BASELINE HIGHLY SENSITIVE TROPONIN T AND OUTCOME PREDICTION IN ADULTS WITH ACUTE CORONARY SYNDROME TREATED AT THE AGA KHAN UNIVERSITY HOSPITAL-KENYA

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DECLARATION

This research project is my original work and has not been presented for a degree in any other University.

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DEDICATION

To GOD Almighty, who owns our heart and mind and has good plans for every mortal.

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ABBREVIATIONS

AMI	Acute Myocardial Infarction
ACS	Acute Coronary Syndrome
AKUH-N	Aga Khan University Hospital-Nairobi
BMI	Basic Metabolic Index
CVD	Cardiovascular Diseases
CKMB	Creatinine Kinase Muscle/ Brain
CJA	Cardiovascular Journal of Africa
CHD	Coronary Heart Disease
CKBB	Creatinine Kinase Brain
CKD	Chronic Kidney Disease
CKMM	Creatinine Kinase Muscle
cTnT	Cardiac Troponin T
CV	Coefficient of Variation
eGFR	Estimated Glomerular Filtration Rate
ECLIA	Electrochemiluminescence
ESC	European Society of Cardiologists
ED	Emergency Department
EDA	Exploratory Data Analysis
HDL	High Density Lipoprotein
hsTnT	Highly Sensitive Troponin T
HMLIS	Hospital Management Laboratory Information System
IFCC	International Federation of Clinical Chemistry
KNGCDM	Kenya National Guidelines for Cardiovascular Disease Management
KNH	Kenyatta National Hospital
LMICs	Low and Middle Class Income countries
LDL	Low Density Lipoprotein
LoD	Limit of Detection
MI	Myocardial Infarction

PPV	Positive Predictive Value
STEMI	ST Elevation Myocardial Infarction
SSA	Sub Saharan Africa
NSTEMI	Non ST Elevation Myocardial Infarction
UA	Unstable Angina
NPV	Negative Predictive Value
UoN	University of Nairobi
USA	United States of America
URL	Upper Reference Limit
WHO	World Health Organization

DEFINITIONS

Cardiovascular diseases- Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels.

Acute Coronary Syndromes- Acute coronary syndrome (ACS) is a **syndrome** (set of signs and symptoms) due to decreased blood flow in the **coronary** arteries such that part of the heart muscle is unable to function properly or dies.

STEMI- ST-Elevation Myocardial Infarction (STEMI) is a very serious type of heart attack during which one of the heart's major arteries (one of the arteries that supplies oxygen and nutrient-rich blood to the heart muscle) is blocked.

NSTEMI- An electrocardiogram or ECG that displays each heartbeat as a waveform is used to determine if an NSTEMI or a STEMI has occurred in a person. When looking at the waveforms of a person who has had an NSTEMI, they appear very distinct from those of someone who has had a STEMI.

Unstable Angina- Unstable angina is chest pain that occurs at rest or with exertion or stress. The pain worsens in frequency and severity. Unstable angina means that blockages in the arteries supplying your heart with blood and oxygen have reached a critical level.

Acute Myocardial Infarction - Acute myocardial infarction is the medical name for a heart attack. A heart attack is a life-threatening condition that occurs when blood flow to the heart muscle is abruptly cut off, causing tissue damage. This is usually the result of a blockage in one or more of the coronary arteries.

Highly Sensitive Troponin-T – The **high-sensitivity** cardiac **troponin** test (Hs-cTnT) is the latest generation of the cardiac enzyme testing that allows for detection of very low levels of **troponin** T, helping to diagnose heart attacks more quickly

Biomarker- A substance produced by the body, often detectable in body fluids such as blood or urine that indicates a specific process, condition or disease

Cardiac biomarkers-Cardiac biomarkers are substances that are released into the blood when the **heart** is damaged or stressed.

Gold Standard- In medicine and statistics, a *gold standard* test is usually the *diagnostic* test or benchmark that is the best available under reasonable conditions. Other times, a *gold standard* is the most accurate test possible without restrictions.

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ABSTRACT

***Background*:** WHO (2017) report indicates that (CVD) is a major concern worldwide and accounts for approximately 10% mortality and 30% morbidity and nearly half of all these deaths are due to ACS. ACS is divided into ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina. The term acute myocardial infarction (AMI) is used in reference to STEMI and NSTEMI and develops when there is an imbalance between demand in oxygen and supply in the heart muscle. Cardiac troponin assays have evolved over the years and is marked with significant improvement in analytical sensitivity that has enabled the measurement of very low concentrations of Troponin as seen in healthy individuals that was previously not possible. Data on the utility of HsTnT assays is scarce from the African continent. The time from onset of symptoms to initial troponin testing impacts on the baseline levels and is an important consideration when interpreting the evolution of troponin levels.

Objectives: We wanted to determine if baseline HsTnT is a useful predictor of in-hospital mortality among patients with ACS seen at AKUH-N. We also wanted to determine the relationship between known risk factors for CVD and baseline HsTnT levels. Finally, we wanted to determine the association of time to presentation on baseline hsTnT levels.

***Methods*:** A cross sectional study Design looking at clinical and laboratory data for patients diagnosed with ACS at the AKUH-N between January 2012 to December 2013. The data was retrieved from the hospital information system and chart reviews where necessary.

Results: 196 patients were in the final analysis. Patients included were 29 - 89 years. 44% had a diagnosis of STEMI, about 40% had NSTEMI diagnoses and 16% diagnosed with unstable

ungina (UA). 16.8% had normal baseline troponin T levels while 83.2%had elevated baseline troponin T levels. Duration of symptom onset to presentation in patients with STEMI was 1-3 hrs 66.7% while for NSTEMI/UA majority took more than 24hrs to present 70.1%. 12 (6.1%, 95% CI: 2.8%-9.5%) died while in hospital and 24 (12.2%, 95% CI: 7.7%- 16.8%) died after discharge. Troponin T level was found to have no statistically significant effect (RR=1.00, 95% CI 0.99-1.00) on the risk of mortality among ACS patients at 0.05 level of significance. CVD risk factors as well as baseline hsTnT levels had no statistically significant effect on the risk of mortality among ACS patients.

Conclusion : Even though there was no sufficient evidence to conclude that baseline hsTnT was a statistically significant predictor of mortality in this study, previous studies indicates that in patients with ACS, hsTnT levels provides useful prognostic information and permits early identification of patients with increased risk of mortality. (Reichlin, T *et al* 2009).

