MEDICAL UNIVERSITY – SOFIA

FACULTY OF MEDICINE - SOFIA

Department of Cardiovascular Surgery and Invasive Cardiology

Head of Department: Prof. Dimitar Petkov, MD, PhD, DSc

Acute Myocardial Infarction in Young Patients - Demographic, Risk, Clinical Profile, Angiographic Characteristics, and Prognosis. Comparative Analysis in Patients Below and Above 45 Years

Dr Iva Nikolaeva Dimitrova

Abstract

Dissertation work for the acquisition of the educational and scientific degree "PhD"
Scientific specialty - Cardiology

Scientific supervisor:

Prof. Diana Trendafilova-Lazarova, MD, PhD

Sofia, 2024

The dissertation is written on 222 pages, illustrated with 9 figures and 43 tables. The bibliography includes 240 literary sources, of which 7 are in Cyrillic.

The dissertation was approved and referred for defense by an extended Departmental Council of the Department of Cardiovascular Surgery and Invasive Cardiology at Medical University – Sofia and is directed for an official defense on 05.03.2024 in Aula "Prof. Dr. Alexandar Chirkov" of University Hospital 'St. Ekaterina' - Sofia; bul. Pencho Slaveikov 52A, before a Scientific Jury composed of:

1. **Prof. Julia Borisova Makedonska (Jorgova), MD, PhD- internal member for MU-Sofia,** a retired professor for less than five years from the academic staff of the Department of Cardiovascular Surgery and Invasive Cardiology at the Faculty of Medicine, MU- Sofia.
2. **Prof. Nikolay Margaritov Runev, MD, PhD- internal member for MU-Sofia,** Department of Propaedeutic of Internal Diseases, UMHAT 'Alexandrovska', at the Faculty of Medicine, MU-Sofia
3. **Prof. Maria Hristova Milanova, MD, PhD, DSc- external member for MU – Sofia,** UMHATEM "N.I. Pirogov"-Sofia
4. **Prof. Elina Baltadjieva Trendafilova, MD, PhD- external member for MU – Sofia,** National Heart Hospital, Sofia
5. **Prof. Mariya Petkova Tokmakova, MD, PhD - external member for MU – Sofia**, UMHAT "Sv. Georgi" MU- Plovdiv.

Reserve members:

1. Prof. Emil Ivanov Manov, MD, PhD- internal member for MU-Sofia, Department of Propaedeutic of Internal Diseases, UMHAT 'Alexandrovska', at the Faculty of Medicine, MU-Sofia
2. Assoc. Prof. Valery Liubenov Gelev, MD, PhD- external member for MU – Sofia, Acibadem City Clinic Tokuda Hospital-Sofia

The materials of this PhD thesis have been published online on the web page of the Medical University – Sofia.

Contents:

LIST OF ABBREVIATIONS:

ACS – acute coronary syndrome
AH – arterial hypertension
AMI – acute myocardial infarction
BMI - Body Mass Index
BMS - Bare Metal Stent
CABG - Coronary artery bypass grafting
CAD- coronary artery disease
CKD - chronic kidney disease -
CPK - Creatine phosphokinase
cTn - cardiac troponin
CV - cardiovascular
CVD - cardiovascular disease
DALY - Disability-Adjusted Life Year
DES - Drug-Eluting Stent
DM – diabetes mellitus
DVD- double vessel diseaseт
ECG- electrocardiogram
ESC - European Society of Cardiology
HDL - high-density lipoprotein
HF – heart failure
IHD- ischemic heart disease
IRA - infarct related artery
IVUS - Intravascular Ultrasound
LAD - Left anterior descending artery
LCX - left circumflex artery
LDL - low-density lipoprotein
LMA - left main artery
LVEF – left ventricular ejection fraction
MACE - Major adverse cardiovascular events
MR – mitral regurgitation
MVD - multi vessel disease
NOCD - nonobstructive coronary disease.
NSTEMI - Non-ST-Elevation Myocardial Infarction
OCT - optical coherence tomography
PAF - population attributable fractions
PCI - percutaneous coronary intervention
RCA - right coronary artery
RCT - randomized controlled trial
RF – risk factor
SCAD - Spontaneous Coronary Artery Dissection
STEMI - ST-Elevation Myocardial Infarction
SVD- single vessel disease
TC – total cholesterol
TIMI - Thrombolysis In Myocardial Infarction
TVR - target vessel revascularization
VF -ventricular fibrillation
VT - ventricular tachycardia

I. INTRODUCTION

Acute myocardial infarction (AMI) currently remains the leading cause of morbidity and mortality worldwide (Gao et al., 2021). Despite a decrease in the frequency of AMI among adults over the past decade, such a trend has not been observed among younger individuals (Gupta et al., 2014). AMI is a rare condition in young individuals, with a frequency ranging between 2 and 10%, depending on the age cutoff (Zimmerman et al., 1995; Fournier et al., 2004; Doughty et al., 2002). Recent studies have shown that the frequency of AMI is 12.9 and 38.2 per 1000 in men and 2.2 and 5.2 per 1000 in women in the age groups of 30–34 and 35–44 years, respectively (Lu et al., 2022).

Most studies use an age cutoff of 40 to 45 years to define "young" patients with coronary artery disease (CAD) or AMI (Gulati et al., 2020; Haider et al., 2023).

Several studies demonstrate that young patients with AMI have different characteristics concerning clinical presentation, risk profile, angiographic profile, and prognosis compared to adults (Rubin and Borden, 2012; Chen et al., 2014).

Young patients typically exhibit traditional risk factors (RFs) for ischemic heart disease (IHD) but also have a unique risk profile. Rubin and Borden (2012) suggested that young patients with cardiovascular diseases (CVD) are predominantly male, smokers, obese, and have a positive family history. Chen et al. (2013) emphasized the high frequency of dyslipidemia in patients under 45 years old with AMI. Despite the relatively favorable prognosis in young individuals, modifying RF is crucial. Treatment for young patients with AMI should be based on contemporary recommendations, including guideline-directed medical therapy and coronary revascularization, similar to treatment in older individuals (Gulati et al., 2020).

Atherosclerotic plaque rupture is the most common cause of AMI in young individuals. However, in these patients, non-traditional RF and etiologies, such as coronary anomalies, autoimmune and connective tissue disorders, coronary microvascular dysfunction, spontaneous coronary artery dissection and recreational drug-related coronary spasm are more common causes of AMI than in older adults (Gulati et al., 2020; Dimitrova and Trendafilova, 2023).

Due to a weaker suspicion of AMI and the occurrence of atypical symptoms in young individuals, there is a greater likelihood of delayed diagnosis of this condition in patients younger than 45 years (Safdar, 2019; Gulati et al., 2020). The classical presentation with accelerating angina preceding the infarct is less common in young patients. First angina symptoms usually rapidly progress to AMI in young adults (Egred et al., 2005). The left anterior descending artery (LAD) is the most commonly affected coronary artery, followed by the right coronary artery (RCA) and the left circumflex artery (LCX) (Haider et al., 2023).

Single-vessel disease (SVD) and less severe atherosclerotic involvement are the main angiographic findings in young patients (Zimmerman et al., 1995; Rosengren et al., 2006; Lei and Bin, 2019). There are hypotheses suggesting that premature coronary artery disease is associated with rapid disease progression (plaque rupture and/or erosion) rather than a gradual developing process, supported by histopathological findings revealing that atherosclerotic plaques in young patients with CAD exhibit lipid-rich cores and a relative lack of fibrous caps (Chen et al., 1995).

Despite recent improvements in the diagnosis and treatment of cardiovascular diseases (CVD) lately, they remain a leading cause of morbidity and mortality among young individuals globally (Roth et al., 2015). Currently, the majority of studies focus on older cohorts, with young patients often being excluded. This population remains underestimated and has a unique risk profile with fewer traditional cardiovascular risk factors than older patients with the same pathology (Gulati et al., 2020). Despite the relatively low incidence of AMI in young individuals and its relatively benign prognosis, the potential for a fatal outcome and long-term disability make it a clinically significant problem (Haider et al., 2023). On the other hand, AMI can cause significant socio-economic and psychological consequences for the patients and their families, as well as economic implications for the government.

Despite the favorable long-term prognosis of young patients with AMI compared to older individuals, they still remain at significantly higher risk of long-term mortality compared to an age- and gender-matched individuals in the general population (Jing et al., 2016). Furthermore, at long-term follow-up, there was no trend toward a decrease in mortality in young AMI patients over the years, which may largely be due to the fact that the benefits of advancements in treatment are attenuated by the worsening risk profile of these individuals (Khawaja et al., 2011). This is the reason for the growing clinical interest in AMI in young patients.

Challenges in young patients include atypical and delayed presentation, non-adherence to lifestyle modification recommendations, and non-compliance with prescribed therapy (Gulati et al., 2020). All these factors should be a focus in the treatment of AMI in young patients.

Within the literature, especially in Eastern Europe—a region with the highest age-standardized levels of Disability-Adjusted Life Years (the sum of years lost due to premature death and years lived with disability)- DALYs, attributed to ischemic heart disease (IHD) (Roth et al., 2021)—there is a scarcity of information regarding baseline characteristics, demographic profiles, risk factors, clinical presentations, angiographic findings, and in-hospital outcomes among young patients with AMI.

II. SUMMARY OF THE LITERATURE REVIEW

1. IHD accounts for 49.2% of deaths due to CVD. Over the past two decades, there has been a negative trend toward sustained or even increased incidence of CVD among patients aged 18 to 50 years, in contrast to the declining rates among those older than 50 years (Andersson and Vasan, 2017). The probable reasons include underrecognition and insufficient data regarding the prevalence of cardiovascular RFs in young individuals, leading to an underestimation of cardiovascular risk and, consequently, primary prevention measures (Dégano et al., 2015). There is a growing interest in the epidemiology, RFs, and prognosis of IHD, particularly AMI, in young patients due to the potential risks of mortality and disability during the prime of life, the psychological impact on the patient, as well as its effects on employability and subsequent socio-economic burdens on both the government and the patient's family.

2. There is no universal definition of 'young' regarding MI in the literature; 'young' is defined within an age range from <30 years to <55 years, with the most common cutoff being <40-45 years.

