UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

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The Impact of Pre-Hospital Emergency Care on Outcome in Patients with Acute Coronary Syndrome

DISSERTATION

Zagreb, 2024

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This dissertation was made at the University of Zagreb School of Medicine and University Clinical Center of Kosovo

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List of symbols and abbreviations

ACS - Acute coronary syndrome

AMI – Acute myocardial infarction

APSAC – Anisoylated plasminogen streptokinase activator complex

ASA – Acetosalicylitic acid

CHD – coronary heart disease

CI - Confidence interval

CPC – Cerebral performance category

CPR – Cardiopulmonary resuscitation

ECG – Electrocardiogram

EMS – Emergency medical service

EMT – Emergency medical technician

ED - Emergency department

ESC – European Society of Cardiology

HEMS – Helicopter emergency medical service

ICH – Intracerebral hematoma

IU – International unit

MI – Myocardial infarction

MACE - Major adverse cardiac events

NSTEMI - Non-ST-elevation myocardial infarction

NS – Not significant

OR – Odds-ratio

PCI – Percutaneous coronary intervention

SD – Standard deviation

STEMI – ST – elevation myocardial infarction

1. INTRODUCTION

Acute coronary syndrome is the leading cause of cardiovascular morbidity and mortality, resulting in substantial health care utilization and costs (1). The increase in cardiovascular diseases burden is largely the result of both an increase in the prevalence of the risk factors and a relative lack of access to well-recognized interventions that prolong survival once CVD is manifest. Extremely limited data are available about the mortality rates of acute CVD in Central and Eastern European countries (2-4) although the available data suggest higher proportion of in-hospital mortality deaths attributed to CVD in these countries when compared with the European member states (2).

The mortality rate of ACS in the first 30 days after the onset of disease ranges from 30-50%, with about half of deaths occurring within the first 2 hours (5.6). Yet, despite parallel reductions in 30 day case fatality rates, the British Heart Foundation reports that acute coronary syndromes remain one of the major causes of premature death in men and women in the UK (7).

The main objective of treating patients with ACS is to re-establish myocardial perfusion within a few hours from the onset of pain, in order to save the ischemic myocardium and increase the chance of survival (8-10). The emergency physician's role in the stabilization, evaluation, and treatment of the patient who has ACS is critical (11). ACS is one of the main causes of death in Kosova (12) and it is among the medical emergencies that benefit most from an efficient system of pre-hospital care (13). Most deaths from ACS occur in the first few hours after the onset of symptoms, mainly from fatal arrhythmias which could be prevented by rapid access to specialized care (5). Recent studies (14-20) have demonstrated the effectiveness of Pre-Hospital Emergency in reducing the time between onset of symptoms, diagnosis and beginning of treatment, as well as in reducing mortality in ACS patients (14,15). Global data on the management and therapies of patients with ACS are needed to improve the outcomes of these patients, especially in countries with low-to-middle income economies (16).

1.1. Emergency Medical Service (EMS) systems

According to the European Society for Emergency Medicine: “Emergency Medicine is a specialty based on the knowledge and skills required for the prevention, diagnosis and management of urgent and emergency aspects of illness and injury affecting patients of all age groups with a full spectrum of undifferentiated physical and behavioral disorders. It is a specialty in which time is critical. The practice of Emergency Medicine encompasses the pre-hospital and in-hospital triage, resuscitation, initial assessment and management of undifferentiated urgent and emergency cases until discharge or transfer to the care of another physician or health care professional. It also includes involvement in the development of pre-hospital and in-hospital emergency medical systems” (17).

Emergency medical service is a link between primary health care and secondary health care. This service addresses to people who have disorders of vital functions, or disruption of these functions. An Emergency Medical Service (EMS) can be defined as "a comprehensive system which provides the arrangements of personnel, facilities and equipment for the effective, coordinated and timely delivery of health and safety services to victims of sudden illness or injury." (18, 19)

For patients with ACS, early symptom recognition, early activation of emergency medical service (EMS), early transportation to the hospital and early administration of definitive treatment are associated with improved clinical outcomes (20) Guidelines from European Society of Cardiology,(21) American College of Cardiology (ACC) and American Heart Association (AHA)(20,22) strongly recommend activation of the EMS, a rapid and effective means of obtaining medical care, for patients who have symptoms consistent with ACS. EMS is critical to provide an opportunity for earlier initiation of evidence-based therapies, faster receipt of initial reperfusion therapies and also earlier coordination with capable centers for efficient delivery of care (23,24).

1.1.1. Background

Advanced emergency medical service for the first time has been displayed in early ‘60ties of XX century in Europe and USA. The first ambulance was used in 1906 (USA). Since 1970s, the mode of emergency health care delivery in pre-hospital environment evolved around two main models of EMS with distinct features. These are the Anglo-American and the Franco-German model. These categorical distinctions were obvious during the 1970s until the end of the 20th century. Today, most EMS systems around the world have varied compositions from each model (25).

In Kosovo, before 1999 EMS has been similar to the system which has been applied in the former Yugoslavia. The development of an Anglo-American model of emergency medicine came post conflict, with the involvement of international governmental and non governmental organizations. These organizations built or renovated hospital emergency departments, donated ambulances and equipment, and trained healthcare professionals. At first the emergency centers were established near the regional hospitals. In October 1999, the emergency center it was established in Kosovo University Clinical Center (UCCK). The organogram of Emergency Center in UCCK is presented in Fig. 1. These centers are equipped with new modern equipment for monitoring, diagnosis and treatment of seriously ill and injured patients. At the same time it has been worked on establishing primary cells in emergency medicine health houses which were being transformed in family medicine bases in all municipalities of Kosovo. These cells were equipped with the necessary equipment and vehicles for transporting patients. The British Department for International Development supported the construction of a new emergency department at the Kosovo University Clinical Center, Pristina, Kosova. The Johns Hopkins University in cooperation with Samaritan's Purse developed an emergency medicine residency program. Various other non governmental organizations such as Die Johan niter, International Medical Corps and the Spanish Red Cross provided training to emergency medical service providers (26). The World Health Organization (WHO) assessed Kosovo's emergency medical services in 2000 and made recommendations to the Joint Interim Administrative Structure—the United Nations/Kosovar government (27).

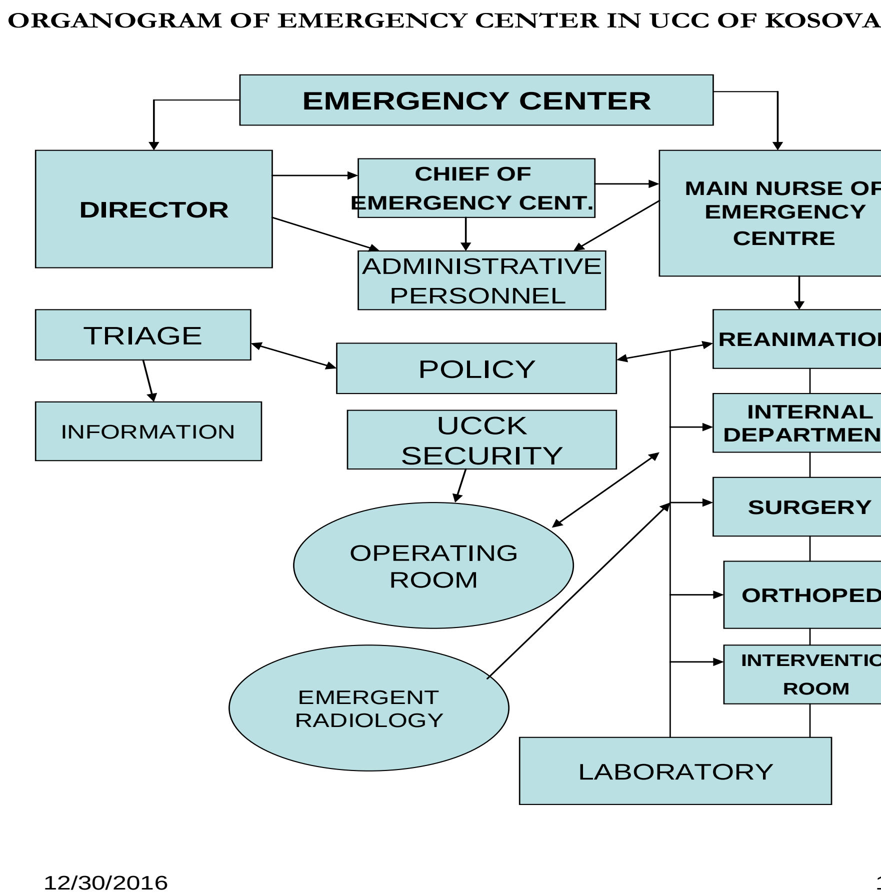

Fig. 1. Organogram of Emergency Center in UCC of Kosova

1.1.2. Human resources, education

For the new system, the existing resources of “acceptance service” from the old establishment were not enough. Therefore, for this purpose a considerable number of new personnel were educated. Today this system counts about 1000 employees distributed in primary and secondary medicine. This system takes care of treating about 200,000 patients per year. Nearly two thirds of the patients are treated at primary health care level and more than one third in regional emergency centers, at the secondary level. UCC Emergency Centre just within a year treats 30,000 emergency patients.

In the fall of 2000, the first generation began its specialization in Emergency Medicine, a step that was made possible by the international staff of the Emergency Medicine John Hopkins University (26). Lecturers and trainers, 21 prominent experts from the US were for two consecutive years. In this plan, Kosovo doctors benefited in different aspects such as: medical logistics, efficient organization and modern medicine.

1.1.3. Working Principle

The working principle is based on the emergency chain: 1) telephone call , 2) recognition of the patient's condition , 3) medical assistance at the scene , 4) medical assistance during transport , 5) further diagnostics in the intensive care unit , 6) if needed transportation and treatment within hospital premises and further in intensive care unit (ICU) , or the surgery room .

Emergency medical assistance is based on three basic principles:1) Actual patient, 2) Emergency medical assistance at the right time, 3) Transport and placement of the patient in the correct hospital. The overall work during first hour, which in medicine is called "golden hour", determines the outcome between life and death. The actions which determine patient’s life are: a) arriving at the spot as fast as possible, b) early cardiopulmonary reanimation (CPR - cardiopulmonary resuscitation). The employees of pre-hospital emergency medical unit (medical technicians and emergency medicine specialists) are in service 24 hours non-stop. They are trained to make endotracheal intubation and defibrillate patients, find intravenous line (intravenous open access), fluid resuscitation with crystalloids, injecting adrenaline or epinephrine, dopamine, amiodarone, pain killers intravenous analgesics and are able making ECG with 12 derivations also known as (12 lead electrocardiography – ECG).

1.1.4. Utstein style

Thirty years ago, a conference was held at Utstein Abbey in 1990 which resulted in the publication of guidelines for uniform reporting of data from out-of-hospital cardiac arrest (OHCA). The term 'Utstein Style' is now synonymous with resuscitation reporting and registries**.** Clear definitions and performance indicators enable a collective approach to measuring and improving patient outcomes. A template for reporting these agreed measures with standardized definitions is now known as the Utstein style or just Utstein. The Utstein Style has had greatest influence in resuscitation, registries, pre-hospital and disaster medicine (28-30).

The Utstein Formula for Survival (31) is now a widely recognized model which includes three elements in hypothesizing potential survival rates from cardiac arrest: medical science, educational efficiency and local implementation (Fig. 2).

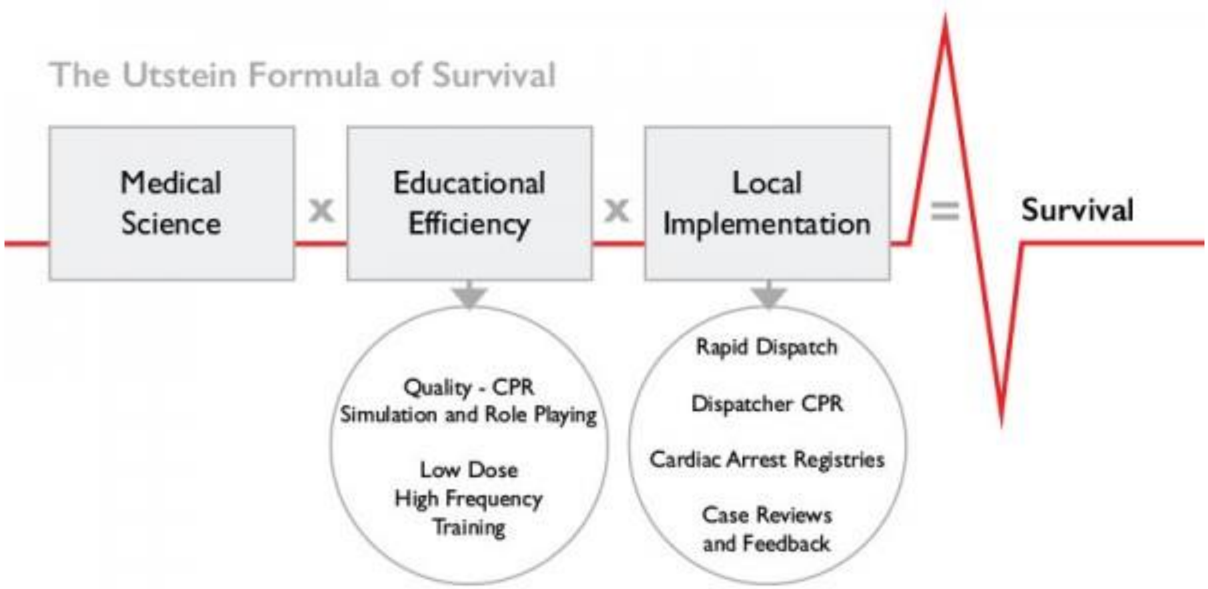

Fig. 2 The Utstein Formula of Survival

1.2. Acute Coronary Syndrome (ACS)

1.2.1 Definition

Acute Coronary Syndrome is the clinical condition in which patient is suffering from signs of myocardial ischemia. So, ACS has to do with overall reduction or complete cessation of blood flow in the coronary arteries and consequently it ends up with heart muscle necrosis. Updated classification of ACS introduced the following conditions: 1) Unstable angina; 2) ST-elevation myocardial infarction (STEMI), 3) non-ST- elevation myocardial infarction (NSTEMI), (32).

1.2.2 The pathogenesis of acute myocardial infarction (AMI)

Acute thrombosis in coronary arteries is caused by detachment of atherosclerotic plaque. Atherosclerotic plaques begin to form very early in a human's life. Atherosclerosis is the pathology in which dominates the extracellular accumulation of lipids and where small lipoprotein particles are deposited within intimate part of arterial. Atherosclerotic plaque extends in advance because the white blood cells migrate into them and also cells of smooth musculature. Even the plate can also develop blood microcirculation, which helps the continued growth of plaque (atheroma). Detachment or (cracks) of atherosclerotic plaque promotes a cascade process of substance action which would put into motion thrombolytic aggregation and the generation of trombones, inside areas (field) of ruptured, forming up clotting and in the worst case causing the sudden thrombotic closure (occlusion) of coronary artery, and as a result acute myocardial infarction. AMI can also be caused by coronary spasm in patients who have normal coronary arteries (33).

1.2.3 Risk factors of atherosclerotic disease

- Dyslipoproteinemia

Many studies have shown that high cholesterol values in serum have an important role in the development of coronary heart diseases. Also increased levels of lipoprotein in the blood speed up atherosclerotic plaque formation. Treating in time the hyperlipidemia prevents coronary heart disease (34, 35)

- Smoking

Smoking increases the risk of coronary heart disease. Smoking increases platelet aggregation and also causes coronary spasm (34, 36)

- Diabetes mellitus

Diabetes increases the risk for cardiovascular disease. Hyperglycemia increases the production of lipoprotein with very low density (VLDL) in the liver, the final products of which increase the risk for vascular damage (34, 37).

.

- Arterial Hypertension

Arterial hypertension increases the risk of coronary heart disease. The main mechanism is the pulsative pressure causing endothelial cell dysfunction and cell hypertrophy of the smooth muscles (34, 38).

1.2.4. Angina Pectoris

Generally, chest pain can be divided into two major groups: cardiac pain and non cardiac chest pain. Chest pain can be categorized as cardiac ischemic pain, pericardial or atypical. Retrosternal pain of unexpected character "tightening" and "the collapse" that lasts a few minutes is pathognomonic sign for angina pectoris. Angina pectoris usually occurs during physical strain or emotional strengths that is associated with a significant fear for existence and this pain then stops and disappears slowly. If for any reason such a pain appears suddenly even during the rest time accompanied by sweating, and not reacting in nitroglycerine, then all chances are that it comes to an acute myocardial infarction. When coronary artery closes the pain is more severe and high intensity and lasts more than 20 minutes. There are times when patients feel no pain (silent myocardial infarction), especially in patients with diabetes mellitus and hypertension. About 2/3 of patients with AMI have prodromal signs first days or weeks characterized by increasing angina, fatigue and difficult breathing. The first symptoms of AMI is usually a deep pain, substernal, visceral, which often spreads to the back, jaw or left arm. In severe episodes the patients are afraid of dying, anxiety, and gloomy thoughts in general; here dominates symptomatic left ventricular failure, pulmonary edema, shock or have cardiac arrhythmia (39).

