"AN ANALYTICAL CROSS-SECTIONAL STUDY TO DETERMINE THE EFFECT OF GLYCEMIC GAP AS A BIOMARKER OF SEVERITY AND OUTCOME AMONG ACUTE MYOCARD IAL INFARCTION PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE CENTRE IN CHENNAI."

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DEPARTMENT OF GENERAL MEDICINE

GOVERNMENT STANLEY MEDICAL COLLEGE, CHENNAI

MAY 2023.

CERTIFICATE BY THE INSTITUTION

This is to certify that this dissertation entitled **"AN ANALYTICAL CROSS-SECTIONAL STUDY TO DETERMINE THE EFFECT OF GLYCEMIC GAP AS A BIOMARKER OF SEVERITY AND OUTCOME AMONG ACUTE MYOCARDIAL INFARCTION PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE CENTRE IN CHENNAI"** is a bonafide work done by Dr. J.Arjun, post graduate student, Department of General Medicine, Stanley Medical College & Hospital, Chennai-600001, in partial fulfilment of the requirement for the award of degree of M.D. General Medicine (Branch-I), carried out by him under direct supervision and guidance, during the academic year 2020 – 2023.

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Introduction
INTRODUCTION Acute Myocardial Infarction (AMI) is a common cardiac emergency with substantial morbidity and mortality. Patients with diabetes mellitus are more prone to develop coronary heart disease and are more likely to have multivessel coronary artery disease compared to those without diabetes.1 Hyperglycaemia is a frequent observation in

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ABBREVIATIONS

DM	Diabetes Mellitus
ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
STEMI	ST Elevation Myocardial Infarction
NSTEMI	Non- ST Elevation Myocardial Infarction
HbA1c	Glycosylated Haemoglobin
ABG	Admission Blood Glucose
eAG	Estimated Average Glucose
ADAG	A1c Derived Average Glucose
GG	Glycemic Gap
SIH	Stress Induced Hyperglycemia
ADA	American Diabetes Association
ACC	American College of Cardiology
AHA	American Heart Association
ESC	European Society of Cardiology
ECG	Electrocardiogram
ECHO	Echocardiogram
CAG	Coronary Angiogram

PCI	Percutaneous Coronary Intervention
AKI	Acute Kidney Injury
ARF	Acute Respiratory Failure
AF	Atrial Fibrillation
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia
VPC	Ventricular Premature Complexes
CABG	Coronary Artery Bypass Grafting
HFrEF	Heart Failure with reduced Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
LVEF	Left Ventricular Ejection Fraction
JVP	Jugular Venous Pressure
TNF alpha	Tumour Necrosis Factor alpha
IFN gamma	Interferon gamma
IL 6	Interleukin 6
HPA	Hypothalamo Pituitary Adrenal axis
AGE	Advanced Glycation End products
CBG	Capillary Blood Glucose
MACE	Major Adverse Cardiovascular Events
CAD	Coronary Artery Disease

"AN ANALYTICAL CROSS-SECTIONAL STUDY TO DETERMINE THE EFFECT OF GLYCEMIC GAP AS A BIOMARKER OF SEVERITY AND OUTCOME AMONG ACUTE MYOCARDIAL INFARCTION PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE CENTRE IN CHENNAI. "

ABSTRACT

BACKGROUND:

Hyperglycemia is a common observation in acute myocardial infarction patients presenting to the emergency department. Stress Induced Hyperglycemia (SIH) is an acute response that has been associated with adverse outcomes in many critical illnesses including acute myocardial infarction. The Admission Blood Glucose (ABG) level may not be a true reflector of the stress-induced rise in blood glucose levels, as it can be influenced by the underlying glycaemic status of patients with diabetes mellitus. Recently, glycemic gap has emerged as a novel glycemic indicator and is defined as the difference between the ABG and ADAG (i.e. A1c Derived Average Glucose which is the estimated three month average blood sugar value derived from the HbA1c using the formula eAG = 28.7 × HbA1c–46.7). The glycemic gap has been studied in various critical illnesses such as community acquired pneumonia, sepsis, acute ischaemic stroke and intracranial haemorrhage but studies in acute MI are very few in number.

OBJECTIVES:

To analyse the effect of the glycemic gap on the severity and outcome of Acute Myocardial Infarction in patients with Diabetes Mellitus admitted in a tertiary care centre.

MATERIALS AND METHODS:

This is a prospective cross-sectional study where 100 diabetes mellitus patients who were admitted with acute myocardial infarction were included in the study. The study spanned over a period of 1 year. The Glycemic gap was calculated for the patients. Patients were classified into two groups based on the glycaemic gap values with one group of patients having a high glycaemic gap and the other group with a low glycaemic gap. The severity of MI and the outcome were assessed in both the groups and compared.

RESULTS:

Patients with an elevated glycemic gap presented with a higher Killip class and were found to have higher risk of adverse outcomes such as cardiogenic shock, acute respiratory failure, a lower LV ejection fraction, longer duration of hospital stay and higher mortality rate when compared to those with a low glycemic gap.

CONCLUSION:

The glycemic gap is superior to admission CBG as well as HbA1c values in predicting mortality in patients with acute MI. The glycemic gap thus provides additional prognostic information beyond that provided by conventional risk factors in diabetic patients presenting with acute MI.

KEY WORDS: Acute MI, Stress Induced Hyperglycemia, Glycemic gap.

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Introduction

INTRODUCTION

Acute Myocardial Infarction (AMI) is a common cardiac emergency with substantial morbidity and mortality. Patients with diabetes mellitus are more prone to develop coronary heart disease and are more likely to have multivessel coronary artery disease compared to those without diabetes.[1] Hyperglycaemia is a frequent observation in acute myocardial infarction patients presenting to the emergency department.[2] An independent predictor of long-term mortality in individuals with or without documented diabetes is the admission blood glucose level following AMI. The hyperglycaemia may be a reflection of the acute stress response or the underlying chronic glucometabolic state in patients with diabetes mellitus.

Stress Induced Hyperglycemia (SIH) is an acute response that is commonly observed in many critical illnesses. It has been reported in critical conditions such as community acquired pneumonia, sepsis, burns injuries, polytrauma, major surgeries and acute myocardial infarction.[3] SIH creates a state of insulin resistance through various mechanisms leading on to deleterious effects. The presence of hyperglycemia in AMI results in a prothrombotic and inflammatory state causing depressed myocardial contractility and resulting in higher short- and long-term mortality.

SIH has been shown to be an independent risk factor for mortality in critically ill patients without diabetes. However, in patients with diabetes mellitus, it is necessary to consider pre-existing glycaemic status when investigating the relationship between SIH and mortality. Therefore the parameter glycaemic gap is used to assess

whether the gap between the Admission Blood Glucose(ABG) value and the A1c Derived Average Glucose(ADAG) could be a predictor of adverse outcomes in patients with diabetes. An international multi-center study termed A1C-derived average glucose (ADAG) study demonstrated a strong correlation between glycosylated haemoglobin (HbA1c) and mean plasma glucose levels in the preceding three months, allowing long-term average glucose levels to be determined using HbA1c values.[4] HbA1c values were converted to the estimated Average Glucose(eAG)/ A1c Derived Average Glucose (ADAG) levels for the previous three months by using the equation ADAG = [(28.7 * HbA1c) – 46.7].

The glycaemic gap is calculated by subtracting the ADAG value from the admission blood glucose (ABG) value. It indicates the changes in blood glucose levels during the current illness. Recent studies have shown that an elevated glycaemic gap is associated with worse outcomes in patients with acute ischemic stroke, intracranial haemorrhage, community acquired pneumonia and COVID-19 but studies pertaining to acute MI are limited. Many studies have been conducted on the impact of admission hyperglycaemia on the short-term as well as long-term outcomes of acute myocardial infarction. However, there is scarce literature available regarding the effect of the glycaemic gap on the severity and outcome of AMI. The aim of this study is to explore the correlation between the glycaemic gap and adverse outcomes in diabetes mellitus patients presenting with acute MI.

Aim & Objectives

AIM AND OBJECTIVES

AIM:

To analyse the effect of the glycaemic gap on the severity and outcome of Acute Myocardial Infarction in patients with Diabetes Mellitus.

OBJECTIVES:

- To determine the glycaemic gap in diabetic patients presenting with acute myocardial infarction.
- To explore the correlation between the glycaemic gap and adverse outcomes among acute myocardial infarction patients with diabetes mellitus.

Review of Literature

REVIEW OF LITERATURE

ACUTE MYOCARDIAL INFARCTION:

Ischemic heart disease encompasses a spectrum of conditions ranging from chronic stable angina to acute coronary syndrome. Acute coronary syndrome is the most frequent cause of death and disability globally. The term Acute Coronary Syndrome includes the diagnoses of ST-segment Elevation Myocardial Infarction (STEMI), non-ST-Segment Elevation Myocardial Infarction (NSTEMI) and Unstable Angina. Acute myocardial infarction is characterized by acute myocardial injury due to myocardial ischemia.[5] Acute myocardial infarction with or without ST-segment elevation (STEMI or NSTEMI respectively) are characterized by elevation of cardiac biomarkers implying myocardial necrosis. Unstable angina is present in patients with symptoms suggestive of myocardial ischemia without elevation in cardiac biomarkers with or without ECG changes suggestive of myocardial ischemia.

DEFINITION OF ACUTE MYOCARDIAL INFARCTION:

The Fourth Universal Definition of MI (2018) proposed by The Joint Task Force of the European Society of Cardiology, the American College of Cardiology, the American Heart Association and the World Heart Federation defined acute MI as acute myocardial injury detected with the help of abnormal cardiac biomarkers in a setting consistent with acute myocardial ischemia.[5]

Myocardial Injury – Myocardial injury has been defined as elevated cardiac troponin values with at least one value above the 99th percentile of the upper reference limit. Myocardial injury can be acute or chronic. Acute myocardial injury is characterized by rise and/or fall of cardiac troponin values whereas chronic myocardial injury is characterized by elevated troponin values but no typical rise and fall demonstrable.[5]

CLASSIFICATION:

Five types of MI have been defined as below:[5]

- Type 1 – MI due to acute athero-thrombotic occlusion of a coronary artery usually precipitated by plaque disruption.
- Type 2 – MI due to ischemia as a result of oxygen supply-demand mismatch.
- Type 3 - Patients who suffer sudden cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation, but expire before blood samples for biomarkers could be obtained, or before elevations in cardiac biomarkers could be detected, or MI was detected by autopsy examination.
- Type 4 – post Percutaneous Coronary Intervention (PCI) MI :
    - Type 4a – PCI related MI
    - Type 4b – Stent / scaffold thrombosis associated with PCI
    - Type 4c – In-stent restenosis
- Type 5 – post Coronary Artery Bypass Grafting (CABG) MI.

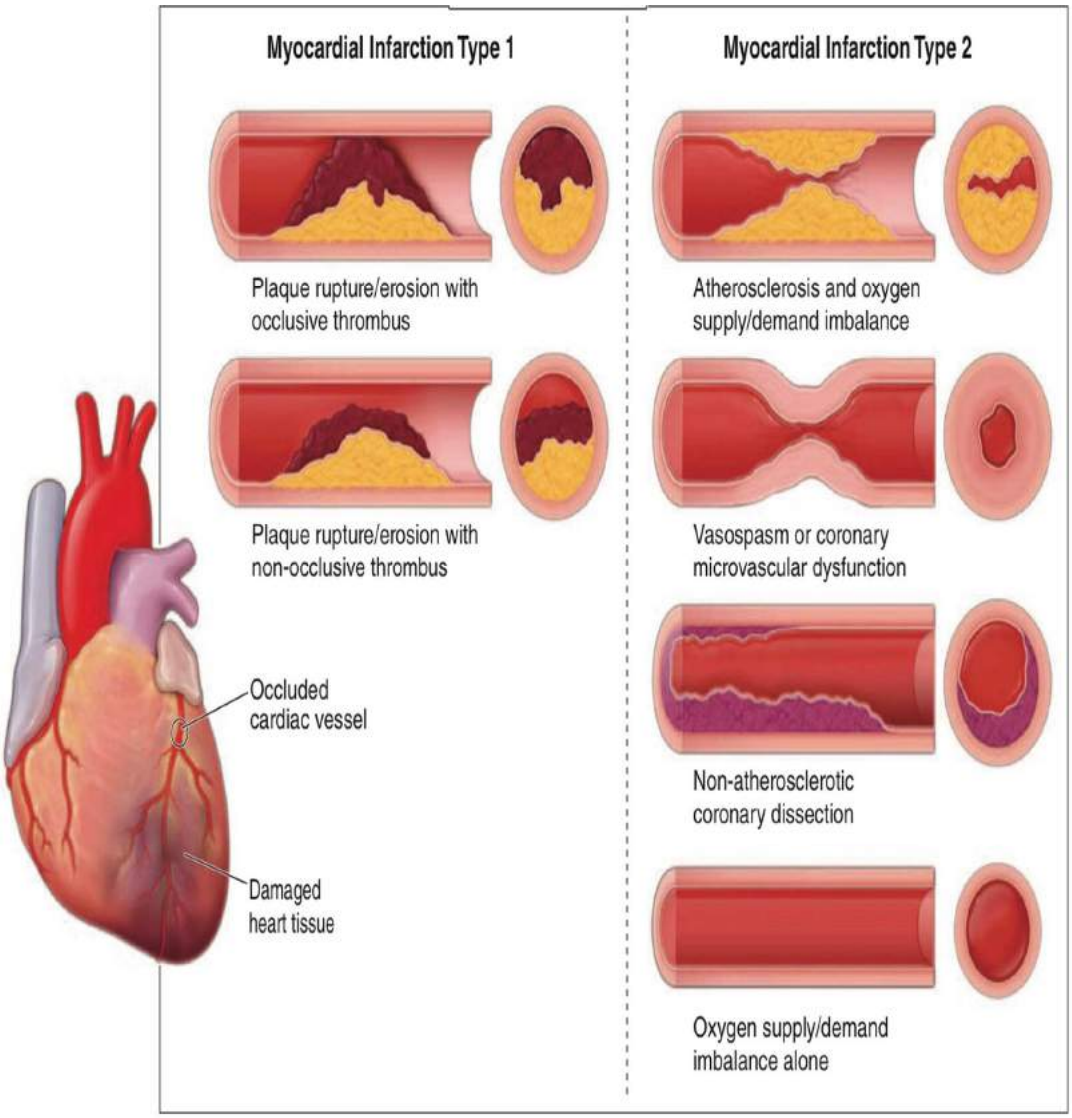


Figure: Depiction of Type 1 and Type 2 myocardial infarction. Type 1 MI occurs in patients with atherosclerotic plaque rupture or erosion and subsequent thrombosis, whereas type 2 MI occurs as a result of myocardial oxygen supply and demand mismatch in the setting of an acute illness causing hypoxia, hypotension or tachyarrhythmias.

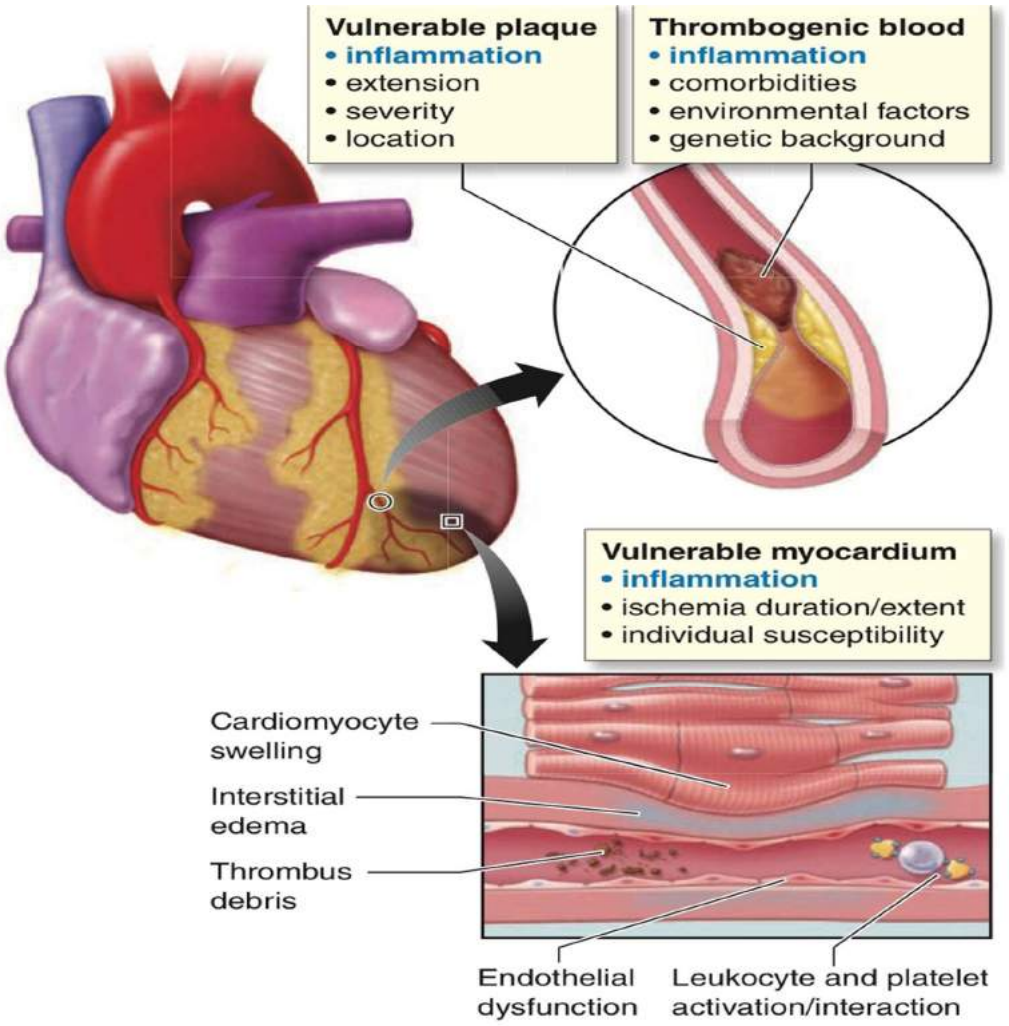
EPIDEMIOLOGY

Despite advances in diagnosis and management, STEMI remains a significant public health problem in the developed world and is on the rise in developing countries.[6] Approximately 5,50,000 new episodes and 2,00,000 recurrent episodes of acute myocardial infarction occur annually.[7] The relative incidence of NSTEMI is on the rise due to the increasing detection of myocardial necrosis by the use of high sensitivity cardiac troponins and also due to the increasing burden of various comorbidities such as diabetes mellitus, obesity and chronic kidney disease in an aging population. On the other hand, STEMI is declining due to the widespread use of aspirin and statins. The in-hospital mortality rate after admission for AMI has declined from 10% to 5%. The 1-year mortality rate after an AMI is approximately 15%. The global burden of acute myocardial infarction has shifted to low and middle income countries which contribute to about 80% of deaths from cardiovascular disease worldwide.[8] According to the findings of the Global Burden of Disease study, India has an age-standardized CVD death rate of 272 per 100,000 people, significantly higher than the global average of 235.[9] Indians are affected by CVDs ten years earlier than the western population. The highest rates of coronary artery disease (CAD) are known to occur in Indians, yet the usual risk factors are unable to account for this elevated risk. In India, diabetic patients have a CAD prevalence of 21.4%, while non-diabetics have a prevalence of 11%. Compared to other ethnic groups, Indians are 2-4 times more likely to get hospitalised for complications of CAD.[10]

PATHOPHYSIOLOGY

Almost all acute coronary syndromes result from underlying atherosclerosis of the coronary arteries with superimposed coronary thrombosis which is caused by rupture or erosion of an atherosclerotic lesion. STEMI occurs when a coronary artery thrombus develops rapidly at a site of vascular injury and the coronary blood flow decreases abruptly. This injury is facilitated by factors such as hypertension, lipid accumulation and cigarette smoking. A totally obstructing thrombus typically leads to STEMI.[11] The cellular effects of ischemia begin within seconds of onset of the hypoxia with the loss of adenosine triphosphate (ATP) production. Myocardial relaxation-contraction is deranged and irreversible cell injury begins as early as 20 minutes. Necrosis is usually complete by 6 hours unless an extensive collateral circulation is present or reperfusion occurs. Plaque rupture is the most common underlying pathology of culprit coronary lesions accounting to 60 to 70 % of cases.[12] Coronary plaques prone to rupture are the ones with a rich lipid core and a thin fibrous cap. Other histopathologic features of vulnerable plaques include increased macrophage infiltration, reduced smooth muscle content, spotty calcification and neovascularisation of plaque. Plaque erosion is the second most common pathology and is seen especially in young females. Calcific nodules can be seen in upto 5 percent of cases particularly elderly patients with a long standing history of coronary artery disease. Initially, a platelet monolayer forms at the site of the disrupted plaque. Various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation. After agonist stimulation of platelets, thromboxane A2, which is a potent local vasoconstrictor is released. Further platelet activation occurs, and potential resistance to fibrinolysis develops. The coagulation cascade is activated on

exposure of tissue factor in damaged endothelial cells at the site of the disrupted plaque. Factors VII and X are activated, ultimately leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to fibrin. The culprit coronary artery eventually becomes occluded by a thrombus containing platelet aggregates and fibrin strands. In a few cases, STEMI may be the result of coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm and a wide variety of systemic inflammatory diseases.[13]



NSTEMI is caused by a mismatch between myocardial oxygen supply and demand that lead to coronary arterial thrombosis as a result of one of the processes mentioned below:

1. disruption of an unstable atheromatous plaque as a result of plaque rupture, erosion or a calcified nodule, which may be driven by inflammation. Patients with NSTE-ACS frequently have multiple such plaques that are at risk of disruption. Although plaque rupture remains the commonest cause of thrombosis, plaque erosion is increasingly being recognised.[14]
2. coronary arterial vasoconstriction
3. gradual narrowing of the lumen of an epicardial coronary artery as a result of progressive atherosclerosis and
4. increased myocardial oxygen demand created by conditions such as tachycardia, fever, thyrotoxicosis in the background of a fixed epicardial coronary obstruction.

Coagulation necrosis and contraction band necrosis are distinctive features, frequently accompanied by patchy myocytolysis near the infarct's edge. Myocytes die in the infarct zone during the acute phase of MI, which is followed by inflammation, the removal of necrotic debris, healing, and eventually scar formation.[13]

CLINICAL FEATURES:

The most common presenting complaint in patients with acute myocardial infarction is chest pain. The pain is deep and visceral, usually described by the objectives- heavy, squeezing or crushing. Occasionally, it is also described as a stabbing or burning pain. The pain is similar in character to the discomfort of angina pectoris but has at least one of three typical features –

- occurs at rest(or with minimal exertion),
- is usually more severe, and
- lasts longer.

The pain is usually substernal and on occasion radiates to the arms. Less common sites of radiation of the pain include the abdomen, back, lower jaw, and neck. The pain of AMI can radiate as high as the occipital area but not below the umbilicus. It is often accompanied by nausea, vomiting, diaphoresis, dyspnoea, anxiety, weakness or a sense of impending doom. Contrary to angina pectoris, the discomfort may start while the patient is at rest, but unlike angina, it typically does not go away when activity is stopped. The primary causes of the commonly held misconception that indigestion exists are the frequent placement of the discomfort beneath the xiphoid and epigastrium and the patients' disbelief that they may be having a heart attack. STEMI pain might mimic the discomfort of acute pericarditis, pulmonary embolism, acute aortic dissection, costochondritis, and gastrointestinal conditions. Patients with STEMI do not experience pain radiating to the trapezius, and this may be a helpful indicator that pericarditis is the cause.[13]

However, pain is not always present in patients with STEMI. The proportion of painless STEMIs is higher in patients with diabetes mellitus and in the elderly. Dyspnoea, syncope, pain limited to the epigastrium, nausea and fatigue represent "anginal equivalents." These atypical findings are more prevalent in the elderly, females and in patients with diabetes mellitus, CKD, or dementia and can lead on to under recognition, undertreatment and worse outcomes.

PHYSICAL FINDINGS:

Most of the patients are restless and anxious. Pallor can be present which is brought on by perspiration and coolness of the extremities. Patients with an anterior wall infarction may show evidence of sympathetic nervous system hyperactivity (tachycardia and/or hypertension), and those patients with an inferior infarction may have manifestations of parasympathetic hyperactivity (bradycardia and/or hypotension). Patients with large territories of myocardial ischemia may present with an audible third and/or fourth heart sound or pulmonary rales.[15] Other signs of ventricular dysfunction include reduced intensity of the first heart sound and paradoxical splitting of the second sound. A transient mid-systolic or late systolic apical systolic murmur may be present if there dysfunction of the mitral valve apparatus. A pericardial friction rub may be heard in patients with transmural infarction at some point in the course of the illness.[13] Potential precipitating factors of ACS, such as fever, tachycardia, profound bradycardia, resistant hypertension, thyroid disease, and gastrointestinal (GI) bleeding can be

identified occasionally. Tenderness of the chest wall, localisation of the pain with a single fingertip or reproduction of the pain on palpation of the chest are pointers which denote that the pain is unlikely to be due to ischemia.

ELECTROCARDIOGRAM:

The ECG is an essential part of the diagnostic workup of patients with suspected ACS. A standard 12 lead ECG should be acquired and interpreted promptly (i.e., target within 10 minutes) of first medical contact. Persistent new convex ST-segment elevation, especially when associated with reciprocal ST-segment depression reflects STEMI. STEMI can be differentiated from pericarditis or early repolarisation syndrome with the help of reciprocal changes. Serial or continuous ECG monitoring should be done in patients with persistent symptoms with a nondiagnostic initial ECG and also to determine the reperfusion or re-occlusion status.[16] Reperfusion is generally associated with a prompt reduction in ST-segment elevation.

