Prevalence of Occlusive Myocardial Infarction (OMI) in patients diagnosed with Non-ST-Elevation Myocardial Infarction (NSTEMI) at a single private facility in Cape Town, South Africa, during 2019

by

Dr Elmari Schoeman

MBChB, DipPEC

SCHELM002

This dissertation is submitted in partial fulfilment of the requirements for the degree Master of Emergency Medicine in the Faculty of Health Sciences at the University of Cape Town.

Supervisors:

A/Prof Willem Stassen (principal investigator)

BTEMC, MPhil EM, PGDip Appl. Ethics, PhD

Division of Emergency Medicine

University of Cape Town

Dr Ibrahim D'Andrea

MBChB, MMed (EM), FCEM

Honorary Lecturer Division of Emergency Medicine

University of Cape Town

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Table of Contents

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PART A: MANUSCRIPT IN ARTICLE FORMAT

Title Page

Prevalence of Occlusive Myocardial Infarction (OMI) in patients diagnosed with Non-ST-Elevation Myocardial Infarction (NSTEMI) at a single private facility in Cape Town, South Africa, during 2019.

Authors:

1. Dr Elmari Schoeman

   MBChB, DipPEC

   Division of Emergency Medicine, University of Cape Town, South Africa

   +27 79 506 4360

   schelm002@myuct.co.za

2. Dr Ibrahim D'Andrea

   MBChB, MMed (EM), FCEM

   Honorary Lecturer Division of Emergency Medicine, University of Cape Town, South Africa

   +27 73 731 4412

   flashhire@gmail.com

3. A/Prof Willem Stassen

   BTEMC, MPhil EM, PGDip Appl. Ethics, PhD

   Division of Emergency Medicine, University of Cape Town, South Africa

   +27 76 502 2187

   willem.stassen@uct.ac.za

Abstract

Background: ST-Elevation Myocardial Infarction (STEMI) is strongly associated with acute coronary occlusion, leading to less urgent management of Non-ST-Elevation Myocardial Infarction (NSTEMI), often perceived as partial occlusion. However, 25.5% of NSTEMIs involve total coronary occlusion, significantly impacting mortality and Major Adverse Cardiovascular Events (MACE).[1] The Occlusive Myocardial Infarction (OMI) vs Non-occlusive Myocardial Infarction (NOMI) paradigm has been proposed for better identification of acute myocardial infarction (AMI).[2–5]

Objectives: This study investigates the prevalence of OMI among NSTEMI patients in a private Cape Town emergency centre in 2019, analysing descriptive data, serial cardiac troponin I (cTnI) results, the proportion undergoing angiography, Thrombolysis in Myocardial Infarction (TIMI) flow grades, and door-to-angiogram times.

Methods: A cross-sectional, observational study was conducted using a retrospective chart review of NSTEMI patients who underwent angiography. Data were analysed using descriptive statistics, Chi-square, and Mann-Whitney U-tests.

Results: Among 31 NSTEMI patients, 83.9% (n=26) had OMI (median age 65 years, IQR 25), and 88.5% were male ($p<0.001$). Significant second cTnI levels (median 1450 ng/L, $p=0.001$) and a median door-to-angiogram time of 34 hours (IQR 48) were noted. The left anterior descending artery (34.6%) was the most common culprit lesion.

Conclusion: The high prevalence of OMI among NSTEMIs highlights the limitations of the current STEMI/NSTEMI classification. Improved diagnostics and timely interventions, including emergent angiography and alternative treatments like thrombolysis, could enhance patient outcomes with reduced healthcare costs in resource-limited settings. The observed disparities and challenges in meeting international guidelines for timely interventions underscore the urgency of addressing accessibility issues. Heightened mortality and MACE risk among NSTEMIs with missed coronary occlusions[1,7] highlight the need for expanded research to understand OMI prevalence and implications in South Africa.

Keywords: occlusive myocardial infarction, myocardial infarction, non-ST-segment myocardial infarction, acute coronary syndrome

Introduction

Ischaemic heart disease (IHD), classified under the International Classification of Diseases, Tenth Revision (ICD-10) codes I20-I25, was the seventh leading underlying natural cause of death in South Africa in 2019, following communicable diseases.[8] Sub-Saharan Africa is currently undergoing an epidemiological transition, suggesting that cardiovascular diseases (CVD) will become one of the leading causes of death, with IHD being the most significant cause of CVD mortality.[9] This growing burden of CVD is concerning, as South Africa lacks the healthcare resources and infrastructure to manage it effectively.[9]

Acute myocardial infarction (AMI) is a common diagnosis in Emergency Centres (EC) across South Africa. In current clinical practice, AMI is classified into ST-Elevation Myocardial Infarction (STEMI) and Non-ST-Elevation Myocardial Infarction (NSTEMI) to identify which patients require emergency coronary reperfusion. In South Africa, 41.1% of patients admitted with acute coronary syndrome (ACS) are STEMIs, with a 30-day mortality rate of 2.4% for STEMI and 1.7% for NSTEMI. The 1-year ACS mortality rate is reported at 5.7%.[10]

International guidelines recommend percutaneous coronary intervention (PCI) as the gold standard treatment for STEMI.[11] However, this is not accessible for many South Africans due to significant healthcare and socio-economic inequalities. A significant 77% of PCI facilities in South Africa are privately owned,[12] making them accessible only to the 15.8% of the population with private healthcare insurance.[13] Consequently, the remaining 84.2% of the uninsured population must rely on the limited 23% of public-owned PCI facilities or pay out of pocket for treatment from a private-owned PCI facility. Notably, the province of Limpopo, which has the highest poverty rate at 78.9%, has no public-owned PCI facilities.[12]

Despite 53.8% of South Africans living within a 60-minute drive of a PCI facility and 71.5% living within 120 minutes,[14] only 32.5% have access to private transport, making them reliant on public transport or ambulance services for emergency healthcare access.[13] Nationally, the median distance to a PCI facility is 123.6 km, and the median driving time is 100 minutes.[14] In emergencies, the wait time for an ambulance can be as long as 12 hours.[15] Low-income individuals, those lacking private healthcare insurance, and patients residing in rural areas face the most significant barriers to healthcare access.[16]

Given these challenges, PCI as the gold standard treatment is not feasible for most South Africans. As a result, current clinical practice in public healthcare facilities involves fibrinolysis as an emergency reperfusion strategy. However, this approach also faces significant challenges. A study conducted in Cape Town reported that achieving the 30-minute door-to-needle goal is challenging in a South African setting. The study found a median door-to-needle time of 54 minutes, with only 20.5% of patients meeting the 30-minute goal.[17] Another study

at a tertiary hospital in Pretoria reported that only 37% of AMI patients received fibrinolytic therapy, and 3% received fibrinolysis within 60 minutes of symptom onset, with patient and transport delays being the most significant obstacles.[18] A study at a tertiary hospital in Johannesburg found that only 19.6% of STEMI patients achieved the 30-minute door-to-needle goal for fibrinolysis, with 53.1% presenting late to the healthcare facility.[19] These studies highlight the significant barriers to timely and effective AMI treatment in South Africa.