CHAPTER ONE

INTRODUCTION

1.1 Background

Early diagnosis of (AMI) is very important in the emergency department (ED) in patients with acute onset of chest pains and is the main reason for ED visits and overall cause of death. AMI commonly referred to as 'heart attack' is a medical emergency that usually occurs when blood flow to the heart muscle is blocked and without this blood, tissue lacks oxygen and dies. AMI may present once or may occur repeatedly among patients with other established disease (Thygesen *et al* 2012). According to WHO 2017 report, AMI is the number 1 cause of death worldwide and that 17.7 M people die every year, more than 75% of these deaths are experienced in developing countries and of all CVD`s, an alarming 80% are due to heart attacks and stroke (WHO. 2015). Cardiovascular diseases (CVDs) Fact sheet (Updated May 2017). ACS seems to be increasing in sub-Saharan Africa and is associated with predisposing risk profile like cigarette smoking hypertension and diabetes similar to that of the developed world (Shavadia, J., Yonga, G., & Otieno, H. 2012). According to a report by Kenya national guidelines for cardiovascular management (KNGCDM), adults who are 65 years and above currently are about 2.7% of the total population of Kenya and are at a higher risk of developing CVD which is associated with higher rates of mortality. The report indicates that the main risk factors for the elderly are high systolic blood pressure, dietary patterns, high body mass index, air pollution and tobacco smoke. Management of these risk factors plays a major role in worldwide burden

reduction of CVD among older people (Grundy, S. M., Pasternak, R., Greenland, P., Smith, S., & Fuster, V. 1999, September 28).

Early management and prevention is important in lessening ACS burden and cardiac biomarkers such as troponin play an important role in diagnosis. Cardiac troponins are proteins that are present in the cardiac myocytes and are released when there is onset of myocardial injury. They are believed to be the most sensitive and specific biochemical markers of cardio-myocyte damage. Cardiac troponin I and T are cardio-specific and are the preferred biomarkers for the diagnosis of ACS (Mueller, C. 2014).

The development of highly sensitive troponin assays that can measure troponin levels in healthy individuals has enabled the determination of an upper reference interval limit that can be used as a cut off to diagnose ACS. The improved analytical sensitivity of these new assays has improved their clinical sensitivity for the diagnosis as well as ability to quickly rule out ACS (Peacock, W. F.*et al* 2008).

Cardiac troponin assays like Roche TnT the current 4^{th} generation are measured using automated equipment such as cobas ® 6000 (Mannheim, Germany), and are believed to be superior to all other biomarkers that are clinically available, including myoglobin (Saunders *et al* 2011). They are therefore most preferred for early diagnosis of AMI because of its high sensitivity (De Lemos, J. A. 2013).

1.2 Problem statement

Pain in the chest and other symptoms that might be suggestive of ACS are majorly encountered by emergency physicians and this account for approximately 5% to 10% of all visits to the ED. High mortality has been associated with ACS. Early and timely diagnosis of such patients attending EDs is of major importance especially ruling in or out of ACS. Guidelines for diagnosis of AMI recommend serial sampling and measurement of cardiac troponins in anyone suspected of having an ACS in order to demonstrate increasing or decreasing levels. This is particularly useful when distinguishing between AMI and unstable angina especially in the absence of electrocardiogram findings. AMI requires immediate intervention to prevent further cardiac damage that can be fatal while unstable angina does not necessarily require an immediate intervention but rather the institution of measures to prevent ACS. A delay in diagnosis due to serial sampling may lead to adverse outcomes as it allows for more cardiac damage and other complications like stroke or heart failure hence increasing the risk of mortality or severe morbidity. The utility of a baseline hsTnT in predicting adverse outcomes needs to be evaluated in different populations due to differences in patient characteristics especially risk factors for CVD, health seeking habits and availability of interventional cardiology services. Clinical data available to establish if initial or baseline analysis of hsTnT can predict outcomes in SSA is scarce.

1.3 Justification

CVD is the number 1 cause of death globally with half of the cases being due to ACS and as such poses a public health concern and currently there is little to no available data that has been studied to determine whether baseline analysis of HsTnT can predict outcomes among patients with AMI in SSA, despite knowledge of the increasing burden of CVD`s in developing countries. There is need to study the association between baseline troponin T and ACS outcomes as this will help reduce the time to diagnosis, improve on patient care, lower the need for cardiac stress testing, shorten the length of stay and saves costs among patients in ED. It will also reduce cases of fatalities and other adverse events reducing the time to initiation of definitive treatment. Serial sampling and measuring of hsTnT may not be required before instituting treatment for AMI diagnosis if we are able to demonstrate that a baseline hsTnT level is an independent predictor of adverse events among patients complaining of chest pains and abnormally high hsTnT concentrations at presentation. Available data on the utility of hsTnT is largely from populations where patient characteristics in particular CVD risk factors differ from those found in SSA and time to presentation to a healthcare facility following the onset of symptoms of myocardial ischemia is much shorter due to better infrastructure and availability of healthcare facilities. Determining whether hsTnT is an independent predictor of ACS outcomes as well as an appropriate cut-off with a good predictive value for ACS in patients seen at AKUHN will reduce the time to commencement of specific treatment.

1.4 Research questions

i) Does a baseline hsTnT independently predict fatal mortality among patients diagnosed with ACS at AKUH-N?

ii) What is the duration of onset of symptoms to presentation to health facility?

iii) What is the survival status ACS patients following admission?

iv) What is the relationship between known risk factors for CVD and baseline HsTnT levels, and mortality?

1.5 Study objectives

1.5.1 Main objective

To determine whether a baseline hsTnT level predicts in-hospital and long term mortality among patients with ACS seen at AKUH-N.

1.5.2 Specific objectives

i) To assess patients demographic characteristics per diagnosis and To determine whether baseline analysis of HsTn T predict mortality events among patients at AKUH-N.

ii) To determine duration of onset of symptoms to presentation.

iii) To determine in hospital and long term mortality among ACS patients.

iv) To determine the relationship between known risk factors for CVD and baseline hsTnT levels and mortality

1.5.3 Secondary objectives

To determine the association between CVD risk factors (smoking, hypertension, diabetes and reduced eGFR), baseline hsTnT levels and outcomes among patients with ACS seen at AKUH-N.

