Addis Ababa University
አዲስ፡አበባ፡ዩኒቨርሲቲ
SEEK WISDOM, ELEVATE YOUR INTELLECT AND SERVE HUMANITY !

COLLEGE OF HEALTH SCIENCES,

SCHOOL OF MEDICINE,

DEPARTMENT OF INTERNAL MEDICINE,

NUCLEAR MEDICINE UNIT

CORRELATION OF ANGINA SYMPTOMS, BASELINE ELECTROCARDIOGRAM ABNORMALITIES AND FINDINGS ON STRESS PROTOCOL WITH MYOCARDIAL PERFUSION SCINTIGRAPHY OUTCOMES

Principal Investigator: Dr. Yonas Shewangizaw (MD, Final Year Resident)

Advisors: Dr. Senbeta Guteta (Associate professor and cardiologist)

Mr. Desalegn Abeje (MSc, MPharm, Lecturer)

Dr. Marco Raddi (MD, Nuclear Medicine Physician)

A THESIS SUBMITTED TO ADDIS ABABA UNIVERSITY, POSTGRADUATE STUDIES, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE SPECIALTY CERTIFICATE IN CLINICAL NUCLEAR MEDICINE

February, 2023

Addis Ababa

Approval by the examining board

This thesis by **Dr. Yonas Shewangizaw** is accepted in its present form by the board of examiners satisfying thesis requirement for the Specialty Certificate in Clinical Nuclear Medicine.

Title of project: Correlation of angina symptoms, baseline electrocardiogram abnormalities and findings on stress protocol with myocardial perfusion scintigraphy outcomes, a retrospective study, in Monadi Hospital, Naples, Italy.

Examiners

1. Dr. Bethlehem Mekonen Signature ___________ Date _____________

2. Mr. Aschalew Alemu Signature ____________ Date_____________

Advisors

1. Dr. Senbeta Guteta Signature ____________ Date ___________

2. Mr. Desalegn Abeje Signature ____________ Date _________

Chairperson of the Nuclear Medicine Unit

____

Head, Department of Internal Medicine or Graduate Program Coordinator

____

Acknowledgment

The development of the thesis for this particular research project has been made possible by the continued support and encouragement of various individuals and institutions.

First and foremost, I would like to thank Addis Ababa University, College of Health Sciences, School of Medicine, Department of Internal Medicine in general, and Nuclear Medicine Unit in particular for their tireless efforts aimed at providing the platform to conduct this research in a foreign institution.

I would like to express my appreciation and sincere gratitude to my advisors, Dr. Senbeta Guteta (MD, MPH, Associate Professor, Consultant Internist, and Cardiologist) and Mr. Desalegn Abeje (MSc, MPharm) for their comments, guidance, and recommendations. I would like to wholeheartedly thank Dr. Marco Raddi (MD, Nuclear Medicine Physician) and Mr. Masresha Ahmed for their valuable contributions.

I would also like to express my sincere gratitude to the staff of Monaldi Hospital, Department of Nuclear Medicine, for providing me the opportunity to study at the facility and for their holistic support.

Finally, I would like to thank the Ethiopian Ministry of Innovation and Technology (MINT) and the International Atomic Energy Agency (IAEA) for organizing, facilitating, and sponsoring the fellowship programs at Pascale and Monaldi Hospitals.

Table of contents

List of Tables

List of Figures

List of Abbreviations

^{201}Tl	Thallium-201
^{99m}Tc	Technetium-99m
ACS	Acute coronary syndrome
CAD	Coronary artery disease
CCS	Canadian cardiac society
CT	Computed tomography
CVD	Cardiovascular diseases
ECG	Electrocardiogram
IHD	Ischemic heart disease
Kg	Kilogram
LVEF	Left ventricular ejection fraction
MBq	Megabecquerel
MET_{score}	Metabolic equivalent score
MI	Myocardial infarction
MPI	Myocardial perfusion imaging
MPS	Myocardial perfusion scintigraphy
NSTEMI	Non-ST segment elevated myocardial infraction
PET	Positron emission tomography
QRS	Segment on ECG which describes ventricular depolarization
SDS	Summed difference score
SMS	Summed motion score
SPECT	Single photon emission computed tomography
SPSS	Statistical package for social sciences
SRS	Summed rest score
SSS	Summed stress score
STEMI	ST segment elevated myocardial infraction
TID	Transient ischemic dilation
TPD	Total perfusion deficit
WHO	World Health Organization

Abstract

Background: Myocardial perfusion scintigraphy is an imaging modality used in the management of coronary artery diseases. Previous studies have shown that the combination of angina symptoms, baseline electrocardiogram abnormalities, and findings on stress protocols can provide valuable information for predicting the likelihood of abnormal imaging findings. However, the correlation and effect between these variables and imaging outcome is not well established.

Objective: To evaluate the correlation and effect between angina symptoms, baseline electrocardiogram abnormalities in coronary artery diseases and during stress exam with abnormal MPS outcomes and their predictive value.

Method: Hospital-based single-center retrospective cross-sectional study was conducted using medical records of 328 patients that underwent myocardial perfusion scintigraphy between 2020 and 2022. A systematic random sampling method was used to attain an appropriate sample size. Data were extracted from an electronic database using a checklist. The collected data were coded, entered, and analyzed using SPSS version 26. Pearson chi-square test and logistic regression were performed to evaluate the association and effect of independent variables. The statistical significance was measured at 95% CI and P-value less than 0.05(95%).

Results: The study population consisted of 328 patients, among them 185(56.4%) were males and 143(43.6%) were females. A significant association was observed between the severity of the chest pain category, baseline electrocardiogram abnormalities, inducible ischemia, and metabolic equivalent score with abnormal myocardial scintigraphy parameters. For each outcome variable, the aforementioned factors exhibited a statistically significant effect upon logistic regression. The odds of abnormal myocardial perfusion scintigraphy parameters were significantly higher for each independent variable.

Conclusions and recommendation: According to results in this study, clinical and electrocardiogram features can help prognosticate coronary artery disease before imaging which can lead to more effective and personalized diagnostic and treatment strategies for patients. Further studies with different methodologies are needed to validate the findings of this study.

Keywords: Myocardial perfusion scintigraphy, Perfusion defect, Metabolic equivalent score, inducible ischemia

Chapter One: Introduction

1.1. Background

Coronary artery disease (CAD) is an atherosclerotic disease of an inflammatory nature that is the leading cause of death in both developed and developing countries. It is manifested by stable angina, unstable angina, myocardial infarction (MI), or sudden cardiac death. In the pathogenesis of CAD, myocardial perfusion abnormalities are the first changes to occur, followed by wall motion abnormalities, electrocardiogram changes, and angina (1). Angina is the commonest presenting feature of CAD. It is caused by atherosclerosis of the coronary arteries, restricting the flow of oxygen to the myocardium which subsequently causes a debilitating pain or sensation of squeezing in the chest (2) . In addition to clinical evaluation, several diagnostic modalities are available for CAD assessment including electrocardiogram (ECG) and myocardial perfusion scintigraphy (MPS).

ECG is a non-invasive and straightforward test that measures the heart's electrical activity, detecting abnormalities in rhythm and conduction. Variables derived from baseline or exercise ECG can yield substantial data for risk stratification, either supplementary to scintigraphy parameters or even without concurrent scintigraphy (3). MPS utilizes radiopharmaceuticals to assess myocardial blood flow during stress as well as rest to identify perfusion defects. It demonstrates the cumulative effect of pathology at epicardial coronary arteries, small vessels, and endothelium, thereby evaluating the overall burden of ischemic heart disease (IHD). Early detection of myocardial perfusion abnormalities followed by aggressive intervention against cardiovascular risk factors may restore myocardial perfusion that may lead to reduced morbidity and mortality (4).

Currently, there is established evidence for using MPS in the diagnosis, follow-up, risk stratification, and prognosis of symptomatic patients with known or suspected CAD. However, the data regarding MPS outcomes are not adequately defined for specific groups such as those with baseline ECG abnormalities, angina-related physical limitations, and inducible ischemia during stress protocol (5).

1.2. Statement of the problem

CAD is an important cause of morbidity and mortality worldwide. According to World Health Organization (WHO), cardiovascular diseases (CVD) are responsible for an estimated death of 18 million per year. Over a third of the cardiovascular diseases are contributed by due to CAD. Over 50% of the mortality due to CVD is caused by CAD. In 2014, the WHO reported that around 30% of the Ethiopian population died due to non-communicable diseases, of which, CVD contributed 9% (2).

Despite considerable improvements in the identification and treatment of CAD, it remains highly morbid and is the most common cause of death in the developed world. Recently, the number of noninvasive radionuclide and echocardiographic scintigraphy studies performed to identify ischemic heart disease has grown considerably. Fortunately, as many as 60% to 70% of MPS studies ordered for CAD detection are normal. However, optimal test selection for symptomatic patients with suspected coronary artery disease requires a patient-centered approach factoring in the risk-benefit ratio and cost-effectiveness (6).

The prevalence of CVD in Italy is significant and was estimated at 38.8%with a high incidence among the older population most prevalent CVD subtype was coronary heart disease (20.8%). According to the World Health Organization (WHO), CAD is one of the leading causes of death in Italy, accounting for approximately 16% of all deaths. The prevalence of CAD in Italy has been increasing over the years, primarily due to a shift in lifestyle choices and an increase in risk factors such as smoking, high blood pressure, high cholesterol, obesity, and diabetes. The age-standardized prevalence of CAD was estimated to be 7.4% in men and 4.4% in women(7).

The pooled prevalence of CVD is reported to be 5% in Ethiopia (7-24%). Among patients who underwent coronary angiography for various indications,76% had single to multivessel coronary artery disease. This is a significant clinical burden that requires an appropriate diagnostic and prognostic test. In the Ethiopian context, the most frequently encountered presentations of patients with suspected or established CAD are heart failure with unrecognized or misdiagnosed preceding acute myocardial infarction, stable anginal symptoms or angina equivalents like dyspnea, faintness, and fatigue as well as acute coronary syndrome presenting with malignant arrhythmia and/or sudden death (2,8).

Prior studies regarding myocardial perfusion scintigraphy have failed to show a strong correlation between angina and ischemic myocardium, as measured on MPS. This lack of significant association was attributed to inaccuracies in the measurement of coronary physiology and errors in the evaluation of severity of angina symptoms. It was also suggested retrospectively that there must be an association between scintigraphy evidence of inadequate blood flow with patient-reported symptom severity due to the improvement in physical symptoms following an intervention like coronary revascularization (6).

One of the important complications of coronary artery disease is left ventricular dysfunction which eventually leads to heart failure and death. It is therefore imperative to make a distinction between viable and non-viable myocardium in patients who are candidates for revascularization which necessitates sensitive diagnostic and prognostic modality (9).

1.3. Significance of the study

Association between MPS findings and patients' pre-imaging health status was found to be an important unmet need in previous literatures. Subsequently, this particular study will aspire to fill this gap by evaluating the correlation between patient-based angina symptom severity assessment, objective baseline ECG abnormalities and findings during stress protocol with myocardial perfusion score and ventricular function. The results of this study will also help widen our understanding of the mechanisms of coronary artery disease, angina and perfusion defects.

The outcome of the study will address an important unmet need in CAD diagnosis and can be used as a potential means of optimizing the decision making in imaging and therapeutic interventions which optimize patients' health status.

This study will provide evidence for a holistic approach during decision making and improves sensitivity and specificity by extrapolating the data from MPS perfusion parameters, patient clinical evaluation, and baseline ECG findings.

Finally, the result of this study will help future researchers design prospective studies to validate the true predictive effect of pre-imaging factors impacting the diagnosis and prognosis of coronary diseases.

Chapter Two: Literature review

2.1. CAD and MPS

MPS is the most commonly used method for diagnosis and risk stratification of CAD. Barstow, Rice, and McDivitt stated that stress myocardial perfusion scintigraphy has a sensitivity and specificity only bettered by cardiac catheterization and has the highest negative predictive value with 98-99%. The location and extent of ischemia can be reliably obtained using MPS, which plays an important role in patient management. The latest advancements in computed tomography (CT), such as faster gantry, multidetector array, and even dual-source detectors, make it possible to noninvasively and intuitively obtain the anatomic morphology of coronary arteries, especially contributing to identifying the magnitude, distribution, and composition of coronary atherosclerosis (10,11).

