Treatment Outcome of Acute Coronary Syndromes and its determinants at Two Tertiary Hospitals in Ethiopia: Prospective cohort Study

BY: KORINAN FANTA (B. Pharm.)

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By: Korinan Fanta (B. Pharm)

Advisor: 1. Fekede Bekele (M. Pharm, RPh.)

        2. Dr. Elsa Tegne (MD, Internist)

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ABSTRACT

Background: The burden of cardiovascular diseases, particularly ischemic heart disease is figured out to escalate in Ethiopia. Despite increasing burden of ischemic heart disease in Ethiopian, acute coronary syndrome is a forgotten domain and a few data are available.

Objective: To assess treatment outcome of Acute Coronary Syndrome in patients admitted to JUMC, and St. Peter Hospital, from March -August, 2018.

Methods: Prospective cohort study was conducted at Jimma University medical center and St. Peter hospital in Ethiopia. Adult patients with confirmed ACS diagnosis were consecutively included from March-August, 2018. Data on patient demography, presentation, management and outcomes were collected and the patients were followed from admission to 30 days. Cox-regression model was used to determine predictors of 30 day survival. Statistical significance was considered at p value <0.05

Results: A total of 181 patients with confirmed ACS were enrolled (61% with ST-elevation myocardial infarction [STEMI], 39% with non–ST elevation–ACS). Mean (SD) age at presentation was 56 (±12) years and did not differ among ACS types. The mean symptom onset to hospital presentation time was 54hr, (±26). In-hospital and discharge anti-platelet and statins use were high (>90%), although none of the patients get any form of early revascularization. The use of beta-blockers and ACEIs were variable (80% vs 72%) in hospital and (71%vs 70%) at discharge respectively. The overall 30 day mortality rate was 20% with higher death in STEMI (26%) compared to non-STMI/UA (11.4%). Non fatal MACE was occurred in 22% patients. Rural residence (AHR=2.4 CI 1.23-4.66), STEMI [AHR 3.05, (1.14- 8.89)], prior stroke [AHR 15.14, (3.61-63.50)], GRACE-Score [AHR 1.026, (1.01-1.04)], and cardiogenic shock [AHR 4.46 2.02-9.81)] were factors associated with high risk of 30 day mortality after adjusted for confounders. Factor associated with a lower risk were hemoglobin at admission (HR 0.843, CI 0.75-0.96).

Conclusion: The overall mortality of ACS in our study was alarmingly high, and reveals the need of instantaneous intervention by government and other stakeholders to improve outcome ACS patients.

Keywords: Acute myocardial infarction, Ethiopia, and Treatment outcomes.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGMENT

ACRONYMS AND ABBREVIATIONS

- **ACEIs:** Angiotensin Converting Enzyme Inhibitors
- **ACS:** Acute coronary Syndrome
- **AF:** Atrial Fibrillation
- **AMI:** Acute Myocardial Infarction
- **BMI:** Body Mass Index
- **CABG:** Coronary Artery By Pass
- **CAD**: Coronary Artery disease
- **DALYs**: Disability Adjusted Life Years
- **CK-MB**: Creatine Kinase- MB
- **DM:** Diabetes Mellitus
- **CVD:** Cardiovascular Disease
- **CVA:** Cerbrovascular Accident
- **ECG:** Electrocardiography
- **ED:** Emergency Department
- **EMS:** Emergency Medical Service
- **GCS**: Glasgow Coma Scale
- **GRACE:** Global Registry of Acute Coronary Events
- **HDL:** High Density Lipoproteins
- **HF:** Heart Failure
- **HICs:** High Income Countries
- **HTN:** Hypertension
- **ICU:** Intensive care Unit
- **IHD**: Ischemic Heart disease
- **IRB**: Institutional Review Board
- **JUMC**: Jimma University Medical Center
- **LDL:** Low density Lipoproteins
- **LMICs**: Low and Middle Income Countries
- **MACEs**: Major Adverse CardiacEvents
- **MDR-TB**: Multi Drug Resistant tuberculosis
- **MI:** Myocardial Infarction
- **MICU:** Medical Intensive Care Unit
- **MRI:** Magnetic Resonance Imaging
- **NCDs:** Non-Communicable disease
- **NSTEMI**: Non ST-segment Elevation Myocardial Infarction
- **STEMI**: ST-segment Elevation Myocardial Infarction
- **SSA:** Sub-Saharan Africa
- **SPSS:** Statistical Package of Social Science
- **PAD:** Peripheral Artery Disease
- **PCI**: Percutaneous Coronary Intervention
- **RHD:** Rheumatic Heart Disease
- **TASH**: Tikur Anbessa Specialized Hospital
- **TIMI:** Thrombolysis In

1. INTRODUCTION

1.1. Background

The term Acute Coronary Syndrome (ACS) refers to spectrum of condition compatible with acute myocardial ischemia and/or infarction that are usually due to an abrupt reduction in coronary blood flow(1). Based on the presentations of electrocardiography (ECG), ACS is categorized into two distinct populations: ST-elevation myocardial infarction (STEMI) and non ST-Elevated-ACS (NSTE-ACS). Patients with ST-segment elevation on ECG usually indicate acute complete coronary occlusion that warrants aggressive therapeutic strategies for rapid coronary reperfusion(2). The other patients presented without persistent ST-segment elevation on ECG are defined as NSTE-ACS which is further divided into non-STEMI and unstable angina (UA) according to whether the cardiac biomarkers are elevated or not(3).

Non communicable diseases (NCDs) accounted for 71% of all death through the world and 41 million people death each year. More than three quarters (32million) of global NCD death with 85% of "premature" (30-69 years) death occurs in Low and middle income countries (LMICs) (4). Cardiovascular diseases (CVDs) are the leading NCD which accounted for one-third of global deaths in 2015(5). Of all CVDs, ischemic heart disease (IHD) is one of the leading causes of mortality and morbidity worldwide, resulting in approximately 8.9 million deaths and 164.0 million disability-adjusted life years (DALYs) globally in 2015(6, 7). Not only mortality, economic burden of ischemic heart diseases is also unacceptably huge. Myocardial infarction (MI) only results in greater than $11 billion hospitalization cost annually, besides being the leading cause of morbidity and mortality in united state; with high recurrent MI or fatal coronary heart disease (CHD) in individual above 45 years the health care cost projected to raise by almost 100% by 2030(8).

High income countries (HICs) have experienced significant declines mortality rates from all cardiovascular conditions since the 1960s(9, 10). Both treatment and prevention have contributed to the observed reductions in IHD mortality in HICs(11). Particularly, advances in the acute management of ACS include many celebrated achievements in intensive care-related and interventional approaches to cardiovascular medicine: the creation of the coronary care unit, the introduction of streptokinase, and later thrombolytic drugs and the development of coronary artery catheterization, balloon angioplasty, and surgical revascularization(10). These advances made it possible, rather than to simply observe the natural history of ACS complications, to intervene and attempt to modify the natural course of illness. However,

LMICs are disproportionately suffering from IHD mortality(4). Many of these countries have experienced transformational economic growth and lifestyle changes over the past several decades that have increased the prevalence of IHD risk factors and rates of mortality(12, 13). A number of factors which have been found associated with IHD such as hypertension, dyslepidemia, Diabetes mellitus, smoking has been increasing dramatically in developing countries(14). Hypertension is arguably the most powerful cardiovascular risk factor in the African context and roughly one in six people has hypertension even in SSA and hardly, only half of the populations with hypertension are aware of their hypertension, indicating un-controlled high blood pressure that causing premature CVD(15, 16).

The treatment and outcomes of ACS in LMICs are variable but often suboptimal. Observational studies do suggest that, to a large extent, the in-hospital treatment of ACS in LMICs includes the use of aspirin, Angiotensin converting enzyme inhibitors (ACEIs), lipid lowering agents and beta-blockers(17, 18). However, Utilization of emergency medical services (EMS), thrombolysis and primary percutaneous coronary intervention (PCI) for STEMI remains low in many developing countries likely secondary to underdeveloped infrastructure and lack of resources. In addition, in-hospital mortality rates were highest in countries with the lowest rates of primary reperfusion. Countries with lower growth domestic product (GDP) rankings tended to have fewer STEMI patients undergoing reperfusion with thrombolysis(19).

Similar to other Sub-Saharan African (SSA) countries, NCDs are causing significant morbidity and mortality in Ethiopia(20). Especially, CVD account for 24% of mortality in Addis Ababa Ethiopia(21) and this figure anticipated to increase in near future as major CVD risk factors such as hypertension, Smoking, alcohol misuse, physical inactivity, higher glucose level, and khat-chewing were rising among urban and population aged 15 and above (22-24). Although exact prevalence of ischemic heart disease in Ethiopia was not known, some hospital based studies were indicated that it has been increasing rapidly(25, 26). Further, IHD has been posing huge economic impact in resource constrained settings like Ethiopia; as treatment of acute myocardial infarction with ACEIs costs at least US$2.4 million annually(27). However, IHD particularly, ACS was forgotten domain in Ethiopia for years; since ACS burden, risk factors, and outcomes were not studied in large. Reliable, up-to-date information on ACS burden, risk factors, management practice and outcome in Ethiopia are necessary to provide effective and efficient preventative, acute care as well as

rehabilitation programs for ACS patients; that may raise awareness on challenges of ACS in LMICs including Ethiopia.

1.2 Statement of the problem

Ischemic heart disease (IHD) is the largest single cause of death and loss of disability adjusted life years (DALYs) worldwide, accounting for approximately seven million deaths and 129 million DALYs annually(28). Cardiovascular disease cause a serious economic toll, accounting for one-third of a projected $47 trillion in economic losses to non-communicable diseases (NCDs) over the next 20 years(29) .While high-income countries (HICs) continue to deal with significant IHD mortality, nearly two-thirds of all IHD DALYs and over half of deaths occur in low and middle income countries (LMICs)(30). Many of these countries have experienced transformational economic growth and lifestyle changes over the past several decades that have increased the prevalence of IHD risk factors and rates of mortality(30, 31).

Although prevalence of IHD in SSA considered relatively uncommon(16), it's expected that most of the case were misdiagnosed or under diagnosed as result of limited diagnostic means (electrocardiographs, markers of myocardial injury, cardiac imaging),and shortages of physicians(32). However, its prevalence is predicted to rise rapidly in the next two decades due to the rising prevalence of risk factors, especially hypertension, diabetes mellitus, overweight and obesity, physical inactivity, increased tobacco use and dyslipidaemia. Not only prevalence, age-standardized mortality rate from IHD was projected to rise by 70% in African men and 74%, in women by 2030(16).

Notably, the burden of ACS in these LMICs is not limited to rich or elderly population but also on the low socioeconomic status and working-age, posing a risk to economic growth and social development(28). According to Global Burden of Disease study, the median age of death from IHD among males was a decade younger in LMICs than in HICs in 2010(33). This may be due to earlier onset of ACS and IHD, as well as shorter survival after ACS. Suggest that earlier age for first ACS in LMICs is a major contributing factor. Registry data from many other LMICs also support the assertion that ACS often occur at younger ages than in HICs (17, 34, 35). Strikingly, a registry from the United Arab Emirates reported a mean age of 50.8 years(36).

In Ethiopia, cardiovascular disease increased remarkably over the past three decade (37-40). Although rheumatic valvular heart diseases (RHD) were the principal cause of cardiac emergency in Ethiopia in the past two decades, hypertension and ischemic heart diseases were steeply increasing over the past two decades(41). Beyond rapidly rising in prevalence, cardiovascular disease specially IHD was resulting in high morbidity and mortality (40, 42, 43). Besides high case fatality rate IHD has been causing a considerable economic loss since it was affecting a very young age population group in Ethiopia unlike developed countries(43). Ischemic heart disease also expected to be doubled in near future in SSA; as a level of cardiovascular risk factors distinctly, increasing and inadequate knowledge of CVD and associated risk factors has been contributing to a great extent throughout SSA and Ethiopia is not exceptional(24, 44).

Ethiopia

1.3 Significance of the Study

Despite rapid rise in ischemic heart disease, particularly acute coronary syndrome over the past three decades, only a few retrospective studies available on coronary artery disease in Ethiopia(43, 45). Those available studies are confined to single center and reviewed patient charts retrospectively. In addition to inherent draw backs of retrospective studies, in Ethiopia it's reliability further hindered by incomplete records, and loss of patient data or part of the data's (since all kept in hardcopy) and medical records are always written manually (not computerized).

To date, only two studies reported in-hospital mortality of ACS(40, 43). Beyond being retrospective, both of them have small sample size and did not reported determinant of in hospital mortality and other in hospital complications as well as short term outcomes of ACS. As much as our knowledge concerned there is no even a single study which followed patients prospectively to capture clinical characteristics, management and short term (30 days) outcome of ACS in Ethiopia. Hence little is known about the burden, clinical characteristics, management and outcome of ACS.

Therefore, creating awareness for all level of society by identifying the risk factors, diagnostic protocols, management patterns and outcome of ACS with in sighted information on ACS in poor settings will be a stepping stone for us. Moreover, the finding may call for attention of concerned bodies to make decision and take measure in the spirit of improving the burden of ACS by forwarding necessary recommendations for possible change and to scale up current intervention programs by providing basic information on burden of ACS and would allow closer follow-up and more targeted interventions in high risk patients that ultimately reduces mortality.

