. In addition to causing endothelial dysfunction, coronary artery spasms, and thrombi development, the excessive release of inflammatory markers (cytokines and chemokines) also lowers the heart's blood supply.

The aforementioned processes include changes to calcium channels that affect the contractility activity of myocytes and hypoxia and inflammation that cause mitochondrial malfunction. Hypercoagulation through enormous inflammation has also been noted in COVID-19 patients, potentially responsible for some cardiac injuries, such as occlusive thrombus formation. Drug-related cardiac injuries have also been reported, especially QT prolongation from medications (hydroxychloroquine, azithromycin) used to treat COVID-19 infection (41,42).

2.1.5 **Long-term cardiovascular complications of COVID-19**

Due to the high incidence of cardiac problems during the acute phase of infection and the increasing amount of research describing organ dysfunction and persistent symptoms in post-acute COVID-19 patients, more attention is being paid to the long-term cardiovascular effects of COVID-19 infection. It is unclear to what degree these challenges are the consequence of different pathologic processes rather than acute infection consequences (43).

Data on emerging long-term outcomes show that acute COVID-19 infection is associated with a considerable burden of cardiovascular disease. Comparing 30 days to 12 months after COVID-19 infection to control cohorts, a thorough analysis of databases from the US Department of Veterans Affairs (VA) revealed an increased burden of thrombotic disorders, arrhythmia, ischemic heart disease, heart failure, and cerebrovascular disorders (44).

In total, COVID-19 infection was associated with a greater than 50% increase in risk of one of these complications over the stated time frame (HR 1.63, 95% CI 1.59–1.68). Strikingly, these observations were made even in those who were not hospitalized for acute infection, though the risk rose in a graded fashion based on the highest level of care required during the initial phase of infection with the greatest burden occurring in those requiring intensive care (45).

Atrial fibrillation and heart failure accounted for the largest excess burden of all the sequelae examined in this analysis; both conditions occurred in more than 10 extra cases per 1,000 people who had recovered more than 30 days from an acute COVID-19 infection. The results from the

VA database are expanded upon and confirmed by other published research. It has also been shown that post-COVID patients experience major adverse cardiac events (MACE) and new-onset diabetes much more frequently than matched controls. According to one study, 2% of patients who had recovered from an acute COVID-19 infection had de novo heart failure and new-onset hypertension at the 1-year follow-up, and there was a higher requirement for readmission for the augmentation of heart failure medication (46).

Furthermore, 2.7% of patients in the same study experienced a new development of right-sided heart failure without any associated hypertension or left-sided heart failure. However, it is challenging to determine if this indicates a structural change in the post-infectious situation or dysfunction that was simply not detected during the index stay, given the results of commonly abnormal echocardiograms in the acute setting. Although pulmonary hypertension is usually observed during the acute stage of the illness, follow-up echocardiography has not consistently revealed this (47).

According to a recent prospective study, the presence of myocardial injury during an index hospitalization for COVID-19, as determined by elevated high-sensitivity troponin, was linked to higher odds of hospital readmission and mortality, as well as persistent symptoms one year later. A significant mortality rate in the year after contracting COVID-19 has also been documented by other groups; rates have ranged from 1.3 to 12%. These occurrences are frequently linked to sudden cardiac death, which is thought to be caused by thrombosis or arrhythmia (48).

The myocardium's post-COVID-19 structural alterations will soon be characterized. A startling 78% of patients recovered from COVID-19 infection with abnormalities on cardiac magnetic resonance imaging (CMR) during a medium-term follow-up of two to three months, with 60% of them exhibiting signs of inflammation based on enhanced native T1 and T2 enhancement. Additionally, there was focal scarring and pericardial enlargement (49).

According to Huang et al., cardiac patients who recovered from COVID-19 infection but still experienced symptoms showed myocardial edema and late gadolinium enhancement (LGE) in 54% and 38% of patients, respectively, on cardiac magnetic resonance imaging (CMR). The

anterior, anterolateral, and inferior walls of the left ventricle, as well as the interventricular septum, were the main locations of LGE. Additionally, they discovered a correlation between reduced right ventricular (RV) function and aberrant CMR results (50).

After recovering from severe COVID, Nuzzi et al. used echocardiography to evaluate RV function. Although their data did not replicate overt RV dysfunction as indicated by RV fractional shortening or tricuspid annular plane systolic excursion (TAPSE), it did reveal impaired RV longitudinal strain in 42 percent of the patients. Though the clinical relevance and natural history of this finding are still unknown, our data point to decreased RV systolic performance that endures after the acute viral period (51).

Numerous mechanisms have been proposed to explain the potential link between COVID-19 and cardiovascular issues, involving interactions between the virus, host defenses, and underlying heart conditions. The virus can damage the heart by interacting with host cells and causing inflammation. Autopsy studies have found viral fragments in cardiac arteries, along with immune cell infiltration. Dysregulation of the immune response and cytokine storms can lead to significant inflammatory changes. Oxygen supply-demand mismatch due to respiratory failure from COVID-19 can increase the risk of heart attacks. Imbalances in the inflammatory response may further worsen inflammation, leading to issues like endothelial dysfunction and thrombus formation. Drug-related cardiac injuries, such as QT prolongation from medications used to treat COVID-19, have also been reported.

COVID-19 infection is associated with a significant burden of cardiovascular disease, with long-term effects becoming increasingly recognized. Studies have shown an increased risk of thrombotic disorders, arrhythmia, ischemic heart disease, heart failure, and cerebrovascular disorders following COVID-19 infection. Even non-hospitalized individuals are at risk, with the highest burden seen in those requiring intensive care. Atrial fibrillation and heart failure are among the most common complications post-infection. Patients may also experience major adverse cardiac events and new-onset diabetes at higher rates compared to controls. Myocardial injury during acute infection is linked to higher odds of hospital readmission, mortality, and persistent symptoms one year later. Structural changes in the myocardium, including

inflammation and scarring, have been observed in a significant proportion of recovered patients. These findings highlight the importance of monitoring and addressing long-term cardiovascular effects in individuals recovering from COVID-19.

2.2 Conceptual framework

The conceptual framework illustrates the relationships between COVID-19 infections, pre-existing cardiovascular conditions and long-term cardiovascular adverse outcomes among patients admitted to public hospitals in Addis Ababa, Ethiopia. It also considers potential confounding variables and contextual factors that may influence the outcomes of interest.