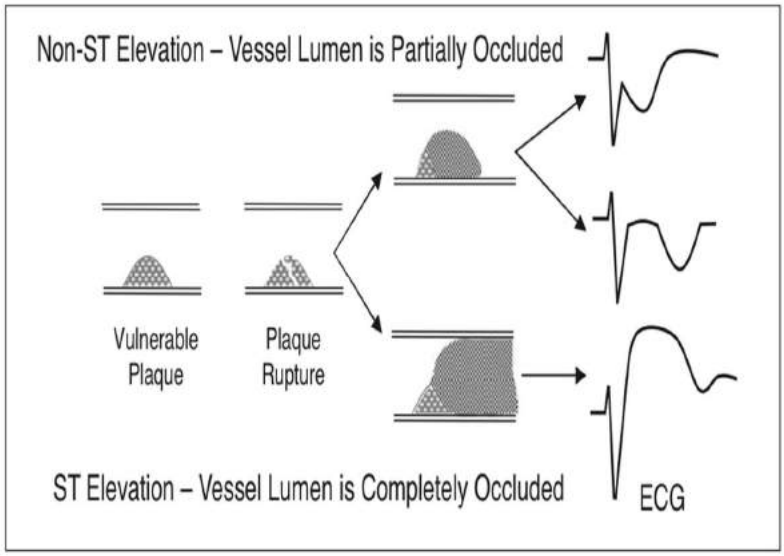


Figure 23.1: Electrocardiogram Changes of Acute Coronary Syndrome. Complete occlusion of the vessel lumen by a thrombus causes ST elevation whereas partial occlusion of the vessel lumen will result in ST depression, T-wave inversion, or other less-specific ST and T-wave abnormalities.

Table 2. Electrocardiographic Manifestations Suggestive of Acute Myocardial Ischemia (In the Absence of Left Ventricular Hypertrophy and Bundle Branch Block)
ST-elevation
New ST-elevation at the J-point in 2 contiguous leads with the cut-point: ≥1 mm in all leads other than leads V_2–V_3 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.*
ST-depression and T wave changes
New horizontal or downsloping ST-depression ≥0.5 mm in 2 contiguous leads and/or T inversion >1 mm in 2 contiguous leads with prominent R wave or R/S ratio >1.
*When the magnitudes of J-point elevation in leads V_2 and V_3 are registered from a prior electrocardiogram, new J-point elevation ≥1 mm (as compared with the earlier electrocardiogram) should be considered an ischemic response. For bundle branch block, see section below.

Intraventricular bundle branch blocks, arrhythmias, atrioventricular conduction delays, and decrease of precordial R wave amplitude are further ECG findings in acute myocardial ischemia.[5]

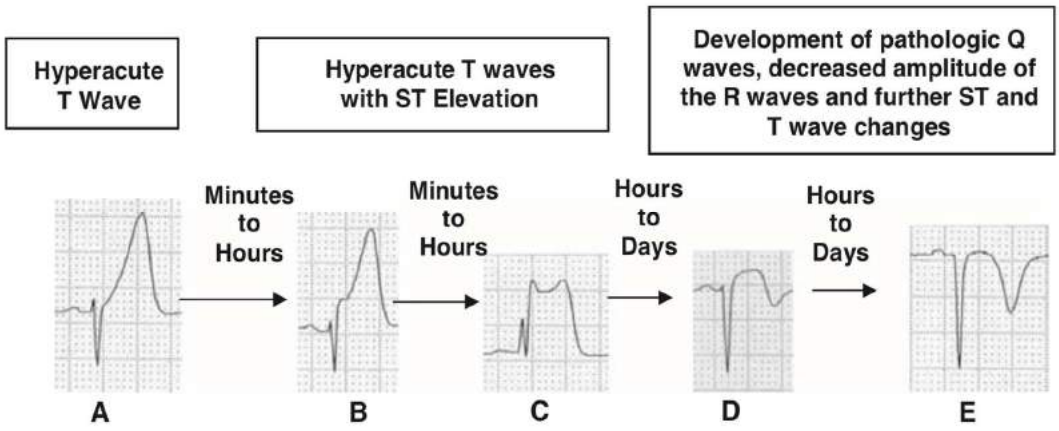


Figure 23.5: ST Elevation Myocardial Infarction (MI). Giant or hyperacute T waves mark the area of ischemia **(A–C)** followed by ST elevation **(B, C)**, diminution of the size of the R wave **(D)** or development of pathologic Q waves **(E)** and inversion of the T waves **(D, E)**. The evolution of ST elevation MI from hyperacute T waves to the development of pathologic Q waves may be completed within 6 hours after symptom onset or may evolve more slowly for several days.

SUPPLEMENTAL LEADS:

Supplemental leads should be deployed with a low threshold in patients presenting with ischemic chest pain and a nondiagnostic initial ECG. Ischemia in the left circumflex arterial territory is often overlooked as it is the least represented on the ECG.[18] Isolated ST-segment depression ≥0.5 mm in leads V_1–V_3 may denote left circumflex occlusion and in such cases posterior leads should be recorded at the fifth intercostal space (V_7 at the left posterior axillary line, V_8 at the left mid-scapular line, and V_9 at the left paraspinal border). A cut-off point of 0.5 mm ST elevation has been recommended in leads V_7–V_9. ST-segment depression in leads V_1–V_3 may also be suggestive of inferobasal myocardial ischemia (previously termed as posterior infarction), particularly when the terminal T wave is positive. In patients with inferior wall and suspected right ventricular infarction, leads aVR or V_1 may denote ST-segment elevation ≥1 mm. Prompt recording of right precordial leads V_3R and V_4R should be

done, since ST-elevation ≥0.5 mm (≥1 mm in men <30 years old) yields supportive criteria for the diagnosis.[17]

LABORATORY TESTING:

CARDIAC BIOMARKERS:

The preferred biomarkers for identifying myocardial necrosis and differentiating between NSTE-ACS and UA are cardiac-specific troponins I(cTnI) and T(cTnT). They are part of the contractile apparatus of the myocardial cells and are thus almost exclusively expressed in the heart. Elevations in cTnI values have not been shown to occur following injury to non-cardiac tissues whereas the scenario is more complex with cTnT. For routine clinical usage, high-sensitivity (hs)–cTn assays are recommended. The sensitivities of different troponin assays in clinical practice vary. Hence the consensus recommendation is to define AMI by a rise in cTnI or cTnT >99th percentile of the normal range of that specific assay used.[19] Troponin values peak at around 24 hours. Elevations in cTnI can persist for 7 to 10 days after MI whereas elevations in cTnT can persist for up to 10 to 14 days because of continuous release from a degenerating contractile apparatus within necrotic myocytes. Hence they can be used for a late diagnosis of MI as well as for detecting re-infarctions. The successful recanalization of the infarct-related artery in STEMI patients results in a rapid release of cardiac troponins, which may signify reperfusion. If patients arrive very early in disease course i.e. within 2 hours, testing of troponins beyond 2 hours of admission is recommended.

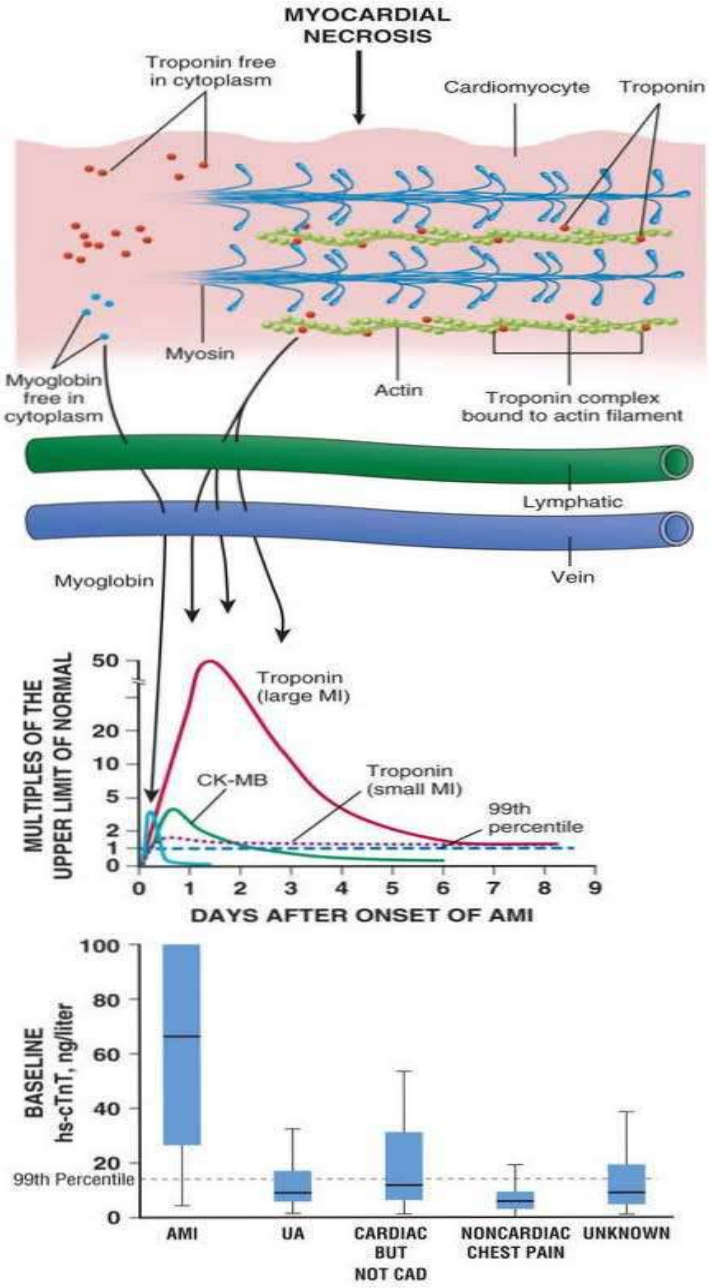


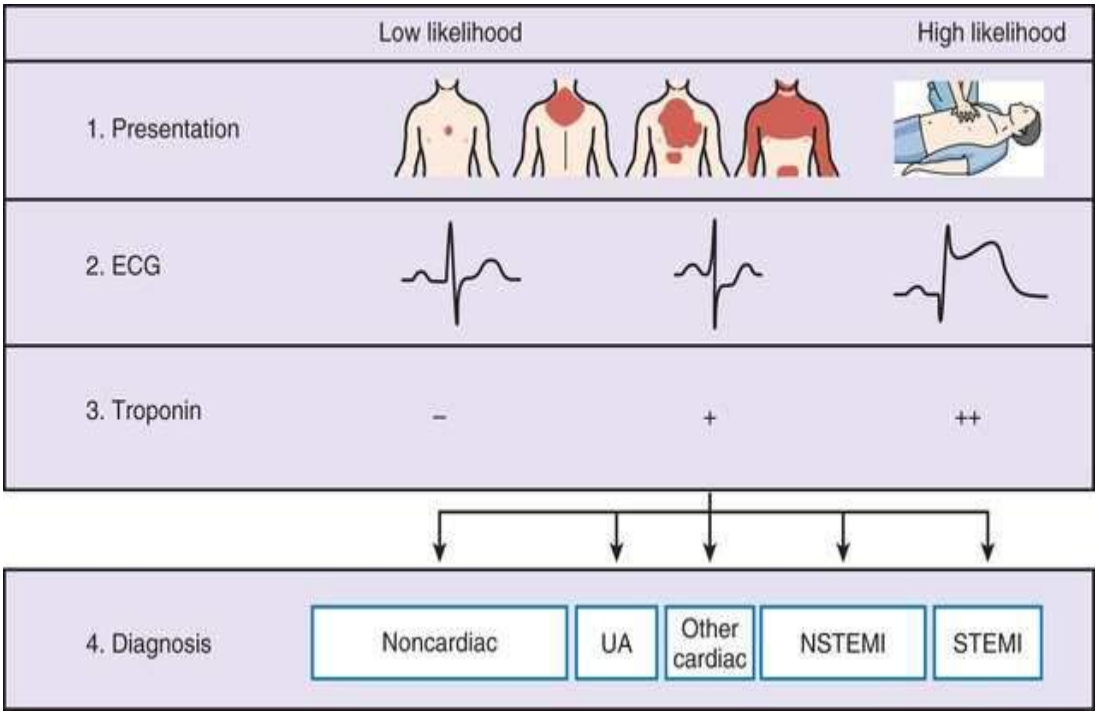
Figure: Myocardial necrosis leads to release of biomarkers into the interstitium which are first cleared by the lymphatics followed by subsequent spill over into the venous system. Markers such as myoglobin and CK are rapidly released followed by cardiac troponins.[20]

In case of non-availability of a cardiac-specific troponin, the best alternative would be CK-MB measured with a mass assay. It rises within 4–8 hours and usually returns to normal by 48–72 hours. Cardiac muscle possesses both the MB and the MM isoenzyme of CK. The MB isoenzyme of CK has the benefit over total CK in that it is significantly more selective and does not exist in appreciable concentrations in extracardiac tissue. However, the small intestine, tongue, diaphragm, uterus, and prostate are some other tissues that may have trace amounts of CK-MB. In situations involving significant skeletal muscular injury, CK-MB may increase. Hence CK-MB is less specific and sensitive compared to cardiac troponins for the detection of myocardial infarction. As with cardiac troponins, an elevated CK-MB value is defined as one which is above the 99th percentile upper reference limit. Sex-specific CK-MB values should be employed.[21]

All patients with a suspected MI should undergo measurement of cardiac troponin as early as possible at the initial presentation. The usage of conventional troponin assays permit the diagnosis of MI by obtaining measurements at initial evaluation and then 3 to 6 hours later. The usage of high-sensitivity troponin assays can decrease the interval between testing to 1 to 2 hours in those patients without diagnostic ECG changes. Testing beyond 2 hours from hospital arrival should be considered for patients who present very early (<2 hours) after symptom onset.[22]

DIAGNOSIS:

A 12 lead ECG should be obtained for all patients presenting with symptoms suggestive of myocardial ischaemia within 10 minutes of arrival. Blood samples should be sent for cardiac troponin testing(ACC–AHA class I recommendation, evidence level A). If the initial ECG is non-diagnostic it should be repeated and, when possible compared with previous recordings. It is important to monitor for dynamic ST-segment changes. Rapid diagnostic triage is performed based on the history and ECG, and the patient is classified as a case of STEMI or likely acute coronary syndrome without ST-segment elevation(NSTE-ACS) or non-ischaemic chest pain. NSTE-ACS is further subclassified into NSTEMI and unstable angina on the basis of serial biomarker testing.[23]



INITIAL MANAGEMENT:

- A brief history should be ascertained regarding the character of the pain and associated symptoms. A focused physical examination should be performed promptly to identify patients who are hemodynamically unstable and contraindications for thrombolysis looked for.
- A 12 lead ECG should be recorded and interpreted within 10 minutes of First Medical Contact (FMC) for all patients with symptoms of myocardial ischemia. If the initial ECG is non-diagnostic, the ECG should be repeated at 15- to 30-minute intervals in patients with a suspicion of ACS.[22]
- Intravenous access should be established and blood drawn for cardiac troponin (ACC–AHA class I recommendation, evidence level A).
- A cardiac monitor should be attached to the patient. A defibrillator should be readily available if the need arises as arrhythmic disturbances like VT and VF are more common in the initial period.
- Intravenous fluids should be administered in cases of right ventricular MI.
- Supplemental oxygen should be given if oxygen saturation is less than 90 % and is not routinely recommended.
- All patients should be given a loading dose consisting of:
    - Aspirin 162-325 mg non-enteric formulation (to be chewed)
    - Clopidogrel 300 mg (if > 75 years, a dose of 75 mg is given)
    - Atorvastatin 80 mg/ Rosuvastatin 20-40 mg

- Sublingual Nitrate should be given at a dose of 0.4 mg every five minutes for a total of three doses. Intravenous nitroglycerin should be administered in case of persistent ischemia, heart failure or uncontrolled hypertension. Patients should be enquired about the use of PDE-5 inhibitors in the last 24-36 hours as nitrate administration in such cases can lead on to profound hypotension. Additionally, when there is a possibility that the right ventricle is involved in case of an inferior myocardial infarction, extreme caution should be used before administering nitrates.
- Intravenous morphine (1 to 5 mg; may repeat in 5 to 30 min if necessary) can be administered for relief of persistent ischemic pain.
- An oral beta blocker should be initiated in the first 24 hours provided there are no contraindications to its administration.
- ACE inhibitors should be started for patients with a left ventricle ejection fraction < 40 % and in those with diabetes mellitus, hypertension and stable CKD.[22]

REPERFUSION THERAPY:

Coronary reperfusion is accomplished by:

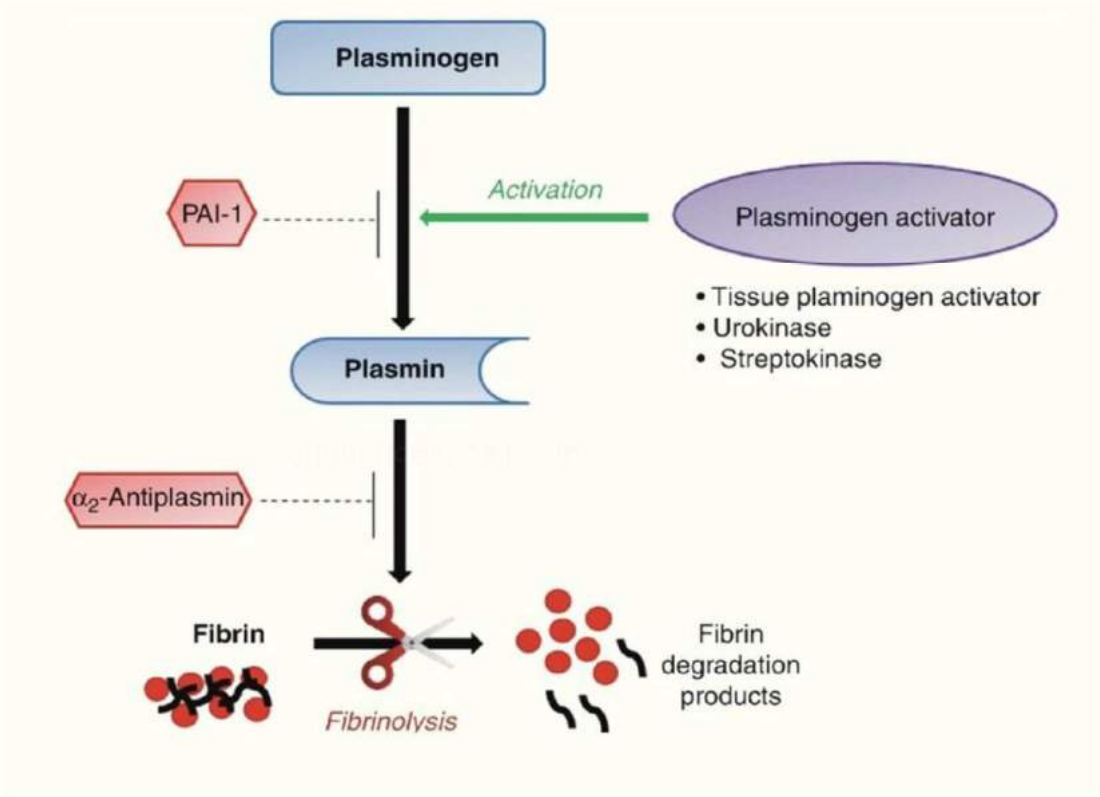
1. Fibrinolysis
2. Percutaneous Coronary Intervention (PCI)
3. Coronary Artery Bypass Grafting (CABG)

The aim of coronary reperfusion is:

- To attain normal epicardial coronary flow (TIMI 3)
- To attain normal microvascular flow (MPG3)

FIBRINOLYSIS:

Intravenous fibrinolysis can recanalize the thrombotic occlusion in patients with STEMI. When recanalized by fibrinolysis, the size of the infarct is decreased, myocardial function is improved, and both short- and long-term survival rates are increased. It is an important reperfusion strategy in scenarios where primary PCI cannot be done in a timely manner. Intravenous fibrinolytic therapy is recommended within 12 hours of onset of symptoms if primary PCI cannot be done within 120 min from STEMI diagnosis, provided there are no contraindications. Patients who are treated within the first 1 to 2 hours of symptom onset appear to have the greatest benefit with respect to long-term survival. Within 2 hours, primary PCI and fibrinolysis yield similar outcomes.[24]



The Fibrinolytic Therapy Trialists' (FTT) Collaborative Group carried out a comprehensive analysis of nine fibrinolytic therapy studies, each of which included more than 1000 patients.[25] The aggregate findings showed an 18% decrease in short-term mortality. Two trials, EMERAS (Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur) and LATE (Late Assessment of Thrombolytic Efficacy), when considered together, yield evidence that a decrease in mortality may still be observed in those patients treated with intravenous thrombolytic agents between 6 and 12 hours after symptom onset.[20] Streptokinase and Urokinase are first generation agents which are not fibrin specific whereas the latest generation agents such as alteplase, reteplase and tenecteplase are relatively fibrin specific.[26] Reteplase and Tenecteplase are bolus fibrinolytics.

	Streptokinase	Alteplase	Reteplase	TNK-t-PA
Dose	1.5 MU in 30-60 min	Up to 100 mg in 90 min (based on weight)	10 U × 2 (30 min apart) each over 2 min	30-50 mg based on weight[*]
Bolus administration	No	No	Yes	Yes
Antigenic	Yes	No	No	No
Allergic reactions (hypotension most common)	Yes	No	No	No
Systemic fibrinogen depletion	Marked	Mild	Moderate	Minimal
90-min patency rates (%)	≈50	≈75[‡]	≈75	≈75[†]
TIMI grade 3 flow (%)	32	54	60	63
Cost per dose (U.S. $)[‡]	568	2750	2750	2750 for 50 mg

Absolute
Previous intracranial haemorrhage or stroke of unknown origin at anytime
Ischaemic stroke in the preceding 6 months
Central nervous system damage or neoplasms or arteriovenous malformation
Recent major trauma/surgery/head injury (within the preceding month)
Gastrointestinal bleeding within the past month
Known bleeding disorder (excluding menses)
Aortic dissection
Non-compressible punctures in the past 24 hours (e.g. liver biopsy, lumbar puncture)
Relative
Transient ischaemic attack in the preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week postpartum
Refractory hypertension (SBP >180 mmHg and/or DBP >110 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer
Prolonged or traumatic resuscitation

Figure: Absolute and relative contraindications to fibrinolysis.

The most frequent adverse effect of fibrinolytic therapy is bleeding, and intracranial haemorrhage is the most dangerous complication.[20] An ECG should be taken 60 to 90 minutes after the administration of the fibrinolytic agent to assess for success of reperfusion. In case of successful fibrinolysis, PCI should be performed within the next 24 hours. This is termed as pharmaco-invasive PCI. In case of a failed thrombolysis, an immediate rescue PCI should be performed.

PERCUTANEOUS CORONARY INTERVENTION (PCI):

Primary PCI is the standard of care for patients with STEMI. The advantage of primary PCI over fibrinolysis is that the underlying plaque is also treated in primary PCI whereas in fibrinolysis, only the thrombus is resolved and the plaque is left behind. The chances of recurrent ischaemia are significantly lesser with primary PCI when compared to fibrinolysis. The variants of primary PCI include:

1. Pharmaco-invasive PCI : It is performed 2 to 12 hours after successful fibrinolysis.
2. Rescue PCI : It is done immediately after a failed fibrinolysis.
3. Facilitated PCI : Immediate PCI following fibrinolysis irrespective of the success of fibrinolytic therapy. It is no longer followed due to high bleeding risk.

During primary PCI, the preferred procedure is coronary stenting compared to balloon angioplasty alone.[27] Stenting with a bare-metal stent (BMS) is associated with a lower risk of reinfarction and target vessel revascularization, but it is not associated with a lower mortality rate when compared to balloon angioplasty alone. Stenting with new generation drug eluting stent (DES) is recommended over BMS for primary PCI.[28] Radial access is recommended over femoral access if PCI is done by an experienced radial operator. Routine thrombus aspiration is not advised; it is used as a bail out procedure. In situations such as cardiogenic shock, culprit-only PCI is recommended whereas in stable patients, non-culprit artery PCI before discharge is advocated.

Figure: Reperfusion strategies in the infarct-related artery and their class of recommendation according to time from symptom onset.[22]

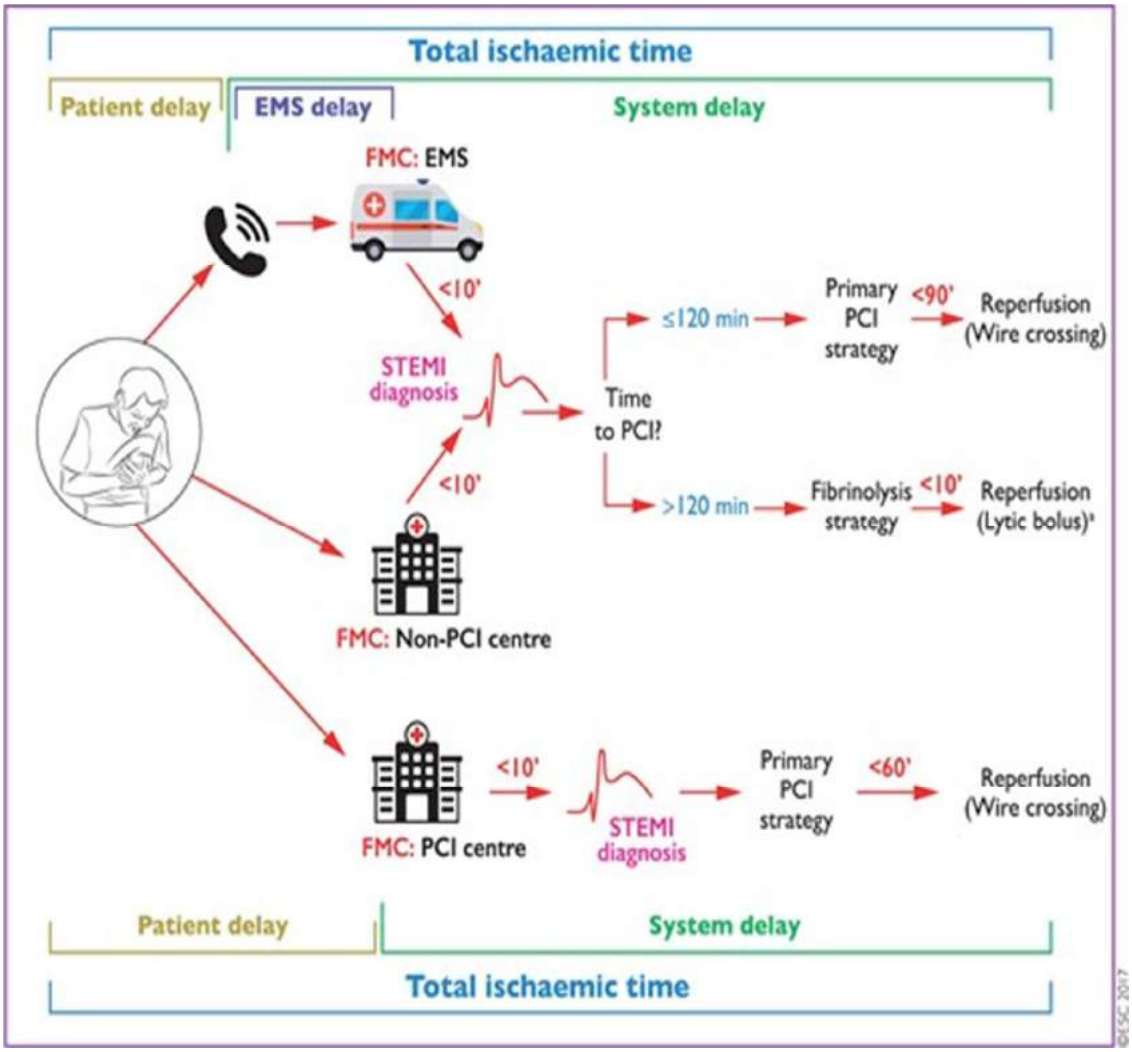


Figure: Target times in STEMI with recommended reperfusion strategies. It signifies the excellence of the system. The greatest delay is usually between the onset of symptoms and the patient's first medical contact. FMC- First Medical Contact; EMS- Emergency Medical Services; PCI- Percutaneous Coronary Intervention.