CHAPTER TWO

2. LITERATURE REVIEW

2.1 Epidemiology of Acute Coronary Syndromes

Coronary heart disease (CHD) is a global public health concern and the leading cause of death in the Western world. Globally it accounts for 30% of mortality and 10% morbidity. In 2005 alone 17 out of a total of 58 million was due to CVD, and among them 7.6 million were due to CHD (WHO. 2015). In the USA, approximately 15 million patients annually present to the ED with pains in the chest or other symptoms that are suggestive of ACS (Kelly, B. S. 2007, May). In developing countries, 80% of the deaths occur from CHD and with the greatest proportion of patients having ACS (Sanchis-Gomar, F. *et al* 2016). ACS is one of the five main manifestations of CHD, this includes: stable and unstable angina pectoris, heart failure, MI and sudden death (Kumar, A., & Cannon, C. P. 2009). MI incidence of a population can be used for estimating the CHD burden (Anderson, J. L., & Morrow, D. A. 2017). Following AMI, patients still remain at high risk of death and other adverse events like heart failure, recurrent MI and stroke. The CHD burden is high in low and middle income countries(LMICs) due to increased population sizes and high exposure to risk factors such as lack of exercise, unhealthy diet, smoking, diabetes, obesity, excessive alcohol consumption, tobacco use, high blood pressure, abnormal lipid levels and other psychosocial factors. Outcome of ACS in SSA is largely due to inability to afford or access treatment and preventive services. Consequences of industrialization, globalization and urbanization also contribute to these factors. There is need to monitor prevalence, incidence and mortality of ACS so as to track global epidemic trends. Different presentations of ACS requires case definition and they need to be scientifically valid, generally applicable, and consistent when applied across different countries, and very robust. Even though ACS mortality has declined in the past four decades in USA as the life expectancy increases, use of age-adjusted rates to

describe the ACS mortality has been thought to obscure the fact that decline largely represents the postponement of ACS deaths until older age. Burden of ACS is therefore on the rise as life expectancy also increases. The more there are people living with heart disease, the more the increase in burden of prevalent disease that is associated with other comorbid complications. Identifying people who are living with heart disease, and measuring the incidence and disease outcome and how the two might have changed with time becomes paramount as it depicts reduction of disease burden. In this context, MI occupies a central role in the burden of heart disease assessment and yearly there are 32.4 million MI`s and strokes worldwide. Patients with history of MI and stroke are at a higher risk of further development of CHD and other adverse events. Survivors are at a higher risk of recurrent infarctions and have an annual death rate of about 5%. (Institute of Medicine. 2010). *Promoting cardiovascular health in the developing world: A critical challenge to achieve global health*. *Challenge* (p. 465).

2.2 Acute Coronary Syndromes in the elderly

The world`s population is growing and longevity in developing countries has improved significantly. As CHD leads in causing death both in men and women above 65 years of age, its severity and prevalence increase with age. More than 50% of the people above the age of 60, have coronary artery disease which increases with old age and this contributes to high morbidity and mortality in that age group. This is attributed to other comorbid conditions like diabetes, depression, cognitive problems, underrepresentation in clinical trials and atypical vague symptoms that increases with age and this forbids the elderly patients to get good access to quality health care. Thrombolytic or percutaneous coronary intervention is the mainstay in ACS management; however there are still scarce guidelines for management of ACS in this kind of

subset population. Risk factors and outcomes are different among the elderly and there is further need for detailed discussion (Alam, S., & Abou-Khamis, A. 1997).

2.3 Biomarkers of Myocardial Infarction

Since MI causes increasingly significant morbidity and mortality, timely diagnosis and risk stratification is importing when selecting appropriate treatment. Higher number of new markers to predict outcome following an AMI attack have been identified and hsTnT is one of the interesting biomarker. (Chan, D., & Ng, L. L. 2010, June 7). Proper ACS diagnosis requires accurate and very reliable biomarker assays to be able to detect evidence of myocardial necrosis. Over the decades several cardiac biomarkers have been available and have been helpful in detection of MI these include, LDH, myoglobin, CKMB, troponin I and T. Although some of the biomarkers are being used in many hospitals, the novel introduction of highly sensitive troponin assays such as hsTnT have made other biomarkers obsolete. HsTnT assays have improved accuracy in early detection of ACS, nonetheless, correct interpretation requires careful consideration in view of slightly reduced specificity compared to contemporary assays (Kehl, *et al* 2012). Cardiac troponins are the preferred biomarkers for the diagnosis of MI because of high specificity and sensitivity for this diagnosis and therapies given to patients with high troponin have shown to have some impact on the outcomes. Even though other markers of inflammation, myocardial necrosis, and neuro hormonal activity have also been shown to have either diagnostic or prognostic utility, no other biomarker has shown to be superior to highly sensitive troponin assays (Aldous, S. J. 2013, April 15)

2.3.2 Highly sensitive Troponin T

Troponin is the best biomarker for detecting cardiac injury and increased levels are highly specific in injury of cardiac muscles. It is a three-piece protein complex comprising troponin I, troponin T and troponin C. Troponin I inhibits interaction of myosin with actin, Troponin T binds troponin components to tropomyosin and troponin C has binding sites for calcium that initiate contractions. Troponin C is located on the actin filament along with tropomyosin and is important for regulation of calcium mediation of cardiac and skeletal muscle contraction. Troponin C is not specificied to cardiac muscle because it is shared by slow-twitch skeletal muscle and it is mainly not used as an assay for cardiac injury diagnosis. Troponin assays have over the last decade become increasingly sensitive due to the latest upgrade in assay technology. Due to its high specificity to the myocardium, quantification of the biomarker has become important in MI diagnosis. The IFCC Task Force has defined troponin assays as highly sensitive based on the assay performance. Low concentration of cardiac troponin as is found in healthy volunteers cannot be detected by conventional assays but highly sensitive troponin assays can. HsTnT assay can detect levels equivalent to that of approximately 100 dead cardiac cells whereas the conventional assays detect approximately 1000 dead cardiac cells. HsTnT assays detect cardiac troponin in 80% of healthy volunteers. (ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: A report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents. 2012). *Journal of the American College of Cardiology, 60*(23),

2.4 Predisposing factors associated with Cardiovascular Diseases

2.4.1 Physical inactivity

WHO reports that more than 60% of the world`s population is not sufficiently active due to increasing urbanization, industrialization and mechanization. If one is physically active, chances of increasing life span is high. Physical activity therefore protects against many chronic health problems including CVD at any given age. It protects the body by regulating weight and is useful for controlling blood pressure, glucose levels, and lipid levels. Being active everyday will reduce risk of CVD by about 30% and may also lower risk of premature deaths compared to those who are inactive with no risk factors for CVD. Being inactive increases risk of developing CVD and other health related problems (Lanas, F *et a*l 2007).