MPS reflects relative differences in the distribution of blood flow in the myocardium at rest and during stress. Unlike during stress, myocardial perfusion at rest is maintained by dilation of myocardial arterioles distal to a significant coronary stenosis through an auto-regulation mechanism. Contrary to rest, stress has no significant effect on vascular beds distal to significant coronary stenosis causing differences in perfusion appearing as “defects” in myocardial perfusion images. These defects are described by a standardized 17-segment model of the left ventricle. An irreversible (fixed) defect that is seen on both at rest and stress images indicate infarction, whereas a perfusion defect seen after stress but reversible on resting images indicates myocardial ischemia (7,8).

MPS is an integral component in the evaluation of the presence and severity of CAD through the detection of flow-limiting disease, assessment, and quantification of patient risk. Nowadays, large number of MPS studies are done with ECG-gated SPECT, and more than 50% are done with pharmacologic stress. Gated MPS provides crucial information such as the severity and the extent of myocardial perfusion abnormalities, mechanical dyssynchrony, myocardial ischemia, and left ventricular (LV) function and size (12).

MPS has been found to have value in the evaluation of perfusion abnormalities during symptomatic stages and asymptomatic in unstable angina patients. A significant association between remote ECG abnormalities and relevant coronary perfusion impairment was revealed, especially between remote ST-segment abnormalities and functional measures of myocardial perfusion defects (12).

In patients with STEMI, remote ECG changes are frequent and associated with global coronary perfusion abnormalities. In those patients, the severity of coronary perfusion abnormalities in remote and culprit vessels is interrelated (12).

MPS is one of the most important and commonly performed tests in nuclear cardiology with major indications such as diagnosis, risk stratification in patients with known CAD, assessment of therapy and intervention, and myocardial viability before percutaneous intervention or bypass surgery. It has been shown to have high accuracy in identifying CAD and providing prognostic information on future cardiac events. The prognostic value of stress MPS has been established and a normal scan is associated with an annual hard cardiac event rate of less than 1%. The annual risks of cardiac death and myocardial infarctions were 0.3% and 0.5%, respectively, in patients with normal perfusion images, in contrast to 6% and 9.8%, respectively, in those with abnormal images. In patients with known coronary artery disease, the physiological information obtained by MPS improves risk stratification beyond the anatomical information of coronary angiography. It also plays a key role in the diagnosis of cardiovascular disease, establishing prognosis, assessing the effectiveness of therapy, and evaluating myocardial viability. Currently, most stress MPS is performed with an ECG gated SPECT for evaluation of both myocardial perfusion and cardiac function simultaneously. Thallium-201 chloride and technetium-99m (sestamibi and tetrofosmin) are the currently used radiopharmaceuticals (7-12).

Myocardial uptake of radiopharmaceuticals during scintigraphy procedure depends on two steps. Transportation of radiopharmaceutical to the cell surface is flow-mediated and the extraction of radiopharmaceutical by the intact cell membrane is directly dependent on blood flow (9). Thallium-201 distributes actively in cardiac myocytes, whereas technetium-based products distribute passively depending on blood flow and viability of the myocardium. Both radiopharmaceuticals are administered when the heart is stressed, either by treadmill test or pharmacologically. Radiotracer uptake indicates areas of perfusion and viable tissue during exercise and at rest. Areas of poor perfusion show improved perfusion at rest, which is referred to as reversible ischemia. Technetium-99m tracers, which have low first-pass extraction, are commonly used in SPECT scintigraphy, resulting in underestimation of both the extent and severity of ischemic changes. Since the redistribution of technetium-99m is minimal, it is more suitable for assessing the myocardial area at risk and delineating zones of hypoperfusion. Within minutes of injection, the ratio of uptake between the normal and ischemic myocardial areas is determined and remains constant for hours (11).

Technetium-99m based radiopharmaceuticals have largely replaced Thalium-201 chloride, because of improved dosimetry, better spatial scintigraphy resolution, and less soft-tissue attenuation, leading to greater test accuracy (13).

MPS is recommended as the first-line diagnostic procedure when exercise electrocardiography is difficult or inconclusive, or when the resting ECG is abnormal. MPS is also an efficient and cost-effective technique in patients presenting with stable chest pain. It provides a reliable assessment of coronary obstruction leading to inducible perfusion abnormalities and prognostic information on coronary artery disease (14).

2.2. Severity of angina symptoms and MPS

Angina or chest pain is the commonest presenting feature of CAD. It is caused by atherosclerosis of the coronary arteries, restricting the flow of oxygen to the cardiac muscle which subsequently causes a debilitating pain or sensation of squeezing in the chest. Angina pain can then radiate to the neck, arms, jaw, and back. Angina is one of the hallmarks of an acute coronary syndrome (ACS) and can be broadly categorized into stable and unstable angina. Stable angina is defined as the occurrence of symptoms with exertion only. Unstable angina is angina at rest, post-revascularization angina, new-onset exceptional angina within two months, or a recent acceleration of previous angina. Unstable angina is suspected if pain occurs at rest with a duration of more than twenty minutes within one week of the index incident and if previously diagnosed angina develops resistance to medication that controlled symptoms (2).

According to the guidelines from Canadian society of cardiology severity of angina is categorized into four depending on the severity of limitation during certain activities. Normal activity does not cause angina in class one, whereas, in class two, angina occurs when walking or climbing stairs quickly, climbing or straining after meals, in cold weather, during emotional stress. In class three, there is a clear limitation of normal activity when walking or during climb of stairs at a normal pace. Finally, class four signifies an inability to perform minor activities without discomfort” or “angina at rest” (15).

The presence of reversible and fixed defects on MPS are independent predictors for cardiac events such as MI and cardiac death. It was suggested by Wiersma et al. that there is an association between the severity of anginal complaints based on the Canadian cardiac society class and reversible perfusion defect on MPS (16).

Furthermore, there was a significant, positive correlation between, myocardial perfusion scores of the and the severity of angina symptoms (17). Despite the clear logic that serves as the foundation for modern ischemia testing, directly associating specific scintigraphy abnormalities with patient-reported angina has been difficult to establish (3,10).

2.3. ECG abnormalities and MPS

ECG is one of the pertinent investigations in the management of CAD. Furthermore, resting ECG was found to be a strong predictor of mortality and major adverse cardiac events such as myocardial infarction in healthy subjects as well as high-risk populations. The presence of a major ECG abnormality was associated with a threefold increased likelihood of myocardial ischemia in patients with an intermediate pretest probability of obstructive CAD. ECG also provided an incremental diagnostic value over pretest probability models and an independent prognostic factor for major adverse cardiac events in patients with known CAD (18).

ECG is a rapid and non-invasive tool that can guide decision-making, especially in a resource-limited setup. Approximately 50% of patients with acute myocardial infarction have abnormalities diagnosed on the ECG. In ACS, ST-segment changes, abnormal Q-waves, and T-wave changes are frequently observed. In chronic settings, ECG can show information like axis deviation, bundle branch blocks, and ventricular hypertrophy (19).

ECG provides useful information regarding prognosis through monitoring for the strength of symptoms, the extent of ST-segment changes, exercise tolerance, arrhythmia, and blood pressure response throughout the procedure and recovery period. ECG also provides valuable information on infarct location, results of reperfusion, as well as prognosis. Baseline ECG abnormalities in the general public even without known CAD have been were found to predict adverse cardiac outcomes. Subsequently, the decision-making by the nuclear medicine physician should follow a holistic approach by extrapolating the data from MPS perfusion parameters, clinical data, and ECG findings. Furthermore, baseline ST and T wave abnormalities were found to predict a greater frequency of abnormal MPS and when abnormal, greater ischemic extent than in those with a normal baseline ECG (18,20,21).

Arash *et al*. found that the only statistically significant difference between ECG changes as well as transient ischemic dilation (TID) ratio between normal scans and scans with ischemia. They suggested a correlation between ECG changes with summed stress score (SSS) as well as summed difference score (SDS). Among patients with ischemia in their scans, 44.3% were found to have ST depression after pharmacological stress (12).

Taywade *et al*. evaluated the correlation between stress-related ECG abnormalities and perfusion defects on the MPS. They found that ECG changes and reversible perfusion defects showed moderate strength of association. They underlined the need for critical evaluation of MPS in patients with ECG abnormality (10).

The sensitivity and specificity of MPS can be improved by extrapolating ECG findings both at baseline and during stress as well as angina symptom severity reported by the patient. Furthermore, some borderline and false negatives perfusion findings such as three-vessel diseases can be eliminated by incorporating these parameters into the interpretation protocol (12).

MPS adds diagnostic and prognostic value in higher-risk populations such as poor functional capacity, diabetes, or chronic kidney disease, variables derived from exercise ECG can yield substantial data for risk stratification, either supplementary to scintigraphy variables or without concurrent scintigraphy. However, the correlation between ECG abnormalities commonly observed in CAD, specifically, in acute coronary syndromes and MPS outcomes is not well studied. MPS evaluates physiological pathways of ischemia, including perfusion abnormalities and myocardial blood flow, which eventually manifest as angina in many patients (3,10).

2.4. Findings during stress protocol and MPS

The prognostic value of exercise capacity is consistent in patients with and without known CAD as well as those with non-revascularized and revascularized CAD. Metabolic score (METscore) defined as a quantity that signifies the amount of oxygen required to perform an activity. Exercise capacity measured in metabolic equivalents (METs) alone was found to be a powerful predictor of cardiovascular events (22,23).

The prevalence of any ischemia on MPS was as low as 4% in patients reaching the target heart rate and a high workload of ≥10 METs. Another composite clinical score called Duke's treadmill score (DTS) which incorporates exercise duration, ST segment changes, and stress-induced angina is a strong predictor of multivessel disease, mortality, and guiding the need for stress MPS. Stress MPS provides minimal incremental value in patients with a low-risk exercise stress test, a low-risk DTS, or a high-rate-pressure product without ST-segment depression (3).

Inducible ischemia on ECG which is defined as flat or down-sloping ST-segment depression of 1.0 mm or greater with or without ST-segment elevation, can yield substantial data for risk stratification, either supplementary to scintigraphy outcome or without concurrent scintigraphy (22). It has also been associated with presence and extent of ischemia on MPS (14). Contrary to the above authors, another study suggested that inducible ischemia on ECG during stress protocol was not correlated with significant ischemia on MPS (24).