3. There are limited data regarding the frequency of MI in young individuals. The most commonly reported frequency of AMI in patients under 40 years old ranges

from 1 to 6% of all patients with this condition (Trzeciak et al., 2017). Concerning the male-to-female ratio, most authors unanimously report a male predominance among young patients with AMI (Gostman et al., 2004; Chaudhary et al., 2016; Goel et al., 2016). Eastern Europe represents a region with one of the highest DALYs, attributable to IHD, particularly AMI—as a comprehensive health measure, However, there is notably scarce of information regarding the specific profile of young patients with AMI in this region.

4. RFs play a significant role in the development and progression of CVD. This highlights the necessity of developing effective strategies to affect the main modifiable RFs in order to reduce the burden of these diseases. RFs in patients with myocardial MI of all ages are traditional IHD. Studies show that over 80–90% of young patients with MI have at least one cardiovascular RF before their MI, but differences in the risk profile between younger and older cohorts are observed (Wu et al., 2020). On the other hand, there is an increase in modifiable RFs among patients surviving MI at a young age. The highest rate of modifiable RFs in young patients was attributed to smoking, followed by dyslipidemia and arterial hypertension (AH) (Yandrapalli et al., 2019). The fact that a significant portion of CVD incidence is still attributable to modifiable RFs underscores the need for governments and health authorities to focus on primary and secondary prevention programs, population education, and the improvement of healthcare access.

5. Compared to the older population, ST-elevation myocardial infarction (STEMI) is more common in young patients than non-ST-elevation myocardial infarction (NSTEMI) (Schoenenberger et al., 2011; Puricel et al., 2013; Zasada et al., 2021). Anterior MI is more frequent in the younger population compared to older patients (Malik et al., 2016; Colkesen et al., 2008; Weinberger et al., 1987; Lv et al., 2021; Tambyah et al., 1996). According to literature data, a significantly higher frequency of left main coronary artery (LMA) involvement is observed in young patients with MI, while triple-vessel disease (TVD) is more common in older patients, with the left anterior descending artery (LAD) being the most affected artery in young patients (Klein et al., 1987; Malik et al., 2016; Sinha et al., 2017; Fennich et al., 2019; Lei et al., 2019; Lv et al., 2021). MINOCA (myocardial infarction with non-

obstructive coronary arteries) is detected in approximately 6% of MI patients and occurs more frequently in young patients, especially women (Pasupathy et al., 2015; Tamis-Holland and Jneid, 2018; Safdar et al., 2018).

6. Compared to older individuals, young patients with acute myocardial infarction (AMI) tend to have a relatively favorable in-hospital, one-year, and long-term prognosis (Hoit et al., 1986; Rosengren et al., 2006; Malik et al., 2016). Despite this benign prognosis, the social burden of CVD in this population is substantial, emphasizing the need for aggressive modification of RFs (Chen et al., 2014). Jing et al. (2016) noted that young patients with AMI are at a significantly greater risk of long-term mortality than is an age-matched general population.

III. AIM AND OBJECTIVES

AIM:

The AIM of the current study is to evaluate the initial characteristics, demographic profile, RFs, clinical features, angiographic findings, in-hospital outcomes, and short-term prognosis of young patients aged ≤45 years with AMI and compare these results with those of patients aged >45 years with AMI. The present study, based on the obtained results and analysis of significant differences, particularly in younger patients, defined their specific profile, identifying the significant predictors of disease outcome and directing attention to possibilities for improved prevention in patients aged ≤45 years with AMI.

OBJECTIVES:

1. Defining the baseline characteristics in both groups, predominant gender, assessing the characteristic risk profile in young patients, examining gender differences in RFs, and exploring the relationship between RFs and prognosis in patients aged ≤45 years with AMI compared to the older population.

2. Evaluation of the clinical presentation, presence of prior angina, time from symptom onset to initial medical contact in both genders, and Killip class at presentation in young versus older patients. Determining the significance of delayed presentation and high Killip class at admission for prognosis.

3. Establishing differences between the groups concerning the degree of left ventricular dysfunction, presence of mitral regurgitation (MR) ≥ 2 degrees, mean peak values of CPK, CPK-MB, cTn in young patients aged ≤45 years with AMI compared to the older population. Determining the influence of reduced ejection fraction for prognosis.

4. Determining the ratio of STEMI/NSTEMI, localization of MI, most common infarct-related artery (IRA), number of involved coronary arteries, presence of non-obstructive coronary disease (NOCD), average number of implanted stents, achieved TIMI III flow in the young group, and comparing these parameters with the older patients. Assessing the influence of localization of AMI and severity of atherosclerotic involvement for prognosis.

5. Determining the rate of in-hospital complications, average length of hospital stay, in-hospital mortality, as well as the frequency of major adverse cardiac events (MACE) at 1 and 2 years in young patients aged ≤45 with MI compared to the older population.

6. Determining the factors negatively impacting prognosis in young patients and subsequently defining high-risk groups to direct attention towards improving preventive programs, public awareness, access to healthcare, and enhancing clinicians' awareness for early recognition and more effective treatment in this specific population to reduce disability and premature cardiovascular disease-related mortality.

IV. MATERIALS AND METHODS

1. Material

1.1. Study population - defining the groups

In accordance with the aim and objectives of the current analysis, 172 patients admitted to the Cardiology Department of University Hospital for Active Treatment "St. Ekaterina"-Sofia during the period 2018-2021 with a diagnosis of acute AMI were included. Patients were divided into two age groups: Group 1, aged ≤ 45 years; and Group 2, aged > 45 years.

Group 1 include 61 consecutively hospitalized patients diagnosed with AMI (STEMI or NSTEMI) in the abovementioned period, between the ages of 18-45 years, inclusively, based on the inclusion and exclusion criteria.

Group 2 include 111 patients, aged over 45 years old, selected randomly using a web-based platform (Research Randomizer), who were hospitalized with a diagnosis of AMI (STEMI or NSTEMI) during the abovementioned period based on the inclusion and exclusion criteria.

Due to the lack of a universal definition of "young" concerning MI and considering that "young" individuals are classified within an age range from <30 years to <55 years, with the most common cutoff being <40-45 years, for the purposes of the present study, an age limit of ≤ 45 years was chosen to differentiate the two groups.

All 172 patients were hospitalized in the clinic with a diagnosis of MI according to the latest Expert Consensus Document from the European Society of Cardiology - the Fourth Universal Definition of Myocardial Infarction (2018):

Presence of acute myocardial injury with clinical data of acute myocardial ischemia and rise and/or fall of cardiac troponin (cTn) to at least one value above the 99th percentile upper reference limit (URL) and at least one of the following features:

- Symptoms of myocardial ischemia;
- New ischemic changes on ECG;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities consistent with ischemic etiology;
- Identification of coronary thrombus by angiography or autopsy (excluding Type 2 MI).

Patients with type 3, 4, or 5 MIs are not included in the study. The classification of patients into STEMI and NSTEMI categories was based on clinical and ECG criteria as defined in the latest guidelines by the European Society of Cardiology.

Patients with STEMI are defined as those experiencing ongoing chest discomfort or other corresponding symptoms suggestive of ischemia, along with detected ST-segment elevation in at least two contiguous leads on an ECG (Ibanez et al., 2018). ST-segment elevation is defined as a new elevation at the J point in two contiguous leads with a magnitude ≥ 1 millimeter in all leads except V2–V3, where these values are ≥ 2 millimeters for men overolder than 40 years, ≥ 2.5 millimeters for men younger than 40 years, or ≥ 1.5 millimeters for women, irrespective of their age, in the absence of left ventricular hypertrophy or bundle branch block (Thygesen et al., 2019). Additionally, patients with new-onset bundle branch block and clinical signs of myocardial ischemia are considered to have STEMI (Ibanez et al., 2018).

Patients with NSTEMI are defined as those experiencing acute chest discomfort without evidence of persistent ST-segment elevation, with ECG changes that may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudonormalization of T waves. Patients can also be categorized as NSTEMI if they present clinical symptoms without ECG changes (Collet et al., 2021). ST depression and T-wave changes were defined as new horizontal or downsloping ST-segment depression ≥ 0.5 millimeters in two contiguous leads and/or T-wave inversion in two contiguous leads and/or T-wave inversion > 1 millimeter in two contiguous leads with prominent R waves or an R/S ratio > 1 in the absence of left ventricular hypertrophy or bundle branch block (Thygesen et al., 2019).

The final diagnosis was retrospectively determined from the electronic database of University Hospital "St. Ekaterina" Sofia and verified through the patients' medical records by the researcher.

Only patients who underwent selective coronary angiography with a detailed description of the findings and subsequent percutaneous coronary intervention, when appropriate according to recommendations, with available data from them in the hospital's Web-based platform SC PACS server (picture archiving and communication system), for further analysis by the interventional cardiologist were included.

1.2. **Inclusion and exclusion criteria**

Inclusion criteria:

- Patients hospitalized during the specified period.
- Patients with MI, type 1 or type 2 according to the definition.
- Patients aged ≥ 18 years.
- Time from onset of the MI ≤ 48 hours.

-Coronary angiography performed according to protocol recommendations and, when indicated, percutaneous intervention.

Exclusion criteria:

-Age < 18 years.

- Patients with MI, type 3–5 as per the definition.

- Onset of MI > 48 hours.

- Patients who did not undergo coronary angiography or lacking precise data from it.

- Any incompleteness in the available medical documentation that might hinder data analysis.

2. Methods

Diagnostic-therapeutic algorithm:

2.1. Medical history and physical examination

The medical history is collected during first medical contact and includes: pain characteristics (typical or atypical), localization, duration, radiation (toward the neck, upper limb, back, epigastrium, lower jaw), triggering factors, and accompanying symptoms. Atypical symptoms include shortness of breath, nausea/vomiting, weakness, palpitations, or syncope. The duration of symptoms in hours was recorded. The patient was asked about any preceding angina symptoms.

Any concomitant diseases are noted, as reported by the patient as well as remarqued in the existing medical documentation - prior MI, previous angioplasty, and the prescribed therapy.

For the purposes of the study, a definition was provided for RF to characterize each patient's profile. For each RF, it's recorded whether it was known before admission or diagnosed during hospitalization.