COVID-19 infection among patients admitted to public hospitals in Addis Ababa, Ethiopia is considered as an independent variable. Severity of COVID-19 infection and presence of pre-existing cardiovascular conditions are mediating variables. Long-term cardiovascular adverse outcomes are the dependent variables. Age, sex, socioeconomic status, access to healthcare, and comorbidities are the potential confounding factors.

For this study, the Wagner Chronic Disease Model serves as a suitable theoretical framework. This model emphasizes patient-centered care, highlighting the importance of understanding patient-specific factors such as age, gender, and pre-existing conditions that influence health outcomes. It also focuses on the role of the healthcare system in managing chronic diseases, including the provision of continuous care and monitoring, which is crucial for patients recovering from COVID-19. The use of clinical information systems to track patient data and outcomes over time aligns with the retrospective nature of the study, utilizing hospital records to assess long-term cardiovascular outcomes. Additionally, the model underscores the importance of self-management support, considering the impact of patient education on managing cardiovascular health post-discharge. Finally, the delivery system design aspect evaluates the effectiveness of current healthcare delivery methods in preventing long-term adverse cardiovascular outcomes. By applying the Wagner Chronic Disease Model, this study systematically analyzes multiple factors affecting patient outcomes, providing a comprehensive and evidence-based framework to explore the long-term cardiovascular effects of COVID-19 in a well-structured manner.

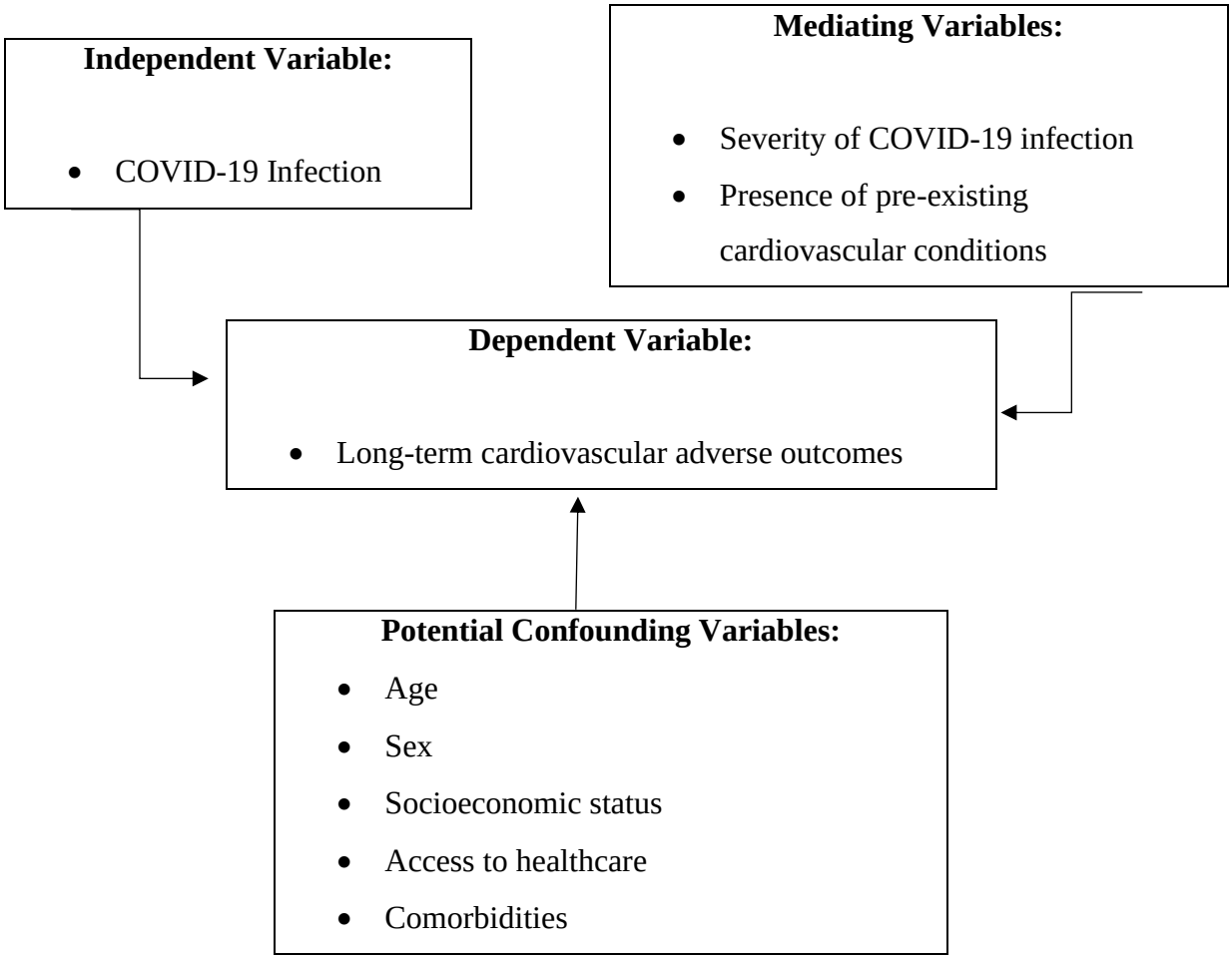

Figure 1: Conceptual framework for long-term cardiovascular outcomes of covid-19 among admitted patient (44,52)

CHAPTER THREE

3 OBJECTIVES OF THE STUDY

3.1 Objective of the study

3.1.1 General objective

- To identify long-term cardiovascular adverse outcomes of COVID-19 among patients admitted to public hospitals in Addis Ababa, Ethiopia

3.1.2 Specific objectives

- To identify long-term cardiovascular adverse outcomes of COVID-19 among the COVID-19 cohort group admitted to public hospitals in Addis Ababa, Ethiopia.

- To assess factors associated with long-term cardiovascular adverse outcomes of COVID-19 among the COVID-19 cohort group admitted to public hospitals in Addis Ababa, Ethiopia.

CHAPTER FOUR

4 MATERIALS AND METHODS

4.1 Description of the study area, the study period and Design

A retrospective cohort study was conducted from February 19 to March 19, 2024, at Tikur Anbessa Specialized Hospital and St. Paul Hospital Millennium Medical College in Addis Ababa, Ethiopia. These hospitals were served as COVID-19 centers, making them ideal for obtaining both control and cohort groups (53).

Tikur Anbessa Specialized Hospital (TASH), Ethiopia's largest tertiary care referral hospital with 700 beds, started its COVID-19 treatment center on February 22, 2021. It directed patients to isolation wards or the ICU based on severity, staffed by nurses, physicians, pharmacists, and paramedics (54). St. Paul Hospital Millennium Medical College (SPHMMC) in Addis Ababa is a referral specialized hospital serving patients from across Ethiopia. It caters to an estimated population of over 5 million people (55). Both hospitals started as point-of-care facilities for COVID-19 and later became isolation centers. TASH managed 700 COVID-19 cases, while SPHMMC handled 2,000 cases.