1.2.5. Electrocardiography findings and biochemical markers in ACS

The two primary approaches for optimizing ACS patient outcomes are to reduce treatment delay and to minimize total ischemic time, defined as time of symptom onset to reperfusion of culprit arteries (20,40). To minimize total ischemic burden time, the American Heart Association and European Society of Cardiology (AHA/ESC) recommend that individuals with chest pain seek medical attention immediately and receive a 12-lead electrocardiogram (ECG) within 10 min of hospital arrival, based on evidence that longer delays are associated with adverse prognoses (20). ECG results should be analyzed in conjunction with patient history and clinical presentation to assess the likelihood of an ACS diagnosis (20).

The most important laboratory procedure that is done in patients suspected of having ACS is the analysis of ECG. STEMI patients are presented with ischemic symptoms and ST elevation of the segment in ECG also develops AMI and "Q" wave. Most of these patients have increased typical biomarkers of necrosis. ECG findings could be relative, but biochemical markers are strong indicators that myocardial cells are suffering from ischemia, or are dead, and known intracellular macromolecules as cardiac marker end up in the bloodstream. These markers known as creatine kinase (CK), cardiac specific isoenzymes (CK. MB) and troponin TnT and TNI. Cardiac troponins are the most sensitive and specific biomarkers for NSTE-ACS. They rise within a few hours of symptom onset and typically remain elevated for several days (but may remain elevated for up to 2 weeks with a large infarction). A negative cardiac troponin obtained with more sensitive cardiac troponin assays on admission confers a >95% negative predictive value for MI compared with high-sensitivity assays that confer a negative predictive value ≥99% (41-43).

Patients with NSTEMI in their ECG don’t have elevation of ST segment neither Q wave, but they have increased level of biomarkers known as cardiac markers. Non stable angina represents third expression spectrum of acute coronary syndrome and it is pathological substrate, similar to NSTEMI, because at unstable angina we do not have the presence of biomarkers (cardiac markers) in the blood (44, 32). Of all patients with acute coronary syndrome, 42% had STEMI, 51% have NSTEMI and 7% have unstable angina.

ACS is divided into "two branches" according to ECG; STEMI and NSTEMI together with AJS. NSTEMI is differentiated from AJS with biomarkers. Differential diagnosis of STEMI should be made with: angina pectoris, dissection aortic aneurysm, pericarditis, pneumothorax, pulmonary embolism etc.

1.2.6. Management of STEMI

A "diagnostic test" can be understood as a laboratory or imaging test: however, the concepts related to "test" also apply to clinical information from other findings, such as physical examination and patient history. The sensitivity of a test is understood as the capacity of the test to detect individuals who present with a particular condition, or the proportion of individuals with a particular condition who have been tested positive for this condition (true positive). Highly sensitive tests can be used at the beginning of the diagnostic process, when a great number of possibilities are being considered, with the intention of excluding as many options as possible. The specificity of a test is defined as the capacity of the test to identify individuals who do not have a particular medical condition, or the proportion of individuals without the condition who have a negative test (true negative). A triage system that presents a good sensitivity can minimize the occurrence of under triage, the same way, systems with suitable specificity can avoid the occurrence of over triage. The assessment of patients with ACS suspected using the MTS, can occur through different flow charts, since the patient does not always have typical symptoms and concerns such as chest pain as the main complaint. For this reason, in addition to the flowchart "chest pain", other flowcharts, including "shortness of breath in adults", "unwell adult", "collapsed adult", and "palpitations", enable distinguishing chest pain and other urgent conditions from non-urgent conditions, and can assist the appraiser to establish the highest priority level to treat patients with these urgent conditions. According to the algorithm from the American Heart Association, every patient who presents symptoms of chest discomfort suggestive of ischemia must receive medical attention within 10 minutes. Therefore, in order to recognize patients in those conditions, the health care professional applying MTS must establish priority levels of "red" or "orange", thereby setting a safe waiting time for these patients. Although there are well-established criteria for the prioritization of patients with suspected ACS, several studies have reported the difficulties of evaluating patients with these conditions. Various factors can interfere with the outcome of this process, such as atypical presentation of symptoms, AMI classification, patient age, and professional skill. Primary studies have addressed the issue from different perspectives. Studies have been conducted to evaluate the ability of nurses using MTS to detect high-risk patients with chest pain, the impact of MTS on short-term mortality in AMI, and the sensitivity and specificity of MTS for patients with ACS, and to assess whether the MTS was used effectively in patients admitted to the hospital with a diagnosis of acute coronary syndrome. These studies concluded that use of the MTS by nurses is a sensitive method for identifying high risk cardiac chest pain, but further studies are required to assess whether additional training can improve the sensitivity of MTS. The MTS safeguards patients with typical AMI presentation and ST elevation during myocardial infarction, and who are under 70 years of age. The MTS has a high sensitivity in prioritization (immediate/very urgent) of patients with ACS. Additionally, most patients admitted for ACS are initially triaged as "orange" or "yellow", an indication for prompt assessment in the emergency department. This has a positive effect on time to first medical assessment, but has no effect on time to hospital admission (45).

The Global Registry of Acute Coronary Events (GRACE) risk score, which is used as a predictor of the risk for death in ACS, is determined based on age, vital signs, creatinine and Killip class (46). However, when trying to determine the mortality in these patients, other laboratory data are not usually included in this score. Furthermore, with the exception of elevated creatinine kinase MB or troponin T, the Thrombolysis in Myocardial Infarction (TIMI) risk score, which is a risk score for patients with non-ST elevated ACS, does not include any other biomarkers used in the calculation of the risk (47).

The GRACE (46) score, which is a well-known and classical predictor of in-hospital mortality, involves checking several items related to a patient's baseline physical data that can be analyzed within the emergency department. However, only one laboratory value (serum creatinine level) is required for this classical risk score. Of note, during the enrollment pe-riod for the GRACE registry, the efficacy of aggressive lipid lowering therapy for ACS patients (48, 49) and the utility of highly sensitive cardiac biomarkers in improving the accuracy of the ACS diagnosis (50, 41) had yet to be definitively established and applied to ACS patients. Several studies comparing the classical risk score with the risk assessment based on the results of biomarkers have suggested that C-reactive protein (51) or troponin T (52) levels can provide a better prognostic accuracy than the GRACE risk score. However, several verification studies that examined the GRACE risk score have reported finding similar accuracies despite differences in the study period, the countries involved and the risk assessments used (52-57).

In-hospital mortality of ACS in North America has decreased from 25-30% to 7-10% in the past 30 years. This decrease can be attributed to the introduction of CCUs (1960s), administration of beta blockers (1970s), introduction of fibrinolytic therapy (1980s) and percutaneous coronary intervention (PCI) (1990s), (5,58). The proportion of ACS with STEMI—when a blood clot completely blocks a coronary artery—is declining (59), possibly due to reductions in smoking, aging of the population (STEMI is more common in middle age, while NSTEMI occurs more in the elderly), and greater use of statin therapy. Similar trends have been seen for sudden cardiac arrest. NSTEMI—usually when a clot partially blocks a coronary artery—is now the dominant type of ACS, and outcomes after the acute phase are significantly worse than for STEMI.

There has been a consistent decline in mortality rates for hospitalized acute MI, thanks in part to better in-hospital management of patients with ACS. There has also been an increasing emphasis on prevention and awareness, as well as advances in diagnostics and treatment, all taking place alongside societal and socio-economic changes and population migration (60). As the evidence base in acute coronary syndromes (ACS) has expanded dramatically over decades, longitudinal data demonstrate improvements in risk factor modification, organization of healthcare systems, and disease management that have substantially attenuated the adverse prognosis of both ST-segment elevation myocardial infarction (STEMI) and non-ST segment elevation ACS (NSTE-ACS). Nevertheless, discrepancies remain between genders, and women with ACS often sustain worse outcomes than men (61).

Triage, or risk classification, is a clinical management tool used in emergency services to guide patient flow when the need for medical attention exceeds that available. The Manchester Triage Group was developed in 1994 in the United Kingdom. The aim was to establish a consensus among physicians and nurses in the emergency room by creating a triage pattern focused on the development of the following: Thus, the Manchester Triage System (MTS) was created. The MTS simplifies the clinical management of each patient, and consequently, the whole service, by utilizing a system that defines the clinical priority for adults and children (62). Despite advances in the treatment of ACS and the dissemination of formal recommendations on approaches to managing NSTE ACS, pharmacologic and reperfusion therapy remain underused and often delayed. This results in an increase in adverse cardiac events for patients and rising health care costs for the public. The key to NSTE ACS management is rigorous adherence and application of evidence-based recommendations. The American Heart Association (AHA) and the American College of Cardiology (ACC) have released comprehensive clinical practice guidelines to manage NSTE ACS. These include a process of risk stratification of patients presenting with NSTE ACS or possible NSTE ACS. Risk stratification can be performed using a number of scoring models, including the Thrombolysis in Myocardial Infarction (TIMI), the Global Registry of Acute Coronary Events (GRACE), and the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) scoring models (63).

Patients with ACSs are a heterogeneous population with varying risks of death and recurrent cardiac events, in long-term as well as short-term follow-up. In these patients, early risk stratification plays a central role, as the benefit of newer and more aggressive and a costly treatment strategy seems to be proportional to the risk of adverse clinical events. The TIMI score was developed with the database from a large clinical trial of NSTE-ACS.[44] The Global Registry of Acute Coronary Events score was developed from the registry, with a population of patients across the entire spectrum of ACS.[47] Even though the prognostic impact of both scores have been confirmed after longer follow-up periods both these scores were initially developed for short-term assessment of risk and to define risk oriented therapies in emergency departments and chest pain units (64, 65).

For the treatment of patients with STEMI guidelines have been prepared by European Society of Cardiology – ESC, American College of Cardiology –ACC and American Heart Association – AHA. Their goal is to improve clinical practice and quality of care for patients in Europe and the USA. The Guide is a book "law to doctors" how to deal with patients in every instance of this life-threatening condition. Guidelines derived from the so-called – Evidence Based Medicine – EBM, which is not experience or opinion of some experts, but large collection of studies of important clinical records, comparisons, analysis, meta-analysis, special clinical studies, and studies of epidemiological things etc.

Treatment of patients with AMI, and especially with STEMI can be organized in three phases (21).

1.2.6.1.The first medical contact with a STEMI patient

Initial diagnosis

- Patient history in chest pain, typical or equivalent, lasting or resistant to therapy.
- Elevation of ST segment or block of the left branch (LBBB) in ECG.
- Increase in blood of biomarkers of myocardial necrosis (CK MB and Troponin).

Reperfusion therapy might be:

- Mechanical, primary PCI, which means swelling of the balloon under pressure and stent implantation to keep the coronary artery open, and
- Pharmacological, thrombolytic therapy (TT) which is intended the merge of thrombus that has clogged coronary artery.

Possibility of the patient with AMI and reperfusion TT will die is 7-8% in the first month, and 3-4% of patients who undergo reperfusion with primary PCI. Medicine based on evidence (Evidence Based Medicine) emphasizes two important things in the treatment of patients with STEMI; Reperfusion and function of time, the probability of survival will be greater the shorter the time of start of reperfusion therapy. Of course, there are other actions that should be undertaken by the doctor who fights AMI.

1.2.6.2. Early Care Hospital

PCI primary should be performed in patients with STEMI, including AMI in the back wall of the left ventricle, or new LBBB, if done within 12 hours of onset of symptoms, especially if done at the right time, which means two hours after the first medical presentation, or within 90 minutes if a large mass of myocardium is at risk. Primary PCI must be performed in patients with expressed heart weakness or pulmonary oedema within 12 hours of onset symptom. Primary PCI must be performed in patients in shock and those with contraindication to thrombolytic therapy regardless of the time of onset of symptoms, or delay time. Rescue PCI is undertaken when thrombolytic therapy fails. Sometimes it happens that the patient is not sent directly to the hospital with possible PCI, then the family doctor or cardiologist should give therapy.

Evidence based medicine (EBM) shows that primary PCI is superior to thrombolysis. PCI provides greater opportunity for the patient with AMI to survive. At some conditions and some forms of AMI, such as cardiogenic shock or severe weakness of the heart, is the only chance to survive. Such patients are known as a "high risk" patient and these are with: Hypotension, congestive heart weakness, sinus tachycardia, age, female gender, diabetes mellitus, uninterrupted pain regardless of drugs, the presence of elevation of the ST segment, anemia, higher number of WBC leukocyte (leukocytosis) and chronic kidney disease. Patients with these findings should be transferred as soon as possible to the PCI center. Sometimes PCI center is too far away and primary PCI can not be done within two hours of first medical contact. Physicians should inform the patient and his family that primary PCI is the best treatment and most favored for AMI.

In this context, in Kosovo the most remote primary PCI is not away more than two hours' drive. In the US there is broad national register of AMI (National Registry of Myocardial Infarction 2 and 3, NRMI 2 AND 3) involving more than 300,000 patients with AMI and primary PCI. The technical success rate of stents in AMI is high with minor procedural complications, even if patients with high-risk are involved. Primary PCI results are excellent when conducted by the operator with experience in interventional center with large volume. In an interventional center with a small volume mortality rate is the same as the TT (thrombolytic therapy). In the US only 20% of hospitals have heart catheterization laboratory, and very few are available for hospitals with primary PCI. Thus, most patients with AMI are transferred, but 87% of these are more than two hours late. The low rate of mortality after primary PCI connects with short time door to balloon, shorter then 90 minutes, which laboratories with 24/7 services are equipped.

Coronarography

Coronarography is a diagnostic method. It is considered the gold standard for diagnosis of coronary disease. When there are, or where other diagnostic elements suggest advanced coronary disease, coronarography is indicated. Through arteries in the legs (rarely hand arteries) a tube is placed (catheter) that is placed at the entrance of the coronary arteries, through this catheter the contrast is injected into the coronary arteries, which enables visualization of the lumen of these arteries, it is obvious whether they are tight how much are tightened and where are the bottlenecks. On the basis of this outcome can decide what the patient should do further- thrombolytic drug therapy or mechanical revascularization with stent (Angioplasty).

Coronarography is an invasive method (with various means we enter into the human body), so there exists the possibility of complications. Complications are infrequent. Only 2% of coronarography have complications. World statistics show the possibility of death in 0.1% of coronarography. In principle (if no new clinical moments occur), the result of coronarography can serve about 6 months. After coronarography doctor may propose the continuation of the procedure (angioplasty). The decision for angioplasty is taken from the patient itself after getting the adequate information.

Percutaneous coronary intervention (PCI)

PCI is an invasive procedure by which a metal stent is placed in the closed coronary artery by atherosclerotic plaques, in order to improve blood flow and prevent restenosis. The first percutaneous transluminal coronary angioplasty was performed in 1977 (Gruentzig, 1979).

Less than 50% of patients receiving thrombolytic therapy have good recovery flow through arteries that caused heart attack (infarct-related artery IRA). To these patients TIMI flow is at 3-rd grade (Thrombolysis in myocardial infarction). This leakage is crucial for reducing the mortality of AMI from 16% to 7%. But a third of these reopened arteries areas with a high degree of obstructive lesions, favorable to be enclosed (most often without symptoms). The reason is that fibrolites' agents are effective in the destruction of the fibrin network in the occlusive thrombin, without having to remove the core rich in platelets. They have no effect on thrombin, which is the most powerful activator of platelets. Their lytic effect is blocked by inhibitors of platelet activator I I (PAI I- platelets -I inhibitor activator), which is the inhibitor of fibrinolysis. The accuracy of the identification of patients who fail thrombolysis is limited. Also, clinical markers reperfusion (removal of pain, partial elevation resolution of ST - segment and reperfusion arrhythmias have limited predicative value).

1.2.6.3. Preventive secondary period

Evidence based medicine (EBM) recommends interventions that can improve prognosis after STEMI. Coronary artery disease is chronic and progressive. Basic disease and risk factors should be treated by the patient, the family and the family doctor or cardiologist. This treatment is called secondary prevention and it is initiated in hospital after PCI. This is a lifelong process and should be controlled by the family doctor. Secondary prevention improves health and prolongs the life of patient who has experienced myocardial infarction (AMI). The patient must take responsibility for their own health. The family should help the patient to change lifestyle and nutrition, as well as controlling diabetes mellitus and arterial tension.

1.3. The strategy of treating patients with angina and unstable NON-STEMI (66).

The first step that must be done in ACS (Acute coronary syndrome) is to identify patients by risk profile.

- Exact treatment by EBM (Evidence Based Medicine).
- Patient to be send for invasive and PCI treatment study
- To be initiated the program of modification of risk factors, early in the hospital, and to be educated the patient and family.
- To be assigned monitoring for coronary artery disease (CAD) and the control of risk factors

1.4. Identifying patients at high risk for ACS.

High-risk patients should be considered for early invasive strategy. It should be risk stratification in three groups according to the **TIMI RISK SCORE** calculation:

- Age> 65 years
- Previous coronary stenosis> 50%
- Three or more risk factors for coronary artery disease (CAD); Hypertension, Hypercholesterolemia, active smoker, diabetes, family history of CAD
- Taking aspirin 7 days ago
- Depression of ST-segment
- Increase of biomarkers of heart
- Two or more episodes of angina in the last 24 hours (de novo angina).