3.Conceptual framework

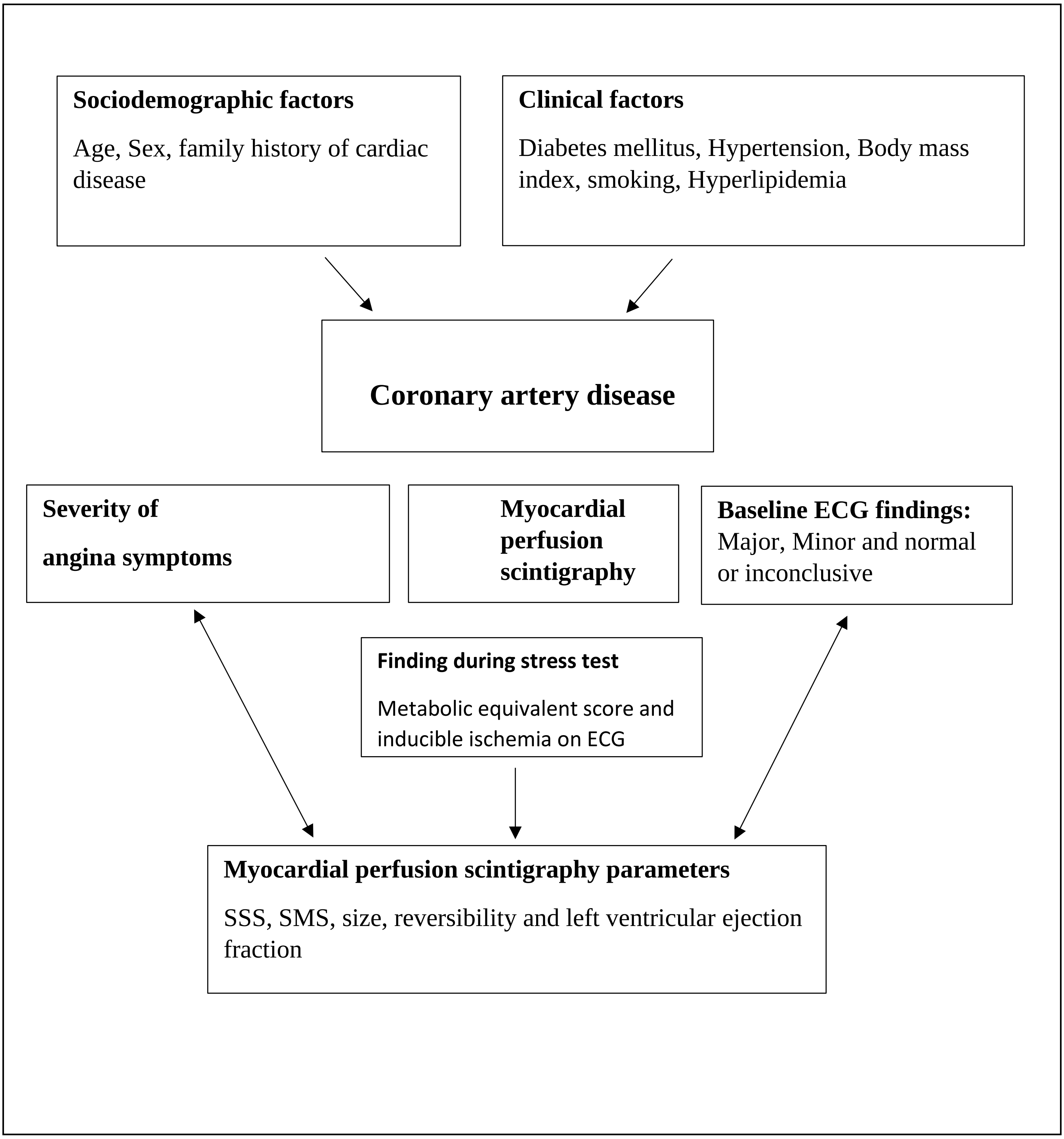

Fig.1: Conceptual framework

4: Objectives

4.1. General objective

To assess the correlation and predictive value of severity of angina symptoms, baseline electrocardiogram abnormalities, and findings during stress protocol with outcomes of myocardial perfusion scintigraphy performed at Monaldi hospital from October,2020 to September,2022.

4.2. Specific objectives

4.2.1. To evaluate the degree of correlation between the severity of angina symptoms and MPS findings

4.2.2 To evaluate the degree of correlation between baseline ECG parameters of coronary artery disease and subsequent MPS findings

4.2.3. To assess the magnitude and direction of correlation between findings during stress (metabolic score and inducible ischemia on ECG) test with abnormal MPS outcomes

4.2.4. To evaluate the impact or effect of each independent variable on dependent variables.

Chapter five: Methodology

5.1. Study Design

This single-center, retrospective, cross-sectional study was performed by revising a medical database of patients to determine the correlation between multiple dependent and independent variables of CAD and MPS outcomes.

5.2. Study area and period

5.2.1. Study area

The study was conducted in Monaldi Hospital which is located in the city of Napoli, Italy. Monaldi hospital is a renowned cardiorespiratory scintigraphy and therapeutic center including nuclear cardiology, cardiothoracic surgery, and pneumonology. The hospital is within a walking distance of Pascale tumor institute in an area known as “zona ospedaliera” which is located in the rione alto district of Napoli. The hospital was founded in 1938 and was named Monaldi in 1978 when it was dedicated to Vincenzo Monaldi who was a famous doctor and politician who served as a specialist in respirology.

5.2.2. Study period

The study was conducted in Monaldi Hospital, Napoli, Italy from September 1,2022 through February 11, 2023.

5.3. Source and study population

5.3.1. Source population

The source population of the study was all patient records in the database of Monaldi Hospital for the Myocardial perfusion scintigraphy procedure from October 1, 2020, through September 30, 2022.

5.3.2. Study population (target population)

The study population was all patients who had myocardial perfusion scintigraphy in Monaldi hospital from October,1,2020 through September 30, 2022, and whose chart or electronic database contains complete data regarding angina classification, baseline ECG parameters regarding coronary artery disease, and interpretation of the myocardial perfusion scintigraphy by a nuclear medicine physician.

5.4. Eligibility criteria

5.4.1. Inclusion criteria

The main inclusion criteria were all patients with suspected or confirmed coronary artery disease who were referred to Monaldi Hospital for MPS from October,1,2020 through September,30,2022 and with complete data concerning baseline ECG investigation and severity of angina symptoms before the scintigraphy procedure and complete interpretation of perfusion defects on myocardial perfusion scintigraphy.

5.4.2. Exclusion criteria

The exclusion criteria included patients with incomplete clinical data regarding angina symptoms and baseline ECG parameters of CAD as well as those who were referred to Monaldi Hospital before September 30, 2020, and after September 30, 2022, as well as patients with severe valvular pathology and cardiomyopathy.

5.5. Sampling size determination and sampling procedure

5.5.1. Sample size determination

The required sample size was determined using single population formula

$$n=\frac{(Z\alpha/2)^2\,p(1-p)}{d^2}$$

where:

p=proportion of myocardial perfusion scintigraphy in CAD patients assumed to be 50%

n=calculated sample size

d=margin of sampling error tolerated (5%)

Z=confidence interval (95%)

Therefore: $n=\frac{(1.96)^2 \times 0.5\,[1-0.5]}{(0.05)^2} = 384$

However, the total population of the study was found to be less than 10,000 and the minimum sample size (n') was obtained by applying the correction formula calculated as follows.

$n' = n/(1+n/N)$

Where: n’ = corrected sample size, n= calculated sample size and N=total source population

The source population represented the total number of myocardial perfusion scintigraphy performed from October 1, 2020, to September 30, 2022. which is found to be 2250. Therefore, the corrected sample size n’=384/ (1+384/2250) =328

5.5.2. Sampling procedure

The sampling procedure was based on the principle of systematic random sampling. After determination of the number of myocardial perfusion scintigraphy performed from October 1 2020 through September 30, 2022, this number was divided by the corrected sample size. The resulting number is (2250/328=6), therefore every 6th electronic database was selected until the sample size is attained provided it fulfilled the inclusion criteria.

5.6. Scintigraphy and interpretation protocol

5.6.1. Patient selection and preparation.

Patients with suspected CAD with a pretest probability of 15-85% or established CAD were referred by clinicians for diagnostic and prognostic assessment respectively. To prevent interference with myocardial perfusion scintigraphy all patients were instructed to withhold beta-blocking medications, calcium antagonists for 48 hours, and nitrates for 12 hours before the examination. For patients undergoing a pharmacological stress test, xanthine-based food stuff or medications regardless of indication were withheld for 24 hours before testing. Stress testing is performed using physical exercise on a treadmill using the modified Bruce protocol. For patients who cannot tolerate exercise stress, a pharmacological stress test was performed using dipyridamole (persantin) 0.56mg/kg. After patient preparation, resting ECG data, blood pressure, and heart rate were entered into the database, and continuously monitored every few minutes throughout the stress test.

5.6.2. Image acquisition.

One-day protocol with a stress-rest sequence was performed in Monaldi Hospital. For stress acquisition, the injected activity was in the range between 2.5-3.5 MBq/kg (megabecquerel per kilogram) of 99mTc-sestamibi (usually 185 MBq) and, for the rest acquisition, in the range between 7.5–10.5 MBq/kg of 99mTc-sestamibi (maximum of 900 MBq). Acquisitions were performed early after the injection of a tracer (15–30 min), if high tracer uptake was present close to the heart (in the liver or digestive tract), the acquisition was repeated 30–60 minutes later. Depending on the nuclear medicine physician's recommendations, rest image acquisition was performed after 30-60 minutes post-injection of at least three times the stress dose.

SPECT scintigraphy was performed while the patient was in a supine position and gated acquisition (step and shoot with 32–64 steps separated by 3°–6°) was undertaken on the stress images. The duration of SPECT acquisitions was adjusted to the counts measured in the myocardium that are estimated by placing a circular region of interest on the cardiac area on the scout view. Iterative reconstruction method was used for image reconstruction.

5.6.3. Image interpretation

After image acquisition, the nuclear medicine physician performs quality control of scintigraphy followed by image analysis which consisted of visual(qualitative), semi-quantitative and quantitative components. The image analysis considered attenuation correction by the low dose CT for artifacts related to extracardiac tissue uptake of the radiopharmaceutical such as breast tissue in women or bowel uptake in obese patients. The low-dose CT was also evaluated for gross abnormalities in the pulmonary field. The nuclear medicine physician ensured that stress and rest images were aligned well to perform a meaningful qualitative and semiquantitative interpretation of the images. First, the quantitative perfusion study was interpreted and reported, and later the quantitative gated study was reported. The report included the location of the perfusion defect with a description using 17 segment model and specific myocardial walls with respective major vasculature involved. It also included qualitative, semiquantitative, and quantitative analysis of perfusion defect severity and extent using parameters such as SSS, SMS, and left ventricular ejection fraction. Prognostic determinants such as left ventricular cavity dilation, lung uptake, or right ventricle uptake were carefully investigated.

5.7. Data collection instruments and techniques

Data extraction included include socio-demographic data, comorbidities, angina types, and severity of chest pain according to the Canadian Society of Cardiology as well as baseline ECG investigation parameters, inducible ischemia, metabolic equivalent score, myocardial perfusion scores, perfusion defect features, left ventricular function, and type of perfusion defects as reported by the nuclear medicine physician. Each study subject was pseudonymized and assigned a study identification code, and clinical, ECG, and myocardial scintigraphic data was collected, de-identified, and entered into a standardized electronic data capture checklist prepared using Epi info version 7.2.5. A pilot study was performed with at least 10% of the study population to ensure the completeness and availability of data as well as the feasibility of the study. Data was collected by the primary investigator who by the time of the study, was a nuclear medicine resident.

5.8. Operational definitions

Acute myocardial infarction: an event of a heart attack that is due to the formation of plaques in the interior walls of the arteries resulting in reduced blood flow characterized by cardiac enzymes, ECG findings, and clinical symptoms.

Major ECG findings: major ST-T changes, left ventricular hypertrophy, conduction abnormalities, and axis deviations.

Minor ECG findings: minor ST-T changes and minor and/or isolated Q-wave abnormalities

Myocardial perfusion scintigraphy: An important nuclear cardiology investigation modality that uses radiopharmaceuticals to diagnose and manage coronary artery disease.

Abnormal findings of myocardial perfusion scintigraphy: Perfusion defects in the scintigraphic image characterized in terms of reversibility, size or extent of the lesion, magnitude expressed with summed scores, and location of the lesion.

Acute coronary syndrome: a group of diseases in which blood flow to the heart is markedly reduced and ranges from ST-elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina.

Coronary artery disease: pathologic process of the epicardial coronary arteries that results from various causes.

Pathologic Q waves: Q waves that have $\geq$ 0.03 seconds and an amplitude of 25% of R wave amplitude in two anatomically contiguous leads.

Inducible ischemia on ECG: defined as flat or down-sloping ST-segment depression of 1.0 mm or greater with or without ST-segment elevation.

Known CAD: patients with previous confirmed MI or prior revascularization procedure

Metabolic equivalent score: a measure of exercise workload capacity in terms of energy required to perform an activity.

Summed stress score: a semiquantitative score that represents the sum of the severity of perfusion defect for all 17 segments of the left ventricle during a stress test.

Summed motion score: a semiquantitative score that represents summed score of wall motion abnormalities of the left ventricle (3,10,11).

5.9. Study variables

5.9.1. Dependent variables

Perfusion defects on myocardial perfusion scintigraphy are expressed in terms of global perfusion parameters such as summed stress score, reversibility of defect, size, summed motion score, and left ventricular ejection fraction.

5.9.2. Independent variables

Angina symptoms severity based on Canadian cardiac society grading, baseline electrocardiogram findings of coronary artery disease, metabolic equivalent score, and inducible ischemia features on ECG during a stress protocol.

5.10. Data analysis

Data was collected using a standardized data collection checklist prepared using Epi info version 7.2.5. The extracted data were entered into and checked using Epi info version 7.2.5 and then exported into IBM SPSS version 26 for analysis. Frequencies, proportions, and descriptive statistics were used to explain the study population with the relevant variables. Continuous variables were summarized using means and standard deviations. Frequency and percentages were used to summarize the central tendency and variability of categorical ordinal variables. The binary data were summarized using the mode and proportion test for hypothesis testing. Pearson's chi-square test of independence with appropriate parameters was used to describe the association between variables, whereas Pearson's correlation was used to evaluate correlation.