In 2018, a paradigm shift was proposed for AMI, distinguishing between Occlusive Myocardial Infarction (OMI) and Non-occlusive Myocardial Infarction (NOMI).[2] An OMI is defined as "acute coronary occlusion or near occlusion with insufficient collateral circulation, such that downstream myocardium will undergo imminent infarction without timely reperfusion."[4] Additionally, an OMI is defined as a Thrombolysis in Myocardial Infarction (TIMI) flow culprit of 0-2 or TIMI flow culprit of 3 with peak cardiac troponin T >1000 ng/L or I >10 000 ng/L."[4] The TIMI flow culprit is used to assess coronary artery flow on cardiac angiography.

Shortcomings of the current STEMI vs. NSTEMI classification support the OMI vs. NOMI paradigm.[2] A 2017 systematic review and meta-analysis demonstrated that 25.5% of NSTEMI patients had an occluded culprit artery, which was associated with increased all-cause mortality and a higher risk of major adverse cardiac events (MACE).[1] A 2014 study found that 86% of patients with subtle ST-elevation myocardial infarction (defined as ST-elevation of 0.1 to 1 mm) had a TIMI flow grade of 0-1, despite not meeting the STEMI ECG criteria.[20] Additionally, a 2010 study involving 1500 patients with complete coronary artery occlusion on angiography revealed that only 72% met the STEMI criteria.[21]

The evolution of the electrocardiogram (ECG) criteria for AMI management has seen multiple changes since its introduction in 1994.[22] In 2000, it changed from Q-wave vs non-Q-wave myocardial infarction (MI) to STEMI and NSTEMI classification, with the refinement of 2mm ST-elevation in V1-V3.[23,24] The first universal definition of an MI, published in 2000, advocated for the global adoption of the STEMI/NSTEMI paradigm.[25] In 2007, the Second Universal Definition of MI introduced gender differentiators.[26] A subsequent recommendation of age-based variations was introduced in 2009.[27] The Third Universal Definition solidified these criteria globally in 2012.[28] The current Fourth Universal Definition states that ECG findings suggestive of a STEMI AMI (in the absence of left ventricular hypertrophy and bundle branch block) are: "New ST-elevation at the J-point in 2 contiguous leads with the cut-point: ≥1 mm in all leads other than leads V2-V3 where the following cut-points apply: ≥2 mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age."[11] It further suggests that immediate reperfusion therapy is indicated in patients with chest discomfort or other ischemic symptoms with new bundle branch blocks with ischemic repolarisation

patterns.[11] Moreover, STEMI equivalents were identified, including ST-elevation in leads V7-V9 and ST-elevation in aVR or V1, accompanied by widespread reciprocal ST-depression in other leads.[11]

Significant emphasis is placed on the STEMI ECG diagnosis to determine AMI management. As a result, STEMI has become synonymous with acute coronary occlusion (ACO) over the years. This strong mental association has led to less urgent management of NSTEMI due to the perception that it involves only partial coronary occlusion. As a result, NSTEMI patients do not receive emergent coronary reperfusion, despite evidence reporting that emergency reperfusion decreases MACE and mortality.[1,7,22]

Predefined OMI ECG findings have been shown to be superior to the STEMI ECG criteria in identifying patients with AMI.[4] Using predefined OMI ECG findings was more sensitive and accurate at identifying AMI than using the STEMI criteria (86% vs 41%; 89% vs 77%).[4] OMI patients are missed using the STEMI criteria and, as a result, have significant delays to cardiac catheterisation. OMI patients may benefit from emergent PCI.[4] Furthermore, in a 2007 study, 14% of patients with suspected STEMI underwent angiography, yet no culprit artery was identified.[29]

This retrospective observational study aims to identify the prevalence of OMI among patients diagnosed with NSTEMI who presented to a single centre private EC in Cape Town during 2019. The objectives are to examine the descriptive data and serial cardiac troponin I (cTnI) results, determine the proportion of NSTEMI patients that undergo cardiac angiography, determine the TIMI flow grade and culprit coronary artery as reported on the angiogram, and the time from EC presentation to angiogram (door-to-angiogram).

Methods

Study design

A cross-sectional, observational study design was undertaken using a retrospective chart review of patients diagnosed with NSTEMI at a single centre private EC during 2019. Ethical approval (with a waiver of informed consent) was obtained from the Health Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (HREC Ref: 078/2023) and the involved private hospital group's Ethics Committee (Ref: CRIP-12042023/10), as well as approval from the EC managing company and involved cardiologists.

Study setting

This study was conducted at the EC of a private hospital in Cape Town, with an on-site cardiac catheterisation laboratory. The calendar year 2019 was chosen for research secondary due

to the possibility of the Coronavirus disease 2019 (COVID-19) pandemic being a confounder. An EC within the private healthcare sector was chosen as the study could not be replicated in the public healthcare sector. Most patients diagnosed with NSTEMI in the public healthcare sector will not undergo angiography as current Western Cape secondary-level hospital best-practice guidelines recommend medical management for NSTEMIs.[30] Only patients meeting specific criteria will be referred to a tertiary hospital for inpatient angiography. The criteria are as follows: hemodynamic instability, persistent or recurrent chest pain, dynamic ischaemic ECG changes, TIMI score of 5 or more, ischaemic chest pain on mobilisation or poor prognostic features on the sub-maximal exercise stress test after 48 hours of medical treatment. All other patients are referred for outpatient angiography.[30]

In one small South African study done in the public healthcare sector, only 69% (n=76) of NSTEMIs underwent inpatient angiography.[30] In contrast, in another study done at New Somerset Hospital (a public hospital in the Western Cape, South Africa), of the 43 NSTEMI patients, only 23% were referred for an angiogram. The remainder (77%) were treated with medical management.[31] Compared to a larger South African study (n=362) done in the private healthcare sector, 95% of NSTEMIs underwent inpatient angiography.[32] Only a small proportion of NSTEMI patients in the public healthcare sector will meet the study's inclusion criteria as they have not undergone angiography unless a tertiary hospital was used. As a result, it will not accurately represent the prevalence of complete coronary occlusion among NSTEMI patients.

Sample, sampling procedures, and data management

This study included all patients who presented to the EC diagnosed with NSTEMI and underwent angiography in 2019. Inclusion criteria were patients diagnosed with NSTEMI who had undergone angiography and presented to the selected private EC from 1 January 2019 to 31 December 2019. Exclusion criteria included patients under the age of 18 and cases with incomplete data (patient age and gender, diagnosis, cTnI results, ECG, and angiogram report).

Study participants were identified by an electronic search of clinical records (Google Drive, a restricted access system) using the ICD-10 coding for NSTEMI and Unstable Angina (UA) (ICD-10 I21.4 and I20.0, respectively). Patients diagnosed with UA were included in the initial search, as the treating cardiologist could later diagnose NSTEMI if the patient's repeat cTnI yielded a positive result. The primary researcher (an emergency medicine registrar) was granted electronic view-only access and used their personal password-protected computer to perform the electronic search.