Some of these findings are sufficient to align the patient in the group with "high risk": depression of ST segment, increase of heart biomarkers (troponin or CK-MB) with angina pectoris in peace. In the group with "high risk" are also more than 4 risk factors. The group of "average risk" has the result of 3-4 risk factors. The group of "low risk" has one or two risk factors mentioned above.

Characteristics that favor early invasive strategy in ACS:

- Repeated angina pectoris (recurrent) ischemia at rest or with small load, despite intensive anti-ischemic therapy.
- Increased levels of troponin
- New depression or depression of ST segment
- Angina / recurrent ischemia with symptoms of heart weakness S3 gallop, pulmonary edema, crackle deterioration, or worsen mitral regurgitation.
- High Risk found in stress test
- Systolic dysfunction of the left ventricle with EF <40%

- Hemodynamic instability
- Stable ventricular tachycardia
- PCI within 6 months
- CABG (coronary artery bypass - graft) Previous

So, these are the situations that should make the doctor to take the decision for early PCI strategy. All other patients who are not considered high-risk, the decision for early PCI should be based on technical feasibility, the experience of the operator and patient’s preference. But, the surveillance is recommended, risk stratification and selective invasive strategy. Sometimes it is difficult for cardiologist to convince the referral physician or patient and his family that the best treatment is coronary angiography with possible PCI.

1.5. Delays in the treatment of AMI

The total delay in the treatment of AMI with thrombolytic therapy includes the patient, the EMS and the hospital delays (Figure 3). It has been shown that nearly half of the AMI patients suitable for thrombolytic therapy are waiting up to three to four hours before calling for help (67,68). Female and elderly (>65 years old) patients have been reported to wait longer before calling for help than others (69). Media campaigns have been shown to have only marginal impact on the help-seeking delay (70,71). Improvement of prehospital management of AMI is expected to cut the delay in the call-to-therapy time (72). Short prehospital EMS door-to-therapy time may save time for the patient, but the time benefit also comes from rapid transportation to the hospital.

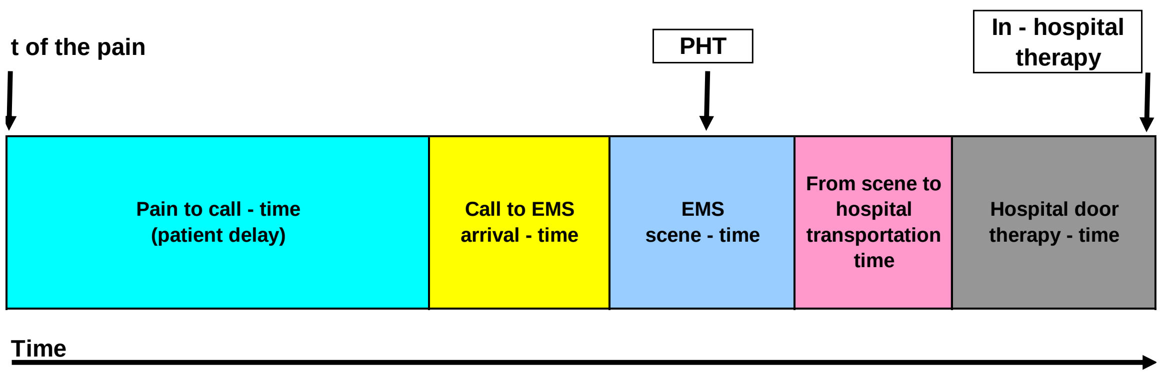

Figure 3. Delays in the treatment of AMI

A study performed at the Vancouver General Hospital (73) showed an average reduction in 67 minutes in the door-to-needle time in patients seen by cardiologists. Patient care performed by a specialized physician is fundamental to reduce the time used to determine the therapy and starts thrombolysis.

The performance of the Kosova emergency system for the acute treatment of ACS patients has not been thoroughly studied. Emergency medicine, a field relatively new to even the most developed societies (74), is in its infancy in Kosova. There has been little formal training, the EMS system lacks organization, equipment, and a reliable communication system, and centralized emergency centers, other than the center at Prishtina Hospital, are inadequate (75)

2. HYPOTHESIS

Pre-hospital and hospital emergency care will improve prognosis of patients admitted to hospital with acute myocardial infarction.

3. AIMS AND PURPOSE OF THE RESEARCH

The general aim of the study was to analyze the most recent trends in acute coronary syndrome care, to evaluate the impact of pre-hospital and hospital emergency care in the management and prognosis of patients admitted to the hospital with ACS.

SPECIFIC AIMS:

1. To analyze the outcome of ACS pts admitted to emergency department through pre-hospital emergency care.
2. To analyze the outcome of ACS patient admitted to emergency department who self-transported to the ED and those who were sent there by a health center or family physician, whatever the type of transport used (including ambulances operated by the fire services).
3. To illustrate the importance of pre-hospital emergency care on outcome of ACS pts.
4. To illustrate the importance of time in minutes between the onset of symptoms as reported by the patient and admission to the hospital, between the onset of symptoms and the first ECG and between entering the ED and the beginning of the therapy.

4. MATERIAL AND METHODOLOGY

Observational prospective clinical study has included all cases of ACS patients (defined in accordance with the criteria of the 2000 consensus document "Myocardial Infarction redefined" of the ESC/ACC Joint Committee) admitted to emergency department of University Clinical Center of Kosova between January 1, 2011 and December 31, 2012. Inclusion criteria were clinical signs and symptoms of acute coronary syndrome, ECG changes and enzyme values in blood analysis. Location of myocardial infarction was determined according to ECG changes. ST elevation more than 1 mm and growing troponin were denoted as STEMI, ST denivelation more than 1 mm and T wave inversion with growing value of troponin were denoted as NSTEMI infarction.

The patients are divided into two groups, depending on whether pre-hospital emergency care was used; and in the three groups of different clinical presentations of ACS: unstable angina, NSTEMI and STEMI. For the purposes of the study, we defined the Pre-hospital emergency (PHE) group as those who were referred to the emergency department (ED) via PHE, and the control group as all other patients. In the control group, we include those who were self-transported to the ED and those who were sent there by a health center or family physician, whatever the type of transport used (including ambulances operated by the fire services).

Self-transport was defined as any mode of transportation that did not involve ambulance, including taking taxis or any public transportation, driving by themselves, driven by others and walking to the hospital.

The final ED diagnosis was defined as the discharge diagnosis for patients discharged home or the admitting diagnosis for patients admitted to an inpatient setting.

Electrocardiographic presentation

The patients' electrocardiographic presentations are divided into two groups, depending on the alterations recorded on the first ECG performed at hospital arrival: with ST elevation or *de novo* LBBB, and without ST elevation or *de novo* LBBB. ST elevation is considered to exist when ECG showed the ST segment > 1 mm above the baseline in the limb leads or > 2 mm in the pre-cordial leads in two or more consecutive leads. *De novo* LBBB is defined as this pattern being previously unknown but found on the admission ECG. All other forms of initial ECG presentation, including ST depression, T wave abnormalities, normal ECG, or previously documented LBBB, were classified as non-ST elevation.

Symptoms-to-ED time

This was taken as the time in minutes/hours between the onset of symptoms as reported by the patient and admission to hospital's emergency department.

Symptoms-to-ECG time

This is the time in minutes/hours between the onset of symptoms and the first ECG in the hospital.

Door-to-needle/balloon time

This is the time between entering the ED and beginning reperfusion therapy (injection of thrombolytic) in patients with ST elevation or *de novo* LBBB.

Ejection fraction

In patients with ACS elevation/*de novo* LBBB on admission, ejection fraction was assessed by 2D transthoracic echocardiography in four-chamber view on the day of discharge.

Follow-up

All the patients were followed in the hospital and for at least six months after discharge. During this time, mortality rates was monitored and readmissions for all causes were recorded directly or by telephone contact.

Statistical analysis

Data are expressed as median and inter quartile ranges (IQR) for continuous variables with non-normal distribution and as percentages for categorical ones. Pearson’s chi-square test or Fisher’s exact test are used for categorical variables. Mann Whitney U test and Kruskal Wallis test are used for testing the difference between quantitative variables when distribution was not normal and Student t-test or ANOVA test when distribution is normal. The odds ratio (OR) and the corresponding 95% confidence intervals (CI) were calculated. Differences in survival were analyzed with the Kaplan-Meier method, data on surviving patients were censored at the date of hospital discharge, and data for non-surviving patients were censored at the date of hospital death, the results were compared with the use of log-rank test. $P<0.05$ was considered statistically significant. Data analysis was performed with the Statistical Package for Social Sciences 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

5. RESULTS

For the sake of easier elaboration, the research results are divided into three parts. In three parts the patients were analyzed according to clinical characteristics, risk factors and survival.

1. Socio demographic characteristics of patients with acute coronary syndrome treated at the University Clinical Center of Kosova for the analyzed period
2. Patients with acute coronary syndrome treated at the University Clinical Center of Kosova for the analyzed period by groups
3. Patients with acute coronary syndrome treated at the University Clinical Center of Kosova for the analyzed period by types of acute coronary syndrome

5.1. Socio demographic characteristics of patients with acute coronary syndrome treated at the University Clinical Center of Kosova for the analyzed period

For the period January 1, 2011 and December 31, 2012, 1498 patients diagnosed as ACS were admitted to emergency department of the University Clinical Center of Kosovo. In 2011 were received much higher numbers compared to 2012 (61.7% versus 38.3%). With the distribution of cases by gender and years we did not earn significant difference (P = 0.636). For the two genders we have had more cases in 2011 compared to 2012 (Table 1).

Table 1. Patients with acute coronary syndrome by socio demographic characteristics

	F	M	Total	OR (95% CI) P-value
Total	**546**	**952**	**1498**	
Year N (%)				
2011	332 (60.8)	592 (62.2)	924 (61.7)	*P*=0.619
2012	203 (39.2)	360 (37.8)	574 (38.3)	
Age (years)				
< 70	343 (62.8)	696 (73.1)	1039 (69.4)	0.746 (0.652 - 0.853) *P*=0.000
≥ 70	203 (37.2)	256 (26.9)	459 (30.6)	
Median (IQR)	65.5 (20-92)	63 (18-99)	64 (18-99)	P=0.0001
Residence N (%)				
Village	185 (33.9)	309 (32.5)	494 (33.0)	1.06 (0.853 - 1.333) P=0.612
Town	361 (66.1)	643 (67.5)	1004 (67.0)	
Acute coronary syndrome N (%)				
UA	123 (22.5)	215 (22.6)	338 (22.6)	0.820* (0.643 - 1.046) P=0.279
STEMI	169 (31.0)	330 (34.7)	499 (33.3)	
NSTEMI	254 (46.5)	407 (42.8)	661 (44.1)	
Group N (%)				
PHE group	73 (13.4)	97 (10.2)	170 (11.3)	1.36 (0.984 - 1.881) P=0.063
Control group	473 (86.6)	855 (89.8)	1328 (88.7)	
Status on discharge N (%)				
Survived	478 (87.5)	866 (91.0)	1344 (89.7)	1.242 (1.025 - 1.504) P=0.041
Deceased	68 (12.5)	86 (9.0)	154 (10.3)	
LVEF N (%)				
< 40%	195 (35.7)	339 (35.6)	534 (35.6)	1.005 (0.806 - 1.251) P=0.988
≥ 40%	351 (64.3)	613 (64.4)	964 (64.4)	

* OR for STEMI/NSTEMI by gender

By age, 1039 or 69.4% were younger than 70 years. In a higher percentage, females were 70 and older compared to males (37.2% versus 26.9%), the difference being statistically significant (P <0.001). Patients with acute coronary syndrome were less likely to be women aged ≥70 years OR 0.746 (95% CI 0.652-0.853). The mean age of patients with acute coronary syndrome was 63.2 years (SD ± 11.2 years), ranging from 18 to 99 years. The mean age of female patients with acute coronary syndrome was 64.6 years (SD ± 11.4 years), the range 20-92 years. The average age of male patients with acute coronary syndrome was 62.4 years (SD ± 11.0 years), ranging from 18 to 99 years. With T-test, we gained significant statistical difference in the average age of patients with acute coronary syndrome by gender (P <0.001). About two-thirds of patients with acute coronary syndrome (67.0%) were living in the city. Patients of both genders were more commonly in the city without any significant difference (OR 1.06, 95% 0.853-1.333), (P = 0.612). For the two-year analysis of 1498 patients in the Emergency Center of the University Clinical Center of Kosovo with acute coronary syndrome, 338 or 22.6% were diagnosed as unstable angina, 499 or 33.3% as STEMI and 661 or 44.1% as NSTEMI. The Odds of STEM is lower in females (OR 0.820, 95% CI 0.643-1.046) but without significant difference (P = 0.279). For the purposes of the study, we defined the Pre-hospital emergency (PHE) group as those who were referred to the emergency department (ED) via PHE, and the control group as all other patients. In the control group, we include those who were self-transported to the ED and those who were sent there by a health center or family physician, whatever the type of transport used (including ambulances operated by the fire services). In PHE group were 170 or 11.3% of patients. Women (13.4%) often used PHE services compared to males (10.2%) OR 1.36 (95% CI 0.984-1.881) but without significant difference (P = 0.063). In hospital mortality rate for ACS was 10.3% more for female 12.5% vs. male patients (9.0%) with significant difference (P=0.041). Female were in higher risk than man OR 1.242 (95% CI 1.025 - 1.504). By LVEF, 534 or 35.6% has LVEF <40%, similar by gender (Females 35.7% versus Males 35.6%), OR 1.005 (95% CI 0.806 - 1.251), (Table 1).

Table 2. Patients with acute coronary syndrome by risk factors

	F	M	Total	OR (95% CI)
Total	**546**	**952**	**1498**	**P-value**
Hypertension N (%)				
Yes	385 (70.5)	461 (48.4)	846 (56.5)	2.547 (2.037 - 3.185)
No	161 (29.5)	491 (51.6)	652 (43.5)	P=0.000
SAP (mmHG)				
Mean ± SD	139.7 ± 24.9	134.6 ± 26.2	136.4 ± 25.9	P=0.0001
DAP (mmHG)				
Mean ± SD	83.7 ± 14.1	82.6 ± 15.1	83.0 ± 14.7	P=0.205
Heart rate				
Mean ± SD	83.2 ± 20.7	81.2 ± 24.0	82.0 ± 22.9	P=0.205
Diabet N (%)				
Yes	218 (39.9)	240 (25.2)	458 (30.6)	1.972 (1.574 - 2.470)
No	328 (60.1)	712 (74.8)	1040 (69.4)	P=0.000
Hiperlipidemia N (%)				
Yes	285 (52.2)	516 (54.2)	697 (46.5)	0.922 (0.747 - 1.139)
No	261 (47.8)	436 (45.8)	801 (53.5)	P=0.487
Obesity N (%)				
Yes	83 (15.2)	70 (7.4)	153 (10.2)	2.259 (1.612 - 3.165)
No	463 (84.8)	882 (92.6)	1345 (89.8)	P=0.000
Smoking N (%)				
Current smoker	80 (14.7)	463 (48.6)	543 (36.2)	0.155
No smoker	441 (80.8)	376 (39.5)	817 (54.5)	(0.121 - 0.199)
Ex smoker	25 (4.6)	113 (11.9)	138 (9.2)	P=0.000
Alcohol N (%)				
Yes	1 (0.2)	18 (1.9)	19 (1.3)	0.142*
No	219 (40.1)	837 (87.9)	1056 (70.5)	(0.021 - 0.963)
No data	326 (59.7)	97 (10.2)	423 (28.2)	P=0.003
Comorbidity N (%)				
Yes	310 (56.8)	346 (36.3)	656 (43.8)	2.301 (1.856 - 2.852)
No	236 (43.2)	606 (63.7)	842 (56.2)	P=0.000
Cardiac event history N (%)				
Yes	210 (38.5)	300 (31.5)	510 (34.0)	1.358 (1.090 - 1.693)
No	336 (61.5)	652 (68.5)	988 (66.0)	P=0.007
Family history for cardiac event N (%)				
Yes	187 (34.2)	331 (34.8)	518 (34.6)	0.977 (0.783 - 1.220)
No	359 (65.8)	621 (65.2)	980 (65.4)	P=0.883

Patients with ACS in 56.5% of cases had hypertension, females more often 70.5% vs. males 48.4% with significant difference (P=0.000). Female were in higher risk for hypertension than man OR 2.547 (95% CI 2.037 - 3.185). The mean systolic arterial pressure of patients with acute coronary syndrome was 136.4 mmHg (SD ± 25.9 mmHg), ranging from 0 to 240 mmHg. The mean systolic arterial pressure of female patients with acute coronary syndrome was 139.7 mmHg (SD ± 24.9 mmHg), the range 70-230 mmHg. The average systolic arterial pressure of male patients with acute coronary syndrome was 134.6 mmHg (SD ± 26.2 mmHg), ranging from 0 to 240 mmHg. With Mann- Whitney test, we gained significant statistical difference in the average systolic arterial pressure of patients with acute coronary syndrome by gender (P =0.0001).