2.4.2 Smoking

From as early as 1940s, smoking has been associated with heart disease and cancer. Tobacco has from then been increasing risk factors for diseases that cause illness and even death. Many people still don't believe that smoking is linked to heart disease with only 4% being aware and most of the smokers do not believe that they are at a higher risk of developing heart disease than nonsmokers. An individual who started smoking as a child has much higher risk of CVD than one who started smoking as an adult. Tobacco damages endothelium, increases clotting factors, increases deposits of fats in the artery, increases low density lipoprotein cholesterol and promotes coronary artery spasm. Nicotine as an additive component of tobacco increases heart rate and raises blood pressure. Some people who smoke have genes that increase genes that

increase risk of CHD by up to 4 times. Statistics indicates that women who smoke are at a higher risk of developing heart attacks than men who smoke. Even though smoking causes damage quitting effectively reduces risk of CVD and reduces even risk of deaths (Mendis S, Puska P, N. B. 2011).

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2.4.3 Diet

Diet plays a very major role in developing and preventing CVD. If diet can be changed it can cause a great impact on all other cardiovascular risk factors. Diet that is high in saturated fats increases risk of stroke and heart disease and is estimated to cause about 31% of CHD and 11% of stroke globally. Diet low in saturated fats reduces risk of developing new major cardiac events by 73%. Previous studies have shown that diet that is high in fat levels is associated with risk of developing CAD, MI, and even coronary death (Masic, I. *et al* 2011). High fat saturated diet is mainly found in animal products and it increases level of cholesterol in blood which in turns leads to atherosclerosis. Diet that is high in sodium may lead to hypertension which is a risk factor in CVD. Eating diet that is high in fresh fruits, vegetables, whole grain cereals and fish protects the heart against heart diseases and even stroke (Mendis S, Puska P, N. B. 2011).

2.4.4 Blood lipids (fats)

Increased lipids in blood is also another risk factors for CVD. Cholesterol is a soft waxy substance found in lipids in the bloodstream of healthy individual cells. It is essential in healthy

functioning of the body and helps in formation of hormones and cell membranes. Cholesterol is carried into the bloodstream by lipoproteins: namely LDL and HDL. Increased levels of LDL cholesterol cause atherosclerosis which increases the risk of ischemic stroke and the risk of heart attack. HDL cholesterol reduces the risk of CVD and it aids in carrying cholesterol to the bloodstream. High triglyceride levels combined with high LDL cholesterol levels speeds up atherosclerosis which increases the risk of MI and strokes (Mendis S, Puska P, N. B. 2011).

2.4.5 Hypertension

Hypertension is also a leading risk factors of CVD today with at least 970 million people globally having it. 330 million have hypertension in developed countries while 640 million people in developing countries have hypertension. WHO report indicates that hypertension is a crucial cause of premature deaths and estimates about 1.56 billion people will have high blood pressure by 2025 (World Health Organization 2002). Hypertension is when levels of blood pressure is raised with systolic levels of 140 and above. Hypertension stresses the blood vessels and causes it to weaken and clog; hypertension can lead to atherosclerosis and narrowing of the blood vessels. Damaging the arteries creates weak places that rupture easily causing aneurism. A person who is less than 50 years old with high blood pressure is associated with high risk of CVD and increases as one gets older, systolic blood pressure becomes essential predictor for risk of cardiovascular damage. High dietary salt intake significantly raises blood pressure in normal people and in people with hypertension (Mendis S, Puska P, N. B. 2011).

2.4.6 Obesity

Obesity is also included as a major risk factors for CVD. Currently globally, 400 million adults are obese and 1 billion are overweight. Being overweight may lead to development of diabetes, hypertension, atherosclerosis or even death. All these conditions pose greater risk of development of CVD. Increased levels of BMI increases the risk of developing a heart disease and stroke. Individuals with BMI of 25 kg/m^2 and above are considered overweight while those with BMI of 30 kg/m^2 and above are considered obese and the latter are at a serious risk of CVD. Risk of developing type 2 diabetes and hypertension increases as one becomes overweight. Statistics indicates that 58% of diabetes and 21% of ischemic heart attacks are attributable to a BMI greater than 21 kg/m^2 (Mendis S, Puska P, N. B. 2011).

2.4.7 Diabetes

Diabetic patients are 2-4 times more likely to have CVD than those without diabetes. CVD is the leading cause of death among people with diabetes. Uncontrolled diabetes damages blood vessels making them prone to damage from hypertension and atherosclerosis. People with diabetes people are 2-3-fold greater risk of developing a heart failure as compared to people who do not have and prognosis is worse. Diabetes damages nerves and blood vessels. Controlling blood glucose levels reduces the risk of CVD between 33%-50% or death from CVD by 57%. Weight loss and healthy diet maintenance improves diabetes status (Mendis S, Puska P, N. B. 2011).

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2.4.8 Chronic kidney disease

About 26 million people are affected by Chronic kidney disease (CKD) in the US and is considered a coronary risk factor. In patients diagnosed with ACS, CKD is highly prevalent and is associated with long and short-term outcome (Marenzi, G. 2012). ACS is common in CKD and contributes as a major cause of mortality and morbidity. Increased CKD could be due to pump failures or arrhythmias; the uremia-related nontraditional cardiac risk modifiers include cardiomyocytes dysfunction, hyperhomocysteinemia and hypervolemia: all this contribute to increased risk in CKD patients (Roberts, J. K., & McCullough, P. A. 2014). American Heart Association science advisory recommend that all patients with CVD be screened for evidence of kidney disease by estimating glomerular filtration rate (eGFR) among the elderly and testing for microalbuminuria by measuring abumin:creatinine ratio (McCullough, P. A *et al* 2008).

CHAPTER THREE
METHODOLOGY

3.1 Study design and site

Cross sectional study, design was used and retrospective chart review carried out for patients admitted with ACS. The study used data previously collected between January 2012 and December 2013 as part of another study to assess ACS outcomes in Aga Khan University Hospital-Nairobi. However, the assessment of hsTnT and its association with ACS outcomes was not part of the study.

3.2 Eligibility criteria

3.2.1 Inclusion criteria

Study included patients admitted to Aga Khan University Hospital –Nairobi with Acute Coronary syndromes or Acute Myocardial Infarction, ST elevation Myocardial Infarction, Non ST-elevation Myocardial Infarction, Unstable Angina.

3.2.2 Exclusion criteria

Patients with ACS or MI secondary to other medical causes such as hypotension or severe anemia.

Patients whose medical records will be unavailable during period of interest.

Patients who survived to discharge but could not be traced or contacted despite

Patients who whose troponin levels were not done during period of study

3.1 Sampling

Hospital registry was used to identify records of all patients admitted during the study period with discharge of ACS, STEMI, Non STEMI or UA.