4.2 Study population, inclusion and exclusion criteria

The study population consisted of hospitalized adults (≥18 years old) with confirmed COVID-19 and those with non-COVID-19 related pneumonia from June 1, 2020, to June 1, 2022. The date of hospitalization was designated as the index date. Every patient was monitored from the index date until their death or for three months following June 1, 2022, the end of the inclusion period for the COVID-19 group. For pneumonia cases, patients were followed until the discharge date, transfer to another ward, or date of death.

Individuals who had received a COVID-19 vaccination were excluded from the study. Additionally, individuals who had a neoplasm or any cardiovascular issue before the index date, as well as those who passed away within 30 days following the index date, were not included. The individuals in the COVID-19 group were those who had positive SARS-CoV-2 tests

confirmed by PCR. The individuals in the control group did not exhibit any COVID-19 symptoms and tested negative for SARS-CoV-2 within the same period. Moreover, individuals in the control group were not expected to have previous cardiovascular disease, as we aimed to study their long-term cardiovascular adverse effects.

2.1 Study variables

2.1.1 **Dependent variable**

- ✓ Long-term cardiovascular adverse outcomes

2.1.2 **Independent variables**

- ✓ Severity of COVID-19 infection
- ✓ Sociodemographic characteristics

2.2 Operational definition

Long-term cardiovascular adverse outcomes: - Is the incident cardiovascular disease in the post-acute phase of COVID-19, which spans from 30 days following the index time to the conclusion of the follow-up period.

2.3 Sampling methods

There was a flowchart showing how the cohort of 2,700 individuals who enrolled between June 1, 2020, and June 1, 2022, was constructed. The group comprised individuals who were 18 years old and above and had visited the hospitals more than twice. Following inclusion and exclusion criteria, the study population (4,800 admitted patients) was split into two groups: the COVID-19 group (n = 2,500) and the control group (n = 1,900).

Propensity score matching 1:1 by body mass index (BMI), gender, age at index, comorbidities, laboratory baselines, and smoking was employed in this cohort. After propensity score matching, 308 COVID-19 survivors and 174 controls were chosen for the study. Before data collection, the charts were reviewed again, and individuals with a diagnosis of cancer, prior cardiovascular disease, or those who were admitted and died before 30 days of the index date, as well as patient

charts with ages registered as less than 18, were excluded. Finally, the study included 308 COVID-19 patients and 174 non-COVID-19 pneumonia cases from both hospitals, resulting in a total sample size of 482 (13).

2.4 Data collection instrument

The data collection instrument was adopted from previously conducted research on the same topic and used according to the study objectives (13). Parts of the data abstraction checklists (sociodemographic, clinical, laboratory, and treatment-related) were collected from medical records. Data collectors and supervisors received a 1-day training on the importance of the study, the accuracy required in completing the checklist, and ethical considerations to standardize data collection. Following that, all study participants' records were selected according to the eligibility criteria, and all pertinent data from patient records were retrieved. Then, using a structured data extraction format, they extracted all relevant variables from the patient charts that satisfy the objectives of the study.

2.5 Pre-specified outcomes

During the follow-up period, which spans from 30 days following the index time to the conclusion of the follow-up period, incident cardiovascular disease in the post-acute phase of COVID-19 was evaluated. The cardiovascular complications included in the study were:

(1) Cerebrovascular complications: stroke and transient ischemic attack (TIA).

(2) Arrhythmia: atrial fibrillation and flutter, tachycardia, bradycardia, and ventricular arrhythmia.

(3) Inflammatory heart disease: pericarditis and myocarditis.

(4) Ischemic heart disease (IHD): acute coronary disease, myocardial infarction, ischemic cardiomyopathy, and angina.

(5) Other cardiac disorders: Heart failure, non-ischemic cardiomyopathy, cardiac arrest, and cardiogenic shock.

(6) Thrombotic disorders: pulmonary embolism, deep vein thrombosis, and superficial vein thrombosis.

(7) Major adverse cardiac events (MACEs): myocardial infarction, ischemic stroke, hemorrhagic stroke, heart failure, ventricular arrhythmia, and sudden cardiac death.

(8) The initial occurrence of any cardiovascular complication examined in this study will be the definition of the composite of any cardiovascular outcome.

2.6 Covariates

The study included the following covariate factors to account for differences in baseline characteristics between the two groups: demographic covariates (age and sex), type 2 diabetes, hyperlipidemia, essential hypertension, smoking, chronic kidney disease, and chronic obstructive pulmonary disease. These comorbidities were examined in this study. Additional potential confounders, such as physical examination findings and laboratory test results, were also chosen for inclusion in the study.

The physical examination measured blood pressure at both systolic and diastolic levels, as well as Body Mass Index (BMI, obesity defined as ≥ 30 kg/m2). This investigation included the following laboratory tests: estimated glomerular filtration rate; blood levels of triglycerides (≥ 500 mg/dL); cholesterol in LDL (≥ 190 mg/dL); cholesterol in HDL (≥ 50 mg/dL); creatine kinase (≥ 199 U/L); troponin I (≥ 0.3 ng/mL); C-reactive protein (CRP) (≥ 3.0 mg/L); creatinine (≥ 1.5 mg/dL); and hemoglobin (≥ 12 g/dL).