Clinical records included standardised consultation forms with the patient's sticker (which included their name and surname, age, gender, date of birth and hospital folder number), clinical history, examination findings, medication, allergies, blood results, ECG and X-ray interpretation, management plan, as well as the ICD-10 diagnosis. The consultation form and supporting documentation, such as the ECG and blood results, are scanned and uploaded electronically by the managing company. All cTnI results recorded on the consultation forms were verified against the patient's necessary pathology laboratory results.

After identifying potential study participants, the subsequent step was to ascertain whether the patient had undergone angiography. The date and time of the angiogram were identified with an electronic search of the cardiac catheterisation laboratory patient register. Once confirmed that study participants had undergone an angiogram, cardiology angiogram reports were sourced electronically via email from the treating cardiologist.

Inclusion and exclusion criteria were applied during the selection process. For purposes of the study, an NSTEMI is defined as a change in the pattern of anginal cardiac pain with ECG features such as ST-segment depression and/or T wave inversion and positive cTnI levels diagnostic of acute myocardial infarction. ST-elevation may also be observed but is never sustained.[11] A positive cTnI is defined as the presence of a rise and/or fall in cardiac troponin (cTn) values, with at least one elevated cTn value above the 99th percentile upper limit reference.[11] The accuracy of the ICD-10 diagnosis was verified by cross-referencing doctor consultation notes, troponin results, and diagnoses made by treating cardiologists.

Data were collected onto password-protected Excel spreadsheets (Microsoft Corporation, Washington DC, United States) from electronic clinical records, cardiac catheterisation laboratory patient register, and the cardiologist's angiogram reports. Age, gender, comorbidities (such as hypertension, diabetes mellitus, dyslipidaemia, ischaemic heart disease, chronic kidney disease, and others), ICD-10 diagnosis, EC presentation date and time, serial cTnI results, angiogram date and time, TIMI flow culprit grade, and culprit coronary lesion as reported on the angiogram were collected. Serial cTnI values were recorded and additionally categorised into positive and negative results. A positive cTnI result is >70 ng/L. TIMI flow of the culprit coronary arteries were divided into two categories, namely grade 0-2 and grade 3 for the study.

All data entries were validated through double entry of a 10% random sample, with a 100% agreement. Further, the second author reviewed all data from the included cases to ensure valid data entry. Confidentiality was rigorously maintained to ensure ethical standards were upheld. Patient identification information, including names, dates of birth, addresses, and folder numbers, were removed. Data were separated into a temporary master data sheet with

patient folder numbers and unique study numbers, and an anonymised study datasheet. All data were securely stored on a password-protected computer and will be retained for the study duration, followed by deletion.

Data Analysis

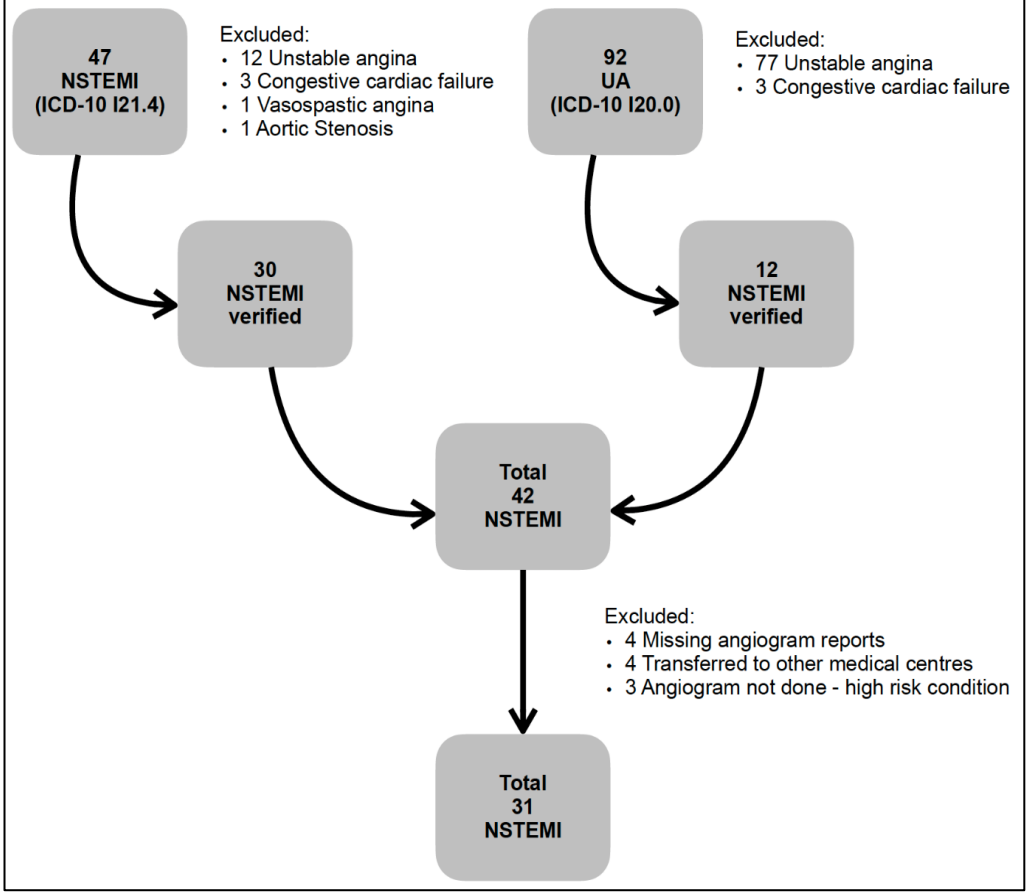
After collation, data were subjected to descriptive analysis. Due to sample size, events per predictor variable assumptions were not met for regression analysis. Chi-square test was used to determine differences between categorical variables for OMI vs NOMI. Differences in continuous variables (age, cTnI results, and EC-to-angiogram time) between the OMI and NOMI groups were tested using Mann-Whitney U-test because assumptions of normality were not satisfied (Shapiro-Wilks < 0.05). A p-value of 0.05 was considered significant. No missing data techniques were employed. Analyses were performed using SPSS V.28 (IBM, Armonk, New York, United States).

Results

The study included 31 validated NSTEMI cases. One hundred thirty-nine cases were initially identified using ICD-10 diagnosis, namely 47 NSTEMIs and 92 UA for 2019. During the first phase, 17 cases were excluded due to an alternative final diagnosis. Of the 92 initially identified UA cases, 12 were identified as NSTEMIs and 3 were excluded due to alternative final diagnosis. During the second phase, an additional 11 were excluded due to various criteria, including missing angiogram reports, transfers to other medical centres, or high-risk conditions that precluded angiography. A flow diagram of study patients is provided in Fig. 1.

As shown in Fig. 1, 42 NSTEMI patients were identified, 83.3% (n=35) underwent angiography, 9.5% (n=4) of the patients it is unclear if angiography was undertaken as these patients were transferred to other facilities, and 7.1% (n=3) of NSTEMI patients were precluded from angiography due to a high-risk medical condition, such as end-stage renal failure.

