IMPACT OF THE SARS-CoV-2 PANDEMIC ON ACUTE CORONARY SYNDROME PATIENTS ADMITTED TO AN URBAN ACADEMIC HOSPITAL IN SOWETO, SOUTH AFRICA.

Candidate:

Dr. Suzan Leon.

MD

Wits student number: 2215610

Registrar training number: W-05-01-116

Degree: MMed Internal Medicine.

Email: leonsuzan13@gmail.com

Supervisor:

Prof. Ruchika Meel.

MBChB, MMed (Cum Laude), Cert. Cardiology (SA), PhD, FEACVI, Post-Doctoral Carnegie Fellow.

Specialist Physician, Cardiologist, Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital.

Email: ruchikameel@gmail.com

Co- Supervisor:

Dr. Priya Parbhoo.

MBChB, MMed, FCP (SA).

Specialist Physician, Fellow in Cardiology, Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital

Email: priya.parbhoo@gmail.com

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Suzan Leon (Student number: 2215610) am a student registered for the degree of Masters in Internal Medicine in the academic year 2019.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: Date: 31/01/2022.

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Suzan Leon, student number 2215610 declare that this Thesis/Dissertation/Research Report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Thesis/Dissertation/Research Report.

Signature of Student **Date**: 31/01/2022

Name of Primary Supervisor

Prof Ruchika Meel

Signature of Primary Supervisor

Date………31/01/2022……………

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of his/her Thesis/Dissertation/Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article 1: Title: Impact of the SARS-COV-2 pandemic on acute coronary syndrome patients admitted to an urban academic hospital in Soweto, South Africa.

Journal name, year, volume, and page numbers:

……………………………………………………………………………………………………

Authors	Name	Signature	Date
1st author	Suzan Leon		31/01/2022
2nd author	Priya Parbhoo		31/01/2022
3rd author	Ruchika Meel		31/01/2022
4th author			
5th author			
6th author			

Comments by primary supervisor:

………
………
………
………
………

PRESENTATIONS / PUBLICATION

1. University of the Witwatersrand Biannual Research Day 2021.

A poster abstract of the research report was displayed at the event.

2. South African Heart Congress 2021.

A poster abstract of the research was accepted and displayed at the event at the end of October 2021.

3. Publication

The research article has been submitted to Southern African Journal of Public Health for publication.

ABSTRACT

Background: Recent worldwide data has shown a concerning decline in the number of acute coronary syndrome (ACS) related admissions and percutaneous coronary intervention (PCI) procedures during the coronavirus disease 2019 (COVID-19) pandemic. We suspected a similar trend at Chris Hani Baragwanath Hospital (CHBAH).

Aim: To evaluate the impact of the COVID-19 pandemic on ACS patients admitted to the cardiac care unit (CCU) in CHBAH.

Methods: A retrospective descriptive study was conducted to evaluate and compare all ACS-related admissions to CCU at CHBAH in the pre-COVID-19 (November 2019 to March 2020) and during COVID-19 periods (April 2020 to August 2020).

Results: The study comprised 182 patients with a mean age of 57.9 ±10.9 years (22.5% females). Of these, 108 patients were admitted in the pre-COVID 19 period. During the pre-COVID-19 period, 42.9% of patients presented with ST-segment-elevation myocardial infarction (STEMI), 39.2% with non -ST segment -elevation myocardial infarction (NSTEMI) and unstable angina (UA) was noted in 18.52%. In contrast, STEMI was noted in 50%, NSTEMI in 43.24% and UA in 6.76% of patients during the COVID-19 period. A statistically significant difference in STEMI and NSTEMI-related admissions was not noted, however there were a greater number of admissions for UA during the pre-COVID-19 period (18.52% vs 6.76%, P =0.013).

Only a third of the patients with STEMI received thrombolysis during the pre- and COVID-19 periods (30.4% vs 37.8%, P=0.47). No difference in the number of PCI procedures was noted between the pre- and COVID-19 periods (78.7% vs 72.9%, P=0.37). There was a trend towards a lower left ventricular ejection fraction (48.6% vs 34.2%, P=0.05) and increased diagnosis of heart block (5.4% vs 0.9%, P=0.06) during COVID as compared to the pre-COVID-19 period. More arrhythmias (8.3%) were noted in the pre-COVID-19 period (P=0.011).

Conclusion: There was no difference in ACS admissions to the CCU during pre- and COVID-19 periods. Although the assessment of the full impact of COVID-19 on ACS admissions to the hospital was limited, in the CCU, there was a higher number of UA admissions during the pre-COVID-19 period. During both periods, the use of

thrombolysis was low for STEMI and no difference in PCI was noted. There were no differences in complications observed between the two periods, except for a higher rate of arrhythmias noted in the pre-COVID-19 period.

ACKNOWLEDGEMENTS

My special thanks and gratitude to my supervisor Prof. Ruchika Meel for helping me in conceptualizing the idea of this research project and providing a detailed review of the manuscript. Her guidance, kind supervision, advice and timely suggestions has helped me to a greater extent in the completion of this research.

I would also like to express my sincere thanks to my co- supervisor Dr Priya Parbhoo for her insight and time given to review this research report at various stages.

I am grateful to my steadfast husband for his enduring love and unwavering support during this project.

Finally, I thank the almighty God who made everything possible.

Table of contents

DECLARATION………………………………………………………………………….. i

PRESENTATIONS / PUBLICATIONS ……………………………………………… iv

ABSTRACT ……………………………………………………………………………. v

ACKNOWLEDGEMENTS …………………………………………………………… vii

ABBREVIATIONS……………………………………………………………………… 1

LIST OF FIGURES…………………………………………………………………….. 2

LIST OF TABLES……………………………………………………………………… 3

CHAPTER ONE: APPROVED PROTOCOL WITH EXTENDED LITERATURE REVIEW

1. Summary……………………………………………………………………… 4
2. Introduction…………………………………………………………………… 5
3. Study Objectives………………………………………………….............. 9
4. Methodology…………………………………………………………………… 9
   - 4.1. Study Design………………………………………………………….. 9
   - 4.2. Study Population and Sample………………………………………… 10
   - 4.3. Study site……………………………………………………………… 10
   - 4.4. Data collection………………………………………………………… 10
5. Data Analysis……………………………………………………............. 11
6. Ethics…………………………………………………………………………… 11
7. Funding………………………………………………………………………… 12
8. Timing………………………………………………………………………….. 12
9. References…………………………………………………………………….. 13

CHAPTER TWO: SUBMISSIBLE ARTICLE

1. Introduction……………………………………………………………………. 18
2. Methods…………………………………………………………………………... 18
3. Results…………………………………………………………………………. 20
4. Discussion……………………………………………………………………… 26
5. Limitations……………………………………………………………………… 30
6. Conclusion…………………………………………………………………… 31
7. Recommendations…………………………………………………………….. 31
8. References…………………………………………………………………… 33

LIST OF APPENDICES

I. Data collection sheet……………………………………………………….. 38
II. Ethics clearance certificate…………………………………………………. 40
III. Turn It In report……………………………………………………………. 41

ABBREVIATIONS

ACE2: Angiotensin converting enzyme-2

ACS: Acute coronary syndrome

CCU: Cardiac care unit

CHBAH: Chris Hani Baragwanath Academic Hospital

COVID-19: Coronavirus disease 2019

ECG: Electrocardiogram

ESC/ACCF/AHA/WHF: European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and the World Heart Federation

MACU: Medical acute care unit

MEU: Medical emergency unit

MI: Myocardial infarction

NSTEMI: Non-ST-elevation myocardial infarction

PCI: Percutaneous coronary intervention

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

STEMI: ST-elevation myocardial infarction

WHO: World health organization

ZAR: South African Rand

LIST OF FIGURES

Figure 1: Flow diagram depicting the methodology used in the study………. 19

Figure 2: Acute coronary syndrome admissions during the pre-COVID-19 and COVID-19 periods ………………………………………………….. 21

Figure 3: Length of stay in days between two groups………………………… 23

Figure 4: Graphic presentation of patients admitted for STEMI, NSTEMI and unstable angina……………………………………………………… 24

Figure 5: The distribution of patients who received thrombolysis for STEMI and those that underwent PCI and referral for CABG for ACS during pre-COVID-19 and COVID-19 periods …………………………………… 25

LIST OF TABLES

Table 1: Demographic and clinical characteristics of study patients ………… 22

Table 2: Summary of specific ACS diagnosis among patients admitted in the pre-COVID-19 and COVID-19 periods ……………………………….. 24

Table 3: Complications encountered in ACS patients during the pre-COVID-19 and COVID-19 periods……………………………….…………………. 26

CHAPTER ONE: APPROVED PROTOCOL WITH EXTENDED LITERATURE REVIEW

1. SUMMARY

Coronavirus disease 2019 (COVID-19) is a viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Elderly individuals and those with significant comorbidities, in particular cardiovascular diseases, are at a higher risk for morbidity and mortality. The highly infectious nature of COVID-19 has led to implementation of strict measures such as lockdowns to combat the spread of infection. Shift of attention to COVID-19, together with lockdown measures has impacted on patients with non- COVID-19 related diseases. Data from developed countries across Europe and North America, as well as developing nations, have demonstrated a concerning decline in the number of acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI) procedures. We suspect a similar trend in South Africa. To the best of our knowledge, such a study has not been formally published within Africa. Therefore, in this retrospective study we aim to systematically study the impact of COVID-19 pandemic on ACS patients at Chris Hani Baragwanath Academic Hospital (CHBAH).