Adjustments or control was made for confounding variables including sociodemographic and clinical factors. Dummy variables were created to transform categorical nominal or ordinal variables with more than two categories into a statistically efficient binary category. The dependent variables in the study were mostly presented in categorical ordinal data form, subsequently, ordinal logistic regression with a proportional odds model assumption was used to assess the relationship between the various variables. However, whenever, the proportional odds assumption was violated or not fulfilled during preliminary analysis, multinomial logistic regression analysis was performed. The preliminary analysis of ordinal logistic regression consisted of model fitting information, goodness of fit, pseudo $R^{2,}$ and test of parallel lines or proportional odds model of the data.

Binary logistic regression was used for the dependent variables with just two outcomes after ascertaining goodness of fit with Hosmer and Lemeshow test as well as the omnibus test. Appropriate regression analysis was selected and the effect or impact of independent variables on the outcomes of myocardial perfusion scintigraphy was calculated. A P-value of 0.05 was regarded as statistically significant.

5.11. Ethical considerations

This study was undertaken after written ethical approval and permission to conduct research was given by Istituto Nazionale Tumori IRCCS Fondazione G. Pascale and the Department of internal medicine, College of Health Sciences, Addis Ababa University. All data collection procedures were conducted per the 2013 amendment of the Helsinki Declaration of 1964 for biomedical research. The ethical review board of the institution provided an ethics vote or a waiver before commencing any study activities. Although informed consent was not needed because the study relied on retrospective data which is characterized by data collection from medical records, lack of patient risk, and lack of directly or indirectly interfering with treatment, the confidentiality of all the data recorded was kept with utmost care throughout the study.

5.12. Method of dissemination

The results of this study with their respective discussions, interpretations, and recommendations will be prepared and disseminated to the college of health sciences, School of Medicine, Internal Medicine Department, Nuclear Medicine Unit, and Instituto Nazionale Tumori-Fondazione Pascale. The result of the study will also be available to all stakeholders in Monaldi Hospital including all staff in the nuclear medicine department. Subsequently, an effort will be undertaken to present the results on various platforms including conferences, seminars, and workshops. Finally, there will also be a plan to publish in international journals.

5.13. Role of the investigator

The investigator was responsible for topic selection, proposal development and planning of the study. The researcher will also analyze and summarize the findings of the study and presents to the appropriate authorities.

Chapter six: Results

The findings of this study are reported in six sections including the sociodemographic characteristics of the study population, baseline clinical and electrocardiogram findings, findings during a stress test, outcomes of myocardial perfusion scintigraphy, bivariate correlation analysis, and regression analysis of the aforementioned factors.

6.1. Sociodemographic characteristics

The total study population included 328 patients of whom 185(56.4%) were female and 143(43.6%) of them were male. The age group of patients ranged from 50 to 84 with a mean of 68.7 and a standard deviation of 6.9. The highest frequency of patients 146(44.9%) was from 61-70 whereas the age group 71-80 has the second highest frequency with 134(40.9%). The sociodemographic data of the study population were summarised in **figure 2** which describes the age group and **figure 3** describes the sex distribution of the study population respectively.

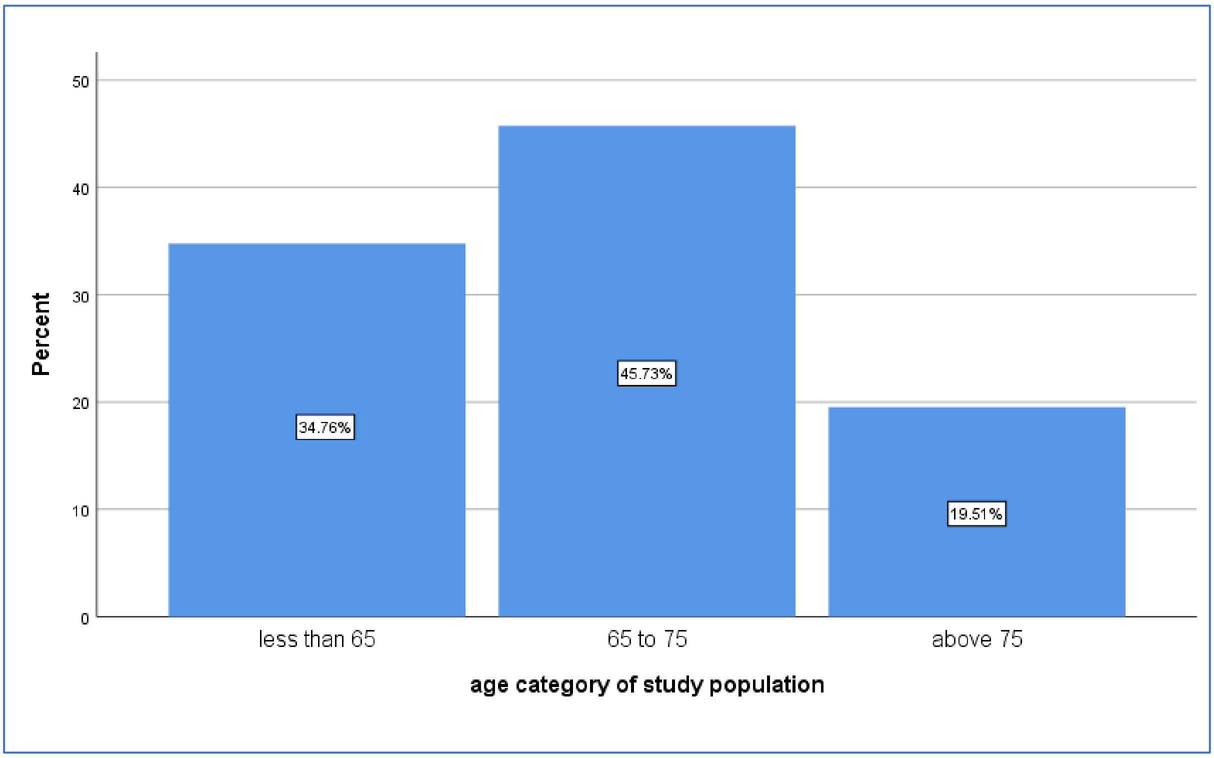

Figure 2: Age group of the study population in Monaldi hospital,2022 (N=328)

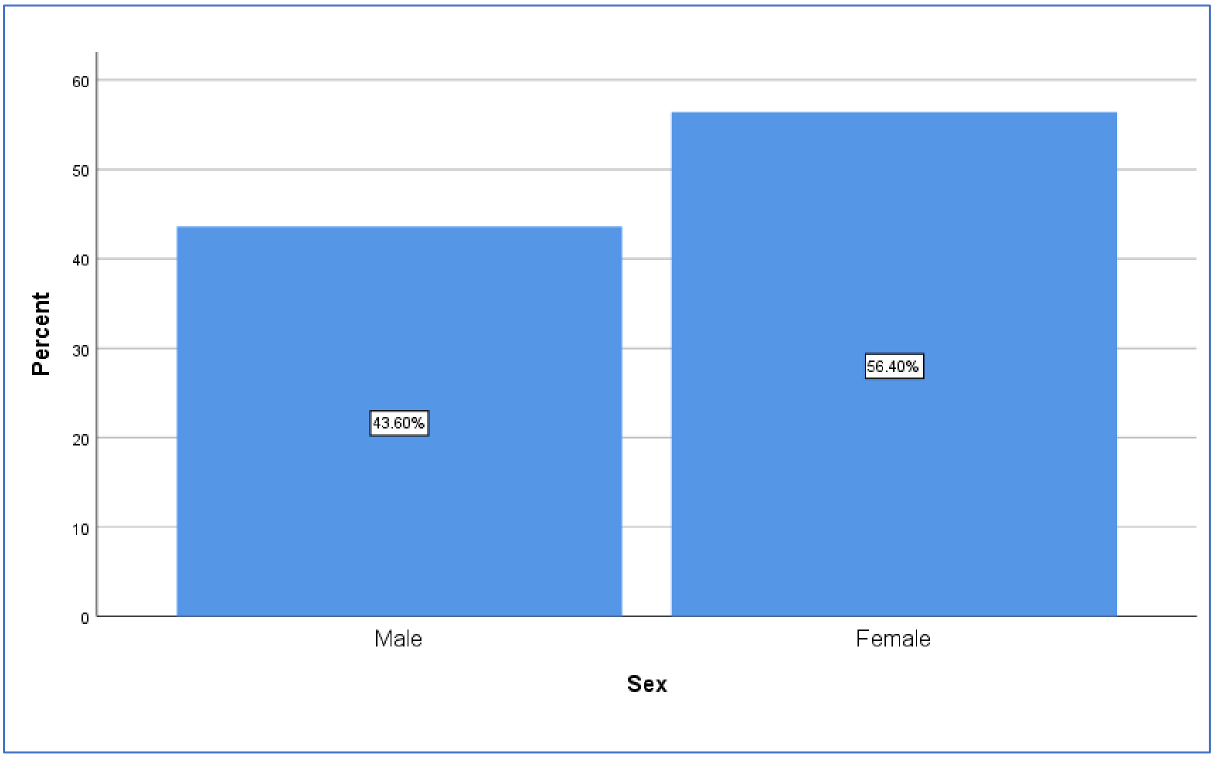

Figure 3: Sex distribution of the study population, Monaldi hospital,2022 (N=328)

6.2. Clinical and Electrocardiogram data

The body mass index of the patients ranged from less than 25 to more than 35, with the largest group 184(56.1%) with a BMI of 25-30, and the second largest group with 130(39.6%) had a BMI of 31-35, whereas the least group had 2(0.6%) with BMI of above 35. Concerning a family history of coronary heart disease,186(56.7%) patients had a family history and 142(43.3%) had no such history. In terms of smoking status,184(56.1%) were previous smokers and 112(34.1%) were current smokers.

Among the study population, 144(45.4%) had diabetes mellitus as comorbidity,148(45.3%) had hypertension,240(73.2%) had hyperlipidemia and 4(1.5%) of the study population had no comorbidity at all. Among those that had comorbidity,60(18.2%) patients had both diabetes and hypertension, whereas 106(32.3%) had diabetes and hyperlipidemia,125(38.1%) patients had hypertension and hyperlipidemia whereas 52(15.8%) patients had all three comorbidities.

With regards to the chest pain category,225(68.6%) patients had typical angina features, whereas 99(30.2%) had atypical chest pain and 4(1.2%) patients had non-cardiac chest pain. In terms of severity of the chest pain according to the Canadian cardiac association classification, the majority of the patients had class 2 or slight limitation of activities 159(48.5%) and class 3 or moderate limitation of activities 139(42.4%).

Among the study population,172(52.4%) patients had major abnormal findings on baseline ECG findings while 140(42.7%) had minor abnormalities and 16(4.9%) had normal or inconclusive findings. The following table **(table 1)** summarised the clinical and ECG data of the study population.

Table 1: Clinical and ECG data of the study population, Monaldi hospital,2022(N=328)

Variable	**Indicators**	**Total**	**Percent (%)**
BMI	Less than 25	12	3.7%
	25-30	184	56.1%
	31-35	130	39.6%
	Above 35	2	0.6%
Family history of coronary heart disease	Yes	186	56.7%
	No	142	43.3%
Smoking status	Previous smoker	184	56.1%
	Current smoker	112	34.1%
	Never smoked	22	9.8%
Chest pain category	Typical	213	64.9%
	Atypical	109	33.2%
	No chest pain	6	1.8%
Severity of chest pain class	Class 1	4	1.2%
	Class 2	159	48.5%
	Class 3	139	42.4%
	Class 4	26	7.9%
Baseline ECG finding	Major abnormality	172	52.4%
	Minor abnormality	140	42.7%
	Normal or Inconclusive	16	4.9%
Comorbidities	Diabetes	176	53.7%
	Hyperlipidaemia	240	73.2%
	Hypertension	149	45.4%
	No comorbidity	4	1.2%

6.3. Findings during a stress test

During the exercise stress test 194(59.1%) patients had inducible ischemia features on the electrocardiogram and 134(41.9%) didn't exhibit inducible ischemia features as shown in **figure 4**. As shown in **figure 5**, the metabolic score during the stress exam ranged from 4 to 11 with a mean of 6.84 and a standard deviation of 1.6.