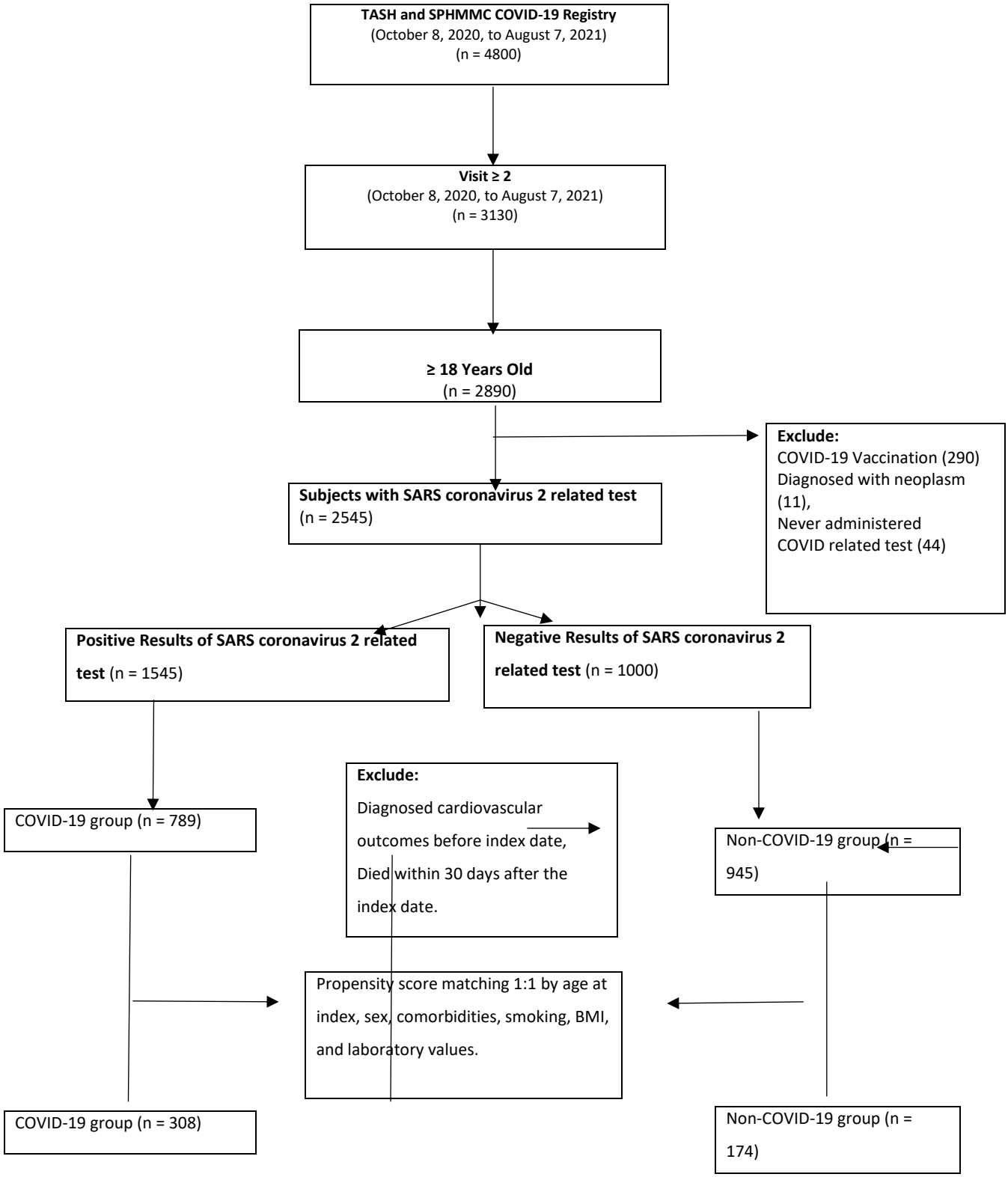

Figure 2: Cohort construction for the COVID-19 and non-COVID-19 pneumonia groups

2.7 Statistical analysis

Data was entered into SPSS version 27, and the following analyses were performed. To lessen the impact of confounding variables, the study matched the two groups at a 1:1 ratio using greedy nearest neighbor matching for age at index, sex, lifestyle-related proxy variables (such as BMI and smoking), and comorbidities. Propensity score matching was used to create groups with matched baseline characteristics.

The baseline characteristic balance of the propensity score-matched populations was assessed using the Standardized Difference (Std diff). A Std diff of less than 0.1 is typically regarded as a small difference. The follow-up began 30 days after the test and lasted for 12 months to prevent reverse causality. The hazard ratio (HR) of incident cardiovascular disease was computed for both the COVID-19 and control groups.

The generalized Schoenfeld technique was used to test the proportional hazard assumption. If the assumptions were not satisfied, the hazard ratios for various time periods were computed independently. A 95% confidence interval (95% CI) was regarded as evidence of statistical significance in all analyses. The survival probability was calculated using the Kaplan-Meier method. A p-value of less than 0.05 was used to indicate statistical significance.

Subgroup analyses examined how age and sex differences in the risks for cardiovascular events affect COVID-19 participants. Additionally, the study aimed to investigate whether variations in COVID-19 infection severity could result in different outcomes. Thus, a sensitivity analysis was also carried out for outpatients (defined as patients utilizing outpatient services and never hospitalized within one month on or after the SARS-CoV-2 test) and hospitalized patients (defined as those hospitalized within one month on or after the SARS-CoV-2 test).

2.8 Ethical considerations

Ethical approval was obtained from the Ethical Review Board of the School of Nursing and Midwifery, College of Health Sciences (CHS), Addis Ababa University (AAU) with a Protocol number of SNM/09/2024. Support letter was be obtained from both TASH and SPHMMC to access the HMIS. Confidentiality was maintained by omitting study participants' names and identifiers.

2.9 Dissemination of the results

The findings of this study were disseminated to AAU's School of Nursing, and copies of the final thesis report will be provided to the two hospitals. With their permission, the principal investigator (PI) will present the research findings to the hospitals' communities. Additionally, to reach a wider audience, the information will be published in a reputable scientific journal.

CHAPTER FIVE

2 RESULT

2.1 Baseline Characteristics

The table provided offers a comparison between COVID-19 and non-COVID-19 groups before and after undergoing propensity score matching. The analysis highlights several key findings regarding demographic, comorbidity, and laboratory measures. Initially, there were noticeable differences in age distribution between the two groups, but after matching, the mean age remained consistent, indicating successful age-based matching. Before matching, significant gender imbalances were observed, with the COVID-19 group skewed towards females and the non-COVID-19 group towards males. However, post-matching, gender distribution became more balanced, suggesting improved comparability between the groups. Similarly, disparities in comorbidity prevalence, including Type 2 DM, Hyperlipidemia, Smoking, Hypertension, CKD, and COPD, were evident before matching. Yet, after propensity score matching, these differences diminished substantially, indicating a more equitable distribution of comorbidities between the groups (Table 1).