DIABETES MELLITUS AND THE HEART – SCOPE OF THE PROBLEM

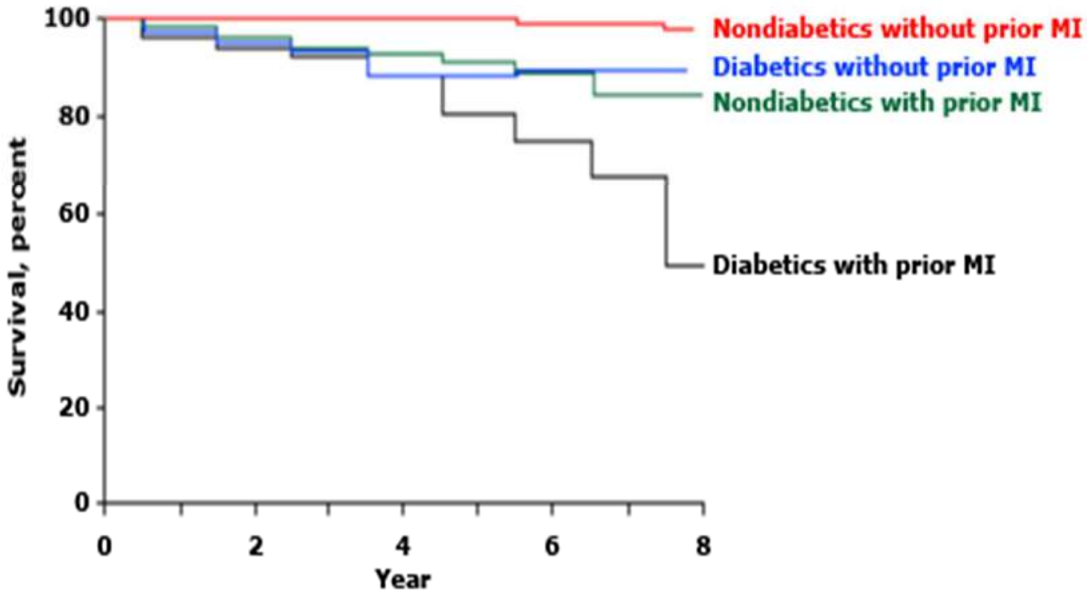
Diabetes mellitus is a leading chronic non-communicable disease and its prevalence has increased significantly globally. In 2017, the prevalence of adult T2DM accounted for 8.8% of the world population.[29] This proportion is expected to increase to 9.9% by 2045.[30] Diabetes mellitus is an under-recognised entity and it has been estimated that approximately 5% of the world's population has undiagnosed diabetes.[33] Diabetes is a significant independent risk factor for atherosclerotic coronary heart disease. Acute Myocardial infarction (MI) is the leading cause of death in patients with T2DM. Among patients with acute MI, those with diabetes have significantly increased risk of subsequent mortality and also future cardiovascular events compared to non-diabetics. There seems to be a graded increase in cardiovascular risk with increasing degree of hyperglycemia.[36] Diabetes mellitus has various adverse effects on the cardiovascular system which include:

- Coronary heart disease
- Heart failure
- Atrial Fibrillation

Patients with diabetes mellitus have also been shown to have an increased risk of other complications, including arrhythmias, cardiogenic shock, renal failure, and recurrent MI.

CORONARY HEART DISEASE IN THE PATIENT WITH DIABETES MELLITUS

Atherosclerotic cardiovascular disease (ASCVD) which includes coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease which is presumed to be of atherosclerotic origin is the leading cause of morbidity and mortality in diabetic patients. Compared to people without diabetes, those with diabetes exhibit a two- to four-fold higher risk of CHD, CV mortality, and overall mortality. Diabetic patients are more likely to have multi-vessel CHD. In addition to CHD, diabetic patients have an increased risk of stroke, cerebrovascular disease, and peripheral arterial disease. Patients with diabetes are two times more likely to experience a stroke than people without diabetes.[39] Patients with diabetes experience worse outcomes following acute MI than patients without diabetes, especially in women.



MECHANISMS IMPLICATED:

In recent years, our understanding of the processes that are responsible for an increased incidence of MI in people with diabetes has greatly expanded. Traditional cardiovascular risk factors such as obesity, hypertension and dyslipidaemia cluster in diabetic patients. The majority of diabetic individuals harbour vascular calcification, insulin resistance, and hyperinsulinemia. These factors not only promote the development of atherosclerosis but also accelerate the transition of stable plaques to unstable plaques by causing plaque rupture or erosion, ultimately leading to thrombus formation and acute coronary events.[20] The principal vascular derangements linked to hyperglycaemia include:

- Endothelial dysfunction – It is the hallmark of diabetic vascular disease. It has been shown to be associated with increased incidence of hypertension and adverse cardiovascular outcomes. The various alterations contributing to endothelial dysfunction include decreased nitric oxide synthesis, increased circulating angiotensin 2 and endothelin 1, decreased prostacyclin production and increased thromboxane A2 activity. Microalbuminuria is a marker of endothelial dysfunction.

- Platelet and coagulation abnormalities – Diabetes is characterised by a prothrombotic milieu as a result of disturbances in platelet activation and

aggregation. Increased levels of circulating tissue factor, von Willebrand factor, factor VII and plasminogen activating inhibitor 1 are observed in diabetes whereas levels of protein C and antithrombin III are decreased, all of which contribute to the prothrombotic state.

- Diabetic dyslipidemia – It is characterised by elevated triglycerides (TG), high small dense LDL particles and low HDL cholesterol, all of which contribute to the accelerated atherosclerosis observed in diabetic patients.

Endothelium	↑ NF-κB activation ↓ Nitric oxide production ↓ Prostacyclin bioavailability ↑ Endothelin 1 activity ↑ Angiotensin II activity ↑ Cyclooxygenase type 2 (COX-2) activity ↑ Thromboxane A_2 activity ↑ Reactive oxygen species ↑ Lipid peroxidation products ↓ Endothelium-dependent relaxation ↑ RAGE expression
Vascular smooth muscle cells and vascular matrix	↑ Proliferation and migration into intima ↑ Increased matrix degradation Altered matrix components
Inflammation	↑ IL-1β, IL-6, CD36, MCP-1 ↑ ICAMs, VCAMs, and selectins ↑ Activity of protein kinase C ↑ AGEs and AGE-RAGE interactions

AGEs, Advanced glycation end products; *ICAMs,* intracellular adhesion molecules; *IL,* interleukin; *MCP,* monocyte chemoattractant protein; *NF,* nuclear factor; *RAGE,* receptor for advanced glycation end products; *VCAMs,* vascular cell adhesion molecules.
Modified from Orasanu G, Plutzky J. The pathologic continuum of diabetic vascular disease. J Am Coll Cardiol 2009;53:S35.

Figure : Mechanisms implicated in the development of CAD in diabetics.

- Inflammation – The accumulation of advanced glycation end products and increased oxidative stress are key drivers of inflammation. Diabetes has been associated with overexpression of reactive oxygen species (ROS); secretion of inflammatory cytokines; activation of protein kinase C and increased aldose reductase (AKR1B1) substrate conversion, all of which accelerate the occurrence of MI. Diabetes is associated atherosclerotic plaque which are lipid-rich with a high inflammatory cell content, expression of tissue factor, and also expression of the receptor for advanced glycation end products.

HEART FAILURE:

Heart failure is another significant contributor of cardiovascular morbidity and mortality. Recent studies have revealed that people with diabetes had two times the rate of incident heart failure hospitalisation (adjusted for age and sex) as those without diabetes. The factors responsible are more severe coronary vascular disease in diabetics in the form of multivessel disease, intrinsic myocardial dysfunction and a high incidence of prior MI. Diabetic patients may present with heart failure with reduced EF (HFrEF) or with preserved EF (HFpEF). A prior myocardial infarction is a major factor in patients with HFrEF whereas hypertension is a precursor in patients with HFpEF as well as HFrEF. In the TAMI trial, diabetic patients were more likely to present in acute pulmonary edema when compared to patients without diabetes - 11 versus 4 percent in TAMI.[38] The rates of hospitalisation for heart failure in diabetic patients have reduced in recent trials with the increasing use of sodium–glucose cotransporter 2 (SGLT2) inhibitors.

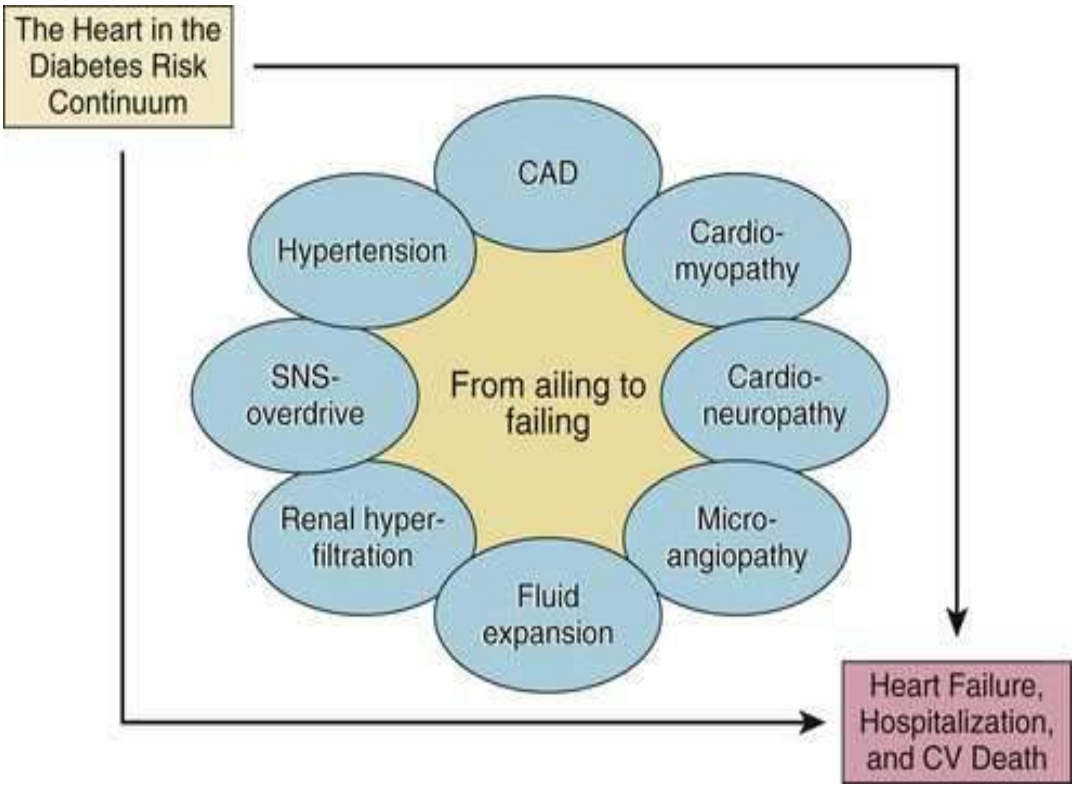


Figure: The 'ominous octet' – the various mechanisms underlying heart failure in patients with diabetes mellitus. CAD is an important contributor to the development of heart failure in diabetes mellitus.[20]

ATRIAL FIBRILLATION:

Diabetes is said to increase the risk of atrial fibrillation. In patients with AF, diabetes has been shown to increase the annual risk of developing stroke by about 2 to 3.5%. Diabetes has been included as one of the components in the $CHA_2DS_2VAS_c$ score thus affirming the risk of stroke associated with diabetes in the setting of AF.

STRESS INDUCED HYPERGLYCEMIA

Uncontrolled hyperglycaemia is commonly observed in critically ill patients and is referred to as stress induced hyperglycaemia or critical illness hyperglycaemia. SIH was defined using the American Diabetes Association Diabetes in Hospitals Writing Committee Guidelines as random blood glucose values in excess of 200 mg/dL (≥11.1 mmol/L).[40] It is usually evident in the first 48 hours of admission to the ICU and can be seen in at least 50% of the patients.[42] Stress induced hyperglycaemia is known to be a marker of disease severity and the magnitude of SIH has been strongly correlated with short-term mortality in acutely ill patients.[43]

Box 1. Causes of hyperglycemia during critical illness.

- Pre-existing conditions
  - Pre-existing diabetes mellitus
  - Obesity with metabolic syndrome
  - Pancreatitis
  - Cirrhosis
- Immunoneuroendocrine changes*
  - Increased level of counter regulatory hormones (e.g., epinephrine, norepinephrine, growth hormone, glucagone and cortisol)
  - Increased level of proinflammatory cytokines (e.g., TNFα, IL-1 and IL-6)
- Iatrogenic
  - Catecholamines infusion
  - TPN (particularly excess amount of dextrose infusion)
  - Drugs (e.g., corticosteroids, thiazide diuretics and phenytoin)
- Hypokalemia (impairs insulin secretion)

*These metabolic alterations increase the rate of glycogenolysis and gluconeogenesis and induce insulin resistance in skeletal muscles, adipose tissues and liver.
IL: Interleukin; TNF: Tumor necrosis factor; TPN: Total parental nutrition.

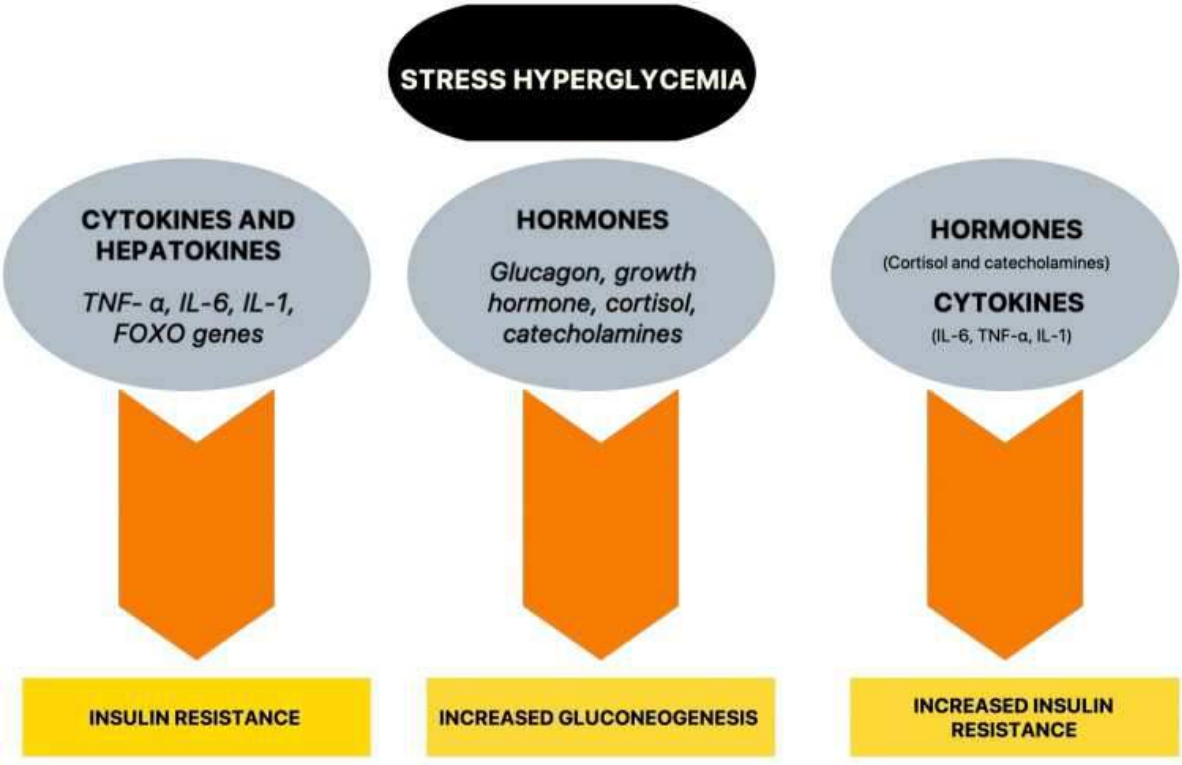
PATHOPHYSIOLOGY OF SIH

Stress induced hyperglycaemia is a state of temporary insulin resistance coupled with relative insulin deficiency, wherein the plasma insulin concentrations are inadequate to compensate for the surge in plasma glucose levels. The metabolic environment that develops in SIH is brought on by counter-regulatory hormones and pro-inflammatory cytokines. These factors lead onto increased gluconeogenesis and insulin resistance. In cases of stress, the hypothalamic-pituitary-adrenal (HPA) axis is activated, increasing the secretion of cortisol from the adrenal gland. Cortisol, glucagon, growth hormone and catecholamines are all counter-regulatory hormones that reduce insulin release by enhancing the activity of pancreatic alpha cells. Catecholamines and cytokines control increased hepatic gluconeogenesis, while glucagon is a key mediator. In addition, catecholamines inhibit tyrosine kinase activity, insulin activation, and glucose uptake by GLUT-4 in the periphery. Glucose uptake in the periphery is also restricted by glucocorticoids whereas the insulin activation on tyrosine residues is prevented by growth hormone.

Interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) are inflammatory cytokines that cause insulin resistance and also suppress insulin release, an effect that is concentration-dependent.[45] Increased levels of IL-6 in the serum are associated with insulin resistance, which promotes hyperglycemia by releasing glucose from hepatic glycogen reserves.[46] Additionally, hyperglycemia raises IL-6 levels in the blood, presumably due to elevated production in monocytes. TNF-α is associated with the severity of sepsis and is the primary mediator in the development of

sepsis. TNF-α causes insulin resistance in animals by itself or by increasing circulating levels of free fatty acids.

Forkhead Box O (FOXO) transcription factors are a significant additional SIH-related pathway. Hepatic glucose-6-phosphatase (G6PC), a gluconeogenic gene controlled in part by FOXO, is expressed more frequently in SIH patients. By altering gene expression, deletion of FOXO transcription factors lowers SIH. The adjustments drive the liver's glycogenolysis and insulin resistance. Indirectly, it reduces adipose tissue lipolysis.[47]



IGFBP-1, a liver-derived protein that prolongs insulin-like growth factor activity and is typically blocked by insulin, is found in high concentrations in critically ill patients. In humans, an increase in IGFBP-1 is linked to death from critical illness and insulin resistance in the liver. The fact that FOXO also controls IGFBP-1 suggests that the transcription factor family may be important in SIH.[47] Lower levels of cytokines and FOXO-regulated hepatokines were associated with lower blood glucose levels in SIH, suggesting that these factors are crucial for the emergence of hyperglycemia.

Stimulation of the sympathetic nervous system leads to an increase in the level of counter regulatory hormones, such as noradrenaline, adrenaline, growth hormone and glucagon. These hormones lead onto increased hepatic cAMP levels, which in turn, promote PEPCK gene transcription and thus increase hepatic gluconeogenesis.[41] Adrenaline promotes glycogenolysis in hepatocytes and skeletal myocytes and, in conjunction with glucagon, has an additive effect on both gluconeogenesis and glycogenolysis. In addition, interruption of the insulin receptor substrate (IRS)-1 activity and inhibition of the insulin signalling pathway by adrenaline leads to the development of insulin resistance. Elevated free fatty acid (FFA) levels secondary to simulation of lipolysis by adrenaline inhibits insulin signalling and, hence, glycogen synthesis. Growth hormone decreases the number of insulin receptors and impairs the activity of tyrosine kinase. Glucagon acts synergistically with epinephrine in the induction of gluconeogenesis and, also activates glycogenolysis.

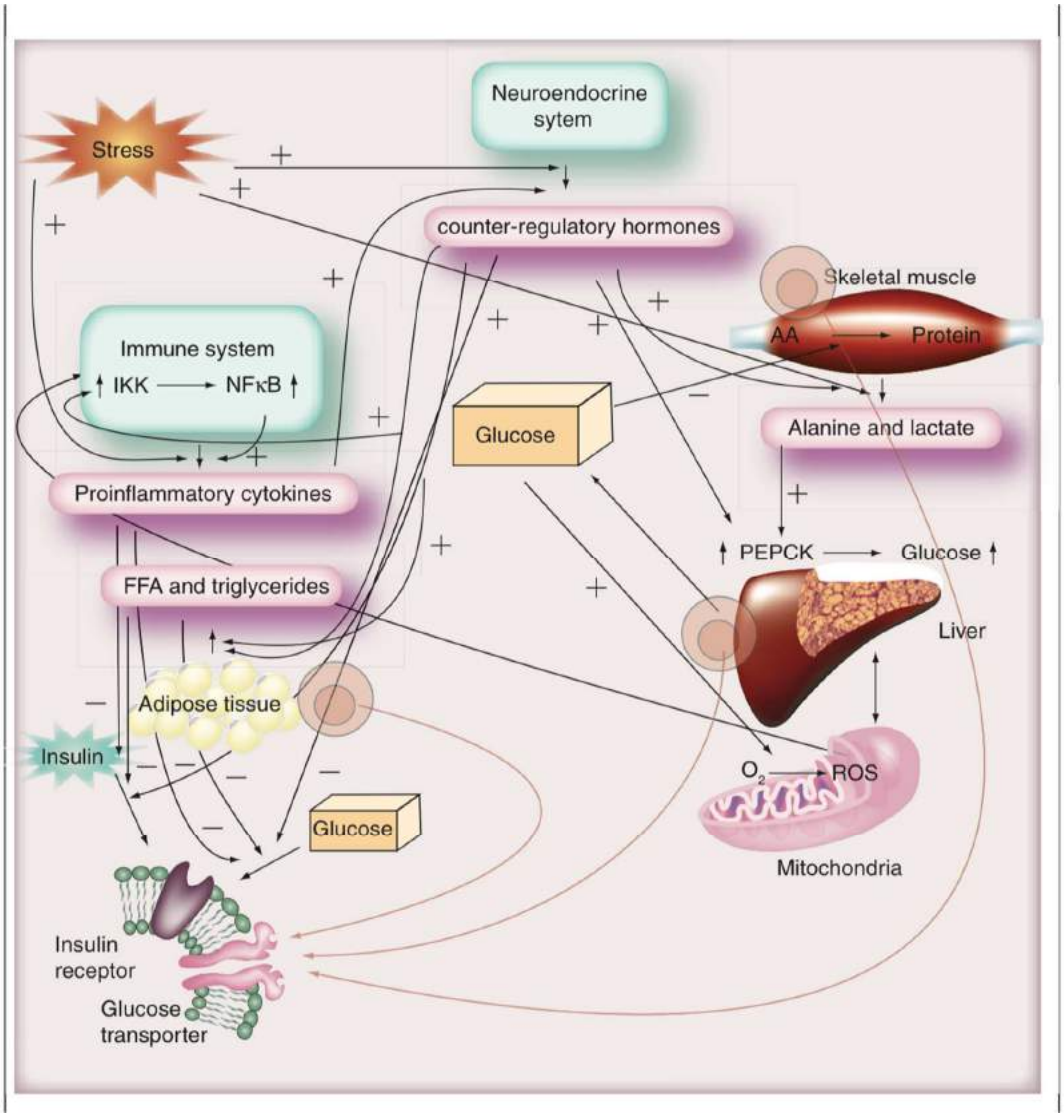


Fig: Interaction between the immuno-neuroendocrine system, adipose tissue, skeletal muscle and the liver during stressful situations. Stress causes release of counter regulatory hormones by the stimulation of the HPA axis and augments the release of proinflammatory cytokines from the immune cells. These cytokines activate the CRF-ACTH-Cortisol axis (HPA axis). Glucose has detrimental effects on the immune system and the skeletal muscle as hyperglycemia exacerbates muscle protein catabolism which leads onto increased gluconeogenesis.[44]

CONSEQUENCES OF SIH

It has been established in various observational studies that hyperglycemia is associated with a poor prognosis in acute illnesses such as AMI, stroke, trauma and complex surgeries. In addition to having proinflammatory properties, glucose overfeed causes immune cells to produce more reactive oxygen species, causing oxidative stress and triggering a cascade of proinflammatory cytokines. Similarly, hyperglycemia by itself promotes insulin resistance. In critical illnesses, there is an increased inflow of glucose into immunological, endothelial, and epithelial cells and hepatocytes which raises intercellular glucose levels and worsens cellular inflammation and mitochondrial function.[41]

Box 2. Deleterious effects of stress-induced hyperglycemia.