2. INTRODUCTION

The Coronavirus disease 2019 is an acute respiratory infection caused by SARS-CoV-2. The first case was reported in Wuhan, China on 8th December 2019. [1] The outbreak originated from Hunan seafood market in Wuhan. [2] Rapid spread of the virus beyond geographical regions led to declaration of COVID-19 a pandemic by the World Health Organisation (WHO) on March 11th, 2020. [3] The statistics to date are mounting with over two hundred million people infected worldwide and more than four million deaths at the time of this writing. [4]

The virus is transmitted through person-to-person contact via respiratory droplets or direct contact. [3,5] Studies have shown that both symptomatic, as well as asymptomatic patients can transmit the virus. Some of the common clinical symptoms include fever, dry cough, myalgia, headache, sore throat, shortness of breath and gastrointestinal symptoms like nausea and diarrhoea. [3,5] SARS-CoV-2 gains access to human cells by binding to angiotensin converting enzyme-2 receptor (ACE-2) which is highly expressed in the lungs and heart. It is also found in the intestinal epithelium, vascular endothelium, and kidneys. [6,7] According to the meta-analysis by Yang J et al, [8] pre-existing comorbidities are associated with disease severity, complications, and higher risk of mortality. These include cardiovascular diseases such as hypertension, coronary artery disease, diabetes, and chronic respiratory diseases.

Long B et al, have highlighted some cardiovascular complications related to COVID-19. These include myocardial injury, myocarditis, acute myocardial infarction, heart failure, cardiomyopathy, dysrhythmias, and venous thromboembolic events. [9] The interaction between SARS-CoV-2 and ACE-2 receptor in its pathogenesis gives insight into the related manifestations and complications of COVID-19 in the cardiovascular system. Among the numerous complications mentioned above, the proposed mechanisms of myocardial injury include: 1) direct myocardial injury due to viral myocarditis, 2) systemic inflammatory response and cytokine storm, 3) increased cardio-metabolic demand associated with systemic infection and 4) plaque rupture and prothrombotic milieu created by systemic inflammation. [10-13]

A Wuhan study by Shi S, et al [14] supports the consequences of myocardial injury associated with SARS-CoV-2. Among 416 hospitalized patients with confirmed COVID-19, 82 (19.7%) had evidence of myocardial injury manifested by elevation of high sensitivity troponin I (hs-TnI) levels. A similar finding was reported by Guo T et al, [15] where 27.8% of the cohort demonstrated myocardial injury with elevated troponin T levels.

Acute coronary syndrome (ACS) includes non-ST elevation myocardial infarction (NSTEMI), ST-elevation myocardial Infarction (STEMI) and unstable angina (UA). [16] According to the Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Heart Federation (ESC/ACCF/AHA/WHF), myocardial infarction is defined as a clinical or pathological event in the setting of myocardial ischemia in which there is evidence of myocardial Injury. [17,18]

The diagnosis is made when there is a rise and /or fall of troponin with at least one value greater than the 99th percentile upper reference limit with at least one of the following: [18]

- Symptoms of myocardial ischemia.
- New ischemic electrocardiogram (ECG) changes.
- Development of pathological Q waves.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic aetiology.
- Identification of a coronary thrombus by angiography or autopsy.

New ischemic ECG changes entails: [18]

- new ST-segment elevation at the J-point in two contiguous leads measuring ≥ 0.1mv in all leads except V2-V3, which require ≥ 2mm in men ≥ 40years; ≥ 2.5 mm in men <40 years or ≥ 1.5mm in women regardless of age for STEMI.
- ST depression and/or T wave inversions without ST-segment elevations or pathologic Q waves for NSTEMI.

The early management goals in myocardial infarction are to relieve pain, evaluation of and correction of hemodynamic abnormalities, antithrombotic, reperfusion and beta blockade therapy. The increase in ischemic time (i.e., more than 6 hours after the onset of symptoms) is directly related to short- and long-term survival. [19]

Fear of contracting COVID-19, together with the lockdown measures instituted by many had led to delayed medical seeking habits and a reduction in the admissions of patients with acute coronary syndrome. Recent publications have confirmed this alarming reduction in the number of patients presenting with myocardial infarction in both developed and developing countries. [20]

A multicentre, observational, national survey in Europe's most severely affected country (Italy) aimed to evaluate the impact of the COVID-19 pandemic on cardiac care unit (CCU) admissions. The study observed a 48.8% reduction in admissions for acute myocardial infarction compared to the equivalent week in 2019 (p<0.0001). The reduction was both significant for STEMI; 26.5%, 95% confidence interval (CI) 21.7-32.3; (p=0.009), and NSTEMI; 65.1%, 95% CI 60.3-70.3; (p<0.001). [21]

A retrospective study conducted in Northern Italy analysed the clinical and angiographic characteristics of patients admitted for acute coronary syndromes at fifteen hospitals. The study period was between the time of the first confirmed case of COVID-19 in Italy (20th February 2020) and 31st March 2020 compared to the same period during the previous year (20th February to 31st March 2019) and an earlier period during the same year (1st January to 19th February 2020). Of the 547 patients who were admitted for ACS, 248 (45.3%) presented with STEMI. The mean hospitalization rate for ACS during the study was 13.3 admissions per day. This rate was significantly lower than the rate in the earlier period in the same year [(where total number of admissions was 899; 18.0 admissions per day; incidence ratio, 0.74; 95% CI, 0.66 to 0.82; p<0.001)] or the rate in the previous year [(number of admissions, 756; 18.9 admissions per day; incidence ratio, 0.70; 95% CI, 0.63 to 0.78; (p<0.001)]. [22]

An Austrian study also reported a similar decline in rates of admission (39.4%) for ACS when compared to the first and last calendar week of 2019. [23]

On 14th March 2020, Spain declared a national state of emergency which led to a decrease in health care activity in interventional cardiology units. [24] A study by Rodrigues-Leor O, et al did a survey to quantify these changes. Eighty-one centres were included. Not only did the number of patients treated in STEMI networks decline, but also the numbers of performed diagnostic procedures (56%), PCI (48%) and structural interventions (81%). [24]

In the United States of America timely primary PCI is the standard of care for STEMI patients. Garcia S, et al performed a study to determine if there was a decrease in the number of STEMI patients for primary PCI in New York during the COVID-19 era. Nine high-volume (>100 primary PCIs per year) cardiac catheterization laboratories were involved. A 38% decrease in STEMI activation was observed (95% CI: 26-49; p<0.001). [25]

These concerning declines have also been reported in the developing countries. In Pakistan, a study by Sharif K.H et al depicted a decline of 37.84% and 66.43% for STEMI and PCI, respectively. [26] A Turkish study by Khalil E, et al also showed reduced numbers in STEMI and PCI procedures during the COVID-19 period compared to the previous five years. [27]

In South Africa, the first confirmed case of COVID-19 was reported by the department of health on 5th March 2020. Since then, the disease has rapidly spread throughout the country with consequent implementation of lockdown measures, starting 26th March 2020. There are to date over 2.5 million infected citizens with more than eighty thousand deaths. [28]

COVID-19 has not only caused a collateral damage economically but has also posed a threat to public health and the care of non-COVID related cases. The decline in acute coronary syndromes presentations have been attributed to 1) change in the threshold for treating patients medically and therefore less referral for PCI, 2) reduced physical/stress activity during lockdown periods (which in itself reduces incidence of MI), 3) patients are less likely to seek medical attention out of concern for an overwhelmed medical system, 4) good health practices i.e. less smoking, 5) good adherence to treatment due to the confines of lockdown.

South Africa is a resource limited country with some impoverished communities. Lockdown measures with the resultant economic collapse and unemployment, has exacerbated financial difficulties and has led to lack of funds for most patients to travel out of rural communities to seek appropriate health care.

Chris Hani Baragwanath Academic Hospital (CHBAH) cardiology unit usually receives ACS patients referred from nearby local clinics or directly from CHBAH medical emergency unit (MEU). During COVID-19, patients from local clinics must be tested and confirmed negative for COVID-19 before being accepted to CHBAH CCU.

Patients from MEU with ACS must temporarily be cared for in medical acute care unit (MACU). Once a negative test result is documented, only then can a patient be admitted to the CCU for appropriate management and PCI. These changes in the flow of ACS patients have affected the required care and may have contributed to a decline in admissions and PCI procedures as hypothesized.

This retrospective study aimed to analyse the impact of COVID-19 on ACS patients admitted to the CCU in CHBAH. The hospital is one of the largest academic hospitals in Africa and South Africa. It is located in Soweto on the outskirts of Johannesburg city. The study assessed the admissions of ACS patients prior to COVID-19 (i.e. November 2019-March 2020) and compared admissions during COVID-19 and lockdown measures (i.e. April 2020-August 2020).

3. STUDY OBJECTIVES

- To describe and compare the demographic and clinical characteristics of the patients admitted to CCU during pre-COVID 19 and COVID-19 periods.
- To determine the number of admissions of patients admitted with ACS and associated co-morbidities in CCU during COVID-19 period and compare findings with the pre-COVID-19 period.
- To determine and compare ACS-related complications pre-COVID-19 and during COVID-19 periods.
- To determine and compare the management of patients in the pre-COVID-19 and COVID-19 periods.

4. METHODOLOGY

4.1. Study design

This was a retrospective analysis of all the patients with ACS who were admitted to the CCU in the pre-COVID-19 (i.e. November 2019 to March 2020) and during COVID-19 (April 2020 to August 2020) eras at CHBAH. ACS was defined according to The Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Heart Federation (ESC/ACCF/AHA/WHF) fourth universal definition for myocardial infarction.

Major complications related to ACS was defined as heart failure with reduced ejection fraction (HFrEF), cardiogenic shock, arrhythmias, thromboembolism (left ventricular clot, critical limb ischemia and stroke), cardiac arrest, varying degrees of atrioventricular block, left ventricular aneurysms and in-hospital mortality.

4.2. Study population and sample.

The study included all patients with ACS that were admitted to the CHBAH CCU in the period between November 2019 and August 2020. Simple consecutive convenient sampling method was used to procure a sample size in the pre-specified study period. The study included both male and female patients irrespective of their age and race.

Inclusion criteria

- All the patients above 18 years of age admitted to CCU with ACS.

Exclusion criteria

- All patients under 18 years of age.
- Patients admitted to CCU for reasons other than ACS.
- Patients with ACS for whom data was missing during the time of admission within the study period

4.3. Study site

The study was conducted at CHBAH CCU, department of cardiology.