Diabetes mellitus (DM) - a known diagnosis documented or newly diagnosed during hospitalization. For newly diagnosed patients during the hospital stay, the diagnostic criteria for diabetes mellitus have been applied according to the guidelines of the World Health Organization from 2006/2011 and the American Diabetes Association from 2019, respectively coinciding with those in the 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases. Accordingly: HbA1c ≥6.5% (48 mmol/mol); fasting blood glucose ≥7.0 mmol/L (126 mg/dL) or plasma glucose 2 hours after ingestion ≥11.1 mmol/L (≥200 mg/dL) (Cosentino et al., 2020).

Arterial hypertension (AH) : a known diagnosis of "arterial hypertension" with ongoing treatment, or newly diagnosed during hospitalization. For newly discovered cases of AH, the criteria from ESC 2021 for cardiovascular disease prevention in clinical practice were applied: blood pressure levels: ≥ 140 mmHg for systolic and ≥ 90 mmHg for diastolic blood pressure.

Dyslipidemia: a known diagnosis of "dyslipidemia" or intake of lipid-lowering therapy. Given that the target levels of therapy differ based on individual risk profiles, for the purposes of this study, the following broadly recognized values were adopted: total cholesterol ≥ 5.2 mmol/l, LDL (low-density lipoprotein) cholesterol ≥ 2.6 mmol/l, triglycerides ≥ 1.7 mmol/l, HDL (high-density lipoprotein) ≤ 1 mmol/l for males and ≤ 1.3 mmol/l for females.

Smoking status: Patients who were currently smoking or had quit smoking within the last year were classified as smokers, while the rest were considered nonsmokers.

Obesity: Obesity status was determined by the Body Mass Index (BMI), where patients with a BMI ≥ 30 kg/m2 were considered obese.

Family history: History of premature coronary artery disease, including fatal MI, non-fatal MI, or coronary revascularization under the age of 55 in first-degree male relatives or under 65 in first-degree female relatives.

Illicit drug abuse: Consumption of cocaine, marijuana, or other prohibited substances was noted in the patient's history and/or reported by close contacts. Drug tests were not utilized.

Anamnesis and physical examination served as the basis for determining the class of heart failure for each patient according to the Killip classification: Class 1: no signs of decompensation; Class 2: rales up to half of the lung fields; S3: gallop rhythm; elevated jugular venous pressure; Class 3: pulmonary edema; and Class 4:

cardiogenic shock. X-ray examination of the lungs and heart as well as laboratory tests are beneficial.

2.2. ECG

The 12-lead ECG is conducted using a GE MAC 1200ST and Fukuda Denshi FX-8322 machines, with the standard paper speed set at 25 mm/s and calibration at 10 mm/mV as fast as possible (up to 10 minutes) from the first medical contact. It is interpreted by a cardiology specialist. Additional leads such as V3R and V4R were recorded when suspecting right ventricular infarction or V7-V9 for suspected posterior MI. The localization of MI is determined.

Follow-up ECGs are performed daily or in case of worsening of the patient's condition.

2.3. Laboratory tests

A standard set of laboratory tests is conducted for each patient, including a complete blood count; blood glucose, creatinine and urea levels; markers for myocardial necrosis (CK, CK-MB, and high-sensitivity troponin I [hsTn-I]; lipid profile (total cholesterol, HDL and LDL cholesterol, triglycerides); liver enzymes (AST, ALT); electrolytes; coagulation status; and serology. Markers for myocardial necrosis are monitored daily, and based on the attending physician's assessment, specific parameters might be tracked in the case of particular comorbidities, complications or to evaluate the treatment's effectiveness.

For the purposes of the comparative analysis, peak values of the markers for myocardial necrosis were utilized and determined as the highest values recorded during hospitalization. These findings, combined with echocardiographic findings, could serve as markers for the extent of myocardial damage.

All laboratory tests were conducted at the Central Clinical Laboratory of the University Hospital for Active Treatment "St. Ekaterina" -Sofia.

Elevated markers for myocardial necrosis were defined according to the laboratory's reference values as follows: CK $\geq$ 171 U/L, CK-MB fraction $\geq$ 24 U/L, and hsTN-I $\geq$ 0.0175 ng/mL.

In patients diagnosed with NSTEMI, the combination of clinical history; symptoms; vital signs; other physical findings; ECG, and laboratory results, including hs-cTn levels, served as the basis for risk stratification to determine the appropriate timing of invasive strategies. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (2015; 2020) were followed for these patients. Additional 12-lead ECG was performed in patients with recurrent symptoms or diagnostic uncertainty, and blood samples were collected for repeat TnI testing at 1 hour or 3 hours in patients with inconclusive data and a clinical condition suggesting AMI.

2.4. Echocardiography

Echocardiographic examination is performed on all patients upon admission to the Intensive Cardiology Care Unit using a Siemens ACUSON X700 echocardiography machine by an experienced cardiologist. Standard echocardiographic views, including the parasternal position (long and short axes), apical views (four-chamber, two-chamber, and five-chamber views), subcostal position, and suprasternal position are emloyed.

The echocardiographic examination involved the utilization of various imaging modalities: Two-dimensional imaging (2D); M mode, Color Doppler, Pulse Wave Doppler, Continuous Wave Doppler, Tissue Doppler.

The echocardiographic assessment involved a comprehensive evaluation of cardiac structure and function, including myocardial thickness and motion, thereby identifying regional wall motion abnormalities. The Left Ventricle Ejection Fraction (LVEF) was measured using the Simpson's method, presented as a percentage. To describe the motion of the left ventricular segments, terms such as normokinesia, hyperkinesia, hypokinesia, akinesia, and dyskinesia were used based on a 16-segment model.

Valve lesions are graded via qualitative, semi-quantitative, or quantitative assessment. Additionally, the pressure in the right chambers was indirectly measured.

Non-coronary heart conditions that could mimic symptoms of AMI have been excluded, such as acute pericarditis, severe aortic stenosis, hypertrophic cardiomyopathy, aortic dissection, massive pulmonary embolism, and several other conditions. This methodology is useful for the diagnosis of mechanical complications in patients with AMI.

A follow-up examination was also conducted for patients who experienced deterioration in their clinical state, new onset heart murmur or pericardial friction rub, and at the time of discharge for each patient.

Two parameters were included for the purposes of the study, retrospectively tracked in the echocardiographic protocols, electronic hospital system and the patient's medical history.

1. LVEF- patients are categorized into three groups: those with reduced LVEF ≤ 40%, those with mildly reduced LVEF (41-49%), and those with preserved LVEF (≥ 50%).

2. The degree of mitral regurgitation is categorized as 0 (none), I, II, III, and IV.

2.5. Medical Therapy

The administered medical therapy during hospitalization and prescribed upon discharge is not part of the current analysis. It was aligned with the latest guidelines from the European Society of Cardiology (ESC) and the American Heart Association (AHA). However, it was individualized for each patient based on the judgment of the physicians, considering the specific patient profile.

2.6. Selective Coronary Angiography (SCAG) and Percutaneous Coronary Intervention (PCI)

The procedures are performed using the PHILIPS ALLURA FD10 and GE HEALTHCARE INNOVA 2100-IQ machines. The indications and timing for these procedures are aligned with established recommendations based on the diagnosis.

-For STEMI patients, reperfusion therapy is indicated for those with ischemic symptoms for a duration of ≤12 hours and persistent ST-segment elevation. For patients whose symptom onset exceeds 12 hours, a primary PCI strategy is recommended if there is ongoing symptomatic ischemia, hemodynamic instability, or life-threatening arrhythmias. This intervention should be conducted as soon as possible following diagnosis (≤ 120 minutes) (Ibanez et al., 2018).

- For patients with NSTEMI, after admission, additional risk stratification is conducted using the GRACE risk score to assess the optimal timing of the invasive strategy and therapy.

* NSTEMI patients at very high risk, namely, those with hemodynamic instability, cardiogenic shock, recurrent/refractory chest pain despite medical therapy, life-threatening arrhythmias, mechanical complications, acute heart failure clearly related to the NSTEMI, or ST-segment depression >1 mm in at least 6 leads plus ST-segment elevation in the aVR and/or V1, are managed similarly to STEMI patients with an urgent invasive strategy implemented within 2 hours.

* NSTEMI patients at high risk factors, including diagnosed NSTEMI, dynamic new or presumed new ST/T-segment changes (symptomatic or silent), resuscitated cardiac arrest without ST-segment elevation, or cardiogenic shock, GRACE risk score >140, are managed with an early invasive strategy within 24 hours.

***** For patients at low risk, meaning the absence of any of the aforementioned criteria, a selective invasive strategy is adopted. These patients were not included in the current analysis because their management aligns with that of patients with chronic coronary syndrome.

Considering that, during the study period, new treatment guidelines for NSTEMI patients were published by the European Society of Cardiology, it is important to note that the management observed in the studied groups aligns with the aforementioned algorithm, consistent with the hospital's institutional protocols. In this context, behavior will be discussed according to the institutional protocol, which remains consistent with the recommendations up to 2020.

Invasive assessment

Patients typically undergo SCAG followed by intervention conducted using standard percutaneous techniques. The choice of tools and techniques is determined by the operator. Radial access (preferred) (Dimitrova et al., 2020) or femoral access was used; 5, 6, or 7 French-sized catheters are used for an intervention. At least four projections are taken to visualize the left coronary artery and at least two for the RCA.

The number of affected arteries, the diameter of the coronary arteries, the degree, and length of the stenosis are visually determined by the operator in urgent conditions or in specific situations using software for assessing the size of the coronary arteries (QCA - Quantitative Coronary Analysis). Based on the angiographic findings and available preceding data, the culprit artery (IRA - infarct-related artery) is identified. The severity of the lesion is assessed in at least two orthogonal projections. Blood flow in the IRA is noted using the TIMI scale.

Percutaneous intervention, based on the operator's assessment, can involve POBA (less frequently) or the implantation of one or more stents. In this study, only a drug eluting stent (DES) was utilized. Blood flow following PCI in the treated artery was classified using the TIMI scale. Individually, a thrombus aspiration catheter may also be used. If multiple significant lesions are present, immediate or staged revascularization can be proposed by the operator or after extensive discussion.