- Electrolyte disturbances
- Increase in the rate of oxidative stress
- Procoagulative effects
- Disturbances in the cardiovascular system
- Impairment in the immune system (which increases the rate of infection and sepsis):
  - Decrease in the complement cascade function
  - Decrease in the neutrophil phagocytic and chemotactic capacity
- Hepatocyte mitochondrial dysfunction
- Increase in the rate of acute renal failure
- Increase in the rate of polyneoropathy
- Increase in the rate of insulin resistance

SIH IN THE CONTEXT OF ACS

In many critical ill conditions, SIH has been associated with adverse outcomes and an increase in mortality. Acute myocardial infarction is one such condition where SIH is commonly observed. It has been shown that regardless of the patient's history of diabetes or glycemic control, adverse events in myocardial infarction (MI) patients increase when SIH is present. Inhibiting platelet aggregation and activating nitric oxide synthase are two ways that insulin exerts a beneficial effect on cardiovascular disease. Recent studies indicate that dermcidin, a stress-induced protein, has been found to impede glucose-induced insulin production and cause hyperglycemia in patients with AMI.[48] By lowering plasma dermcidin levels and shrinking infarct size in AMI patients, aspirin can further raise plasma insulin levels. During the early stages of an inflammatory response, hyperglycemia decreases vascular dilatation and increases permeability, possibly through activating protein kinase C. Nuclear factor-kB and protein kinase C pathways can be activated by glucose fluctuations, increasing the expression of adhesion molecules and producing more advanced glycation end products than steady glucose in vitro. Due to increased oxidative stress, inflammation, and activation of stress-responsive kinases, patients with SIH may be more vulnerable to myocardial ischemia-reperfusion injury. During coronary revascularization procedures, acute hyperglycemia induces endothelial dysfunction and is linked to plaque instability and infarct size.[49]

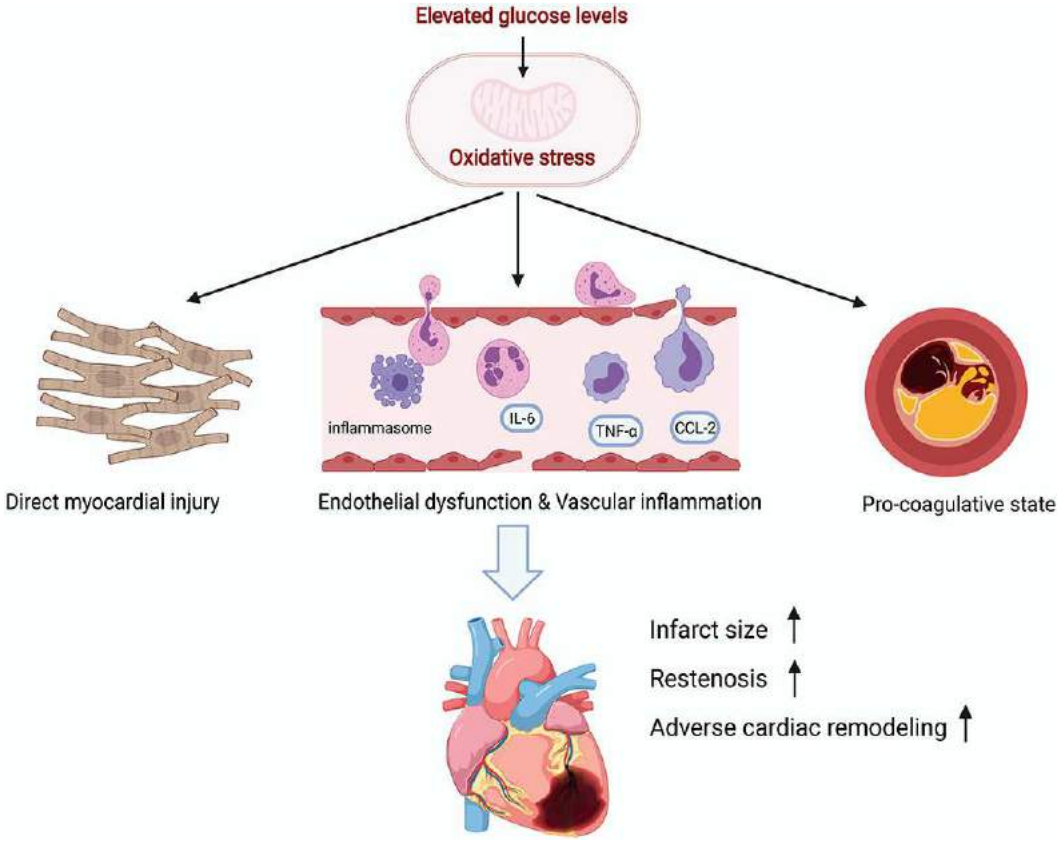


Fig: Mechanisms underlying the detrimental effects of SIH on the cardiovascular system.

In a study by Rajpurohit et al. 100 individuals over the age of 18 who had been admitted to the ICU with an acute MI were analysed to determine the impact of stress induced hyperglycemia in acute MI. Out of the 100 patients, 50 patients with blood glucose above 180mg/dl admitted to the ICU were grouped under SIH, and the remaining 50 patients were categorised as normoglycemic. The study revealed a considerable rise in mortality as well as an increased incidence of complications such as cardiogenic shock, arrhythmias and progression to severe heart failure, thus elucidating that SIH in acute MI patients had a deleterious effect on the outcome.[50]

In a study done by Chen et al, the sequelae in elderly AMI patients with SIH was analysed by determining the relationship between stress hyperglycemic ratio (SHR) and in-hospital outcomes among elderly patients presenting with AMI. SHR was defined as the ratio of the fasting glucose concentration at admission to the HbA1c level. It is an index of the relative stress hyperglycemia prevailing in the acute scenario and is used as a prognostic indicator in AMI. In this study, 341 patients presenting with AMI over 75 years were analyzed to look for a link between the SHR and in-hospital outcomes. All-cause mortality and adverse cardiac events and cerebrovascular events namely reinfarction, cardiogenic shock, mechanical complications of MI, severe bleeding and stroke comprised the in-hospital outcomes. This study showed that SIH is an independent predictor of adverse outcomes in elderly patients with AMI. The study also showed that the outcome and increased mortality rate in a patient with an acute illness such as AMI can be predicted using the parameter called SHR.[51]

Another study done by Khalfallah et al. conducted on 660 patients with ST-elevation MI who were managed with percutaneous coronary intervention elobarated the adverse outcomes of SIH. Patients were analysed based on the presence or absence of SIH. On analysis, the study findings suggested an increased incidence of cardiogenic shock, the no-reflow phenomenon, contrast-induced nephropathy and higher mortality in those patients with SIH.[52]

INSULIN AND THE CARDIOVASCULAR SYSTEM

Insulin has a wide range of favourable metabolic and nonmetabolic effects that can counteract nearly all unfavourable effects of the stress response and ameliorate the glucotoxicity. Intensive glycemic control has been shown to reduce the morbidity and mortality rate in critically ill patients.

Box 3. Beneficial effects of insulin therapy and glycemic control.

- Anti-inflammatory effects
  - Decrease in proinflammatory cytokines (e.g., TNFa)
  - Decrease in NFkB level
  - Increase in IkB level
  - Suppression of EGR-1 action
  - Suppression of AP-1 action
  - Reduction in MBL and CRP level
- Enhanced coagulation profile
  - Suppression of tissue factor
  - Suppression of plasminogen activator inhibitor
  - Suppression of pro-MMP-1
- Enhanced cardiovascular profile
  - Increase NO formation and NO synthesis expression in endothelium
  - Cardio–protective effects
  - Decrease in iNOS expression
- Prevent mitochondrial dysfunction
- Improvement in lipid profile
- Antiapoptotic effects

AP: Activator protein; CRP: C-reactive protein; EGR: Early growth response factor; iNOS: Inducible nitric oxide synthase; MBL: Mannose-binding lectin; MMP: Matrix metalloproteinase; NFκB: Nuclear factor κ B; NO: Nitric oxide; NOS: Nitric oxide synthase; TNF: Tumor necrosis factor.

GLYCEMIC GAP

The admission blood glucose level is influenced by the acute physiological stress as well as chronic baseline glucose levels, particularly in patients with pre-existing diabetes mellitus. The link between high glucose levels and increased in-hospital and long-term mortality in ACS patients, particularly in non-diabetic individuals, has long been known. While studying the association between SIH and adverse outcomes in diabetic individuals, it is important to consider pre-existing hyperglycaemia as hyperglycaemia is the cardinal feature of diabetes mellitus. Hence a single cut-off value of admission blood glucose to define SIH, regardless of the patient's prior glycemic status is not convincing. This led to exploration of newer metrics such as glycemic gap and stress hyperglycemia ratio. The Glycemic Gap is calculated by subtracting the HbA1c derived average glucose level (eAG)/ ADAG from the admission CBG.

$$\text{Glycemic Gap (GG)} = \text{ABG} - \text{ADAG}$$

The glycemic gap reflects "additional" glucose homeostasis in response to acute stress on the chronic glycemic control. The consistent findings regarding the association between elevated glycemic gaps and adverse outcomes in diabetic patients with liver abscess and CAP allowed us to strengthen our hypothesis that an acute surge of glucose levels beyond the long-term average (or in nondiabetic patients) serves as a surrogate marker for acute physiological stress.[53]

Methodology

METHODOLOGY

1. **Study design:** Hospital based prospective cross-sectional study.
2. **Study period:** April 2021 – March 2022
3. **Study population:** Patients with diabetes mellitus from the general population presenting to our hospital with acute myocardial infarction.

INCLUSION CRITERIA:

1. Patients with established diabetes mellitus previously diagnosed as per the ADA guidelines:

- Fasting blood glucose more than or equal to 126 mg/dl.
- Postprandial blood glucose more than or equal to 200 mg/dl.
- Patients with symptoms of hyperglycemia with random blood sugar more than or equal to 200 mg/dl.
- HbA1c value more than or equal to 6.5 %.
- Patients discharged from a hospital with a diagnosis of Diabetes Mellitus.
- He/she who has a prescription of Insulin/ oral hypoglycemic agents from a Registered Medical Practitioner.

2. Patients presenting with acute myocardial infarction diagnosed as per the 4th Universal Defintion of MI by the Joint Task Force recommendation, which defined Acute MI as the presence of acute myocardial injury detected by elevated cardiac biomarker Troponin I in the setting of acute myocardial ischemia as evidenced by the clinical presentation and the ECG findings.

3. Patients aged more than 18 years.

EXCLUSION CRITERIA :

1. Patients on treatment with steroids.

2. Patients presenting with hypoglycemia (blood glucose < 70 mg/dl).

3. Patients with anaemia. (Hb < 13 g/dl in males and Hb < 12 g/dl for females as per the WHO definition of anaemia).

4. Patients who received a blood transfusion within the past 3 months.

5. Pregnant patients.

SAMPLE SIZE:

Based on the reference study done by Liao et al, Taiwan

Formula:

$n = 2(Z_a+Z_B)^2Sd^2/(M_1-M_2)^2$

Where $Z_a = 1.96$ (statistical significant constant for 95% CI)

$Z_B = 0.84$ (80% power)

Sd = 84.8 (Standard deviation of glycemic gap in mg/dl among survivors of Acute myocardial infarction patients with Type 2 diabetes mellitus from previous study)

M_1 =95.7 (Mean glycemic gap in mg/dl among non survivors of Acute myocardial infarction patients with Type 2 diabetes mellitus from previous study)

M_2 = 58.3 (Mean glycemic gap in mg/dl among survivors of Acute myocardial infarction patients with Type 2 diabetes mellitus from previous study.)

$(M_1-M_2)^2 = 1398$ (37.4 x 37.4)

On substituting in the formula

n = 15.6 x 84.8 x 84.8 / 1398

n = 81

Adding 10% non response rate (ie 10% of 81= 8)

n = 89 (minimum sample size)

Therefore Sample size **n = 100 (1 group)**

SAMPLING METHOD: Consecutive sampling.

ETHICAL COMMITTEE APPROVAL: Obtained.

DATA COLLECTION AND METHODS:

Patients were given a patient information chart and informed consent was obtained. In Diabetic patients presenting with Acute MI fulfilling the inclusion criteria, glucose level was obtained upon admission to the ED. Physical examination was performed promptly to identify patients in shock or in acute heart failure using vital signs such as BP, elevated JVP and/or presence of rales. The severity of AMI was determined using the Killip classification. Killip class I refers to individuals with no clinical signs of heart failure; Killip class II indicates individuals with crackles in the lungs, elevated jugular venous pressure and an S3; Killip class III refers to individuals with frank acute pulmonary oedema; and Killip class IV denotes individuals in cardiogenic shock. A 12 lead ECG was done for all the patients within 10 minutes of presentation to the ED. Blood samples were sent for Troponin I, Complete Blood Count, Renal function test and HbA1c apart from other routine investigations. The three month estimated average glucose level(eAG)/ ADAG was calculated from HbA1c using the equation eAG = 28.7 × HbA1c–46.7. Glycaemic gap was calculated using the formula GG = ABG - eAG. Patients were classified into two groups based on the glycaemic gap values with one group of patients having a high glycaemic gap and the other gap with a low glycaemic gap. The cut-off value for the glycaemic gap was determined as 38.5 mg/dl using the Youden's index with a sensitivity and specificity of 66% and 67% respectively. The severity of MI and the outcome were assessed in both the groups and compared. Echocardiogram was done for all the patients and the left ventricular ejection fraction was determined. Disease severity was assessed by complications such as acute

heart failure, cardiogenic shock, acute kidney injury, acute respiratory failure and arrhythmias in addition to in-hospital mortality and duration of stay in the hospital.

In our study, the following criteria were used to define the various complications.

- Cardiogenic shock – Systolic Blood pressure < 90 mmHg with evidence of end organ hypoperfusion like cold clammy extremities, decreased mentation and decreased urine output in the presence of adequate volume status.
- Acute Kidney injury – AKI is defined by KDIGO guidelines as follows
    - Rise in serum creatinine by ≥ 0.3 mg/dl within 48 hours (or)
    - Rise in serum creatinine to ≥ 1.5 times the baseline value which is known or presumed to have occurred within the previous 7 days (or)
    - Urine volume < 0.5 ml/kg/hour for 6 hours.
- Acute respiratory failure – requirement of ventilatory support in the form of either invasive or non-invasive ventilation.
- Arrhythmia – both tachyarrhythmias and bradyarrhythmias were looked for.

STATISTICAL ANALYSIS:

After collection, the data was compiled and entered in Microsoft Excel Sheet. Analysis was done using Statistical software SPSS version 16. All Continuousvariables were expressed as Mean and Standard Deviation. All Categorical variables were expressed as Percentages and Proportions. Chi-square test was used as test of significance. The test was considered Significant if $P<0.05$, at 95% Confidence Interval.

ETHICAL CONSIDERATION:

Patients will be given a Patient Information sheet and informed consent form that will be verbally explained to the patients orally in a language they understand. Confidentiality will be maintained.

CONFLICT OF INTEREST: None to declare

FINANCIAL DISCLOSURE: None to declare

PERMISSION:

Written permission will be obtained from the Heads of the Departments of General Medicine, Cardiology, Diabetology and Biochemistry.

Observation and Results

Age distribution table

The mean age is 58.6 years (S.D. =13.1) ranging between 31 years and 85 years.

N		100
	Missing	0
Mean		58.630
Median		60.500
Std. Deviation		13.1392
Minimum		31.0
Maximum		85.0

Table 1: Age distribution table

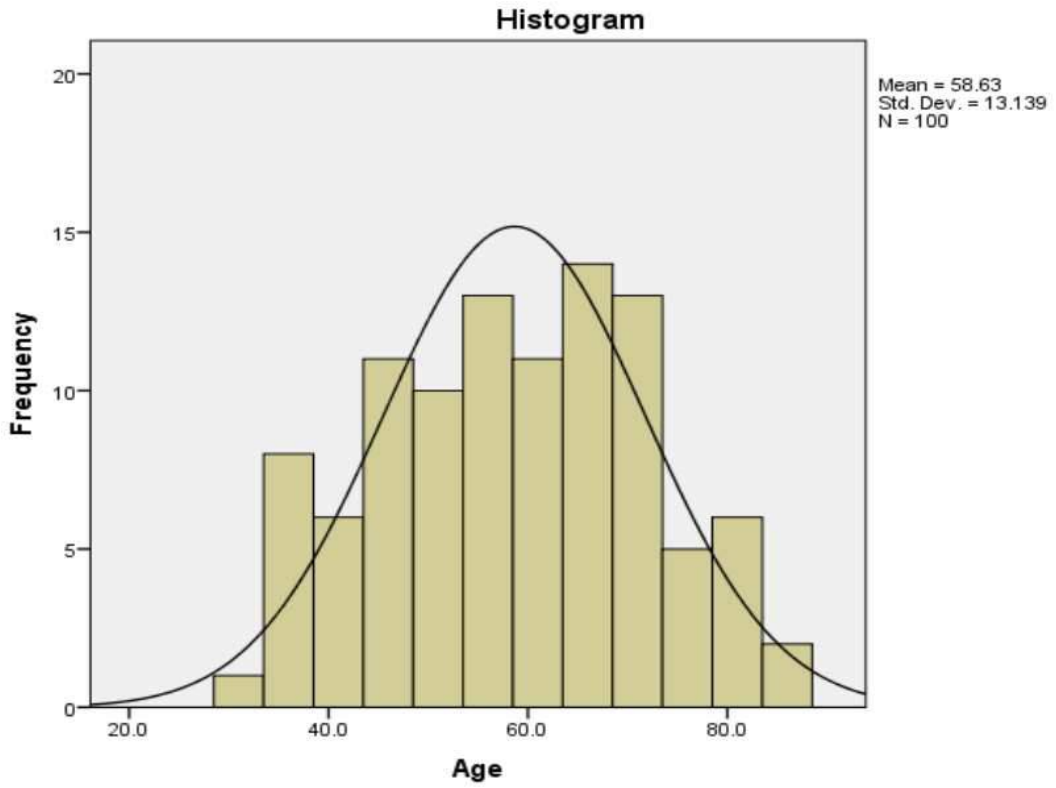


Figure 1: Age distribution table

Gender distribution table

Majority of the study population were males (n=61, 61%).

Gender		Frequency	Percent
	Female	39	39.0
	Male	61	61.0
	Total	100	100.0

Table 2: Gender distribution table

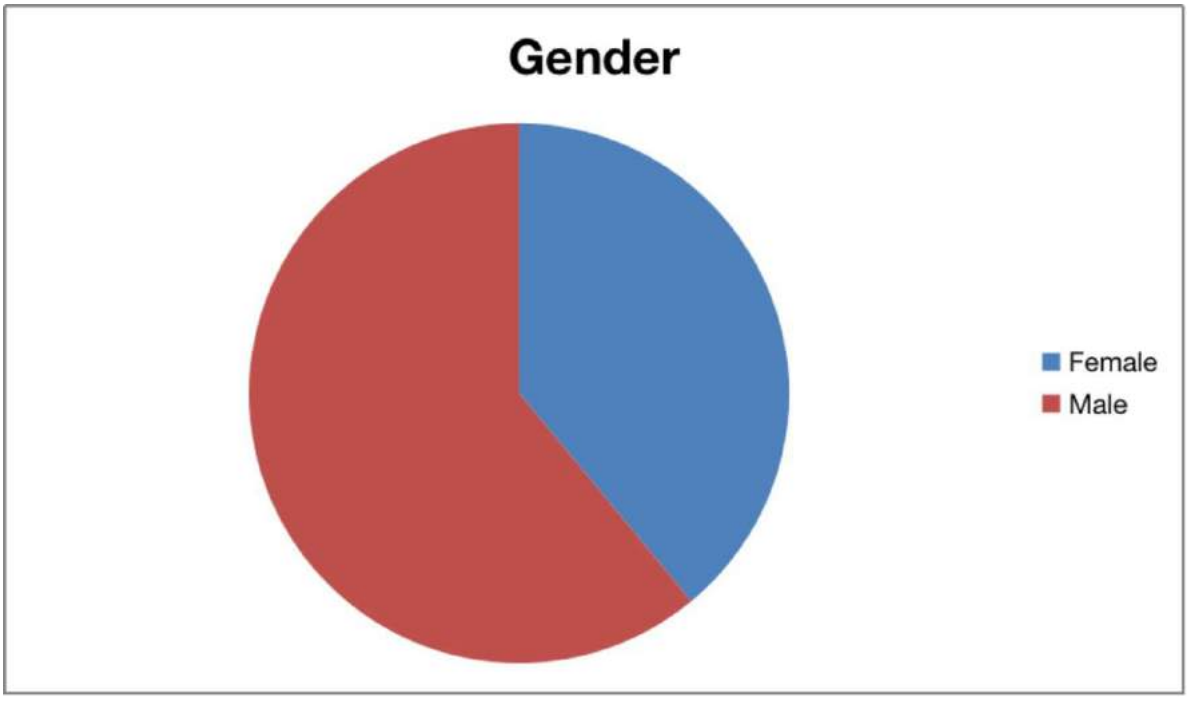


Figure 2: Gender distribution table

Prevalence of comorbidities

Around 59% had hypertension and 40% had dyslipidaemia.

		Frequency	Percent
Hypertension	Absent	41	41.0
	Present	59	59.0
	Total	100	100.0
Dyslipidaemia	Absent	60	60.0
	Present	40	40.0
	Total	100	100.0

Table 3: Prevalence of comorbidities

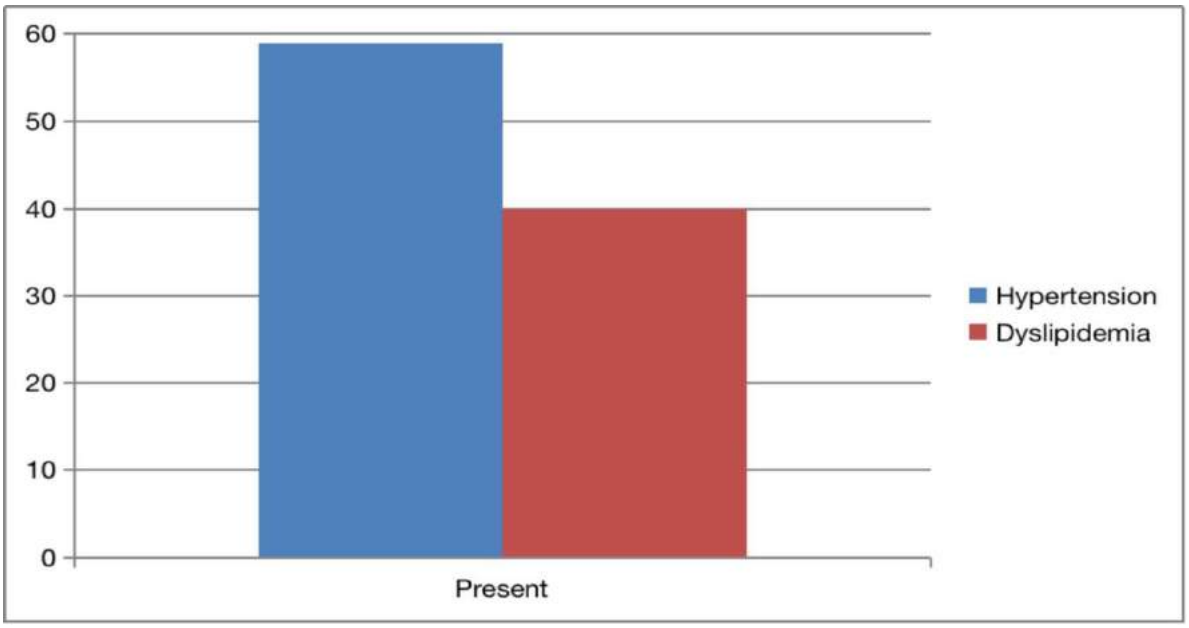


Figure 3: Prevalence of comorbidities

Prevalence of smoking

Around 44% of them were smokers.

Smoking		Frequency	Percent
	Absent	56	56.0
	Present	44	44.0
	Total	100	100.0

Table 4: Prevalence of smoking

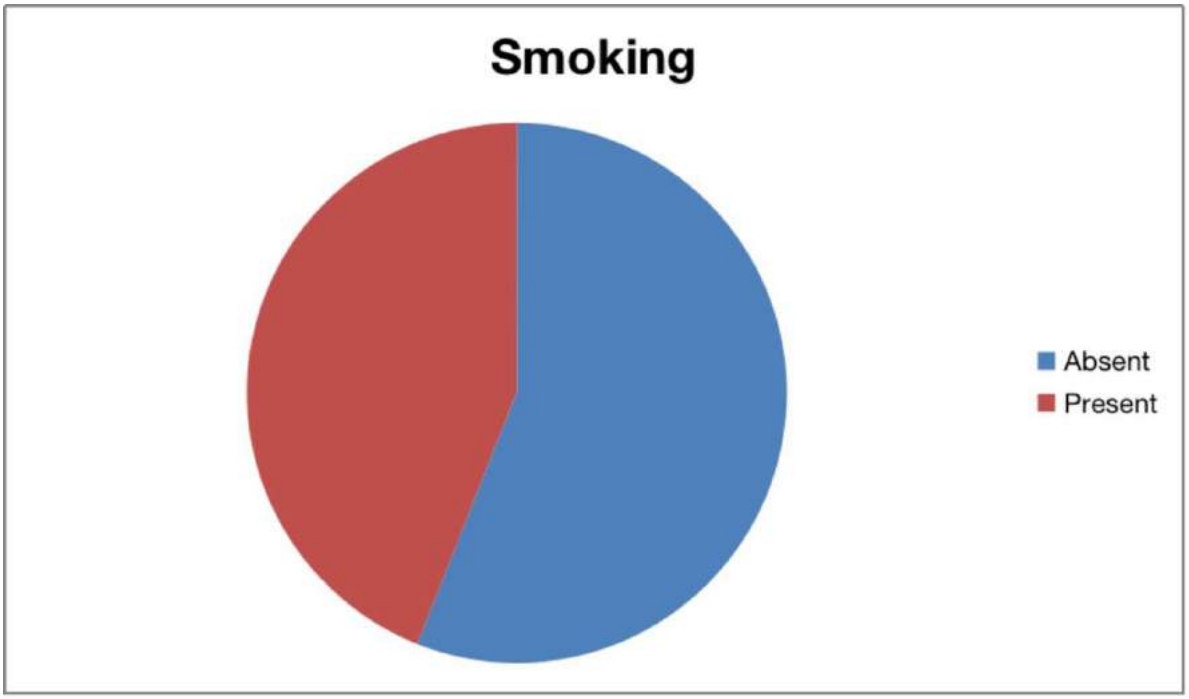


Figure 4: Prevalence of smoking

Symptoms at presentation

Around 88% of them had chest pain, 41% had breathlessness, 24% had palpitations and 8% had syncope.