4.4. Data collection

Data was collected by the principal investigator. The principal investigator reviewed all discharge summary notes filed at the CCU and identified all patients with ACS admitted during the study period. A data collection sheet was used (see appendix I).

5. DATA ANALYSIS

In line with the study objectives, data analysis was performed in the following way:

1. In the descriptive statistics phase of our analysis, patients' socio-demographic and clinical characteristics, co-morbidities, complications, and mortality was summarized and analysed using measures of central position (mean and median) and their distributions described using measures of location (quantiles) and appropriate graphs.
2. Using results and tables obtained in the descriptive statistics phase, the number of patients admitted with ACS (with or without comorbidities or complications) for the period spanning from April 2020 to August 2020 was compared to that of patients admitted between November 2019 and March 2020. Comparisons were performed using appropriate hypothesis testing for sample proportions. Other relevant continuous variables were compared either using Students T-test or Mann-Whitney test, and the Chi-Square test of association for categorical variables.
3. For all hypothesis tests, a p-value of less than 0.05 was considered statistically significant. Stata version 15 was used for statistical analysis.

6. ETHICS

The protocol was submitted for approval at the University of the Witwatersrand Human Research Ethics Council. The study was performed in accordance with guidelines set out in the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. It adhered to the integrity standards as set out by the Singapore Statement June 2019.

All patient information was kept confidential through the allocation of a case number for each patient. The case number allocated was only known to the principal investigator.

7. FUNDING

The costs of the study will be minimal and will include stationery and printing. All costs will be covered by the principal investigator.

8. TIMING

	June 2020	July 2020	August 2020	Sept to Nov 2020	Dec 2020 to March 2021	April to June 2021	July to Oct 2021
Literature review							
Protocol development							
Protocol Assessment							
Ethics application							
Data collection							
Data analysis							
Writing up research report							

9. REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019(COVID-19) outbreak in China. Summary of a report of 72314 cases from the Chinese Centre for Disease Control and Prevention (published online February 24, 2020). JAMA. 2020; 323(13):1239-1242. doi: 10.1001/jama.2020.2648.

2. Shereen MA, Khan S, Kazmi A, et al. COVID-19 infections: origin, transmission and characteristics of human coronaviruses. Journal of Advanced Research. July, 2020. Vol 24; page 91-98.

3. World Health Organization, Report of the WHO-China joint mission on coronavirus disease 2019(COVID-19). https://www.who.int/publication-details/ report-of-the-who-china-joint-misssion-on-coronavirus-disease-2019-(covid-19). Published 2020.

4. World Health Organization. Coronavirus disease (COVID-19) situation reports 162. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Published 30, June 2020.

5. Zou L, Ruan F, Huang M, et al. SARS-Cov-2 viral load in upper respiratory specimens of infected patients. N. Engl J Med. 2020; 382:1177-1179. doi: 10.1056/NEJMc200173.

6. Hoffman M, Kleine-weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically protease inhibitor (published online March 5,2020). Cell. Doi: 10.1016/j.cell.2020.02.052. https://www.sciencedirect.com/science/article/pii/S0092867420302294

7. Zhao Y, Zhao Z, Wang Y, et al. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov (published online January 26, 2020). bio.Rxiv.doi:10.1101/2020.01.26.919985. https://www.biorxiv.org/content/10.1101/2020.01.26.919985v1.

8. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection, a systemic review and meta-analysis. Int J Infect Dis 2020. 1201-9712(20) 3136-3. doi: 10.1016/j.ijid.2020.03.017.

9. Long B, Brady WJ, Koyfman A, et al. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020 April 18. pii: S0735-6757(20)30277-1. Doi: 10.1016/j.ajem.2020.04.048.

10. Xiong TY, Redwood S, Prendergast B, et al. Coronavirus and the cardiovascular system: acute and long term implications. Eur Heart J 2020. Vol 41; page 1798-1800. https://doi.org/10.1093/eurheartj/ehaa231.

11. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic disease on COVID-19 in China. Clin Res cardiol 109; 531-538(2020). https://doi.org/10.1007/s00392-020-01626-9.

12. Zhou F, Yu T, Du R, et al. Clinical course and risk factor for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study (published online March 9, 2020). Lancet 2020; 395: 1054-1062. https://doi.org/10.1016/S0140-6736 (20)30566-3.

13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, china. Lancet 2020; 395: 497-506. https://doi.org/10.1016/S0140-6736 (20)30183-5.

14. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan china (published online March 25, 2020). JAMA Cardiol. 2020; 5(7):802-810. doi: 10.1001/jama cardio. 2020.0950.

15. Guo T, Fan Y, Chen M, et al. Cardiovascular complications of fatal outcomes of patients with coronavirus disease 2019(COVID-19) (published online March 27, 2020). JAMA Cardiol. 2020; 5(7):811-818. doi:101001/jamacardio.2020.1017.

16. Robert PG, Christopher PC, Eugene B. Non-ST Segment Elevation Acute Coronary Syndrome (non-ST-segment Elevation Myocardial Infarction and Unstable Angina). In: Kasper D, Fauci A, Longo D, Hauser S, Jameson J.L., Loscalzo J (Eds). Harrison’s Principle of internal medicine. 20th edition. United States of America: McGraw-Hill Education; 2018. p 1866-1872.

17. Anderson JL, Morrow DA. Acute myocardial infarction. N Engl J Med 2017; 376:2053-2064. DOI: 10.1056/NEJMra1606915.

18. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol. 2018 Oct, 72(18) 2231-2264. Doi: 10.1016/j.jacc.2018.08.1038.

19. Scholz KH, Maier SKG, Maier LS, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with or without hemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. Eur Heart J 2018; 39:1065-1074. https://doi.org/10.1093/eurheartj/ehy004.

20. Helal A, Shahin L, Abdelsalam M, et al. Global effect of COVID-19 pandemic on the rate of acute coronary syndrome admissions: a comprehensive review of published literature. Open Heart 2021;8: e001645. doi:10.1136/ openhrt-2021-001645

21. De Rosa S, Spaccarotella C, Basso C, et al. Reduction of hospitalization for myocardial infarction in Italy in the COVID-19 era. Eur Heart J 2020; 14: 2083-2088. https://doi.org/10.1093/eurheartj/ehaa409.

22. De Fillippo O, D'Ascenzo F, Angelini F, et al. Reduced rate of hospital Admissions for ACS during Covid-19 outbreak in Northern Italy. N Engl J Med 2020; 383:88-89. DOI: 10.1056/NEJMc2009166.

23. Metzler B, Siostrzonek P, Binder RK, et al. Decline acute coronary syndrome admissions in Austria since the outbreak of covid-19: the pandemic response causes cardiac collateral damage. Eur Heart J 2020; 41: 1852-1853. https://doi.org/10/1093/eurhearj/ehaa314.

24. Rodrigues-Leor O, Cid-Alvarez B, Ojeda S, et al. Impact of the covid-19 pandemic on interventional cardiology activity in Spain. REC Interv Cardiol. 2020; 2(2):82-89. https://doi.org/10.24875/RECICE.M20000123.

25. Garcia S, Albaghdadi MS, Meraj PM, et al. Reduction in ST-segment Elevation Cardiac Catheterization Laboratory Activations in the United States during COVID-19 Pandemic. J Am Coll Cardiol 2020. doi: https://10.1016/j.jacc.2020.04.011.

26. Sharif K. H, Mohsin M, Saif M. Impact of covid-19 pandemic associated lockdown on admissions secondary to cardiac ailments in a tertiary cardiac centre of Pakistan. Pak Armed Forces Med J 2020; 19:342–6 https://www. pafmj. org/ index. php/ PAFMJ/ article/view/ 4930.

27. Khalil E, Üniversitesi O, Özcan S. Comparison of the number of cardiovascular admissions before and after COVID-19: experience from turkey, 2020. Available: https://www.researchgate. net/publication/ 342611022.

28. Department of Health, South Africa: https://www.gov.za/covid-19/resources/regulations-and-guidelines-coronavirus-covid-19.

CHAPTER TWO: SUBMISSIBLE ARTICLE

Title: Impact of the SARS-COV-2 pandemic on acute coronary syndrome patients admitted to an urban academic hospital in Soweto, South Africa

Authors: Suzan Leon [1], MD; Priya Parbhoo [2], MBChB, Mmed, FCP(SA); Ruchika Meel [2], MBChB, Mmed, Cert. Cardiology, PhD, FEACVI

Affiliations: *Department of Internal Medicine and University of the Witwatersrand [1], Department of Internal Medicine, Division of Cardiology, Chris Hani Baragwanath Academic Hospital and University of the Witwatersrand [2].*

Conflicts of Interest: Nil

Corresponding Author:

Dr. Suzan Leon

Cell no: 0027727626150

Address; Unit 13, 44 Edward Avenue, Vistasun, Glenvista

Email: leonsuzan13@gmail.com

1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a life-threatening respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case was reported in Wuhan China on 8th December 2019.[1] Rapid spread of the virus worldwide led to the declaration of COVID-19 a pandemic by the World Health Organization (WHO) on March 11 2020, a mere 3 months from the index case.[2] As a means to combat and contain the spread of the virus, many countries implemented stringent lockdown measures.[3] In South Africa, the first confirmed case of COVID-19 was reported by the Department of Health on 5th March 2020, with subsequent introduction of stringent lockdown measures on 26th March 2020.[4]

Reports around the globe have confirmed a significant reduction in the number of hospitalizations for patients with acute coronary syndrome (ACS) and those requiring percutaneous coronary intervention (PCI) during the pandemic. [5] Different datasets from countries within Europe, [6-10] Asia, [11-13] North and Latin America, [14-16] have demonstrated 30% to 50% reductions in ACS admissions and PCI procedures. The decrease in ACS admissions was associated with an increase in morbidity and mortality. [6-9] There is limited data of this nature emanating from Africa. In a survey conducted by the European Society of Cardiology (ESC), only 4.7% of responses confirming the above reductions originated from the African continent. [5] A report from few private hospitals in South Africa have corroborated similar findings. [17]

It is evident that data from Africa and South Africa is scarce. Whilst statistics are available for a few private hospitals within the country [17], similar information from tertiary state hospitals are lacking. In a developing country such as South Africa with already strained public health care facilities and numerous socioeconomic challenges, we suspected a poor outcome of patients with ACS during the pandemic. This study therefore sought to analyse the impact of COVID-19 on ACS admissions to the cardiac care unit (CCU) in Chris Hani Baragwanath Academic Hospital (CHBAH), Africa's largest tertiary state hospital, located in Soweto on the outskirts of Johannesburg city.