Figure 1: Sample size flow diagram



Of the 31 NSTEMI patients included in the study, 83.9% (n=26) had an OMI with a TIMI culprit flow 0-2, and 16.1% (n=5) had a NOMI. All OMI patients required intervention on angiography. The median NSTEMI age was 64 (IQR 23), with the youngest and oldest patients at 42 and 83, respectively. A larger portion of the sample included men (77.4%, n=24) compared to women (22.6%, n=7). 93.5% (n=29) of patients had comorbidities, with hypertension (HTN) accounting for the most common comorbidity among NSTEMI patients (74.2%, n=23). All the patients received an initial cTnI, 3.2% (n=1) did not receive a second cTnI, and 54.8% (n=17) had a third cTnI. Of those, 64.5% (n=20) of patients had a positive initial cTnI, followed by 93.3% (n=28) of patients with a positive second cTnI result and 85.7% (n=12) with a positive third cTnI result. The median time elapsed from door-to-angiogram was 40 hours (IQR 48).

Patient clinical characteristics are shown in Table 1. The median age did not differ significantly between the OMI and NOMI groups (65 vs 60 years, p=0.358). There was a significant difference in the proportion of men and women between OMI and NOMI patients; 88.5% of OMI patients were male (p<0.001), and 80% of NOMI patients were female (p<0.001).

Almost all (93.5%; n=29) patients had comorbidities; however, no significant difference was shown between the two groups (p=0.521). Additionally, comorbidities were assessed

individually, and no significance was shown between the two groups. Among the OMI patients, 92.3% (n=24) had pre-existing comorbidities, and the other 7.7% (n=2) were subsequently diagnosed after presentation. A large percentage (76.9%, n=20) of OMI patients had IHD, accounting for the most common comorbidity; however, this was not significantly different compared to NOMI cases (p=0.096).

The first cTnI result was positive in 64.5% (n=20) of patients. This median cTnI value did not differ significantly between OMI and NOMI patients (85 ng/L vs 140 ng/L, p=0.257). There was, however, a statistically significant difference in the second mean cTnI results when comparing the two groups (1450 ng/L vs 130 ng/L, p=0.011). The second cTnI was positive in 93.3% (n=28) of patients. The third cTnI was significantly positive in 85.7% of patients (n=12; p<0.001). The median third cTnI significantly differed between the OMI and NOMI groups (1695 ng/L vs 55 ng/L; p=0.011).

The median door-to-angiogram time was similar between the OMI and NOMI groups (34 hours vs 40 hours; p=0.775). The shortest and longest time were 1.6 hours (NOMI patient) and 281.8 hours (OMI patient), respectively. 41.9% (n=13) of patients underwent angiography within 24 hours, of which 84.6% (n=11) were from the OMI group and 15.4% (n=2) from the NOMI group.

Table 1: Patient clinical characteristics

		OMI n=26 (83.9%)	NOMI n=5 (16.1%)	TOTAL N=31	Sig.
Age, years, median (IQR)		65 (25)	60 (15)	64 (23)	0.358
Gender	Male	23 (88.5%)	1 (20%)	24 (77.4%)	**<0.001**
	Female	3 (11.5%)	4 (80%)	7 (22.6%)	**<0.001**
Comorbidities	Yes	24 (92.3%)	5 (100%)	29 (93.5%)	0.521
	HTN	19 (61.3%)	4 (12.9%)	23 (74.2%)	0.746
	DM	9 (34.6%)	2 (40%)	11 (35.5%)	0.818
	DLD	15 (57.7%)	2 (40%)	17 (54.8%)	0.467
	IHD	20 (76.9%)	2 (40%)	22 (71%)	0.096
	CKD	3 (11.5%)	0	3 (9.7%)	0.424
	Other	7 (26.9%)	3 (60%)	10 (32.3%)	0.147

First cTnI	Positivity (>70 ng/L)	15 (57.7%)	5 (100%)	20 (64.5%)	0.070
	Value, ng/L, median, (IQR)	85 (523)	140 (1255)	110 (723)	0.257
Second cTnI	Positivity	25 (100%)	3 (60%)	28 (93.3%)	**0.001**
	Value	1450 (2458)	130 (940)	1250 (2840)	**0.011**
Third cTnI	Positivity	12 (100%)	0	12 (85.7%)	**<0.001**
	Value	1695 (3638)	55 (N/A)	1565 (3443)	**0.022**
Door-to-angiogram time, hours, median (IQR)		34 (48)	40 (79)	40 (48)	0.775

cTnI = cardiac troponin I; HTN = hypertension; DM = diabetes mellitus; DLD = dyslipidaemia; IHD = ischaemic heart disease; CKD = chronic kidney disease. Unless otherwise indicated, results are reported as number (percentage).

The culprit coronary artery on angiogram revealed 34.6% (n=9) related to the left anterior descending artery, 30.8% (n=8) of the left circumflex artery, 23.1% (n=6) of right coronary artery occlusion, 7.7% (n=2) linked to the left coronary artery, and 3.8% (n=1) associated with the posterior descending artery.

Discussion

This retrospective observational study aimed to discern the prevalence of OMI among patients diagnosed with NSTEMI at a single private EC in Cape Town during 2019. Our findings revealed a remarkably high prevalence of OMI (83.9%) in the NSTEMI patient cohort. This contrasts with the systemic review and meta-analysis by Khan *et al.*[1] in 2017, which, with more restrictive criteria, identified total culprit artery occlusion in 25.5% of 40,777 patients. The differences in prevalence may stem from the varied defining criteria, with our study adopting the TIMI flow culprit criteria in alignment with Meyers *et al.*[4] thus capturing more OMI cases. To evaluate the statistical power of our study, we employed the Z-test methodology, considering the effect size, sample size, and significance level as input parameters. With a null hypothesis prevalence of 25.5%,[1] our post-hoc power analysis, based on a sample size of 31 and an observed prevalence of 83.9%, yielded an approximate power of 99.95%. This high level of power is justified as OMI appears to be a common outcome within our sample.

Our NSTEMI patients, with a median age of 64 years, align with the South African ACCESS registry's NSTE-ACS patients, whose mean age was 60.5 years.[33] NSTEMI patients are generally older than their STEMI counterparts in sub-Saharan African countries.[34] Notably, OMI patients in our study had a median age of 65 years, resembling similar findings from a Canadian study by McLaren *et al*.,[35] reporting a mean age of 69.5 years. The predominantly male distribution in both NSTEMI (77.4%) and OMI (88.5%) groups, akin to McLaren *et al.*[35] and Schamroth *et al.*[33] observations, underscores consistent demographic patterns across studies.