List of patients was generated from hospital registry using patient Aga Khan Number which was be used to retrieve charts, hsTnT levels, and electronic medical records was also used to collect data where applicable. Review of records was performed to ascertain diagnosis and eligibility and diagnosis prior to inclusion into the study.

3.2 Data collection

Data of interest will be obtained from patient's charts, hospital registry and laboratory information system. Measures obtained will be:

- Hs Troponin T levels
- Date of admission
- Date of birth where we get the age on admission
- Duration to presentation
- Gender
- Race
- Blood pressure
- Pulse rate, weight, height, BMI calculated
- Comorbidities: diabetes mellitus, hypertension, smoking, creatinine levels lipids, cholesterol

- Diagnosis :STEMI, NSTEMI and Unstable Angina
- Dead or alive status in hospital and out of hospital

3.3 Highly Sensitive Troponin T assay

The "ECLIA" Principle is intended for use on Elecsys and **cobas e** 601 analyzers

It is Immunoassay done in vitro to determination quantitatively cardiac troponin T in human blood either serum or plasma. New hsTn T is a modification of 4th generation cardiac troponin levels and is determined by auto analyzer cobas e601 (Roche diagnostics). HsTnT assay improved significantly by increasing ruthenium concentration of detected antibody and signal background being lowered via buffer optimization. Definition of MI and IFCC recommend using a troponin test which measure 99th percentile URL with analytical precision of less or equal to10% CV (Frankenstein, L. *et al* 2011).

Roche diagnostics achieves this CV and percentile at 14 pg/ml and this complies with the recommendations. IFCC further defines HsTnT as the one that measures troponin above LoD in >50% of healthy subjects and this has also been achieved by Roche cobas e601. (Roche)

3.4 Statistical analysis

3.4.1 Descriptive statistics

Descriptive statistics was performed in form of percentages and frequencies for categorical variables. With regards to base-line characteristics, patients with cardiac troponin levels of at least 14ng/l were compared with patients who had lower levels. Demographics and socio-demographics were performed in form of pie charts histograms and tables.

3.4.2 Log binomial regression model

Log binomial regression model used to model binary outcome. It models relative risk (risk ratio or prevalence ratio) and combines set of predictors to estimate the probability that a particular event will occur. The prevalence ratio calculated shows the amount of change in the outcome variable expected from each unit change in the predictor variable when other predictors are held constant. This model was fitted to evaluate the relationship between the baseline Troponin T levels and mortality among ACS patients. In this model the Troponin T was the independent variable (used a continuous variable) and mortality was the response.

3.4.3 Survival analysis

Survival analysis was performed using Kaplan – Meier survival curves to determine the survival experience between the two groups and log rank tests performed to check for difference in survival curves. Receiver Operating Characteristics (ROC) curves was not employed since our analysis was insignificant. Time to presentation was analyzed using graphs.

3.4.4 Poisson regression model with robust standard errors

This is a model is an approach adapted for binary data, especially as an alternative to the logistic regression. Poisson regression is regarded appropriate model for analyzing rare events. With binomial data when Poisson regression is applied, the error for the estimated relative risk will be over dispersed and this is rectified using Poisson regression model with robust standard errors.

3.1 Ethical consideration

- The KNH-UON Ethics and Research Committee approved the study.
- Data from AKUH-N required institutional approval by AKU Ethics and Research Committee of which a waiver was saught.
- Patient`s data and clinical information were highly confidential no names were used during the research period only principal investigators had access to the data.

3.2 Limitation of the study

1. Missing data for troponin T levels which was either not reported or requested by the doctor or troponin I levels done which was not in our main interest of study.

2. The proportion of patients who died was 6% and those who survived during the study period was around 82% and this difference might have contributed to the statistically insignificant results
3. Missing outcomes due to missing records or that which could not be traced since it was a retrospective study design and also other patients died after study period and this significantly affected prediction

CHAPTER FOUR

RESULTS

4.1 Patient characteristics

228 patients were retrieved from the hospital admission registry. They included patients whose discharge diagnosis was either UA, STEMI or Non STEMI. 196 patients were in the final analysis; excluding 32 whose baseline Troponin T levels were not recorded.

Patients aged between 29 years and 89 years; mean age was 60.6 years (SD=12.3years). The figure 1 shows the patients` percentage by diagnosis.

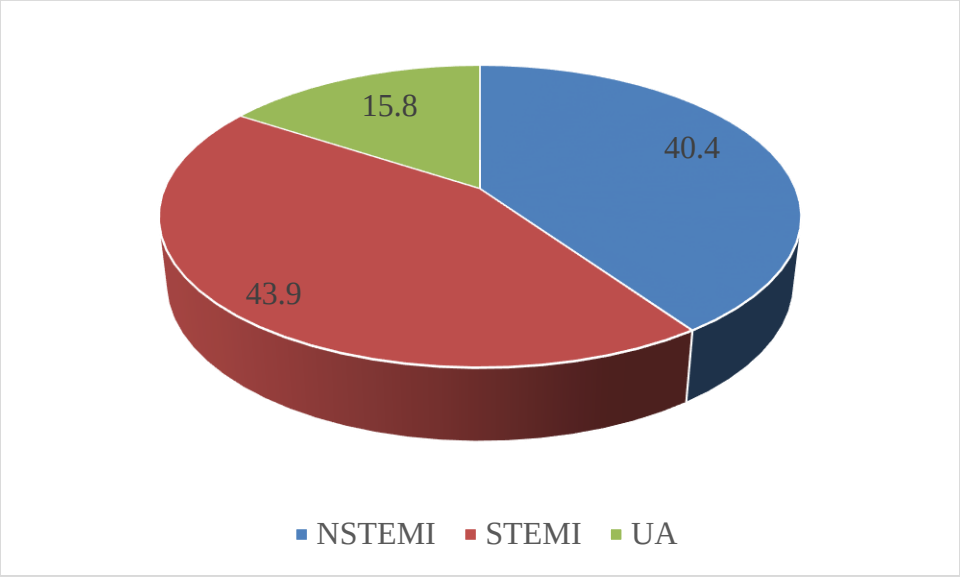

Figure 1: Pie chart by diagnoses

Figure: 2 shows patients' age distribution which appears to be normally distributed.