2. METHODS

A retrospective observational analysis was performed to evaluate all patients with ACS who were admitted to the CCU at CHBAH in the pre-COVID-19 era (November 2019 to March 2020) and compared with patients during the COVID-19 period (April 2020 to August 2020). ACS was defined according to The Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association and the World Heart Federation (ESC/ACCF/AHA/WHF) fourth universal definition for myocardial infarction. [18,19]. Patients admitted to CCU for reasons other than ACS and all patients with missing data during the predefined time periods were excluded (Figure 1).

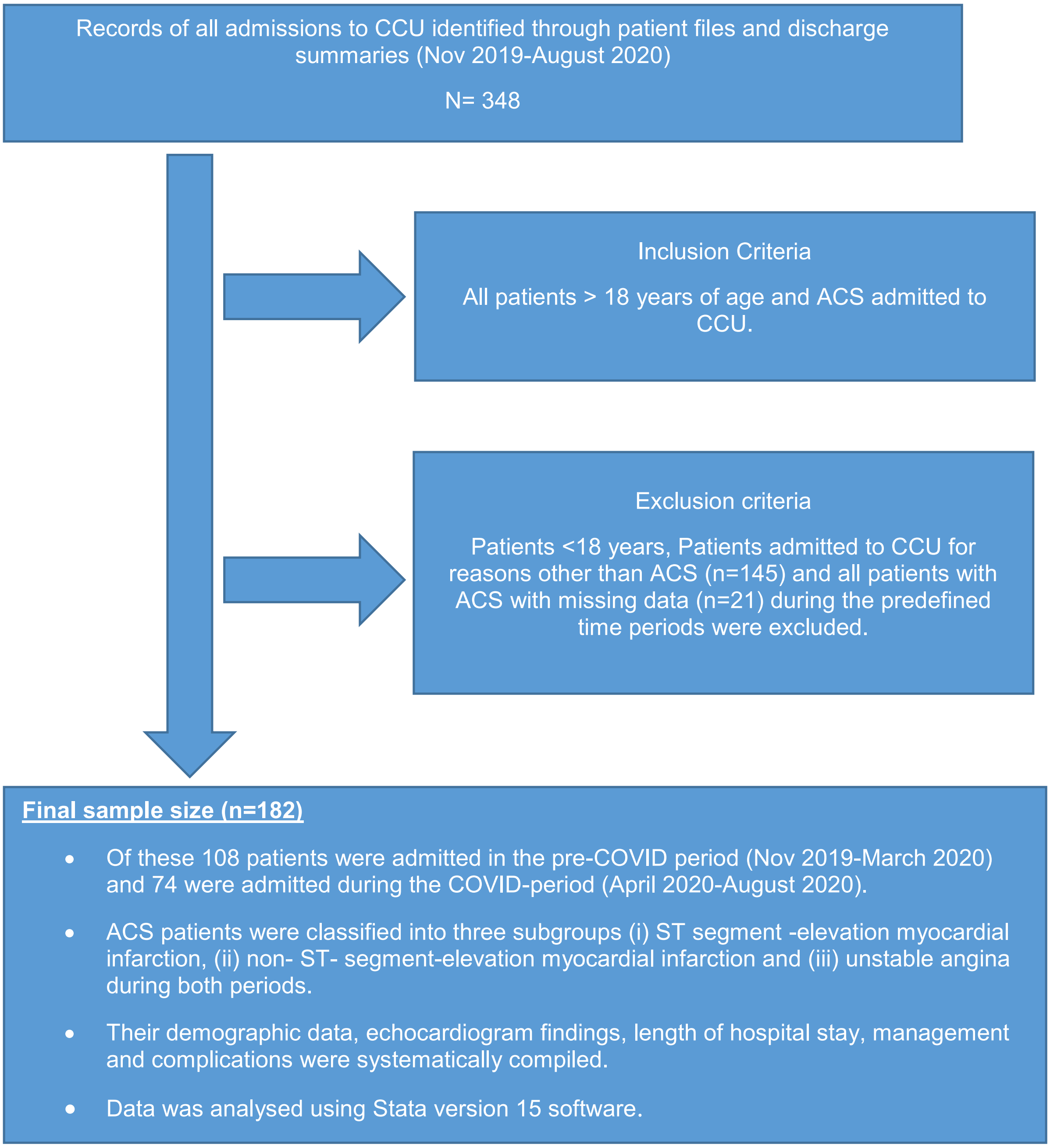

Figure 1: Flow diagram depicting the methodology used in the study. ACS, acute coronary syndrome; CCU, Coronary care unit; COVID, Corona virus disease.

Major complications related to ACS were defined as heart failure with reduced ejection fraction (HFrEF), cardiogenic shock, arrhythmias, thromboembolism (left ventricular clot, critical limb ischemia and stroke), cardiac arrest, varying degrees of atrioventricular block, left ventricular aneurysms and in-hospital mortality.

Data was analysed for the three ACS groups: (i) ST segment-elevation myocardial infarction (STEMI), (ii) non-ST-segment-elevation myocardial infarction (NSTEMI) and (iii) unstable angina (UA).

Data was collected by the principal investigator by reviewing all discharge summaries and PCI reports of patients admitted to CCU. Consecutive convenience sampling method within the defined study period was used. The number of admissions, demographic data, echocardiogram findings, length of hospital stay, management and complications were obtained, and the corresponding data sheet compiled.

All statistical analyses were conducted in Stata version 15. Descriptive statistics were summarized using frequencies and percentages for categorical variables. Mean and standard deviation (SD) were used to summarize normally distributed continuous variables while median and interquartile range (IQR) were used to summarize non-normal continuous data. Comparison of socio-demographic characteristics and clinical information (risk factors) between the two groups were done using Chi-square test for categorical variables while the Mann Whitney U test was used to compare continuous variables between the two periods. The significance level was set at 5%.

3. RESULTS

A total of 182 patients with ACS were admitted to the CCU during this study period. As depicted in *Figure 2*, more admissions were observed during the pre-COVID period [59.34% (n=108)] compared to the COVID period [40.66% (n=74)]. However, there was no statistically significant difference between the number of admissions (P =0.9945) during the two periods.

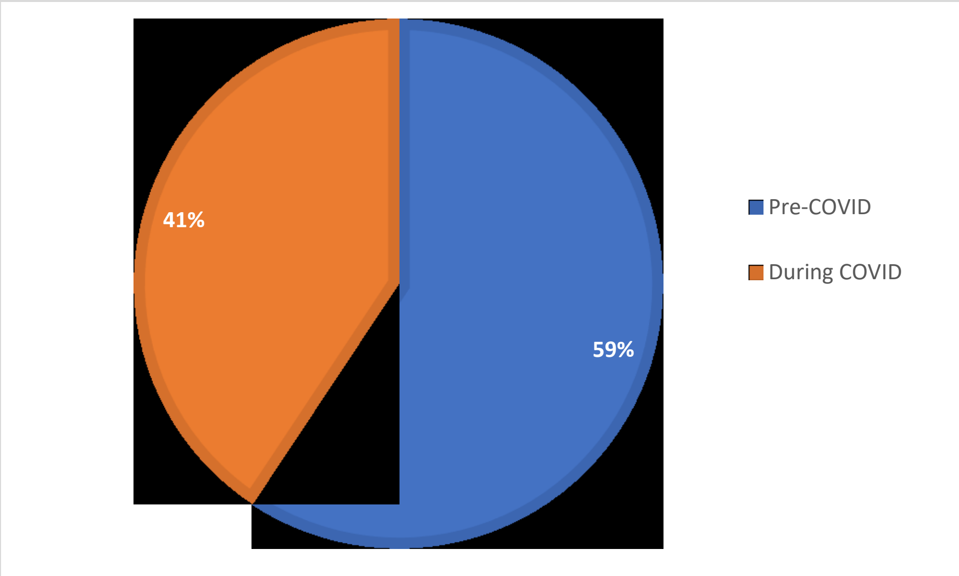

Figure 2: Acute coronary syndrome admissions during the pre-COVID-19 and COVID-19 periods

Demographic and clinical characteristics of the study cohort are summarised in *Table 1*. In the overall group, males predominated. The number of males and females admitted in the two periods were similar, and therefore no significant difference in the admissions by gender was noted (P=0.905).

Patients of black race formed the majority of those admitted, as expected by the considerable proportion of black communities serviced by CHBAH. Pre-COVID-19 (48.07%) and COVID-19 (47.3%) numbers were similar for black patients. Although more Asian (31.3%) patients were seen in the pre-COVID and more Caucasians (37.84%) in the COVID-19 period, there was no difference in the admissions by ethnicity between the two groups (P=0.387).