Definitions

Coronary lesion significance: Obstructive coronary artery disease (CAD) was defined as at least 70% narrowing of the lumen in the LAD, LCX, RCA, or their branches, or $\geq$ 50% reduction in the lumen of the LMA (left main artery). CAD is classified based on the number of affected arteries as single, double, or triple-vessel disease, while patients with minimal or no atherosclerotic involvement are categorized as having non-obstructive coronary artery disease (NOCD).

TIMI (Thrombolysis in Myocardial Infarction) Scale:

TIMI 0 - Blood flow: no antegrade flow beyond the occlusion zone.

TIMI I - Blood flow: contrast material passes distal to the lesion but does not opacifies the distal segments of the artery.

TIMI II - Blood flow: contrast material passes distal to the lesion and visualizes the coronary artery, but the penetration or "washout" speed distally is noticeably slower than that in the artery unaffected by the respective lesion.

TIMI III - Blood flow: contrast material passes rapidly distal to the lesion, comparable to the area before the occlusion, with clearance as fast as that in the unaffected artery.

All procedural details are noted in the invasive reports by the operator, remaining in the patient's medical history, stored in the electronic database and the Excel table "Journal", and the film is recorded on a disk and transferred to PACS.

These data serve as the basis for a retrospective analysis of the examined parameters: arterial access, IRA, number of affected arteries, significant involvement of LMA, PCI-yes/no, stent implantation, number of implanted stents, and postprocedural TIMI blood flow.

2.7. In-hospital complications

We defined complications during the hospital stay as follows: 1) Heart rhythm or conduction disturbances, requiring medical or instrumental therapy (ventricular tachycardia/ventricular fibrillation); (high-degree heart block, requiring or not temporary pacemaker implantation); 2) Heart failure (maximum Killip class during hospitalization, including at admission); 3) Mechanical complication of the infarct (confirmed by echocardiography and/or computed tomography); 4) Cardiac arrest; 5) Post-infarction angina (syndrome of ischemic chest pain occurring at rest or with minimal activity 24 hours or more after the index event); 6) Reinfarction during hospital stay.

The duration of hospital stay in days and vital status upon discharge were noted.

2.8. Follow-up

The follow-up of each patient was performed at the end of the first and second years after discharge or until the occurrence of a fatal outcome. A longer follow-up period was not conducted due to the expected higher frequency of adverse events in the older age group attributed to age-related comorbidities.

The follow-up process was conducted using multiple methods:

- By reviewing the hospital information system for outpatient visits or subsequent hospitalizations in the clinic for each specific patient, identified by their unique civil registration number (personal identification number) until the end of the 1st and 2nd years.

- Through personal visits by the patient during scheduled outpatient check-ups, conducting a survey based on a prepared questionnaire, and reviewing medical documentation.

- Through telephone interviews with the patient and/or their close relatives, conducting a survey based on a preprepared questionnaire.

- In cases where it was impossible to determine the date of death using any of the aforementioned methods, after verification through the electronic hospital information system, a check was conducted in the Unified Civil Registration and Administrative Services System. It was a method to track down 5 patients that died in the follow-up period, all falling within age group 2.

Given that it was not always possible to determine the exact cause of death that occurred after discharge (whether cardiovascular or non cardiovascular death), we analyzed all-cause death.

We collected data regarding all-cause death, recurrent MI; non-fatal stroke, rehospitalization due to heart failure, unplanned revascularization, and the recurrence of angina symptoms requiring hospitalization. These adverse cardiovascular events are defined as MACE – major adverse cardiac events.

- A recurrent MI is defined as an acute coronary syndrome occurring after discharge and meeting the criteria of the 'Fourth Universal Definition of Myocardial Infarction'.

- A non-fatal stroke is defined as a cerebrovascular accident documented in a discharge summary or confirmed by computed tomography, which did not result in the patient's death and occurred after discharge.

- Rehospitalization due to heart failure is defined based on data in the hospital information system, in cases of subsequent admission for heart failure in the institution or upon presentation of medical documentation from the patient from another medical center.

- Unplanned revascularization: any revascularization after discharge involving the target or another artery that was not planned at the time of discharge.

- Recurrence of angina: high-class angina pectoris, not adequately relieved after the administration of medical therapy and requiring hospitalization.

2.9. Statistical analysis

1. Descriptive statistics

- The quantitative variables are presented through summary statistical characteristics - mean, median, and standard deviation (SD).

- The categorical variables are presented as absolute frequencies (n) and relative frequencies (%).

2. The One-Sample Kolmogorov-Smirnov test is used to assess the conformity of a sample's distribution to a particular theoretical distribution or to compare the sample's distribution against a standard theoretical distribution.

3. The Chi-square test and Fisher's Exact Test are both utilized to analyze associations or dependencies between categorical data with two or more categories.

4. The Mann-Whitney U test, also known as the Wilcoxon rank-sum test, is employed when comparing two independent groups with ranked or ordinal data. It serves as a non-parametric alternative to the independent samples t-test when the assumptions of normality aren't met or when dealing with ordinal data.

5. Binary logistic regression is a statistical method used to examine the relationship between one binary dependent variable and several independent variables, which can be categorical or quantitative. The resulting statistic, Odds Ratio (OR), quantifies the impact and direction of the studied factors on the binary variable. It estimates the likelihood of an event occurring concerning the presence or absence of a particular factor or variable.

6. Kaplan-Meier analysis –estimation of the survival function or survival curve for time-to-event data.

7. The Log-Rank test - comparing the survival curves of two or more independent groups in Kaplan-Meier survival analysis.

Mean: The arithmetic average value

Median: The middle values in a dataset when arranged in ascending order

SD: Standard deviation, a measure of the amount of variation or dispersion in a set of values

Min: The minimum value in a dataset

Max: The maximum value in a dataset

X2: Statistical criterion (Chi-square)

df: Degrees of freedom

p: Level of statistical significance

The accepted threshold level of significance is $\alpha = 0.05$. Statistical significance is accepted when the p-value is less than α ($p < 0.05$).

The specialized statistical software package SPSS (Statistical Package for the Social Sciences) version 20.0 was used for data processing in the study.

V. Results

1. Comparative analysis of age, gender, risk factors, and baseline characteristics between the two groups of patients with myocardial infarction.

A total of 172 patients, admitted to the Cardiology Clinic at University Hospital 'St. Ekaterina'- Sofia between 2018 and 2021 with a diagnosis of MI (STEMI and NSTEMI) are included in the study.

1.1. Distribution by age

The patients are divided into two age groups:

-Group 1 - aged 18 to 45 years (n= 61)

-Group 2 - aged > 45 years (n= 111)

The average age of patients in Group 1 is 39.74±4.97 years, with the youngest being 23 years old and the oldest 45 years old. The average age of patients in Group 2 is 67.21±10.18 years, with the youngest being 46 years old and the oldest 89 years old **(Table 1).**

Group	**N**	**Age**			
		Mean	SD	Min	Max
Age ≤ 45	61	39,74	4,97	23,00	45,00
Age >45 г.	111	67,21	10,18	46,00	89,00

Table 1. Distribution of patients by age.

1. 2. Distribution by gender

The distribution of patients by gender in both groups is shown in **Table 2**, indicating a statistically significant predominance of males in both groups (p=0.001). There is a noticeable increase in the proportion of females in the overall followed population in Group 2 compared to Group 1.

Chi-Square Tests

Group		Male	Female	Total	X^2	df	p
Age≤ 45	N	56	5	61	10,61	1	0,001
	%	41,8%	13,2%	35,5%			
Age >45	N	78	33	111			
	%	58,2%	86,8%	64,5%			
Total	N	134	38	172			
	%	100,0%	100,0%	100,0%			

Table 2. Distribution of patients by gender.

In Figure 1, a statistically significant predominance of males in the ≤ 45 years group compared to the same in the >45 years group is evident (p=0.001).

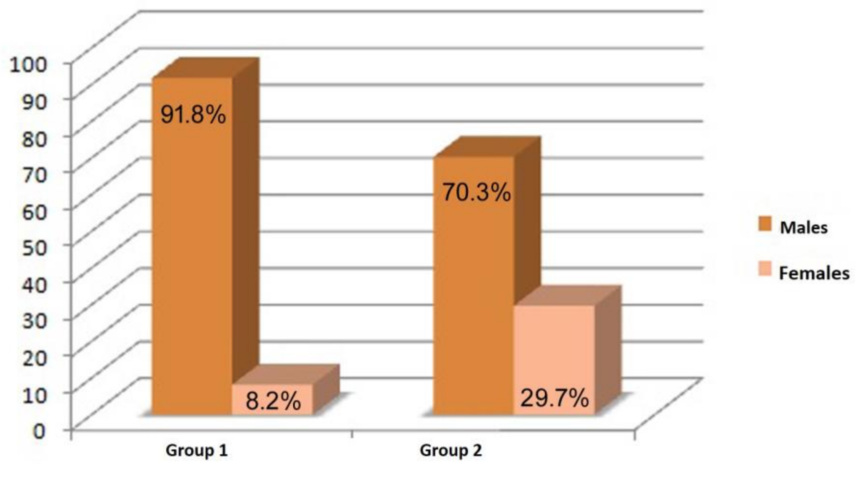


Figure 1: Distribution of patients by gender in each group.

1.3. Comparative analysis of the risk profile in the two groups

- In the present study, eight RFs were examined, and their percentage distribution in the groups is presented in **Table 3:**
- The predominant RFs in the entire studied patient population are male gender (77.9%), AH (84.3%), and dyslipidemia (88.3%).
- There's **no** significant differences observed between the two groups regarding the incidence of DM, dyslipidemia, family history, and illicit drug abuse.
- There's a relatively high frequency of DM in group 2 without reaching a significant difference (p=0.093)- borderline significance.