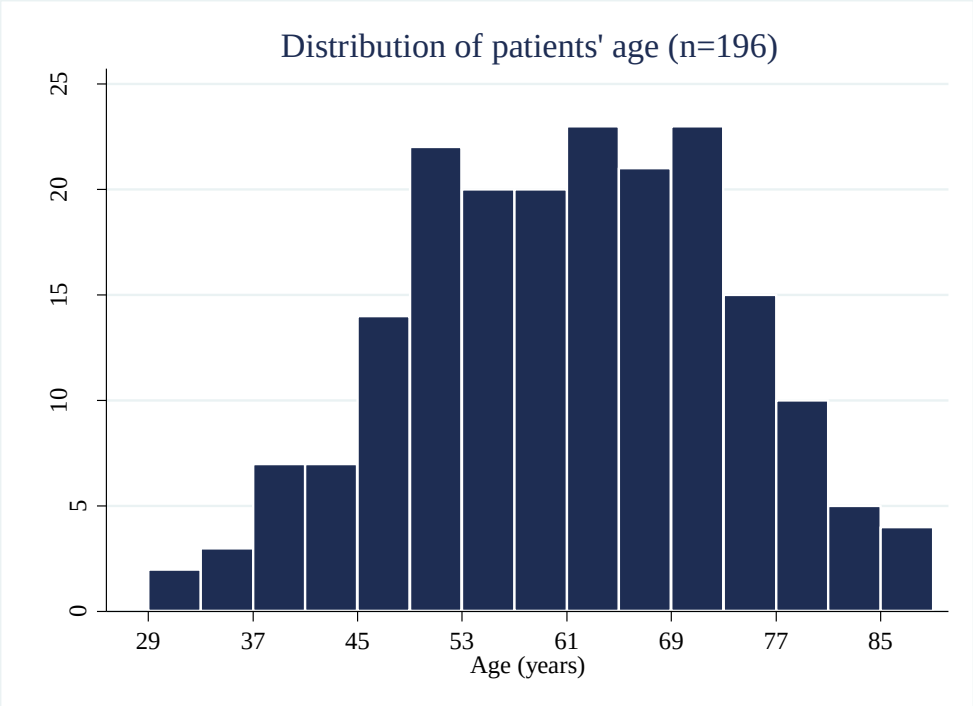

Figure 2: Histogram showing distribution of patient age in years

Male patients were the majority representing 84.2% of the sample. At least half (33.2%) were Asians and one-third (33.2%) were Africans, the rest were Caucasian. A quarter (24.5%) of these patients were smokers. Table 1 presents the summary of the patients' socio-demographic characteristics.

Table 1: Socio-demographic characteristics of patients

Variable	Category	Frequency	Relative frequency (%)
Gender	Female	31	15.8
	Male	165	84.2
Ethnicity	African	65	33.2
	Asian	117	59.7
	Caucasian	14	7.1

Smoker?	No	148	75.5
	Yes	48	24.5

It was noted that more than 50% of the patients weighed above their expected normal weight range; either overweight (40.2%) or obese (32.0%). (37.8%) of the cases were diabetic and at least (59.7%) were hypertensive. Duration between onset of symptoms and presentation to hospital varied from less than 1 hour to 24 hours with majority presenting after 24hrs as shown in **Table 2**. Majority (79.1%) had normal pulse (60-100 beats/minute). (28.1%) had normal systolic blood pressure (<120 mmHg) at admission. High creatinine levels were recorded in a few patients (15.1%).

Table 2: Patients' medical history

Variable	Category	Frequency	Relative frequency (%)
BMI	Underweight	2	1.0
	Normal weight	52	26.8
	Overweight	78	40.2
	Obese	62	32.0
Diabetic?	No	122	62.2
	Yes	74	37.8
Hypertensive?	No	79	40.3
	Yes	117	59.7
Presentation	<1 hour	19	9.7
	1-3 hours	12	6.1
	4-6 hours	33	16.8
	7-12 hours	22	11.2
	13-24 hours	33	16.8
	>24 hours	77	39.3
Pulse rate	Low (<60 beats/min)	10	5.1
	Normal (60-100 beats/min)	155	79.1
	Elevated (>100 beats/min)	31	15.8

Systolic pressure	Normal (<120mmHg)	55	28.1
	Elevated (120-139mmHg)	62	31.6
	High (≥140mmHg)	79	40.3
Creatinine level	Low	112	57.7
	Normal	53	27.3
	High	29	15.0
Baseline Troponin T levels	Normal (≤14pg/ml)	33	16.8
	Elevated (>14pg/ml)	163	83.2

Following admission, 41.8% of the patients were diagnosed with NSTEMI, 43.4% had STEMI and the remaining 14.8% were diagnosed with UA. Approximately 87.0% presented with Angio, and 28.2% were reported to experience heart failure while still in hospital. About 83.0% of the patients had elevated Troponin T levels. (**Table 3**).

Table 3: In-hospital patient history

Variable	Category	Frequency	Relative frequency (%)
Diagnosis	NSTEMI	82	41.8
	STEMI	85	43.4
	UA	29	14.8
Angio (n=196)	No	26	13.3
	Yes	170	86.7
Culprit (n=160)	Graft	1	0.6
	LAD	73	45.6
	LCX	35	21.9
	LMS	2	1.3
	Non atherosclerotic	5	3.1
	RCA	44	27.5
In-hospital heart failure (n=195)	No	140	71.8
	Yes	55	28.2

4.2 Time to presentation by diagnosis

From figure 4.2, it can be deduced that a higher proportion of patients diagnosed with STEMI presented themselves for medical attention earlier than those diagnosed with NSTEMI/UA.