Table 1: Demographic and clinical characteristics of study patients

Variable	Categories	Pre-COVID-19 admission n=108 (%)	COVID-19 admission n=74 (%)	Total admission n=182 (%)	P-value
Age (years)		58.12 (10.4)	57.77 (11.88)	57.97 (10.99)	0.833
Gender (n/%)	Male Female	84 (77.78) 24 (22.22)	57 (77.03) 17 (22.97)	141 (77.47) 41 (22.53)	0.905
Ethnicity (n/%)	Black Asian Caucasian	53 (49.07) 23 (31.30) 32 (29.63)	35 (47.3) 11 (14.86) 28 (37.84)	88 (48.35) 34 (18.69) 60 (32.97)	0.387
Heart rate (bpm)		77 (72-88.5)	82.5 (74-92)	79 (72-91)	0.027
Systolic BP (mmHg)		121 (107-137.5)	118.5 (104-140)	120 (105-139)	0.577
Diastolic BP (mmHg)		75 (65-82.5)	70 (64-80)	73 (64-82)	0.701
Presenting symptoms	Chest pain Other	101 (93.52) 7 (6.48)	66 (89.19) 8 (10.81)	167 (91.76) 15 (8.24)	0.297
Length of stay (days)		3(2-5)	4 (3-7)	3(2-5)	0.016
MEDICATIONS n (%)					
Beta blockers		70 (64.81)	58 (79.38)	128 (70.33)	0.049
ACE-I		53 (49.53)	44 (59.46)	97 (53.59)	0.188
DAPT (Aspirin & Clopidogrel)		106 (98.15)	72 (97.3)	178 (97.8)	0.701
Statins		97 (89.81)	74 (100)	171 (93.96)	0.005
Nitrates		21 (19.44)	3 (4.05)	24 (13.19)	0.003
Mineralocorticoid receptor antagonists		11 (10.19)	14 (18.92)	25 (13.74)	0.093
Hypoglycemic drugs		15 (13.89)	16 (21.62)	31 (17.03)	0.173
Anticoagulants		4 (3.7)	6 (8.11)	10 (5.49)	0.2
Furosemide		3 (2.78)	7 (9.46)	10 (5.49)	0.052
Anti-arrhythmic drugs		4 (3.7)	0	4 (2.2)	0.094
Calcium channel blockers		3 (2.78)	3 (4.05)	6 (3.3)	0.636
RISK FACTORS n (%)					
Hypertension		70 (64.81)	47 (63.10)	117 (64.29)	0.857
Diabetes mellitus		46 (42.59)	26 (35.14)	72 (39.56)	0.312
Dyslipidemia		38 (35.19)	49 (66.22)	87 (47.80)	<0.001
Smoking		64 (59.26)	48 (64.86)	112 (61.54)	0.445
Family history of CAD		2 (1.85)	12 (16.22)	14 (7.69)	<0.001
Previous IHD		36 (33.33)	16 (21.62)	52 (28.57)	0.086
BMI >25kg/m2		9 (8.33)	12 (16.22)	21 (11.54)	0.102

Abbreviations: ACE-I: angiotensin converting enzyme inhibitor, bpm: beats per minutes, BP: blood pressure, BMI: body mass index, CAD: coronary artery disease, DAPT: dual antiplatelet therapy, IHD: ischemic heart disease, IQR: interquartile range, SD: standard deviation.

Beta blockers, angiotensin converting enzyme inhibitors, dual antiplatelet therapy and statins were the most prescribed drugs in both periods.

Traditional cardiovascular risk factors and their prevalence in the pre-COVID-19 and COVID-19 groups are indicated in *Table 1*. Of note, there was a significantly lower number of patients with dyslipidaemia (P<0.001) and a family history of CAD (P<0.001) in the pre-COVID-19 group.

Figure 3 shows a line plot of the hospital length of stay between the two periods. Although total length of hospital stay was separated by a median of 1 day between the groups, patients admitted during the COVID-19 period [4 (IQR 3-7)] stayed for a significantly longer duration (P =0.016) than those in the pre-COVID-19 period [3 (IQR 2-5)].

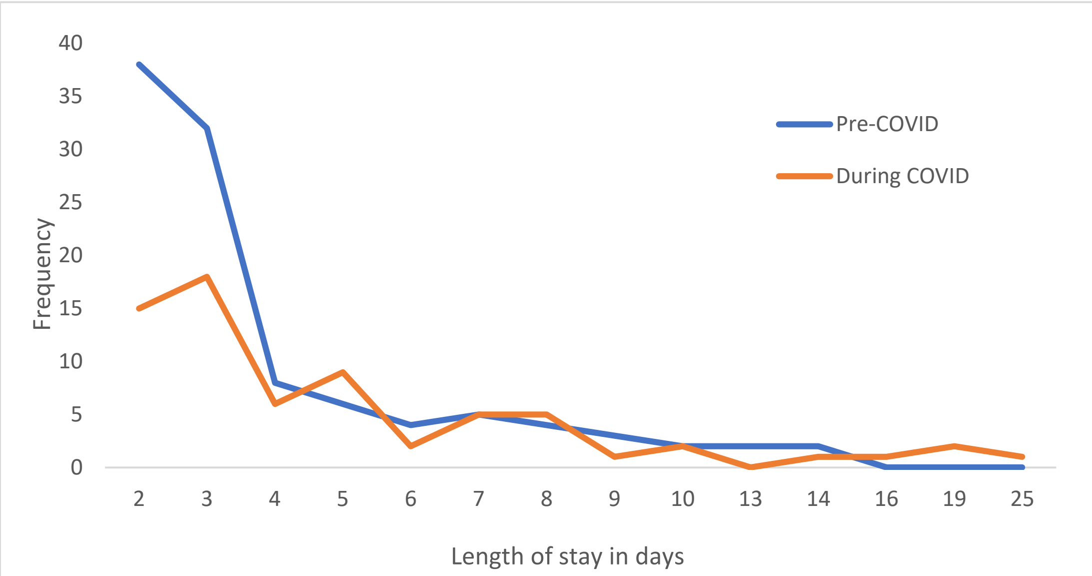

Figure 3: Length of stay in days between the two groups. COVID, Coronavirus disease.

Table 2 and *Figure 4* summarize the specific diagnosis for which patients were admitted. STEMI accounted for the bulk of admissions in both groups, followed by NSTEMI, however there was no statistically significant difference between STEMI and NSTEMI admissions between the two periods. More patients with UA were admitted during the pre-COVID period (18.52% vs 6.76%, P=0.013). Nonetheless, the proportions of UA admissions were higher during the pre-COVID-19 (18.52%) compared to the COVID-19 (6.76%) group (P=0.013).

Table 2: Summary of specific ACS diagnoses among patients admitted in the pre-COVID-19 and COVID-19 periods

Variable	Categories	Total Admissions n (%)	Pre-COVID Admissions n (%)	During COVID Admissions n (%)	Percentage change (difference) in admissions (95% CI)	P-value
ACS	STEMI	83 (45.86)	46(42.99)	37(50)	7% (2.1 - 6.7%)	0.321
	NSTEMI	74 (40.88)	42(39.25)	32(43.24)	4% (-9.6 - 17.6%)	0.5652
	UA	25 (13.74)	20(18.52)	5(6.76)	-12% (-21.2 - 2.8%)	0.013
STEMI	Inferior	34 (40.96)	17 (36.96)	17 (45.95)	9% (-4.6 - 22.6%)	1.29
	Anterior	49 (59.04)	29 (63.04)	20 (54.05)	-9% (-22.6 - 4.6%)	0.196

ACS: Acute coronary syndrome, CI: confidence interval, non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, UA: unstable angina.

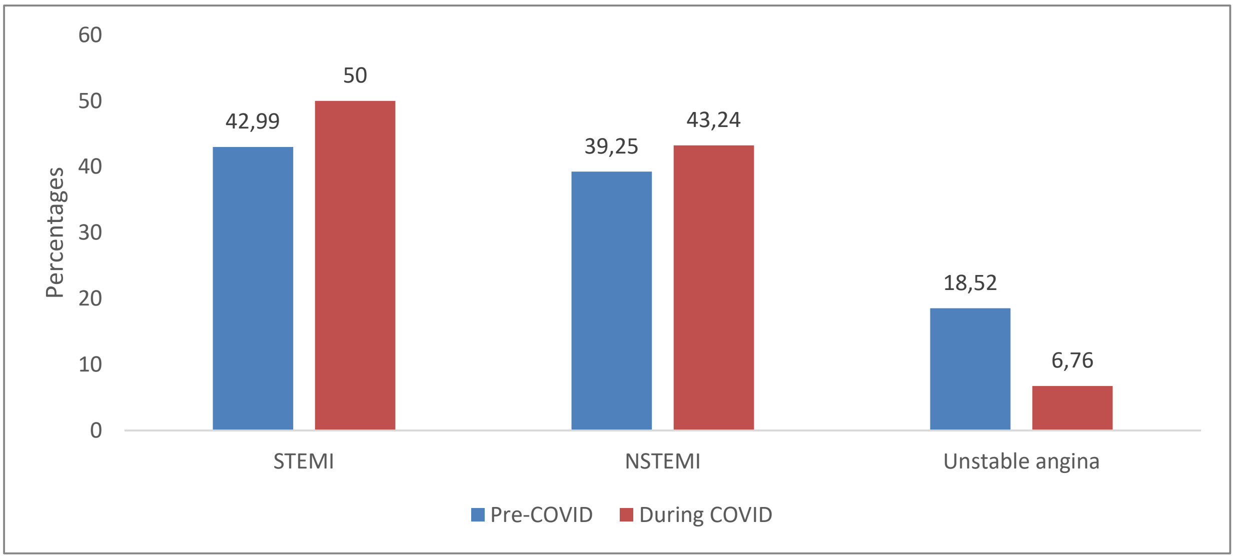

Figure 4: Graphic representation of patients admitted for STEMI, NSTEMI and unstable angina. COVID, Coronavirus disease

Management of patients with ACS during Pre-COVID-19 and COVID-19 periods (Figure 5).

Only a third of STEMI patients received thrombolytic therapy during both periods and there was no difference noted in the two groups (P=0.478). A total of 139 PCI procedures were performed during the study period. There was no statistically significant difference in the vascular (coronary artery) territories affected for the patients who presented with STEMI. Concurrent with overseas findings, more PCI procedures were done during the pre-COVID-19 period [85 (78.70%)] compared to the COVID-19 period [54 (72.97%)], however, this did not reach statistical significance (P =0.371) in our study. There was no difference in the number of patients that underwent coronary artery bypass grafting (CABG) (P =0.495).