- There's a significant difference between the groups regarding the prevalence of 3 RFs – in group 1, there's a relatively higher proportion of smokers (55.7% vs. 28.8%; p=0.001), while in group 2, there's a higher prevalence of hypertension (70.5% vs. 91.9%; p<0.001) and obesity (16.4% vs. 31.5%; p=0.031).
- Only 2 patients in group 1 reported illicit substance abuse **(Table 3).**

Chi-Square Tests

Variable		**Group**		**Total**	X^2	**df**	**p**
		Age ≤ 45	Age>45				
Male	**N**	**56**	**78**	**134**	**10,61**	**1**	**0,001**
	%	**91,8%**	**70,3%**	**77,9%**			
Smoking	**N**	**34**	**32**	**66**	**12,05**	**1**	**0,001**
	%	**55,7%**	**28,8%**	**38,4%**			
AH	**N**	**43**	**102**	**145**	**13,62**	**1**	**<0,001**
	%	**70,5%**	**91,9%**	**84,3%**			
DM	N	11	33	44	2,83	1	0,093
	%	18,0%	29,7%	25,6%			
Dyslipidemia	N	54	98	152	0,00	1	0,963
	%	88,5%	88,3%	88,4%			
Family history of CAD	N	17	29	46	0,06	1	0,805
	%	27,9%	26,1%	26,7%			
Obesity	**N**	**10**	**35**	**45**	**4,67**	**1**	**0,031**
	%	**16,4%**	**31,5%**	**26,2%**			
Drug abuse	N	2	0	2			0,124*
	%	3,3%	0,0%	1,2%			

Table 3. Risk profile of the two groups. Abbreviations: AH, hypertension; DM, diabetes mellitus; CAD, coronary artery disease. **Note:** * Fisher's Exact Test

The results from **Table 4** indicate the following:

Upon conducting a sub-analysis to establish gender differences in the risk profile, no significant difference in the prevalence of any RF was observed in both groups.

Fisher's Exact Test

Group	Variable		Male	Female	Total	p
Age≤ 45	Smoking	N	32	2	34	0,460
		%	57,1%	40,0%	55,7%	
	AH	N	40	3	43	0,591
		%	71,4%	60,0%	70,5%	
	DM	N	9	2	11	0,182
		%	16,1%	40,0%	18,0%	
	Dyslipidemia	N	49	5	54	0,401
		%	87,5%	100,0%	88,5%	
	Family history of CAD	N	14	3	17	0,094
		%	25,0%	60,0%	27,9%	
	Obesity	N	10	0	10	0,301
		%	17,9%	0,0%	16,4%	
	Drug abuse	N	2	0	2	1,000
		%	3,6%	0,0%	3,3%	
Age> 45	Smoking	N	21	11	32	0,496
		%	26,9%	33,3%	28,8%	
	AH	N	73	29	102	0,314
		%	93,6%	87,9%	91,9%	
	DM	N	20	13	33	0,147
		%	25,6%	39,4%	29,7%	
	Dyslipidemia	N	70	28	98	0,464
		%	89,7%	84,8%	88,3%	
	Family history of CAD	N	17	12	29	0,110
		%	21,8%	36,4%	26,1%	
	Obesity	N	22	13	35	0,246
		%	28,2%	39,4%	31,5%	
	Drug abuse	N	0	0	0	n/a
		%	0,0%	0,0%	0,0%	

Table 4. Gender subgroup analysis of risk factors in the two groups

The majority of patients in both groups presented with 2 or more RFs, with a tendency towards a higher frequency among patients in the >45 years age group, without a significant difference observed between the two groups (p= 0.154) **(Table 5).**

Fisher's Exact Test

Number of RF		**Group**		**Total**	**p**
		Age≤ 45	**Age> 45**		
No	N	2	1	3	0,154
	%	3,3%	0,9%	1,7%	
1 RF	N	8	7	15	
	%	13,1%	6,3%	8,7%	
≥ 2 RFs	N	51	103	154	
	%	83,6%	92,8%	89,5%	
Total	N	61	111	172	
	%	100,0%	100,0%	100,0%	

Table 5. Comparative analysis of the number of risk factors in the groups

1.4. Comparative analysis of other baseline characteristics (previous MI and prior revascularization) between the two groups

- A significant difference is observed in terms of the frequency of prior revascularization in favor of Group 2 (p < 0.001).
- In Group 2, the frequency of previous MI is twice as high (13.5%) compared to Group 1 (6.7%), but it does not reach statistical significance (p = 0.174) **(Table 6).**

			Group		Total	X^2	df	p
			Age≤45	Age>45				
Previous MI	No	N	56	96	152	1,85	1	0,174
		%	93,3%	86,5%	88,9%			
	Yes	N	4	15	19			
		%	6,7%	13,5%	11,1%			
	Total	N	60	111	171			
		%	100,0%	100,0%	100,0%			
Prior revascularization	No	N	59	84	143	12,44	1	<0,001
		%	96,7%	75,7%	83,1%			
	Yes	N	2	27	29			
		%	3,3%	24,3%	16,9%			
	Total	N	61	111	172			
		%	100,0%	100,0%	100,0%			

Table 6. Comparative analysis regarding previous MI and prior revascularization

2. Comparative analysis of clinical presentation

2.1. Differences in the presence of prior angina between the two groups

The proportion of patients reporting prior angina is almost identical in the two studied groups (p = 0.459) **(Table 7).**

Chi-Square Tests

Prior angina		Group		Total	X^2	df	p
		Age≤ 45	**Age> 45**				
No	N	36	59	95	0,55	1	0,459
	%	59,0%	53,2%	55,2%			
Yes	N	25	52	77			
	%	41,0%	46,8%	44,8%			
Total	N	61	111	172			
	%	100,0%	100,0%	100,0%			

Table 7. Comparative analysis regarding the presence of prior angina

2.2 . **Comparison between the two groups regarding symptoms at presentation.**

Figure 2 illustrates the presenting symptoms of patients in each group.

The majority of patients in both groups experienced typical chest pain. Upon subanalysis of patients presenting with typical chest pain and those without pain in both groups, it was found that more patients in Group 1 presented with typical pain compared to those in Group 2, but the difference was not significant (90.16% versus 85.6%; p = 0.534).

In Group 1, the most commonly reported symptoms following typical chest pain were shortness of breath (16.4%) and sweating (14.7%), while in Group 2, the most common symptoms were shortness of breath (14.4%) and nausea/vomiting (8.1%).

In the group aged ≤ 45 years, none of the patients presented with syncope or palpitations, whereas in the group aged > 45 years, their prevalence was 4.5% and 1.8%, respectively.

The total percentage of symptoms in each group exceeds 100% because some patients presented with more than one symptom.

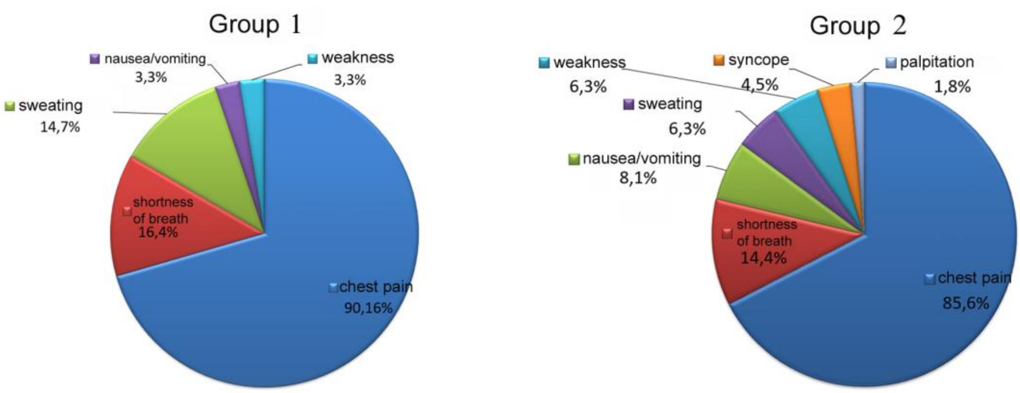


Figure 2: Percentage distribution of symptoms at admission in the groups.

When conducting a gender subanalysis to determine differences in presentation with or without pain, differences were not found in either of the age groups **(Table 8).**

Fisher's Exact Test

Group	Chest pain		Male	Female	Total	p
Age≤ 45	No	N	5	1	6	0.4153
		%	8,9%	20,0%	9,8%	
	Yes	N	51	4	55	
		%	91,1%	80,0%	90,2%	
Age > 45	No	N	9	7	16	0.2374
		%	11,5%	21,2%	14,4%	
	Yes	N	69	26	95	
		%	88,5%	78,8%	85,6%	

Table 8. Gender subgroup analysis concerning presentation with and without chest pain.

2.3. Comparative analysis between the two groups regarding the time delay from symptoms onset to presentation.

Table 9 presents the parameters characterizing the time delay from the symptoms onset to the patient's presentation at the hospital. It is evident that the mean time delay of young patients with AMI is nearly 4 hours shorter, leading to a significant statistical difference when comparing this parameter (p= 0.004). The maximum time in both groups is 48 hours, as specified in the inclusion criteria during patient selection.

Mann-Whitney Test

Parameter	Group	N	Mean	Median	SD	Min	Max	p
Time from symptom onset in hours	Age≤ 45	61	**7,76**	3,00	11,04	0,30	48,00	0,004
	Age> 45	111	**11,67**	5,00	13,89	0,50	48,00	

Table 9. Comparative analysis between the groups regarding the time delay from the symtoms onset to presentation at the hospital.

When dividing all patients in the study into two groups—those who arrived within six hours of symptom onset and those who arrived more than six hours after symptoms onset—a significant trend is once again observed among the young individuals who presented earlier to the healthcare facility. Notably, nearly 28% of patients in Group 1 had a delay of more than six hours **(Table 10).**

Chi-Square Tests

Time from symptoms onset		**Group**		**Total**	X^2	**df**	**p**
		Age≤ 45	**Age>45**				
< 6 ч.	N	44	63	107	3,96	1	0,047
	%	72,1%	56,8%	62,2%			
>6 ч.	N	17	48	65			
	%	**27,9%**	43,2%	37,8%			
Total	N	61	111	172			
	%	100,0%	100,0%	100,0%			

Table 10. Proportion of patients in the two groups presenting before and after 6 hours from symptoms onset.

A subanalysis was performed to determine sex differences at delays > 6 hours, and it is found that only in Group 1 the proportion of women presenting late is higher than men, yet statistical significance is not reached (p= 0.612) **(Table 11).**

Fisher's Exact Test

Group	**Time from symptoms onset**		**Males**	**Females**	**Total**	**p**
Age≤ 45	< 6 ч.	N	41	3	44	0,612
		%	73,2%	60,0%	72,1%	
	>6 ч.	N	15	2	17	
		%	26,8%	40,0%	27,9%	
Age> 45	< 6 ч.	N	43	20	63	0,677
		%	55,1%	60,6%	56,8%	
	>6 ч.	N	35	13	48	
		%	44,9%	39,4%	43,2%	

Table 11. Gender sub-analysis regarding the time from the symptoms onset to presentation.