The mean diastolic arterial pressure of patients with acute coronary syndrome was 83.0 mmHg (SD ± 14.7 mmHg), ranging from 0 to 160 mmHg. The mean diastolic arterial pressure of female patients with acute coronary syndrome was 83.7 mmHg (SD ± 14.1 mmHg), the range 30 - 160 mmHg. The average diastolic arterial pressure of male patients with acute coronary syndrome was 82.6 mmHg (SD ± 15.1 mmHg), ranging from 0 to 140 mmHg. With Mann-Whitney test, we didn’t gained significant statistical difference in the average diastolic arterial pressure of patients with acute coronary syndrome by gender (P =0.205).

The mean heart rate of patients with acute coronary syndrome was 82.0 (SD ± 22.9), ranging from 0 to 244. The mean heart rate of female patients with acute coronary syndrome was 83.2 (SD ± 20.7), the range 30-200 mmHg. The mean heart rate of male patients with acute coronary syndrome was 81.2 (SD ± 24.0), ranging from 0 to 244. With Mann- Whitney test, we gained significant statistical difference in the average heart rate of patients with acute coronary syndrome by gender (P =0.0018).

Patients with ACS in 30.6% of cases had diabetes, females more often 39.9% vs. males 25.2% with significant difference (P=0.000). Female were in higher risk for diabetes than man OR 1.972 (95% CI 1.574 - 2.470). Patients with ACS in 10.2% of cases were Obese, females more often 15.2% vs. males 7.4% with significant difference (P=0.000). Female were in higher risk for obesity than man OR 2.259 (95% CI 1.612 – 3.165). Patients with ACS in 36.2% of cases were Current smoker, males more often 48.6% vs. females 14.7% with significant difference (P=0.000). Female were in lower risk for smoking than man OR 0.155 (95% CI 0.121 – 0.199).

Male patients were more often alcohol users (1.9%) compared to female patients (0.2%) with significant difference (P=0.003). Generally speaking, the rate of reporting alcohol use is low.

Patients with ACS in 46.5% of cases had hyperlipidemia, females less often 52.2% vs. males 54.2% with no significant difference (P=0.487). Female were in lower risk for hyperlipidemia than man OR 0.922 (95% CI 0.747 - 1.139). Patients with ACS in 43.8% of cases had Comorbidity, females more often 56.8% vs. males 36.6% with significant difference (P=0.000). Female were in higher risk for comorbidity than man OR 2.301 (95% CI 1.856 - 2.852). Patients with ACS in 34.0% of cases had Cardiac event history, females more often 38.5% vs. males 31.5% with significant difference (P=0.007). Female were in higher risk for Cardiac event history than man OR 1.358 (95% CI 1.090 - 1.693). Patients with ACS in 34.6% of cases had Family history for cardiac event, with similar percent according to gender females 34.2% vs. males 34.8% with no significant difference (P=0.883, OR 0.977 (95% CI 0.783 - 1.220), (Table 2).

Table 3. Patients with acute coronary syndrome by gender and duration of symptoms

	F	M	Total	OR (95% CI)
Total	**546**	**952**	**1498**	**P-value**
Duration of simptoms N (%)				
< 6 hours	174 (31.9)	343 (36.0)	517 (34.5)	1.271* (1.005-1.607) P=0.051
6-12 hours	4 (0.7)	14 (1.5)	18 (1.2)	
> 12 hours	277 (50.7)	437 (45.9)	714 (47.7)	
Unknown	91 (16.7)	158 (16.6)	249 (16.6)	
Onset of symptoms as reported by the patient and admission to the hospital (hours)				
Median (IQR)	8 (1-16)	8 (1-14)	8 (1-16)	P=0.278
Time between the onset of symptoms as reported by the patient and first ECG (hours)				
Median (IQR)	8.5 (1-17)	8.5 (1-17)	8.5 (1-17)	P=0.798
Time between entering the ED and the beginning of the therapy (minutes)				
Median (IQR)	50 (15-60)	40 (15-65)	40 (15-65)	P=0.923

* OR for 12 hours and less/ >12 hours by gender

For the two-year analysis of 1498 patients in the Emergency Center of the University Clinical Center of Kosovo with acute coronary syndrome, at 517 or 34.5% duration of symptoms from the onset of symptoms as reported by the patient and admission to the hospital were < 6 hours, 18 or 1.2% from 6 to 12 hours, 714 or 47.7% more than 12 hours and 249 or 16.6% was unknown. The Odds of > 12 hours is higher in females (OR 1.271, 95% CI 1.005- 1.607) but without significant difference (P = 0.051), (Table 3).

5. 2. Patients with acute coronary syndrome treated at the University Clinical Center of Kosova for the analyzed period by groups

In 2012, twice more patients with ACS requested PHE assistance compared to 2011, this difference was with statistical significance (P=0.000). According to the gender females have frequently sought PHE service assistance compared to men OR 1.312 (95% CI 0.986 to 1.745) but without significant difference (P=0.063). Patients older than 70 years of age have more often requested PHE assistance than those <70 years OR 0.625 (95% CI 0.450 - 0.869) with significant difference (P=0.006). Patients who used PHE services to be admitted to the Emergency Center were older than the control group. The average age of patients in the PHE group was 66.2 years (SD ± 11.2 years) ranging from 37 to 92 years. The average age of patients in the control group was 62.8 years (SD ± 11.1 years) ranging from 18 to 99 years. This difference with significant statistical significance (P = 0.0001).

Frequently, PHE assistance has required STEMI patients (47.1%) or 1.780 (95% CI 1.343 - 2.358), while with less AI (10.6%) OR 0.406 (95% CI 0.253 - 0.652), with significant difference by groups.

Rarely PHE services have been used by patients living in the village (19.4% vs. 80.6%) and compared to the control group (34.7% vs. 65.3%) this difference was significant statistical significance (P <0.0001), OR 0.489 (95% CI 0.340 - 0.705).

The mortality rate was higher in PHE patients 28.8% compared to that of the control group 7.9% OR 3.534 (95% CI 2.652 - 4.709), with significant statistical difference (P = 0.000).
This high mortality rate of patients who have been using pre-emergency services can be explained by the fact that they were more often STEMI patients, older than patients of control group, 40.0% who were 70 years or older.

Patients of PHE group on 45.9% of cases had LVEF < 40% compared to Control group 34.3% with significant difference (P=0.004), PHE group were in higher risk for LVEF < 40% than Control group OR 1.621 (95% CI 1.175 – 2.238), (Table 4).

Table 4. Patients with acute coronary syndrome by groups and year of treatment

	PHE group	Control group	OR (95% CI) P-value
Total	**170**	**1328**	
Year N (%)			
2011	48 (28.2)	876 (66.0)	0.203 (0.142 - 0.288) P=0.000
2012	122 (71.8)	452 (34.0)	
Gender N (%)			
F	73 (42.9)	473 (35.6)	1.312 (0.986 - 1.745) P=0.063
M	97 (57.1)	855 (64.4)	
Age (years)			
< 70	102 (60.0)	937 (70.6)	0.662 (0.497 - 0.883) P=0.006
≥ 70	68 (40.0)	391 (29.4)	
Mean ± SD	66.2 ± 11.2	62.8 ± 11.1	P=0.0001
Runk	37 - 92	18 - 99	
Residence N (%)			
Village	33 (19.4)	461 (34.7)	0.489 (0.340 - 0.705) P=0.000
Town	137 (80.6)	867 (65.3)	
Acute coronary syndrome N (%)			
UA	18 (10.6)	320 (24.1)	0.406 (0.253 - 0.652) P=0.000
STEMI	80 (47.1)	419 (31.6)	1.780 (1.343 - 2.358) P=0.000
NSTEMI	72 (42.4)	589 (44.4)	0.930 (0.698 - 1.239) P=0.681
Status on discharge N (%)			
Survived	121 (71.2)	1223 (92.1)	4.717 (3.202 - 6.947) P=0.000
Deceased	49 (28.8)	105 (7.9)	
LVEF N (%)			
< 40%	78 (45.9)	456 (34.3)	1.621 (1.175-2.238) P=0.004
≥ 40%	92 (54.1)	872 (65.7)	

Table 5. Patients with acute coronary syndrome by groups and hypertension

	PHE group	Control group	OR (95% CI) P-value
Total	**170**	**1328**	
Other deseases N (%)			
Hypertenson	89 (52.4)	735 (55.3)	0.898 (0.677 - 1.193) P=0.462
Diabet	72 (42.4)	386 (29.1)	1.668 (1.256 - 2.216) P=0.000
Obesity	11 (6.5)	142 (10.7)	0.608 (0.337 - 1.095) P=0.105
Hiperlipidemia	101 (59.4)	700 (52.7)	1.313 (0.949 - 1.817) P=0.117
SAP (mmHG)			
Mean ± SD	132.0 ± 29.1	136.9 ± 25.4	P=0.018
DAP (mmHG)			
Mean ± SD	79.1 ± 16.8	83.5 ± 14.4	P=0.690
Heart rate			
Mean ± SD	88.3 ± 20.5	81.2 ± 21.6	P=0.008
Smoking N (%)			
Current smoker	56 (32.9)	487 (36.7)	
Ex smoker	17 (10.0)	93 (7.0)	0.970* (0.703 - 1.339) P=0.000
No smoker	97 (57.1)	748 (56.3)	
Alcool N (%)			
Yes	2 (1.2)	17 (1.3)	0.926 (0.247 - 3.465) P=0.999
Comorbidity N (%)			
Yes	95 (55.9)	561 (42.2)	1.732 (1.255 - 2.389) P=0.045
Cardiac event history N (%)			
Yes	70 (41.2)	440 (33.1)	1.413 (1.020 - 1.958) P=0.045
Family history for cardiac event N (%)			
Yes	77 (45.3)	441 (33.2)	1.665 (1.206 - 2.300) P=0.002

* OR for current+ex-smoker/ No smoker by groups

According to risk factors for ACS, hypertension was similar in structure to patients of both groups (PHE group 52.4% vs. Contr. Gr. 55.3%) without significant difference (p = 0.511). The mean systolic arterial pressure of PHE group patients with acute coronary syndrome was 132.0 mmHg (SD ± 29.1 mmHg), the range 70-240 mmHg. The average systolic arterial pressure of Control group patients with acute coronary syndrome was 136.9 mmHg (SD ± 25.4 mmHg), ranging from 0 to 230 mmHg. With Mann- Whitney test, we gained significant statistical difference in the average systolic arterial pressure of patients with acute coronary syndrome by groups (P =0.018).

The mean diastolic arterial pressure of PHE group patients with acute coronary syndrome was 79.1 mmHg (SD ± 16.8 mmHg), the range 10-120 mmHg. The average diastolic arterial pressure of Control group patients with acute coronary syndrome was 83.5 mmHg (SD ± 14.4 mmHg), ranging from 0 to 160 mmHg. With Mann- Whitney test, we gained significant statistical difference in the average diastolic arterial pressure of patients with acute coronary syndrome by groups (P =0.028).

The mean heart rate of PHE group patients with acute coronary syndrome was 88.3 beats (SD ± 30.9), the range 30- 244. The average heart rate of Control group patients with acute coronary syndrome was 81.2 (SD ± 21.6), ranging from 0 to 231. With Mann- Whitney test, we gained significant statistical difference in the average heart rate of patients with acute coronary syndrome by groups (P =0.008).

As seen in Table 5, out of the 170 patients of PHE group with diabetes were 42.4% compared to 29.1% of patients with diabetes from the control group, with significant statistical significance (P = 0.001). The Odds of using PHE services was greater in patients with diabetes OR 1.668 (95% CI 1.256-2.216). Obese patients were often patients of control group (PHE group 6.5% vs. Contr. Gr. 10.7%), but without significant difference (p = 0.115). Patients of PHE groups were often Ex smoke compared to the control group (10.0% vs. 7.0%), with significant difference (P = 0.000). Patients of PHE group on 1.2% of cases were alcohol users compared to control group 1.3% with no significant difference (P=0.706), OR 95%CI 0.926 (0.247-3.465). Patients of PHE group on 59.4% of cases had hiperlipidemia compared to

Control group 52.7% with no significant difference (P=0.706), PHE group were in higher risk for hyperlipidemia than Control group OR 1.313 (95% CI 0.949 - 1.817).

Patients of PHE group on 55.9% of cases had comorbidity compared to Control group 42.2% with significant difference (P=0.001), PHE group were in higher risk for comorbidity than Control group OR 1.732 (95% CI 1.255 - 2.389).

Patients of PHE group on 41.2% of cases had Cardiac event history compared to Control group 33.1% with significant difference (P=0.045), PHE group were in higher risk for Cardiac event history than Control group OR 1.413 (95% CI 1.020 - 1.958). Patients of PHE group on 45.3% of cases had Family history for cardiac event compared to Control group 33.2% with significant difference (P=0.002), PHE group were in higher risk for Family history for cardiac event than Control group OR 1.665 (95% CI 1.206 – 2.300), (Table 5).

Table 6. Patients with acute coronary syndrome by groups and duration of symptoms

	PHE group	Control group	OR (95% CI) P-value
Total	170	1328	
Duration of simptoms N (%)			
< 6 hours	81 (47.6)	436 (32.8)	1.630* (1.171-2.269) P=0.004
6-12 hours	6 (3.5)	12 (0.9)	
> 12 hours	76 (44.7)	638 (48.0)	
Unknown	7 (4.1)	242 (18.2)	
Onset of symptoms as reported by the patient and admission to the hospital (hours)			
Median (IQR)	7 (1-13)	11 (1-16)	P=0.008
Time between the onset of symptoms as reported by the patient and first ECG (hours)			
Median (IQR)	8 (1-14)	12 (1-17)	P=0.008

* OR for 12 hours and less/ >12 hours by groups

Patients of PHE group on 47.6% of cases duration of symptoms from the onset of symptoms as reported by the patient and admission to the hospital were < 6 hours compared to Control group 32.8% with significant difference (P=0.004), PHE group were in higher risk for from the onset of symptoms as reported by the patient and admission to the hospital were < 6 hours than Control group OR 1.630 (95% CI 1.171 – 2.269).

Of the 499 patients with ST elevation/de novo LBBB, 331 underwent thrombolysis and the other 168 primary angioplasty, but only 65 has done angioplasty in UCCK other go to private institutions. Door-to-needle (67 vs. 135 min) and door-to-balloon (89 vs. 142 min) times were shorter in the PHE group, but not significantly (p = 0.08), (Table 6).

Table 7. Univariate Cox regression analysis for the predictors of mortality

	HR	95% CI	P-value
Age ≥ 70 yr	2.81	1.99 - 3.97	< 0.001
Female sex	1.39	1.00 - 1.93	0.041
UA	1.00	-	-
STEMI	8.51	5.88 - 12.31	< 0.001
NSTEMI	2.18	1.19 - 3.98	< 0.001
PHE group	3.92	2.35 - 6.54	< 0.001
Urban residence	1.02	0.73 - 1.43	0.928
Hypertension	0.36	0.26 - 0.49	< 0.001
Diabetes	2.39	1.69 - 3.37	< 0.001
Hiperlipidemia	1.68	1.22 - 2.31	0.032
Obesity	0.06	0.03 - 0.09	0.001
No smoker	1.00	-	-
Current smoker	0.76	0.53 - 1.08	0.130
Ex smoker	1.86	1.09 - 3.17	0.006
LVEF < 40%	15.95	9.11 - 27.91	< 0.001

Abbreviations: STEMI: ST-segment elevation myocardial infarction, NSTEMI: non- ST- elevation myocardial infarction; LVEF: left ventricular ejection fraction; PHE: pre-hospital emergency treatment

Age, female sex, STEMI, NSTEMI, PHE treatment, diabetes, hiperlipidemia, smoking and low LVEF were significant risk factors for in-hospital mortality in patients admitted for ACS, in univariate Cox regression analysis (Table 7). However, only age, the presence of STEMI, the luck PHE treatment, diabetes mellitus, low LVEF and smoking remain independent predictors of mortality in patients admitted for ACS, in multivariate Cox regression analysis (Table 8).