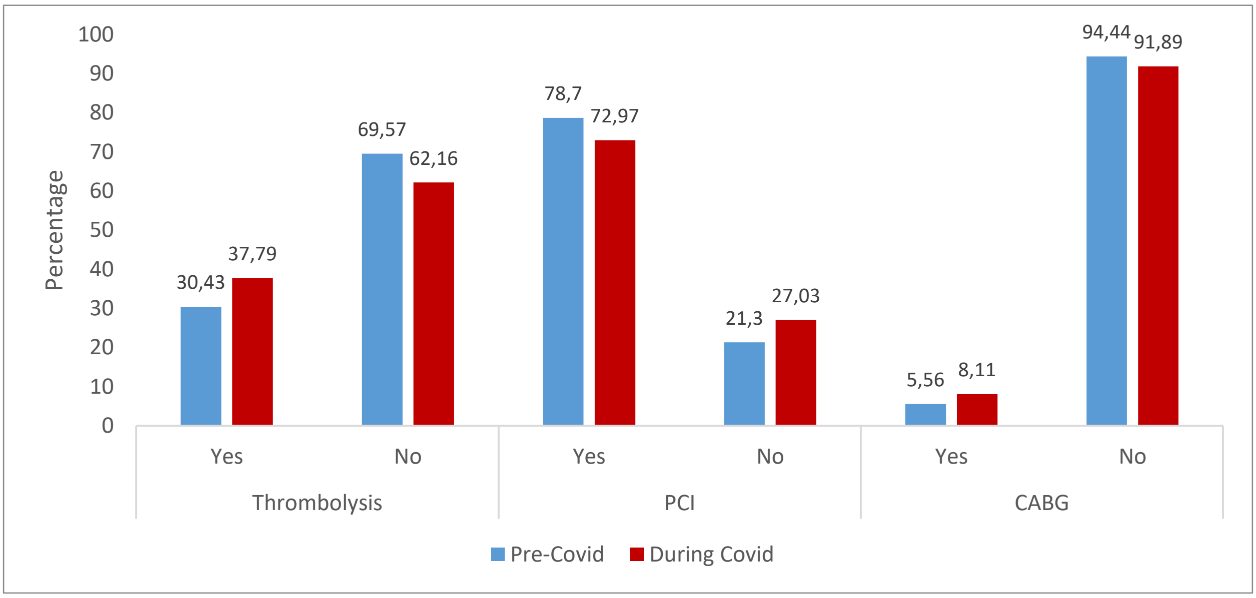

Figure 5: The distribution of patients who received thrombolysis for STEMI and those that underwent PCI and referral for CABG for ACS during pre-COVID-19 and COVID-19 periods. ACS, acute coronary syndrome; CABG, Coronary artery bypass grafting; COVID, Coronavirus disease; PCI, percutaneous coronary artery intervention.

Complications related to ACS admissions during pre-COVID-19 and COVID-19 periods

Table 3 depicts complications related to ACS observed during the study period. The only significant between-group difference was that of a higher incidence of arrhythmias in patients admitted during the pre-COVID-19 period (P= 0.011). Other complications that had a trend towards statistical significance included heart failure and atrioventricular block. Six in-hospital mortalities were observed. Five patients died in the pre-COVID-19 period and one patient during the COVID-19 period.

Table 3: Complications encountered in ACS patients during the pre-COVID-19 and COVID-19 periods.

Variable	Pre-COVID-19 Admissions n (%)	COVID-19 admissions n (%)	Total Admissions n (%)	P-value
Complications	43 (38.81)	38 (51.35)	81 (44.51)	0.124
HFrEF	37 (34.26)	36 (48.65)	73 (40.11)	0.052
Cardiogenic shock	1 (0.93)	0	1 (0.55)	0.407
Arrhythmias	9 (8.33)	0	9 (4.95)	0.011
Left ventricular clot	2 (1.85)	1 (1.35)	3 (1.65)	0.794
Cardiac Arrest	2 (1.85)	1 (1.35)	3 (1.65)	0.794
Atrioventricular blocks	1 (0.93)	4 (5.41)	5 (2.75)	0.069
Critical limb ischemia	0	2 (2.7)	2 (1.1)	0.086
Left ventricular aneurysm	0	1 (1.39)	1 (0.56)	0.219

HFrEF- Heart failure with reduced ejection fraction

4. DISCUSSION

This is the first South African study to assess the impact of the COVID-19 pandemic at a public tertiary level hospital. The most striking finding was a lack of anticipated reduction in ACS admissions, no difference in the rates of thrombolysis and the number of PCI and CABG procedures during the COVID-19 pandemic compared to the pre-COVID-19 period.

We noted no reduction in the number of ACS admissions during the COVID-19 period compared to the pre COVID-19 period. In contrast to several international studies that showed significant reduction in ACS admissions, [6-16] our study shows no significant reduction in ACS admissions. Multiple factors might have contributed to this finding. First, most other studies compared the time during lockdown measures to a similar period in the previous year. Therefore, this finding might have been influenced by the month-to-month variability of admissions. Secondly, it is not unreasonable to assume that the de-escalation of the stringent lockdown rules from 31st May 2020 may have eased the anxiety and fear to seek medical care, hence allowing more patients to attend the hospital instead of ignoring their symptoms. Thirdly, CHBAH is the largest referral hospital receiving a high volume and sicker patients, thus consequently obscuring the reduction in ACS.

Two studies undertaken in Taiwan and Australia respectively, where strict lockdown measures were implemented early, reported a lack of reduction in ACS admissions. [20,21] In yet another report from a large referral centre in the United States, Baystate medical centre, no significant change in STEMI volumes was noted during the COVID-19 pandemic. Similar to CHBAH, this finding was attributed to the large volumes of patients seen at this hospital. In contrast to the current study, the aforementioned studies did not evaluate the influence of the pandemic on other forms of ACS admissions.

Moreover, we found that the number of admissions for UA decreased by 75% during the COVID-19 period. This finding was also highlighted amongst patients attending South African private hospitals. [17] A meta-analysis which included forty studies, concluded a 48.1% reduction in admission rates for UA during the COVID-19 pandemic (Helal et al). [22] This finding was attributed to less severe symptoms associated with UA as opposed to STEMI/NSTEMI. Thus, patients likely tended to wait instead of seeking urgent medical attention. This is particularly relevant in the South African context, where this behaviour is not uncommon even under normal circumstances due to poor socioeconomic status of the patients compounded by the lack of access to public transport. [23,24] Other factors such as underestimation/misinterpretation of symptoms as well as reluctance to seek healthcare for fear of contracting the infection may have also played a role. [11]

Male gender was the most prevalent across all periods comprising 77.4%. Historically, male gender has been demonstrated as a risk factor for CAD compared to females of the same age. [25] The latter may be explained by the protective effects of oestrogen that women derive benefit from during their pre-menopausal years. This defence is lost during the postmenopausal period, during which atherosclerotic coronary events rapidly reach the rates seen in men. [26] Additionally, the prevalence of smoking, identified as an important risk factor for CAD, is much lower in females compared to males. [27] Furthermore, the small percentage of females observed might be attributed to the general underdiagnoses of ACS in females due to atypical symptom presentation as stipulated in the previous studies. [28,29]

It is important to note that only one third of STEMI patients received fibrinolysis in both periods. This finding is akin to the study by Meel et al and the larger Acute Coronary Events-a Multinational Survey of Current Management Strategies (ACCESS) registry study conducted approximately a decade ago in the pre-COVID- 19 period.[30,31] It again highlights the failing South African health care system and an inability to implement measures to improve care of STEMI patients, despite attempts to establish strategies and networks in South Africa for the care of these patients.[32] The findings of the current study may be related to a combination of factors such as: 1) poorly educated patients with ignorance regarding ACS symptoms and therefore late presentations beyond the thrombolysis period; 2) poor STEMI activation systems[33] and/or 3) increase in under- and misdiagnosis during the pandemic due to fear amongst health care workers of contracting COVID-19 infection;[22] 4) the growing number of broadcasts from national authorities emphasizing chest discomfort and dyspnoea as the dominant symptoms of COVID-19 may have been misleading for many patients with ACS and [22] 5) a strained healthcare system coupled with restructuring to accommodate acutely ill COVID-19 patients may have accounted for the misdiagnoses and inappropriate down-referral of ACS patients. We did not document the time to thrombolysis in this study during the two periods. Based on prior data, a minority of patients in South African hospitals receive fibrinolytic therapy within the optimal one- to - six hours window period due to previously reported factors. [30,32] This translates into increased morbidity and mortality in these patients.

There was no difference in PCI procedures or CABG referral during the pre-COVID-19 period compared to the COVID-19 period. This was an interesting finding. As per initial data from China and Italy [34], we advocated use of thrombolysis over PCI in patients with ACS during the COVID-19 period to the avoid risk of COVID-19 infection to operators in our Cardiology unit. Despite postponing elective procedures at CHBAH, advocating for use of thrombolysis, awaiting COVID swab results prior to PCI, and discharging of low-risk patients with ACS, no difference in the rates of PCI was noted during the two periods. This lack of difference in PCI during the two periods again is likely a result of high volumes of ACS referrals to CHBAH that nullified the effect of the pandemic on overall PCI procedures. This finding is similar to other large volume referral centres in the world. [21]

There was a trend toward higher admissions secondary to ACS-related HFrEF and higher atrioventricular block in the COVID-19 period. This was likely due to delayed presentations and lack of timeous PCI or thrombolysis during this period. Arrhythmias in ACS generally occur during the first few hours following the onset of symptoms. [35] As patients likely presented late during the pandemic, it may explain why arrhythmias were less frequently observed during this period, resulting in a significant difference between the two groups. The increased incidence of complications related to delayed presentation of ACS during the COVID-19 pandemic has been observed and reported previously in Chinese and Italian studies. [33] Nevertheless, in the South African context, these findings are of grave concern as it is likely due to overburdened health care facilities subsequent to repeated hospitalisations of such patients with heart failure and other related complications. This has a direct effect on the costs incurred by these facilities. It has been shown that the cost of a heart failure-related admission can cost between ZAR 135 to ZAR 733 per night at CHBAH. [36] Additionally, the high rates of complications post-MI impairs quality of life of these patients and places economic and psychological burden on patients and their families. [37,38] These problems must be anticipated, and plans need to be put in place to limit the effects of the aforementioned issues during the post-COVID period.