2.4. Comparative analysis of the severity of acute heart failure at presentation between the two groups

- The majority of patients in both groups, after a physical examination, were identified as having a low class of heart failure - Killip 1, comprising 78.7% of patients in Group 1 and 75.7% of patients in Group 2.
- When dividing patients in both groups into those with Killip classes 1 and 2 and those with 3 and 4, meaning high grade, it is observed that a larger proportion in Group 2 had a high Killip class compared to young patients with borderline significance (p= 0.057) **(Table 12).**

Chi-Square Tests

Killip class		**Group**		**Total**	X^2	**df**	**p**
		Age ≤ 45	**Age>45**				
≤2	N	58	95	153	3,6	1	0,057
	%	95,1%	85,6%	89%			
> 2	N	3	16	19			
	%	4,9%	14,4%	11%			
Total	N	61	111	172			
	%	100,0%	100,0%	100,0%			

Table 12. Comparative analysis between the two groups regarding presentation with high Killip class (> 2) heart failure.

2.5. Distribution of STEMI/NSTEMI patients in the groups

According to the definitions provided by the European Society of Cardiology and following a detailed review of the final diagnoses recorded in the hospital information system and the patient's medical history, the distribution by diagnosis of myocardial infarction with or without ST elevation (STEMI/NSTEMI) was established, as presented in **Table 13.**

There is a predominance of patients with STEMI in both groups, without a significant difference in the prevalence of STEMI or NSTEMI between the groups.

Chi-Square Tests

Diagnosis STEMI/NSTEMI		Group		Total	X^2	df	p
		Age≤45	Age >45				
STEMI	N	46	80	126	0,22	1	0,636
	%	75,4%	72,1%	73,3%			
NSTEMI	N	15	31	46			
	%	24,6%	27,9%	26,7%			
Total	N	61	111	172			
	%	100,0%	100,0%	100,0%			

Table 13. Comparative analysis of the groups regarding the final diagnosis (STEMI/NSTEMI).

2.6. Comparative analysis of the two investigated groups based on the localization of the infarction.

The results in **Table 14** show that the majority of patients in both Group 1 and Group 2 presented with anterior MI (over 40% in both groups), followed by inferior MI. No significant difference was found in the predominance of any localization of the MI between the two investigated groups (p= 0.822).

Chi-Square Tests

AMI localization		Group		Total	X^2	df	p
		Age≤ 45	Age> 45				
Anterior	N	29	46	75	0,91	3	0,822
	%	47,5%	41,4%	43,6%			
Inferior	N	17	38	55			
	%	27,9%	34,2%	32,0%			
Inferolateral	N	9	15	24			
	%	14,8%	13,5%	14,0%			
Lateral	N	6	12	18			
	%	9,8%	10,8%	10,5%			
Total	N	61	111	172			
	%	100,0%	100,0%	100,0%			

Table 14. Comparative analysis of the two investigated groups based on the localization of the MI.

2.7. Comparative analysis between the groups regarding echocardiographic and laboratory variables

2.7.1. Echocardiographic parameters

- Two echocardiographic parameters were compared—specifically, the LVEF and the degree of mitral regurgitation.
- Regarding the LVEF, after categorizing into three groups—preserved LVEF, mildly reduced LVEF, and reduced ejection fraction—it appears that the majority of patients in both groups had preserved LVEF (≥ 50%), 62.3%, compared to 59.5%.
- The lowest proportion of patients in both groups had a reduced ejection fraction (≤ 40%).
- There is no statistically significant difference observed regarding this parameter between the groups (p=0.932) **(Table 15).**

LVEF (%)		**Group**		**Total**	***X^2***	**df**	**p**
		Age≤45	**Age>45**				
≤ 40	N	12	24	36	0,14	2	0,932
	%	19,7%	21,6%	20,9%			
41-49	N	11	21	32			
	%	18,0%	18,9%	18,6%			
≥ 50	N	38	66	104			
	%	62,3%	59,5%	60,5%			
Total	N	61	111	172			
	%	100,0%	100,0%	100,0%			

Table 15. Comparative analysis regarding the LVEF.

- In terms of the severity of mitral regurgitation, significant differences were identified.
- A significantly larger proportion of patients in Group 1 exhibited mild mitral regurgitation - 98.4% compared to 73.0% (p <0.001).

•Only one patient in Group 1 (1.6%) had a mitral insufficiency ≥ 2 degrees, and she died during the index event. In comparison, 30 patients (27.0%) in Group 2 had moderate or severe MR insufficiency **(Table 16).**

Chi-Square Tests

Mitral insufficiency		**Group**		**Общо**	X^2	**df**	**p**
		≤45 г.	**>45 г.**				
< 2 grade	N	60	81	141	17,17	1	<0,001
	%	98,4%	73,0%	82,0%			
≥ 2 grade	N	1	30	31			
	%	1,6%	27,0%	18,0%			
Total	N	61	111	172			
	%	100,0%	100,0%	100,0%			

Table 16. Comparative analysis based on the severity of mitral regurgitation

2.7.2. Laboratory parameters

- The mean peak values of cardiac biomarkers were compared between the two groups (CK-MB, CPK-MB, and hsTN-I) and were recorded during the hospital stay. Along with echocardiographic data of the LVEF, these markers could potentially serve as indicators for the extent of myocardial necrosis.
- The results are presented in **Table 17**. There is no statistically significant difference observed for any of the markers between the groups, aligning with the data concerning the baseline LVEF.

Mann-Whitney Test

Biomarker	**Group**	**N**	**Mean**	**Median**	**SD**	**Min**	**Max**	**p**
Peak CPK	Age≤ 45	61	2657,08	525,00	7325,39	56,00	46556,00	0,995
	Age>45	111	997,66	650,00	1061,51	48,00	6000,00	
Peak MB	Age≤ 45	61	161,37	50,00	222,86	11,00	1060,00	0,987
	Age>45	111	100,52	69,00	107,14	8,00	636,00	
Peak TN-I	Age≤ 45	61	17,96	7,10	19,80	0,04	50,00	0,546
	Age>45	111	16,96	12,00	15,75	0,02	50,00	

Table 17. Comparative analysis regarding the peak values of cardiac biomarkers.

3. Comparative analysis of the angiographic characteristics and procedural features

3.1. Arterial vascular access

Mainly, two arterial vascular accesses were used during procedures - radial and femoral. Brachial access was not utilized.

The distribution in the two groups is presented in **Table 18.**

- The radial approach is preferred, with a high frequency in both groups. Among the younger patients, it reaches 95.1%.
- The radial access is more frequently used in Group 1 compared to Group 2 (95.1% vs. 85.6%), and borderline significance is observed (p= 0.057).

Chi-Square Tests

Radial access		**Group**		**Total**	X^2	**df**	**p**
		Age≤ 45	**Age> 45**				
No	N	3	16	19	3,61	1	0,057
	%	4,9%	14,4%	11,0%			
Yes	N	58	95	153			
	%	95,1%	85,6%	89,0%			
Total	N	61	111	172			
	%	100,0%	100,0%	100,0%			

Table 18. Comparative analysis of the two investigated groups by arterial vascular access.

3.2. IRA-infarct related artery

- The infarct-related artery was determined following coronary angiography and documented in the protocol.
- The LAD was the most frequently targeted artery in patients in Group 1 (40.9%), followed by the RCA in 27.9% of patients.
- The RCA was the most common IRA in patients in Group 2 (37.8%), followed closely by the LAD (left anterior descending artery) at 36.9%.

- The frequency of involvement of the LCX as an IRA was almost the same in both groups (18.03% versus 17.11%).
- LMA as the target artery was observed in only one patient from Group 1 and in four from Group 2, and the difference not being significant.
- Arterial or venous grafts were not used for the IRA in any patient in Group 1.
- No significant difference was recorded in the predominance of a concrete IRA between the two groups **(Table 19).**
- The total percentage of patients in both groups is less than 100% since some of the patients were diagnosed with non-obstructive coronary artery disease (NOCD).
-

IRA	Age≤ 45 (N =61)	Age> 45 (N= 111)	p
LAD	25 (40,9%)	41 (36,9%)	0,601
RCA	17 (27,9%)	42 (37,8%)	0,18
LCX	11 (18,03%)	19 (17,11%)	0,87
LMA	1 (1,6%)	4 (3,6%)	0,46
LIMA	0 (0,0%)	1 (0,9%)	
svg- RCA	0 (0,0%)	1 (0,9%)	
svg- RIM	0 (0,0%)	1 (0,9%)	

Table 19. Comparison of the frequency of IRA in both groups. Abbreviations: IRA, infarct-related artery; LAD, left anterior descending artery; RCA, right coronary artery; LCX, circumflex artery; LMA, left main artery; SVG, saphenous vein graft; RIM, ramus intermedius artery.

3.3. Comparative analysis of the two studied groups regarding the number of involved arteries (SVD, DVD, MVD, and NOCD)

- The distribution of patients based on the presence of SVD, DVD, or MVD and NOCD is presented in **Table 20**, and the definitions of lesion significance are outlined in the Materials and Methods section.
- Single-vessel coronary involvement was the main angiographic finding in patients in the younger age group (49.2%), followed by DVD (27.9%) and MVD (11.5%).
- For patients in older age group the most commonly encountered was MVD (46,8%).

- A significant difference was noted in the presence of SVD and MVD between the two groups (p <0.001), whereas there was no difference in terms of the frequency of DVD (p= 0.894).
- Notably, the prevalence of non-obstructive coronary artery disease was significantly greater in the younger group than in the older group (p = 0.006).
- One of the younger patients with NOCD had coronary arterial vasospasm, another had Takotsubo cardiomyopathy, and in the other 5 cases, the cause remains unclear.
- One of the patients in Group 2 with NOCD had Takotsubo cardiomyopathy, while in the other patient, the cause remains unclear.
- Patients with an unclear cause of MI in the setting of NOCD or a normal coronary artery were classified as patients with MINOCA.
- The data noted in **Table 20** demonstrate a less severe coronary atherosclerotic involvement in patients in Group 1 compared to those in Group 2.