A substantial proportion of patients across the studies exhibited comorbidities. The comorbidities, hypertension, dyslipidaemia, and diabetes mellitus, showed similarity to the South African ACCESS registry for the NSTE-ACS population and the Canadian OMI population (HTN 74.2% vs 65.7% vs 63.0%; DLD 54.8% vs 63.0% vs 51.6%; DM 35.5% vs 26.8% vs 37.4%).[33,35]

Serial cTnI assessment in our study revealed that approximately one-third of OMI patients exhibited an initial negative cTnI, followed by a positive result, emphasising the crucial role of serial troponins in the EC, particularly when the initial result is negative. Elevated second cTnI levels were significantly associated with OMI when compared to NOMI (median 1450 ng/L vs 130 ng/L; p=0.011), indicating the importance of this marker in prompting further evaluation. A cTnI >1000 ng/L accompanied by OMI ECG findings[4] might prompt emergency angiography.

In the context of angiography, 83.3% of our NSTEMI patients underwent the procedure, with all patients receiving PCI. Only 41.9% underwent angiography within 24 hours. Our study revealed a median door-to-angiogram time of 40 hours for NSTEMI patients, longer than McLaren *et al*[35] 14.6 hours; this aligns with the challenges faced in a South African setting. The international 90-minute door-to-balloon time for STEMI[36,37] should be extended to OMI, considering both groups exhibit occlusive myocardial infarction. Our study, along with Khan *et al*.,[1] reveals comparable median times to angiogram for OMI patients (40 hours vs. 31.3 hours), raising concerns as none of the OMI patients underwent PCI within the recommended door-to-balloon time, emphasising the increased risk of MACE and all-cause mortality for NSTEMI patients with total occlusion culprit arteries.[1] Given that there is no significant difference in median door-to-angiogram time between OMI and NOMI groups, it suggests that the high proportion of OMI in this study was not explained by variations in the timing of angiograms, eliminating the argument that they resulted from an evolving AMI while in hospital.

In South Africa, public healthcare sector guidelines recommend medical management for NSTEMI patients, reserving emergent angiography for specific criteria, such as hemodynamic

instability, persistent or recurrent chest pain, dynamic ischaemic ECG changes, TIMI score of 5 or more, ischaemic chest pain on mobilisation or poor prognostic features on the sub-maximal exercise stress test (EST) after 48 hours of medical treatment.[30] This approach aligns with international guidelines, emphasising an invasive strategy for NSTEMI patients with very high-risk criteria with the addition of specific criteria such as signs or symptoms of heart failure or new mitral regurgitation, signs or symptoms of mechanical complications and life-threatening arrhythmias.[38] Our study sheds light on the critical issues within the STEMI/NSTEMI paradigm, emphasising the potential oversight of cases with near or total occlusion that lack significant ST-segment elevation or depression on ECG. While guidelines recommend scoring systems such as Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) to identify high-risk NSTEMI patients, there is still a risk of missing cases with occlusion that does not manifest significant ST-segment elevation or depression.[1,39] Perhaps thrombolysis as an alternative treatment for OMI in a resource-constrained setting merits consideration.

OMI ECG findings have demonstrated superiority over STEMI ECG criteria in identifying AMI, as demonstrated by two senior clinicians/authors.[4] However, the intricacy of OMI ECG diagnosis, encompassing eight specific findings,[4] poses challenges. The existing STEMI criteria also present a diagnostic challenge due to subjectivity and poor interrater reliability.[40–43] This complexity is especially pertinent given that a considerable portion of EC staff in South Africa, particularly interns (newly qualified clinicians working under senior supervision) and community service doctors (mandatory one-year public service after internship), are junior doctors.[6] These junior doctors, often assigned to rural facilities within the public health sector,[44] may encounter difficulties in interpreting such intricate ECG criteria, especially in settings with limited supervision. A 2023 observational cohort study (n=7313) developed machine learning models for OMI ECG diagnosis that outperformed doctors in precision and sensitivity.[45] Given the complexity of OMI ECG diagnosis and the varying experience levels within our emergency service workforce, artificial intelligence (AI) interpretation of ECGs could be a logical advancement. Additionally, the same challenges may be experienced in the prehospital setting in notification of AMI. These findings suggest that AI could play a crucial role in improving early detection and management of OMI, warranting further research in this area.

The challenges extend beyond diagnosis, and concerns about the accessibility of PCI facilities and primary PCI, particularly for individuals with limited resources or residing in geographically remote areas. In South Africa, correlations between the number of private and public-owned PCI facilities, socio-economic factors, and patients' medical insurance status highlight potential disparities in access.[12] While emergent management is crucial for OMI, addressing these issues necessitates a comprehensive approach, with potential solutions such as

thrombolysis for OMI in resource-strained settings, contingent on reliable ECG diagnosis, prompting further research on OMI ECG criteria and the potential use of fibrinolytics.

Limitations

Our study was conducted at a single-centre EC within the private healthcare sector in South Africa, which affects the external validity. Extending the study to multiple hospitals with PCI facilities, especially in the public healthcare sector, is recommended. The study's small sample size should be acknowledged, impacting the generalisability of results. No missing data techniques were employed because the sample size was small. The impact of missing data on the results is likely negligible since none of the key variables were missing. While about 10% of the sample was excluded due to a missing angiogram report, it is reasonable to assume that these patients were not significantly different from those included in the study, reinforcing the decision not to use missing data techniques.

Further exploration is required despite identifying a significant prevalence of OMI among NSTEMI cases. The authors acknowledge that having an on-site cardiac catheterisation laboratory may have introduced selection bias into the study population. Additionally, they recognise the importance of accounting for symptoms' duration before emergency centre presentation, as it could introduce bias. Future research should include symptom-to-angiogram times better to understand disease progression and its impact on angiographic outcomes. Inherent to retrospective chart reviews are limitations tied to the completeness of documentation, leading to incomplete capture of relevant variables and a lack of comprehensive context. Furthermore, retrospective data cannot inherently establish causality or assess real-time trends.

While recognising these limitations, our study (and many others on OMI) is not practice-changing but emphasises the imperative for in-depth exploration, considering the prevalence of OMI in the NSTEMI population in South Africa. Future research, expanding beyond a private healthcare setting to include both public and private sectors, would offer a more comprehensive understanding of this phenomenon. Additionally, future investigations should delve into the ECG findings of OMI patients, comparing them to STEMI ECG diagnosis for a more nuanced understanding.

Conclusion

Our study has demonstrated that many NSTEMI patients require intervention on angiography, emphasising the urgent need for refined diagnostic approaches, especially in regions where junior clinicians dominate in emergency centres. The observed disparities and challenges in meeting international guidelines for timely interventions underscore the urgency of addressing

accessibility issues. Furthermore, the heightened mortality and risk of MACE among NSTEMI patients with missed coronary occlusion[1,7] highlight the imperative for expanded research beyond private healthcare settings to achieve a comprehensive understanding. The authors of this study recommend that South African cardiovascular societies consider reassessing current guidelines to ensure they incorporate the latest evidence and address the practical realities of healthcare delivery. Addressing these concerns is vital for the timely and appropriate management of all NSTEMI patients, which can potentially lead to societal benefits, such as reduced healthcare costs, improved patient outcomes, and enhanced healthcare equity.

Funding

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Accessibility of protocol, raw data, and programming code

Raw, anonymised data are available on reasonable request and are subject to additional approvals by the organisations involved.