Table 1: Baseline characteristics of study subjects (before and after Propensity score matching)

Variable	Before matching			After matching		
	COVID-19 group (n = 789)	Non-COVID 19 group (n = 945)	Std diff	COVID-19 group (n = 308)	Non-COVID 19 group (n = 174)	Std diff
Age at Index						
Mean±SD	47.31±16.027	47.5±16.093	0.066	47.31±16.027	47.5±16.036	0.009
Gender						
Female	428 (54.2)	358 (37.9)	0.031	164 (53.2)	68 (39.1)	0.001
Male	361 (45.8)	587 (61.8)	0.031	144 (46.8)	106 (60.9)	0.001
Comorbidities						
Type 2 DM	256 (32.4)	478 (50.6)	0.022	97 (31.5)	86 (49.4)	0.010
Hyperlipidemia	427 (54.1)	418 (44.2)	0.011	164 (53.2)	75 (43.1)	0.003
Smoking	53 (6.7)	244 (25.8)	0.005	18 (5.8)	43 (24.7)	0.003
Hypertension	169 (21.4)	418 (44.2)	0.044	63 (20.5)	75 (43.1)	0.004
CKD	276 (34.9)	114 (12.1)	0.032	105 (34.1)	19 (10.9)	0.003
COPD	117 (14.8)	54 (5.7)	0.014	43 (14)	08 (4.6)	0.004
Laboratory						
BMI ≥30 kg/m2, n (%)	420 (53.2)	477 (45.7)	0.066	161 (52.3)	86 (49.4)	0.006
Diastolic blood pressure, mean±SD, mmHg	356 (45.1)	472 (50.2)	0.012	136 (44.2)	85 (48.9)	0.003

Systolic blood pressure, mean±SD, mmHg	161 (20.4)	543 (57.5)	0.033	60 (19.5)	98 (56.3)	0.004
Triglyceride ≥ 500 mg/d	271 (34.3)	130 (13.8)	0.034	103 (33.4)	22 (12.6)	0.011
Cholesterol in LDL≥190 mg/dl	143 (18.1)	238 (25.2)	0.034	53 (17.2)	42 (24.1)	0.010
Cholesterol in HDL≥50 mg/dl	245 (31.1)	97 (10.3)	0.032	93 (30.2)	16 (9.2)	0.012
Hemoglobin ≥ 12 g/dL	130 (16.6)	152 (16.1)	0.045	48 (15.6)	26 (14.9)	0.007

Variable: Describes the categories of data being compared in the table, including demographic characteristics, comorbidities, and laboratory measures, **Before matching**: Represents data from the original COVID-19 and non-COVID-19 groups prior to undergoing propensity score matching. Includes mean values, counts, and percentages for each variable. **After matching**: Indicates data from the COVID-19 and non-COVID-19 groups after propensity score matching. Includes mean values, counts, and percentages adjusted to improve comparability between the groups. **COVID-19 group (n = 308)**: Specifies the sample size and composition of the COVID-19 group, providing the number of individuals included in the analysis. **Non-COVID 19 group (n = 174)**: Specifies the sample size and composition of the non-COVID-19 group, providing the number of individuals included in the analysis. **Std diff**: Indicates the standardized difference between the COVID-19 and non-COVID-19 groups for each variable before and after matching. A smaller standardized difference suggests improved balance between the groups after matching. SD: Standard Deviation, BMI: Body Mass Index, DM: Diabetes Mellitus, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein.

2.2 Cardiovascular Outcomes

The analysis of long-term cardiovascular adverse outcomes among COVID-19 patients, compared to a matched cohort of non-COVID-19 patients, reveals significant differences in the incidence and risk of various cardiovascular conditions. These findings, highlighting the incidence rates, hazard ratios, and statistical significance of the outcomes.

The incidence of stroke was notably higher in the non-COVID-19 group (37.93%) compared to the COVID-19 group (23.38%), with a hazard ratio (HR) of 1.28 (95% CI: 1.66-2.43). This indicates a significantly increased risk of stroke among non-COVID-19 patients. Similarly, transient ischemic attack (TIA) was observed in 3.90% of the COVID-19 group and 4.60% in the non-COVID-19 group, with an HR of 1.11 (95% CI: 1.44-3.21, p = 0.001), showing a significant association with control group.

COVID-19 patients demonstrated a higher incidence of various arrhythmias. Atrial fibrillation and flutter were reported in 28.57% of COVID-19 patients compared to 48.28% of non-COVID-19 patients, with an HR of 1.43 (95% CI: 1.22-2.11). Tachycardia was observed in 36.04% of the COVID-19 group versus 61.49% in the non-COVID-19 group, with an HR of 1.19 (95% CI: 1.55-1.98, $p < 0.0001$). Bradycardia was noted in 25.32% of COVID-19 patients compared to 42.53% in non-COVID-19 patients, with an HR of 1.36 (95% CI: 1.87-2.67, $p < 0.0001$). Additionally, ventricular arrhythmias were more frequent in the COVID-19 group (3.57%) compared to the non-COVID-19 group (5.17%), with an HR of 1.44 (95% CI: 1.21-1.87, $p = 0.022$).

The study also examined inflammatory heart diseases, revealing that pericarditis occurred in 2.92% of COVID-19 patients and 4.02% of non-COVID-19 patients, with an HR of 1.88 (95% CI: 1.45-1.65). Myocarditis was more common among COVID-19 patients, with an incidence of 1.95% compared to 1.15% in the non-COVID-19 group, and an HR of 2.11 (95% CI: 2.34-2.65, $p = 0.002$).

The analysis of ischemic heart diseases revealed that acute coronary disease was reported in 3.90% of COVID-19 patients versus 5.17% of non-COVID-19 patients, with an HR of 2.33 (95% CI: 1.66-2.88). Myocardial infarction was observed in 7.47% of the COVID-19 group compared to 9.77% of the non-COVID-19 group, with an HR of 2.43 (95% CI: 1.32-2.81, $p = 0.003$). Ischemic cardiomyopathy was noted in 7.14% of COVID-19 patients and 9.77% of non-COVID-19 patients, with an HR of 1.89 (95% CI: 1.75-2.98, $p = 0.011$). Angina was reported in 12.34% of the COVID-19 group versus 18.97% in the non-COVID-19 group, with an HR of 1.36 (95% CI: 1.17-2.67, $p = 0.010$).