Chi-Square Tests

Variable		**Group**		**Total**	X^2	**df**	**p**
		Age≤ 45	**Age> 45**				
SVD	N	30	25	55	12,86	1	<0,001
	%	49,2%	22,5%	32,0%			
DVD	N	17	32	49	0,02	1	0,894
	%	27,9%	28,8%	28,5%			
MVD	N	7	52	59	21,86	1	<0,001
	%	11,5%	46,8%	34,3%			
NOCD	N	7	2	9	7,43	1	0,006
	%	11,5%	1,8%	5,2%			

Table 20. Comparative analysis of the two studied groups regarding the number of involved arteries. Abbreviations: SVD, Single-Vessel Disease; DVD, Double-Vessel Disease; MVD, Multi-Vessel Disease; NOCD, Non-Obstructive Coronary Disease.

3.4. Comparative analysis between the groups regarding involvement of the Left Main Artery (LMA).

There is a significant difference between the groups regarding the presence of significant LMA stenosis, with younger patients significantly less likely to present with it (p = 0.007) **(Table 21).**

Chi-Square Tests

LMA		**Group**		**Total**	X^2	**df**	**p**
		≤ 45 г.	**>45 г.**				
No	N	60	95	155	7,21	1	0,007
	%	98,4%	85,6%	90,1%			
Yes	N	1	16	17			
	%	1,6%	14,4%	9,9%			
Total	N	61	111	172			
	%	100,0%	100,0%	100,0%			

Table 21. Comparative analysis between the groups regarding the LMA involvement.

3.5. Comparative analysis between the groups regarding PCI/POBA (Plain Old Balloon Angioplasty) or stent implantation and the mean number of implanted stents

The type of interventional revascularization is chosen by the operator. **Figure 3** represents the ratio of patients with implanted stents and those with POBA. According to the results, the majority of procedures in both groups were related to stent implantation, with no significant difference observed between the groups (p= 0.82).

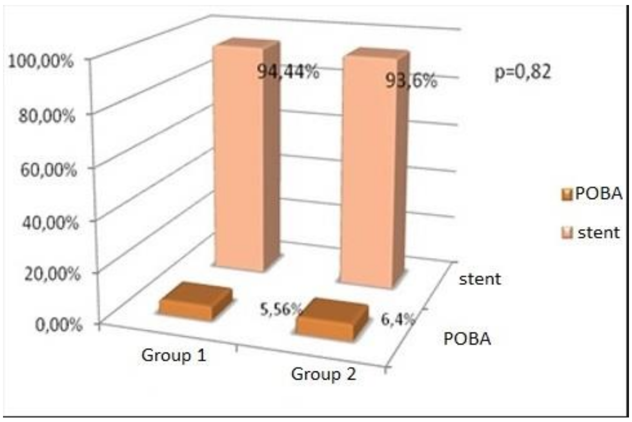


Figure 3. Comparative analysis between the groups regarding the type of interventional revascularization – stent implantation/POBA.

- All stents were drug-eluting stents (DES).

According to the results in **Table 22**, the mean number of implanted stents in the ≤ 45 years age group was significantly lower than that in the > 45 years age group (p= 0.045).

Mann-Whitney Test

Variable	Group	N	Mean	Median	SD	Min	Max	p
Mean number of implanted stents	Age ≤ 45	61	1,00	1,00	0,61	0,00	2,00	0,045
	Age> 45	111	1,23	1,00	0,71	0,00	4,00	

Table 22. Comparison regarding the mean number of implanted stents.

3.6. Comparative analysis between the groups based on achieved TIMI III blood flow in the IRA.

Procedural success, defined by achieving TIMI III blood flow in the IRA, was high in both groups, with no significant difference observed between them (p= 0.754) **(Table 23).**

Fisher's Exact Test

TIMI III		Group		Total	*p*
		Age≤ 45	Age>45		
No	N	5	7	12	0,754
	%	8,6%	6,4%	7,2%	
Yes	N	53	102	155	
	%	91,4%	93,6%	92,8%	
Total	N	58	109	167	
	%	100,0%	100,0%	100,0%	

Table 23. Comparative analysis based on achieved TIMI III blood flow in the IRA.

4. Comparative analysis between the groups regarding in-hospital complications and length of stay

The overall frequency of observed in-hospital complications, which were overviwed for the purpose of this study, is presented in **Figure 4**. It's evident that the proportion of younger patients experiencing complications was significantly lower

(N=13; 21%) than that of older patients (N=47; 42%). There was a twofold greater percentage of complications recorded in Group 2 (p = 0.009).

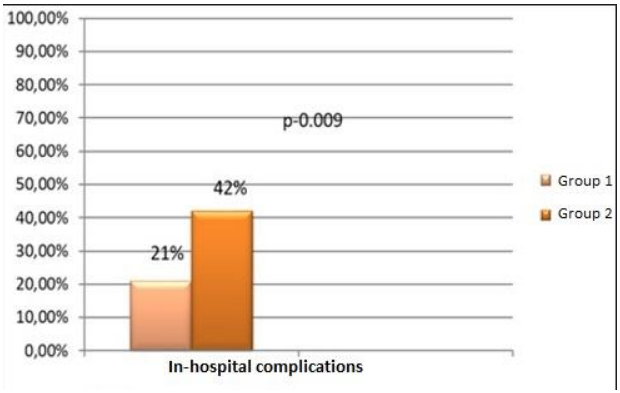


Figure 4. Comparison of the frequency of in-hospital complications in both groups.

- **Table 24** presents the proportions of patients with each observed complication in the two groups. The most frequent complications in Group 1 were ventricular tachycardia or fibrillation (VT/VF) at 4.9%, cardiogenic shock at 4.9%, resuscitated cardiac arrest at 4.9%, and post-infarction angina at 4.9%. On other hand, in Group 2, the highest frequency is observed for cardiogenic shock at 13.5%, followed by cardiac arrest at 11.7%, and high-degree or complete AV block or permanent pacemaker implantation at 9.0%. The only complication with a higher frequency among younger patients was post-infarction angina (4.9% vs. 0.0%). None of the patients in either group experienced reinfarction during the hospital stay.
-

In-hospital complications		**Group**		**Total**
		Age≤ 45	**Age>45**	
VT/VF	N	3	6	9
	%	4,9%	5,4%	5,2%
Third-degree AV block/temporary pacemaker	N	1	10	11
	%	1,6%	9,0%	6,4%
cardiogenic shock	N	3	15	18
	%	4,9%	13,5%	10,5%
cardiac arrest	N	3	13	16
	%	4,9%	11,7%	9,3%

Mechanical complications	N	0	3	3
	%	0,0%	2,7%	1,8%
post-infarction angina	N	3	0	3
	%	4,9%	0,0%	1,7%
reinfarction	N	0	0	0
	%	0,0%	0,0%	0,0%

Table 24. Percentage distribution of in-hospital complications in both groups.

- Comparison of the mean length of hospital stay between the two groups.

Table 25 shows no significant difference in the mean hospital stay in days between the studied groups (p=0.204).

Mann-Whitney Test

Variable	**Group**	**N**	**Mean**	**Median**	**SD**	**Min**	**Max**	**p**
Hospital stay/days/	Age≤45	61	4,16	4,00	2,20	2,00	16,00	0,204
	Age>45	108	4,48	3,00	5,81	1,00	60,00	

Table 25. Comparative analysis of the mean hospital stay.

5. In-hospital mortality in both groups

5.1. Comparative analysis of in-hospital mortality between the two groups

Despite the nearly half mortality rate in Group 1 compared to Group 2 (4.9% versus 10.8%), no statistical difference is observed regarding this variable (p= 0.190) **(Table 26).**

Hospital mortality		**Group**		**Total**	***X²***	**df**	**p**
		Age≤45	**Age>45**				
No	N	58	99	157	1,72	1	0,190
	%	95,1%	89,2%	91,3%			
Yes	N	3	12	15			
	%	4,9%	10,8%	8,7%			
Total	N	61	111	172			
	%	100,0%	100,0%	100,0%			

Table 26. Comparison of in-hospital mortality between the two groups

After running a binary logistic regression with a reference category- age of ≤ 45 years shows an odds ratio (OR) for in-hospital mortality of 2.343, with a 95% confidence interval (CI) ranging from 0.635 to 8.651, and a p-value of 0.201.

5.2. Evaluation of the influence of factors such as gender, AH, dyslipidemia, DM, presence of >2 RFs, reduced LVEF, delayed patient presentation, Killip class >2, anterior MI localization, presence of MVD, and hospital stay duration on in-hospital mortality for each group separately

- After analyzing the influence of the abovementioned 11 variables on in-hospital mortality in both groups, we suggest that two factors could have negative predictive value in Group 1: reduced LVEF <50% (p-0.049) and Killip class >2 at admission (p<0.001). In Group 2, similar negative prognostic value could have- reduced LVEF <50% (p<0.001), Killip class >2 (p<0.001) and having >2 RFs (p-0.039). These characteristics show a higher likelihood of fatal outcomes during the index hospitalization **(Table 27).** Individual analysis of each risk factor (hypertension, dyslipidemia, diabetes) did not reveal a correlation, so the combination of >2 RFs was investigated.