Table 8. Multivariate Cox regression analysis of in-hospital mortality

	HR	95% CI	P-value
Age ≥ 70 yr	2.37	1.67 - 3.52	< 0.001
Female sex	1.01	0.87 - 1.23	0.067
STEMI	6.17	3.22 - 15.31	< 0.001
PHE group	3.92	2.35 - 6.54	< 0.001
Diabet	3.01	1.98 - 3.78	< 0.001
Hiperlipidemia	1.2	0.98 - 1.89	0.054
Ex smoker	2.34	1.57 - 3.85	0.01
LVEF < 40%	17.63	11.2 - 30.54	< 0.001

Abbreviations: STEMI: ST-elevation myocardial infarction; LVEF: left ventricular ejection fraction; PHE: pre-hospital emergency treatment

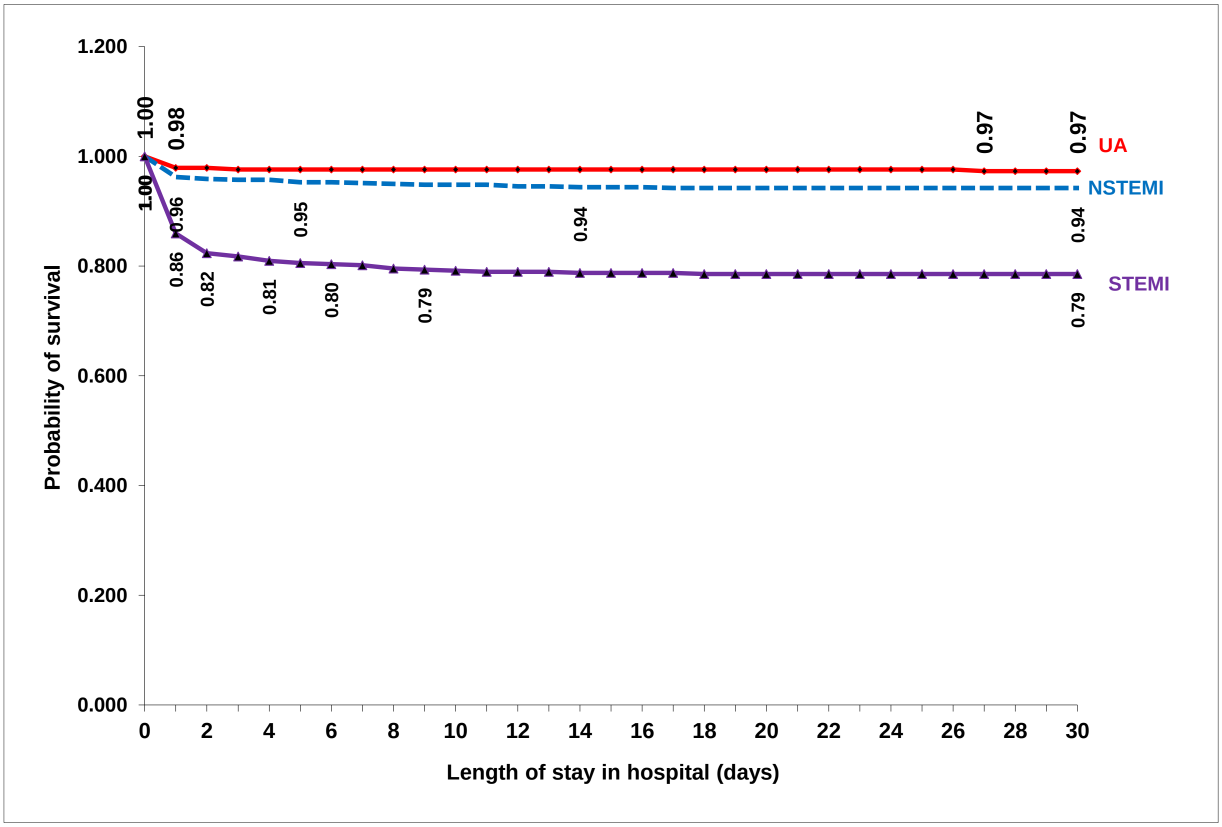

Figure 1. The Kaplan Meier survival curve of patient with STEMI, NSTEMI

The Kaplan-Meier survival curve revealed that STEMI patients had a higher in-hospital mortality rate and a lower survival rate when compared to patients admitted for ACS and having NSTEMI or UA (Figure 1).

Using the Log rank test, we discovered a significant difference on in- hospital mortality between STEMI and NSTEMI patients (P < 0.001), STEMI and UA patients (P < 0.001) and NTEMI and UA patients (P < 0.001).

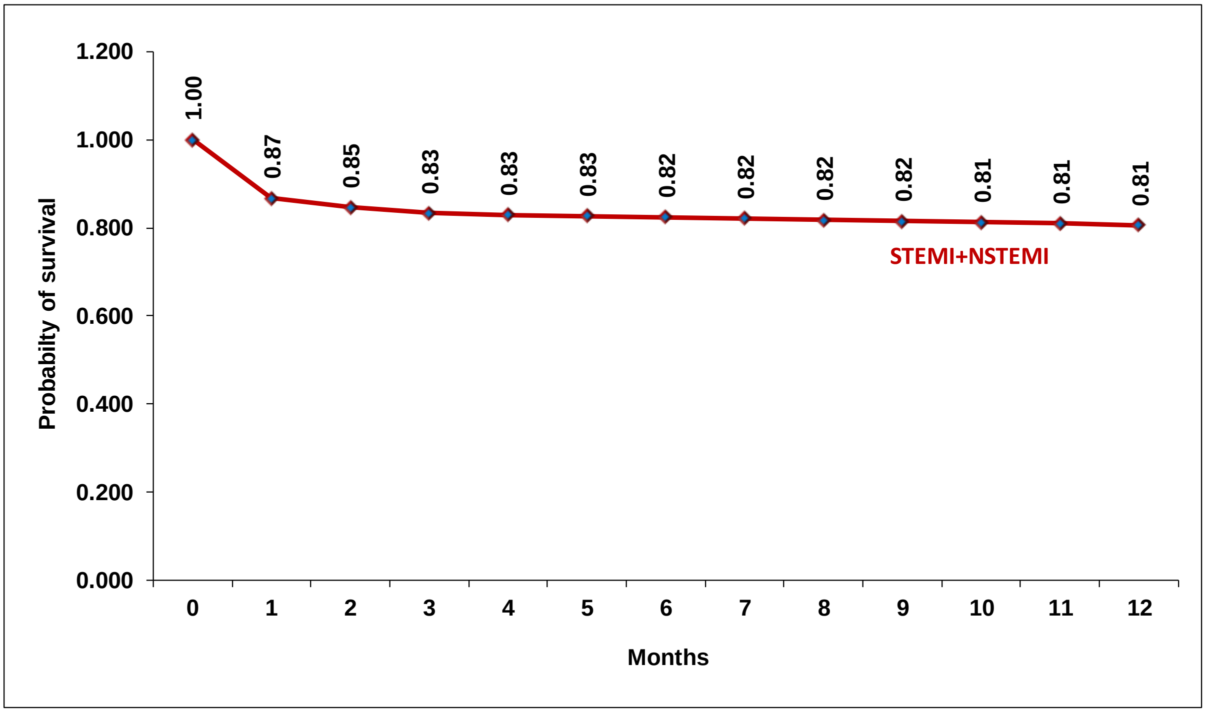

Figure 2. The Kaplan Meier survival curve of patient with STEMI, NSTEMI after 1 year follow up

After one year, when the patients were contacted by phone, the probability of survival was 0.81, and the mortality rate from admission to 12 months was 19.4%. (Figure 2)

Patients over the age of 70 (18.3%), female patients (12.5%), STEMI patients (21.4%), PHE treated patients (28.8%), patients who did not have arterial hypertension prior to hospitalization (15.4%), diabetics (17.0%), non-obese patients (10.8%), and ex-smokers (18.8%) had a higher in-hospital mortality rate. The mortality rate did not differ between patients living in cities and those living in rural areas (Table 9).

Table 9. Risk factor for in hospital mortality

	Deceased on discharge	X^2-test
Total, n=1498	154 (10.3)	
Gender		
F, n=546	68 (12.5)	0.041
M, 952	86 (9.0)	
Clinical presentation		
UA, n=338	9 (2.7)	
STEMI, n=499	107 (21.4)	0.000
NSTEMI, n=661	38 (5.7)	
Group		
PHE group, n=170	49 (28.8)	0.000
Control group, n=1328	105 (7.9)	
Age group		
<70, n=1039	70 (6.7)	0.000
≥70, n=459	84 (18.3)	
Residence		
Rural, n=494	50 (10.1)	0.928
Urban, n=1004	104 (10.4)	
Hypertension		
Yes, n=846	50 (6.1)	0.000
No, n=652	104 (15.4)	
Diabet		
Yes, n=458	78 (17.0)	0.000
No, n=1040	76 (7.3)	
Obesity		
Yes, n=153	1 (1.2)	0.001
No, n=1345	153 (10.8)	
Smoking		
No smoker, n=817	85 (10.4)	
Current smoker, n=543	43 (7.9)	0.000
Ex smoker, n=138	26 (18.8)	
Duration of symptoms		
< 6 hours, n=517	68 (44.2)	
6-12 hours, n=18	10 (6.5)	0.000
> 12 hours, n=714	73 (47.4)	
Unknown, n=249	3 (1.9)	

5. 3. Patients with acute coronary syndrome treated at the University Clinical Center of Kosova for the analyzed period by types of acute coronary syndrome

In 2011 we had the largest number of admissions in general, especially patients with Unstabile angina and NSTEMI. In 2012, we had less patients with ACS, especially we had a decrease in the number of patients with UA and NSTEMI, while the number of patients with STEMI was similar (240 vs 259), the difference with significant statistical significance (P = 0.000).

According to the clinical presentation of ACS we had a similar structure at both genders without significant difference (P = 0.279). In the two genders the most frequent cases were NSTEMI cases (F 46.5% versus M 42.8%), then STEMI (F 31.0% versus M 34.7%) and UA (F 22.5% vs. M 22.6%).

By clinical presentation of ACS and age group we have earned significant difference (P=0.000). At age group ≥ 70 years 37.0% were patients with STEMI compared to those aged <70 years 31. 7% (Table 10). However, between the average age of the patients by clinical presentation of ACS we didn't earn significant difference. The mean age of patients with unstable angina was 62.7 years (SD ± 10.7 years), ranging from 33 to 88 years. The mean age of STEMI patients was 63.6 years (SD ± 11.7 years), the range 18-99 years. The mean age of NSTEMI patients was 63.0 years (SD ± 11.1 years), the range 20-92 years. With Krusckal – Wallis test, we didn't distinguish significant statistical difference in the average age of patients with acute coronary syndrome by clinical presentation of ACS (P=0.406).

The number of patients by residence and clinical presentation of ACS is presented in table 10. The STEMI patients were more often from town (36.4%) compared to village (27.1%), with significant difference (P=0.000).

The STEMI patients were more often from PHE group (16.0%) compared to NSTEMI (10.9%) and UA patients (5.3%) with significant difference (P=0.000). The survival of ACS patients varied significantly according to the clinical presentation. STEMI patients had a lower rate (78.6%) than UA patients (97.3%) and NSTEMI patients (94.3%), with a significant difference (P=0.000) (Table 10).

Table 10. Patients with acute coronary syndrome by clinical presentation of ACS and year of treatment

	UA	STEMI	NSTEMI	
Total	**338**	**499**	**661**	**P-value**
Year N (%)				
2011	250 (74.0)	240 (48.1)	434 (65.7)	P=0.000
2012	88 (26.0)	259 (51.9)	227 (34.3)	
Gender N (%)				
F	123 (36.4)	169 (33.9)	254 (38.4)	P=0.279
M	215 (63.6)	330 (66.1)	407 (61.6)	
Age (years)				
< 70	238 (22.9)	329 (31.7)	472 (45.4)	P=0.000
≥ 70	100 (21.8)	170 (37.0)	189 (41.2)	
Mean ± SD	62.7 ± 10.7	63.6 ± 11.7	63.0 ± 11.1	
Runk	33 - 88	18 - 99	20 - 92	
Residence N (%)				
Village	133 (39.3)	134 (26.9)	227 (34.3)	P=0.000
Town	205 (60.7)	365 (73.1)	434 (65.7)	
Group N (%)				
PHE group	18 (5.3)	80 (16.0)	72 (10.9)	P=0.000
Control group	320 (94.7)	419 (84.0)	589 (89.1)	
Status on discharge N (%)				
Survived	329 (97.3)	392 (78.6)	623 (94.3)	P=0.000
Deceased	9 (2.7)	107 (21.4)	38 (5.7)	
LVEF N (%)				
< 40%	5 (1.5)	255 (51.1)	274 (41.5)	P=0.000
≥ 40%	333 (98.5)	244 (48.9)	387 (58.5)	

Table 11. Patients with acute coronary syndrome by clinical presentation of ACS and hypertension

	UA	STEMI	NSTEMI	
Total	**338**	**499**	**661**	**P-value**
Other deseases N (%)				
Hypertenson	207 (61.2)	242 (48.5)	397 (60.1)	P=0.000
Diabet	82 (24.3)	176 (35.3)	200 (30.3)	P=0.003
Obesity	40 (11.8)	29 (5.8)	84 (12.6)	P=0.000
Hiperlipidemia	161 (47.6)	319 (63.9)	321 (48.6)	P=0.000
SAP (mmHG)				
Mean ± SD	138.6 ± 25.2	134.5 ± 29.0	136.7 ± 23.6	P=0.021
DAP (mmHG)				
Mean ± SD	83.0 ± 13.1	82.7 ± 17.6	83.2 ± 13.2	P=0.690
Heart rate				
Mean ± SD	80.9 ± 20.5	83.8 ± 22.6	81.2 ± 24.1	P=0.002
Smoking N (%)				
Current smoker	106 (31.4)	222 (44.5)	199 (30.1)	
Ex smoker	28 (8.3)	28 (5.6)	58 (8.8)	P=0.000
No smoker	204 (60.4)	249 (49.9)	404 (61.1)	
Alcohol N (%)				
Yes	4 (1.2)	8 (1.6)	7 (1.1)	
No	212 (62.7)	425 (85.2)	419 (63.4)	P=0.706
No data	122 (36.1)	66 (13.2)	235 (35.6)	
Comorbidity N (%)				
Yes	148 (43.8)	179 (35.9)	329 (49.8)	P=0.000
No	190 (56.2)	320 (64.1)	332 (50.2)	
Cardiac event history N (%)				
Yes	133 (39.3)	98 (19.6)	279 (42.2)	P=0.000
No	205 (60.7)	401 (80.4)	382 (57.8)	
Family history for cardiac event N (%)				
Yes	120 (35.5)	286 (57.3)	112 (16.9)	P=0.000
No	218 (64.5)	213 (42.7)	549 (83.1)	

Patients with UA (61.2%) and NTEMI (60.1%) were more often hypertensive compared to STEMI patients (48.5%) with significant difference (P=0.000), (Table 11). STEMI patients had more often diabetes (35.3%) compared to NSTEMI patients (30.3%) and UA patients (24.3%) with significant difference (P=0.003). Patients with UA (11.8%) and NTEMI (12.7%) were more often obese compared to STEMI patients (5.8%) with significant difference (P=0.000). Patients with STEMI in 63.9% of cases had hyperlipidemia, NSTEMI patients in 48.6% and rarely UA patients with 47.6% of cases had hyperlipidemia with significant difference (P=0.000).

The mean systolic arterial pressure of patients with unstable angina was 138.6 mmHg (SD ± 25.2 mmHg), ranging from 0 to 210 mmHg. The mean systolic arterial pressure of STEMI patients was 134.5 mmHg (SD ± 29.0 mmHg), the range 0 - 240 mmHg. The mean systolic arterial pressure of NSTEMI patients was 136.7 mmHg (SD ± 23.6 mmHg), the range 25 - 230 mmHg. Using Krusckal – Wallis test, we gained significant statistical difference in the average systolic arterial pressure of patients with acute coronary syndrome by clinical presentation of ACS (P=0.0215).

The mean diastolic arterial pressure of patients with unstable angina was 83.0 mmHg (SD ± 13.1 mmHg), ranging from 0 to 130 mmHg. The mean diastolic arterial pressure of STEMI patients was 82.7 mmHg (SD ± 17.6 mmHg), the range 0 - 150 mmHg. The mean diastolic arterial pressure of NSTEMI patients was 83.2 mmHg (SD ± 13.2 mmHg), the range 30-160 mmHg. Using Krusckal– Wallis test, we didn't distinguish significant statistical difference in the average diastolic arterial pressure of patients with acute coronary syndrome by clinical presentation of ACS (P=0.690). The mean heart rate of patients with unstable angina was 80.9 beats (SD ± 20.5 beats), ranging from 0 to 219. The mean heart rate of STEMI patients was 83.8 (SD ± 22.6), the range 1 - 230 beats. The mean heart rate of NSTEMI patients was 81.2 (SD ± 24.1), the range 30-244. Using Krusckal – Wallis test, we gained significant statistical difference in the average heart rate of patients with acute coronary syndrome by clinical presentation of ACS (P=0.0024).

At 1.5% of patients with unstable angina, at 51.1% of STEMI patients and at 41.5% of NSTEMI patients the LVEF were < 40%. With X2- test, we gained significant statistical difference on percent of LVEF by clinical presentation of ACS (P=0.0000).

STEMI patients were more often current smoker (44.5%) compared to UA patients (31.4%) and NSTEMI patients (30.1%) with significant difference (P=0.000). STEMI patients were more often alcohol users (1.6%) compared to UA patients (1.2%) and NSTEMI patients (1.1%) without significant difference (P=0.706). Generally speaking, the rate of reporting alcohol use is low.