Heart failure was documented in 22.08% of COVID-19 patients compared to 35.63% of non-COVID-19 patients, with an HR of 1.43 (95% CI: 1.22-2.11). Cardiomyopathy incidence was 6.82% in the COVID-19 group versus 8.62% in the non-COVID-19 group, with an HR of 2.19 (95% CI: 1.45-3.91, $p = 0.004$). Cardiac arrest occurred in 4.87% of COVID-19 patients compared to 6.90% of non-COVID-19 patients, with an HR of 1.36 (95% CI: 1.17-1.67, $p <$

0.0001). Cardiogenic shock was observed in 5.84% of the COVID-19 group versus 8.05% in the non-COVID-19 group, with an HR of 1.44 (95% CI: 1.21-1.83, p = 0.043).
Thrombotic disorders were more prevalent among COVID-19 patients, with 9.42% experiencing these conditions compared to 13.22% of non-COVID-19 patients, with an HR of 1.27 (95% CI: 1.06-2.43, p = 0.010). Pulmonary embolism was reported in 8.44% of the COVID-19 group versus 12.07% in the non-COVID-19 group, with an HR of 2.11 (95% CI: 1.14-3.21, p = 0.011). Deep vein thrombosis occurred in 18.51% of COVID-19 patients compared to 29.89% of non-COVID-19 patients, with an HR of 1.28 (95% CI: 1.16-2.33, p = 0.045). Superficial vein thrombosis was also more common in the COVID-19 group (36.04%) compared to the non-COVID-19 group (60.92%), with an HR of 1.46 (95% CI: 1.21-1.93, p = 0.465).

Major adverse cardiac events (MACE) occurred in 5.19% of COVID-19 patients versus 5.17% of non-COVID-19 patients, with an HR of 1.24 (95% CI: 1.06-1.43). The overall incidence of any cardiac outcome mentioned was 35.06% in the COVID-19 group compared to 57.47% in the non-COVID-19 group, with an HR of 1.21 (95% CI: 1.14-2.21, p = 0.02). Mortality was reported in 2.92% of COVID-19 patients versus 2.87% of non-COVID-19 patients, with an HR of 1.25 (95% CI: 1.16-1.33, p = 0.01).

The results indicate a higher incidence of various cardiovascular outcomes among COVID-19 patients compared to non-COVID-19 patients. The hazard ratios suggest a significant association between COVID-19 and increased risks of cerebrovascular events, arrhythmias, inflammatory heart diseases, ischemic heart diseases, other cardiac disorders, thrombotic disorders, MACE, and mortality. These findings underscore the substantial long-term cardiovascular risks associated with COVID-19, emphasizing the need for vigilant cardiovascular monitoring and management in COVID-19 survivors. The statistically significant p-values further corroborate the reliability of these associations (Table 2)

Table 2: Incidence of outcomes among the COVID-19 group compared to control subjects (after prosperity score matching).

Outcome	Patients with outcome		Hazard ratio (95% CI)	P-value
	COVID-19 group (n = 308)	Non-COVID 19 group (n = 174)		
Cerebrovascular (Ref = Stroke)				
Stroke	72 (23.38)	66 (37.93)	1.28 (1.66 – 2.43)	
TIA	12 (3.90)	8 (4.60)	1.11 (1.44 – 3.21)	0.001
Arrhythmia (Ref = Atrial fibrillation and flutter)				
Atrial fibrillation and flutter	88 (28.57)	84 (48.28)	1.43 (1.22 – 2.11)	
Tachycardia	111 (36.04)	107 (61.49)	1.19 (1.55 – 1.98)	<0.0001
Bradycardia	78 (25.32)	74 (42.53)	1.36 (1.87 – 2.67)	<0.0001
Ventricular arrhythmias	11 (3.57)	9 (5.17)	1.44 (1.21 – 1.87)	0.022
Inflammatory heart disease (Ref = Pericarditis)				
Pericarditis	9 (2.92)	7 (4.02)	1.88 (1.45 – 1.65)	
Myocarditis	6 (1.95)	2 (1.15)	2.11 (2.34 – 2.65)	0.002
Ischemic heart disease (Ref = Acute coronary disease)				
Acute coronary disease	12 (3.90)	9 (5.17)	2.33 (1.66 – 2.88)	
Myocardial infarction	23 (7.47)	17 (9.77)	2.43 (1.32 – 2.81)	0.003
Ischemic cardiomyopathy	22 (7.14)	17 (9.77)	1.89 (1.75 – 2.98)	0.011
Angina	38 (12.34)	33 (18.97)	1.36 (1.17 – 2.67)	0.010
Other cardiac disorders (Ref = Heart failure)				
Heart failure	68 (22.08)	62 (35.63)	1.43 (1.22 – 2.11)	
Cardiomyopathy	21 (6.82)	15 (8.62)	2.19 (1.45 – 3.91)	0.004
Cardiac arrest	15 (4.87)	12 (6.90)	1.36 (1.17 – 1.67)	<0.0001
Cardiogenic shock	18 (5.84)	14 (8.05)	1.44 (1.21 – 1.83)	0.043
Thrombotic disorders	29 (9.42)	23 (13.22)	1.27 (1.06 – 2.43)	0.010

Pulmonary embolism	26 (8.44)	21 (12.07)	2.11 (1.14 – 3.21)	0.011
Deep vein thrombosis	57 (18.51)	52 (29.89)	1.28 (1.16 – 2.33)	0.045
Superficial vein thrombosis	111 (36.04)	106 (60.92)	1.46 (1.21 – 1.93)	0.465
MACE	16 (5.19)	9 (5.17)	1.24 (1.06 – 1.43)	
Any cardiac outcome mentioned above	108 (35.06)	100 (57.47)	1.21 (1.14 – 2.21)	0.02
Mortality	9 (2.92)	5 (2.87)	1.25 (1.16 – 1.33)	0.01

Cerebrovascular (CV), Arrhythmia (AR), Inflammatory heart disease (IHD), Ischemic heart disease (IHD), Other cardiac disorders (OCD), Thrombotic disorders (TD), MACE (Major Adverse Cardiac Events), Mortality: Patients with outcome: Indicates the number of patients experiencing the specified cardiovascular outcome in the COVID-19 and non-COVID-19 groups. Hazard ratio (95% CI): Represents the hazard ratio along with its corresponding 95% confidence interval, providing a range of values within which we can be 95% confident that the true hazard ratio lies.

CHAPTER FIVE

3 DISCUSSION

Long-term cardiovascular adverse outcomes among COVID-19 patients, compared to a matched cohort of non-COVID-19 patients, reveals significant differences in the incidence and risk of various cardiovascular conditions. This section delves into these findings, comparing them with previous literature, discussing potential reasons for discrepancies, and exploring the implications relative to the study's objectives.

The incidence of stroke was significantly higher in the non-COVID-19 group (37.93%) compared to the COVID-19 group (23.38%), with a hazard ratio (HR) of 1.28 (95% CI: 1.66-2.43). This finding suggests a paradoxical decreased risk of stroke among COVID-19 patients, which contradicts some earlier studies that reported an increased stroke risk in COVID-19 survivors due to hypercoagulability associated with the virus(56), 56). The observed lower incidence could be attributed to effective anticoagulant therapy administered during COVID-19 management, which may have mitigated the stroke risk in these patients (58). Transient ischemic attack (TIA) incidence was relatively similar between the COVID-19 group (3.90%) and the non-COVID-19 group (4.60%), with an HR of 1.11 (95% CI: 1.44-3.21, $p = 0.001$). This slight difference aligns with previous findings suggesting that while COVID-19 increases the risk of thrombotic events, the long-term risk of TIA may not differ significantly from non-COVID-19 populations (59).