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PART B: ADDENDA

Cardiovascular Journal of Africa (CVJA) - Instructions to authors

All submissions should be written in a clear and succinct manner, following the journal's style. Title page should include a descriptive title, authors' surname and forename, address of each author and full address, telephone, fax, and email contacts for the corresponding author. In text: tables and figures are either inserted as part of the sentence, for example Table 1, or in parentheses, for example (Fig. 1). Each table should carry a descriptive heading. References numbered in order of appearance in the text, according to Vancouver style.

Original articles:

Title page as above.

Abstract: a short inclusive statement suitable for direct electronic abstracting, identifying the purpose of the study, key methods, the main results, and the main conclusion. Keywords: A maximum of six keywords are needed for indexing.

Introduction: A concise description of the background is sufficient for the non-specialist to appreciate the context of the work—a clear statement of the purpose of the study.

Methods: a brief description of study design, procedures, analytical techniques, and statistical evaluation.

Results: a clear account of the study findings using quantitative language where possible and cross-referenced to tables and figures.

Discussion: an interpretation of the study placed within the context of current knowledge, leading to specific conclusions where possible.

Acknowledgements.

References, figures, and tables are above.

Research Protocol

Prevalence of Occlusive Myocardial Infarction (OMI) in patients diagnosed with Non-ST-Elevation Myocardial Infarction (NSTEMI) at a single private facility in Cape Town, South Africa, during 2019

by

Dr Elmari Schoeman

MBChB, DipPEC

SCHELM002

This proposal is submitted in partial fulfilment of the requirements for the degree Master of Emergency Medicine in the Faculty of Health Sciences at the University of Cape Town

Supervisor(s):

Dr Willem Stassen (principal investigator)

BTEMC, MPhil EM, PGDip Appl. Ethics, PhD

Division of Emergency Medicine

University of Cape Town

Dr Ibrahim D'Andrea

MBChB, MMed (EM), FCEM

Honorary Lecturer Division of Emergency Medicine

University of Cape Town

May 2022

Declaration

I, Elmari Schoeman, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I authorise the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever. I further declare the following:

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Background

Acute myocardial infarction (AMI) is a common diagnosis in Emergency Centres (EC) across South Africa with high morbidity and mortality. Ischaemic heart disease (IHD) (I20-I25) is ranked 9th as the leading underlying natural cause of death in 2017 in South Africa, of which communicable diseases are the leading causes (1). Sub-Saharan Africa is currently undergoing an epidemiological transition which suggests that cardiovascular diseases (CVD) will become one of the leading causes of death, with IHD as the most significant cause of CVD mortality. The growing burden of CVD is concerning as South Africa does not have the health care resources and infrastructure to treat this burden (2).

In current clinical practice, AMI is classified into ST-segment Elevation Myocardial Infarction (STEMI) and Non-ST-segment Elevation Myocardial Infarction (NSTEMI) to determine which patients require emergency coronary perfusion with Percutaneous Coronary Intervention (PCI) as the gold standard. Emphasis has been placed on the ECG diagnosis of STEMI to determine management; as a result, STEMI has become synonymous with AMI over the decades. Emergency coronary reperfusion has been shown to decrease Major Adverse Cardiac Events (MACE) and mortality among patients who present with AMI (3).

In 1994 the ECG millimetre criteria were born and over the years were updated (3). In 2000, AMI management changed from Q-wave vs non-Q-wave MI to STEMI/NSTEMI (4). Furthermore, ST elevation is increased to 2mm in V1-V3 (5). Later that same year, in 2000, the First Universal Definition of MI was published, and the STEMI/NSTEMI paradigm was recommended for the management of AMI worldwide (6). Since 2000, there have been minor changes to this paradigm. In 2007, a difference between genders in interpreting ST elevation in V2 and V3 was published in the Second Universal Definition of MI (6). In 2009, an age difference in the interpretation of ST elevation in V2 and V3 was recommended (7). In 2012, this criterion was recommended worldwide by the Third Universal Definition of MI (8).

The Fourth Universal Definition of MI states that ECG findings suggestive of a STEMI AMI (in the absence of Left Ventricular Hypertrophy (LVH) and Bundle Branch Block (BBB)) are as follows: "new ST-elevation at the J-point in 2 contiguous leads with the cut-point: ≥1 mm in all

leads other than leads V2-V3 where the following cut-points apply: ≥2 mm in men ≥40 years; ≥2.5 mm in men <40 years, or ≥1.5 mm in women regardless of age." It is further suggested that immediate reperfusion therapy is indicated in patients with chest discomfort or other ischemic symptoms with new bundle branch blocks with ischemic repolarisation patterns (9).

STEMI equivalents have also been identified as ≥0.5 mm ST-elevation in leads V7-V9, suggestive of inferobasal MI (previously termed posterior MI). Another STEMI equivalent has been identified as ST-segment elevation ≥1 mm in aVR or V1, with widespread reciprocal ST-depression in the other leads (9).

A STEMI has become synonymous with acute coronary occlusion (ACO), while NSTEMI is associated with partial coronary occlusion and therefore does not receive emergent coronary reperfusion. In 2017 a sizable systemic review and meta-analysis demonstrated that 25.5% of patients diagnosed with NSTEMI had a total occluded culprit artery. The all-cause mortality and risk of MACE were increased (10). Although these patients had an AMI with an occluded coronary artery, they did not meet the STEMI ECG criteria. In 2010, a study was done where 1500 patients had complete coronary artery occlusion on angiography, and only 1077 (72%) met the STEMI criteria (11).

A new paradigm shift has been suggested for identifying patients who present with AMI, called the Occlusive Myocardial Infarction (OMI) vs Non-occlusive Myocardial Infarction (NOMI). An OMI is defined as "acute coronary occlusion or near occlusion with insufficient collateral circulation, such that downstream myocardium will undergo imminent infarction without timely reperfusion" (12). Additionally, an OMI is defined by a TIMI (Thrombolysis in Myocardial Infarction) flow of 0-2 on cardiac catheterisation (12). The TIMI flow grade is commonly used to assess coronary artery flow in acute coronary syndromes.

It has been shown that using predefined OMI ECG findings was superior to the STEMI ECG criteria in identifying patients with AMI. Using predefined OMI ECG findings was more sensitive and accurate at identifying AMI than using the STEMI criteria (86% vs 41%; 89% vs 77%) (12). OMI patients are missed using the STEMI criteria and, as a result, have significant delays to cardiac catheterisation. OMI patients may benefit from emergent PCI (12). Additionally, 14% of patients during a study in 2007 who had suspected STEMI underwent angiography and no culprit artery was found (13).

This retrospective observational study aims to identify the prevalence of OMI amongst patients diagnosed with NSTEMI who present to a single centre private EC in Cape Town during 2019.

The objectives include identifying how many patients diagnosed with NSTEMI undergo cardiac angiography, describing the angiogram findings, and the time from EC presentation to time of the angiogram.

Methodology

Study design

A cross-sectional, observational study design will be undertaken by utilising a retrospective chart review of patients diagnosed with NSTEMI [redacted] Emergency Centre during 2019.