Patients with NSTEMI in 49.8% of cases had Comorbidity, patients with UA more often 43.8% vs. STEMI patients 35.9% with significant difference (P=0.000). Patients with UA in 39.3% of cases had history for cardiac event, STEMI patients in 19.6% and NSTEMI patients on 42.2% of cases had history for cardiac event with significant difference (P=0.000).
Patients with UA in 35.5% of cases had Family history for cardiac event, STEMI patients in 57.3% and NSTEMI patients on 16.9% of cases had Family history for cardiac event with significant difference (P=0.000), (Table 11).

Table 12. Patients with acute coronary syndrome by clinical presentation and duration of symptoms

	UA	STEMI	NSTEMI	
Total	**338**	**499**	**661**	**P-value**
Duration of symptoms N (%)				
< 6 hours	88 (26.0)	246 (49.3)	183 (27.7)	P=0.000*
6-12 hours	-	10 (2.0)	8 (1.2)	
> 12 hours	154 (45.6)	223 (44.7)	337 (51.0)	
Unknown	96 (28.4)	20 (4.0)	133 (20.1)	
Onset of symptoms as reported by the patient and admission to the hospital (hours)				
Median (IQR)	8 (1-16)	7 (1-14)	8 (1-16)	P=0.002
Time between the onset of symptoms as reported by the patient and first ECG (hours)				
Median (IQR)	8.5 (1-17)	7 (1-17)	8 (1-17)	P=0.002
Time between entering the ED and the beginning of the therapy (minutes)				
Median (IQR)	50 (15-65)	30 (10-45)	40 (15-65)	P=0.0002

* for 12 hours and less/ >12 hours by clinical presentation

The duration of symptoms from the onset of symptoms as reported by the patient to admission to the hospital was more than 12 hours in 61.2% of patients with unstable angina, 46.1% of STEMI patients, and 60.8% of NSTEM patients. With X^2- test, found a statistically significant difference in the duration of symptoms from the onset of symptoms as reported by the patient to admission to the hospital due to clinical presentation of ACS (P=0.0000), (Table 12).

6. DISCUSSION

6.1. Socio demographic characteristics of patients with acute coronary syndrome

The Republic of Kosovo has an area of 10 905.25 km², located on the south-eastern Europe, bordering Albania in south-west, Montenegro in northwest, Serbia to the north-east and Macedonia to south. Currently there are 38 municipalities with 1,469 settlements organized by the laws of the country. According to the KAS estimates, the resident population in Kosovo is about 1.78 million people.24% of the population in under 14 years old and 9% are over 65. Life expectancy at birth in 2011 was 76.7 years, 74.1 years for males and 79.4 for females (76).

The performance of the Kosovo emergency system in terms of acute care for ACS patients has not been thoroughly studied. Even in the most developed societies, emergency medicine is a relatively new field (75), whereas it is in its infancy in Kosovo. There has been little formal training, the EMS system lacks organization, equipment and a reliable communication system, and all of these were inadequate also for the UCCK emergency center (77 – 79) and it is expected to find specific in-hospital mortality rates of patients with ACS.

The use of EMS services for patients experiencing chest pain or who are suspected of having ACS is complicated (80) and major public health initiatives have encouraged the activation of emergency services as soon as possible in order to optimize timely diagnosis and treatment.

Two key findings from our study merit consideration. First, despite a publicly funded health system, only one-nine patients in this study were transported to the emergency department by pre-emergency services. Second, several factors such as older age, comorbidity, in higher risk for LVEF < 40 more often STEMI patients, Family history for cardiac event, cardiac event history were associated with higher PHE use, which may indicate that those who are most vulnerable are using PHE. The use of PHE for cardiac symptoms, the rate of ambulance use increased in this patient population from year 2011 to 2012. The increase in PHE use over

time that we observed in this study may not be a widespread global phenomenon and the pattern might be different in other jurisdictions (80).
In the study that include 50,881 patients with main ED diagnosis of acute coronary syndrome, stable angina or chest pain in the metropolitan areas of Edmonton and Calgary in the years of 2007–2013, 30.5% presented by emergency medical services. Same with our study use of emergency medical services was linked to an increased risk of 7-day and 30-day clinical events (80).

Triage, or risk classification, is a clinical management tool used in emergency services to guide patient flow when the need for medical attention exceeds that available. The Manchester Triage Group was developed in 1994 in the United Kingdom. The aim was to establish a consensus among physicians and nurses in the emergency room by creating a triage pattern focused on the development of the following: Thus, the Manchester Triage System (MTS) was created (45).

According to our findings, our patients have a higher percentage of in-hospital mortality. The in-hospital mortality rate for ACS was 10.3% higher in female patients (12.5% vs. 9.0%), with a significant difference (P=0.041). Females were at a higher risk than men, with an OR of 1.242 (95% CI 1.025 - 1.504). According to Bajraktari et al. (81), the overall in-hospital mortality rate for AMI patients in a Cardiology Department without a primary PCI centre in 2008 was 10.3% (12.3% for women and 9.5% for men).

The average age of AMI patients increased between 1999 and 2012, but the mortality rate remained stable. The in-hospital mortality rate for unstable angina was 2.7%, STEMI patients 21.4%, and NSTEMI patients 5.7%. In the study of Ishida at al. (53), the overall in-hospital mortality from ACS was 5.9%. The European Society of Cardiology (ESC) recommends timely coronary artery reperfusion in patients with ST-elevation myocardial infarction (STEMI) and emphasizes that primary percutaneous coronary intervention (PPCI) is the preferred strategy if available (82). Despite its benefits, PPCI is not universally used, and thrombolysis is still used in many patients. Furthermore, a large number of STEMI patients do not receive reperfusion therapy (83-84). The reasons for these disparities in reperfusion therapy use across ESC countries are unknown (85). And in other states the in-hospital mortality rate was higher before percutaneous coronary intervention (PCI), (2,3,4). In the study of Mirić et al. (86) in Split/Croatia the number of hospitalized patients with AMI, in ten years, were 5339 (67.5% males vs. 32.5% females). before percutaneous coronary intervention (PCI) mortality rate was 13,5% after PCI procedures 7.6%. The mortality in the first group was significantly higher in females (22.7 vs. 12%) and in males (9 vs. 5.5%) comparing with second group. In-hospital mortality in the patients with STEMI was significantly higher in the first group (16.6 vs. 9%). Among the patients with NSTEMI there were no significantly differences in the in-hospital mortality (4 vs. 2.5%). The most frequent trigger of death in males were ventricular fibrillation in both groups such as heart failure in females. Cx occlusion is more often among the male patients treated with PCI. In-hospital mortality in patients with STEMI treated with PCI was 5.7%. A in-hospital mortality in the patients with AIM after PCI was almost halved. Females had two times higher in-hospital mortality before and after PCI introduction

The lack of percutaneous coronary intervention procedures in AMI patients may have contributed to the high in-hospital mortality in our population. Kosovo University Clinical Center - Cardiac Surgery Service with Invasive Cardiology is the only public institution in the country that offers invasive cardiology services. From February 2018 it was introduced primary PCI for STEMI in Kosovo University Clinical Center (88). In some hospitals in the private sector, PCI has been done since 2011.

In an effort to reduce disparities in a number of European countries, the Stent for Life Initiative, which supports timely PPCI implementation, was established in September 2008, as a coalition of the European Society of Cardiology, European Association for Percutaneous Cardiovascular Interventions and Eucomed. The goal is to raise awareness of the life-saving indications for percutaneous coronary interventions, particularly in all types of acute myocardial infarction. The participating countries have already reported significant increases in PPCI utilization, mortality reductions, and overall, more effective management/organization of the STEMI treatment system, which strongly calls for the continuation of an implementation strategy and support for countries with low activity (89- 91).

To improve the rate of timely PPCI for STEMI patients, quality improvement initiatives such as "Stent for Life" in Europe, the "D2B Alliance," and "Mission: Lifeline" in the United States were established The SFL initiative established three main goals: (1) to treat 70% of STEMI patients by pPCI; (2) to perform 600 pPCI/year/million population; and (3) to ensure that centers with pPCI perform this procedure 24/7 (92-96).

The ACCA-EAPCI STEMI registry will document the current status of management and outcomes of patients admitted with an initial diagnosis of STEMI in a large number of ESC (European Society of Cardiology) member countries. This registry allows researchers to assess whether current ESC STEMI guidelines are being followed in clinical practice (97). Kosova is member of this registry from 2017. In Kosovo is not yet implemented Utstein Style (98).

Over the last 30 years, the in-hospital mortality rate for ACS in North America has decreased from 25-30% to 7-10%. This reduction can be attributed to the introduction of the Coronary Care Unit (1960s), the administration of beta blockers (1970s), the introduction of fibrinolytic therapy (1980s), and percutaneous coronary intervention (PCI) (1990s) (6), as well as improvements in risk factor modification, healthcare system organization, and disease management, which have significantly reduced the adverse prognosis of both STEMI and NSTEMI (61). According to the British Heart Foundation, despite reductions in 30-day case fatality rates, acute coronary syndromes remain one of the leading causes of premature death in both men and women in the UK (7). In their systematic review, Sarkees et al. (99) discovered that older age groups, previous atheromatous cardiovascular disease, diabetes, smoking, hypertension, hypercholesterolemia, male sex, and a family history of premature ischemic heart disease are risk factors for ACS. Between 9% and 19% of patients with ACS die within the first 6 months of being diagnosed, with roughly half dying within 30 days. The mortality rate in different countries remains different as there are differences in the application of methods for diagnosis and treatment.

Prospective cohort (EURObservational Research Programme STEMI Registry) of hospitalized STEMI patients with symptom onset within 24 hours in 196 centers across 29 countries, enrolling 11 462 patients who received primary percutaneous coronary intervention (PCI) (total cohort frequency: 72.2%, country frequency range 0-100%), fibrinolysis (18.8%; 0-100%), and no reperfusion therapy (9.0%; 0-75%). Reperfusion therapy was widely used for STEMI in ESC member and affiliated countries. Primary PCI was the most commonly used treatment, with an associated total in-hospital mortality rate of less than 5%. However, there was geographic variation in primary PCI use, which was linked to differences in in-hospital mortality (100).

In our study, female patients had a higher in-hospital mortality rate for ACS (12.5% vs. 9.0%). Females were more likely to die than men, with an OR of 1.242 (95% CI 1.025 - 1.504). A number of studies, including the effects of age, oestrogen, and different patterns of atherosclerosis, support a biological mechanism for sex-based differences in clinical presentation (82, 101-106). Furthermore, in the study of Novak et al. (107), women were significantly older than men (71,11 years vs. 64 .12 years, p 0.001) and had a higher in-hospital mortality rate and complications as a result of this age difference. When examining sex differences in mortality following acute ST-STEMI, there are numerous debates (108,109). Some studies indicate a disadvantage for women in the context of STEMI (110,111). Others show comparable outcome profiles for men and women (112). However, the majority of these studies focused solely on clinical covariates, which should be interpreted with caution given that therapeutic interventions have a large impact on outcomes (113,114). According to Bugiardini et al. (115), the gender disparity in mortality after STEMI persists and appears to be driven by prehospital delays in hospital presentation. Women appear to be more susceptible to untreated ischemia over longer time periods.

6.2. Patients with acute coronary syndrome treated at the University Clinical Center of Kosovo for the analyzed period by groups

According to the American Heart Association, the best option in the event of a suspected ACS event is to call the mobile emergency medical service (EMS) (116). This recommendation is based on the possibility of safer transportation and shorter time-to-treatment intervals. Despite guidelines, the majority of patients with symptoms suggestive of an acute coronary syndrome do not use emergency medical services to reach the emergency department (ED), (75) In LMICs, ambulance and emergency medical services (EMS) are underdeveloped, particularly outside of large urban areas. Typically, patients experiencing ACS symptoms will use available public transportation and private cars to get around (117,118). In large urban cities where EMS is more fully developed and available, it has contributed to significant improvements in the timely management of patients with an ACS, but it is estimated that only 5% of patients use these services (119, 120). In our study, only 11.3% of patients received pre-hospital emergency care, with females receiving 13.4% and males receiving 10.2%. Emergency Medical Services were utilized by 53.4% of MI patients in developed countries such as the United States (24).

From 2010 to 2019, Valent et al. (121) examined EMS use by patients with AMI, factors associated with EMS use, and outcomes in 14,900 AMI patients in the Italian region of Friuli Venezia Giulia. Only half of the people used EMS, and there were no changes over time. Patients transported by EMS had a higher mortality rate, most likely due to residual confounding from AMI severity (121).

So et al. (122) compare patients who arrived via EMS to those who arrived via self-transport. Among the 401 patients, 59.9% arrived via EMS and 40.1% via self-transport. Patients who arrived by EMS were older (p 0.001) and had higher Killip's scores (p 0.001). Patients who arrived via EMS had shorter door-to-needle and door-to-balloon intervals (42 vs 57 minutes, p 0.001, and 124 vs 154 minutes, p 0.001, respectively). In-hospital mortality was higher in patients who used EMS (13.3% vs 5.0%, p 0.001). Patients who arrived by EMS also had a higher mortality rate within the first hour (4.2% vs 0%, p = 0.007). Only age and systolic blood pressure were found to be predictors of mortality in a multivariate analysis. Despite the fact that patients who arrived by EMS received reperfusion therapy sooner, mortality was higher. Almost 33% of these deaths occurred during the early in-hospital period, owing to the tendency of older and sicker patients to arrive via EMS.

Boothroyd et al. (123) conducted a study that included 82 acute care hospitals in Quebec (Canada) that treated 1,956 patients, 1,222 (62.5%) of whom arrived by ambulance. Users of an ambulance were older, more often women, and more likely to have co-morbidities, low systolic pressure, an abnormal heart rate, and a higher Thrombolysis in Myocardial Infarction risk index at presentation when compared to non-users. Ambulance users were less likely than nonusers to receive fibrinolysis or be sent for primary angioplasty (78.5% vs 83.2%, p = 0.01), but if they did, treatment delays were shorter (p 0.001). The 1-year mortality rate for users was 18.7% compared to 7.1% for nonusers (p 0.001). STEMI ambulance users were older and sicker than nonusers. After adjusting for clinical risk factors, user mortality was significantly higher, despite receiving faster reperfusion treatment overall.

Sepehrvand et al. (80) included all patients who presented to an ED in the metropolitan areas of Edmonton and Calgary between 2007-2013 with the primary ED diagnosis of acute coronary syndrome, stable angina, or chest pain. EMS used 30.5% of the 50,881 patients. Patients who were older, female, had an acute coronary syndrome diagnosis in the ED, had more comorbidities, and had a lower household income were more likely to use EMS to get to the hospital. Longer travel distance was associated with greater use of EMS, but it was not a predictor of clinical events.

Kodama et al. (124) analyzed 1,172 STEMI patients from the AMI Kyoto Registry who underwent PPCI between January 2009 and December 2013. The self-transport group (n=368) was younger and had a significantly longer DBT (115 min vs. 90 min, P0.01) than the EMS group (n=804), with fewer patients having a Killip classification of 2 or higher. The self-transport group had a lower in-hospital mortality rate than the EMS group (3.3% vs. 7.1%, P0.01). In EMS patients, a DBT of more than 90 minutes was an independent predictor of in-hospital mortality, but not in self-transport patients (118). The same findings were found in a prospective observational study of all patients who presented to the ED of Basel University Hospital (125).

According to a study conducted by the Medical Center University of Alabama (126), in-hospital mortality was 8% in patients with a pre-hospital ECG and 12% in those without (p 0.001). In our study, the PHE group had a higher in-hospital mortality rate (28.8%) than the control group (7.9%). This can be explained by the fact that the usage of pre-emergency services was very scarce (11.3%) and they were only used for patients with a more severe health condition. The self-transport patients with STEMI have the prolonged treatment periods compared to the EMS-transported patients (127).

A substantial part of ACS mortality occurs during the first hours of symptoms (128). Furthermore, timely diagnosis and treatment have an impact on the occurrence of long-term fatal (129) and non-fatal (130) complications. In the emergency department, timely prescription may also be a sign of adequate monitoring and quick decision-making. Exploring bottlenecks in early medication use is important in this regard, as it may reveal alternative options in the ACS patient care system. The majority of evidence for factors influencing time to treatment is based on data on aspirin administration (131) and, in STEMI patients, thrombolytic treatment (9) or revascularization procedures (132).

Thuresson et al. (133) found that half of the patients went to the hospital by ambulance. Factors associated with ambulance use were knowledge of the importance of quickly seeking medical care and calling for an ambulance when having chest pain, abrupt onset of pain reaching maximum intensity within minutes, nausea or cold sweat, vertigo or near syncope, ST-elevation ACS, increasing age (per year), previous history of heart failure, and distance to the hospital of >5 km. Those who did not call for an ambulance thought self-transport would be faster or did not believe they were sick enough.