2. LITERATURE REVIEW

2.1 Characteristics of ACS

In the United States, the median age at ACS presentation is 68 years with male-to female ratio of approximately 3:2. Some patients have a history of stable angina, whereas in others, ACS is the initial presentation of CAD(46). Studies conducted in developing countries were reported earlier onset of ACS and IHD. According to CREATE(17): a prospective analysis of register data in India, of the 20 468 patients who were given a definite diagnosis, 60% had STEMI, and the mean age of these patients was 57·5 (±12) years; patients with STEMI were younger 56 (±12) years than were those with non-STEMI or unstable angina 59 (±12) years). In the same way, The ACCESS(47) (ACute Coronary Events-a multinational Survey of current management Strategies) registry reported, of A total of 1687 patients with confirmed ACS, 59% had STEMI and the midian age of the patients was 59 [IQR 52, 68] years, and 76% were men.

The median pre-hospital delay time in seeking medical care for chest pain varied from country to country; ranging from1.6h in Brazil to 12.9h in Saudi Arabia, according to Global review of delay time in seeking medical care for chest pain(48). According to this study, the mean pre-hospital delay time was 3.4h. The delay time in Europe, America, and Asia ranged between 2.0 and 4.0h, 1.6 and3.3h, and 1.8and 4.0 h respectively. Studies from the Middle East region showed the broadest range of delay times being between1.8h and 12.9h.

Atypical clinical presentation in ACS patients is not uncommon. Global Registry of Acute Coronary Events(GRACE)(49) show that up to 30% of AMI patients presented with atypical symptoms, such as nausea/vomiting, shortness of breath, fatigue, palpitations, or syncope. Similarly, the National Registry of Myocardial Infarction (NRMI)(50) study reported that 35.5 presented with atypical symptoms. Another study from French, The FAST-MI 2010 registry showed that 18% of patients with acute myocardial infarction (AMI) had an atypical presentation (ie, without typical isolated chest pain)(51). In addition these studies have suggested that atypical symptoms predicted adverse outcomes. In the NRMI(50) study, in-hospital mortality was 20.0% in patients with atypical symptoms and 7.2% in those with typical symptoms.10 The GRACE study also reported that atypical symptoms were associated with higher in-hospital mortality (13.0% vs 4.3%). In the same way, the FAST-MI 2010 registry(51) showed that, in-hospital complications (recurrent MI, stent thrombosis, stroke, arrhythmia, and bleeding) were similar regardless of the initial clinical presentation.

However, At 30 days, the rate of death was higher in all groups of patients with atypical presentation compared with patients with typical isolated chest pain. These symptoms are more often observed in the elderly, in females, and in patients with diabetes mellitus (DM), chronic renal disease, or dementia.

2.2 Risk Factors of ACS

INTERHEART(14) was a standardized case-control study that screened all patients admitted to the coronary care unit or equivalent cardiology ward for a first MI at 262 participating centers in 52 countries throughout Africa, Asia, Australia, Europe, the Middle East, and North and South America. Final analysis was carried out for 12,461 cases and 9459 controls. The study has identified 9 easily measured risk factors (smoking (45%), lipid, hypertension (39%), diabetes (18.5%), abdominal obesity (46%), diet, physical activity (14.3%), alcohol consumption (24.3%), and psychosocial factors) that account for over 90% of the risk of acute myocardial infarction (AMI). Abdominal obesity was demonstrated to be a stronger risk factor than body mass index (BMI), suggesting that this measurement should replace BMI as an indicator of obesity. Globally, all 9 risk factors were significantly associated with AMI (all $P < .0001$ except alcohol, $P = .03$). The study demonstrated that risk factors in African population were not different from the overall INTERHEART study.

The Euro heart survey(52) of ACS with 10,253 patients participated from countries in Europe and the Mediterranean basin showed Smokers, overweight/obese, and hypertensive ACS patients were more likely present with ST elevation. In contrast, men with diabetes mellitus were associated with less ST elevation. In addition Prior history of infarction, chronic angina, revascularisation and patients on treatment with (aspirin, beta-blockers, or statins) before admission were also associated with less ST elevation. Even after adjustment for patient's demography, prior medication and disease, smoking was significantly associated with increased risk of ST elevation. But, hypertension was associated with reduced risk. Obesity (BMI >30 kg/m2 versus, <25 kg/m2) was independently associated with less risk of presenting with ST elevation among women, but not among men.

A chart review of 126 ACS patients admitted to Durban hospital, South Africa(53) reported that, one hundred ten (87.3%) met criteria for hyperlipidemia. Not only hyperlipidaemia, other traditional cardiovascular risk factors such as, hypertension (60%) smoking (72%) Diabetes mellitus (54%) and family history of CAD (69%) were also common in the study participants. All most all of the study participants were Indian decent in which previous

7

studies [66] also reported high prevalence of CAD risk factors. This study showed high prevalence of visceral obesity (82%), hyperlipidaemia (78%) and three quarters of the patients had family history of CVD. Additionally, study done in rural India(54) reported high prevalence of hypertension (82.3) in ACS patients. The study also revealed that hypertension, smoking, diabetes mellitus and prior history of MI were associated with ACS.

Population based survey(24) of CVD risk factors showed disparity between rural and urban residents. Urban population had more prevalence of hypertension, obesity and physical in activity which is more common in females compared to male. However tobacco smoking and alcohol misuse were not significantly different between the two populations. Khat (*Catha edulis* Forsk) chewing which anticipated raising risk of acute myocardial infarction was common in both urban and rural populations. Although it was not consistent with optimal cardiovascular health intake of vegetable and fruit were comparatively better in rural are in comparison to urban.

Community based study of prevalence of metabolic syndrome in Ethiopia(55) showed high prevalence of low high density lipoprotein (HDL 69%) as major type of dyslipidemia. In addition the study also demonstrated prevalence of other metabolic syndrome such as hypertension (16%), diabetes mellitus (3%), and impaired fasting glucose (9%). The authors highlighted that; urban residence, old age and physical in activity were associated with metabolic syndrome. Other hospital based study in Ethiopia(25) reported that high prevalence of hypertension (73%), hyperlipidaemia (86%), and ischemic heart disease (73%) were associated with urban population. The authors also showed that, Patients from rural area or those with comorbid disease were more likely to have poor CVD outcome.

Another cross sectional study conducted in Jimma, Ethiopia(56) found, Majority (70.9%) of the respondents have one or more of the seven cardiovascular disease risk factors assessed. The author founded, Hypertension in nearly one forth (23.8%) of the study participants, diabetes 6.2% and smoking in 11.8% among males 2% among females. According to this study, the prevalence of overweight/obesity was 26.8 %. Study on cardiovascular risk factors among diabetic patients on follow up at Jimma, Ethiopia(57) high prevalence of dyslipidemia (63.5%). Followed by; physical inactivity (55%), Hypertension (46.5%) and smoking (5.5%)

2.3 Management of ACS

The management of ACS in Low and middle income countries (LMICs) are inconsistent but often substandard. Observational studies do advocate that, to a great extent, the in-hospital management of ACS in developing countries includes the use of Anti-platelet (e.g. Aspirin), ACE inhibitors, Statins, and beta-blockers(18, 58). The ACCESS Study, a prospective observational registry of patients hospitalized for ACS between 2007 and 2008 in 19 LMICs, found that aspirin and lipid-lowering therapies were each given to more than 90% of patients, while uptake of beta-blockers and Angiotensin converting enzyme inhibitors (ACEIs) were at 78% and 68%, respectively(18). However, comparison of countries participating in the OASIS registries(59) found lower use of heparin in LMICs than in HICs, while the ACCESS investigators found that only 39% of patients presenting with ST-elevation myocardial infarction received fibrinolytics.

Analysis of prospectively collected data on 25 748 consecutive ACS admissions from 2007 to 2009 in 125 hospitals in Kerala, India(58) reported that antiplatelets use was high (>90%). Whereas the use of beta-blocker (70%) was low and ACEIs (27%) were even lower. Thrombolytics were used in 41% of STEMI, 19% of non-STEMI, and 11% of unstable angina admissions. Percutaneous coronary intervention rates were marginally higher in STEMI admissions. Discharge medication rates were variable and generally suboptimal (80%).

World health organizations (WHO) study on Prevention of Recurrence of Myocardial Infarction and StrokE (WHO-PREMISE)(60) in LMICs on demonstrated that an enormous proportion of coronary heart disease (CHD) patients did not received optimal medication at discharge for secondary prevention. The use key medication like: Aspirin (81%), Beta-blockers (48%), ACEIs (40%) and Statins (30%) were almost suboptimal. Only half of the participants received reperfusion therapy.

Acute coronary syndrome registry from four large centers in United Arab Emirates (UAE-ACS) registry(36) reported that, the overall use of in-hospital key medications (Aspirin (99%), Statins (96%), beta-blockers (76), and (48%) clopidogrel) were in line with guidelines and majority of STEMI patients (81%) gets reperfusion therapy. At hospital discharge more than 90% gets anti-platelets and lipid lowering drugs; while Beta-blockers and ACEIs were given for 82% and 74% respectively for secondary prevention. Almost, the use of aspirin was high in LMICs. The low cost of Aspirin and its universal availability may explain the similarity of the findings.

Brazilian Intervention to Increase Evidence Usage in Acute Coronary Syndromes (BRIDGE-ACS)(61), a pragmatic 2-group, cluster-randomized controlled trial with blinded adjudication of outcomes and intention-to-treat analysis was evaluated the effect of a multifaceted quality improvement (QI) intervention on the prescription of therapies proven efficacious for patients with ACS within the first 24 hours and at hospital discharge as well as on the incidence of major cardiovascular events. Among eligible patients (923/1150 [80.3%]), 67.9% in the intervention vs 49.5% in the control group received all eligible acute therapies (population average odds ratio [OR_{PA}], 2.64 [95% CI, 1.28-5.45]). Similarly, among eligible patients (801/1150 [69.7%]), those in the intervention group were more likely to receive all eligible acute and discharge medications (50.9% vs 31.9%; $OR_{PA,}$, 2.49 [95% CI, 1.08-5.74]).

Analysis of medical record of twenty one patients admitted to Tikur Anbessa Specialized Hospital, Ethiopia(43) showed high utilization of in hospital medication such as: Aspirin (100%), Clopidogrel (81%), Heparin (95%), Statins (91%), Beta-blocker (91%), ACE inhibitors (91%), Morphine (52%), Nitrates (10%), and Furosemide (57%). However, none of the patients were received fibrinolytics or underwent primary percutaneous coronary intervention (PCI)/ coronary artery bypass graft surgery (CABG).

Chart review of 999 STEMI patients in Kenya(62) reported that all patients received reperfusion therapy with fibrinolytics therapy (62%) or primary PCI (38%). In the same way antiplatelets (Aspirin and Clopidogrel) were used in (>90%) of the patients at presentation. Rewardingly all patients survived till discharge. Another study from Kenya(63) also reported comparable finding. Majority of STEMI patients were revascularized with thrombolytics (80%) and one in four patients received rescue PCI while the rest (2.2%) were managed medically. Evidence based medications such as Aspirin, Clopidogrel, and Lipid lowering agents were used in around 95% of the patients at discharge, while the use of beta-blockers and ACEIs were low (84% and 48%) respectively.

2.4 Outcomes of ACS

Currently developed countries have experienced significant decrease in mortality rates from all cardiovascular conditions since the 1960s(31, 64). Both treatment and prevention have contributed to the observed reductions in IHD mortality in HICs(64). However, the ACS and IHD situation in LMICs today is strikingly increased more similar to that of HICs in decades past. In particular, the burden of ACS is not solely on the rich nor on the elderly, but also on the poor and working-age(30).

Treatment and outcomes of acute coronary syndromes in India (CREATE)(17): a prospective analysis of registry data, showed significant difference on outcome between ACS subtypes. The investigators reported that, STEMI patients had higher rate of mortality (8·6%), reinfarction (2·3%), and stroke (0·7%) at 30 day than non-STEMI/unstable angina [death (3·7%), reinfarction (1·2%), and stroke (0·3%, p<0·0001) for all comparisons]. Additionally, poor patients had higher mortality at 30 day than rich patients (8·2% vs5·5%, p<0·0001). But adjustments for management eliminate this discrepancy in outcome between economic strata without balancing for risk factors and baseline characteristics.

Another ACS registry from India(58) also demonstrates that in-hospital mortality and MACE rates were highest for STEMI (8.2 and 10.3%, respectively). Even after adjustment for potential confounders, patients presenting with STEMI had a four times risk of in-hospital death (OR=4.06, CI=2.36, 7.00) and three times in-hospital MACE (OR = 2.75 CI, 1.81, 4.17) than patients presenting with unstable angina. According to this registry, symptom-to-door time >6 h [OR = 2.29 (1.73, 3.02)], and inappropriate use of thrombolysis [OR =1.33 (0.92, 1.91)] were associated with higher risk of in-hospital mortality and door-to-needle time <30 min [OR = 0.44 (0.27, 0.72)] was associated with lower mortality. Similar trends were seen for risk of MACE.

ACute Coronary Events—a multinational Survey of current management Strategies (ACCESS) registry(18): prospective observational registry, 12,068 adults hospitalized with a diagnosis of ACS, enrolled 19 countries in Africa, Latin America, and the Middle East. According to ACCESS-Registry report, the rate of all-cause death at 30 days was 3.6% which was higher in STEMI (5.0%) in comparison to no-STEMI (2.4%). This figure rose to 7.3% by 12 months and yet with significant mortality difference between STEMI (8.4%), and non-STEMI (6.3%). The combined end point (cardiovascular death, nonfatal stroke, or MI) was higher among patients with STEMI (11% vs 9%), whereas patients with NSTE-ACS were more likely to be re-hospitalized for an ischemic event. Five variables were significantly

associated with high risk of death at 12 month: cardiac arrest on admission advanced, cardiogenic shock, Stroke/TIA, and antithrombotic treatment (bivalirudin, fondaparinux, and lowmolecular-weight heparin). Factors associated with a better outcome were antiplatlets use (Aspirin and Clopidogrel), and angiography.