Study setting

This study will take place at the EC [redacted], a private hospital in [redacted], Cape Town, with an on-site cardiac catheterisation laboratory. The EC is managed by a [redacted].

The study population will only include patients who can fund their treatment privately or through insurance or medical aid. It is noted that this is a limitation of the study. Because of the nature of this study, the study cannot be replicated in a public hospital sector. Most patients in the public sector diagnosed with NSTEMI will not undergo angiography as current Western Cape secondary level hospital best-practice guidelines recommend medical management for NSTEMIs. Only patients who meet specific criteria will be referred to a tertiary institution to undergo inpatient angiography. The criteria are as follows: hemodynamic instability, persistent or recurrent chest pain, dynamic ischaemic ECG changes, TIMI score of 5 or more, ischaemic chest pain on mobilisation or poor prognostic features on the sub-maximal exercise stress test (EST) after 48 hours of medical treatment. All other patients are referred for outpatient angiography (14).

In one small South African study done in the public health sector (76 NSTEMIs), 69% of NSTEMIs underwent inpatient angiography (14). In contrast, in another study done at New Somerset Hospital (a public hospital in the Western Cape, South Africa), of the 43 NSTEMIs, only 23% were referred for an angiogram. The remainder (77%) were treated with medical management (15). Compared to a larger South African study (362 NSTEMIs) done in the private health sector, 95% NSTEMIs underwent inpatient angiography (16). Only a small proportion of NSTEMIs in the public health sector will meet the study's inclusion criteria as they have not undergone angiography unless a tertiary institution is

used in the study. As a result, it will not accurately represent the prevalence of complete coronary occlusion amongst NSTEMIs.

The year 2019 was chosen for research secondary due to the possibility of the COVID pandemic being a confounder.

Study sample

This retrospective cross-sectional study will include all patients who presented to [redacted] EC and were subsequently diagnosed with an NSTEMI and underwent angiography between 1 January 2019 and 31 December 2019. The estimated sample size is 300 patients. The specific inclusion and exclusion criteria are listed below.

Inclusion criteria:

- Patients diagnosed with NSTEMI and undergone an angiogram.
- Presented to [redacted] EC.
- EC presentation from 1 January 2019 to 31 December 2019.

Exclusion criteria:

- Patients under the age of 18.
- Cases with incomplete data (patient age and gender, patient diagnosis, cardiac troponin levels, ECG, or angiogram report).

Data collection and management

[redacted] EC is run and managed by [redacted]. During each patient consultation, the EC doctor (employed by [redacted]) completes a written consultation form. [redacted] utilises a standardised consultation form that prompts EC doctors to fill out all fields. This form includes the patient's sticker (which includes their name and surname, age, gender, date of birth, physical address, medical aid and hospital number), clinical history, examination findings, medication, allergies, blood results, ECG and X-ray interpretation, management plan, as well as the ICD diagnosis. The consultation form and supporting documentation such as ECGs and blood results are scanned and uploaded by [redacted] onto their electronic database, Google Drive, a restricted access system.

Once the proposal has been granted ethics approval, [redacted] will grant the primary researcher electronic view-only access. The researcher will use their personal password-protected computer to perform the electronic search and collect data. The researcher will be sent a link via email to access the records. The researcher will collect all data onto password-protected Excel spreadsheets (Microsoft Corporation, Washington DC, United States). Data will be

collected from three different sources ([redacted]'s electronic patient database, [redacted] Catheterization Laboratory register, and the cardiologist's angiogram reports). For this reason, a temporary master datasheet will be created to record the patient's file number and their research identification code. Once all data is collected from various resources, the master datasheet will be deleted. See Appendix A.

Data required for the study will be captured into a standardised data capture Excel spreadsheet and include data variables as outlined in Appendix B. Inclusion and exclusion criteria will be applied both before and after extraction to obtain the final datasheet.

Study participants will be identified by performing an electronic search [redacted]'s database using the ICD 10 coding for NSTEMI and UA (I21.4 and I20.0, respectively). Patients diagnosed with Unstable Angina will be included in the initial search as the diagnosis of NSTEMI maybe later made by the treating cardiologist if the patient's repeat troponin is positive.

Once the study sample has been identified as described above, the researcher will verify the diagnosis of NSTEMI. For purposes of the study, an NSTEMI is defined as a change in the pattern of anginal cardiac pain with ECG features such as ST-segment depression and/or T wave inversion and positive troponin levels diagnostic of acute myocardial infarction. ST-segment elevation may also be observed but is never sustained (17). A positive troponin is defined as the presence of a rise and/or fall in cardiac troponin (cTn) values, with at least one elevated cTn value above the 99th percentile upper limit reference (URL) (9). The researcher (an emergency medicine registrar) will review the ECG findings and cardiac troponin values to ensure the diagnosis of NSTEMI is met, as stated above. If the troponin blood result is not documented on [redacted]'s doctor consultation form, the necessary pathology laboratory will be contacted by the researcher, namely [redacted] Laboratories.

The date and time of the angiogram will be identified with an electronic search of [redacted]'s catheterisation laboratory patient register. Once confirmed that study participants have undergone an angiogram, cardiology angiogram reports will be sourced electronically via email from the treating cardiologist, using the researcher's student email address schelm002@myuct.ac.za. The angiogram reports will be assessed to record the TIMI flow and then deleted. If the TIMI flow has not been documented, the respective cardiologist will be contacted via email for an assessment. For the purposes of the study, the TIMI flow grades will be divided into no flow and flow of the infarct-related coronary artery (grade 0-2 and grade 3, respectively), which is consistent with the definition of OMI, i.e., TIMI flow grade 0-2 (12). See Appendix C for the TIMI flow grading system. [redacted]

has preliminary approval in principle from cardiologists at [redacted] Hospital to provide angiogram reports and data to answer the research question.

To validate the findings, a 10% random sample will also be drawn and verified by the co-supervisor, an emergency medicine physician. Percentage agreement will be reported in the report.

Data analysis

Descriptive statistics will be presented for all variables. Most data are nominal categorical, except time to angiogram, a continuous numerical data set.

Depending on the data type, patient demographics will be presented as frequency and proportions (%) and mean and standard deviation. EC presentation time to the angiogram will be recorded as means and standard deviations. Logistic regression will be performed to determine the effect of clinical and demographic factors on OMI risk. Variance inflation Factors will be calculated to determine the presence of multicollinearity, and model fit will be assessed with the Hosmer-Lemeshow (HL) goodness of fit test. A p-value of 0.05 will be considered significant within the 95% confidence interval. A statistician will be employed to support the analyses.

Ethics

Ethics approval for the study will be sought from the Health Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town.

Access to [redacted]'s Cardiac Catheterization Laboratory register will be required. Approval for the study and access to the register will be sought from [redacted] Hospital's Ethics Committee.

Preliminary approval for the study and use of [redacted]'s data has been granted by one of the directors of [redacted]. Additionally, approval will be sought from the involved cardiologists.

Description of risks and benefits

Given the retrospective observational nature of the study, no direct involvement of patients will be required. The study will not affect patient management. The most significant risk to the participant will be breaches in confidentiality. As noted in the data management plan below, this will be mitigated through de-identification.