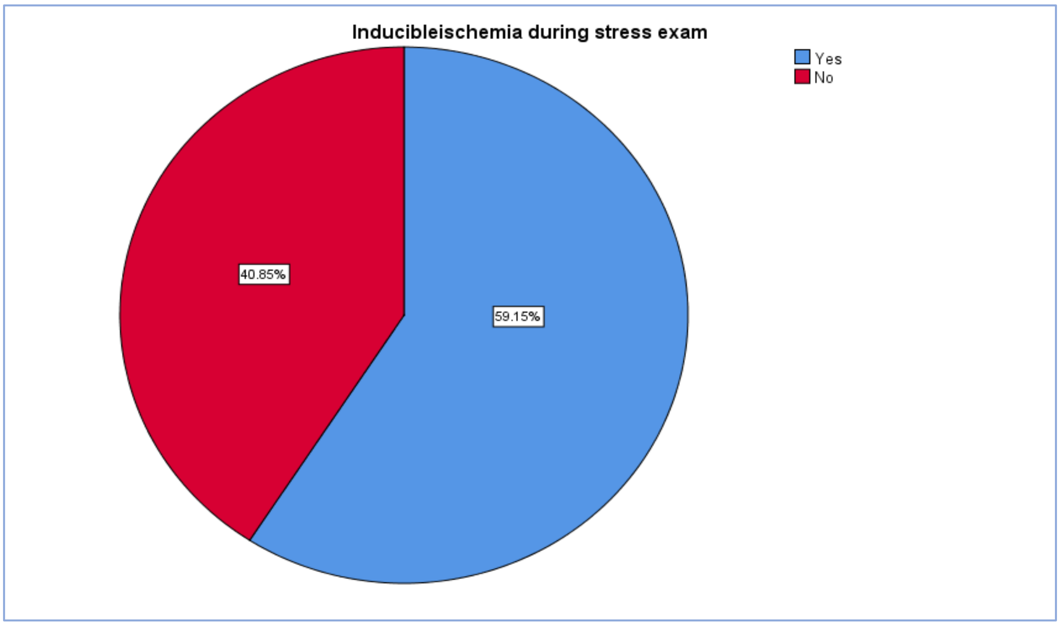

Figure 4: Inducible ischemia in the study population, Monaldi hospital,2022 (N=328)

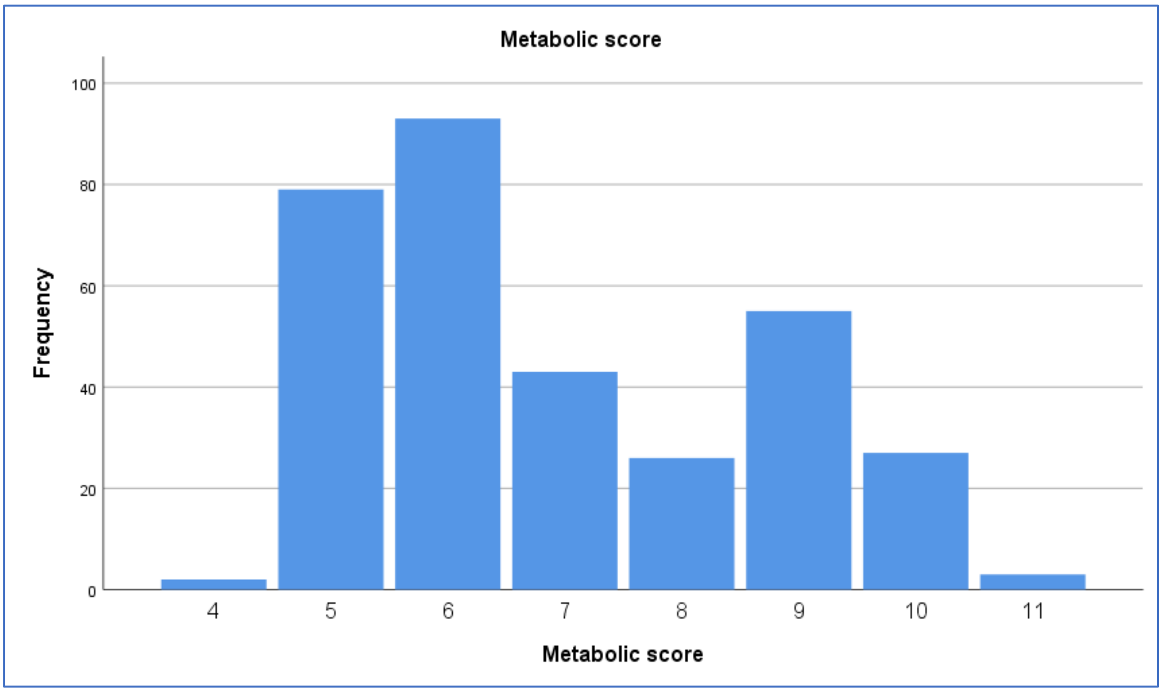

Figure 5: Metabolic equivalent score of the study population, Monaldi hospital,2022(N=328)

6.4. Outcome of myocardial perfusion scintigraphy

6.4.1. Size and reversibility of the perfusion defect

Out of 328 patient records,169(51.5%) had small perfusion defects on myocardial perfusion scintigraphy, whereas 106(32.3%) had a medium-sized defect. In terms of reversibility of the perfusion defects,220(67.1%) patients had a reversible defect while 108(32.9%) patients had an irreversible defect on their myocardial scan. In the following illustrations, **figure 6** represents the size of the perfusion defect, **figure 7** depicts the reversibility of defects on myocardial scintigraphy whereas **figure 8** depicts a cross-tabulation of the size perfusion defect by the reversibility of the defect.

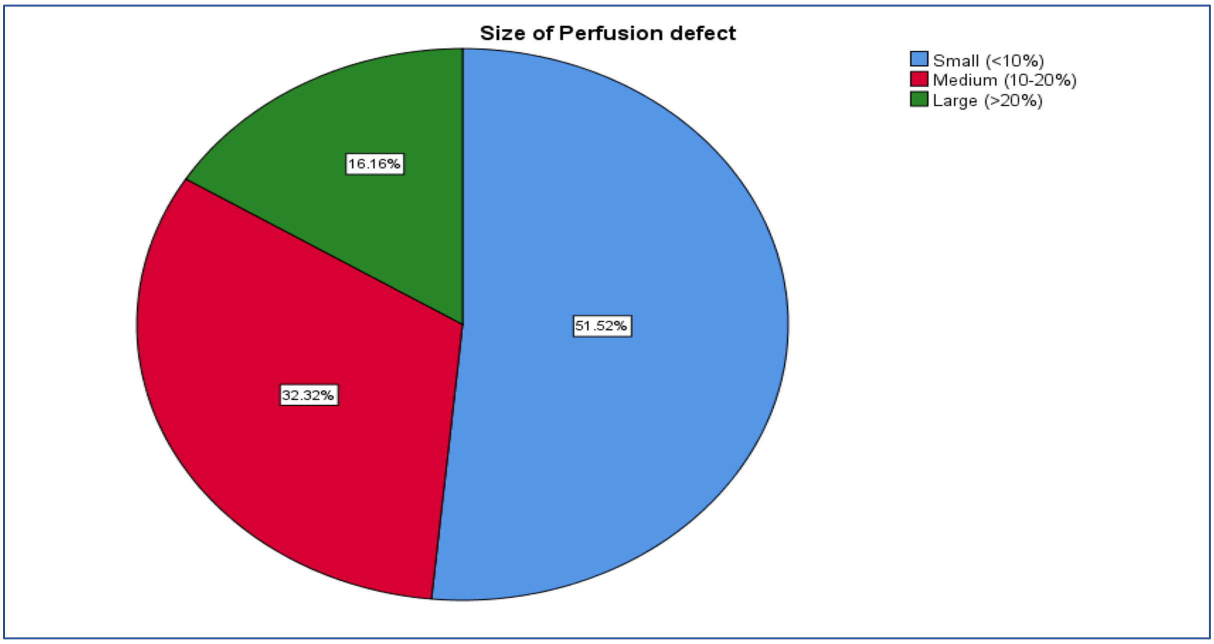

Figure 6: Size of the perfusion defect of study population, Monaldi hospital,2022 (N=328)

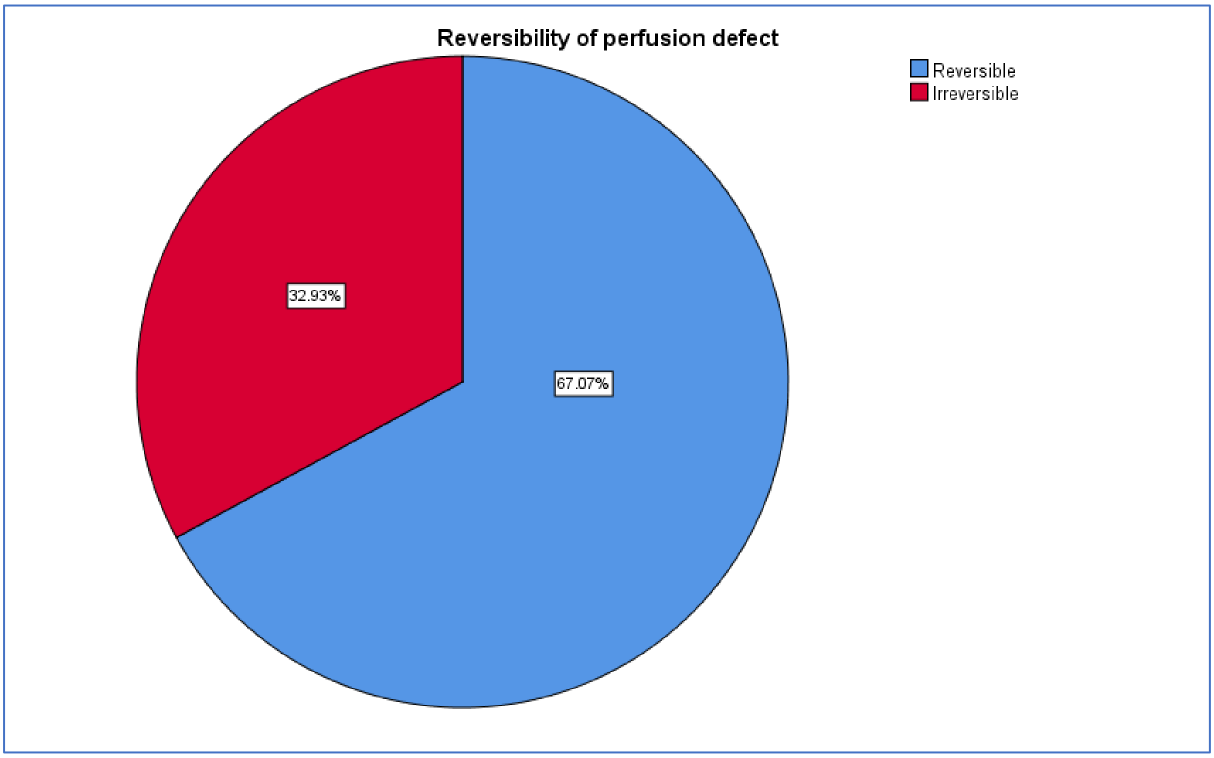

Figure 7: Reversibility of perfusion defect of study population, Monaldi hospital,2022(N=328)