BRIDGE-ACS(61) registry which categorized ACS patients into two groups based provision of quality improvement (QI) intervention or not, reported overall high 30 day mortality rate (7.0% vs 8.4%). Likewise the rate of in-hospital cardiovascular events was 5.5% in the interventional group vs 7.0% in the control groups. However study from UAE-ACS(36) registry reported, low rates of in-hospital complication. Recurrent ischemia occurred in 7.3% which resulted in congestive heart failure (CHF) in 3.3% of them. Ventricular fibrillation/ventricular tachycardia were reported in 3.5%, Inotropes used in 3.5% and cardiogenic shock occurred in 2.2% of the patients during their hospital stay. In the same way the overall in hospital mortality was low (1.68%).

The outcomes of patients with ACS in sub-Saharan Africa are affected by factors that have been clearly identified across the reported studies, including delay from symptom onset to reperfusion therapy, limited numbers of primary emergency facilities, especially in rural areas, limited EMS pre-hospital management and transportation to the hospital, and hence limited numbers of patients eligible for myocardial reperfusion intervention/ therapy(65)

Data from GULF-RACE-2 registry showed that, 30 day mortality of acute coronary syndrome in Yemen(66) population (14.7%) was higher compared to the overall outcome of GULF-RACE-2 registry (7.2%). Not only mortality other in hospital complications was also high in Yemen (recurrent ischemia (28%) and CHF (19.5%). STEMI patients had more in hospital complication and 30 day mortality (16.2%) than NSTEACS (12.1%). The authors pointed out that, high in hospital mortality in Yemen population might be due to late presentation as well as low coronary revascularization rate in STEMI patients as well as high risk NSTEACS.

A prospective review of acute coronary syndromes in an urban hospital in sub-Saharan Africa(34) reported that, in hospital mortality rate was high in STEMI (9.7%) compared to non-STEMI (6.0%). Late presentation to hospital is common and accounts for the increased mortality associated with this condition. Another study from keniya(63) further strengthen the finding by reporting the overall high in hospital mortality rate (9.4%). The investigators reported that the predicted in hospital mortality according to grace score was even around twice (16.1%) the observed mortality rate. Even though the mortality rate reported by these

two studies from Kenya was high, other reports from different sub-Saharan countries were reporting even higher in hospital mortality rate. Prospective study of 21 cases of ACS in young Sub-Saharan Africans(67) also reported similarly high in hospital mortality (14.3%). Another analysis of medical record of twenty one patients admitted to tertiary hospital in Ethiopia(43), reported three (14%) patients died within two weeks of admission. Though small number of patient included in the study, the in hospital mortality rate reported was eminently high.

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2.3 Conceptual frame work

PATIENT RELATED FACTORS
Socio-demography
- o Age , Sex, Residence, occupation, Income,

Behavioral Measures
- o Smoking
- o Alcohol
- o Khat
- o Physical activity

DISEASE RELATED FACTORS
- o DM, HTN, Renal eimparement
- o CVA, , MI, Anemia, Obesity, etc

Clinical Presentation
- o Chest pain/discomfort
- o Atypical symptoms
- o Killip class

Vital Sign at Arrival
ACS-subtypes

Outcomes of ACS
All-Cause Mortality & MACE

Management protocol
Medications
Inhospital medications
- ✓ Antiplatlets
- ✓ Beta blockers
- ✓ ACEIs/ARBs
- ✓ Anticoagulants
- ✓ **Reperfusion therapy**

Discharge medications
Setting of treatment

Laboratory and Diagnostic finding
- o Cardiac biomarkers
- o RFT, Lipid profiles
- o Caugulation abnormality
- o Hyperglycemia
- o CBC(HGB, WBC)
- o Electrolyte abnormality
- o Ejection Fraction

Figure 1 conceptual frame work

3. OBJECTIVES

3.1 General Objectives

- ✓ To assess treatment outcome of Acute Coronary Syndrome and its determinant among patients admitted to Jimma University medical center (JUMC) and St. Peter Specialized Hospital (SPSH).

3.2 Specific objectives

- ✓ To identify clinical characteristics of patients admitted with acute coronary syndrome at JUMC and SPSH.
- ✓ To assess management practice of acute coronary syndrome at selected tertiary settings of Ethiopia.
- ✓ To determine in-hospital major adverse cardiac events (MACE) in ACS at JUMC and SPSH.
- ✓ To determine predictors of 30 day mortality of ACS patients at JUMC and SPSH.

4. METHODS AND PARTICIPANTS

4.1 Study setting and periods

The study was conducted at two tertiary hospitals in Ethiopia (Jimma University Medical Center (JUMC) and St. Peter Specialized Hospital [SPSH]). Jimma university medical center (JUMC) is a tertiary hospital in south-west Ethiopia, which is 352 kilometers from Addis Ababa. It is providing services for approximately 15,000 inpatient, 160,000 outpatient attendants, and 11,000 emergency cases per a year. The hospital serves a more than 15 million coming to the hospital from the catchment area. Investigation modalities including electrocardiography (ECG), echocardiography, CT-scan, basic hematologic and chemistry tests are readily available. It has emergency department, intensive care unit (ICU), and Cardiac unit. The hospital has no modern cardiac catheterization laboratory and there is no any form of reperfusion therapy. www.ju.edu.et

St. Peter Hospital is located in Addis Ababa. The hospital has been serving as a referral unit for multi drug resistance tuberculosis. Currently, the hospital has internal medicine unit, emergency department, intensive care unit and pediatric unit. In addition it has Cardiac center with cardiac catheterization laboratory which was jointly founded by St. Paul hospital and SPSH. The hospital gives a service for around 50,000 - 100,000 patients a year for patients coming from Addis Ababa and allover Ethiopia. The hospital has cardiologists serve as a referral center for angiography and percutaneous coronary intervention (PCI). So the study was conducted at this two selected tertiary teaching hospital concurrently from March 25-August 25, 2018.

4.3 Study design

Hospital based prospective cohort study was conducted.

4.4 Population

4.4.1 Source population

✓ All patients admitted to internal medicine ward of JUMC, and SPSH.

4.4.2 Study population

✓ All consecutive patients who were diagnosed with ACS and admitted to JUMC, and SPSH during the study period and fulfilling the inclusion criteria.

4.5 Eligibility criteria

4.5.1 Inclusion criteria

- ✓ All patients ≥18 years
- ✓ Patient or attendant willing to give valid consent to participate in the study.
- ✓ Confirmed diagnosis of ACS.
    - o ACS was defined as patients admitted with ST-elevation myocardial infarction (STEMI), and non-ST-elevation ACS [non-STEMI/unstable angina (UA)].
    - o STEMI -was diagnosed if new ST elevation at the J point in two contiguous leads with the cut-points: ≥1 mm in all leads other than leads V2–V3 or a new left bundle branch block (LBBB) was found on the electrocardiogram (ECG) with biochemical evidence of myocyte necrosis.
    - o NSTEMI -required at least one elevated cardiac biochemical marker of necrosis without new STEMI on the admission or subsequent ECGs.
    - o UA- was considered to be present in patients with ischaemic symptoms and when markers of myocardial necrosis were below the diagnostic threshold for myocardial infarction.
    - o Markers of myocyte necrosis utilized in our study was serum troponin I

4.5.2 Exclusion criteria

- ✓ Failed to give informed consent.
- ✓ Patients admitted with a diagnosis of chest pain of noncardiac origin.
- ✓ Died before evaluation and confirmation of ACS.

4.6 Variables of the study

4.6.1 Dependent variable:

- o Treatment outcome (30 day all-cause mortality)

4.6.2 Independent Variables

1) **Socio-demographic characteristics**
    - o Age, Sex, Residence, Educational level, Occupation, and Income.
2) **Behavioral measures and key risk factors**

- o Smoking, Alcohol, Khat, abdominal obesity, BMI, Family history of CVD, Hypertension, Diabetes mellitus, prior Coronary artery disease (CAD), and Stroke.

3) **Clinical presentation**
   - o Delay time (symptom onset to hospital arrival), Symptom at presentation, Vital signs, ACS subtypes, and Killip class.

4) **Biochemical measures and imaging findings**
   - o Cardiac biomarkers (troponin I), Serum Creatinine, Lipid profiles, Random blood glucose, and hemoglobin, Ejection fraction, ECG finding, and Angiography finding

5) **In-hospital and discharge medication**
   - o Aspirin, Clopidogrel, Statins, Beta-blockers, Angiotensin converting enzyme inhibitors (ACEIs), and Antithrombotic.

4.7 Sample size and Sampling technique

4.7.1 Sample size determination

The sample was determined using a single population proportion formula, taking the proportion of in-hospital mortality of ACS from previous research (14%)(43). Using α=0.05, 95% CI, p= 0.14 and margin of error= 5%, the sample size can be determine as follows

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

Sample size (n) = 185 and adding 5% for non response rate, the final sample size is = **194**

Over previous 6 month (September, 2017-Feburuary, 2018), 118 and 56 ACS patients were admitted to SPSH and JUMC respectively (taken from medical record at each hospital). Based on this data, the final sample size was allocated for the two hospitals with 2:1 ratio (131 patients form SPSH and 63 from JUMC)

4.8 Outcome endpoints validation

4.8.1 Primary outcome

- ✓ All cause mortality (30days): was defined as all cause mortality from index admission to 30 days. Mortality was ascertained by, death summary from

healthcare records/physicians or Interviews with witnesses and family members for out-of-hospital death.

4.8.2 Secondary outcomes

✓ Secondary endpoints were in-hospital non-fatal major adverse cardiac events (MACE) such as stroke, re-infarction, heart failure, and cardiogenic shock**.**

- o **Stroke**: was diagnosed when new focal motor deficit after hospital admission appear and further confirmed by brain computed tomography.

- o **Reinfraction:** was diagnosed when a recurrent myocardial infarction confirmed by ECG changes or elevation of cardiac markers (Re-elevation of the CK-MB to above the ULN and increased by at least 50% over the previous value).

- o **Cardiogenic shock:** was diagnosed when sustained systolic blood pressure < 90 mmHg and no improvement with fluid challenge, or inotropes (dopamine) required to achieve a blood pressure ≥90 mmHg and signs of impaired organ perfusion with at least one of the following: altered mental status; cold, clammy skin, or oliguri.

- o **Heart failure:** was diagnosed when new onset of clinical sign and symptom of heart failure in patients without previous history of chronic heart failure with structural and/or functional abnormality

4.9 Data collection tool and process

Data regarding patient demography, behavioral measure were assessed by using WHO STEPS. Past medical history was assed based on patient self-report or from patient medical record, and vital sign at admission, biochemical data, diagnostic findings, medications/interventional therapy were abstracted from patient medical record. The GRACE-score for all ACS patients and TIMI-score for non-STEMI/UA were calculated on admission by using GRACE Risk Score MDcalc version 2.2 and TIMI-SCORE for non-STEMI/UA MDcalc respectively. Variables included in GRACE-score were (Age, Heart rate, Systolic blood pressure, serum creatinine, cardiac arrest on admission, ST-segment change, positive cardiac biomarkers and killip class). Enrolled patients followed starting from admission to 30 days to assess in-hospital non-fatal major adverse cardiac events (MACE: Heart failure, cardiogenic shock, Stroke, and Reinfarction) and all cause mortality over 30 days. Three clinical pharmacists collected data prospectively on admission to hospital (baseline), at discharge, and at 30 day follow-up visits. Vital event (mortality) was collected via telephonic interviews of care giver/family/relatives for patients who did not attend the follow-up appointments.

Data quality control and management

Training was given for data collectors for two days on data abstraction and proper patient case recording. Data collection process and quality was supervised by one internist and medical resident. At both sites, completeness of patient case report forms for all enrolled patients were monitored for source documentation and accuracy by cross checking with patient medical record. The data collection tool was first tested on 5 % of the study participants to check the consistency, applicability and understandability of the format. Modifications were made to the abstraction format based on data quality checks.

4. 10 Data processing and analysis

Data entry was done by using Epidata version 4.2, and analyzed by using statistical package for social science (SPSS version 23). Continuous variables were presented in means (standard deviation) or median (inter-quartile range), when skewed in distribution. Categorical variables were expressed as frequency, and percentages. ACS types were grouped under two arms: STEMI and non-STEMI/UA since we encountered small number of unstable angina and comparisons by ACS type were made via independent t-test for continuous variables and Chi-square for

categorical variables. Step wise Cox regression model was used to compute crude hazard ratios and 95% confidence intervals to examine the individual relation between each predictor and death during follow-up (0 to 30 days). All variables identified by the crude regression analysis with $p < 0.25$ were interred into the stepwise multiple Cox regression (backward) analysis to produce final models for predicting 30 day all cause mortality. Comparison of 30 day mortality by ACS subtypes was done by using Kaplan–Meier survival analysis and Log Rank test for significance. P value less than 0.05 with 95% confidence interval was considered statistically significant.

4.11 Ethical consideration

Ethical clearance was obtained from the Institutional Review Board (IRB) of Jimma University, institute of health. Verbal and written consent were given for all study participants before including in the study. The data from the case records and interview were handled with strong confidentiality. Neither the case records nor the data extracted were used for any other purpose. The confidentiality and privacy of patients were assured throughout by removing identifiers from data collection tools using different codes.

4.12 Plan for data dissemination and utilization

The result of the study will be presented and disseminated to Jimma University, Institute of health, JUMC, St. Peter specialized hospital and other concerned bodies. Then the result will be published in reputable journals. The result will be published on reputable journal.

4.4 Operational definition

ACS -was defined as patients admitted with ST-elevation myocardial infarction (STEMI), and non-ST-elevation ACS [non-STEMI/unstable angina (UA)].