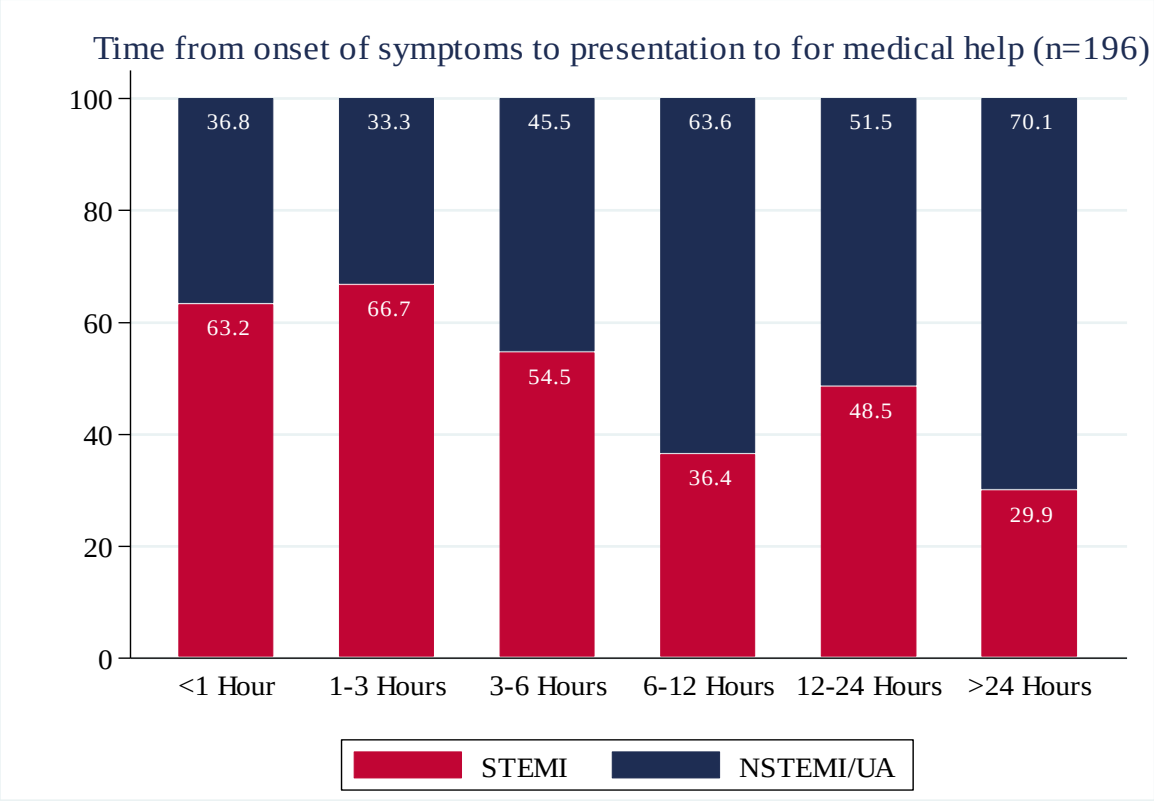

Figure 3: Duration from onset of symptoms to presentation to health facility

4.3 In-hospital and long term mortality among ACS patients

Of the 196 patients, 1ess than a quarter 36 (18.4%) died; 12 (6.1%, 95% CI: 2.8%-9.5%) died while in hospital and 24 (12.2%, 95% CI: 7.7%- 16.8%) after discharge.

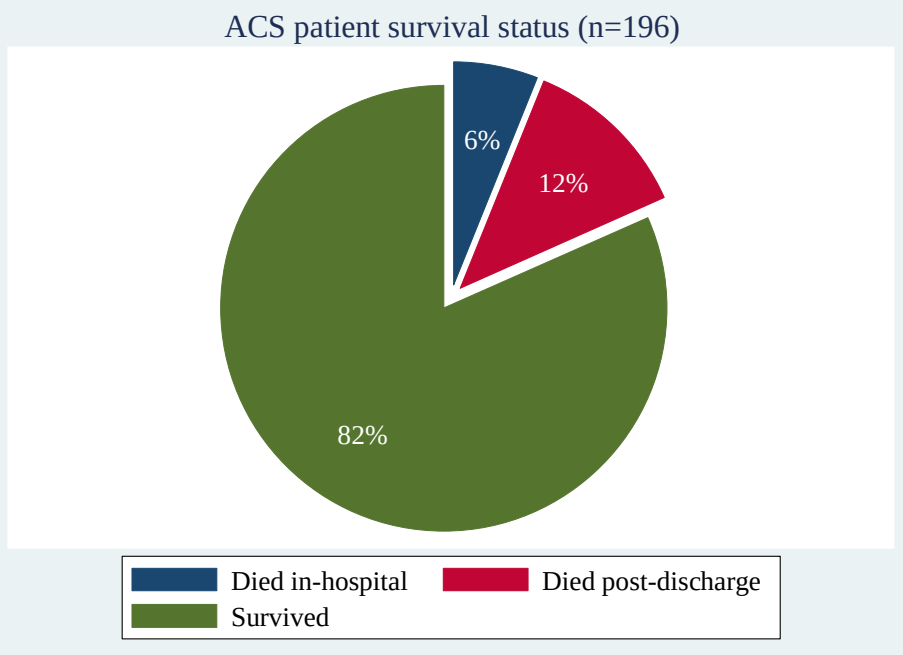

Figure 4: Graph showing patient survival status following admission

4.4 Survival experience by diagnosis

Kaplan-Meier survival estimates were plotted by diagnosis. The outcome was time from admission with ACS to death (event). There was no significant difference in the survival experience between the two groups of patients (Log-rank test P-value = 0.388) as illustrated in figure 4. It was concluded that patients who, upon admission are diagnosed with STEMI had similar survival experience with those diagnosed with NSTEMI/UA.