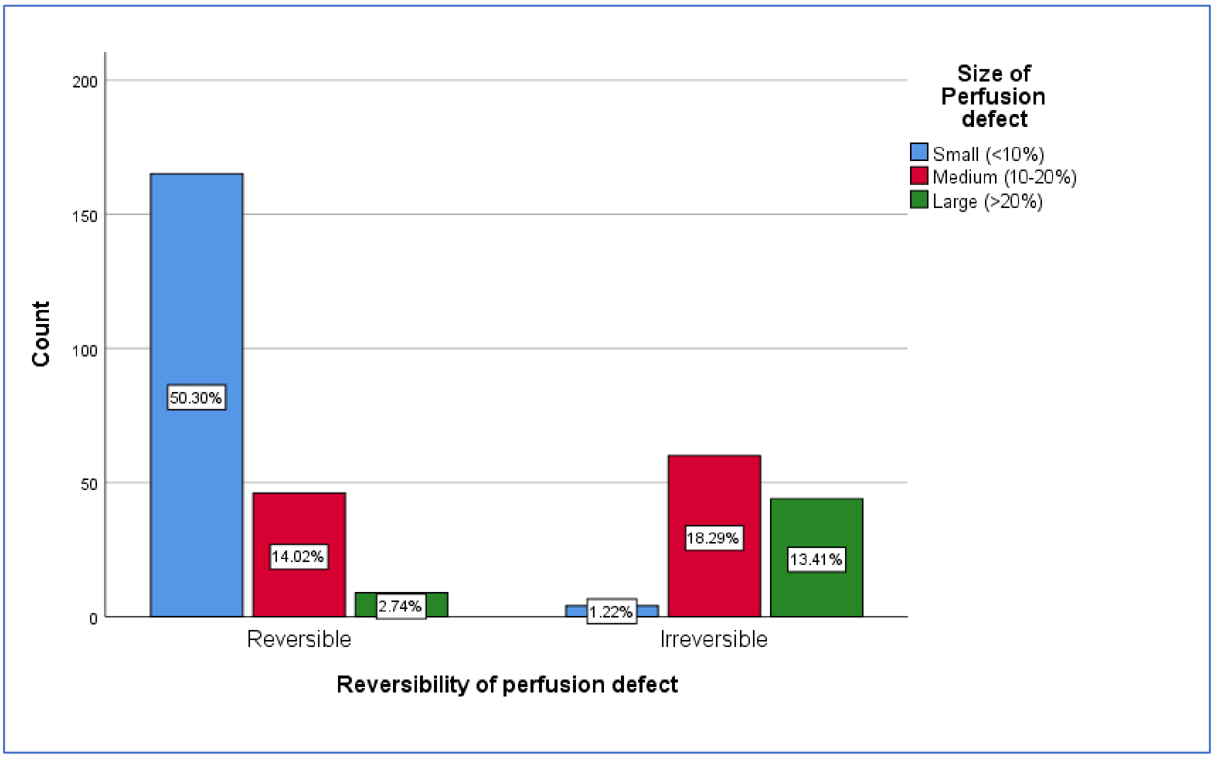

Figure 8: Cross tab of the size of the defect by reversibility of study population, Monaldi hospital,2022(N=328)

6.4.2. Summed stress score

Among the study population,146(44.5%) exhibited mildly abnormal summed stress scores,54(16.5%) showed moderately abnormal scores, and 74(22.6%) patients had severely abnormal scores as shown in **figure 9**.

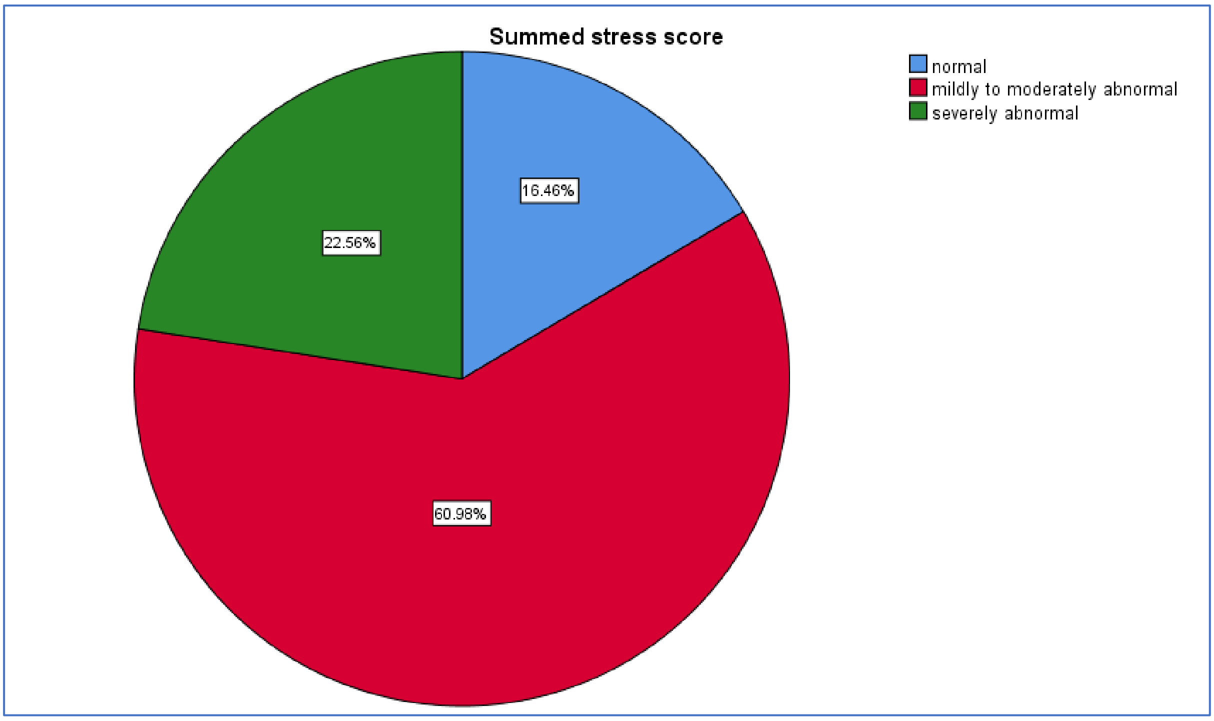

Figure 9: Summed stress score of study population, Monaldi hospital,2022(N=328)

6.4.3. Summed motion score

The following figure (**figure 10**) depicts the wall motion abnormalities of the study population by using summed motion score as a parameter

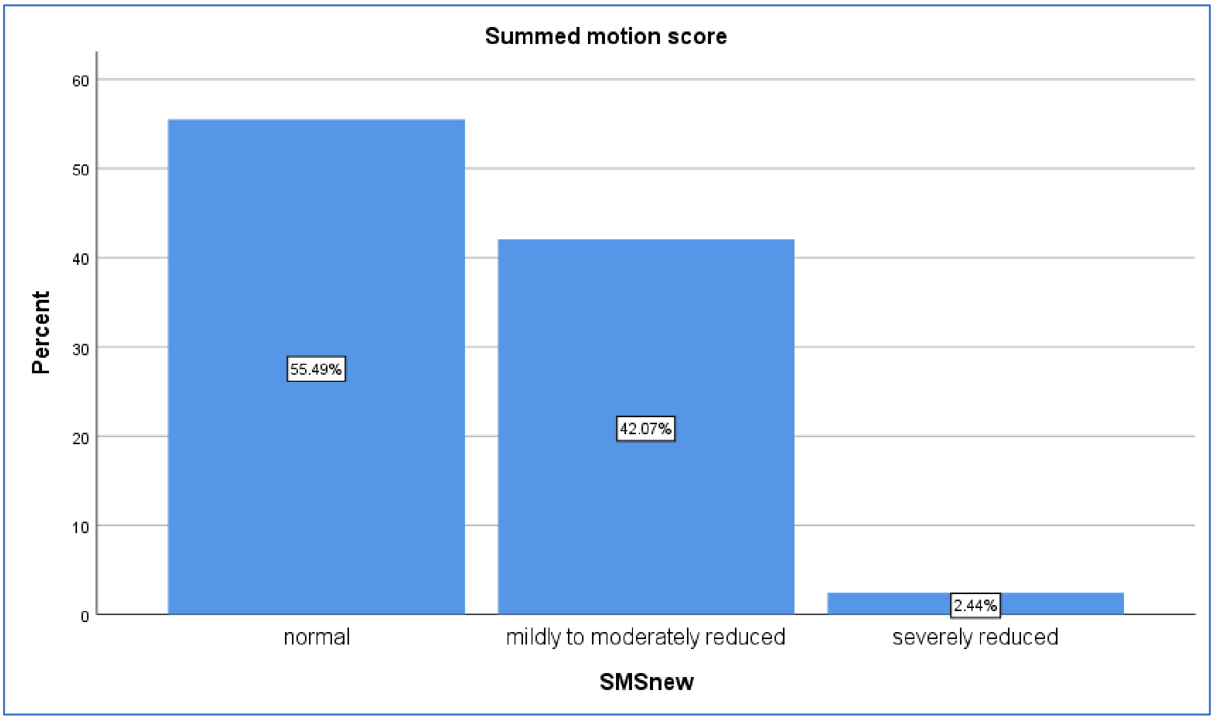

Figure 10: Summed motion score of the study population, Monaldi hospital,2022(N=328)

6.4.4. Left ventricular ejection fraction during stress

The following table (**table 2**) describes the ejection fraction status of the study population during stress.

Table 2: LVEF data of the study population, Monaldi hospital,2022(N=328)

Parameter	Outcome	Frequency	Percent (%)
Left ventricular ejection fraction	Normal (51-75%)	178	54.3
	Borderline (40-50)	104	31.7
	Abnormal (<40%)	46	14.0
	Total	328	100

6.5. Association among independent and dependent variables

One of the main objectives of this retrospective study was to assess the magnitude and direction of association between the independent and dependent variables. The association between categorical variables was examined by using cross-tabulation with the pearson chi-square test. Bivariate correlation analysis with Pearson's coefficient and two-tailed tests of significance at 0.01(99%) and 0.05(95%) levels were performed among five dependent and seven independent variables for 328 patients to determine the direction and magnitude of correlation. Presented below are highly statistically significant($P<0.01$) results together with the pearson correlation coefficient (where $r>0.69$: strong correlation and $r=0.30$-0.69: moderate strength). Selected results of bivariate correlation analysis are presented in **table 3** below.

The severity of chest pain based on the Canada cardiac society grading has a moderate strength negative correlation with the metabolic equivalent score, whereas it has moderate strength positive correlation with the size of the defect, summed motion score, summed stress score, and reversibility of the defect. Typical chest pain or angina has a moderate strength negative correlation with the size of perfusion defect and summed stress score.

Baseline ECG findings exhibited a strong negative correlation with the size of the defect, whereas it showed moderate strength negative correlation with summed stress score and left ventricular ejection fraction.

Inducible ischemia has moderate strength negative correlation with the size of the defect, summed stress score, and left ventricular ejection fraction.

The metabolic equivalent score showed a strong negative correlation with the size of the perfusion defect; however, it showed moderate strength negative correlation with left ventricular ejection fraction, summed stress score, summed motion score, and reversibility of the defect($r=-0.61$).

The comorbidities diabetes mellitus, hypertension, and hyperlipidemia had weak but statistically significant ($P<0.01$) correlation with the size of the defect($r=-0.32$), reversibility($r=-0.34$), ejection fraction($r=-0.36$) and summed stress score($r=-0.35$).

Among the study population who were taking various medications for their comorbidities those that were on aspirin, antianginal, and lipid-lowering medications showed weak but significant($P<0.01$) correlation with the size of perfusion defect($r=-0.24$), reversibility of defect($r=-0.25$) and summed stress score($r=-0.25$).

6.6. Regression analysis of associated factors

The other objective of the study was to evaluate the impact or effect of independent variables on the outcome or dependent variables.

Binary logistic regression was applied to the dependent variable with only two outcomes after ascertaining the omnibus test($p<0.05$) and Hosmer and Lemeshow test ($P>0.05$), to check for the goodness of fit. For the rest of the dependent variables in the study, ordinal logistic regression was performed because most of the outcomes were of nominal categorical data type. Proportional odds model assumptions for the ordinal regression model such as model fitting information, the goodness of fit, and the test of parallel lines were fulfilled before proceeding to the execution of the regression model.