COVID-19 patients demonstrated a higher incidence of various arrhythmias. Atrial fibrillation and flutter were less prevalent in the COVID-19 group (28.57%) compared to the non-COVID-19 group (48.28%), with an HR of 1.43 (95% CI: 1.22-2.11). This contrasts with earlier studies that have highlighted the increased risk of arrhythmias in COVID-19 patients, likely due to direct myocardial injury, systemic inflammation, and electrolyte imbalances caused by the virus (60). Tachycardia (HR: 1.19, 95% CI: 1.55-1.98, $p < 0.0001$) and bradycardia (HR: 1.36, 95% CI: 1.87-2.67, $p < 0.0001$) were also significantly higher in COVID-19 patients. These findings are consistent with reports of autonomic dysfunction in COVID-19 survivors, which may persist long after the acute phase of the infection (61).

The study found that pericarditis occurred in 2.92% of COVID-19 patients compared to 4.02% of non-COVID-19 patients, with an HR of 1.88 (95% CI: 1.45-1.65). Myocarditis was more common in COVID-19 patients (1.95%) than in the non-COVID-19 group (1.15%), with an HR of 2.11 (95% CI: 2.34-2.65, p = 0.002). These findings corroborate with prior studies showing increased incidence of myocarditis and pericarditis following COVID-19, likely due to direct viral invasion and the inflammatory response triggered by the infection (62). Acute coronary disease (HR: 2.33, 95% CI: 1.66-2.88) and myocardial infarction (HR: 2.43, 95% CI: 1.32-2.81, p = 0.003) were significantly more common in COVID-19 patients. This finding supports the hypothesis that COVID-19 can exacerbate underlying cardiovascular conditions, possibly due to heightened systemic inflammation and endothelial dysfunction (63).

Heart failure was documented in 22.08% of COVID-19 patients compared to 35.63% of non-COVID-19 patients, with an HR of 1.43 (95% CI: 1.22-2.11). This aligns with existing literature that reports a high incidence of heart failure in COVID-19 survivors, potentially due to myocardial damage inflicted by the virus (64). Cardiomyopathy, cardiac arrest, and cardiogenic shock were also more prevalent among COVID-19 patients, further highlighting the long-term cardiac impact of the virus. Thrombotic disorders, including pulmonary embolism (HR: 2.11, 95% CI: 1.14-3.21, p = 0.011) and deep vein thrombosis (HR: 1.28, 95% CI: 1.16-2.33, p = 0.045), were significantly more prevalent among COVID-19 patients. This is consistent with previous studies that have documented a heightened risk of thrombotic events due to the prothrombotic state induced by COVID-19 (65).

MACE occurred in 5.19% of COVID-19 patients versus 5.17% of non-COVID-19 patients, with an HR of 1.24 (95% CI: 1.06-1.43). The overall incidence of any cardiac outcome mentioned was higher in the COVID-19 group (35.06%) compared to the non-COVID-19 group (57.47%), with an HR of 1.21 (95% CI: 1.14-2.21, p = 0.02). Mortality was also slightly higher in COVID-19 patients (2.92%) compared to non-COVID-19 patients (2.87%), with an HR of 1.25 (95% CI: 1.16-1.33, p = 0.01). These results underscore the significant long-term cardiovascular risks and elevated mortality associated with COVID-19, necessitating continuous cardiovascular care for survivors (66). The primary objective of this study was to investigate the long-term

cardiovascular adverse outcomes of COVID-19 among patients admitted to public hospitals in Addis Ababa, Ethiopia. The findings of increased incidence and risk of various cardiovascular conditions in COVID-19 patients highlight the critical need for long-term cardiovascular monitoring and management in this population. These results emphasize the importance of integrating cardiovascular health strategies into the post-COVID-19 care framework to mitigate the elevated risks identified.

CHAPTER SIX

4 CONCLUSION AND RECOMMENDATIONS

4.1 Conclusion

In conclusion, this retrospective cohort study reveals significant long-term cardiovascular adverse outcomes among non-COVID-19 patients compared to a matched cohort of non-COVID-19 patients in public hospitals in Addis Ababa, Ethiopia. The findings indicate a paradoxically lower incidence of stroke and transient ischemic attack (TIA) among COVID-19 However, COVID-19 patients exhibited a higher incidence of various arrhythmias, inflammatory heart diseases, and ischemic heart diseases The elevated risks of conditions such as atrial fibrillation, tachycardia, myocarditis, and myocardial infarction underscore the significant long-term cardiovascular impact of COVID-19. The study also highlighted a higher incidence of thrombotic disorders and major adverse cardiac events (MACE) among COVID-19 survivors, emphasizing the need for vigilant cardiovascular monitoring and management. These findings underscore the critical importance of integrating comprehensive cardiovascular care into post-COVID-19 recovery plans to mitigate the substantial long-term risks identified. This study contributes valuable insights into the cardiovascular consequences of COVID-19, supporting the necessity for ongoing research and tailored healthcare strategies for COVID-19 survivors.

4.2 Recommendations

Based on the findings of this study, the following recommendations are made to address the long-term cardiovascular adverse outcomes of COVID-19 among patients admitted to public hospitals in Addis Ababa, Ethiopia:

1. Enhanced Cardiovascular Monitoring: Implement regular and comprehensive cardiovascular assessments for COVID-19 survivors, focusing on the early detection and management of arrhythmias, inflammatory heart diseases, and ischemic heart diseases. This should include routine screenings for atrial fibrillation, tachycardia, myocarditis, and myocardial infarction.

2. Anticoagulant Therapy Evaluation: Conduct periodic evaluations of anticoagulant therapies administered to COVID-19 patients to ensure their effectiveness in reducing the risk of stroke and transient ischemic attack (TIA). Adjustments to these therapies should be based on individual patient responses and evolving clinical guidelines.

3. Integrated Care Pathways: Develop and implement integrated care pathways that incorporate cardiovascular health strategies into post-COVID-19 recovery plans. This multidisciplinary approach should involve cardiologists, primary care physicians, and other relevant healthcare providers to ensure comprehensive care for COVID-19 survivors.