STEMI -was diagnosed if new ST elevation at the J point in two contiguous leads with the cut-points: ≥1 mm in all leads other than leads V2–V3 or a new left bundle branch block (LBBB) was found on the electrocardiogram (ECG) with biochemical evidence of myocyte necrosis.

NSTEMI -required at least one elevated cardiac biochemical marker of necrosis without new STEMI on the admission or subsequent ECGs.

UA- was considered to be present in patients with ischaemic symptoms and when markers of myocardial necrosis were below the diagnostic threshold for myocardial infarction. Markers of myocyte necrosis utilized in our study was serum troponin I

Reinfarction: Diagnosis of a recurrent myocardial infarction confirmed by ECG changes or elevation of cardiac markers (Re-elevation of the CK-MB to above the ULN and increased by at least 50% over the previous value).

Cardiogenic shock: was diagnosed when sustained systolic blood pressure < 90 mmHg and no improvement with fluid challenge, or inotropes (dopamine) required to achieve a blood pressure ≥90 mmHg and signs of impaired organ perfusion with at least one of the following: altered mental status; cold, clammy skin, or oliguria.

Prior Stroke: was considered when there is a record of brain computed tomography confirmed diagnosis.

Cardiac/heart disease*:* had history of CAD, RHD, non-rheumatic valvular heart disease, patent foramen ovale, chronic heart failure, infective endocarditis, IHD, MI, angina, AF or any current use of cardiac medications

Previous myocardial infarction (MI): if the patient has at least 1 documented previous MI before admission.

Family history of premature CAD: Any direct blood relatives (parents, siblings, and children) who have had any of the following at age less than 55 years (for first degree male relatives) and 65years (for first degree female relatives): angina, MI, or sudden cardiac death without obvious cause

Diabetes mellitus: If the patient is previously on oral hypoglycemic agents/insulin treatment or had the diagnosis any type of DM or FBS ≥126 mg/dl or had a documented RBS ≥200 mg/dl or glycosylated hemoglobin of ≥6.5%

Dyslipidemia or hyperlipidemia: previous had history of hyperlipidemia or using lipid lowering medication or total cholesterol ≥200 mg/dl, LDL cholesterol ≥100 mg/dl, and HDL-cholesterol <40 mg/dl for men or <50 mg/dl for women, and/or serum triglyceride level ≥150 mg/dl

Hypertension: previously receiving antihypertensive medication or when the patient was previously diagnosed with hypertension or detecting blood pressure of >140/90 mm/Hg for two measurements

Obesity: according to the WHO, Body Mass Index (BMI) ≥ 30 kg/m^2

Alcohol abuse/ consumption :> 7 unit per week for male and >5 unit drinks per week for females (according to International diabetic federation)

Treatment outcome: treatment outcome of patients with ACS was explained by all cause mortality from admission to 30 days ascertained by, death summary from healthcare records/physicians or Interviews with witnesses and family members for out-of-hospital death
The rate of death was calculated by taking the denominator; all ACS patients participated in the study at beginning and the numerator patients who died during 30 day follow up. In-hospital mortality is defined as the percentage of patients who died during their hospital stay. Confirmed by, death summary from healthcare records/physicians.

MACE-non fatal major adverse cardiac events: composite end point of in hospital stroke, reinfraction, cardiogenic shock and heart failure (diagnosed as defined above).

Killip class- was defined according to the classification of Killip and Kimball (Killip T 3rd. et al. 1996): class I, no signs of heart failure; class II, rales in the lungs; class III, pulmonary oedema; class IV, cardiogenic shock.

5. RESULTS

Of the 193 patients enrolled, 12 with ''no-cardiac chest pain'', ''reject consent'' or died before diagnosis confirmed were excluded. A total of 181 patients had a confirmed ACS diagnosis: 111 with STEMI and 70 with non-ST-elevation ACS (NSTE-ACS) or unstable angina (UA). Over the course of the study, 37 patients died, 4 were lost to follow-up. Data were available for 181 patients, 140 of who had 30 days follow-up data.

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┌─────────────────────────────────┐        ┌──────────────────────┐
│ Exclusions (n=12)               │        │ Patients enrolled    │
│ Non cardiac chest pain (n=7)    │        │ (n=193)              │
│ Reject consent (n=3)            │        └──────────────────────┘
│ Died before diagnosis confirmed │                  │
│ (n=2)                           │        ┌──────────────────────┐
└─────────────────────────────────┘        │ ACS Patients (n=181) │
                                           └──────────────────────┘

        ┌─────────────────────┐          ┌────────────────────────────┐
        │ STEMI (n=111)       │          │ Non-STEMI /UA (n=70)       │
        └─────────────────────┘          └────────────────────────────┘

  ┌──────────────┐  ┌──────────────┐   ┌──────────────┐  ┌──────────────┐
  │ JUMC (n=32)  │  │ SPSH (n=79)  │   │ JUMC (n=29)  │  │ SPSH (n=41)  │
  └──────────────┘  └──────────────┘   └──────────────┘  └──────────────┘

        ┌─────────────────────────┐
        │ Died (n=37)             │
        │ Lost to follow up (n=4) │
        └─────────────────────────┘

              ┌───────────────────────┐
              │ Patients with 30 day  │
              │ follow up (n=140)     │
              └───────────────────────┘
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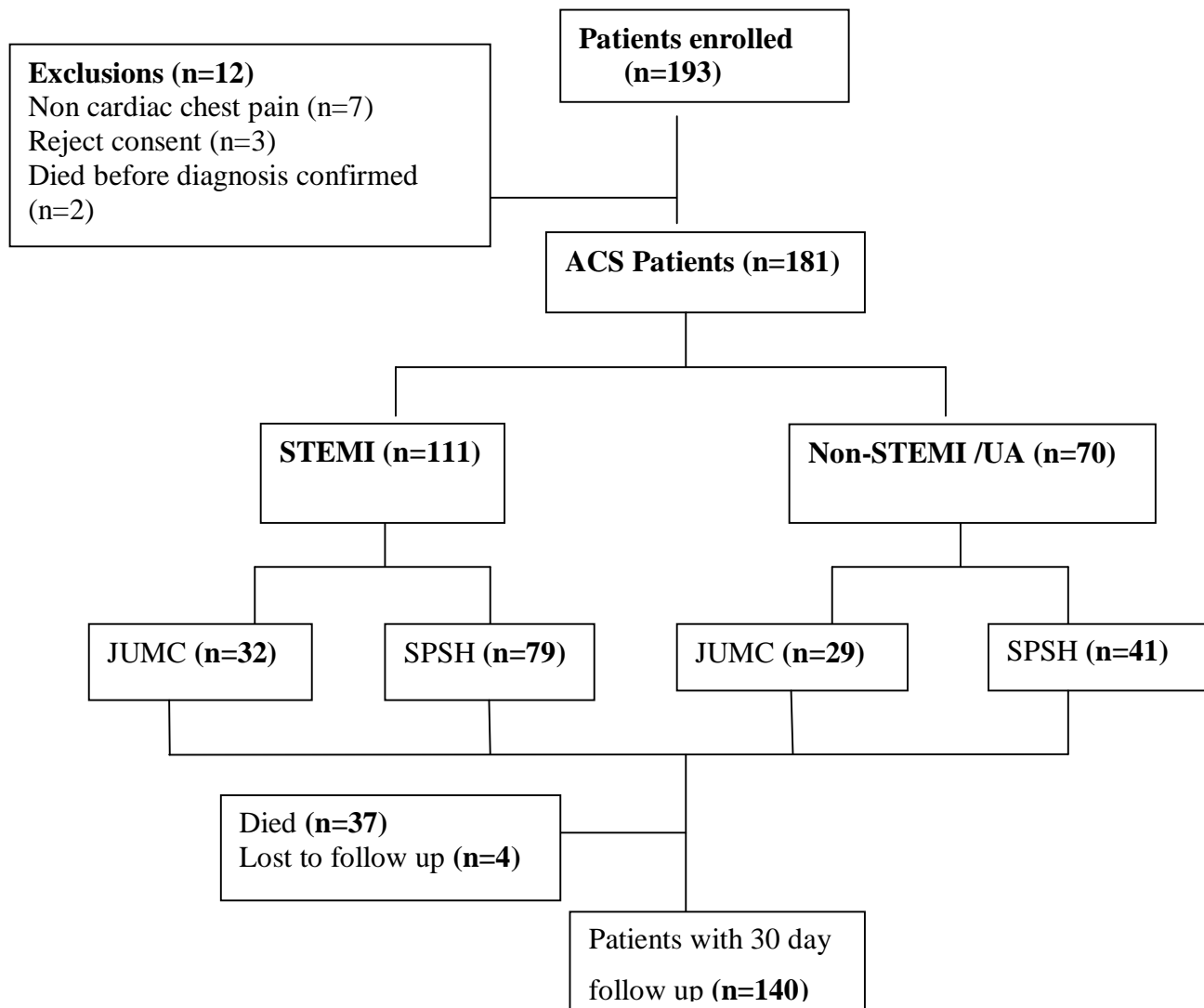
Figure 2: Study flow chart

4.1 Socio-demographic characteristics

The mean age of participants was 56 (±12) years, and men were accounted for more than half (62.4%). Majority of patients were presented with STEMI (61.3%). Majority of the participants were urban resident (76%), and around one third (29%) of the participants were unemployed.

Table 1: Baseline characteristics of participants, by ACS subtypes

Baseline characteristics N (%)	Total 181	STEMI 111(61.3)	NSTEMI 70 (38.7)	P value
Sex (Male)	113 (62.4)	70 (63.1)	43 (61.4)	.825
Age, years (SD)	55.9 ± 12.08	55.3 ±11.1	57.0 ±13.0	.079
Age strata				
<45	36 (19.8)	21 (18.9)	15 (21.4)	
45-64	94 (51.9)	64 (57.6)	30 (42.8)	
≥65	51 (28.2)	26 (23.4)	25 (35.7)	
Residence				.726
Urban	137 (75.7)	85 (76.6)	52 (74.3)	
Rural	44 (24.3)	28 (25.2)	18 (25.7)	
Educational level				.262
Unable to read/write	60 (33.1)	37(33.3)	23(32.8)	
Able to read and write	41 (22.6)	25 (22.5)	16 (22.8)	
Primary education	28 (15.5)	13 (11.7)	15 (21.4)	
Secondary and above	52 (28.7)	36 (32.4)	16 (22.8)	
Occupation				.651
Unemployed	53(29.3)	32 (28.8)	23 (32.9)	
Farmer	30(16.6)	20 (18.0)	10 (14.3)	
Merchant/labor work	53 (30.4)	35 (31.5)	18 (25.7)	
Employee (Govt./private)	43 (23.7)	24 (21.6)	19 (27.1)	
Marital Status				.824
Single	4	2	2	
Married	153 (84.5)	95 (85.6)	58 (82.8)	
widowed	24 (13.3)	14 (12.6)	10 (14.3)	
Average monthly income (ETB)				.780
<1650	73 (40.3)	46 (41.4)	27 (38.6)	
1651-3200	49 (27.1)	28 (25.2)	21 (30)	
≥3200	59 (32.6)	37 (33.3)	22 (12.2)	
Setting				.081
JUMC	61 (33.7)	32 (28.8)	29 (41.4)	
SPSH	120 (66.3)	79 (71.2)	41 (58.6)	
Mode of transportation				
Ambulance	13(7.2%)	9(8.1)	4(5.7)	.896

ETB: Ethiopian birr, **Govt**.: Governmental, **JUMC**: Jimma University Medical Center, **SD**: Standard deviation, **SPSH**: St. Peter Specialized Hospital

4.2 Clinical Presentation and medical history

More than two third (68%) of ACS patients were arrive after 12 hour of symptom onset and non-STEMI patients (48.6%) were more likely to present with atypical presentations (p=0.005). whereas, STEMI patients were more likely to present with Killip class 3 and 4 than NSTEMI. More than half (54%) of the study participates had Prior hypertension (Table: 2).

Table 2: Clinical presentation and key medical history, by ACS subtypes

N (%) Clinical features on presentation	Total 181	STEMI 111(61.3)	NSTEMI 70 (38.7)	P value
Symptom onset to presentation >12 hr, N (%)	123 (67.9)	78 (70.3)	45 (64.3)	.088
Typical chest pain	116 (64.1)	80 (72.1)	36 (51.4)	2.43
Atypical presentations	65 (35.9)	31 (27.9)	34 (48.6)	.005
Heart rate (bpm), mean (SD)	92.1±24.2	91.8±21.7	92.5±27.7	.836
Systolic BP (mmHg), mean (SD)	129.7±29.2	129.8±31.0	129.7±26.0	.997
Diastolic BP (mmHg), mean (SD)	79.5 ±15.7	79.4±16.3	79.6±14.7	.946
Body mass index (kg/m2)	23.2± 4.3	23.6± 4.1	22.7±4.6	.180
Random plasma glucose, >200 mg/dL	37 (20.4)	22 (19.8)	15 (21.4)	.794
Creatinine >2 mg/dl, N (%)	25 (13.8)	16 (14.4)	9 (12.8)	.762
Killip class				.007
Class I	73 (40.3)	44 (39.6)	29 (41.4)	
Class II	69 (38.1)	35 (31.5)	34 (48.6)	
Class III	26 (14.5)	21 (18.9)	5 (7.1)	
Class IV	12 (6.6)	11 (10)	1 (1.4)	
EF ≤ 30%, N (%)	39 (21.5)	27 (24.3)	12 (17.1)	.273
GRACE-Scrore	116.6±36.6	120.4 ±36.4	110.7± 36.5	.084
TIMI-Score non-STEMI/UA				
Key risk factors				
Hypertension	97 (53.6)	59 (53.2)	38 (54.3)	.882
Diabetes mellitus	45 (24.8)	26 (23.4)	19 (27.1)	.573
Dyslipedemia	87(48.1)	54 (48.6)	33 (47.1)	.843
Myocardial infarction	20 (11.0)	11 (9.9)	9 (1.8)	.538
Stroke/TIA	3	2	1	.325
Family history of CVD	46 (25.4)	23 (20.7)	22 12.1)	
PCI	3	2	1	.133
Smoking	29 (16.0)	16 (14.4)	13 (18.5)	.458
Alcohol misuse	55 (30.4)	35 (31.5)	20 (28.6)	.673
Abdominal obesity	60 (33.1)	41 (36.9)	19 (27.1)	.453
Over weight	61 (33.7)	41 (36.9)	20 (28.6)	.327
Khat	42 (23.2)	23 (20.7)	19 (27.1)	.319

BP: Blood pressure, CVD: cardiovascular disease, LVEF: left ventricular ejection fraction, GRACE: global registry of acute coronary events, PCI: Percutaneous coronary intervention, SD: Standard deviation, TIMI: Thrombolysis in myocardial infarction UA: unstable angina

4.3 Key laboratory and imaging findings

Majority of the patients had positive cardiac biomarkers (Troponin I) > 3 times upper limit normal (ULN). One in four patients had random blood glucose above 200 mg/dl and the average high density lipoprotein was less than the normal value for female and at the margin of the lower limit of normal for males. Slightly STEMI patients had higher hemoglobin level relative to NSTEMI patients. Angiography was performed for 42% of the total ACS patients with significant difference in results between ACS subtypes. Around half of STEMI patients have single vessel disease, whereas half of non-STEMI with angiography finding has normal/non-significant disease.