Table 3: Correlation matrix of selected variables, Monaldi hospital,2022(N=328, P<0.01, two tailed test)

Variables	Chest pain type	Severity of chest pain	Baseline ECG	Inducible ischemia	METs	SSS	SMS	Size of defect	LVEF	Reversibility of the defect
Chest pain type	1	-.39	.34	.32	.36	-.47	-.30	-.40	-.29	-.32
Severity of pain	-.39	1	-.60	-.60	-.66	.62	.58	.69	.58	.56
Baseline ECG	.34	-.59	1	.65	.75	-.65	-.54	-.69	-.60	-.54
Inducible ischemia on ECG	.32	-.60	.65	1	.74	-.58	-.49	-.68	-.57	-.53
METscore	.36	-.66	.75	.74	1	-.62	-.54	-.72	-.60	-.60
SSS	-.47	.62	-.65	-.58	-.62	1	.71	.84	.77	.77
SMS	-.30	.58	.54	-.49	-.54	.71	1	.74	.78	.66
Size of defect	-.40	.69	-.69	-.68	-.72	.84	.74	1	.79	.68
LVEF	-.29	.59	-.60	-.57	-.60	.77	.78	.79	1	.71
Reversibility of defect	-.32	.56	-.55	-.53	-.60	.69	.66	.68	.71	1

6.6.1. Reversibility of the perfusion defect

Firstly, since the reversibility of the perfusion defect is a categorical dependent variable, a binary logistic regression model was applied to assess the effect of independent variables. The omnibus test and Hosmer and Lemeshow goodness of fit test were fulfilled because they were $p<0.05$ and $P>0.05$ respectively. The Nagelkerke R2 value was found to be 0.714. The relatively high value signified the fitness or power of the predictive model and was interpreted as meaning 71.4% of the change in the dependent variable could be explained by the independent variables.

Among the study population,220(67%) had a reversible perfusion defect whereas 108(33%) had fixed defect. Out of small perfusion defects,50% were reversible while 18% of large perfusion defects were fixed or irreversible.

Among the independent variables age, male sex, presence of inducible ischemia on ECG, severity of angina symptoms, typical angina, and metabolic equivalent score during stress test were found to have a significant effect on the irreversibility of the myocardial perfusion defect. The odds ratio values are presented with a 95% confidence interval and at a significance level of $P<0.05$. In each categorical parameter, the last member of the group is kept constant. The binary logistic regression in **table 4** depicts membership into the irreversible(fixed) perfusion defect group.

Table 4: Binary logistic regression of reversibility of perfusion defect of study population, Monaldi hospital,2022(N=328)

Parameter	B	Sig.	OR	95% CI	
				Lower bound	Upper bound
Sex(male)	-1.843	.001	0.158	0.066	0.381
Age	.007	.001	1.08	1.02	1.13
Inducible ischemia on ECG	1.656	.026	5.238	1.223	22.32
Slight to moderate chest pain	-2.28	.016	0.107	0.019	0.585
Typical angina	1.90	.002	6.74	2.08	22.71
Metabolic equivalent score	-1.32	.001	0.265	0.146	0.484

6.6.2. Summed stress score

Among the independent variables, age, hyperlipidemia, slight to moderate severity of chest pain, typical chest pain, inducible ischemia on ECG, and major baseline ECG findings were found to significantly affect the summed stress score as shown in **table 5**.

Table 5: Ordinal logistic regression of summed stress score of study population, Monaldi hospital,2022(N=328)

Parameter	B	Sig.	OR	95% CI	
				Lower bound	Upper bound
Slight to moderate chest pain	-2.64	.001	0.071	0.021	0.237
Hyperlipidemia	0.680	.029	1.973	1.070	3.63
Inducible ischemia on ECG	0.885	.039	2.424	1.047	5.612
Major baseline ECG findings	2.83	.001	16.93	6.16	46.64

6.6.3. Summed motion score

Shortness of breath or dyspnea, hyperlipidemia, slight to moderate severity of chest pain, metabolic equivalent score, major baseline ECG findings, and inducible ischemia had a significant impact on summed motion score as presented in **table 6.**

Table 6: Ordinal logistic regression of summed motion score of study population, Monaldi hospital,2022(N=328)

Parameter	B	Sig.	OR	95% CI	
				Lower bound	Upper bound
Dyspnea	-2.891	.034	0.057	0.004	0.786
Hyperlipidemia	0.943	.011	2.567	1.23	5.32
Slight to moderate severity chest pain	-2.82	.001	0.059	0.023	0.153
Metabolic equivalent score	-0.488	.001	0.614	0.454	0.829
Major baseline ECG	1.35	.002	3.88	1.63	9.22
Inducible ischemia ECG	1.151	.014	3.161	1.262	7.918

6.6.4. Size of the perfusion defect

Factors significantly affecting the size of the perfusion defect were dyspnea, metabolic equivalent score, typical chest pain, major baseline ECG, slight to moderate chest pain severity, and inducible ischemia during stress as presented in **table 7** below.

Table 7: Ordinal logistic regression of size of perfusion defect of study population, Monaldi hospital,2022(N=328)

Parameter	B	Sig.	OR	95% CI	
				Lower bound	Upper bound
Dyspnea	-5.09	.002	0.006	0.000	0.148
Metabolic score	-1,8	.001	0.164	0.091	0.297
Typical chest pain	1.819	.001	6.165	2.08	18.2
Major baseline ECG	3.13	.001	23.06	6.67	79.8
Slight to moderate chest pain severity	-2.73	.001	0.065	0.021	0.205

6.6.5. Left ventricular ejection fraction at stress

Age, male sex, hyperlipidemia, slight to moderate chest pain severity, metabolic equivalent score, major baseline ECG and inducible ischemia during stress were found to have a significant impact on the left ventricular stress during stress as shown below in **table 8**.

Table 8: Ordinal logistic regression of left ventricular fraction during stress of study population, Monaldi hospital,2022(N=328)

Parameter	B	Sig.	OR	95% CI	
				Lower bound	Upper bound
Age	-0.143	.008	0.867	0.781	0.963
Sex(male)	-0.753	.014	0.471	0.259	0.855
Hyperlipidemia	1.602	.001	4.693	2.19	11.2
Slight to moderate chest pain severity	-2.070	.001	0.126	0.049	0.323
Metabolic equivalent score	-0.618	.001	0.539	0.392	0.742
Major baseline ECG	1.435	.001	4.199	1.696	10.3
Inducible ischemia ECG	1.441	.003	4.226	1.650	10.82

7. Discussion

MPS acts as a gatekeeper for coronary angiography as well as revascularisation interventions by detecting early abnormalities of myocardial perfusion by evaluating physiological pathways of ischemia, myocardial blood flow and severity of angina symptoms.

Several studies have explored the relationship between severity of angina symptoms, baseline ECG abnormalities, stress protocol findings such as metabolic equivalent score, and MPS outcomes. This single-centre hospital-based retrospective cross-sectional study was done to assess pre-imaging factors and their predictive value or effect on MPS outcomes. Contrary to multiple prior studies, this study showed there is strong, statistically significant correlation between severity of chest pain, baseline major ECG findings, METscore and inducible ischemia with MPS outcomes. According to the current study, there is a significant association as well as an effect between the abovementioned factors with parameters of MPS outcomes such as the size of perfusion defect, reversibility of defect, summed stress score, summed motion score and left ventricular ejection fraction.

A study by Patel *et al*. failed to establish a direct link between myocardial perfusion scintigraphy abnormalities especially reversible perfusion defects and patient-reported severity of angina. However, they found that impaired left ventricular ejection fraction was strongly associated with significant angina-associated functional limitation (6). Their study analysed data from PET-based MPS, included multi-centers, and had a fourfold more sample size which may have led to different conclusions from this study.

In contrast, the current study showed that the severity of chest pain or angina has a significant positive correlation with reversibility as well as the size of the perfusion defect. This finding is in concordance with Wiersma *et al*. who suggested that there is an association between the severity of anginal complaints based on the Canadian cardiac society class and the reversibility of perfusion defect on MPS (18).

Similarly, a study by Cho *et al*. also discovered that patients with angina symptoms and abnormal ECG findings were more likely to have positive MPS outcome indicating myocardial ischemia (25). In agreement with Cho *et al*. this study found out there is a significant, positive correlation between myocardial perfusion scores and grading of angina severity. According to the results, for patients with severe chest pain compared to a reference group of mild to moderate severity, the odds of having an abnormal summed stress score, irreversible defect, and abnormal summed motion score were 14,9 and 16 times more likely for patients in the reference group respectively. In addition, the severe chest pain group was 88% likely to have abnormal LVEF.

With regards to angina category, in this study, the odds of having a large perfusion defect were 6.1 times more likely for patients with typical angina than for atypical or non-cardiac chest pain. For patients having typical chest pain, the odds of having an irreversible defect were 6.84 more likely than those in the reference group.

In concordance with this study, Cho *et al*. didn't find a significant difference in myocardial perfusion scintigraphy outcomes among symptomatic and asymptomatic patients concerning dyspnea (25). However, in the current study, although hyperlipidemia had weak positive correlation with MPS outcomes, it did have statistically significant effect on SMS and SSS.

Although the correlation between ECG abnormalities in coronary artery diseases and MPS outcomes is not well studied (6), Patel *et al*. found that impaired LVEF was strongly associated with significant angina-associated limitation of activities, however, their study didn't find a link between reversibility of perfusion defect and patient-reported severity of angina symptoms. In contrary, the current study showed baseline major ECG findings have a significantly strong negative correlation with size, reversibility of the perfusion defect, semiquantitative perfusion scores and LVEF as well. The contrasting conclusions from the previous authors, may have stemmed from them analysing data from PET based perfusion imaging, inclusion of multi-centers and having fourfold more sample size.

According to the results, compared to normal or minor ECG findings, the odds of having an abnormal summed stress score was 16.9 more likely for patients with major baseline ECG abnormalities. For the same group, the odds of having an abnormal left ventricular ejection fraction and large perfusion defects were 4.19 and 23 times more likely than the reference group. In this study, a significant effect was not observed between the reversibility of perfusion defect and baseline ECG findings.

Similarly, a study done in Iran by Hekmat al., found that the presence of baseline ECG findings such as fragmented QRS is associated with perfusion defect findings on myocardial perfusion scans. They concluded that this inexpensive and readily available investigation can help stratify patients who may benefit from subsequent scintigraphy and intervention (21).

In concordance with the current study, Thomas and Thagav found that Baseline ST and T wave abnormalities predict a greater frequency of abnormal MPS and when abnormal, greater ischemic extent than in those with a normal baseline ECG (16).

Furthermore, Rahman *et al*. concluded that QRS changes on baseline ECG are highly sensitive and reasonably specific for detecting perfusion defects in MPS stress tests and significantly more sensitive than analysis of conventional ST segments (26). However, in this study the effect observed between baseline major ECG findings and reversibility of perfusion defect was not statistically significant.

The current study found that inducible ischemia on ECG during stress tests has a strong positive association with perfusion scores such as summed motion score, summed stress score, reversibility, and left ventricular ejection fraction.

For patients with inducible ischemia, the odds of having reversible perfusion defect were 19% less likely than those without those features. The odds of having an abnormal summed stress score, abnormal summed motion score, and abnormal left ventricular ejection fraction were 2.4,3.1, and 4.2 times more likely for the inducible ischemia category respectively.

Similarly, Akil *et al*. found out stress-induced ST elevation, with or without concomitant ST depression, is predictive of the presence, amount, and location of myocardial ischemia assessed by MPS (14). Contrary to this study, Thakur *et al*. concluded that ischemic changes during stress were not correlated with significant ischemia on MPS (24). The current study didn’t find statistically significant effect between inducible ischemia and size of perfusion defect.

In this study, metabolic equivalent scores during stress tests had a significant negative correlation with myocardial perfusion scores. According to the results, as the metabolic equivalent score increased by one unit the odds of having an irreversible perfusion defect decreased by 26%. Furthermore, the odds of having a large perfusion defect were 16.4% less likely for a unit increase in metabolic score. In this study, as the metabolic equivalent score increased by unit, the odds of having an abnormal LVEF decreased by 54%.

In concordance with the current study, Bourque *et al*. performed prospective analysis and found out that patients with a metabolic equivalent score of 10 or more had negligible features of ischemia on myocardial perfusion scintigraphy especially if they didn’t have inducible ischemia during stress exam (22,23).

Similarly, Loffler *et al*. advocated the independent use of metabolic score for prognostic purposes and forwarded a strategy for the provisional use of myocardial perfusion scintigraphy only for patients with low functional capacity and/or abnormal stress ECG to minimize cost and radiation exposure in patients with high functional capacity and negative for inducible ischemia on ECG (5).

The predictive value of these factors which can be identified before myocardial scintigraphy can provide relevant diagnostic and prognostic information which subsequently can be utilized for patient risk stratification, to identify scintigraphy targets for coronary artery disease, and selection of different management strategies.

8. Conclusion

This study has underlined the importance of understanding the relationship between MPS outcomes and patient-reported symptoms as well as baseline ECG abnormalities by providing statistically significant predictive values among the variables evaluated.