		Frequency	Percent
Chest pain	Absent	12	12.0
	Present	88	88.0
	Total	100	100.0
Breathlessness	Absent	59	59.0
	Present	41	41.0
	Total	100	100.0
Palpitations	Absent	76	76.0
	Present	24	24.0
	Total	100	100.0
Syncope	Absent	92	92.0
	Present	8	8.0
	Total	100	100.0

Table 5: Symptoms at presentation

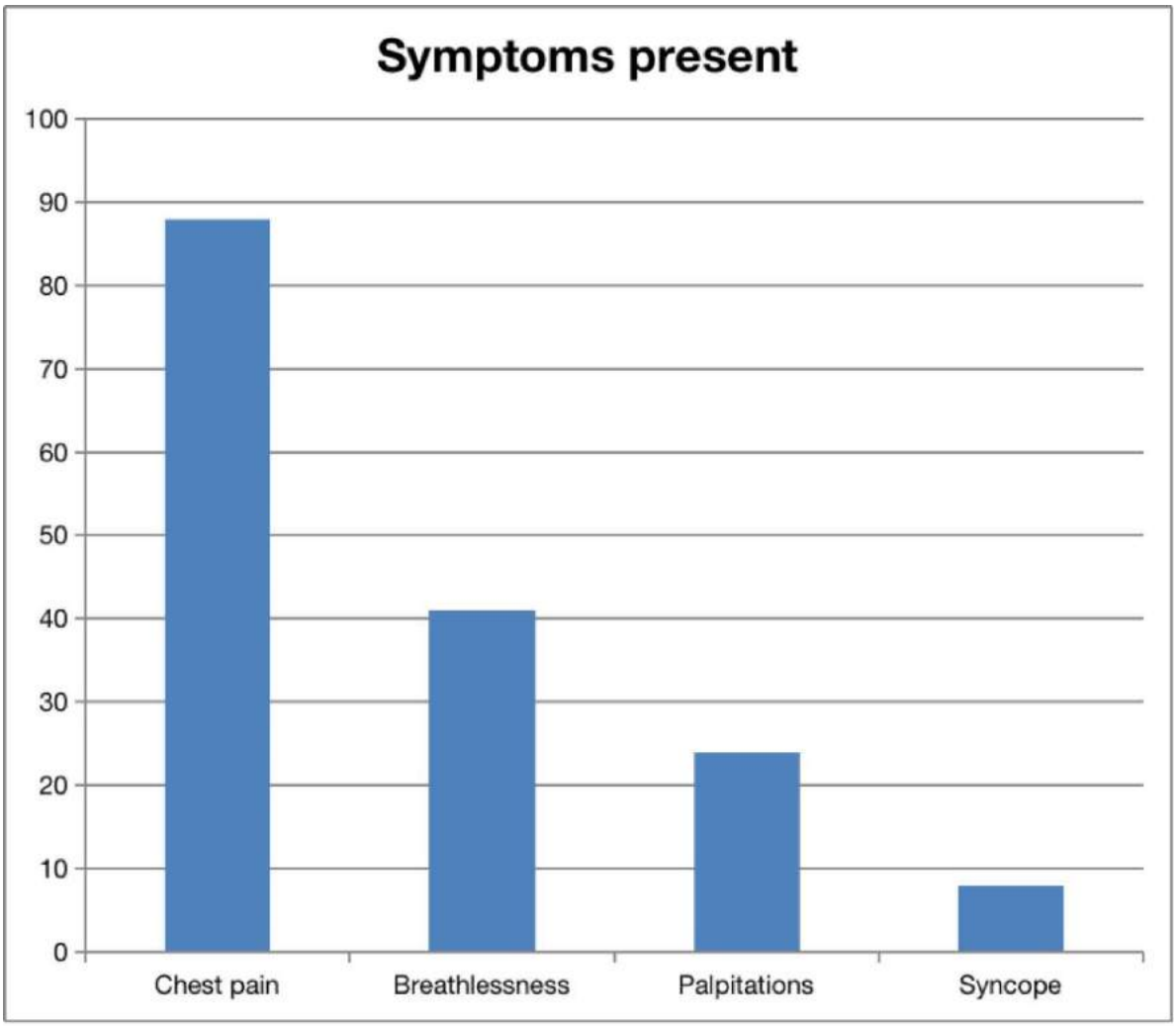


Figure 5: Symptoms at presentation

Killip class distribution

In Killip class distribution, around 53% were class I, around 21% were class II, around 14% were class III and around 12% were class IV.

Killip class		Frequency	Percent
	1.0	53	53.0
	2.0	21	21.0
	3.0	14	14.0
	4.0	12	12.0
	Total	100	100.0

Table 6: Killip class distribution

Figure 6: Killip class distribution

ACS category

In the study population, around 58% patients had NSTEMI and 42% had STEMI.

ACS category		Frequency	Percent
	STEMI	42	42.0
	NSTEMI	58	58.0
	Total	100	100.0

Table 7: ACS type

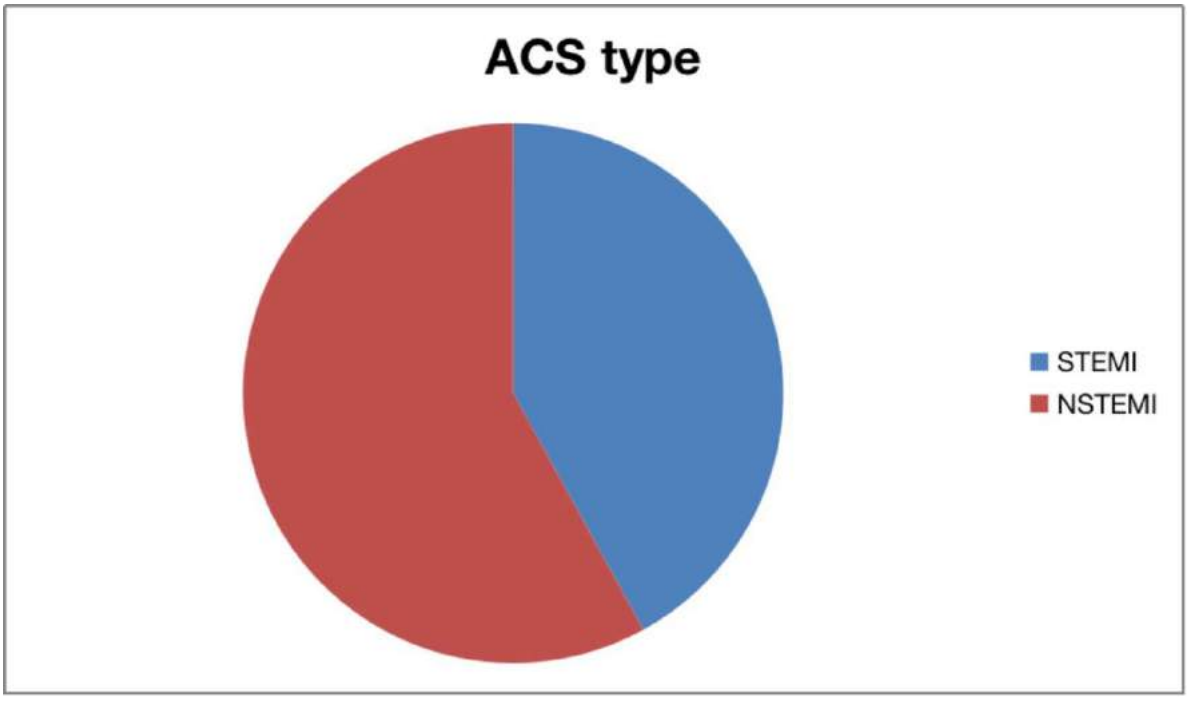


Figure 7: ACS type

Admission CBG distribution

The mean admission CBG is 262.67 (S.D=86.5) ranging between 147 and 672.

		CBG
N		100
	Missing	0
Mean		262.670
Median		249.500
Std. Deviation		86.5241
Minimum		147.0
Maximum		672.0

Table 8: Admission CBG distribution

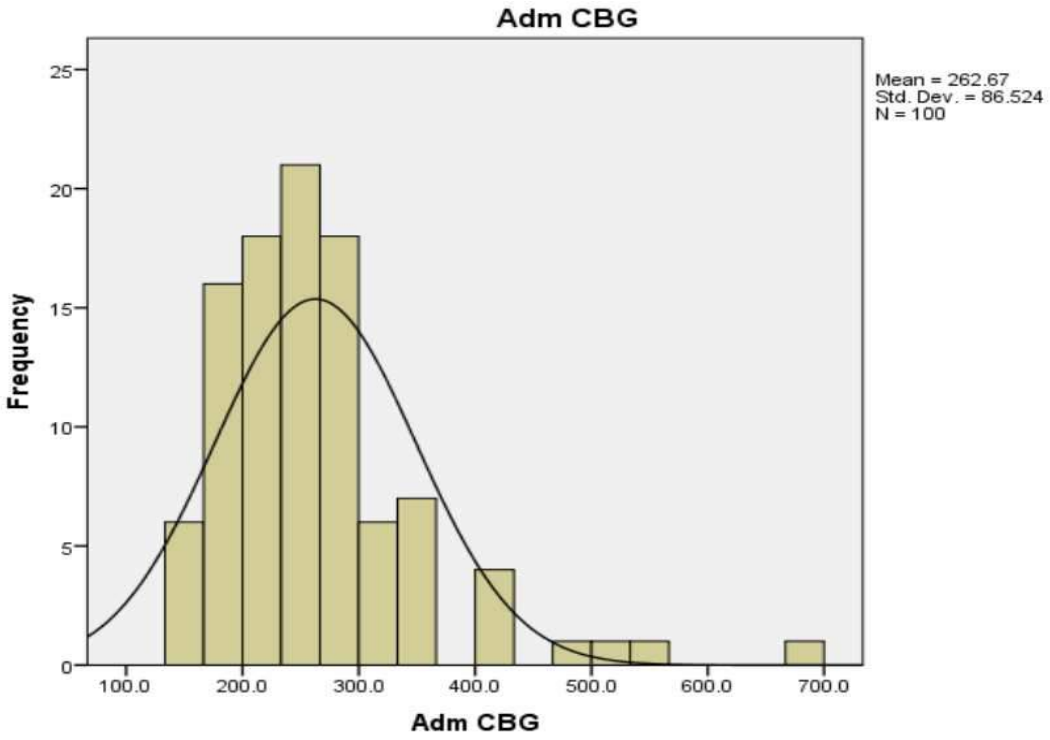


Figure 8: Admission CBG distribution

HbA1c distribution

Mean HbA1c is 8.4 (S.D.=1.5) ranging between 6.5 and 13.2.

		HbA1c %
N		100
	Missing	0
Mean		8.429
Median		8.200
Std. Deviation		1.4847
Minimum		6.5
Maximum		13.2

Table 9: HbA1c distribution

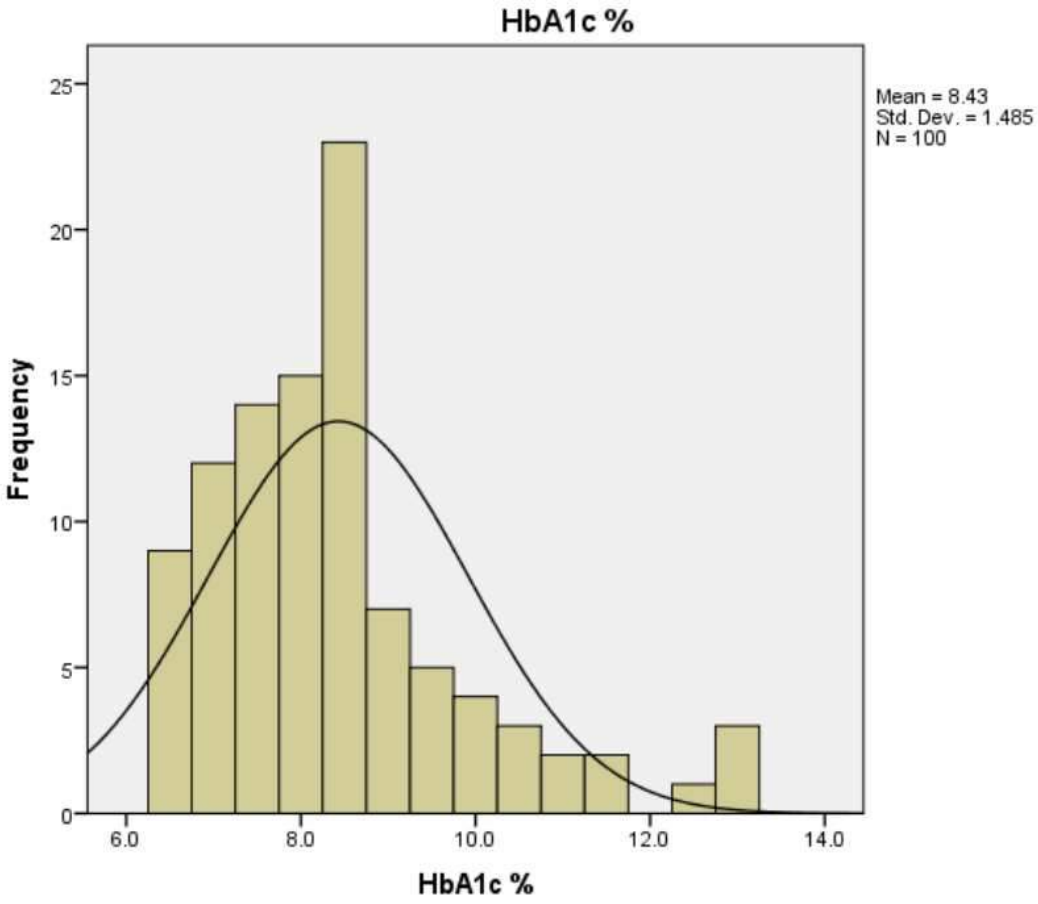


Figure 9: HbA1c distribution

Glycemic Gap distribution

Mean glycemic gap distribution is 67.4 (S.D. =70.6) ranging between -46 and 392.

		Glycemic Gap
N		100
	Missing	0
Mean		67.360
Median		37.000
Std. Deviation		70.6080
Minimum		-46.0
Maximum		392.0

Table 10: Glycemic Gap distribution

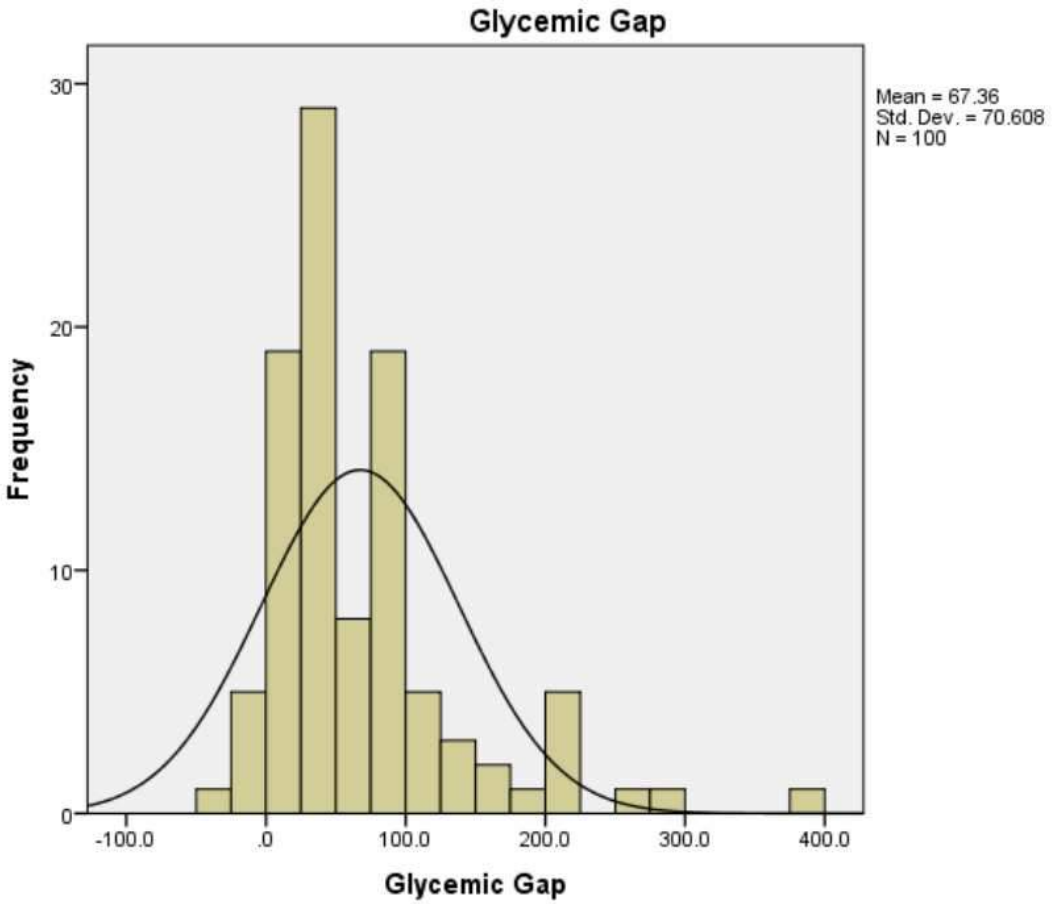


Figure 10: Glycemic Gap distribution

Correlation between Glycemic Gap and Killip Class

Correlation between Glycemic Gap and Killip Class shows that higher Killip class is associated with high glycemic gap. This is statistically significant ($p<0.005$).

		Glycemic gap (category)		Total	p-value
		Low	High		
Killip class	1.0	38	15	53	.002
	2.0	9	12	21	
	3.0	4	10	14	
	4.0	3	9	12	
Total		54	46	100	

Table 11: Correlation between Glycemic Gap and Killip Class

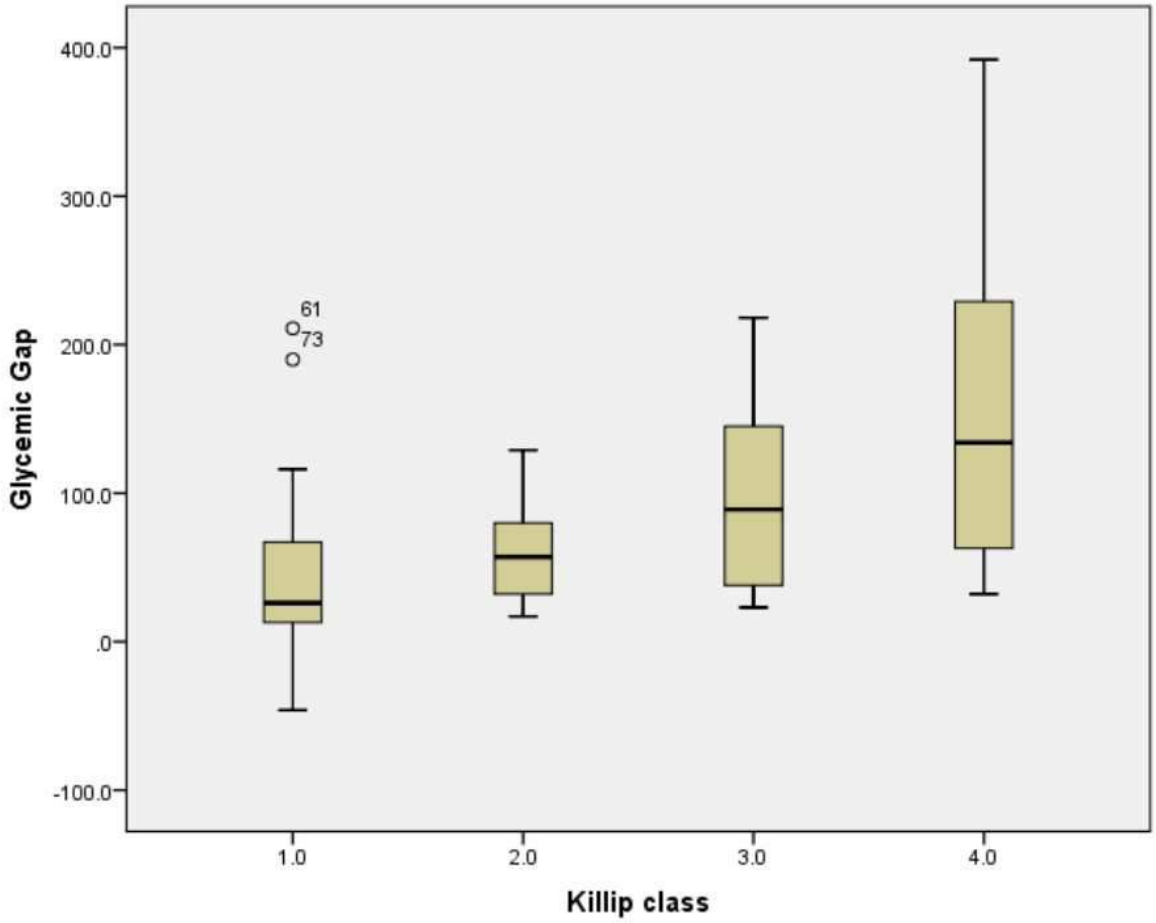


Figure 11: Correlation between Glycemic Gap and Killip Class

Correlation between Glycemic Gap and ACS type

Correlation between Glycemic Gap and ACS type shows that high glycemic gap is associated more with STEMI. This is statistically significant ($p<0.005$).

		Glycemic gap (category)		Total	p-value
		Low	High		
ACS type	STEMI	13	29	42	.000
	NSTEMI	41	17	58	
Total		54	46	100	

Table 12: Correlation between Glycemic Gap and ACS Type

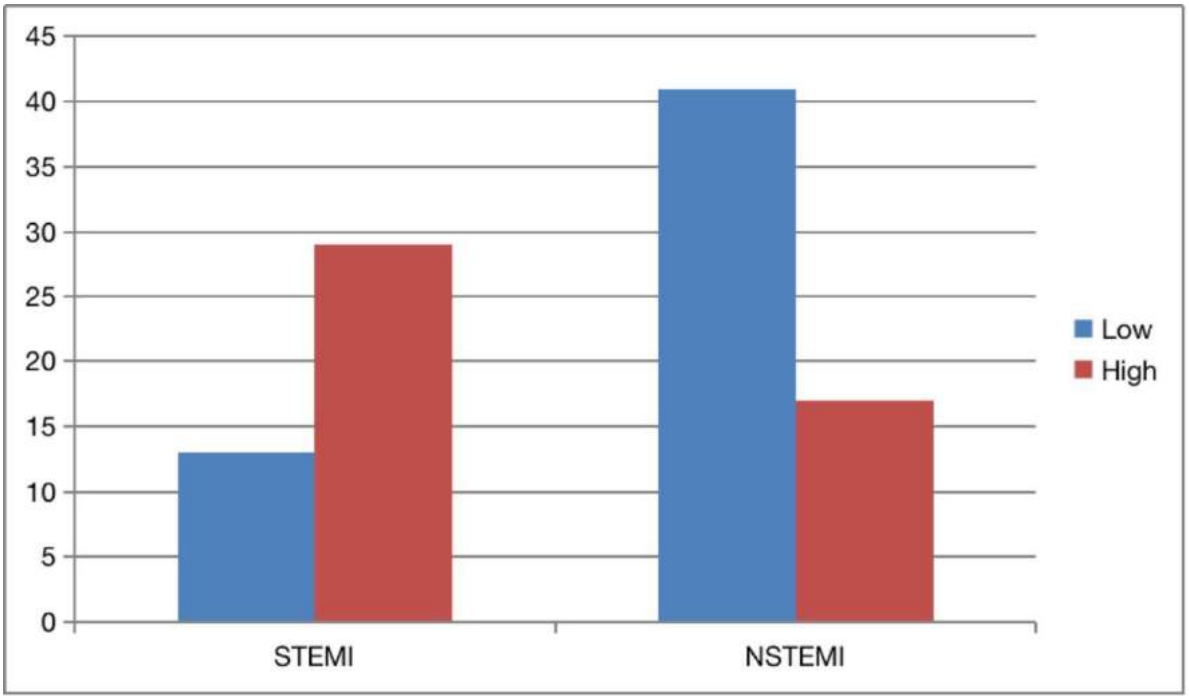


Figure 12: Correlation between Glycemic Gap and ACS Type

Correlation between Glycemic Gap and Acute heart failure

Correlation between glycemic gap and acute heart failure shows that incidence of heart failure is higher in subjects with high glycemic gap. This is statistically significant ($p<0.005$).

		Glycemic gap (category)		Total	p-value
		Low	High		
Acute Heart Failure	Absent	38	15	53	.001
	Present	16	31	47	
Total		54	46	100	

Table 13: Correlation between Glycemic Gap and acute heart failure

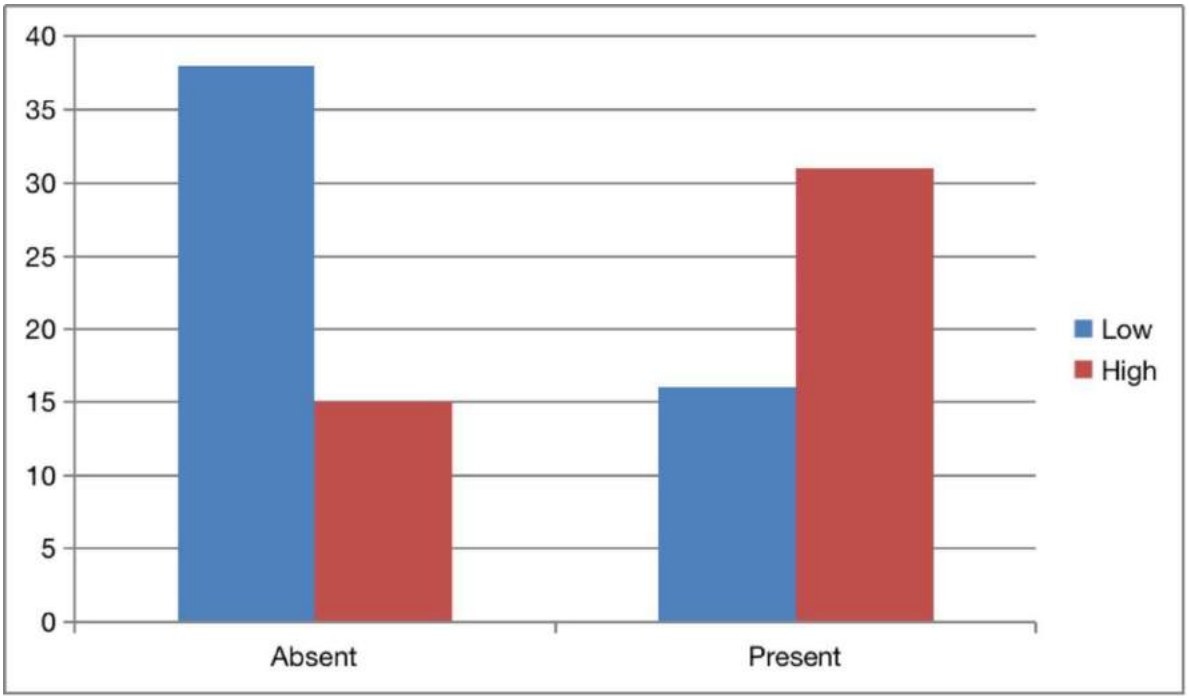


Figure 13: Correlation between Glycemic Gap and Acute heart failure

Correlation between Glycemic Gap and Cardiogenic Shock

Among 12 subjects who had cardiogenic shock, nine of them had high glycemic gap.