Table 3: Biochemical measurements and imaging results

N (%)		Total 181	STEMI 111(61.3)	NSTEMI 70 (38.7)	P value
Biochemical data					
Troponin I	Normal	23 (12.7)	5 (4.5)	18 (27.5)	<.001
	<3times ULN	27 (14.9)	17 ((9.4)	10 (14.3)	
	>3times ULN	131 (72.4)	89 (80.2)	42 (60)	
Random blood glucose, >200 mg/dl		37 (20.4)	22 ((19.8)	15 (21.4)	.794
Serum creatinine (mg/dl), SD		1.1±0.8	1.14±0.6	1.3±1.1	.439
BUN mg/dl (SD)		40.2±27.1	43.9±30.5	34.3±19.4	.629
Lipid panel test					
Total cholesterol		166.7±64.0	168.9±63.0	163.3±65.8	.563
HDL-C		42.3±11.6	41.8±12.6	42.7±9.9	.663
LDL-C		99.3±33.1	97.3±36.5	102.3±41.3	.388
Triglyceride		131.0±61.6	128.0±59.4	135.3±65.1	.439
Coagulation profile					
Prothrombine time		16.8±6.5	16.5±6.5	17.2±6.6	.654
aPTT		32.0±8.5	31.7±8.7	32.1±8.3	.789
INR		2.2±4.4	2.3±5.5	1.9±0.8	.432
Serum electrolyte					
Potassium		4.2±0.7	4.3±0.6	3.9±0.8	.007
Sodium		136.7±6.5	136.5±6.2	136.9±6.8	.618
Chlorine		104.3±6.9	104.4±7.1	104.1±6.7	.786
Hemoglobin (mg/dl)		13.8±2.6	13.9± 2.3	13.6±3.0	.044

aPTT: Activated partial thromboplastin, **BUN**: Blood urea nitrogen, **HDL-C**: High density lipoprotein cholesterol, **INR:** International normalized ratio, **LDL-C**: Low density lipoprotein cholesterol, **ULN**: Upper limit normal, **SD:** Standard deviation

4.3.1 Angiography reports

Out of 120 patients enrolled from SPSH, angiography was done for 76(63.3%) patients. The most common finding was single vessel disease (39%) which was followed by normal or non-significant disease (34%), (**Fig.2**).
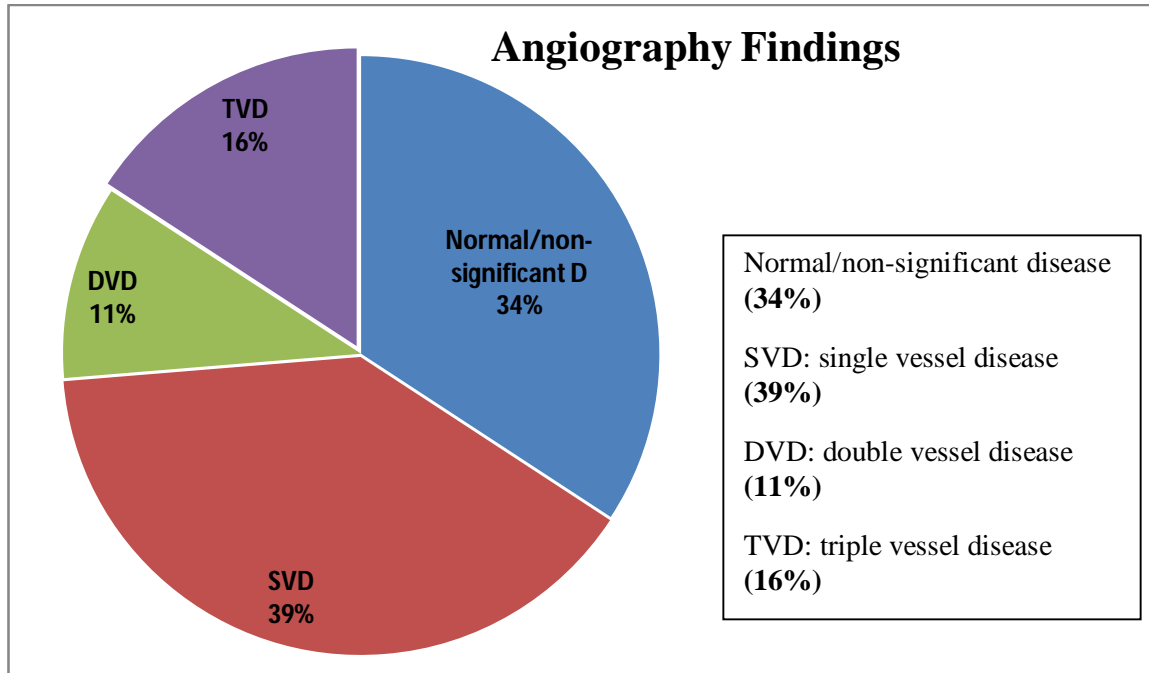
Angiography Findings

Normal/non-significant disease **(34%)**	
SVD: single vessel disease **(39%)**	
DVD: double vessel disease **(11%)**	
TVD: triple vessel disease **(16%)**	

Figure 3: Angiographic finding among ACS patients enrolled from SPSH

4.3 In-hospital management of ACS patients

Coronary angiography was performed in 42% of all patients with significant statistical differences across ACS types (Table 4). None of the STEMI patients were received thrombolysis therapy. None of STEMI patients received any form of reperfusion therapy (thrombolysis, PCI, or CABG), while STEMI (9%) and non-STEMI (5%) patients underwent elective reperfusion with PCI. On the other hand, in-hospital aspirin (99%) and Statins (98%) were given almost for all ACS types. followed by Clopidogrel (92%), Beta-blockers (81%), heparin (76%) and ACE-inhibitors (72%). STEMI (49%) patients were more likely to receive Morphine on presentation compared to non-STEMI patients (31%, p=0.022) (Table 4).

Table 4: Selected in hospital management: Medications and Interventions

N (%)	Total 181	STEMI 111(61.3)	NSTEMI 70 (38.7)	P value
In-hospital medical therapy				
Aspirin	180 (99.4)	111(100.0)	69 (98.6)	.207
LD. Aspirin	154 (85.1)	96 (86.5)	58(82.8)	.504
Clopidogrel	166 (91.7)	103 (92.8)	63 (90.0)	.507
LD. Clopidogrel	150 (82.7)	93 (83.7)	53 (75.7)	.682
Statins	178 (98.3)	109 (98.2)	69 (98.6)	.848
Beta-blockers	146 (80.6)	90 (81.1)	56 (80.0)	.761
ACE-inhibitors	131 (72.4)	84 (75.7)	47 (67.1)	.211
Any heparin	138 (76.2)	86 (77.5)	52 (74.3)	.623
Nitrates	53 (29.3)	32 (28.8)	21 (30.0)	.818
Morphine	76 (42.0)	54 (48.6)	22 (31.4)	**.022**
Furosemide	97 (53.6)	59 (53.2)	38 (34.2)	.882
Dopamine	20 (11.0)	16(11.4)	4(5.7)	**.043**
Antibiotics	46 (25.4)	23 (20.7)	23 (32.8)	
Omeprazole	85 (47.0)	53 (47.7)	32 (45.7)	.790
Elective PCI	13 (7.2)	10 (9.0)	3 (4.3)	.231

ACEIs: Angiotensin converting enzyme inhibitors, **LD:** Loading dose, **PCI**: Percutaneous coronary intervention

4.4 Discharge medication based on discharge diagnosis

Over all use of evidence based medication was variable with high use of Aspirin and high intensity satins (95%). However, the use of clopidogrel, beta blockers and ACEIs were low (74%, 71%, and 70%) respectively (Fig: 4).
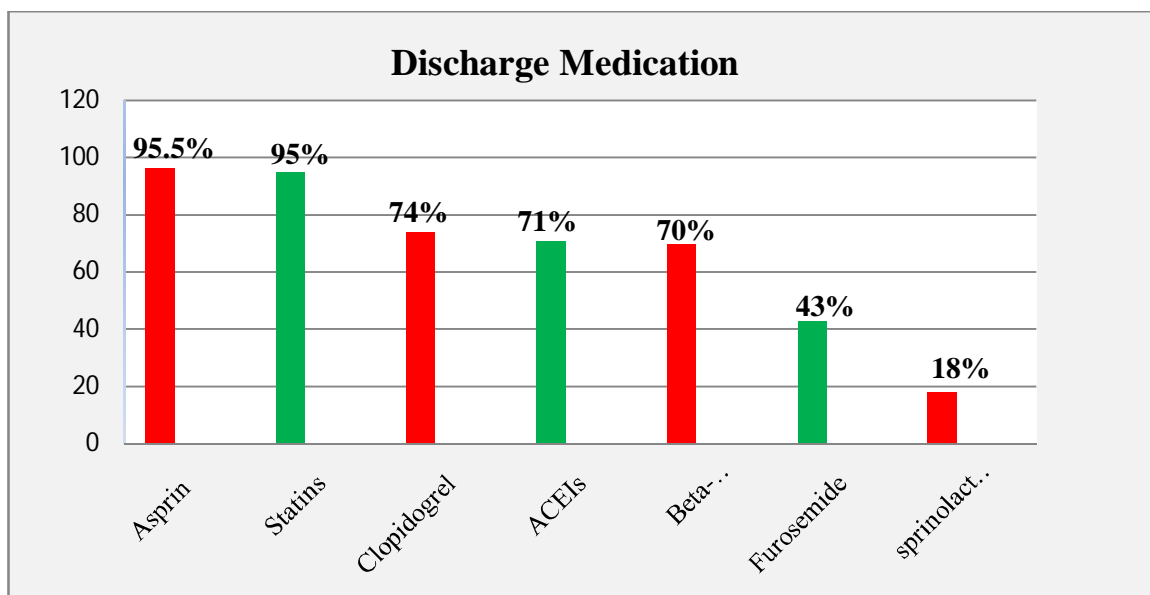

Figure 4: percentage of discharge medication prescribed for ACS patients

4.5 Process of care as quality indicators of ACS

Loading dose of dual antiplatelets therapy (DAPT) was given for 69% of the total ACS; and Aspirin and Clopidogrel was initiated within 24 hr first medical contact (FMC) for majority of the patient (78% and 80%) respectively. However less than three quarter discharged with DAPT which was significantly differ between STEMI (91.4%) and non-STEMI (66.4) (Table 5).

Table 5: process of care as quality indicators for ACS

Process of care	Total 181	STEMI 111	NSTEMI 70	P value
Presentation within 12 hr.	55(30.4)	38(34.2)	17(24.3)	0.366
DAPT-LD within 24 hr	125(69%)	82(74)	43(61.4)	0.780
Aspirin 24 hr of FMC	140 (78.2)	92(83.6)	48(69.6)	0.026
Clopidogrel in 24hr of FMC	132(79.5)	88(85.7)	44(69.7)	0.016
Anticoagulant in 24hr FMC	111(61.3)	73 (65.7)	38 (54.3)	.060
High intensity statin in 24 hr FMC	135(78)	90(83)	45(69)	0.030
Beta- blockers in 24 hr FMC	121(66.8)	80 (72.1)	41(58.6)	0.023
ACEIs in 24hr FMC	111(61.3)	73(65.7)	38 (54.3)	.449
Discharge medication	**Total 144**	**STEMI 82**	**NSTEMI 62**	
DAPT	116 (64.1)	75 (91.4)	41(66.4)	0.014

DAPT: dual antipltelets therapy, FMC: First medical contact, LD: Loading dose

4.6 In-hospital complications and mortality

The unadjusted in-hospital mortality rate was 13.4% in over all ACS patients with marginal statistics difference across ACS subtypes. STEMI patients, more likely to develop cardiogenic shock compared to no-STEMI (13.5 Vs 4.3 p= 0.043). However, non-fatal MACEs such as Heart failure, stroke, and re-infarction were not significantly different across ACS subtypes.