We also noted a more aggressive usage of medical therapy in the form of beta blockers, statins, nitrates, and furosemide during the COVID-19 period compared to the pre-COVID-19 period. The current literature suggests no difference in the medical management of ACS patients during the COVID-19 period, except for an emphasis on anticoagulation in patients that are confirmed COVID positive. [34] The patients admitted to CCU during the COVID 19 period were sicker with higher risk features and complications such as heart failure. This would have led to the significant difference in usage of prior medication by the clinician in this study. This finding was in contrast to the multicentre study conducted in Israel by Fardman et al [39], whereby no difference in distribution of medication was noted in the COVID-19 and non-COVID periods amongst STEMI patients. A greater prevalence of dyslipidaemia and a strong family history of CAD were in our view, coincidental findings that may not have contributed to the higher complication rates.

Furthermore, this study found that patients admitted during the COVID-19 period had a longer hospital stay compared to pre-COVID-19 with a median of 4 days. This is in contrast to a French study by Matsushita K et al and an English study by Kwok CS et al where hospital stay was shorter. [40,41] This discrepancy in our hospital is explained by the fact that patients required a negative COVID-19 polymerase chain reaction (PCR) test before admittance to CCU. This was further aggravated by laboratory delays and the need for repeat testing in patients who were transferred from outlying hospitals. The longer hospital stay has cost implication and also increases a patient's risk of acquiring COVID-19 during the hospitalisation period.

5. LIMITATIONS

The retrospective nature of the study suffers from common limitations inherent in such a study design. As previously mentioned, we were unable to compare admissions during COVID-19 with a similar period in the previous year. However, as CHBAH attends to high volumes of patients daily, we did not believe that this would have a substantial effect on the results of this study. In addition, the paucity of data for patients who demised in CCU, or those with ACS who were not admitted to CCU greatly impacts on the cohort size as well as deductions that can be made about hard endpoints such as morbidity and mortality. All patients admitted to CCU were COVID negative and therefore patients who were COVID-19 positive with concurrent ACS were inevitably excluded from the analysis. Further, it will be difficult to ascertain the true number of ACS admissions outside of CCU that were admitted to the COVID ward due to high number of confounders for troponin leakage in the setting of concurrent COVID-19 infection, also lack of meticulous record keeping and missing data make it difficult to access such information in a large volume centre. In a recent study by Meel et al [42], a prevalence of 6.5% for ACS in patients with COVID-19 was noted in a study conducted in late 2020-2021 at CHBAH and we suspect a similar trend may have occurred in the early part of the pandemic. Further it must be noted that the intent of the study was not to study effect/pathophysiology of COVID-19 and concurrent ACS but rather the influence of the pandemic on ACS admissions and management irrespective of their COVID-19 status. Lastly, this study focused on a single centre and therefore the results cannot be extrapolated to assess the effect of the COVID-19 pandemic at the district, provincial and national levels.

6. CONCLUSION

There was no difference in STEMI and NSTEMI admissions during COVID-19 and pre-COVID-19 periods in the current study. However, fewer cases of unstable angina were seen during the COVID-19 period. During both periods only a third of the patients with STEMI received fibrinolysis and no difference in PCI or CABG were noted. There were no differences in complications observed between the two periods, except for higher rate of arrhythmias noted in the pre-COVID-19 period. The COVID-19 pandemic has had an unprecedented impact on cardiology services worldwide and has had an even greater impact on the already under-resourced developing world as suggested by mostly anecdotal reports in the absence of formal large studies. We hope that this study, despite its limitations, has shed light regarding the impact of COVID-19 on ACS admissions at a tertiary hospital in South Africa. Below, we outline some brief recommendations regarding management of ACS in the era of COVID-19 pandemic in the South African context.

7. RECOMMENDATIONS

1. Education of the general population through social media platforms about early recognition of ACS symptoms and immediate referral to emergency departments is of utmost importance. The dangers of MI-related complications that may result from delays in seeking medical help must be emphasised. Anxiety and fears associated with acquisition of COVID-19 infection at health institutions must be addressed and patients must be reassured regarding the preventative protocols that are implemented at most hospitals to prevent transmission of infection.

2. STEMI activation networks must be put in place during this time to prevent delays in transfer of patients from peripheral hospitals to larger, more specialized centres. This requires co-operation between government, healthcare personnel and hospital administration.

3. The management of patients with ACS must be stratified according to risk. All low risk NSTEMI/ unstable angina and completed STEMI patients must have COVID tests done and may be given elective dates for coronary angiograms to minimise lengthy hospital stays. In general, STEMI patients, high risk NSTEMI/unstable angina patients must be managed where possible according to the standard guidelines. In the South African setting, thrombolysis must remain the first-line treatment of patients with STEMI due to resource and personnel limitations. All decisions must be led by a senior cardiologist in equivocal cases.
4. All patients with ACS requiring emergency care and who are not candidates for thrombolytic therapy or who require rescue PCI, must be assumed to be COVID positive and time should not be wasted whilst awaiting results of the COVID swab. The catheterisation laboratory personnel must be trained in the management of these patients and should have undergone appropriate personal protective equipment (PPE) training. Only the minimum number of staff needed for the case must be present in the catheterisation laboratory. The case must be performed by an experienced operator to minimise prolonged exposure to a patient with possible COVID-19 infection. The catheterisation laboratory must be sanitised upon completion of the procedure. A dedicated isolation area in the hospital must be reserved for ACS patients where they can be monitored post-procedure whilst awaiting results of COVID-19 test.
5. Each unit in the country must establish their own dedicated protocols regarding management of these patients and these must be constantly reviewed to improve care as more data becomes available.
6. Follow-up visits of patient's post-discharge must be minimised, and telemedicine consultation must be encouraged to avoid transmission of infection. Lifestyle modification and strict adherence to prescribed medication must be emphasised to prevent future events.
7. A multidisciplinary team comprising a cardiologist, dietitian, psychologist, social worker and bio-kineticist becomes even more relevant at this time.

8. REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019(COVID-19) outbreak in China. Summary of a report of 72314 cases from the Chinese Centre for Disease Control and Prevention (published online February 24, 2020). JAMA. 2020; 323(13):1239-1242. doi: 10.1001/jama.2020.2648.

2. World Health Organization, Report of the WHO-China joint mission on coronavirus disease 2019(COVID-19). https://www.who.int/publication-details/ report-of-the-who-china-joint-misssion-on-coronavirus-disease-2019-(covid-19). Published 2020.

3. Wilder-Smith A, Bar-Yam Y, Fisher D. Lockdown to contain COVID-19 is a window of opportunity to prevent the second wave, *Journal of Travel Medicine*, Volume 27, Issue 5, July 2020, taaa091. https://doi.org/10.1093/jtm/taaa091.

4. Department of Health, South Africa. https://www.gov.za/covid-19/resources/regulations-and-guidelines-coronavirus-covid-19.

5. Amorim GP, Camm CF, Gajendragadkar P, et al. Admission of patients with STEMI since the outbreak of the COVID-19 pandemic: a survey by the European Society of Cardiology. European Heart Journal-Quality of care and clinical outcomes, Vol 6:2020; p 210-216. https://doi.org/10.1093/ehjqcco/qcaao46.

6. De Rosa S, Spaccarotella C, Basso C, et al. Reduction of hospitalization for myocardial infarction in Italy in the COVID-19 era. Eur Heart J 2020; 14: 2083-2088. https://doi.org/10.1093/eurheartj/ehaa409.

7. Metzler B, Siostrzonek P, Binder RK, et al. Decline acute coronary syndrome admissions in Austria since the outbreak of covid-19: the pandemic response causes cardiac collateral damage. Eur Heart J 2020; 41: 1852-1853. https://doi.org/10/1093/eurhearj/ehaa314.

8. Rodrigues-Leor O, Cid-Alvarez B, Ojeda S, et al. Impact of the covid-19 pandemic on interventional cardiology activity in Spain. REC Interv Cardiol. 2020; 2(2):82-89. https://doi.org/10.24875/RECICE.M20000123.

9. Mesnier J, Cottin Y, Coste Pierre, et al. Hospital admissions for acute myocardial infarction before and after lockdown according to regional prevalence of COVID-19 and patients profile in France: a registry study. The Lancet Public Health, Vol 5:2020; p e536-e542. http://doi.org/10.1016/s2468-2667(20)30188-2.

10. Schmitz T, Meisinger C, Kirchberger I, et al. Impact of COVID-19 pandemic lockdown on myocardial infarction care. European Journal of Epidemiology (2021) 36:619-627. https://doi.org/10.1007/s10654-021-00764-2.

11. Tam C-CF, Cheung K-S, Lam S, et al. Impact of coronavirus disease 2019 (COVID-19) outbreak on outcome of myocardial infarction in Hong Kong, China. Catheter Cardiovasc Interv. 2021;97: E194-E197. https://doi.org/10.1002/ccd.28943.

12. Shams P, Faheem O, Adnan G, et al. Cardiovascular Interventions in Face of Covid-19 Pandemic in a Low to Middle Income Country of South Asia Region-A Pre and Post Covid Era Comparison. Circulation.2020;142: A14710. https://doi.org/10.1161/circ.142.suppl_3.14710.

13. Morishita T, Takada D, Shin J-ho, et al. Trends, Treatment Approaches, and In-Hospital Mortality for Acute Coronary Syndromes in Japan During the Coronavirus Disease 2019 Pandemic. Journal of Atherosclerosis and Thrombosis. https://doi.org/10.5551/jat/62746.

14. Braiteh N, Rehman W, Alom M, et al. Decrease in acute coronary syndrome presentations during the COVID-19 pandemic in upstate New York. American Heart Journal. Vol 226:2020, p147-151. https://doi.org/10.1016/j.ahj.2020.05.009.