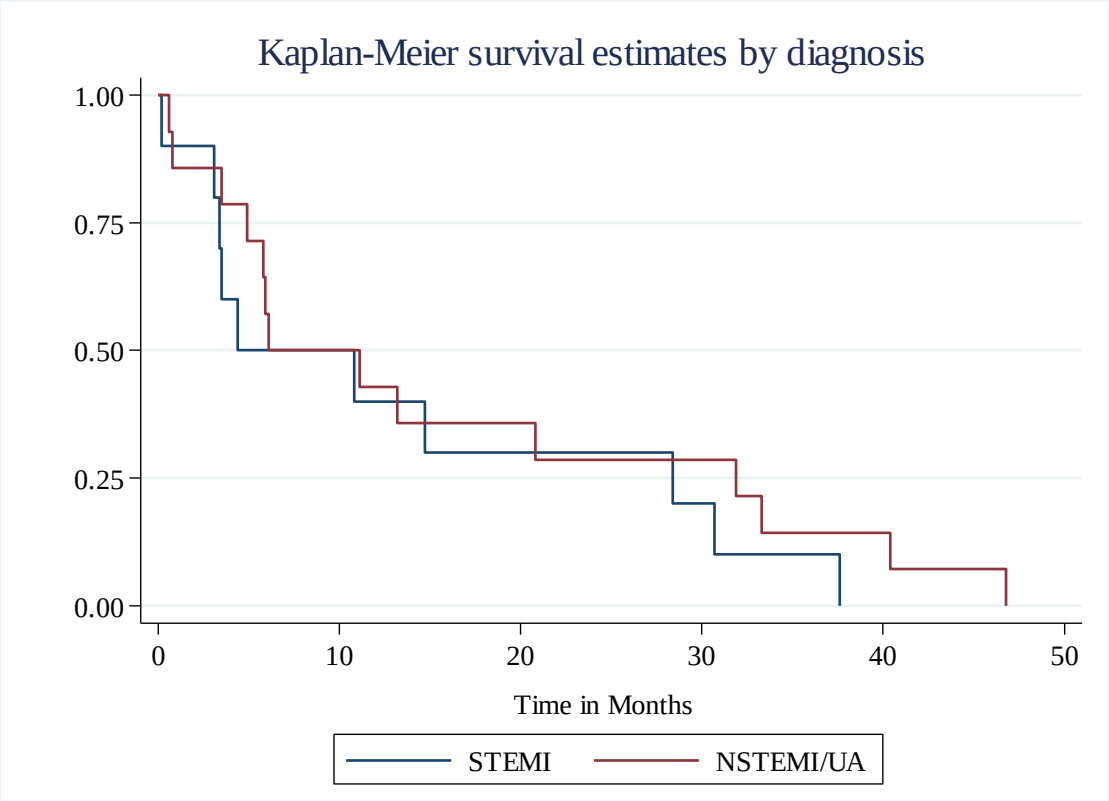

Figure 5: Survival experience based on diagnosis

4.5 Relationship between Baseline hsTnT and mortality among patients with ACS.

Log binomial regression model was fitted to evaluate the relationship between the baseline Troponin T levels and mortality among ACS patients. In this model the Troponin T was the independent variable (used a continuous variable) and the survival status was the response. Due to the limited number of mortality, patients that died in hospital and those that died after discharge were considered as one group (died). The hypothesis being tested was that baseline hsTnT had no effect on the risk of mortality among ACS patients. Troponin T level was found to have no significant effect (RR=1.00, 95% CI 0.99-1.00) on the risk of mortality among ACS patients at 0.05 level of significance. The conclusion was that there is no sufficient evidence to conclude that baseline Troponin T levels independently predict mortality among ACS cases.

4.6 Association between CVD risk factors, baseline Troponin T and mortality

A Poisson regression model with robust standard errors was fit to evaluate the relationship between CVD risk factors, baseline Troponin T levels and mortality while adjusting for the socio-demographic characteristics of the patients. CVD risk factors as well as baseline Troponin T levels were found not to have a statistically significant effect on the risk of mortality among ACS patients as shown in the Table 4.

Table 4: Poisson regression model with robust standard errors to evaluate the relationship between CVD risk factors, Troponin T levels and mortality among ACS patients

Independent variables	Prevalence Ratio (P.R)	P-value	[95% Conf.	Interval]
Troponin	1.00	0.65	1.00	1.00
BMI				
Underweight **(Ref)**				
Normal weight	1.49	0.70	0.19	11.78
Overweight	1.58	0.66	0.20	12.24
Obese	1.61	0.65	0.21	12.44
Creatinine level				
Low**(Ref)**				
Normal	0.92	0.65	0.63	1.33
High	0.84	0.54	0.49	1.45
Systolic BP				
Normal**(Ref)**				
Elevated	1.34	0.19	0.87	2.06
High	1.35	0.17	0.88	2.07
Pulse rate				
Low**(Ref)**				
Normal	0.88	0.72	0.44	1.76
High	0.80	0.59	0.36	1.79
Gender				
Female**(Ref)**				
male	1.04	0.86	0.64	1.70
Diabetic				
No**(Ref)**				
yes	1.00	0.98	0.71	1.40
Hypertension				

No**(Ref)**				
yes	0.96	0.82	0.69	1.34
Smoker				
No**(Ref)**				
yes	1.16	0.46	0.79	1.70
Age (years)	0.99	0.24	0.98	1.01

4.7 Association between CVD risk factors and baseline Troponin T levels

The association between risk factors for CVD and Troponin T levels was determined using Poisson regression with robust standard errors. The outcome variable was Troponin T (categorized into normal (reference) and elevated). Predictor variables consisted of CVD risk factors. There was no statistically significant association between risk factors for CVD and baseline Troponin T levels at 5% level of significance, as presented in table 5.

Table 5: Poisson regression model with robust standard errors to evaluate the association between CVD risk factors and Troponin T levels

Independent variables	Prevalence Ratio (P.R)	P-value	[95% Conf.	Interval]
B.M.I				
Underweight (Ref)				
Normal weight.	0.87	0.86	0.19	3.99
Overweight	0.77	0.74	0.17	3.49
Obese	0.79	0.75	0.18	3.52
Creatinine level				
Decreased (Ref)				
Normal	1.00	0.99	0.69	1.45
High	1.01	0.97	0.62	1.64
Systolic BP				
Normal (Ref)				
Elevated	0.74	0.16	0.48	1.13
High	0.97	0.88	0.66	1.42
Pulse rate				
Low (Ref)				
Normal	1.06	0.87	0.51	2.20
High	1.20	0.66	0.54	2.66
Gender				

Female (Ref)				
Male	1.08	0.77	0.66	1.75
Diabetes				
No (Ref)				
Yes	1.14	0.45	0.82	1.59
Hypertension				
No (Ref)				
Yes	0.96	0.81	0.69	1.34
Smoker?				
No (Ref)				
Yes	1.06	0.77	0.72	1.57
Age	1.00	0.54	0.99	1.02

DISCUSSIONS

The development of STEMI, NSTEMI and UA, shows that a person has gone into a phase of ischemic heart disease and it is associated with high mortality risk. Of importance therefore is to determine whether detection of even low elevated levels of serum myocardial markers like

highly sensitive troponin t can predict outcome. From this study baseline highly sensitive troponin T did not predict in-hospital (30 day and one year) mortality and was not a significant independent predictor of mortality in both univariate and multivariate analysis with known predisposing risk factors of ACS. In-hospital mortality in our study was 6% while out of hospital mortality was 18% and this could have been the major cause of our insignificant results. Time of onset of symptom to presentation was earlier in patients diagnosed with STEMI presenting within 1-3 hours than those diagnosed with NSTEMI of whom majority presented after 24hrs.

Previous studies suggests measurement of highly sensitive troponin T as a useful cardiac biomarker in predicting mortality risk in patients with STEMI or NSTEMI/UA and is known to be superior to all other cardiac biomarkers due to its specificity and sensitivity. This study provides data on highly sensitive troponin T and suggests use of initial baseline measurement at presentation and describes the relation between measurement of highly sensitive troponin T and mortality. Highly sensitive troponin T levels of at least 14 pg/ml when a patient presents with STEMI or NSTEMI/UA.

CONCLUSIONS

Even though there was no sufficient evidence to conclude that baseline hsTnT was a statistically significant predictor of mortality in this study, previous studies indicates that as levels of highly sensitive troponin T increase, the risk of mortality increases. Elevated levels of this marker is used in prognostication and permits early identification of patients at increased risk of mortality. Time to presentation is also paramount as delays could lead to other complications.

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