Table 6: In-hospital complications and mortality

N (%)	Total 181	STEMI 111(61.3)	NSTEMI 70(38.7)	P value
Event rates				
In-hospital Mortality	24 (13.4)	18 (16.7)	6 (8.6)	.059
Heart failure	18 (9.9)	13 (11.7)	5 (7.1)	.317
Cardiogenic shock/cardiac arrest	18 (9.9)	15 (13.5)	3(4.3)	.043
Stroke	5(2.7)	3 (2.7)	2 (2.8)	.951
Re-infarction	6 (3.3)	5 (5.4)	1(1.4)	.038
Heart failure, stroke, Cardiogenic shock and re-infarction	37 (20.4)	27 (24.3)	10 (14.3)	.134
Atrial fibrillation	13(7.2)	7(6.3)	6 (8.6)	.565
Acute kidney injury	22(12.2)	13(11.7)	9 (12.8)	.818
Hospital acquired infection	17 (9.4)	10 (9.0)	6 (8.6)	.824
Hospital Stay in days, Mean, (SD)	9.2±4.4	9.0 ±4.3	9.4± 4.6	.635

4.5 Thirty day mortality, by ACS subtypes

A general cohort of 181 patients was followed for 4651 person days. Over this follow up period about 37 patients were died. The overall incidence rate of mortality was in ACS patients were 7.99 per 1000 person days. Incidence rate of mortality in STEMI patients were 10.65per 1000 person days and non-STEMI was 4.19 per 1000 person days. Kaplan—Meier survival curves show risk of death from admission to 30 days by ACS subtypes, which showed patient presented with STEMI had more risk of death from admission to 30 days compared to non-STEMI (Fig. 2, Log Rank = 0.017).
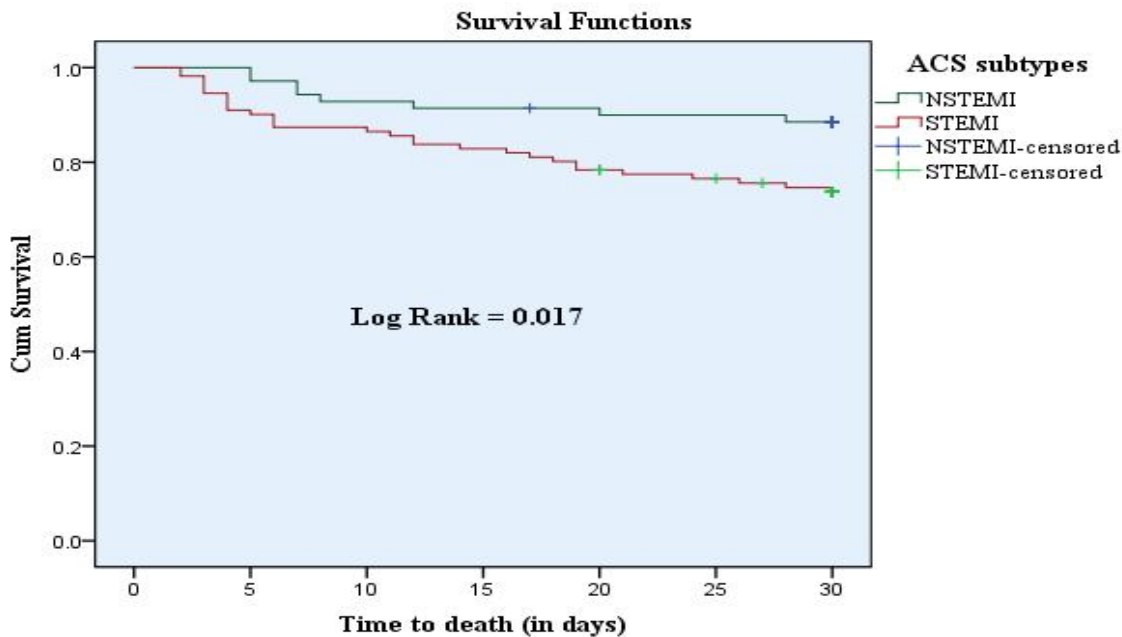
Figure 5: Kaplan-Meier survival curves from admission to 30 days, by ACS subtypes

4.7 Predictors of 30 day all cause mortality by ACS subtypes

Binary and multivariate Cox-regression was performed to determine predicators of 30 day all cause mortality. After adjustment for potential confounder (patient demography, clinical finding, key risk factors, in-hospital medication and complication), factors associated with a higher risk of death at 30 days were Rural residence (AHR=2.4,CI 1.23-4.66), STEMI (AHR 3.05, CI 1.42-8.89), Prior stroke (HR 15.14, CI 3.61-63.50), GRACE-score (AHR 1.026, CI 1.01-1.04) and Cardiogenic shock (AHR 4.46, CI 2.02-9.81), Factor associated with a lower risk were hemoglobin level at admission (HR 0.843,CI 0.75-0.96).

Table 7: Predictors of 30 day all cause mortality

Variables		Total	30 days mortality		Unadjusted model		Adjusted model	
		181	Alive 144(79.6)	Dead 37(20.4)	HR	P value, 95% CI	HR	P value, 95%CI
Demographics								
Sex	Female	68 (37.5)	53 (36.8)	15 (40.5)	1.210	.569(.628-2.333)		
	Male	113 (62.4)	91 (63.2)	22 (59.5)				
Age			54.9(12.1)	59.5(10.4)	1.634	.043(1.014-2.632)	1.033	.125(.991-1.036)
Residence	Urban	137 (75.7)	116 (80.5)	21 (56.7)				
	Rural	44 (24.3)	28 (19.4)	16 (43.2)	2.75	.002(1.434-5.273)	2.39	**.010**(1.23-4.66)
Occupation	Unemployed	53 (29.3)	41 (22.6)	12 (32.4)	3.502	.052 (.989-12.426))	.503	.344(.121-2.002)
	Farmer	30 (16.6)	19 (13.2)	11 (29.7)	6.280	.005(1.751-22.524)	2.347	.461(.415-6.948)
	Merchant	55 (30.4)	44 (30.5)	11 (29.7)	2.989	.093(.834-10.714)	1.349	.670(.340-5.350
	Employee	43 (23.7)	40 (27.7)	3 (8.1)		.001		
Education	Unable to read and write	57 (31.5)	38 (26.4)	19 (51.4)	3.373	.009(1.347-8.488)	1.471	.585(.369-5.869)
	Able to read and write	42(23.2)	34 (23.6)	8 (21.6)	1.706	.323 (.592-4.919)	.903	.875(.252-3.302)
	Primary school	29 (16.0)	25 (17.4)	4 (10.8)	1.119	.786 (.336-4.222)	.670	574 (.166 -2.705)
	Secondary and above	53 (29.3)	47 (32.6)	6 (16.2)		.001		
Income, ETB (monthly)	<1650	73 (40.3)	51(35.4)	22 (59.4)	2.433	.031(1.083-5.446)	1.069	.912(.328-3.485)
	1651-3200	49 (27.1)	42 (29.2)	7 (18.9)	1.050	.924(.381-2.897)	.874	.807(.279-2.572)
	>3200	59 (32.6)	51 (35.4)	8 (21.6)		.035		
Hospital	JUMC	61 (33.7)	43 (29.8)	18 (48.6)	2.304	.031(1.067-3.877)	1.54	.276(.722-1.132)
	SPSH	120 (66.3)	101 (70.1)	19 (51.4)				
Clinical data and risk factors								
Symptom onset to arrival	<12 hr	55(30)	50 (34.7)	5 (13.5)	.036			
	12-24hr	19(10.5)	16 (11.1)	3 (8.1)	1.971	.425(.428-7.497)		
	>24 hr	107(59.1)	78 (54.2)	29 (78.4)	3.309	.013(1.281-8.551)		
Symptom on arrival	Typica	113 (62.4)						
	Atypical	68 (37.6)			3.956	000(1.987-7.878)	1.695	151(.824-3.488)
Heart rate			89.6(18.2)	100.8(38.8)	1.041	.011(1.003-1.024)	1.004	.452(994-1.014)
Systolic-BP		130.09	134.0±27.45	115.6±29.9	.975	.001(.961-.989)	.985	.168(.965-1.006)
Diastolic-BP			81.6±14.7	72.3±16.7	.958	.001(.933-.983)	.984	.283(986-1.049)
Serum-Cr.			1.1(0.9)	1.4(1.0)	1.012	.933(.763-1.342)		
Troponi t (>3timesULN)		131 (72.4)	105 (72.9)	26 (70.3)	1.402	.427(.609-3.231)		
Killip class	Class 1 and 2	145 (80.1)	127 (88.2)	18 (48.6)	1			
	Class 3 and 4	36 (19.9)	17 (11.8)	19 (51.4)	5.432	.000(2.845-10.370)	1.765	**.220**(.711-4.381
ACS types	STEMI	111 (61.3)	82 (56.9)	29 (78.4)	2.507	.021(1.456-5.485)	3.051	**.015**(1.418- 8.889)
	NSTEMI	70 (38.7)	62 (43.1)	8 (21.6)				
GRACE-SCORE					1.041	.000(1.031-1.051)	1.026	<.001(1.014-1.038)
Hemoglobin		13.8	14.2±2.4	12.2±2.9	.835	.000(.756-.924)	.843	**.005**(.747-.951)
LVEF<30%		39 (21.5)	22	17	4.24	.000(2.143-8.422)	1.889	.135(.820-4.381).
BUN		40.2	37.9±24.2	49.0±35.2	1.009	.036(1.001-1.018)	.999	.869(.989-1.009)
Hypertension		97 (53.6)	83 (57.6)	14 (37.8)	.503	.043(.259-.978)	1.793	.214(.715-4.449)
DM		45 (24.9)	35 (24.3)	10 (27.0)	1.137	.729(.550-2.349)		
MI/angina		20 (11.0)	17 (11.8)	3 (8.1)	.654	.481(.201-2.131)		
Anemia		53 (29.3)	34(23.6)	19(51.4)	2.780	.002(1.458-5.300)	1.722	.116(.875-3.388)
Stroke		3 (1.6)	0	3 (8.1)	12.278	.001(3.707-40.661)	15	**<0.001**(3.613-63.497)

Family history of CVD	45 (24.9)	42 (23.2)	3 (8.1)	.245	.019(.075-.797)	.768	.076(.076-1.137)
Dyslipdemia	87 (48.1)	72 (	15	.764	.388 (.387-1.439)		
Smoking	29 (16.0)	24 (13.4)	5 (13.5)	.840	.717(.327-2.156)		
Alcohol	55 (30.4)	42 (23.2)	13 (35.1)	1.293	.456(.658-2.539)		
Khat	42 (23.2)	33 (22.9)	9 (24.3)	1.053	.891 (.497-2.223)		
BMI>=25kg/m^2	61 (33.7)	49 (34.0)	12 (32.4)	1.068	.851(.537-2.126)		
Abdominal obesity	60 (33.1)	49 (34.0)	11 (29.7)	.837	.622(.414-1.695)		
Charlson comorbidty index		1.76(1.5)	1.97(1.3)	1.073	.502(.874-1.316)		
In-hospital medication							
Aspirin	180 (99.4)	144 (100)	1 (2.7)	.216	.131(.030-1.580)	.899	.933(.075-10.822)
Aspirin(LD)	154 (85.1)	125	29 (78.4)	.560	.065(.256-1.225)	1.94	.395(.426-8.680)
Clopidogrel	166 (91.7)	135	31 (91.2)	.049	.049(.173-.997)	1.234	.805(.233-6.536)
Clopidogrel LD	150 (82.8)	124	26 (14.4)	.480	.048 (.231-.995)	.466	.076(.200-1.082)
Statins	178 (98.3)	142	36 (97.3)	.672	.695(.092-4.904)		
Beta-blockers	130 (71.8)	126	20 (54.1)	.228	.000(.119-.437)	1.570	.156(.758-6.690)
ACEIs	131 (72.4)	115	16 (8.8)	.251	.000(.131-.481)	.424	.096 (.267-1.113)
Heparin	138 (76.2)	109	29 (78.4)	1.114	.735 (.523-2.504)		
Morphine	76 (41.9)	65	11 (29.7)	.554	.100(.274-1.121)	.600	.177(.286-1.260)
nitroglycerin,	53 (29.3)	43	10 (27.0)	.964	.889(.431-1.837)		
In-hospital complication							
Cardiogenic shock	14 (19.8)	4(2.8)	14 (37.8)	4.317	.000(2.498-7.459)	4.456	**<.001**(2.023-9.813)
AF	13 (7.2)	7 (4.8)	6 (16.2)		.003(1.456-9.645)	.958	.930(365-2.510)
HAI	16 (8.8)	8 (5.5)	8 (21.6)	3.254	.003(1.485-7.132)	1.252	.581(.564-2.777)
AKI	22 (12.2)	13 (9.0)	9 (24.3)	2.454	.019(1.157-5.206)	.992	.984(.440-2.222)

ACEIs: Angiotensin converting enzyme inhibitors, **ACS:** Acute coronary syndrome, **AF**: Atrial fibrillation, **AKI:** Acute kidney injury, **BMI**: Body mass index, **BUN**: blood urea nitrogen, **BP**: blood pressure, **CVD**: cardiovascular disease, **DM**: diabetes mellitus, **LD**: loading dose, **LVEF**: left ventricular ejection fraction, **MACE**-Major adverse cardiac events, **STEMI**: ST-elevated myocardial infarction, **ULN:** Upper limits normal,

6. DISCUSSION

Majority of the patients in our study were diagnosed with STEMI (61%), and the mean age of the patients was 56 years. previous studies such as CREATE(17) (STEMI 60%, mean age 57.5), ACCESS(47) (STEMI 59%, mean age 59 years) reported similar pattern. However, a decade younger and higher proportion of ST-elevation was observed when compared to studies from HICs: GRACE(68) (STEMI 32%, mean age 66 years), EURO HEART SURVEY(52) (STEMI 47%, mean age 63 years). Earlier age for first ACS is likely due to earlier acquisition of adverse health behaviors such as alcohol, smoking and inactivity and IHD risk factors (hypertension, diabetes mellitus) with concomitant poor management of IHD risk factors. High proportion of STEMI in our patient might be due to younger age at presentation and under diagnosis of non-STEMI due to atypical presentation.