Ma et al. (134) found that only 21.6% patients with ACS chose taking ambulance to hospital. Factors associated with ambulance use were single, taking Suxiaojiuxin pills or nitrates before going to hospital, diagnosed as STEMI, with persistent symptoms and symptoms accompanied with vomiting.

EMS transport to hospital is recommended in acute coronary syndrome (ACS) guidelines, but Cartledge et al. (135) found in the study with patients admitted to an Australian tertiary hospital with a diagnosis of ACS only 54% of them used EMS for transport to hospital. A large proportion of patients (43%) using other transport thought it would be faster. In this study, factors associated with EMS use for ACS were: age >65 years, ST-elevation myocardial infarction, a sudden onset of pain and experiencing vomiting.

Studies (136) suggest that patients who got to the hospital by ambulance present a shorter door-to-needle time. In the study of Muller et al (137), 28.1% of the patients got to the hospital by ambulance, but the total time taken to start the therapy was not reduced (P=0.81). Studies have shown a reduction in mortality after thrombolytic therapy in patients that received pre-hospital care (8% *versus* 13%) (P = 0.04), (14, 138)

According to studies conducted in various parts of the world (139-143), a significant proportion of patients with ACS do not use EMS, with the percentage ranging from 4.5% to 50.4% and the social demographics such as old age (22, 23, 142) and female sex (23) as well as a history of heart disease (23, 143, 144), hemodynamic complications (22) and living far from the hospital (22, 143) were associated with increased ambulance use. Several studies have documented that delays can occur from different sources, including patients and providers and the healthcare system itself (145,146).

Previous research has found that patients who arrived by ambulance with a STEMI had a two-fold higher in-hospital mortality rate than self-presenters, highlighting the fact that the sickest patients are more likely to use EMS. EMS use is supported by practice guidelines and consensus documents (147, 148), and it has been shown to reduce time to treatment and improve survival in STEMI patients (149–152) As a result, we do not believe that the medical community should change the value of the EMS in caring for patients with CP.

According to the standard guidelines, an ECG should be obtained within the first 10 minutes of arrival at the hospital in patients suspected of having acute coronary syndrome, and the ideal door to needle time should be less than 30 minutes (153). The average door to needle time in our study was 34 ± 24 minutes, and the average door to ECG time was 16 minutes, both of which were longer than the recommended guidelines. In a study by Mohannan et al. (154), less than one-third of STEMI patients who received thrombolysis had door-to-needle times longer than 30 minutes. Door-to-needle time of less than 30 minutes was associated with lower in-hospital mortality (154). Indoor admittance delays (time delays in OPD/IPD registration), indoor transport delays (lack of personnel, insufficient transportation carrier), and indoor ECG recording and interpretation delays are regarded to be the most likely reasons of these indoor delays. This indoor time delay can be shortened by commencing thrombolytic treatment in the emergency department or in pre-hospital cardiac ambulances. The widespread availability of cardiac ambulances outfitted with trained doctors and facilities for capturing and electronically transmitting ECGs to an experienced Cardiologist/physician, as is done routinely in numerous countries, can be a valuable strategy to achieve reduced ischemia periods. However, major management guidelines (117,155) emphasize the need of early detection and treatment as a helpful method for lowering the risk of mortality associated with an untreated ACS incident. Time to treatment may be a valuable measure of the quality of care provided during an ACS episode in this scenario.

The success of this treatment is contingent on providing thrombolysis as soon as symptoms occur, and the time it takes the patient to decide that their symptoms require medical attention is the main reason of delay in patients arriving at the hospital after MI. Although it is advised that the time from the onset of pain to hospitalization be shorter than 90 minutes, urban patients admitted for MI in Central Dalmatia required a median of 2 hours after the onset of pain to call the emergency, and the total pre-hospital delay was 4.3 hours (156).

The reperfusion time of STEMI patients in China is evidently delayed when compared to the time required by the guidelines. (157). Provincial and municipal hospitals had door-to-balloon times of 172±13 and 251±14 minutes, respectively, for patients undergoing primary percutaneous coronary intervention. In patients receiving thrombolysis treatment, the door-to-needle times of provincial hospitals, municipal hospitals and country hospitals were 86±7, 91±7 and 123±11 minutes, respectively.

In recent years, enormous progress has been made in treating acute coronary syndrome (ACS) and shortening the time between the onset of pain and intervention. However, the time between the onset of pain and the request for assistance is still far too long.

According to a study conducted by the Institute of Cardiology in Warszawa (158), the time between the onset of symptoms and the call for medical assistance ranged from 4 to 1140 minutes. Patients aged 56-70 years experienced the longest delay. Half of them requested assistance after 3 hours. Women waited longer than men. They also waited 20 minutes longer for an ambulance (p 0.01). The main reasons for the delay were: being confident that the symptoms would go away (201 patients - 57.6%) or believing that the symptoms were not related to heart disease (45 patients - 12.9%).

The only component of the pre-hospital delay that is entirely dependent on patients rather than the health-care system is the pain-to-call time. Dalmatia's median pain-to-call time was 2 hours in 2005, and it remained constant in 2010-2011 (156). This means that residents of Central Dalmatia wait far too long before calling for assistance, wasting valuable time required for optimal reperfusion. Improvements in the health-care system are not accompanied by increased patient awareness of AMI symptoms. According to a recent study, up to half of coronary patients are not taught how to respond to heart attack symptoms (159).

Most of the patients in this study were treated with conservative therapy due to a late arrival of patients into the hospital. Reperfusion treatment (whether PCI or fibrinolysis) is most successful when performed within the 1st hour from the onset of pain, but in the studied cohort only 5.7% of patients arrived at the hospital within 90 minutes from the onset of pain.

Coronary heart disease is the leading cause of morbidity and mortality in both men and women in the United States. Despite dramatic changes in the management of patients hospitalized with acute myocardial infarction over the last several decades, a significant proportion of AMI patients continue to delay seeking medical care. A systematic review of the literature from 1960 to 2008 was conducted, including publications that provided data on the duration of prehospital delay in AMI patients hospitalized. The current study included 44

articles (42 studies) in total (160). When compared to other groups, the elderly and women were more likely to delay seeking medical care after developing symptoms suggestive of AMI. More research is required to fully understand the causes of delay in these vulnerable groups.
In the Rucker et al (161) study, 32% of patients who completed the survey reported a delay in seeking ED care. 71% of patients who reported a delay believed their problem would go away or was not serious. Patients who were older, had higher acuity, or used the ED frequently reported less delay, whereas patients without a regular physician or who were African American reported more delay. Frequent ED users and those with lower baseline physical function reported an increased number of days ill prior to visiting the ED, whereas patients with higher acuity reported fewer days ill prior to visiting the ED.

Ting et al. (162) discovered that longer time to treatment, as measured by door-to-balloon or door-to-needle time, was linked to higher in-hospital mortality rates.
Primary PCI has emerged as an effective treatment strategy for acute STEMI; however, patient survival and outcome are dependent on the time to treatment. The international standard for all programs dealing with STEMI patients with acute coronary syndrome has been established as 90 minutes or less from the time the patient arrives at the hospital to the opening of the affected vessel in the cardiac catheterization laboratory, known as "door-to-balloon time" or D2B. During the year 2014, the STEMI, D2B time of 90 minutes was attained in 25% of patients at the King Faisal Cardiac Center (one of the key centers that conduct primary PCI as treatment for STEMI in Jeddah, Saudi Arabia). Several reasons have contributed to the delays in meeting the objective level of more than 90%, including late diagnosis of STEMI patients, delays in acquiring the ECG, activation of the catheterization laboratory, and patient transportation delays (163).

Wilson et al. (164) compared 101 STEMI patients transported in 2007 to 442 STEMI patients transferred after launching these STEMI initiatives from 2008 to 2011, with the median door-in-to-door-out time decreasing from 44 to 35 minutes, the median first D2B decreasing from 109.5 to 88.0 minutes, and the percentage under 90 minutes increasing from 22.8% to 55.9%. Overall, transport durations remained stable (median 36.5 vs. 36.0 min) from 2007 to 2011, whereas PCI hospital D2B fell from 20.0 to 16.0 min. The average length of stay was 3.0 days, and the in-hospital death rate was less than 4%. Significant developments in STEMI workflow over the last decade have led in most hospitals reporting door-to-balloon (D2B) timings within the 90-minute norm (165). For STEMI, the In-House Interventional Team Program (IHIT) might achieve D2B times of less than 60 minutes. The availability of a 24-hour STEMI team in-house considerably reduced reperfusion time, resulting in improved clinical outcomes and a shorter duration of stay for PCI-treated STEMI patients. If performed promptly, primary percutaneous coronary intervention for STEMI is favorable. Individuals who self-transport with STEMI have longer treatment periods than patients who are transferred by Emergency Medical Services. Shavelle et al. (127) compared patients with D2B times greater than 90 minutes to those with D2B times less than 90 minutes. Using logistic generalized estimating equations, the factors associated with extended D2B (>90 minutes) were investigated. Off-hour presentation (weekends and 7 p.m. to 7 a.m. weekdays), failure to obtain an electrocardiogram within 10 minutes of hospital arrival, previous coronary artery bypass surgery, black race, older age, and female gender were the key characteristics related with longer treatment time. In conclusion, while delayed arrival to electrocardiographic acquisition is a modifiable factor contributing to prolonged D2B times among self-transport STEMI patients, other factors (age, race, and gender) indicate that historic disparities in cardiovascular care persist in terms of contemporary metrics for STEMI reperfusion.

Chen et al. (166) investigated the connection between delayed coronary care unit (CCU) admission and clinical outcomes in patients with ACS with non-ST-segment elevation (NSTE-ACS). Patients were separated into two groups based on their CCU wait duration (12h and >12h). There were no significant differences in in-hospital mortality, stoke incidence, or hospital stay duration across groups.

In their investigation, Bugiardini et al. (167) discovered that in patients with ACSs, earlier administration of oral blocker medication should be prioritized with a higher possibility of improving LV function and in-hospital survival rate. This early treatment regimen should be avoided in patients who present with acute pulmonary edema or cardiogenic shock.

In another study by Heitzler et al. (168), 1190 acute STEMI patients treated with primary PCI were studied prospectively in eight locations across Croatia (677 non-transferred, 513 transferred). All patients were divided according to door-to-balloon time in three subgroups (< 90, 90-180, and > 180 minutes) and according to symptom onset-to-balloon time in three subgroups (<180, 180-360, and > 360 minutes). Considering the symptom onset-to-balloon time subgroups, a statistically significant difference at multivariate level was highest for in-hospital mortality in the subgroup of patients with longest onset-to-balloon time (4.5 vs. 2.6 vs. 5.7%). Door-to-balloon time is one of the indicators of primary PCI network organization quality and targets for quality improvement, however it has little effect on early and six-month follow-up results of therapy for acute STEMI. The symptom onset-to-balloon time is more accurate for this purpose; however, reducing the latter is more complex than reducing the former.

Out of 1386 patients with STEMI, delayed presentation was seen in 1148 (> 2 hrs) and 805 (> 4 hrs) patients. The duration from onset of symptoms to the presentation in the emergency room (pre-hospital delay) was 228 ± 341 minutes. The door to needle time was 34 ± 24 minutes. The major factors for pre-hospital delay were misinterpretation of symptoms (45%) and transportation problems (27%), (169).

In a study of 6704 consecutive patients with ACS from Middle Eastern nations, 61% had NSTEACS and 39% had STEMI). Female gender, advanced age, diabetes, hypertension, dyslipidemia, and obesity were more common in NSTEACS patients. Prior to the index admission, STEMI patients were more likely to be smokers and less likely to be taking aspirin. CRF and diabetes were independent predictors of in-hospital cardiac failure in NSTEACS, whereas CRF and hypertension were predictors of STEMI. Female gender and CRF were both independent predictors of mortality in STEMI patients (170).

The rise in CVD burden is mostly due to an increase in the incidence of risk factors as well as a relative lack of access to well-recognized therapies that prolong survival once CVD has occurred. Risk factors (hypertension, diabetes, obesity) are more prevalent. Patients with AMI in Kosovo are younger than those in other developed countries. In our analysis, smoking was related with a decreased risk of death in ACS, owing to smokers' younger age and less severe CAD. Similar data was discovered, as well as other authors (171-173).

Obesity at the time of ACS manifestation is related with a decreased in-hospital death rate. The "obesity paradox" may be due to younger age at presentation, earlier referral for angiography, and more aggressive care of ACS. The established CVD risk factors, such as high blood pressure, an abnormal blood lipid profile, diabetes mellitus, obesity, and smoking, have been addressed in recommendations and guidelines for at least a half-century. These well-known risk factors account for 80% of the ischemic heart disease burden (174).
Increased population aging and rising rates of several cardiovascular risk factors, such as obesity (175) and diabetes (176), have contributed to an increase in the number of people who have had an ACS event in recent decades.

The CroHort study published in 2012 highlighted trends in behavioral and biological CVD risk factors in Croatia, demonstrating that smoking and alcohol intake in men declined dramatically compared to 2008, whereas alcohol consumption, obesity, and hypertension in both sexes increased significantly (177). The study's negative findings indicate that more attention should be paid to CVD risk factors and CVD prevention.

According to the Euro Heart Survey, the majority of patients diagnosed with CAD, including ACS, have impaired glucose regulation (178), and two prior investigations that included previously healthy persons found that IGT increases the risk of CVD and death (179, 180).

AlHabib et al. (181) examined data from a cohort analysis of 7,930 post-ACS patients from six Middle Eastern nations and discovered that 50.1% had central obesity, 39.5% had diabetes, 47.2% had hypertension, 32.7% had hyperlipidemia, and 35.7% were current smokers.

There is currently no cardiac-specific serum marker that fits all of the criteria for a "ideal" AMI marker. No test is both highly sensitive and highly specific for acute infarction within 6 hours of the beginning of chest pain, which is the timeframe most emergency physicians consider when making diagnostic and therapeutic decisions. Patients presenting to the ED with chest pain or other symptoms suggestive of acute cardiac ischemia cannot therefore rule out AMI based on a single cardiac marker value obtained within a few hours after symptom onset (136).

Tsai et al. (182) found that overall, ED concordance with guideline-recommended processes of care was low to moderate in their evaluation of quality of care for acute myocardial infarction in 58 U.S. emergency departments. Buclin et al. (183) and Tanzi et al. (184) discovered that the emergency medical team's diagnosis was adequate in 91% of cases, resulting in a 5% rate of unnecessary admissions to the critical care unit. Schewe et al. (185) assess the diagnostic accuracy of physician-staffed emergency medical teams (PEMTs) outside of the hospital. After matching the prehospital diagnosis with the appropriate hospital diagnosis, the overall diagnostic accuracy (correct or false) of PEMTs was assessed. PEMTs' overall diagnosis accuracy increased from 87.5% in 2004 to 92.6% in 2014. According to data from a Canadian study, 4.6% of patients with acute myocardial infarction and 6.4% of patients with unstable angina were misdiagnosed (186).

Gilutz et al. (187) investigated adherence to guidelines for NSTEMI in the ED and discovered a lack of timely detection and early medical treatment of NSTEMI in the ED. Better computerized medical history collection, attention to normal and atypical clinical presentation, and use of an appropriate cardiologic risk stratification tool may help to unblind treating teams at the point of treatment and enhance adherence to NSTEMI recommendations.

Percutaneous coronary intervention (PCI) within 120 minutes of commencement is indicated for patients with acute coronary syndrome (ACS). A helicopter emergency medical service (HEMS) can deliver ACS patients. Homma et al. (188) discovered that while HEMS reduced transport time when compared to ground emergency medical services, it did not contribute to PCI access within 120 minutes. The most critical component was direct transport to a PCI hospital (P.01).

6. 3. Patients with acute coronary syndrome treated at the University Clinical Center of Kosova for the analyzed period by types of acute coronary syndrome

Several investigations (189-191) showed significant variations in the incidence of heart failure and mortality among STEMI, NSTEMI, and UA patients. Kaul et al. (189) discovered that the incidence of heart failure and mortality differs significantly across STEMI, NSTEMI, and UA patients. Piva e Mattos et al. (190) examined data from the Acute Coronary Care Evaluation of Practice Registry (ACCEPT study), a multicenter post-ACS Brazilian study with 2,485 patients between August 2010 and December 2011, and discovered 30-day mortality rates of 1.8% in patients with UA, 3.0% in NSTEMI patients, and 3.4% in STEMI patients. From 2.485 individuals, 31.6% had unstable angina, 34.9% had acute coronary syndrome without and 33.4% had acute coronary syndrome with ST-segment elevation. At 30 days, cardiac mortality was 1.0% vs. 2.3% in patients with UA (p = 0.268), 1.9% vs. 4.2% (p = 0.070) in patients with NSTEMI, and 2.0% vs. 8.1% (p = 0.001) in patients with ST-segment elevation.

Santos et al. (191) found an overall one-year case-fatality rate of 12.0% for patients hospitalized to a community hospital with a diagnosis of ACS in their ERICO research. When the results were stratified by ACS type, there was a substantial difference in the death rate (5.4%, 9.6%, and 19.2% for patients with UA, STEMI, and NSTEMI diagnoses, respectively). A study of 1,027 patients with NSTEMI from a single tertiary cardiology clinic in So Paulo (191) discovered that 5.3% died or had a second infarction within 30 days.