15. Garcia S, Albaghdadi MS, Meraj PM, et al. Reduction in ST-segment Elevation Cardiac Catheterization Laboratory Activations in the United States during COVID-19 Pandemic. J Am Coll Cardiol 2020. doi: https://10.1016/j.jacc.2020.04.011.

16. Mayol J, Artucio C, Batista I, et al. An international survey in Latin America on the practice interventional cardiology during the COVID-19 pandemic,

with a particular focus on myocardial infarction. Neth Heart J (2020) 28:424-430. https://doi.org/10.1007/s12471-020-01440-y.

17. Delport R, Vachiat A, Snyders A, et al. Decline in acute coronary syndrome hospitalization rates during COVID-19 lockdown in private hospitals in South Africa. SAHeart 2020; 17:264-265.

18. Anderson JL, Morrow DA. Acute myocardial infarction. N Engl J Med 2017; 376:2053-2064. DOI: 10.1056/NEJMra1606915.

19. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol. 2018 Oct, 72(18) 2231-2264. Doi: 10.1016/j.jacc.2018.08.1038.

20. Li Y-H, Huang W-C, Hwang J-J. No Reduction of ST-segment Elevation Myocardial Infarction Admission in Taiwan During Coronavirus Pandemic. The American Journal of Cardiology, 2020; Vol.131: p133-134. https://doi.org/10.1016/j.amjcard.2020.06.030.

21. Toner L, Koshy AN, Hamilton GW, et al. Acute coronary syndromes undergoing percutaneous coronary intervention in the COVID-19 era: comparable case volumes but delayed symptom onset to hospital presentation. European Heart Journal-Quality of Care and Clinical Outcomes. 2020 Jul 1;6(3):225-6.

22. Helal A, Shahin L, Abdelsalam M, et al. Global effect of COVID-19 pandemic on the rate of acute coronary syndrome admissions: a comprehensive review of published literature. Open Heart 2021;8e001645. doi: 10.1136/openhrt-2021-001645

23. Poverty and Health - OECD iLibraryhttps://www.oecd-ilibrary.org

24. The state of public transport in South Africa - SaferSpaceshttps://www.saferspaces.org.za.

25. Wake R, Yoshiyama M. Gender difference in Ischemic Heart disease. Recent Patents Cardiovasc Drug Discov. 2009: 4:234-240.

26. Iorga A, Cunningham CM, Moazeni S, et al. the protective role of oestrogen and oestrogen receptor in cardiovascular disease and the controversial use

of oestrogen therapy. Biol Sex Differ 8, 33 (2017). https://doi.org/10.1186/s13293-017-0152-8.

27. Keates, A., Mocumbi, A., Ntsekhe, M. *et al.* Cardiovascular disease in Africa: epidemiological profile and challenges. *Nat Rev Cardiol* **14,** 273–293 (2017). https://doi.org/10.1038/nrcardio.2017.19

28. Shah AS, Griffiths M, Lee KK, et al. High sensitivity cardiac troponin and the under- diagnosis of myocardial infarction in women: prospective cohort study. *BMJ* 2016; 354 doi: https://doi.org/10.1136/bmj.i4840.

29. Canto JG, Goldberg RJ, Hand MM, et al. Symptom presentation of women with acute coronary syndromes: myth vs reality. Arch Intern Med 2007; 167:2405-2413.

30. Meel R, Goncalves R. Time to fibrinolytics for acute myocardial infarction: Reasons for delay at Steve Biko Academic Hospital, Pretoria, South Africa. South African Medical Journal (2016) vol. 106 No.1. DOI: 10.7196/SAMJ.2016.v106i1.9801.

31. Schamroth C; ACCESS South Africa investigators. Management of acute coronary syndrome in South Africa: insights from the ACCESS (Acute Coronary Events - a Multinational Survey of Current Management Strategies) registry. Cardiovasc J Afr. 2012 Aug;23(7):365-70. doi: 10.5830/CVJA-2012-017. Epub 2012 Mar 13. PMID: 22447241; PMCID: PMC3721828.

32. Snyders A, Delport R. Referral pathways for reperfusion of STEMI-developing strategies for appropriate intervention: the SA heart STEMI early intervention project. SA Heart. 2015 Sep 1;12(2):74-80.

33. Cameli M, Pastore MC, Mandoli GE, et al. COVID-19 and Acute Coronary Syndromes: Current Data and Future Implications. Frontiers in Cardiovascular Medicine. 2021 Jan 28; 7:369.

34. Nijjer SS, Petraco R, Sen S. Optimal management of acute coronary syndromes in the era of COVID-19. Heart. 2020 Oct 1;106(20):1609-1616.

35. O'Doherty M, Tayler DI, Quinn E, et al. Five hundred patients with myocardial infarction monitored within one hour of symptoms. BMJ,1983;286: 1405-1408.

36. Revision of uniform patient fee schedule relating to the. Classification of and fees payable by patients at provincial. Hospitals, 2019 (online) http://www.gpwonline.co.za

37. Mollon L., Bhattacharjee S. Health related quality of life among myocardial infarction survivors in the United States: a propensity score matched analysis. *Health Qual Life Outcomes* **15,** 235 (2017). https://doi.org/10.1186/s12955-017-0809-3

38. Petersen I., Bhana A., Folb, N. *et al.* Collaborative care for the detection and management of depression among adults with hypertension in South Africa: study protocol for the PRIME-SA randomised controlled trial. *Trials* **19,** 192 (2018). https://doi.org/10.1186/s13063-018-2518-6

39. Fardman A, Zahger D, Orvin K, et al. Acute myocardial infarction in the Covid-19 era: Incidence, clinical characteristics and in-hospital outcomes—A multicentre registry. Plos one. 2021 Jun 18;16(6): e0253524.

40. Matsushita K, Hess S, Marchandot B, et al. Clinical features of patients with acute coronary syndrome during the COVID-19 pandemic. Journal of Thrombosis and Thrombolysis (2021) 52:95-104. https://doi.org/10.1007/s11239-020-02340-z.

41. Kwok CS, Gale CP, Kinnaird T, et al. Impact of COVID-19 on percutaneous coronary intervention for ST-elevation myocardial infarction. Heart 2020; 106:1805-1811.

42. Meel R, Van Blydenstein SA. Demographic, clinical, electrocardiographic and echocardiographic characteristics of patients hospitalized with COVID-19 and cardiac disease at tertiary hospital, South Africa. Cardiovasc Diagn Ther 2021;11(6):1228-1240. Doi:10.21037/cdt-21-459.

APPENDICES.

I. DATA COLLECTION SHEET

1. Case number: ……………….

2. Month of admission………………

3. Demographic data:

a. Age: ………………..

b. Gender: ☐

Female (1); Male (2)

c. Ethnic group: ☐

African (1); Asian (2); Colored (3); White (4); Unknown (5)

4. Patient's risk factors: ☐

Hypertension (1); Diabetes Mellitus (2); Dyslipidemia (3); Cigarette Smoking (4).

Body mass index >25kg/m^2 (5); Family history of ischemic heart disease (6); none (7);

Others (8); specify……………………

5. Clinical presentation:

a. Symptoms: ☐

Typical chest pain (1); others (2); specify………………….

b. Time to referral to CHBAH: ☐

Waiting time at peripheral hospital (1); COVID-19 test results and how long was it delayed (2)

c. Cardiac biomarker:

Highly-sensitive Troponin T – elevated- Y/N

d. Electrocardiogram changes: ☐

ST elevation (1); ST depression (2); T wave inversion (3)

e. Echocardiogram findings:

LVEF preserved (>50%)-Y/N, reduced (<40%)- Y/N……………………………..

Valvular heart disease. Yes /No [ ]

Regional wall motion: Normal (1); Abnormal (2); Anterior (3); Septal (4); Inferior (5); Lateral (6)

………………..………………….

6. Associated complications: [ ]

Heart failure (1); cardiogenic shock (2); left ventricular aneurysm (3); Arrhythmias (4); cardiac arrest 5); Thromboembolism (6); Others, specify……………………..

7. Management: [ ]

Conservative management (1); fibrinolysis (2); percutaneous coronary intervention (3); referral for cardiopulmonary bypass (4)

8. Outcomes: [ ]

Morbidity (1); In-hospital Mortality (2); discharged (3).

II. ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R49 Dr SN Leon

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M201078

NAME: **(Principal Investigator)**	Dr SN Leon
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	Impact of the SARS-CoV-2 pandemic on acute coronary syndrome patients admitted to an urban academic hospital in Soweto, South Africa
DATE CONSIDERED:	2020/10/30
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs M Ruchika and P Parbhoo
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/12/15

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **October** and therefore reports and re-certification will be due in the month of **October** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

___________________________ ____________________

Signature of Principal Investigator Date

III. TURN IT IN REPORT

ORIGINALITY REPORT

11%	12%	7%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	v3r.esp.org Internet Source	2%
2	www.nejm.org Internet Source	2%
3	Submitted to Universidad de Costa Rica Student Paper	2%
4	jfin-swufe.springeropen.com Internet Source	1%
5	www.healthandlifestyle.com.ph Internet Source	1%
6	academic.oup.com Internet Source	1%
7	www.jtraumainj.org Internet Source	1%
8	worldwidescience.org Internet Source	1%
9	Samuel Seidu, Setor K. Kunutsor, Xavier Cos, Kamlesh Khunti. "Indirect impact of the COVID-19 pandemic on hospitalisations for	1%

cardiometabolic conditions and their management: A systematic review", Primary Care Diabetes, 2021
Publication

10	J.E. Siegler, M.E. Heslin, L. Thau, A. Smith, T.G. Jovin. "Falling stroke rates during COVID-19 pandemic at a Comprehensive Stroke Center: Cover title: Falling stroke rates during COVID-19", Journal of Stroke and Cerebrovascular Diseases, 2020 Publication	1 %
11	216.226.177.68 Internet Source	1 %

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		