In our study, there was an undue delay in presenting to the hospital; the mean duration between symptom onset and hospitalization was 54 hr. which is by far longer than mean delay time (3.4hr.) reported by Global review of delay time in seeking medical care for chest pain(48). In the same way, 68% of patients in our study presented after 12 hr of symptom onset, which is more than two times higher when set side by side with the report from CREATE(17) registry in which 31% of patients presented after 12hr of the onset of chest pain. This undue delay of our study participants in seeking health care might be due to lack of emergency transport facilities, economic reasons, and lack of awareness about the importance of the symptoms. Since majority of the patients in our study have no formal education and from low economic class.

More than one third of patients in our study presented with atypical symptoms, which is more common in non-STEMI. This finding was similar with the report of NRMI(50), GRACE(49), but high compared to FAST-MI(51)registry. This discrepancy might be due to high proportion of female (38% Vs 24%) and DM (25% Vs 18%) in our study compared to FAST-MI respectively. Patients presented with atypical symptoms have worse outcome unlike those presented with typical chest pain in present study which further strength the reports of previous studies.

More than half of our study participants had history of hypertension and dyslipedemia and one fourth had history of type 2 diabetes mellitus. Our finding was doubled compared to the report of INTERHEART(14) study that, reported hypertension in (39%), and diabetes in (18.5%). our findings indicate that majority of ACS patients had one or more comorbidty that alert the clinicians and healthcare providers to focus on primary prevention by early screening (<45 years) and management of metabolic syndromes and other risk factors to decrease burden of ACS. Physical inactivity, abdominal obesity, and alcohol misuse was also high in urban compared to rural residents in our study participants. Overall high rate traditional cardiovascular risk factor in our study participant might be partly due to urbanization and increased sedentary life style; since majority of our study participants were from urban area. This finding further strengthen previous studies of cardiovascular risk factor in Ethiopia that reported, hypertension, obesity, and physical inactivity were more concentrated in urban populations(24, 25).

Early restoration of perfusion is the corner stone of ACS management to rescue jeopardized myocardium as soon as possible(2). Despite it is a life saving intervention, none of STEMI patients or high risk non-STEMI received medical (fibrinolytics) or mechanical means (primary PCI or CABG) of early reperfusion therapy in our study. Unavailability of fibrinolytics drugs (even generic streptokinase) and public cardiac center/tertiary hospital capable of PCI with or without onsite cardiac surgery in our country contributed almost zero rate of revascularization observed in present study. This largely contributed in discrepancy of outcome observed in our study even compared to our neighbor Kenya in which all most all STEMI patients were revascularized (tenecteplase 62% and primary PCI 38%).

The use of evidence based medical treatments such as Anti-platelet dugs (Aspirin and Clopidogrel), lipid-lowering drugs were high (> 90%) and similar with report of previous studies such as ACCESS South Africa(35) and and Kerala ACS(58) registry, also showed high use of in-hospital antiplatlets and lipid lowering agents. Although the use of beta-blockers (80%) and ACEIs (72%) in our study was low, it was better than CREATE(17), ACESS(18) and Kerala ACS(58) registry. However acute (within 24 hr of FMC) initiation of loading dose of dual antiplatlets therapy (DAPT 69%) was not in line with international guideline recommendation. Over all initiation of evidence based therapy within 24 hr of hospital arrival was low (2, 3).

Use of anticoagulants is area which need clarification and further research as almost all of our study participants were received fixed subcutaneous UFH in contrast to ACCESS-South Africa(35) and Kenya(34) were majority of the patients received Enoxaparin. The practice also contradicts with international guideline recommendation; weight-based intravenous bolus dose followed by a continuous infusion UFH or weight based LMWHs (2, 3). These discrepancies in management may be partly explained by unavailability with superimposed unaffordability of LMWH and low experience of clinicians with the use of LMWHs in our setup.

Further the use of DAPT at hospital discharge was low compared to FAST-MI(51)registry (DAPT 85% at discharge). International guidelines (2, 3), recommend the use of DAPT irrespective of therapeutic strategy (invasive or conservative) even for prolonged time (12 month) for high risk patients; so clinicians should give due attention on use of DAPT to prevent recurrence and mortality in ACS patients. Majority of the patients were discharge with high intensity statins even though the use of beta-blocker and ACEIs were low. Despite, emerging body of evidence that aldostrone antagonist is associated with mortality benefit in STEMI patients irrespective or in absence of heart failure (72, 73); only quarter of our study participants were discharge with spironolactone. So this is an area which needs further improvement by our physicians for better reduction of mortality and morbidity in STEMI patients.

Thirty days mortality rates in our study (20.4%) were alarmingly high even compared to reports from LMIC countries; with significant difference between STEMI and non-STEMI (26% vs 11.4% HR: 3.1, p=). The finding was higher compared to CREATE(17) registry which reported 30 day mortality in STEMI 8.6% vs 3.7% in non-STEMI/UA and ERICO study reported also low rate of 30 day mortality STEMI (4.9%) and non-STEMI (7.2%). The difference is even more pronounced compared to reports from developed countries. GRACE(68) (STEMI (8%) vs non- STEMI (3%),and Euro Heart Survey-2(52)reported 30 day death 6% vs 3% for STEMI and non-STEMI patients respectively. ACESS-South Africa(35), even reported low rate of thirty day mortality (STEMI 2.4% vs non-STEMI/UA 1.7%).

Even though the reported mortality rate in our study was high, the actual mortality is likely to be higher than reported here since rural residents and more poor patients might died before hospital arrival. The high mortality rate in our population is not surprising since we are still in the pre-interventional/revascularization era. None of STEMI patients or high risk non-STEMI/UA

received any form revascularization due to unavailability of fibrinolytics (even generic streptokinase) and PCI center. Even if fribrinolytics and PCI center available, majority of the patients arrive hospital after 12 hour of symptom onset which make them ineligible. Low use of key medication like loading dose of early DAPT, beta blockers and ACEIs/ARBs with high rate of in-hospital MACE complicated management and contributed to high rate of early mortality in our population.

Not only mortality, the rate of non fatal major adverse cardiac event (MACE: such as stroke, re-infarction, heart failure, or cardiogenic shock) were also more common in our study participants. Cardiogenic shock and re-infraction were more common in STEMI patients, whereas stroke and heart failure had no significant difference between ACS subtypes. Our finding was partly supported by previous studies such as Kerala ACS(58) registry which showed that Patients presenting with STEMI had a higher risk in-hospital MACE [OR = 2.75 (1.81, 4.17)] than patients presenting with NSTE-ACS, even after adjustment for potential confounders, and ACCESS(18) registry also found that, the combined end point (cardiovascular death, nonfatal stroke, or MI) was higher among patients with STEMI. Non fatal MACE were also associated with higher risk of mortality at 30 day (HR 4.4, p <0.001).

Cardiogenic shock was associated with four times high risk of 30 day mortality compared to those who didn't developed cardiogenic shock and 78% patients of ACS complicated with cardiogenic shock died during their hospital stay. Previous studies also reported similar finding that, cardiogenic shock remains the most common cause of death in patients with acute myocardial infarction(74). Although mortality was reduced from formerly 80% to 40–50% in HICs(75), it is still exceedingly high (70-80%) in LMIC those treated conservatively(76). Early revascularization is the cornerstone treatment of acute myocardial infarction complicated by cardiogenic shock. In addition to PCI/CABG, catecholamines, fluids, intraaortic balloon pumping (IABP), and also active assist devices are widely used for CS management (74-76). However, invasive strategy in a poor setting like ours is not only costly but also technically demanding. Despite studies(77, 78) were reported dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days, all of ACS complicated with cardiogenic shock was treated by dopamine only. Poor management of cardiogenic shock partly

contributed to high early mortality rate observed in our study participants, particularly STEMI patients.

More than one in four (29%) of patients participated in our study were anemic. Anemia was not only common in our study participants, it was also associated with three times higher risk of 30 day mortality compared to those with normal hemoglobin value(>13mg/dl: Male and >12.5:Female). In addition 1g/dl increase in hemoglobin decrease 30 day mortality by 16%.This finding is also supported by other previous observational studies such as: The (MINAP)(79) Registry in England and Wales, reported that, more than quarters of participants were anemic and the condition increased risk of 30 days mortality (27.7%) and Others have also shown excess risk such as ischemia and major bleeding were associated with anemia in the setting of ACS and the effect remained evident up to 5 years (80, 81). This partly explained by the fact that anemia exacerbate further imbalance of oxygen demand and supply which is the "sine qua non" of ACS both by decreasing oxygen-delivery capacity and simultaneously raising myocardial oxygen consumption through increased cardiac output. So, clinician should approach an ACS patient with concomitant anemia by substantiating current recommendations to transfuse at more restrictive levels of 7 to 8 g/dl; and measures should be taken to minimize risks for bleeding and dosing of antithrombotic therapy by weight and renal function should be emphasized to further minimize bleeding risks.

7. STRENGTH AND LIMITATION

The primary strengths of our study was that we followed patients and captured mortality rate over thirty days, in-hospital complications and predictors of outcome which didn't get attention in our setup previously (GRACE risk score, and Anemia). In addition our study demonstrated process of care for ACS in resource limited setting. However, our study has several limitations. First, our study suffers the same limitations as all observational studies: namely, no causality can be asserted between parameters that are correlated. Second, comparisons between patients according to ACS subtypes were not randomized and, despite careful adjustments on a large number of potentially confounding variables, our findings can only be considered indicative. Third, limited sample size although we prolonged study period on our own cost still the final sample size was limited. So, our study was underpowered to analysis difference between UA and AMI. Fourth, study site were not randomly selected and only two sites participated in the study, so the finding/practice might not necessarily represent all hospitals in the country. However geographical location of the site favored inclusion of diverse population which indicate usefulness of our data.

8. IMPLICATION FOR QUALITY IMPROVEMENT

Desperately high 30 day mortality has implications for national and local ACS management improvement efforts. Ministry of health (MoH) and Pharmaceutical fund and supply agency (PFSA) should jointly work on availing at least cardiac interventional therapy such as standalone PCI. Additionally priority should be given for fibrinolytic drugs (at least the generic streptokinase) should be accessible to tertiary hospitals currently managing ACS patients. Public health officers and health professionals should work on creating public awareness on common cardiovascular risk factors in particular, importance of screening for metabolic syndrome in decreasing future complications. Clinicians should create public awareness on importance early presentation to hospital and government should develop emergency medical service (EMS) system to decrease lag time between symptom onset and presentation to the hospital for emergency care, which might improve patient outcome. Appropriate in-hospital and discharge medical therapy are key targets with some areas of high performance (in-hospital ACEIs and Beta-blockers). Tertiary hospital and future researchers should conduct nationwide ACS registry jointly with tertiary hospital to determine the full image of ACS burden nationwide, to design protocol on prevention of ACS, and to improve future of patients with ACS in our country.

9. CONCLUSIONS

More than one in three patients had atypical presentation which associated poor outcomes, so clinicians should be more suspicious enough to identify the patients and manage timely to improve outcome of the patients. Majority of the patients were presented to hospital after more than 12 hour of symptom onset which is undesirably high and predicted adverse outcome. So creating public awareness on importance of "warning symptom" and health-seeking behavior has worth enough to improve patient outcome. Use of in hospital and discharge medication was variable and suboptimal, with some area needs further improvement (DAPT, beta-blockers and ACEIRs). Rural residence, STEMI, cardiogenic shock and GRACE score were factors predicted poor outcome at 30 days. So, government should focus on strategies that improve the health of rural residents and facilitate EMS. Hospitals should also conduct risk assessment for ACS patients since it determine therapeutic strategy and patient prognosis. Unavailability of any form of reperfusion therapy for STEMI patients and high risk non-STEMI resulted in unacceptably high rate of early mortality. So high-priority should be given for implementation of evidence-based medications and interventions, including reperfusion therapy are needed.