According to a study conducted in the city of Zagreb in 2009 (192) that included patients with the diagnosis of ACS, intrahospital mortality was 14% and 22% died outside of the hospital. There were 56% of patients with STEMI, 34% with NSTEMI, and 10% with probable MI and MI with unclear ECG. The time from onset of symptoms to hospital attendance was less than 6 hours in 49.8% of patients, 6 to 12 hours in 13.8%, and more than 12 hours in 36.1%. In 19.0% of patients, the beginning of symptoms was uncertain. In 41% of patients, angiography and reperfusion therapy were performed; PCI/PCI + stent in 33% of males with ST or non-ST segment elevation, and 25% of women with ST segment elevation and 19% of women with non-ST segment elevation. Fibrinolytic therapy was administered to 86 patients, 53 (7%) of whom were men and 30 (5%) of whom were women. Aspirin was taken by 85% of ACS patients (N=966), beta-blockers by 70%, angiotensin-converting enzyme inhibitors by 69%, and statins by 63%.

In the study of Novak et al. (107) women were significantly older compared to men (71 ± 11 years vs. 64 ± 12 years, $p < 0.001$) and had higher in-hospital mortality and complications due to this age difference. In women, regardless of age, smoking was less common, whereas hypertension and a history of angina pectoris were more common. PTCA with or without stenting, as well as coronary catheterization, significantly reduced in-hospital mortality and sequelae, but thrombolytic treatment was linked with a 3.3 times greater mortality odds ratio (OR, $p = 0.01$). Other significant predictors of in-hospital mortality were in-hospital complications (OR 25, $p < 0.001$) and ST segment elevation myocardial infarction (STEMI, OR 4.5, $p < 0.001$).

Bugiardini et al. (2) examine the results of coronary reperfusion treatments and ST-segment elevation myocardial infarction (STEMI) in patients from Eastern nations with transitional economies. From January 1st to December 31st, 2009, there were 23,486 consecutive patients admitted to hospitals. In Western countries, in-hospital mortality was between 4% and 5%. Mortality rates were much higher in Serbia (10.8%) and Bosnia and Herzegovina (11.2%), intermediate in the Russian Federation (7.2%), and similar in Hungary (5.0%). Primary percutaneous coronary intervention (primary PCI) rates in Bosnia and Herzegovina were very low (18.3%), low in the Russian Federation (20.6%) and Serbia (22%), and high in Hungary (70%).

Aune et al. (193) reported a 16% one-year mortality rate in 307 post-MI patients treated in a non-tertiary hospital in Norway following the establishment of a reference system for invasive cardiac treatments in a cardiology referral center.

Data from the Australian and New Zealand SNAPSHOT ACS research (194) demonstrate that STEMI (16.2%) and non-STEMI (16.3%) patients had the highest all-cause mortality after 18 months, while those with unstable angina (6.8%) and non-cardiac chest pain (4.8%; P 0.0001 for trend).

Other researchers looked into post-ACS mortality as well. The Swedish Register of Cardiac Intensive Care was prospective observational research conducted in 58 Swedish hospitals' coronary care units from 1995 to 1998. Stenestrand et al. (195) discovered a one-year post-MI mortality rate of 7.8% in a cohort study with 19,599 participants. The usage of statins affected death rates. The unadjusted mortality rate in the no-statin group was 9.3%, while it was 4.0% in the statin treatment group.

Other researchers investigated post-ACS mortality as well. The Swedish Register of Cardiac Intensive Care was prospective observational research conducted in coronary care units at 58 Swedish hospitals from 1995 to 1998. Stenestrand et al. (195) discovered a 7.8% one-year post-MI mortality rate in their cohort analysis of 19,599 patients. The usage of statins had an effect on mortality rates. Unadjusted mortality was 9.3% in the no-statin group and 4.0% in the statin treatment group.

Skelding et al. (196) discovered a one-year mortality rate of 8% in 2,066 patients who received invasive examination after reviewing observational data from a single tertiary institution in Pennsylvania.

Similarly, Kleopatra et al. (197) examined data from 1,986 women with NSTEMI in 155 hospitals from the German Acute Coronary Syndromes registry between June 2000 and November 2002 and divided them into two groups: 1215 (61.2%) received coronary angiography, while 771 (38.8%) received conservative treatment. One-year death rates were 8.1% in those who underwent invasive stratification and 24.0% in those who did not, with in-hospital mortality rates of 3.2% vs. 10.5%.

Ruano-Ravina et al. (198) recently discovered a one-year mortality rate of 9.3% and a 30-day mortality rate of 6.8% in a sample of 1,461 people presenting with STEMI who received primary angioplasty in two hospitals in Spain.

Potočnjak et al. (199) discovered that the most common cause of acute heart failure was worsening of chronic heart failure in their prospective observational analysis at the University Hospital Center Emergency department in 2010. Females were more likely to suffer from hypertensive acute heart failure, while males were more likely to suffer from acute heart failure associated with acute coronary syndrome. Females were older, had a higher BMI, atrial fibrillation, urinary tract infections, a history of hypertension, hypertension upon admission, and a SAPS II score at admission. Males had a greater rate of ST-elevation myocardial infarction and dilated cardiomyopathy, as evidenced by lower ejection fraction and left ventricular dilatation with reduced ejection fraction on ultrasonography. Male smokers with a history of chronic obstructive pulmonary disease were more common.

Older age, past atheromatous cardiovascular disease, diabetes, smoking, hypertension, hypercholesterolemia, male sex, and a family history of early ischemic heart disease are all risk factors for ACS. ACS can occur in the presence of valvular disease, arrhythmias, and cardiomyopathies. Between 9% and 19% of people with ACS die within the first 6 months of being diagnosed, with around half dying within 30 days (99).
CVD was the top cause of death in Croatia in 2017, accounting for 44.0% of all deaths in both men and women (200).

In the study of Pocock et al. (201) within two years of discharge 5.5% of patients died. The 17independent mortality predictors were: age, low ejection fraction, no coronary revascularization/thrombolysis, elevated serum creatinine, poor EQ-5D score, low hemoglobin, previous cardiac or chronic obstructive pulmonary disease, elevated blood glucose, on diuretics or an aldosterone inhibitor at discharge, male sex, low educational level, in-hospital cardiac complications, low body mass index, ST-segment elevation myocardial infarction diagnosis, and Killip class.

In the study of McNamara et al. (202) the in-hospital mortality rate was 4.6%. Age, heart rate, systolic blood pressure, presentation after cardiac arrest, presentation in cardiogenic shock, presentation in heart failure, presentation with ST-segment elevation myocardial infarction, creatinine clearance, and troponin ratio were all independently associated with in-hospital mortality. Observed mortality rates varied substantially across risk groups, ranging from 0.4% in the lowest risk group (score <30) to 49.5% in the highest risk group (score >59).

7. CONCLUSIONS

The results of our research do not confirm our hypothesis that the use of pre-hospital emergency care will improve prognosis of patients admitted to hospital with acute myocardial infarction. The mortality rate was higher in PHE patients 28.8% compared to that of the control group 7.9% OR 3.534 (95% CI 2.652 - 4.709), with significant statistical difference (P = 0.000). This high mortality rate of patients who have been using pre-emergency services can be explained by the fact that:

1. They were more often STEMI patients, older than patients of control group, 40.0% who were 70 years or older, were in higher risk for LVEF < 40% than Control group with significant difference.
2. Significant difference on Family history for cardiac event (PHE group 45.3% vs. Control group 33.2%), Cardiac event history (PHE group 41.2% vs. Control group 33.1%), comorbidity (PHE group 55.9% vs. Control group 42.2%), diabetes (PHE group 42.4% vs. Control group 29.1%), Ex-smoker ((PHE group 10.0% vs. Control group 7.0%).
3. Door-to-needle (67 vs. 135 min) and door-to-balloon (89 vs. 142 min) times were shorter in the PHE group.
4. Patients of PHE group on 47.6% of cases duration of symptoms from the onset of symptoms as reported by the patient and admission to the hospital were < 6 hours compared to Control group 32.8% with significant difference (P=0.004), PHE group were in higher risk for from the onset of symptoms as reported by the patient and admission to the hospital were < 6 hours than Control group OR 1.630 (95% CI 1.171 – 2.269).
5. Age, female sex, STEMI, NSTEMI, PHE treatment, diabetes, hyperlipidemia, smoking and low LVEF were significant risk factors for in-hospital mortality in patients admitted for ACS, in univariate Cox regression analysis.
6. Age, the presence of STEMI, the luck PHE treatment, diabetes mellitus, low LVEF and smoking remain independent predictors of mortality in patients admitted for ACS, in multivariate Cox regression analysis.

7. The Kaplan-Meier survival curve showed that STEMI patients had higher in-hospital mortality rate compared with patients that were admitted for ACS and had NSTEMI or UA.
8. With Log rank test was found significant difference on in- hospital mortality between STEMI and NSTEMI patient ($P < 0.001$), STEMI and UA patients ($P < 0.001$) and NTEMI and UA patients ($P < 0.001$).
9. After one year patient are called by phone mortality rate from admission to 12 month was 19.4 %.
10. Of the 499 patients with ST elevation/de novo LBBB, 331 underwent thrombolysis and the other 168 primary angioplasty, but only 65 has done angioplasty in UCCK other go to private institutions.
11. In-hospital mortality of patients admitted with ACS in Kosovo remains high, compared with developed countries.
12. The luck of pre-hospital emergency treatment, in addition to the old age, diabetes, STEMI type and compromised LV systolic function, was shown independent predictor of in-hospital mortality in ACS patients.
13. Major risk factors for death appear to be lack of reperfusion therapy, longer time delay from symptoms onset to hospital presentation as well as the higher percentage of patients with clinical presentation STEMI.
14. The usage of ambulance in patients with ACS presenting to the ED was low in Kosova.

Proposed measures

We believe that the findings of this survey will help the policymakers in developing policy and programs on reducing the mortality rates of patients with ACS, especially by developing a better strategy for the pre-hospital emergency in Kosovo.

The following initiatives need to addressee: established hospital referral system, goal-oriented performance protocols, expedited transport by ground or air, first hospital activation of the

PCI hospital catheterization laboratory and outreach coordinator and patient-level web-based feedback to the referring hospital; institutional measures should be taken to reduce door-to-needle time and improve patients' life expectancy, such as implementing health care protocols for patients with chest pain and administering thrombolytics in the emergency department.

- Future education programs should focus on these factors and increase people's knowledge on ACS and the benefits of ambulance use. The fact that knowledge increases ambulance use and the need for behavioral change pose a challenge for health-care professionals. Public and targeted campaigns on primary prevention are urgently needed and could potentially lower morbidity and mortality rates due to ACS. Regular training of EMS personnel and public campaigns should be implemented to improve the diagnostic accuracy in the future.
- There is a urgent need to establish both an emergency medical system infrastructure and health coverage for life-saving treatments in order to improve the morbidity and mortality associated with ACS
- Training of multi-disciplinary emergency medical personnel in community hospitals and primary care settings on diagnostic procedures is a vital step.
- Emergency physicians should continue to work with other stakeholders in AMI care, such as emergency medical services (EMS) and cardiologists, to develop strategies to improve care processes.
- Lack of an organized health care system often delays transfer of ACS patients to cardiac intervention facilities. A country-wide or regional referral plan is urgently needed to insure timely transfer of patients from non-cardiac centers to interventional facilities.
- Public campaigns and screenings to increase awareness of hypertension, diabetes and other cardiovascular risk factors may potentially improve morbidity and mortality rates
- A major challenge for improvement of the care and outcome of STEMI patients in Europe is the lack of accurate and comprehensive data. The availability of complete reperfusion data and patient outcome is a prerequisite to address the full diversity of access to treatment in order to improve treatment availability and outcomes for STEMI

patients in the future. Systematic use of large data-based registries on STEMI treatment is highly needed. Also, the establishment of key indicators underpinned by key items of data with data definitions and clear analytical steps as used in other organizations might be helpful.

- Increasing national educational campaigns to improve knowledge about typical and atypical ACS symptoms and the importance of seeking early treatment is central for reducing the high morbidity and mortality in LMICs.
- Improving Red Crescent infrastructure, establishing integrated STEMI networks, and launching educational public campaigns are top health care system priorities.

8. ABSTRACT IN CROATIAN

Utjecaj izvanbolničke skrbi na ishod bolesti u bolesnika s akutnim koronarnim sindromom

Hitna medicina, djelatnost medicine koja je relativno nova čak i u najrazvijenijim društvima, u povojima je na Kosovu. Opći cilj ove studije bio je procijeniti utjecaj pred-bolničke i bolničke hitne skrbi na ishod bolesti u bolesnika koji su primljeni u bolnicu radi ACS. Ova opservacijska, prospektivna, klinička studija uključila je sve slučajeve bolesnika s ACS-om koji su primljeni u hitnu službu UCCK-a između 1. siječnja 2011. i 31. prosinca 2012. godine. U tom razdoblju bolnički je liječeno 1498 bolesnika s dijagnozom ACS, od čega su žene činile 36,4%, a 69,4 % bolesnika bilo je mlađe od 70 godina. Žene su bile 70 i više godina starosti u odnosu na muškarce (37,2% prema 26,9%; p=0,000). Klinička prezentacija nestabilnom anginom bila je u 22,6%, 33,3% STEMI i 44,1% NSTEMI bolesnika. U skupini PHE bilo je 170 ili 11,3% bolesnika. Žene su češće koristile PHE usluge u odnosu na muškarce (13,4% naprama 10,2%; p=0,063). Ukupna bolnička smrtnost za ACS bila je 10,3% sa statistički značajnom razlikom prema spolu (žene 12,5%, muškarci 9,0%; p=0,941). Bolesnici s ACS-om u 56,5% slučajeva bolovali su od arterijske hipertenzije, u 30,6% od šećerne bolesti, 10,2% bili su pretili i 36,2% bili su aktivni pušači. Stopa smrtnosti bila je veća u bolesnika s PHE 28,8% u odnosu na kontrolnu skupinu 7,9%; p=0,000. Ova visoka stopa smrtnosti bolesnika koji su koristili PHE uslugu može se objasniti činjenicom da su ti bolesnici češće imali STEMI i da su bili stariji od 70 godina.

Ključne riječi: ishod biolesti, akutni koronarni sindrom, pre-bolnička hitna skrb

9. ABSTRACT IN ENGLISH

The Impact of Pre-Hospital Emergency Care on Outcome in Patients with Acute Coronary Syndrome, Musli Gashi, 2023

Emergency medicine, a field relatively new to even the most developed societies, is in its infancy in Kosova. The general aim of the study was to evaluate the impact of pre-hospital and hospital emergency care in the prognosis of patients admitted to the hospital with ACS. This observational prospective clinical study has included all cases of ACS patients admitted to emergency department of UCCK between January 1, 2011 and December 31, 2012. During this period 1498 patients diagnosed as ACS, from which 36.4% were females. By age, 69.4% were younger than 70 years. In a higher percentage, females were 70 and older compared to males (37.2% vs 26.9%; p=0,000). 22.6% were diagnosed as UA, 33.3% as STEMI and 44.1% as NSTEMI. In PHE group were 170 or 11.3% of patients. Women often used PHE services compared to males (13.4% vs.10.2%; p=0,063). In hospital mortality rate for ACS was 10.3% with significant difference by gender (F 12.5% vs. M 9.0%; p=0,941). Patients with ACS in 56.5% of cases had hypertension, 30.6% diabetes, 10.2% Obese; 36.2% Current smokers. The mortality rate was higher in PHE patients 28.8% vs. control group 7.9%, with significant statistical difference (p=0,000). This high mortality rate of patients who have been using PHE services can be explained by the fact that they were more often STEMI patients, older than patients of control group, 40.0% who were 70 years or older.

Key words: outcome, acute coronary syndrome, pre-hospital emergency care

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11. CURRICULLUM VITAE

Musli (Mon) Gashi was born on June 5, 1968 in Osek Hyle – Gjakova, Republic of Kosova. In the school year 1987/88 he enrolled in Medical Faculty brunch general medicine at the University of Prishtina where he graduated on 02.02.1994. Immediately after graduating he worked as a physician at the humanitarian association “Mother Tereza” in Gjakova. On December 1, 1995 he started working as a school doctor in two primary schools in the municipality of Gjakova, where he worked until 01.10.1998. In 1998 he was accepted as assistant at the Faculty of Medicine in Prishtina in the field of Emergency Medicine where is still working. In 2004 he completed master's studies at the Medical Faculty University of Prishtina. In 2010 has enrolled in PhD studies program in English at the School of Medicine, University of Zagreb. Specialization in the field of Emergency Medicine has finished in 2007. During his specialization, he was trained by a team of professors and emergency medicine specialists from John Hopkins University in USA. From 2007 till now is working in Emergency Center in University Clinical Center of Kosova. He is the author and coauthor of several scientific and professional works. Is married, has a son. He lives in Prishtina.