Privacy and confidentiality

The researcher will ensure patient confidentiality by removing patient identification information such as first and last name, date of birth, address, and folder numbers. Patients will be allocated a Research Identification Code (RIC) to allow the researcher to enter the necessary information onto the Study Datasheet. Data will be collected and kept on the researcher's personal password-protected computer. Data will be kept for the study period and, after that, deleted. All data will be backup onto UCT OneDrive.

The researcher is aware that there is a risk of breach of confidentiality and therefore has implemented various steps in data management to prevent this. For example, angiogram reports will be received via the researcher's UCT email address using a password-protected computer and password-protected Excel spreadsheets. Once data is collected, it will be deleted. It will not be stored.

Informed consent process

A waiver of informed consent is requested. The study is a retrospective observational study that involves no patient participation.

The research study involves no more than minimal risk to the participants as the study involves no direct patient participation; the data management plan will ensure confidentiality and mitigate breach thereof. Data will be de-identified on collection, and the research and its findings will not affect the management of the participants. For these reasons, a waiver will not adversely affect the rights and welfare of participants.

Reimbursement for participation

No participants will receive reimbursement in any form.

Strengths and limitations

The study will take place at a single private unit (the EC at [redacted] Hospital), limiting the findings to one setting and introducing sample bias. It would be beneficial to perform this study at more hospitals with PCI capabilities and in the public sector.

Two variables are being measured (prevalence of OMI amongst NSTEMI patients and the culprit lesion involved). It would be more informative if the study included the ECG findings. Due to the extra time required to investigate the above variable and the complexity of ECG interpretation, this is not feasible for an MMed study and, therefore, not done.

Despite the limitations mentioned above, this study aims to assess if this does occur in a private South African health care setting and whether it could be translated to more extensive studies conducted in the public and private sectors.

Dissemination of findings

The study will be written up as an MMed thesis and submitted for publication in a scientific journal. This study could serve as a foundational study for future studies. We hope more research will be undertaken in South Africa regarding the topic and our practices and management regarding NSTEMI to be reviewed.

Timeline

EMDRC	2 months
HREC (ethics):	2 months
Data collection:	2 months
Analysis:	2 months
Write up:	3 months

Budget

1) Stationary, transport and communication - estimation of R1500.

2) Statistician @ R500/hr for 10 hours - R5000.

3) Publication in open-source Journal - R15 000.

4) Presentation at Local Emergency Medicine Conference - R20 000.

Appendices

Appendix A

Master Datasheet	
Research identification code (RIC)	Patient file number
001	
002	

Appendix B

Study Datasheet									
RIC	Age	Gender	Comorbidities	ICD-10 diagnosis	Diagnosis verified	Date & time Presentation	Date & time Angiogram	TIMI flow grade	Culprit lesion
001									
002									

Appendix C

Thrombolysis in myocardial infarction (TIMI) flow grading system	
Grade 0	Complete occlusion of the infarct-related artery
Grade 1	Some penetration of contrast material beyond the point of obstruction but without perfusion of the distal coronary bed
Grade 2	Perfusion of the entire infarct vessel into the distal bed but with delayed flow compared with a normal artery
Grade 3	Full perfusion of the infarct vessel with normal flow

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HREC approval letters

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

13 March 2023

HREC REF: 078/2023

Dr W Stassen
Division of Emergency Medicine
F-51 OMB
Email: willem.stassen@uct.ac.za
Student: schelm002@myuct.ac.za

Dear Dr Stassen

PROJECT TITLE: PREVALENCE OF OCCLUSIVE MYOCARDIAL INFARCTION (OMI) IN PATIENTS DIAGNOSED WITH NON-ST-ELEVATION MYOCARDIAL INFARCTION (NSTEMI) AT A SINGLE PRIVATE FACILITY IN CAPE TOWN, SOUTH AFRICA, DURING 2019 (MMED CANDIDATE-DR ELMARI SCHOEMAN)

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, subject to contingent on approval from the hospital group.

Approval is granted for one year until the 30 March 2024.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student : Dr Elmari Schoeman will also be involved in this study.

Please quote the HREC REF 078/2023 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

HREC/ref 078.2023

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/ref 078.2023

[redacted] [redacted]

REF: REF: CRIP-12042023/10

Date: 25 May 2023

Dear Dr Schoeman

RE: PERMISSION TO CONDUCT

Title of study: Prevalence of Occlusive Myocardial Infarction (OMI) in patients diagnosed with Non-ST-Elevation Myocardial Infarction (NSTEMI) at a single private facility in Cape Town, South Africa, during 2019

The Committee for Research Institutional Committee (CRIP) hereby grant permission for you to conduct your above-titled research study at the abovementioned hospitals under the following conditions:

1. Permission is herewith grated for a period of 12 months from the date of this letter.
2. No direct reference may be made to [redacted] its subsidiaries or any of its facilities or institutions in the research report or any publications thereafter. The Company and its facilities, patients and staff must be de-identified in the study, and remain so for any other studies which may utilise this information. Any abstracts submitted or presentations given which will utilise the results of any research done in a [redacted], must comply with the same conditions.
3. If patient or institutional confidentiality is breached, [redacted] is entitled to withdraw this permission immediately. The Company reserves the right to take legal action against you, should [redacted] feel that this is warranted.
4. An electronic copy of the research report or compiled results, in the case of a clinical trial, must be submitted to CRIP on completion of the project or trial. This copy of the research report, and any publications which may develop from it will be placed on the Company's Gateway research page for reference purposes. The researcher is required to make these documents available in PDF format.
5. Research being done for educational purposes must be completed within the time allotted by the higher education institution. If the research is being done in an individual capacity by an employee of the [redacted], the research must be conducted within one year of permission being given by the Company, OR must be completed in the proposed time period specified in the approved proposal. Permission may be withdrawn if the research extends beyond the approved time period.
6. Six to 12 months after receiving permission/ethics clearance from [redacted] HREC to conduct a research study at [redacted] it is mandatory for the researchers to report on the progress of their stud b com letin a monitorin and evaluation form which is accessible on the research website a [redacted] The completed form must be returned to [redacted]
7. [redacted] will not take responsibility for any unforeseen circumstances within its institutions which may materially change the context and potential outcomes of a student's research. Should this occur, the student will be required to approach their Higher Learning institution for guidance around alternatives.

[redacted]

8. [redacted] will not be liable for any costs incurred during or related to this study.

9. In cases where a researcher is found to be guilty of misconduct, or in contravention of any national or international legislation or [redacted] policies or guidelines, permission to continue with the research will be withdrawn immediately pending investigation. In the case of student research, the higher education institution under which the researcher is registered will be notified. In the case of a clinical trial, The South African Health Products Regulatory Authority (SAHPRA) will be notified, as well as the trial sponsor and any other necessary parties.

Yours sincerely,

[redacted]

Dr [redacted]
CRIP Chairperson

[redacted]

Prof [redacted]
Research Specialist

On behalf of CRIP