The findings of this study showed that there is a significant correlation between angina severity in terms of limitation of daily activities, baseline electrocardiogram abnormalities and findings during stress exams, and MPS parameters. This data can be utilized to stratify high-risk patients make clinically sound decision in terms of the need for urgent imaging or therapeutic intervention.

By assessing the impact of specific variables on MPS, this study has pointed out possible entry points for future longitudinal studies which can assess validity or the true effect of such pre-imaging factors.

The current study has shown that it is feasible to predict the prevalence of abnormal myocardial perfusion parameters especially the size of perfusion defect and reversibility by using clinical factors as well as ECG abnormalities, although further validation is required.

Further understanding of the independent prognostic impact of clinical and exercise ECG features can lead to efficient utilization of radionuclide-based myocardial perfusion scintigraphy and reduce patient exposure to unnecessary radiation.

9. Recommendations

Optimal test selection for symptomatic patients with suspected CAD requires a patient-centred approach factoring in the risk to benefit ratio and cost-effectiveness.

The decision-making by the nuclear medicine physician should follow a holistic approach by extrapolating the data from MPS perfusion parameters, patient clinical evaluation, and complementary ECG findings.

The results of this study are plagued by the inherent shortcomings of retrospective designs and the need to conduct a prospective study with a longitudinal design to appreciate the true impact of the aforementioned variables on myocardial perfusion parameters and to identify confounding factors. The effects observed in this single-centre study with small sample should be validated in prospective, large sample, multicentre studies.

10. Strength and limitations

10.1. Strength

To the best of the researcher's knowledge, this is the first study to evaluate the strength of the association of factors with specific MPS parameters.

The cross-sectional study design is the best choice for studies constrained by time, space, and resources to collect secondary data.

All myocardial perfusion scintigraphy interpretation was performed by a single nuclear scintigraphy specialist and which eliminated any possibility for inter-rater variability in this study as MPS variables may be affected by the interpretive accuracy of the reading physician.

To ascertain the quality of data collected, the researcher performed a pilot study and also vigorously crossmatched each patient database with the checklist for completeness of records and necessary adjustment was made.

Potential confounder control was attempted by using logistic regression analysis.

10.2. Limitations

Reliance was placed on the accuracy of available medical records and a piece of important information may not have been collected in the first place.

Furthermore, the study is limited by referral bias or selection bias because the majority of patients were referred for MPS based on the presence of symptoms and had multiple CAD risk factors, and not randomly selected from the population.

Impact and generalisability may be limited due to the single-centre nature of this study.

Unlike multi-centre studies, they may also suffer from a lower sample size, poor control over the exposure factor, covariates, and potential confounders which may lead to spurious associations.

The current study was based on SPECT which might be hampered by poor image quality and false positive studies due to attenuation, especially in obese patients resulting in substandard interpretation. Furthermore, SPECT MPS has been shown to underestimate disease extent and severity when there is a balanced flow reduction especially in multivessel abnormalities. This particular study faced time constraint challenges in both the data collection and analysis phases.

11. References

1. Ora M, Gambhir S. Myocardial Perfusion Imaging: A Brief Review of Nuclear and Nonnuclear Techniques and Comparative Evaluation of Recent Advances. Indian J Nucl Med. 2019;34(4):263–70.

2. Shashu BA. The Management of Coronary Artery Disease in Ethiopia: Emphasis on Revascularization. Ethiop J Health Sci. 2021 Mar;31(2):439–54.

3. Taywade SK, Ramaiah VL, Basavaraja H, Venkatasubramaniam PR, Selvakumar J. Prevalence of ECG changes during adenosine stress and its association with perfusion defect on myocardial perfusion scintigraphy. Nucl Med Commun. 2017 Apr;38(4):291–8.

4. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. J Cell Physiol. 2019 Aug;234(10):16812–23.

5. Löffler AI, Perez MV, Nketiah EO, Bourque JM, Keeley EC. Usefulness of Achieving ≥ 10 Metabolic Equivalents (METS) with a Negative Stress Electrocardiogram to Screen for High-Risk Obstructive Coronary Artery Disease in Patients Referred for Coronary Angiography after Exercise Stress Testing. Am J Cardiol. 2018 Feb 1;121(3):289–93.

6. Patel KK, Patel FS, Bateman TM, Kennedy KF, Peri-Okonny PA, McGhie AI, et al. Relationship Between Myocardial Perfusion Imaging Abnormalities on Positron Emission Tomography and Anginal Symptoms, Functional Status, and Quality of Life. Circulation: Cardiovascular Imaging. 2022 Feb;15(2):e013592.

7. Russo GT, Corigliano G, Arturi F, Cavallo MG, Bette C, Mannucci E. CAPTURE: A cross-sectional study on the prevalence of cardiovascular disease in adults with type 2 diabetes in Italy. Nutrition, Metabolism and Cardiovascular Diseases. 2022 May 1;32(5):1195–201.

8. The prevalence of cardiovascular disease in Ethiopia: a systematic review and meta-analysis of institutional and community-based studies | BMC Cardiovascular Disorders | Full Text [Internet]. [cited 2023 Feb 24]. Available from: https://bmccardiovascdisord.biomedcentral.com/articles/10.1186/s12872-020-01828-z

9. Elfigih IA, Henein MY. Non-invasive imaging in detecting myocardial viability: Myocardial function versus perfusion. Int J Cardiol Heart Vasc. 2014 Dec;5:51–6.

10. Comparative Analysis between SPECT Myocardial Perfusion Imaging and CT Coronary Angiography for Diagnosis of Coronary Artery Disease - PMC [Internet]. [cited 2023 Feb 24]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3405566/

11. Barstow C. Acute Coronary Syndrome: Presentation and Diagnostic Evaluation. FP Essent. 2020 Mar;490:11–9.

12. Datta S, Singh Waila S, Ganti A, Kalayci A. Review of myocardial perfusion imaging in the state of unstable angina. Nucl Med Biomed Imaging [Internet]. 2018 [cited 2023 Feb 24];3(2). Available from: https://www.oatext.com/review-of-myocardial-perfusion-imaging-in-the-state-of-unstable-angina.php

13. Gholoobi A, Ayati N, Baghyari A, Mouhebati M, Atar B, Dabbagh Kakhki VR. Relationship between gated myocardial perfusion SPECT findings and hemodynamic, electrocardiographic, and heart rate changes after Dipyridamole infusion. Int J Cardiovasc Imaging. 2017 Jun;33(6):951–6.

14. Akil S, Sunnersjö L, Hedeer F, Hedén B, Carlsson M, Gettes L, et al. Stress-induced ST elevation with or without concomitant ST depression is predictive of presence, location and amount of myocardial ischemia assessed by myocardial perfusion SPECT, whereas isolated stress-induced ST depression is not. J Electrocardiol. 2016;49(3):307–15.

15. Assessment of activity status and survival according to the Canadian Cardiovascular Society angina classification - PMC [Internet]. [cited 2023 Feb 24]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2723031/

16. Thomas GS, Taghav A. Integrating baseline electrocardiography and myocardial perfusion imaging. J Nucl Cardiol. 2022 Apr;29(2):822–5.

17. Zimetbaum PJ, Josephson ME. Use of the electrocardiogram in acute myocardial infarction. N Engl J Med. 2003 Mar 6;348(10):933–40.

18. Wiersma JJ, Verberne HJ, ten Holt WL, Radder IM, Dijksman LM, van Eck-Smit BLF, et al. Prognostic value of myocardial perfusion scintigraphy in type 2 diabetic patients with mild, stable angina pectoris. J Nucl Cardiol. 2009;16(4):524–32.

19. ECG Diagnosis and Classification of Acute Coronary Syndromes - PMC [Internet]. [cited 2023 Feb 24]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6931956/

20. Singh A, Museedi AS, Grossman SA. Acute Coronary Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2023 Feb 24]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459157/

21. Hekmat S, Pourafkari L, Ahmadi M, Chavoshi MR, Zamani B, Nader ND. Fragmented QRS on surface electrocardiogram as a predictor of perfusion defect in patients with suspected coronary artery disease undergoing myocardial perfusion imaging. Indian Heart Journal. 2018 Dec 1;70:S177–81.

22. Bourque JM, Charlton GT, Holland BH, Belyea CM, Watson DD, Beller GA. Prognosis in patients achieving ≥10 METS on exercise stress testing: Was SPECT imaging useful? J Nucl Cardiol. 2011 Apr;18(2):230–7.

23. Bourque JM, Holland BH, Watson DD, Beller GA. Achieving an exercise workload of > or = 10 metabolic equivalents predicts a very low risk of inducible ischemia: does myocardial perfusion imaging have a role? J Am Coll Cardiol. 2009 Aug 4;54(6):538–45.

24. Thakur U, Levy S, Sivaratnam D, Herath D, Nadesapillai S, Toh H, et al. The Relationship Between Ischaemia on Myocardial Perfusion Imaging and Chest Pain or Electrocardiogram Changes During Exercise. Heart, Lung and Circulation. 2018;27:S282.

25. Cho SG, Park KS, Kang SR, Kim J, Jun HM, Cho JY, et al. Correlation of Angina Pectoris and Perfusion Decrease by Collateral Circulation in Single-Vessel Coronary Chronic Total Occlusion Using Myocardial Perfusion Single-Photon Emission Computed Tomography. Nucl Med Mol Imaging. 2016 Mar;50(1):54–62.

26. Rahman MA, Gedevanishvili A, Birnbaum Y, Sarmiento L, Sattam W, Kulecz WB, et al. High-frequency QRS electrocardiogram predicts perfusion defects during myocardial perfusion imaging. J Electrocardiol. 2006 Jan;39(1):73–81.

12. ANNEXES

12.1. Annex 1: Checklist for extraction of patient data

PART 1: Sociodemographic information

1. Patient code ___________

2. Age ___________

3. Sex of the patient

    1. Male   2. Female

4. Body mass index (Kg/m^2)

    1.<25(normal)   2.25-30(overweight)   3.>30(obesity)

5. Smoking

    1. Yes   2. No   3.Previous smoker

6. Family history of CAD

    1. Yes   2. No

PART 2: Clinical factors

1. Dyspnea

    1. Yes   2. No

2. Chest pain

    1. Typical   2. Atypical   3. Non-cardiac chest pain

3. The severity of chest pain

    1. Ordinary activity does not cause angina at all
    2. Slight limitation of ordinary activity fast walking
    3. Marked limitation of ordinary activity like walking
    4. Severe limitation at rest or minor activity

4. Comorbidities

    1. Diabetes mellitus   2. Hypertension   3. Hyperlipidemia   4. No comorbidity

PART 3: Baseline Electrocardiogram findings according to Minnesota code

1. Normal ECG

2. Minor ECG findings (Minor ST and T wave abnormalities, Isolated Q-waves abnormality)

3. Major ECG findings

    Major ST-segment and T-wave abnormalities

    Atrial fibrillation or atrial flutter

    Multiple abnormal Q waves

    Bundle branch blocks (LBBB or RBBB)

    Left ventricular hypertrophy (LVH)

PART 4: Findings during a stress test

1. Metabolic score (METscore rounded to a single digit) ________________

2. Inducible ischemia features on ECG during stress 1. Yes 2. No

PART 5: Myocardial perfusion outcomes

5.1. Perfusion outcomes

1. Reversibility of defect 1. Reversible 2. Irreversible

2. Size of the perfusion defect

    1. small (<10%) 2. Medium (10-20%) 3. Large (>20%)

4. Global perfusion score assessment

4.1. Summed stress score

1. <4 normal 2. 4-8 mildly abnormal 3. 9-13 moderately abnormal
4. >13 severely abnormal

5.2. Left ventricular function

1. Summed motion score

1. normal 2. mildly reduced 3. moderately reduced 4. significantly reduced

2. Ejection fraction:

1. Normal (50-75%) 2. Borderline (41-50%) 3. Abnormal<40%

12.2. Annex 2: Declaration

I, the undersigned declare that this thesis is my original work and has not been presented for a degree in Addis Ababa university or any other universities. I also declare that all sources of materials used for the thesis have been duly acknowledged.

Name of the candidate: **Dr. Yonas Shewangizaw**

Signature: ____________

Date of submission: __________

The thesis has been submitted for examination with my approval as university advisor.

Name of Advisors	Signature	Date
1. Dr. Senbeta Guteta	__________	_________
2. Mr. Desalegn Abeje	__________	_________