This is statistically significant ($p<0.05$).

		Glycemic gap (category)		Total	p-value
		Low	High		
Shock	Absent	51	37	88	.032
	Present	3	9	12	
Total		54	46	100	

Table 14: Correlation between Glycemic Gap and Cardiogenic Shock

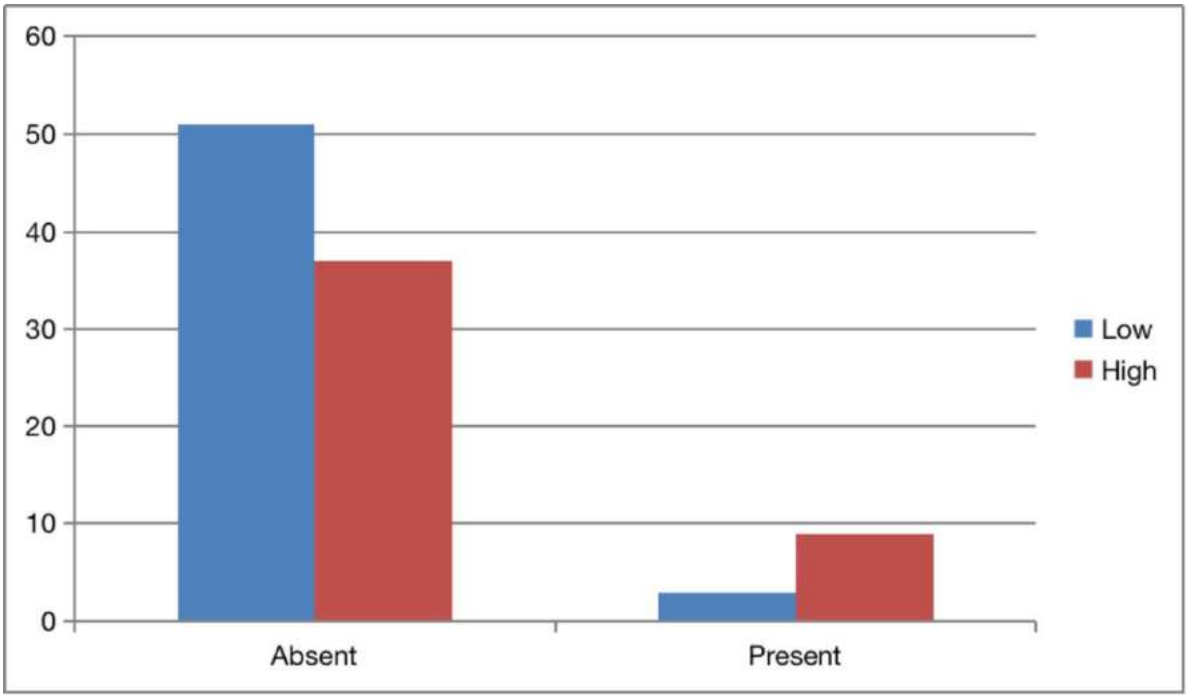


Figure 14: Correlation between Glycemic Gap and Cardiogenic Shock

Correlation between Glycemic Gap and AKI (Acute Kidney Injury)

Majority of the subjects with acute kidney injury had high glycemic gap (13 out of 21 subjects). This is statistically not significant (p>0.05).

		Glycemic gap (category)		Total	p-value
		Low	High		
AKI	Absent	46	33	79	.100
	Present	8	13	21	
Total		54	46	100	

Table 15: Correlation between Glycemic Gap and AKI (Acute Kidney Injury)

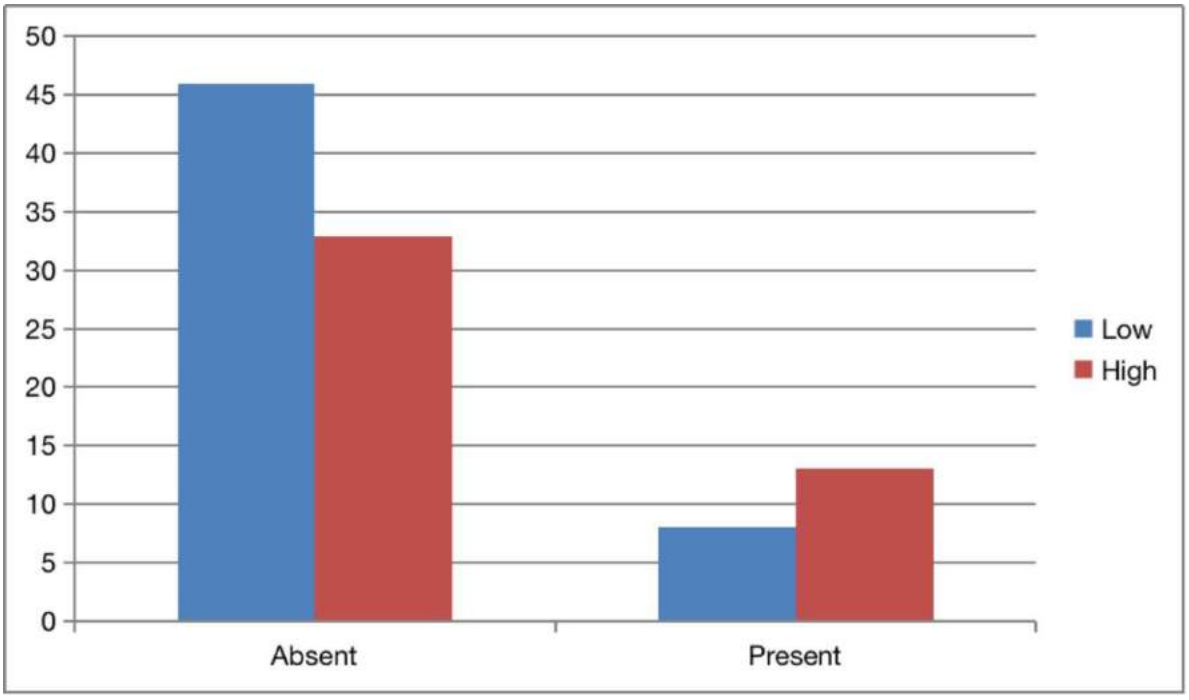


Figure 15: Correlation between Glycemic Gap and AKI (Acute Kidney Injury)

Correlation between Glycemic Gap and Acute respiratory failure

Among 18 subjects who had acute respiratory failure, 13 of them had high glycemic gap. This is statistically significant ($p<0.05$).

		Glycemic gap (category)		Total	p-value
		Low	High		
ARF	Absent	49	33	82	.014
	Present	5	13	18	
Total		54	46	100	

Table 16: Correlation between Glycemic Gap and ARF (Acute respiratory failure)

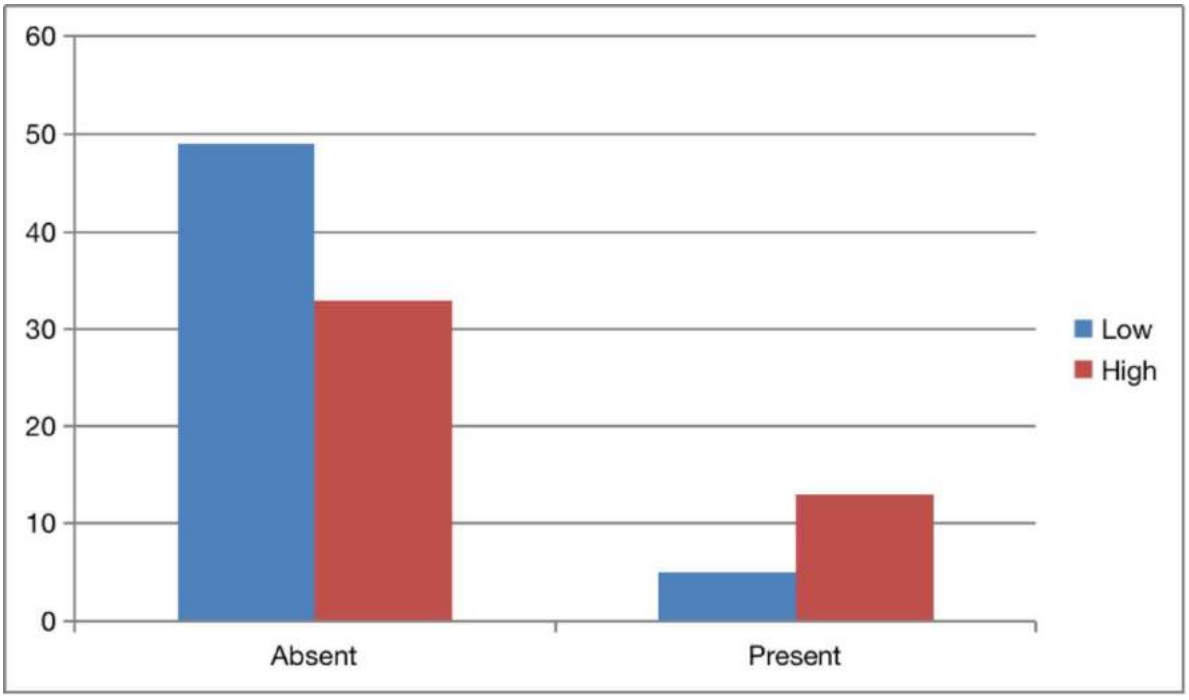


Figure 16: Correlation between Glycemic Gap and ARF (Acute respiratory failure)

Correlation between Glycemic Gap and Arrhythmias

Majority of the subjects with arrhythmias had high glycemic gap (seven out of 11 subjects). This is statistically not significant ($p>0.05$).

		Glycemic gap (category)		Total	p-value
		Low	High		
Arrhythmia	Absent	50	39	89	.213
	Present	4	7	11	
Total		54	46	100	

Table 17: Correlation between Glycemic Gap and Arrhythmias

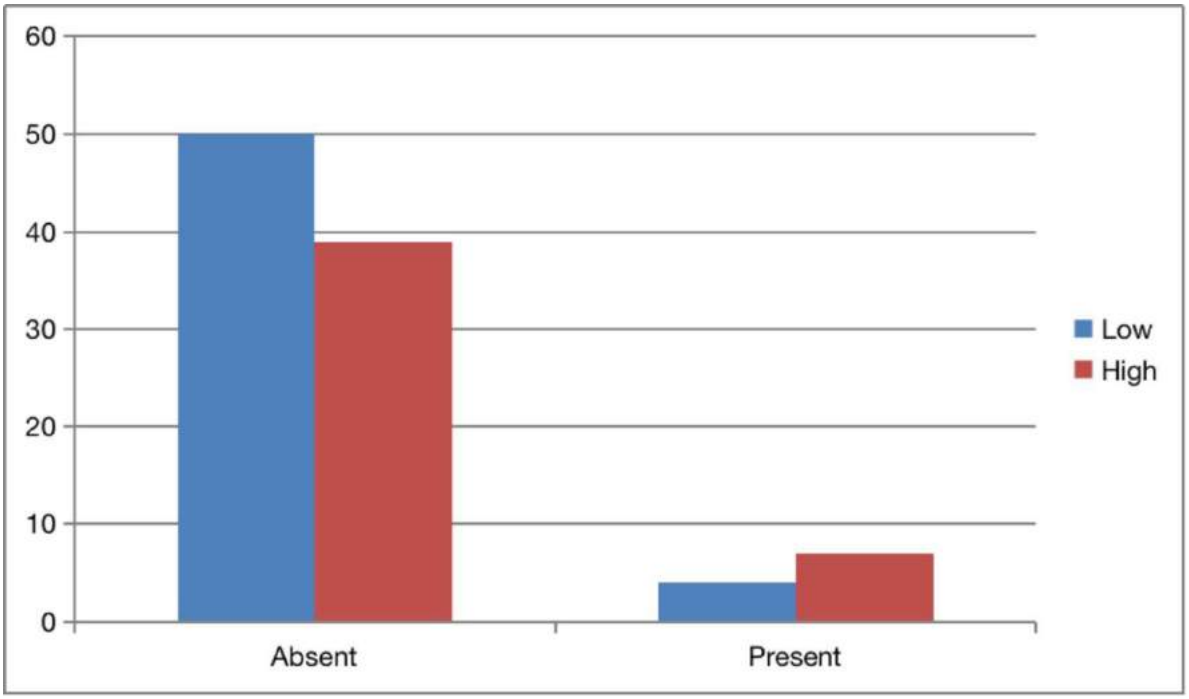


Figure 17: Correlation between Glycemic Gap and Arrhythmias

Correlation between Glycemic Gap and LVEF

Correlation between glycemic gap and LVEF shows that higher glycemic gap is associated with lower LVEF. This is statistically significant ($p<0.005$).

		Glycemic gap (category)		Total	p-value
		Low	High		
LVEF (Category)	50-60 %	31	7	38	.000
	40-50 %	15	14	29	
	30-40 %	8	25	33	
Total		54	46	100	

Table 18: Correlation between Glycemic Gap and LVEF

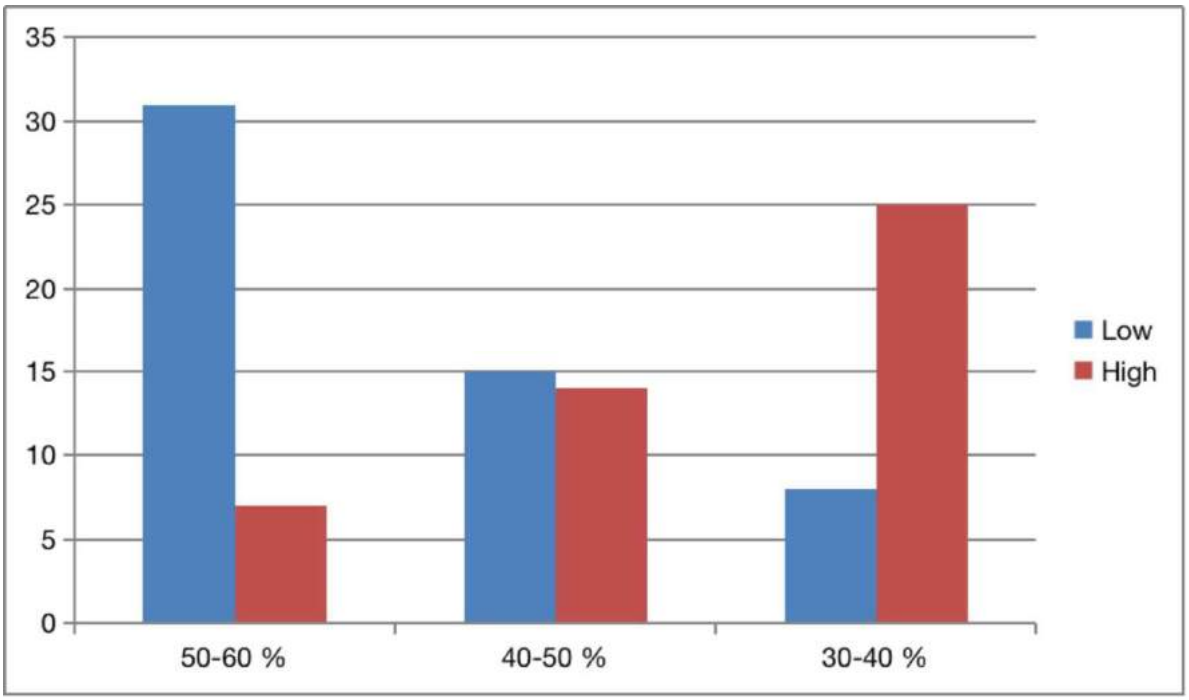


Figure 18: Correlation between Glycemic Gap and LVEF

Correlation between Glycemic Gap & PCI- No of vessels

Among 46 subjects with high glycemic gap, 12 of them had single vessel disease, 15 of them had double vessel disease and 12 of them had triple vessel disease. This is statistically significant (p<0.005).

		Glycemic gap (category)		Total	p-value
		Low	High		
CAG- No of vessels	Not done	2	7	9	.000
	Single vessel disease	39	12	51	
	Double vessel disease	12	15	27	
	Triple vessel disease	1	12	13	
Total		54	46	100	

Table 19: Correlation between Glycemic Gap & PCI- NO OF VESSELS

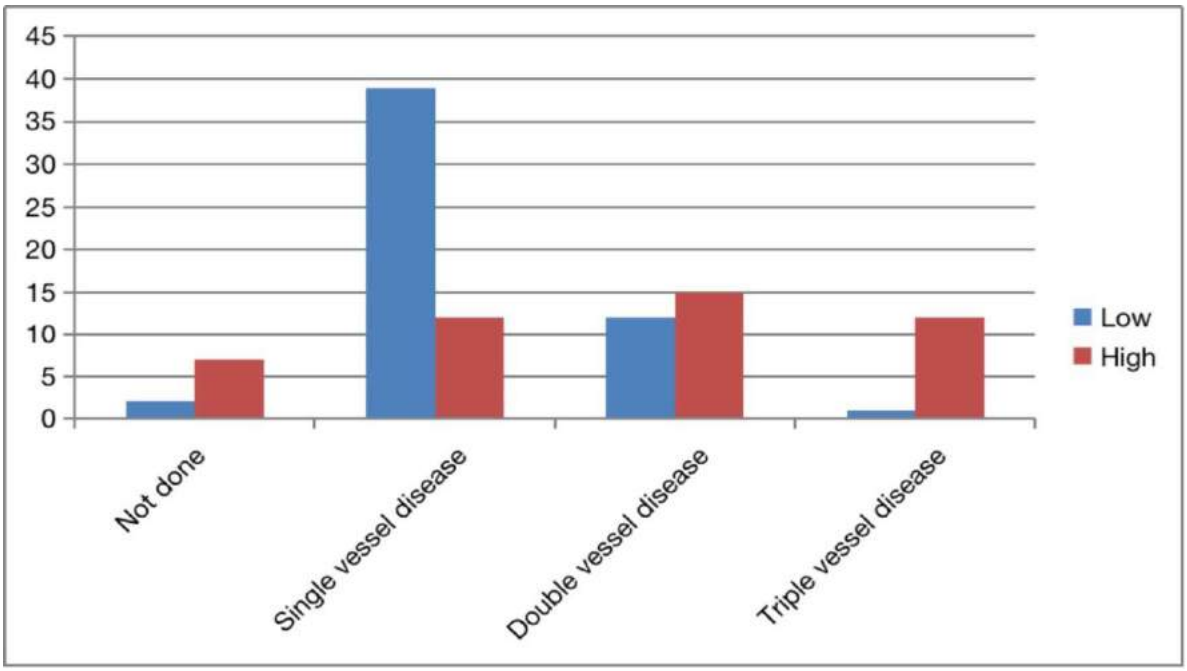


Figure 19: Correlation between Glycemic Gap & PCI- NO OF VESSELS

Correlation between Glycemic Gap and Duration of Hospital Stay

Higher glycaemic gap was associated with increased hospital stay.

This is statistically significant ($p<0.005$).

		Glycemic gap (category)		Total	p-value
		Low	High		
Duration of hospital stay	3.0	29	3	32	.000
	4.0	7	7	14	
	5.0	12	12	24	
	6.0	3	8	11	
	7.0	2	7	9	
	9.0	1	3	4	
	10.0	0	3	3	
	11.0	0	2	2	
	12.0	0	1	1	
Total		54	46	100	

Table 20: Correlation between Glycemic Gap and Duration of Hospital Stay

Correlation between Glycemic Gap and Duration of Hospital Stay

Higher glycemic gap was associated with increased hospital stay.

This is statistically significant ($p<0.005$).

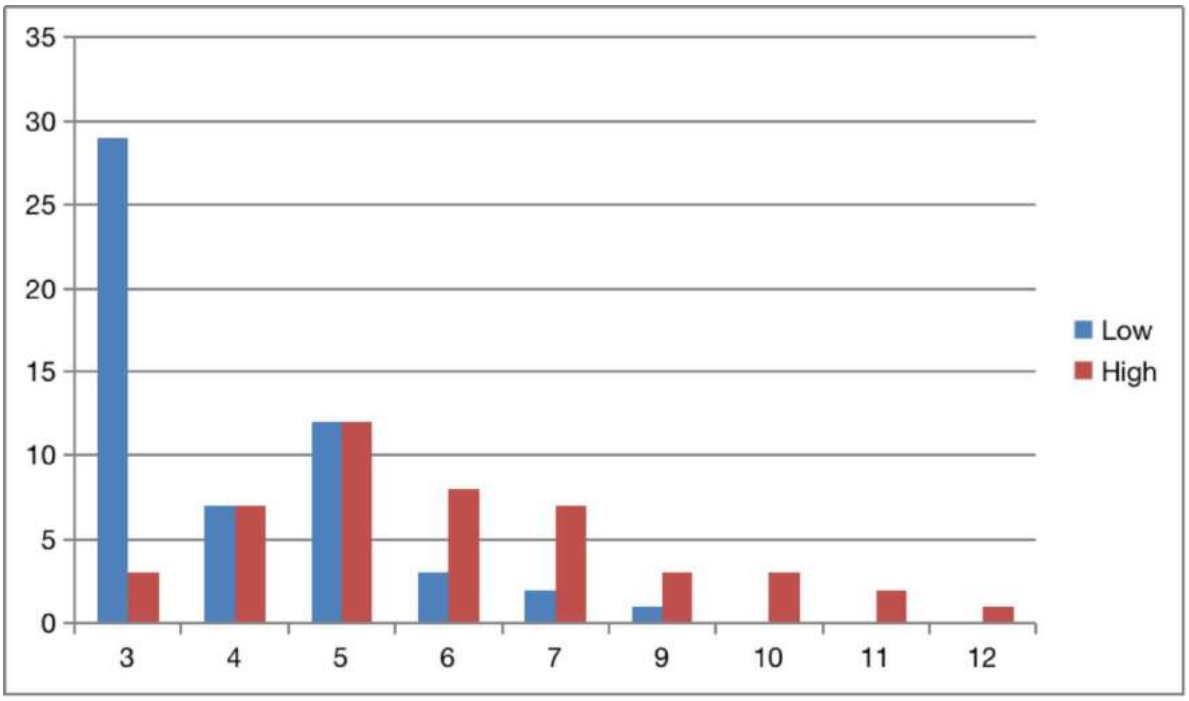


Figure 20: Correlation between Glycemic Gap and Duration of Hospital Stay

Correlation between Glycemic Gap and Death (Mortality)

Among seven subjects who died, six of them had high glycemic gap. This is statistically significant ($p<0.05$).

		Glycemic gap (category)		Total	p-value
		Low	High		
Survival	Alive	53	40	93	.029
	Dead	1	6	7	
Total		54	46	100	

Table 21: Correlation between Glycemic Gap and Death (Mortality)

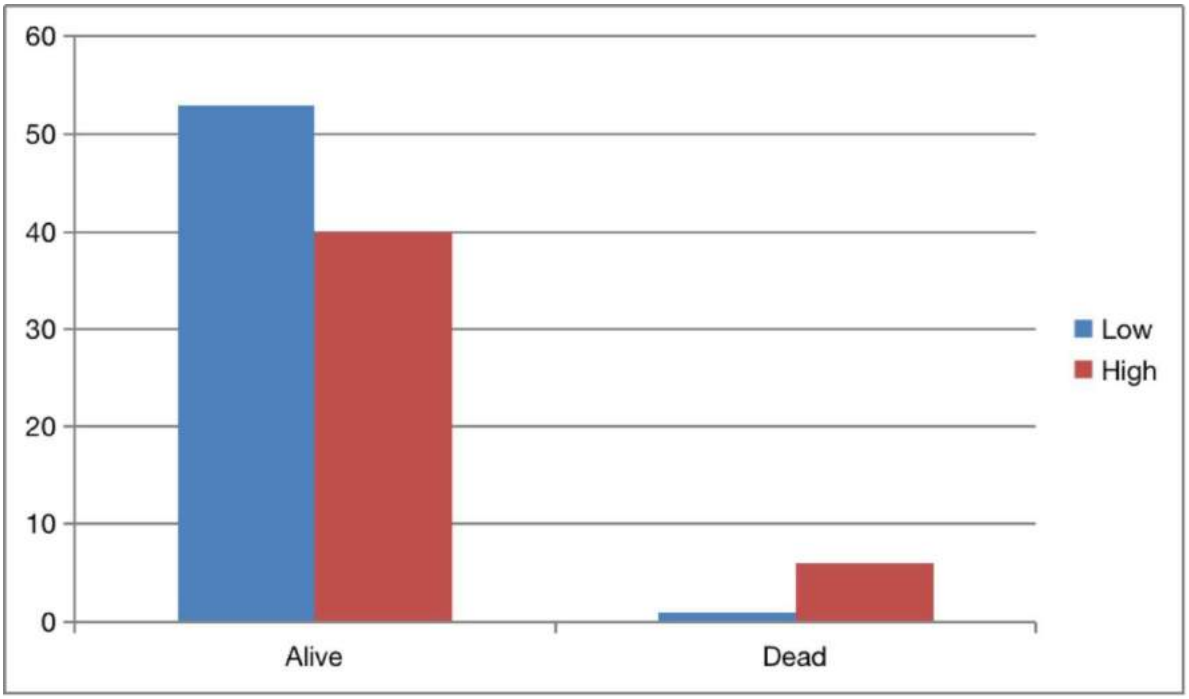


Figure 21: Correlation between Glycemic Gap and Death (Mortality)

Correlation between Age and Glycemic Gap

Comparison of age and glycemic gap shows that the mean age was higher in subjects with higher glycemic gap (59.4 vs 58 years). This is statistically not significant ($p>0.05$).