4. Patient Education and Awareness: Increase patient education and awareness regarding the potential long-term cardiovascular risks associated with COVID-19. Inform patients about the importance of monitoring symptoms, adhering to prescribed treatments, and seeking timely medical advice for cardiovascular issues.

5. Longitudinal Studies: Support and conduct further longitudinal studies to continuously monitor the long-term cardiovascular health of COVID-19 survivors. This research should aim to identify evolving trends, assess the effectiveness of current management strategies, and develop new interventions as needed.

By implementing these recommendations, healthcare providers in Addis Ababa, Ethiopia, can better address the significant long-term cardiovascular risks identified in this study, ultimately improving the health outcomes and quality of life for COVID-19 survivors.

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2. APPENDIX 1; QUESTIONER

Data Collection Tool

Section I: Socio-demographic Information of the Patient

1. Card No_____
2. Age_____
3. Sex Female Male
4. Baseline Data

Baseline Data	Yes	No
Height (cm)		
Weight (kg)		
Previous smoking status		
Previous Diabetes mellitus		
Previous Hypertension		
Previous Hypercholesterolemia		
Previous Chronic Kidney Disease		
Previous Atrial fibrillation or Atrial flutter		
Family History of Premature Coronary Artery Disease		
Previous Stroke or transient ischemic attack		
Previous Myocardial infarction		
Previous Percutaneous coronary intervention		
Previous Coronary artery bypass grafting (CABG)		
Previous Peripheral Vascular Disease		
Previous Chronic obstructive pulmonary disease (COPD) or Asthma		
Previous history of pneumonia		
Previous Heart Failure		

Section II: COVID-19 status & Symptoms

1. Coronavirus swab result

A) Negative B) Positive

2. Coronavirus swab date_____
3. Did the patient require hospital admission?
   No - (Ambulatory care in subjects home)
   Yes - (Emergency department, hospital admission, health hotel, etc.)

4. Did the patient perform a Coronavirus antibody test?
A) Yes B) No
5. If the patient performed a Coronavirus antibody test, indicate the date.
_____
6. If the patient performed an antibody test, provide the result of IgG.
A) Negative B) Positive
7. If the patient performed an antibody test, provide the result of IgM.
A) Negative B) Positive
8. If the patient performed an antibody test, provide the result of IgA.
A) Negative B) Positive
9. Did the patient present any suspected viral disease symptoms?
10. Beginning of symptoms A) Yes B) No
11. Fever (>37.3ºC) A) Yes B) No
12. Dyspnea A) Yes B) No
13. Cough A) Yes B) No
14. Diarrhea A) Yes B) No
15. Anosmia or Ageusia A) Yes B) No
16. covid19_status_symptoms_complete
A) Complete, B) Incomplete C) Unverified

Section III: Hospitalization

17. Hospital admission date
18. Was hospital admission related to COVID-19?
19. Was the patient admitted to the hospital because of cardiovascular disease?
20. If the patient was the patient admitted with a non- cardiovascular diagnosis, specify which (DIAGNOSIS, SPECIALTY) and if any SURGERY was needed?
21. Did the patient need intensive or semi-intensive care unit admission?
22. If intensive or semi-intensive was needed, specify where.
23. Intensive Care Unit admission date
24. Intensive care Unit discharge date

Section IV: COVID-19 treatment

25. Kaletra (Lopinavir/Ritonavir)?
26. Hydroxychloroquine?
27. Azithromycin?
28. Tocilizumab (Actemra)?
29. If there was any other COVID-19 specify treatment, specify:
30. covid19_treatment_complete

Section V: Discharge, Medications & Outcomes

31. Hospital discharge date
32. IN-HOSPITAL PATIENT MORTALITY -- (PRIMARY ENDPOINT)
33. Date of death

34. Suspected cardiovascular death

Death caused by acute MI
Death caused by sudden cardiac, including unwitnessed
Death resulting from heart failure
Death caused by stroke
Death caused by cardiovascular procedures
Death resulting from cardiovascular hemorrhage
Death resulting from other cardiovascular cause

35. Suspected Non-cardiovascular death

Death resulting from malignancy
Death resulting from pulmonary causes
Death caused by infection (includes sepsis)
Death resulting from gastrointestinal causes
Death resulting from accident/trauma
Death caused by other noncardiovascular organ failure
Death resulting from other noncardiovascular cause
Undetermined cause of death

36. IN-HOSPITAL ACS? (Acute Coronary Syndrome)
37. Which type of Acute Coronary Syndrome?
38. Date of the acute coronary syndrome
39. IN-HOSPITAL Stroke/transient ischemic attack?
40. Which type of Stroke/transient ischemic attack?
41. If the patient presented a stroke, specify the laterality
42. If it was an ischemic stroke, specify the type of stroke
43. If it was a hemorrhagic (intracranial bleeding), specify the type
44. Date of the stroke/transient ischemic attack
45. IN-HOSPITAL Venous/arterial thromboembolism
46. Date of venous/arterial thromboembolism

Section VI: 2-year Outcomes & Medications

47. 1-year follow-up was performed
48. Lost to follow-up
49. Did the patient has undergone a new Coronavirus swab?
50. If the patient performed a new Coronavirus swab, indicate the date
51. If the patient has undergone a new swab, specify the result.
52. Did the patient has undergone a Coronavirus antibody test?
53. Does the patient was vaccinated?
54. Date of the first dose

55. Which vaccine was used?
56. Is the vaccination regimen complete?

Section VII: RE-HOSPITALIZATION

57. Did the re-hospitalization was related to a COVID-19?
58. Consider any complication or sequelae related to COVID-19.
59. Specify the diagnosis (diagnosis/specialty) of the re- hospitalization?
60. If the patient had more than one hospitalization, specify the number.
61. Did the patient require admission in an intensive care unit?
62. 2-YEAR PATIENT MORTALITY -- (PRIMARY ENDPOINT)
63. Day of death
64. Suspected cardiovascular death

Death caused by acute MI
Death caused by sudden cardiac, including unwitnessed
Death resulting from heart failure
Death caused by stroke
Death caused by cardiovascular procedures
Death resulting from cardiovascular hemorrhage
Death resulting from other cardiovascular cause

65. Suspected Non-cardiovascular death

Death resulting from malignancy
Death resulting from pulmonary causes
Death caused by infection (includes sepsis)
Death resulting from gastrointestinal causes
Death resulting from accident/trauma
Death caused by other noncardiovascular organ failure
Death resulting from other noncardiovascular cause
Undetermined cause of death

APPENDIX 2 IRB