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Annex 1: Data Collection Tool

I.	**BASELINE SOCIO-DEMOGRAPHIC CHARACTERISTICS**

Date of admission_____ Time:_____ AM/PM	**Sex:** ☐ Male ☐ Female	**Age**:_____ (yrs)	Kebele:_____ Woreda:_____ Region:_____	**Residence** ☐ Urban ☐ rural

Education status
- ☐ Unable to read and write
- ☐ Able to read and write, informal education (eg religious education) (Less than primary school)
- ☐ Elementary school (1-8)
- ☐ Secondary school (9-12)
- ☐ College/university or above

Occupational-status (over the last 1years)
- ☐ Employee (GOvt./NGO)
- ☐ Merchant (business work)
- ☐ Agriculture / farmer
- ☐ Unemployed

Other(specify)_____ _____

Religion
- ☐ Orthodox
- ☐ Protestant
- ☐ Muslim
- ☐ Catholic
- ☐ Traditional belief

Others_____

Marital status
- ☐ Single
- ☐ Married
- ☐ Divorced
- ☐ Widowed
- ☐ Other_____

Socio-economic status
- ☐ Average monthly income_____(ETB)

Mode of transportation_____

Medical record No._____

Contact No._____

Hospital _____ Ward_____

II.	**BEHAVIORAL MEASURES**

Tobacco smoking 1, yes   2,No
- ☐ Current smoker
- ☐ X-smoker _____how long ago did you stop_____
- ☐ Average daily cigarette _____

Alcohol intake
- ☐ No
- ☐ Yes
- ☐ Average weekly intake_____

Bottles, litres etc)

Khat chewing
- ☐ No
- ☐ Yes

Diet (in a week)
- ☐ How many days do you eat fruit_____
- ☐ on how many days do you eat vegetables_____

Contraceptive (females only)
- ☐ OCP
- ☐ Others_____
- ☐ No

Physical activity
- ☐ Does your work involve vigorous-intensity activity that causes large increases in breathing or heart rate
  - o Yes
  - o No
- ☐ In a typical week, on how many days do you do vigorous-intensity activities as part of your work_____
- ☐ How much time do you usually spend sitting or reclining on a typical day? _____

Herbal or other traditional medicine use
- ☐ No
- ☐ Yes (specify)_____duration _____

Therapeutic life style change
- ☐ Advice to reduce salt intake
- ☐ Advice or treatment to lose weight
- ☐ Advice or treatment to stop smoking
- ☐ Advice to start or do more exercise
- ☐ Special prescribed diet
- ☐ 0thers_____
- ☐ No

III. DISEASE RELATED FACTORS

A. CO-MORBIDITY and RISK FACTORS

Diabetes Mellitus	Hypertension	Heart Failure		Renal failure
☐ Yes ☐ No If yes, ☐ Controlled ☐ Uncontrolled	☐ Yes ☐ No If yes, ☐ Controlled ☐ Uncontrolled	☐ Yes ☐ No If yes, ☐ NYHA class_____ ☐ Grade (AHA)_____		☐ Yes ☐ No
Previous MI ☐ Yes ☐ No	**PAD** ☐ Yes ☐ No	**Stroke/TIAs** ☐ Yes ☐ No	**Malignancy** ☐ Yes ☐ No **If-yes ,** **Specify_____**	**Anemia** ☐ Yes ☐ No **If yes,** **Severity_____**
Rheumatic heart disease ☐ Yes ☐ No	**VTE** ☐ Yes ☐ No	**Endocrine disorder** ☐ Hyperthyroidism ☐ Hypothyroidism		**Inflammation** ☐ **Yes** ☐ **No**
Chronic lung disease ☐ Asthma ☐ COPD ☐ ILD	**CLD** ☐ Yes ☐ No	**GERD/PUD** ☐ Yes ☐ No	**Psychiatric/neurologic disorder** ☐ Dementia/Alzihmer ☐ Depression ☐ Epilepsy	**HIV/AIDS** ☐ Yes ☐ No
Family history of ☐ HTN ☐ DM ☐ CHF ☐ Stroke ☐ CAD	**Abdominal obesity** ☐ Waist circumference _____	BMI _____		

B. CLINICAL PRESENTATION

			Killip Class

☐ Symptom onset to Hospital arrival (hr)_____
Vital sing at arrival
☐ Temperature(c°) _____
☐ Heart Rate_____
☐ Respiratory Rate_____
☐ **Blood pressure**
  ✓ Systolic (BP)_____
  ✓ Diastolic (BP) _____
	☐ Chest pain/discomfort
	☐ Shortness of breath
	☐ Nausea/vomiting
	☐ Sweating
	☐ Dysponea
	☐ Syncope
		☐ Abdominal pain
		☐ headache
		☐ isolated dysponea
		☐ Epigastric pain
		☐ Cardiogenic shock
			☐ I
			☐ II
			☐ III
			☐ IV

Serum Cr_____(at admission) **GCS_____(if needed)**	**Cardiac Biomarkers** ☐ Troponin_____ ☐ CK-MB_____	Type of ACS ☐ STEMI ☐ NSTMI ☐ Undetermined	

IV. LABORATORY FINDINGS and DIAGNOSTIC WORKUP

Lipid panel tests	Serum electrolytes,	RFT	LFT
☐ Total cholesterol _____ ☐ HDL-C _____ ☐ Non HDL-C_____ ☐ LDL-C _____ ☐ Triglyceride _____	☐ Ca^{+2}(Tor iCa)_____ ☐ K$^+$_____ ☐ Na$^+$_____ ☐ Cl^{+2}_____	☐ S.Cr____ ☐ BUN _____ ☐ S.Cr_____ ☐ S.Cr_____	☐ AST_____ ☐ ALT_____ ☐ ALP_____ ☐ Bilurubin (T/D)_____

Coagulation profile	CBC	Cardiac biomarkers	Others
☐ PT_____ ☐ aPTT____ ☐ INR_____ **O$_2$ Saturation_____,_____,_____**	☐ WBC_____ ☐ HGB_____ ☐ HCT_____ ☐ MCV_____ ☐ PLT_____	☐ Troponin I____ ☐ CK-MB_____	ESR_____ Sero-status_____ **UOP_____,_____,_____**

Urine Analysis	Serial BP	Blood glucose	
☐ Ketone ☐ Gluc. ☐ Protein ☐ WBC ☐ RBC ☐ Cast	**#1_____** **#2_____** **#3_____**	**#1_____** **#2_____** **#3_____**	

Echocardiographic Findings (if done)	ANGIOGRAPHY	ECG Findings
☐ EF%_____ ☐ Left ventricular hypertrophy ☐ Rheumatic Valvular heart disease ☐ Dilated cardiomyopathy ☐ Ischemic heart disease with mural thrombus/LV apical thrombus ☐ Ventricular wall motion abnormalities ☐ Patent foramen ovale ☐ Carotid artery stenosis	_____ _____ **CT-SCAN**_____ _____ **Abdominal US** _____ _____ **MRI**_____	☐ ST elevation ☐ ST depression ☐ No. of leads with ST elevation/depression ☐ BBB ☐ Atrial fibrillation ☐ Left ventricular hypertrophy ☐ LVH+ Ischemia ☐ Sinus tachycardia ☐ Sinus bradycardia ☐ Normal finding. ☐ other abnormalities _____

Dx. (Initial)_____

Dx.(modified)_____

_____

V.   Medication for ACS

A. Past medications history

List all medications (generic name dose, frequency, and duration if available)

B. Past Medication Given For ACS (if previously admitted for MI)
Number of admission _____, Type of ACS (STEMI, NSTEMI, BBB/MI, UA, Undetermined)

Medication Given (list all)

C. Medication during hospitalization

☐   **ASPIRIN** #time to Rx_____(hr), LD_____ MD_____

☐   **CLOPIDOGREL**   #Time to Rx_____(hr), LD_____ MD_____

☐   **STATIN** #Time to Rx_____(hr), Dose_____, any modification_____

☐   **Beta blocker**   #Time to RX_____(hr), dose_____ adjustment _____

☐   **ACEIS/ARBS** #Time to Rx_____(hr) dose_____ Adjustment_____

☐   **Anticoagulant (UFH, LMWH) Time To Rx_____(hr) LD_____, MD_____**

List other medications given

PROCEDURES (IF DONE) ,

 PCI

CABG

D. Discharge medication

List medications given (Generic name, Dose, Frequency and Duration)

Drug Therapy Problem ,   YES ☐ NO ☐

Specify _____

VI.   OUTCOMES

In hospital complication		Post discharge
☐ Major Bleeding ☐ Atrial fibrillation ☐ Heart failure/pulmonary edema ☐ Re-Infraction ☐ Stroke/TIA ☐ Thrombocytopenia ☐ Venous thromboembolism ☐ Sustained ventricular thachycardia ☐ Heart block	☐ Left Ventricular dysfunction ☐ Cardiac arrest/cardiogenic shock ☐ Hospital acquired infection ☐ Acute kidney injury ☐ Pericarditis ☐ Others(specify)_____ _____	**Patient discharge information** ☐ Patient Alive ☐ Patient Died **Outcome of the patient during discharge (if alive)** ☐ Improved ☐ The same/complicated ☐ Referred ☐ Left against medical advice ☐ Discharge date: _____ **Within 30 day mortality after admission** ☐ No (alive) ☐ Yes (date _____ ☐ Lost to follow up/unknown

Mortality
- ☑ Discharge Status : Alive=1 Dead=2
- ☑ If Dead, Date of Death (mm/dd/yyyy) _____
- ☑ Primary Cause of Death (Select Only One) : **Cardiac=1 Neurologic=2 Renal=3 Vascular=4**

Infection=5 Pulmonary=6 Valvular=7 Other=8 Unknown=9

Patient Written Consent Form

Dear Sir/madam;

My name is Korinan Fanta. I am Master's Degree student in clinical pharmacyin Jimma University. As part of my academic requirements, I am expected to conduct a research. This study is aimed to assess treatment outcome of Acute coronary syndrome (ACS) and it s determinant at Jimma university medical center (JUMC) and St. Peter specialized hospital (SPSH). The information obtained from this study will facilitate clinicians to improve the provision of care and policy makers in their planning activities. During participation in this study we will ask information regarding demography social drugs use and past medication and medical conditions. In addition we follow your outcome for one month so we need your willingness to start follow up at this hospital or willingness to give information through mobile interview at the end of this month. Your participation in this study is voluntary and all data provided will be treated as confidential and anonymous. You have a right not to participate in this study. Therefore; we politely request your cooperation to participate in this study. But your input has great value for the success of the objectives the research.

So, do you agree? 1. Yes 2. No

Thank you for your cooperation!!!

Consent Form

While putting my signature in this sheet, I am giving my consent to participate in this study. I have been informed that the purpose of this study is assessing treatment outcome of acute coronary syndrome and I have understood that participation in this study is entirely voluntarily. I have been told that my answers and other profiles to the questions will not be given to anyone else and no reports of this study ever identify me in any way. I have also been informed that my participation or non-participation or my refusal to participate in this study will have no effect on me. I understood that participation in this study does not involve risks.

Participant/caregiver`s	Data collector	Supervisor
Sign……………………..	Sign……………………….	Sign………………………
Phone number: ………….....	Phonenumber……………….	Phone number…………….

<u>የአማርኛየመረጃመስጫናየስምምነትቅፅ</u>

ስሜኮሪናልፋንታ፤በጅማዩኒቨርሲቲየሁለተኛድግሪየክሊንካልፋርማሲተማሪስሆንበአሁኑግዜለድህረ-ምረቃጽሁፍየማሆንጥናትከ ልብሕመምጋርተያይዘያሉትንንችግሮችእናስለውጠየቶች፤ስለጤንነትህ/ሽናሌሎችየህይወትዘርፎችላይምርምርንእያደረኩስለሆነከዕርሶጋርዕንዳደርግእንድሁም ከካርዶመረጃንእንድወስድእንድፈቀድልኝበትህትናእጠይቆታለው፡፡በተጨማሪ ከ 30 ቀንበኋላበሽታያመጣውጤትእጠይቆታለው፡፡በዝህምርምርውስጥበመሳተፍየምደርስቦትጉዳትወይም ባለመሳተፍዎበፈትከምያገኙየህክምናአገልግሎትየሚቀርቦትየለም፡፡እርስዎየስጡንመረጃሁሉምበም ስጢርይያዛል፡፡ አንድምየግሌዎመረጃአይጻፍም፡፡ በተጨማሪምበዝህምርምርውስጥመሳታፍዎሉበሙሉበፍላጎትዎላይየተመሰረተነው፡፡ ስለምርምሩምሆነስለምትጠየቁትነገርያልገባዎትነገርካለበማንኛውም ግዜዎናውንተመራማሪመጠየው ይችላሉ፡፡

የተሳታውፈርማ-------------------------------

ቀን---

የመረጃሰብሳቢፈርማ-------------------------

ቀን--

የዋናውተመራማሪመረጃ፤ 1 ኮሪናንፋንታ

2.ስልክቁጥር 0911598485

2. E-mail= korif53@gmail.com

Guca walii-galtee Afaan Oromootin

Obbo/Addee….. kanaa. Animaqaankoo barataa Koriinaan Faantaan Jedhama. Yunivarsitii Jimmaatti barataa kilinikaal faarmaasii waggaa lammaffaa yoon ta'u, yeroo ammaa kana hospitaala kanatti qorrannoo fi qu'annoo dhibee onnee hatattaamaa irratti gegeessaa wanan jiruf. Odeffaannoo barbaachisuu fedhaa keessaannin irraatti hirmaachuudhan naf kennuun akka galmaga'iinsa qorannoo kaanaf na gargartaan kabajaan isiin gaaffaadha. Akkasumaas qorannoo kanaaf kan na barbachisu oddeeffaannoo kaardii keessaan irraa akkan fudhaadhu kabajaan issiin gaaffaa. Oddeffaannoon argaamu hunduu dhimmaa qoraannoo kaanan ala fayyiddaa biraf kan hin ollee ta'u isiin beksiisa. Akkaasumas Ji'a took booda bilbilaalan haala irraa gessaan kanan isin gafadhu ta'u beektani odeffaannoo lakkobsa bilbila kan matii ykn fira kessaani kan isiin faan jiraatu akka naf lattan isiin gafadha.

Walii galuu kessaan mallattoo kessaani fi maqaa keessaanin naf mirkanessaa.

Mallaattoo……..

Maqaa……………………..

Koorinaan Faantaa Jimma University, IHS, School of Pharmacy, Department of Clinical Pharmacy

Bilbilaa: 0911598485

Email: *korif53@gmail.com*

Jimma University, Institute of Health, School of Pharmacy

Declaration

This is to certify that this thesis is prepared by Korinan Fanta which is entitled by**:** Treatment Outcome of Acute Coronary Syndrome and it's Determinants at two Tertiary Hospitals in Ethiopia: Prospective Cohort Study. For partial fulfillment of Masters Degree in clinical pharmacy.

I declare that this thesis is my own original work and that has not been presented to any other university for a similar or any other degree award

Signature..

Date..

Advisor: Mr. Fekede Bekele (M. Pharm, RPh.)

Signature...

Date...

Dr. Elsah Tegne (MD, Internist)

Signature...

Date...

Internal examiner:…………………………………………………

Signature...

Date...

External examiner: …………………………………………………

Signature…………………………………………………………

Date…………………………………………………………………