Glycemic gap (category)	Mean	Std. Deviation	N	p-value
Low	58.000	13.9555	54	.606
High	59.370	12.2227	46	
Total	58.630	13.1392	100	

Table 22: Correlation between Age and Glycemic Gap

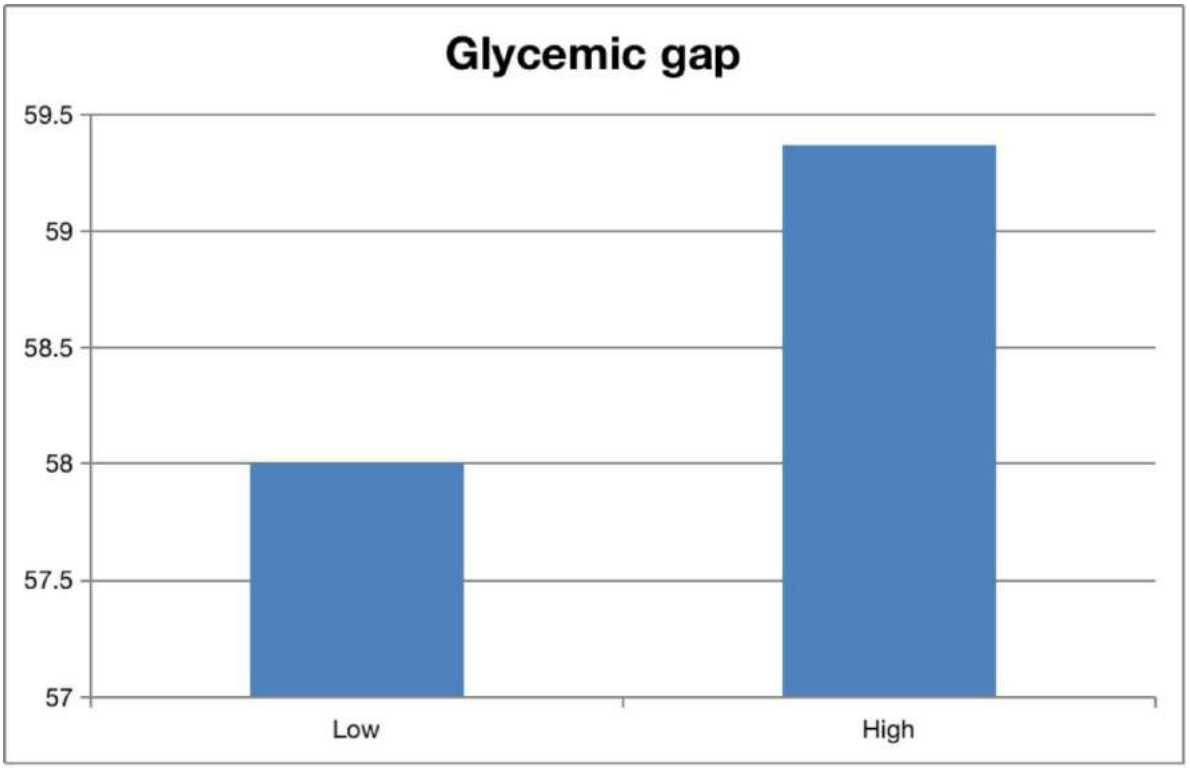


Figure 22: Correlation between Age and Glycemic Gap

Correlation between Gender and Glycemic Gap

There is no statistically significant correlation between gender and glycemic gap ($p>0.05$).

		Glycemic gap (category)		Total	p-value
		Low	High		
Gender	Female	21	18	39	.980
	Male	33	28	61	
Total		54	46	100	

Table 23: Correlation between Gender and Glycemic Gap

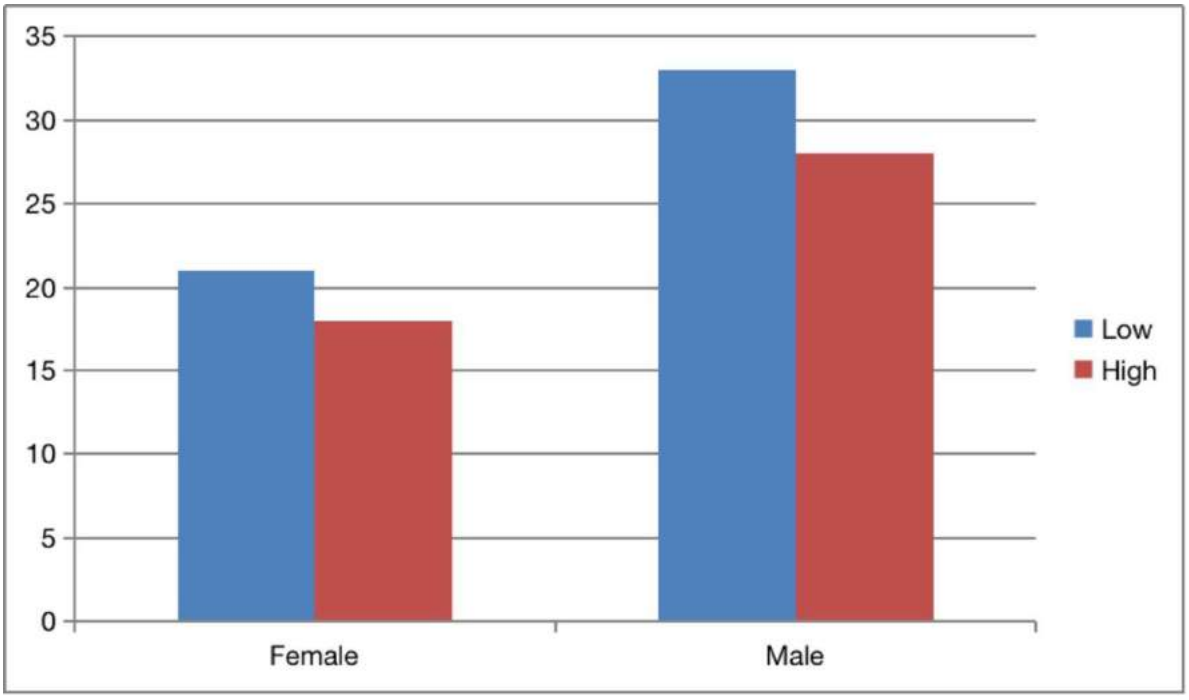


Figure 23: Correlation between Gender and Glycemic Gap

Correlation between Hypertension and Glycemic Gap

There is no statistically significant correlation between prevalence of hypertension and glycemic gap ($p>0.05$).

		Glycemic gap (category)		Total	p-value
		Low	High		
Hypertension	Absent	21	20	41	.642
	Present	33	26	59	
Total		54	46	100	

Table 24: Correlation between Hypertension and Glycemic Gap

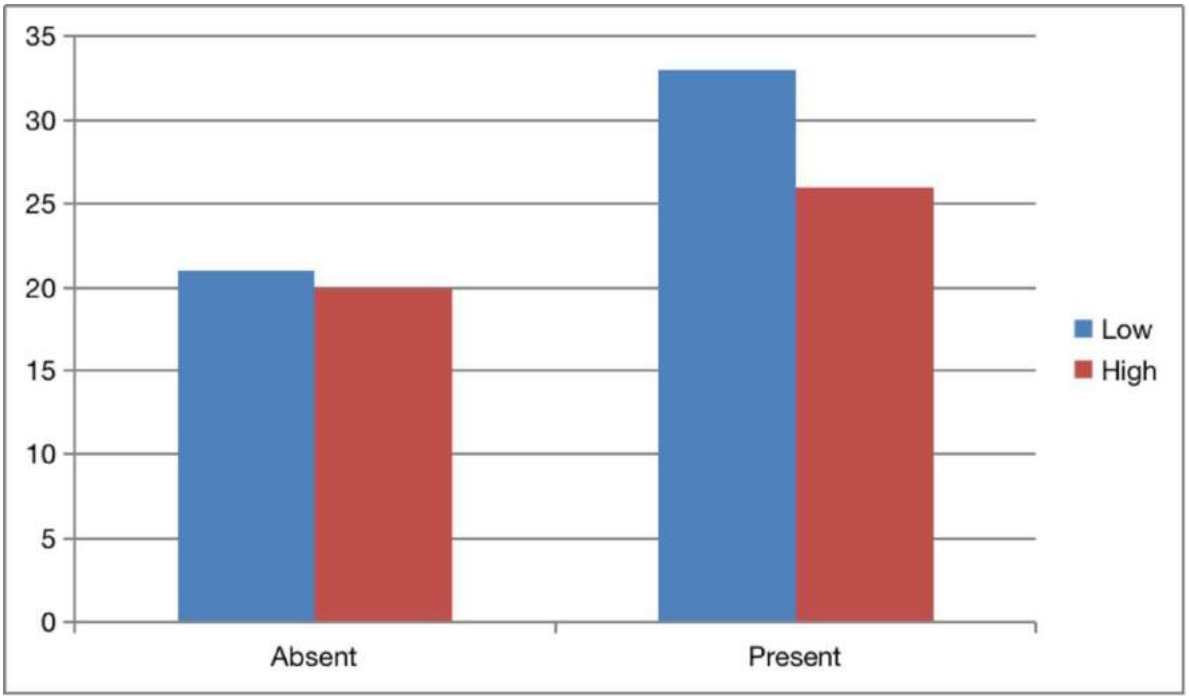


Figure 24: Correlation between Hypertension and Glycemic Gap

Correlation between Dyslipidaemia and Glycemic Gap

There is no statistically significant correlation between prevalence of dyslipidaemia and glycemic gap ($p>0.05$).

		Glycemic gap (category)		Total	p-value
		Low	High		
Dyslipidaemia	Absent	31	29	60	.566
	Present	23	17	40	
Total		54	46	100	

Table 25: Correlation between Dyslipidaemia and Glycemic Gap

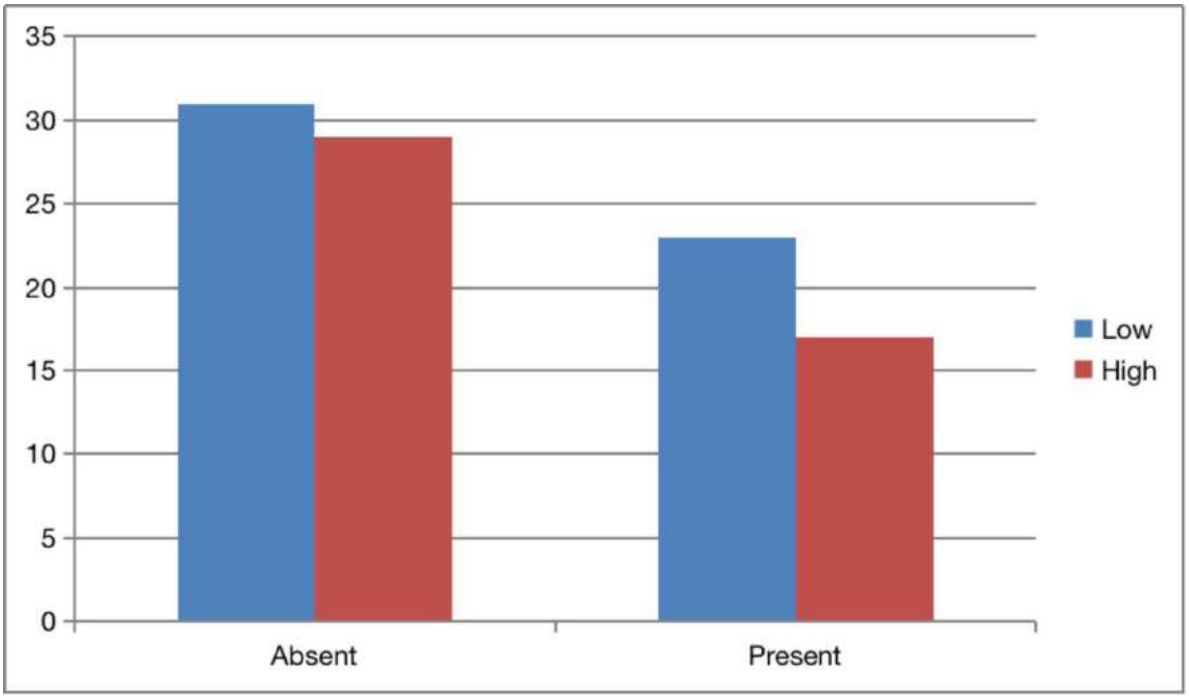


Figure 25: Correlation between Dyslipidaemia and Glycemic Gap

Correlation between Smoking and Glycemic Gap

There is no statistically significant correlation between smoking and glycemic gap ($p>0.05$).

		Glycemic gap (category)		Total	p-value
		Low	High		
Smoking	Absent	29	27	56	0.616
	Present	25	19	44	
Total		54	46	100	

Table 26: Correlation between Smoking and Glycemic Gap

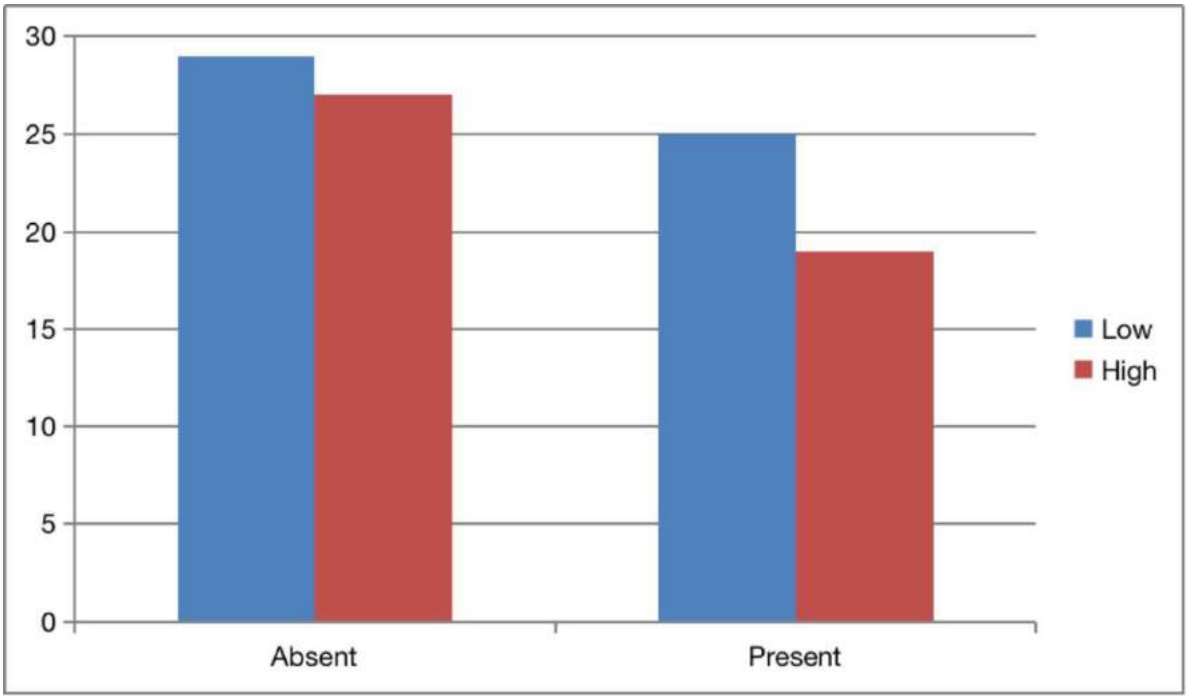


Figure 26: Correlation between Smoking and Glycemic Gap

Kaplan-Meier survival analysis

Kaplan-Meier survival analysis shows that higher duration of hospitalisation was observed in subjects who died. Among seven subjects who died, six of them had high glycemic gap.

Glycemic gap (category)	Total N	N of Events	Censored	
			N	Percent
Low	54	1	53	98.1%
High	46	6	40	87.0%
Overall	100	7	93	93.0%

Means and Medians for Survival Time

Glycemic gap (category)	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Low	8.889	.110	8.673	9.105	.	.	.	.
High	10.648	.502	9.663	11.632	.	.	.	.
Overall	10.889	.417	10.071	11.706	.	.	.	.

a. Estimation is limited to the largest survival time if it is censored.

Overall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	1.154	1	.283
Test of equality of survival distributions for the different levels of Glycemic gap (category).			

Table 27: Kaplan-Meier survival analysis

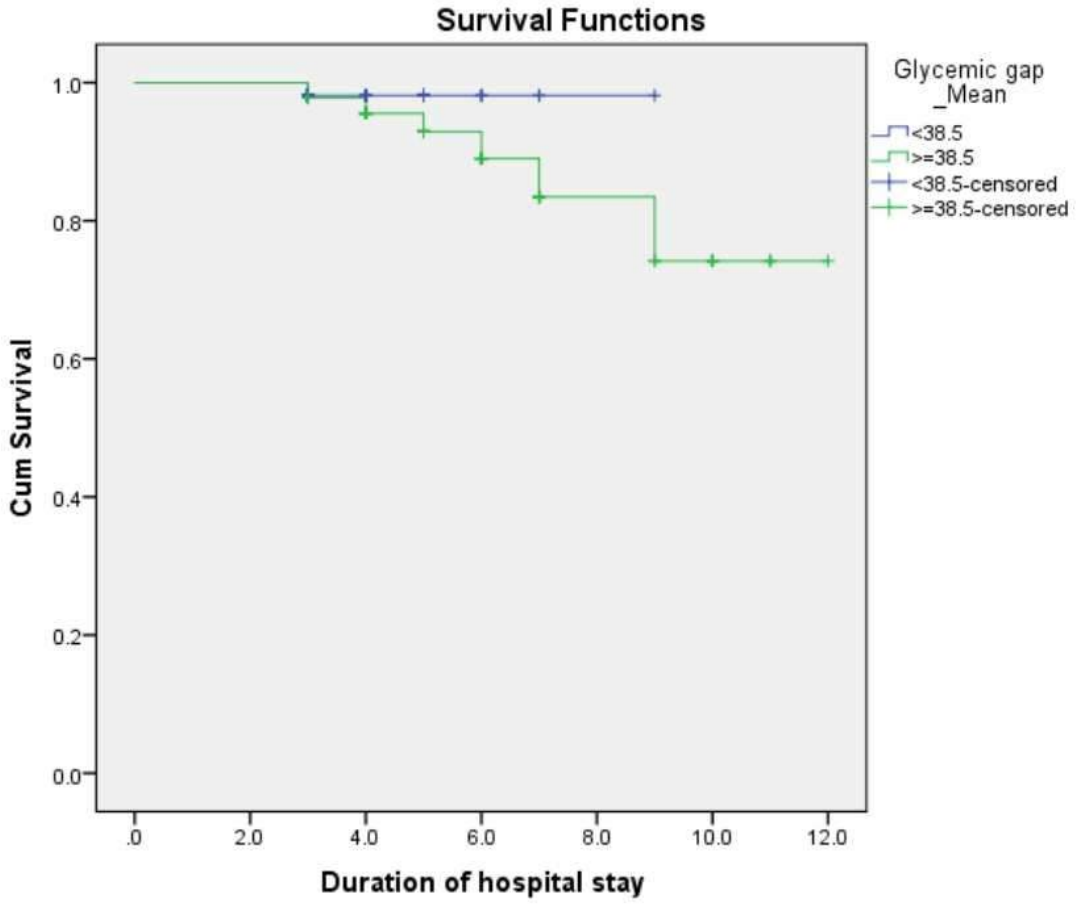


Figure 27: Kaplan-Meier survival analysis

ROC curve

Receiver Operator Characteristic (ROC) curve analysis shows that glycemic gap is a better predictor of mortality than HbA1c and admission CBG.

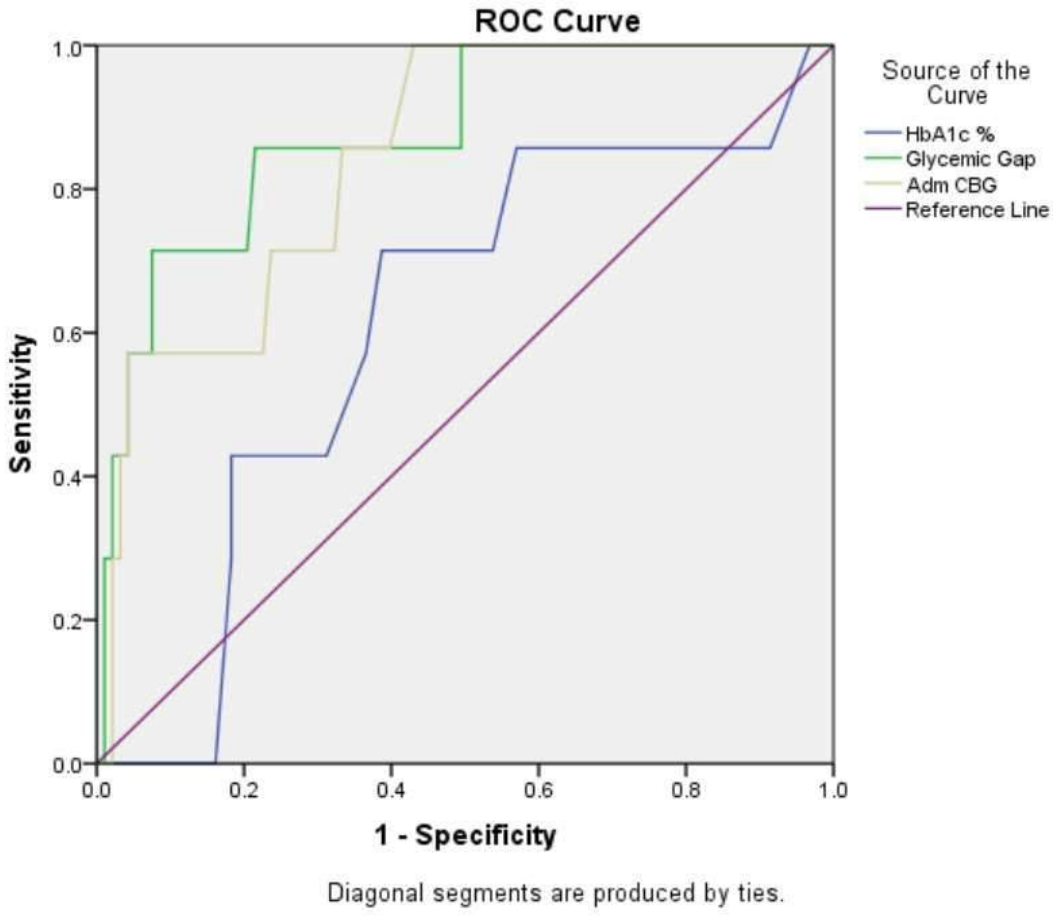


Figure 28: ROC curve

ROC curve

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
HbA1c %	.609	.104	.337	.405	.813
Glycemic Gap	.876	.065	.001	.748	1.000
Adm CBG	.844	.063	.002	.720	.968

Table 28: Area under the curve

SUMMARY

The mean age is 58.6 years (S.D. =13.1) ranging between 31 years and 85 years. Majority of them were males (n=61, 61%). Around 59% had hypertension and 40% had dyslipidaemia. Around 44% of them were smokers. Around 88% of them had chest pain, 41% had breathlessness, 24% had palpitations and 8% had syncope.

In Killip class distribution, around 53% were class I, around 21% were class II, around 14% were class III and around 12% were class IV. In ACS type, around 58% were NSTEMI and 42% were STEMI. The mean CBG is 262.67 (S.D=86.5) ranging between 147 and 672. Mean HbA1c is 8.4 (S.D.=1.5) ranging between 6.5 and 13.2.

Mean glycemic gap distribution is 67.4 (S.D. =70.6) ranging between -46 and 392. The cut-off value for the glycaemic gap was determined as 38.5 mg/dl using the Youden's index (0.34) with a sensitivity and specificity of 65.85 % and 67.8 % respectively.

Correlation between Glycemic Gap and Killip Class shows that higher Killip class is associated with high glycemic gap. This is statistically significant ($p<0.005$). Correlation between Glycemic Gap and ACS Type shows that high glycemic gap is associated more with STEMI. This is statistically significant ($p<0.005$).

Correlation between glycemic gap and acute heart failure shows that incidence of heart failure is higher in subjects with high glycemic gap. This is statistically significant ($p<0.005$). Among 12 subjects who had cardiogenic shock, nine of them had high glycemic gap. This is statistically significant ($p<0.05$).

Majority of the subjects with acute kidney injury had high glycemic gap (13 out of 21 subjects). This is statistically not significant ($p>0.05$). Among 18 subjects who had ARF, 13 of them had high glycemic gap. This is statistically significant ($p<0.05$).

Majority of the subjects with arrhythmias had high glycemic gap (seven out of 11 subjects). This is statistically not significant ($p>0.05$). Correlation between glycemic gap and LVEF shows that higher glycemic gap is associated with lower LVEF. This is statistically highly significant ($p<0.005$).

Among 46 subjects with high glycemic gap, 12 of them had single vessel disease, 15 of them had double vessel disease and 12 of them had triple vessel disease. This is statistically significant ($p<0.005$). Higher glycemic gap was associated with increased hospital stay. This is statistically significant ($p<0.005$). Among seven subjects who died, six of them had high glycemic gap. This is statistically significant ($p<0.05$).

Comparison of age and glycemic gap shows that the mean age was higher in subjects with higher glycemic gap (59.4 vs 58 years). This is statistically not significant ($p>0.05$). There is no statistically significant correlation between gender and glycemic gap ($p>0.05$). There is no statistically significant correlation between prevalence of hypertension and glycemic gap ($p>0.05$). There is no statistically significant correlation between prevalence of dyslipidaemia and glycemic gap ($p>0.05$). There is no statistically significant correlation between smoking and glycemic gap ($p>0.05$).

Kaplan-Meier survival analysis shows that higher duration of hospitalisation was observed in subjects who died. Among seven subjects who died, six of them had high glycemic gap. ROC curve analysis shows that glycemic gap is a better predictor of mortality than HbA1c and admission CBG.

Discussion

DISCUSSION

Stress hyperglycaemia is accompanied by increased insulin resistance, increased gluconeogenesis and increased lipolysis as a result of the oxidative stress and elevated levels of counter-regulatory hormones and pro-inflammatory cytokines. The admission blood glucose (ABG) level may not be a true reflector of the stress-induced rise in blood glucose levels, as it can be influenced by the underlying glycaemic status of patients with diabetes mellitus. Recently, glycaemic gap has emerged as a novel glycaemic indicator and is defined as the difference between the ABG and ADAG (eAG). It is a better indicator of the stress hyperglycaemia compared with the ABG as it eliminates the influence of chronic hyperglycaemia. The glycemic gap has been studied in various critical illnesses such as community acquired pneumonia, sepsis, acute ischaemic stroke and intracranial haemorrhage but studies in acute MI are very few in number.[3]

We conducted a prospective study involving 100 diabetes mellitus patients presenting to the ED with acute MI. The glycemic gap was calculated and correlated with the severity and outcome of the myocardial infarction. There were more male patients in the study population compared to females. Most patients in the study belonged to the age group of 51-70 years. Most of the patients presented with chest pain. Breathlessness, palpitations and syncope were the other presenting complaints observed among the patients in the study.

We observed that patients with an elevated glycemic gap had a higher Killip class at presentation indicating the severity of heart failure. An elevated glycemic gap

was strongly related to the development of acute heart failure. These findings were consistent with those of a retrospective observational study conducted by Liao et al. (2016), in which 331 patients were enrolled and a significant relationship was established between elevated glycemic gap and Major Adverse Cardiovascular Events (MACE) including acute heart failure.[3]

We noted that patients with an elevated glycemic gap had a higher incidence of cardiogenic shock as compared to those with a low glycemic gap. This finding was consistent with the findings of a multi-center observational study conducted across 274 centers in China by Shuang Wu et al.[54] We observed that patients with an elevated glycemic gap had lower values of left ventricular ejection fraction as compared to this with a low glycemic gap. 33 patients were found to have an EF of less than 40 percent, out of which 25 patients had an elevated glycemic gap. These findings were similar to the study done by Liao et al.[3]

We noted that patients with an elevated glycemic gap had a higher mortality rate compared to those with a low glycemic gap. This finding was consistent with the findings of Shuang Wu et al[54] and Liao et al. The duration of hospital stay was also higher in those with an elevated glycemic gap. This finding was consistent with a prospective study done by Ghanem et al in Egypt.[55]

The development of acute respiratory failure with the need for mechanical ventilation was found to be higher in patients with an elevated glycemic gap as compared to those with a low glycemic gap in our study. This was similar to the finding reported by Liao et al. There was no significant difference in the development of acute

kidney injury between the two groups. There was no significant difference in the occurrence of arrhythmias between the two groups in our study. These observations were similar to the findings reported by Liao et al in their study.

In a study done by Capes et al, the ABG levels were associated with poor prognosis in STEMI patients without diabetes, but the association was relatively weaker in diabetic patients. Capes et al. reported that the ABG correlated with an elevated risk of heart failure and cardiogenic shock in non-diabetic patients, but the correlation was not significantly observed in diabetic patients. This observation highlighted the confounding nature of the underlying glycaemic status of patients with diabetes in predicting adverse outcomes. Instead of the ABG, the glycemic gap was correlated with major adverse cardiac events (MACEs) in a study done by Gao S et al, and the results showed that an elevated glycemic gap is a predictor for the occurrence of MACEs in AMI patients with diabetes.[56] In accordance to the findings of the above study, our study revelaed that the glycemic gap showed greater AUROC values for mortality when compared to admission blood glucose and HbA1c. The Receiver Operating Characteristic curve analysis revelaed that the glycemic gap was superior to admission CBG as well as HbA1c values in predicting mortality in patients with acute MI. This finding was also observed in the study conducted by Liao et al and Ghanem et al.[55]

Kaplan-Meier survival analysis shows that higher duration of hospitalisation was observed in patients who died. Majority of the deaths occurred in the group of patients with an elevated glycemic gap. This observation was similar to the findings of Shuang Wu et al.[54]

Conclusion

CONCLUSION

Stress Induced Hyperglycemia (SIH) is commonly observed in patients with diabetes mellitus hospitalised for acute myocardial infarction and is associated with adverse outcomes and a higher mortality rate. The Admission Blood Glucose (ABG) is not an ideal indicator of the magnitude of SIH as it is unable to differentiate whether the surge in blood glucose is caused by the acute stress response or the chronic glucometabolic state in diabetic patients. The glycemic gap, defined as the difference between the ABG and the ADAG is superior to the ABG and HbA1c values in predicting the severity and outcome of acute myocardial infarction in diabetic patients. Patients with an elevated glycemic gap presented with a higher Killip class and were found to have higher risk of adverse outcomes such as cardiogenic shock, acute respiratory failure, a lower LV ejection fraction, longer duration of hospital stay and higher mortality rate when compared to those with a low glycemic gap. The glycemic gap thus provides additional prognostic information beyond that provided by conventional risk factors in diabetic patients presenting with acute MI. Hence, the glycemic gap should be considered for inclusion in the risk stratification of patients presenting with acute MI.

Limitations

LIMITATIONS

- The sample size of our study is relatively small compared to previous studies.

- The present study is a single center study. Experimental and multi-center clinical studies with large sample size are needed to further verify our findings in the future.

- The level of glycemic control during hospital admission might have influenced the outcomes. In our study, we did not address the effect of glycemic control on the outcome of the patients during hospitalization.

- We only recruited STEMI and NSTEMI patients in the present study. Patients with Unstable Angina were not included. Thus, our findings remain to be verified in patients with the entire spectrum of acute coronary syndrome.

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ANNEXURES

IEC CERTIFICATE

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL,CHENNAI_-01
INSTITUTIONAL ETHICS COMMITTEE

TITLE OF THE WORK	:	"AN ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECTIVENESS OF GLYCEMIC GAP AS A BIOMARKER OF SEVERITY AND OUTCOME AMONG MYOCARDIAL INFARCTION PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE CENTRE IN CHENNAI"
PRINCIPAL INVESTIGATOR	:	DR. J. ARJUN,
DESIGNATION	:	PG IN GENERAL MEDICINE,
DEPARTMENT	:	DEPARTMENT OF GENERAL MEDICINE

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 24.03.2021 at the Council Hall, Stanley Medical College, Chennai-1 at 11 am.

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

29/3/21

MEMBER SECRETARY,
IEC, SMC, CHENNAI.

PROFORMA

Name :

Age :

Gender :

IP No :

Contact No :

Date of Admission **:**

Date of Discharge/death **:**

Presenting Complaints:

SYMPTOM	YES	NO	DURATION
Chest pain			
Breathlessness			
Palpitations			
Syncope			
Others (specify)			

Past history:

- Diabetes Mellitus – YES / NO
- Systemic Hypertension – YES / NO
- Prior H/o Coronary Artery Disease - YES / NO
- Chronic Kidney Disease – YES / NO
- Dyslipidaemia – YES / NO
- H/o Blood transfusion in the past 3 months – YES / NO

Personal history:

Smoker – YES / NO Duration -

Alcoholic – YES / NO Duration -

Treatment history:

H/o Steroid intake – YES / NO. (If yes, specify type and duration)

General Examination -

Pallor - YES/ NO

Icterus - YES/ NO

Cyanosis - YES/ NO

Pedal edema - YES/ NO

JVP – elevated / not elevated

Tachypnea – YES / NO

Vitals:

Pulse rate (/min)	
Blood Pressure (mmHg)	
SpO2 %	
Respiratory rate (/min)	

Systemic Examination:

CVS -

RS -

P/A -

CNS -

Investigations:

ECG –

Troponin I –

Admission Blood Glucose (ABG) –

HbA1c –

A1c Derived Average Glucose (ADAG) =

Glycemic Gap =

Hemoglobin -

Serum Creatinine -

ECHO –

LV Ejection Fraction -

Coronary Angiogram –

Complications:

Complication	Yes	**No**
Acute heart failure		
Cardiogenic Shock		
Acute Kidney Injury		
Acute Respiratory Failure		
Arrhythmia		

PATIENT INFORMATION SHEET

TITLE OF THE STUDY - **"AN ANALYTICAL CROSS-SECTIONAL STUDY TO DETERMINE THE EFFECT OF GLYCEMIC GAP AS A BIOMARKER OF SEVERITY AND OUTCOME AMONG ACUTE MYOCARDIAL INFARCTION PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE CENTRE IN CHENNAI."**

We are conducting a study among diabetic patients admitted with acute myocardial infarction at Government Stanley Hospital, Chennai. The purpose of this study is to find out whether the glycemic gap can be used as a predictor of the severity and adverse outcomes of acute myocardial infarction in diabetic patients. A detailed history and physical examination will be done for all the patients. ECG, ECHO and blood samples will be collected from all the patients. Glycemic gap will be calculated for all the patients. Patients with a low glycemic gap will be compared to those with a low glycemic gap. The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared. Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled. The results of the study will be intimated to you at the end of the study to aid in the management or treatment.

Signature of Investigator Signature of participant

Date :

ஆராய்ச்சி தகவல் தாள்

TITLE OF THE STUDY - **"AN ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECT OF GLYCEMIC GAP AS A BIOMARKER OF SEVERITY AND OUTCOME AMONG ACUTE MYOCARDIAL INFRACTION PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE CENTRE IN CHENNAI."**

இதனால் தங்களது ஆய்வறிக்கையோ, அன்றாட செயல்பாடுகளோ பாதிக்கப்படாது என்று தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியின் முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ தங்கள் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துகொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது அதன் முடிவில் அறிவிக்கப்படும் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

பங்கேற்ப்பாளர் கையொப்பம் ஆராய்ச்சியாளர் கையொப்பம்

இடம் :
நாள் :

PATIENT CONSENT FORM

STUDY:

AN ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECT OF GLYCEMIC GAP AS A BIOMARKER OF SEVERITY AND OUTCOME AMONG ACUTE MYOCARDIAL INFRACTION PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE CENTRE IN CHENNAI.

Study Centre: Dept. of General Medicine, Government Stanley Hospital, Chennai.

Patient's Name:
Patient's Age/sex:
ID No:

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected. ❑

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permissionto look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to thisaccess. However, I understand that my identity will not be revealed in any informationreleased to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately informthe study staff if I suffer from any deterioration in my health or wellbeing or any unexpected or unusual symptoms. ❑

e) I hereby consent to participate in this study. ❑

f) I hereby give permission to undergo detailed clinical examination, ECG, ECHO and blood investigations. ❑

Signature/thumb impression Signature of Investigator

Patient's Name: Study Investigator's Name:

ஆராய்ச்சி ஒப்புதல் படிவம்

TITLE OF THE STUDY - **"AN ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECT OF GLYCEMIC GAP AS A BIOMARKER OF SEVERITY AND OUTCOME AMONG ACUTE MYOCARDIAL INFRACTION PATIENTS WITH TYPE 2 DIABETES MELLITUS IN A TERTIARY CARE CENTRE IN CHENNAI."**

பெயர்:
வயது:
பாலினம் : ஆண் / பெண்
பங்குபெறுபவர் அடையாளஎண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும்மு ழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

இந்த சோதனையில் நான் கலந்து கொண்டு ரத்தபரிசோதனைக்கக சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை புரிந்துகொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சம்மதத்துடன் இந்த ஆராய்ச்சிக்கு என்னை பரிசோதிக்க சம்மதிக்கிறேன்.

பங்கேற்ப்பாளர் கையொப்பம் ஆராய்ச்சியாளர் கையொப்பம்

இடம் :
நாள் :

MASTER CHART

ENTRY KEYS

GENDER	M-MALE	F-FEMALE				
Hypertension	0 - No	1- Yes				
Dyslipidemia	0 - No	1 - Yes				
Smoking	0 - No	1 - Yes				
Chest pain	0 - No	1 - Yes				
Breathlessness	0 - No	1 - Yes				
Palpitations	0 - No	1 - Yes				
Syncope	0 - No	1 - Yes				
ACS TYPE	1 - STEMI	2 - NSTEMI				
GLYCEMIC GAP	0 - LOW	1 - HIGH				
Acute Heart Failure	0- No	1 - Yes				
Cardiogenic Shock	0 - No	1 - Yes				
Acute Kidney Injury	0 - No	1 - Yes				
Acute Respiratory Failure	0 - No	1 - Yes				
ARRHYTHMIAS	0 - No	1 - Yes				
Mortality	0 - No	1 - Yes				
LVEF %	1 : 50-60 %	2 : 40-50 %	3 : 30-40 %			
CAG- No of vessels	0 - not done	1- single vessel disease	2 - double vessel disease	3- triple vessel disease		

	Age	Gender	Hypertension	Dyslipidemia	Smoking	Chest pain	Breathlessness	Palpitations	Syncope	Killip class	ACS type	Adm CBG	HbA1c %	eAG	Glycemic Gap	Glycemic gap (category)	Acute Heart Failure	Shock	AKI	ARF	Arrhythmia	LVEF %	LVEF (Category)	No. of vessels	Duration of hospital stay	Death
1	57	M	1	0	1	0	1	0	0	2	1	240	7.2	160	80	1	1	0	0	0	0	40	3	2	5	0
2	37	F	0	0	0	1	0	0	0	1	2	313	8.5	197	116	1	0	0	0	0	0	48	2	2	6	0
3	74	F	1	0	0	1	0	0	0	1	2	244	9.2	217	27	0	0	0	1	0	0	54	1	1	5	0
4	45	M	0	0	0	1	1	0	0	2	1	231	7.3	163	68	1	1	0	0	0	0	56	1	1	5	0
5	69	M	1	0	1	1	0	0	0	1	1	157	8.7	203	-46	0	0	0	0	0	0	52	1	1	3	0
5	65	M	0	0	1	1	0	1	0	1	2	266	11.4	280	-14	0	0	0	0	0	0	45	2	1	4	0
6	61	F	0	1	0	1	1	0	0	2	2	211	7.9	180	31	0	1	0	0	0	0	45	2	1	4	0
7	81	F	1	1	0	1	1	1	0	3	1	362	6.9	151	211	1	1	0	1	1	0	30	3	0	10	0
8	43	F	0	1	0	1	0	0	0	1	2	170	6.9	151	19	0	0	0	0	0	0	58	1	1	3	0
9	37	M	0	1	1	1	1	0	0	2	1	291	7.7	174	117	1	1	0	1	0	0	36	3	3	6	0
10	65	F	1	0	0	1	0	0	0	1	2	194	8.1	186	8	0	0	0	0	0	0	65	1	1	4	0
11	66	F	1	1	0	1	0	0	0	1	2	176	8.6	200	-24	0	0	0	0	0	0	60	1	1	3	0
12	58	F	1	0	0	1	0	0	0	1	2	264	10.1	243	21	0	0	0	0	0	0	58	1	1	3	0
13	71	F	1	1	0	1	0	0	1	3	1	411	8.5	197	214	1	1	0	0	1	1	36	3	2	6	1
14	37	F	0	0	0	1	0	0	0	2	2	239	7.4	166	73	1	1	0	0	0	0	48	2	2	5	0
15	55	F	0	0	0	1	0	0	0	1	2	192	7.4	166	26	0	0	0	0	0	0	60	1	1	3	0
16	67	M	1	0	1	1	1	0	0	2	1	203	6.7	146	57	1	1	0	0	0	0	42	2	1	5	0
17	85	M	1	1	1	1	1	0	0	3	2	277	8.3	192	85	1	1	0	0	1	0	25	3	3	7	0
18	66	F	0	1	1	0	1	0	0	2	2	211	8.4	194	17	0	1	0	0	0	0	46	2	1	5	0
19	51	F	0	0	0	1	0	0	0	1	2	156	7.8	177	-21	0	0	0	0	0	0	62	1	1	3	0
20	37	F	0	0	0	1	0	0	0	1	2	197	8.7	203	-6	0	0	0	0	0	0	54	1	1	3	0
21	45	M	0	0	1	1	0	0	0	1	2	272	8.4	194	78	1	0	0	0	0	0	48	2	1	3	0
22	49	M	0	0	1	1	0	0	0	1	2	198	7.4	166	32	0	0	0	0	0	0	56	1	1	3	0
23	47	M	1	0	1	1	1	0	0	2	2	273	6.7	146	127	1	1	0	0	0	0	36	3	3	7	0
24	38	M	0	0	1	1	1	0	0	3	1	259	7.3	163	96	1	1	0	1	1	0	38	3	2	5	0
25	79	M	1	1	1	0	1	1	0	2	1	193	7.4	166	27	0	1	0	1	0	0	36	3	2	6	0
26	72	M	1	0	1	1	0	0	0	1	2	162	6.7	146	15	0	0	0	0	0	0	56	1	1	3	0
27	46	M	1	1	1	1	1	1	0	3	1	254	7.9	180	74	1	1	0	1	1	0	38	3	0	7	0
28	81	F	1	1	0	0	1	1	1	3	1	269	10.2	246	23	0	1	0	1	1	1	38	3	2	5	0
29	54	F	1	0	0	1	1	0	0	2	1	294	10.7	260	34	0	1	0	0	0	0	48	2	2	4	0
30	75	M	1	0	1	1	1	1	0	4	1	403	8.6	200	203	1	1	1	1	0	0	26	3	3	7	1
31	49	M	0	0	1	1	0	0	0	1	2	227	7.2	160	67	1	0	0	1	0	0	54	1	1	4	0
32	58	F	1	1	0	1	0	0	0	1	2	279	8.6	200	79	1	0	0	0	0	0	54	1	1	4	0
33	61	M	1	0	0	1	0	0	0	1	2	237	9	212	25	0	0	0	0	0	0	62	1	1	3	0
34	66	F	1	0	0	1	0	0	0	1	2	237	8.6	200	37	0	0	0	1	0	0	54	1	1	6	0
35	65	M	1	0	1	0	1	1	0	3	1	432	9.1	214	218	1	1	1	0	1	0	30	3	0	12	0
36	39	F	0	0	0	1	0	0	0	1	2	216	8.7	203	13	0	0	0	0	0	0	60	1	1	3	0
37	70	F	0	0	0	1	1	0	0	2	1	287	8.6	200	87	1	1	0	0	0	0	34	3	1	6	0
38	67	F	1	1	0	0	1	1	1	4	1	506	9.6	229	277	1	1	1	0	1	1	30	3	0	4	1
39	83	M	1	1	0	0	1	1	1	4	1	259	9.4	223	36	0	1	1	0	1	0	36	3	0	3	1
40	54	M	0	1	0	0	1	0	0	1	2	309	13.2	332	-23	0	0	0	0	0	0	45	2	1	3	0
41	54	M	1	1	0	1	0	1	0	3	1	279	8.1	186	93	1	1	0	0	1	0	25	3	3	10	0

42	48	M	1	0	1	1	0	0	0	1	2	218	8.9	209	9	0	0	0	0	0	0	60	1	1	5	0
43	66	M	1	1	1	0	1	1	0	2	2	259	8.1	186	73	1	1	0	1	0	0	38	3	2	6	0
44	68	M	0	0	0	1	0	0	0	1	2	164	6.9	151	13	0	0	0	1	0	0	54	1	2	5	0
45	78	M	1	1	1	1	0	1	0	1	2	211	7.7	174	37	0	0	0	0	0	0	46	2	2	5	0
46	61	F	1	1	0	1	1	1	0	3	1	273	7.9	180	93	1	1	0	0	1	0	30	3	3	5	1
47	52	F	0	0	0	1	1	0	1	4	1	672	11.4	280	392	1	1	1	1	1	0	32	3	0	11	0
48	43	M	0	1	0	1	0	0	0	2	1	221	8.1	186	35	0	0	0	1	0	0	48	2	2	6	0
49	64	M	1	0	1	1	0	0	0	1	2	167	6.6	143	24	0	0	0	0	0	0	60	1	1	3	0
50	52	F	0	0	0	1	0	0	0	1	1	307	9	212	95	1	0	0	0	0	0	35	3	2	5	0
51	64	M	1	0	1	1	1	1	0	3	1	291	6.7	146	145	1	1	0	0	1	1	25	3	3	3	1
52	43	F	0	1	1	1	0	0	0	1	2	335	12.4	309	26	0	0	0	0	0	0	56	1	1	3	0
53	42	M	0	0	1	1	0	0	0	1	2	247	9.6	229	18	0	0	0	0	0	0	54	1	1	3	0
54	61	M	0	0	0	1	1	0	0	2	1	339	10.8	263	76	1	1	0	1	0	0	38	3	3	6	0
55	69	M	1	0	1	1	1	1	0	3	1	241	8.7	203	38	0	1	0	0	1	0	42	2	1	7	0
56	72	F	1	1	0	1	0	0	0	1	2	303	8.3	192	111	1	0	0	0	0	0	36	3	2	5	0
57	61	M	0	0	1	1	1	0	0	2	1	306	7.8	177	129	1	1	0	0	0	0	48	2	1	4	0
58	74	M	1	1	0	1	0	0	0	1	1	229	8.3	192	37	0	0	0	1	0	0	48	2	1	5	0
59	60	F	1	0	0	1	1	0	0	2	1	297	8.4	194	103	1	1	0	0	0	0	48	2	1	5	0
60	70	F	1	0	0	1	0	0	0	1	2	537	13	326	211	1	0	0	1	0	0	60	1	2	6	0
61	61	M	0	1	0	1	1	0	0	3	2	259	7.7	174	85	1	1	0	0	0	0	48	2	2	7	0
62	37	M	0	0	0	1	0	0	0	1	2	178	7.4	166	12	0	0	0	0	0	0	60	1	1	3	0
63	61	M	1	1	0	1	0	0	0	1	2	169	6.9	151	18	0	0	0	0	0	0	52	1	1	3	0
64	81	M	0	0	0	1	1	0	0	2	2	215	7.2	160	55	1	1	0	0	0	0	54	1	0	5	0
66	67	M	1	0	1	1	1	0	0	4	1	366	8.3	192	174	1	0	1	1	1	0	28	3	3	11	0
67	31	M	0	0	0	1	0	0	0	1	2	151	6.7	146	5	0	0	0	0	0	0	45	2	1	3	0
68	56	M	1	0	1	0	1	1	0	1	2	234	8.6	200	34	0	0	0	0	0	0	48	2	0	3	0
69	55	F	1	1	0	1	1	0	0	2	1	264	9.7	232	32	0	1	0	0	0	0	38	3	2	5	0
70	51	M	1	0	1	1	0	0	0	1	2	252	7.8	177	75	1	0	0	0	0	0	46	2	1	3	0
71	49	M	1	1	1	1	0	0	0	1	2	184	7.1	157	27	0	0	0	0	0	0	54	1	1	3	0
72	58	F	1	0	1	1	1	0	0	2	2	213	7.9	180	33	0	1	0	0	0	0	54	1	1	4	0
73	56	F	0	0	0	1	0	1	0	1	2	404	9.1	214	190	1	0	0	0	0	1	54	1	1	5	0
74	62	M	1	0	0	0	0	0	0	1	1	288	8.4	194	94	1	0	0	0	0	0	45	2	2	9	0
75	71	M	1	0	1	0	1	1	0	2	2	198	7.4	166	32	0	1	0	0	0	1	58	1	1	4	0
76	55	M	1	1	0	1	0	1	0	1	2	218	6.9	151	67	1	0	0	0	0	0	42	2	2	4	0
77	64	M	1	1	1	1	0	0	0	1	1	275	8.1	186	89	1	0	0	0	0	0	52	2	3	4	0
78	39	M	0	0	1	1	0	0	0	2	1	289	10.6	258	31	0	1	0	0	0	0	45	2	2	3	0
79	76	M	1	1	1	1	1	0	1	4	1	231	8.3	192	39	0	0	1	0	1	0	32	3	2	9	0
80	45	M	1	1	0	1	0	0	0	1	2	255	10.2	246	9	0	0	0	0	0	0	42	2	1	3	0
81	36	M	0	0	1	1	0	0	0	1	2	355	13.2	332	23	0	0	0	0	0	0	60	1	1	3	0
82	85	F	1	1	0	1	1	1	0	3	1	215	7.8	177	38	0	1	0	0	1	0	36	3	2	5	0
83	46	F	0	0	0	1	0	0	0	2	1	237	6.7	146	91	1	1	0	0	0	0	45	2	2	5	0
84	79	F	1	1	0	1	1	0	0	4	2	347	10.7	260	87	1	0	1	0	0	1	34	3	2	7	0
85	52	M	1	0	0	1	0	0	0	1	2	211	8.5	197	14	0	0	0	0	0	0	62	1	1	4	0

86	47	M	1	1	1	1	0	0	0	1	2	262	9.8	235	27	0	0	0	0	0	0	54	1	1	3	0
87	71	M	1	1	1	1	1	0	1	4	1	487	9.7	232	255	1	1	1	1	1	0	25	3	0	9	1
88	49	M	0	0	0	1	0	0	0	1	2	174	6.8	148	26	0	0	0	0	0	0	62	1	1	3	0
89	47	F	1	1	1	1	0	0	0	3	2	203	7.7	174	29	0	1	0	0	0	0	54	1	1	5	0
90	69	M	1	1	1	1	1	0	1	4	2	235	8.7	203	32	0	1	1	1	0	0	30	3	3	7	0
91	69	F	0	1	0	1	0	1	0	4	1	317	7.4	166	151	1	0	1	1	0	1	38	3	3	10	0
92	38	F	0	0	0	1	0	0	0	1	2	173	6.8	148	25	0	0	0	0	0	0	54	1	1	3	0
93	57	M	0	0	1	1	0	0	0	1	2	276	7.8	177	99	1	0	0	0	0	0	60	1	1	4	0
94	71	M	1	1	1	1	0	0	0	1	1	174	6.6	143	21	0	0	0	0	0	0	42	2	1	3	0
95	63	M	1	1	1	1	0	0	0	1	2	186	6.9	151	35	0	0	0	0	0	0	38	3	2	5	0
96	53	M	0	0	0	1	1	0	0	2	1	294	7.8	177	117	1	0	1	0	0	0	30	3	3	9	0
97	47	F	1	0	0	1	0	1	0	1	1	297	9.1	214	83	1	0	0	0	0	1	42	2	2	6	0
98	73	F	0	0	0	1	0	1	0	1	2	147	6.5	140	7	0	0	0	0	0	1	58	1	1	3	0
99	62	M	0	0	0	1	0	0	0	1	1	362	10.8	263	99	1	0	0	0	0	0	48	2	1	7	0
100	47	M	1	0	1	1	0	1	0	1	2	205	7.6	171	34	0	0	0	0	0	1	48	2	2	5	0