Group	**Variable**			Death		Total	p
				No	Yes		
Age≤ 45	**Gender**	Male	N	54	2	56	0,230
			%	93,1%	66,7%	91,8%	
		Female	N	4	1	5	
			%	6,9%	33,3%	8,2%	
Age>45	**Gender**	Male	N	69	9	78	1,000
			%	69,7%	75,0%	70,3%	
		Female	N	30	3	33	
			%	30,3%	25,0%	29,7%	
Age≤ 45	**Time from symptoms onset**	< 6 ч.	N	41	3	44	0,553
			%	70,7%	100,0%	72,1%	
		>6 ч.	N	17	0	17	
			%	29,3%	0,0%	27,9%	

Age>45	**Time from symptoms onset**	<6 ч.	N	59	4	63	0,122
			%	59,6%	33,3%	56,8%	
		> 6 ч.	N	40	8	48	
			%	40,4%	66,7%	43,2%	
Age≤ 45	**LVEF %**	< 50	N	20	3	23	0,049
			%	34,5%	100%	37,7%	
		≥50	N	38	0	38	
			%	65,5%	0,0%	62,3%	
Age>45	**LVEF%**	< 50	N	34	11	45	<0,001
			%	34,3%	91,7%	40,5%	
		≥50	N	65	1	66	
			%	65,7%	8,3%	59,5%	
Age≤ 45	**Killip class**	1-2	N	58	0	58	<0,001
			%	100,0%	0,0%	95,1%	
		3-4	N	0	3	3	
			%	0,0%	100,0%	4,9%	
Age>45	**Killip class**	1-2	N	95	0	95	<0,001
			%	96,0%	0,0%	85,6%	
		3-4	N	4	12	16	
			%	4,0%	100,0%	14,4%	
Age≤ 45	**Number of RFs**	≤2 RF	N	25	1	26	0,738
			%	43,1%	33,3%	3,3%	
		>2 RF	N	33	2	35	
			%	56,9%	66,7%	13,1%	
Age>45	**Number of RFs**	≤2 RF	N	38	1	39	0,039
			%	38,4%	8,3%	35,1%	
		>2 RF	N	61	11	72	
			%	61,6%	91,7%	64,9%	

Age≤ 45	**MI localization**	Anterior	N	27	2	29	0,496
			%	46,6%	66,7%	47,5%	
		Other	N	31	1	32	
			%	53,4%	33,3%	52,5%	
Age>45	**MI localization**	Anerior	N	41	5	46	0,986
			%	41,4%	41,7%	41,4%	
		Other	N	58	7	65	
			%	58,6%	58,3%	58,6%	
Age≤ 45	**MVD**	No	N	51	3	54	1,000
			%	87,9%	100,0%	88,5%	
		Yes	N	7	0	7	
			%	12,1%	0,0%	11,5%	
Age>45	**MVD**	No	N	54	5	59	0,543
			%	54,5%	41,7%	53,2%	
		Yes	N	45	7	52	
			%	45,5%	58,3%	46,8%	

Table 27. Determining factors, predictive for fatal outcomes during index hospitalization for each group separately (Fisher's Exact Test). (Univariate analysis)

- When conducting binary logistic regression for a quantitative assessment of the factors' impact on mortality, the odds ratio (OR) for the significant predictive factors was determined **(Tables 28 and 29).**

	Factor	OR	95% CI		p
Age≤45	Killip class 3-4	-	-	-	-
	LVEF < 50%	13,146	0,647	267,054	0,03

Table 28. Odds ratio for factors with a negative prognostic value concerning the in-hospital mortality in Group 1.

Note: All patients in Group 1 with Killip class 3-4 died during the index hospitalization, constituting 100% of the fatal cases.

	Factor	OR	95% CI		p
Age>45	Killip class 3-4	-	-	-	-
	LVEF < 50%	21,029	2,604	169.810	0,001
	Number of RFs (> 2)	6,852	0,850	55,226	0,070
	Time from symptoms onset (> 6 ч.)	2,950	0,832	10,458	0,094

Table 29. Odds ratio for factors with a negative prognostic value regarding in-hospital mortality in Group 2.

Note: All patients who had fatal outcome (N-12) in Group 2 had a Killip class of 3-4, and there were no patients with Killip class 1-2. Four patients classified as Killip 3-4 did not have a fatal outcome. The statistical method does not allow the introduction of a cell with a value of 0 for quantitative assessment of the degree of impact.

Killip class 3-4 had an evident high risk impact in both groups and was more pronounced in Group 1.

There is no significant relationship found between the longer hospital stay and the lethal outcome during the index hospitalization in either of the age groups **(Table 30).**

Group	Variable		N	Hospital stay				p
				Mean	SD	Min	Max	
Age≤45	death	No	58	3,88	1,39	2,00	9,00	n/a
		Yes	3	9,67	6,51	3,00	16,00	
Age>45	death	No	99	3,83	1,91	1,00	12,00	0,167
		Yes	10	10,50	17,86	0,00	60,00	

Table 30. Impact of Hospital Stay Duration on In-Hospital Mortality

6. One- and two-year follow-up

The follow-up for each patient, without a lethal outcome during the index hospitalization, was conducted at the end of the first and second years from the discharge date and for patients with a lethal outcome until the date of its occurrence. The data for two patients in group 2 were missing, leading to their exclusion from the postdischarge follow-up.

6.1. Comparative analysis regarding all-cause mortality at the one and two-year follow-up

Given that it is not always possible to determine the exact cause of death occurring after discharge in some cases (cardiac or non-cardiac), all-cause mortality was analyzed.

Within the first year after the index event, a significant difference is noted between the groups in terms of all cause mortality (3.4% compared to 13.3%; p=0.044). Over the two-year period, the significance is more pronounced given the absence of lethal cases in group 1 (p-0.021) (**Tables 31 and 32**).

Regardless the definition of the variable, the mortality was cardiovascular in both cases for group 1.

Chi-Square Tests

1 year all-cause death		Group		Total	p
		Age≤ 45	Age> 45		
No	N	56	85	141	0,044
	%	96,6%	86,7%	90,4%	
Yes	N	2	13	15	
	%	3,4%	13,3%	9,6%	
Total	N	58	98	156	
	%	100,0%	100,0%	100,0%	

Table 31. Comparitive analysis regarding the one-year all-cause death.

2- year all-cause death		Group		Total	p
		Age≤ 45	Age> 45		
No	N	56	82	138	0,021
	%	96,6%	84,5%	89,0%	
Yes	N	2	15	17	
	%	3,4%	15,5%	11,0%	
Total	N	58	97	155	
	%	100,0%	100,0%	100,0%	

Table 32. Comparitive analysis regarding the two-year all-cause death (until the end of follow-up) .

The Kaplan–Meier curves for the cumulative incidence of all-cause death are shown in **Figure 5**. The curve for Group 1 demonstrates a peak in the first few months after the index event, followed by a plateau until the end of the second year. The curve for Group 2 displays divergence from that of Group 1 up to the initial months of the second year, after which it also forms a plateau.

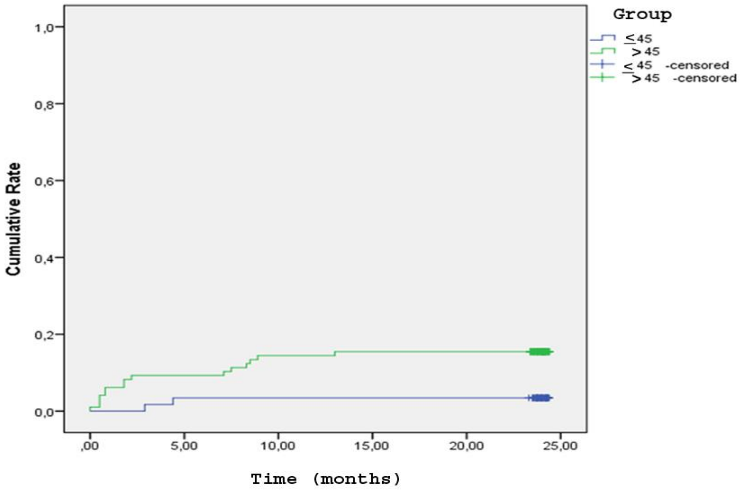


Figure 5. Kaplan–Meier curves for all-cause death stratified by age.

6.2. Comparative analysis regarding the occurrence of major adverse cardiovascular events (MACE) in the first and second years.

We collected data on all-cause death; recurrent MI; non-fatal stroke; rehospitalization due to heart failure; unplanned revascularization; recurrence of angina requiring hospitalization. The combination of these adverse cardiovascular events is defined as MACE.

The number of patients with at least one event is less than the total number of events since some patients experienced more than one MACE.

Table 33 represents the frequency of each adverse event in both groups through the end of the first year. Only concerning the all-cause death, the occurence was significantly lower in younger patients. For the remaining factors, including overall MACE, there was no significant difference. The most common events among younger patients were recurrent angina (19.6%), readmission due to heart failure (7.1%), and unplanned revascularization (5.4%), with even greater frequencies observed for the first two than for Group 2.

MACE at 1-year follow-up		Group		Total	p
		Age≤45	Age>45		
All-cause death	N	2	13	15	0,044
	%	3,4%	13,3%	9,6%	
Recurrent MI	N	1	3	4	0,650
	%	1,8%	3,6%	2,9%	
Non-fatal stroke	N	0	0	0	n/a
	%	0,0%	0,0%	0,0%	
Readmission for HF	N	4	5	9	0,741
	%	**7,1%**	5,9%	6,4%	
Unplanned revascularization	N	3	10	13	0,198
	%	**5,4%**	11,8%	9,2%	
Recurrent angina	N	11	14	25	0,652
	%	**19,6%**	16,7%	17,9%	
Patients with MACE	N	17	34	51	0,461
	%	29,3%	35,1%	32,9%	

Table 33. Rate of MACE at the one-year follow-up.

- **Table 34** presents the frequency of MACE in the 2nd year. Recurrent angina had the highest frequency of MACE in both groups, with a higher occurrence among younger individuals. In group 1, there were no deaths during this period. There was no significant difference in total MACE between the two groups (8.9% compared to 10.7%; p=0.57).
- For the entire follow-up period, there were no patients who experienced a non-fatal stroke.

MACE for the 2nd year		Group		Total
		Age≤ 45	Age>45 г.	
Unplanned revascularization	N	1	0	1
	%	1,8%	0,0%	0,7%
Recurrent MI	N	0	1	1
	%	0,0%	1,2%	0,7%
Readmission for HF	N	0	3	3
	%	0,0%	3,6%	2,1%
Recurrent angina	N	4	3	7
	%	**7,1%**	3,6%	5,0%
All-cause death	N	0	2	2
	%	0,0%	2,4%	1,4%
Patients with MACE	N	5	9	14
	%	8,9%	10,7%	10,0%

Table 34. Rate of MACE for the 2nd year in the two groups.

- **Figure 6** presents the frequency of MACE over the entire follow-up period and compares it between the groups, excluding the event of mortality previously discussed. Similar incidences are observed in both groups, with no significant difference for any event, including the combination of events.

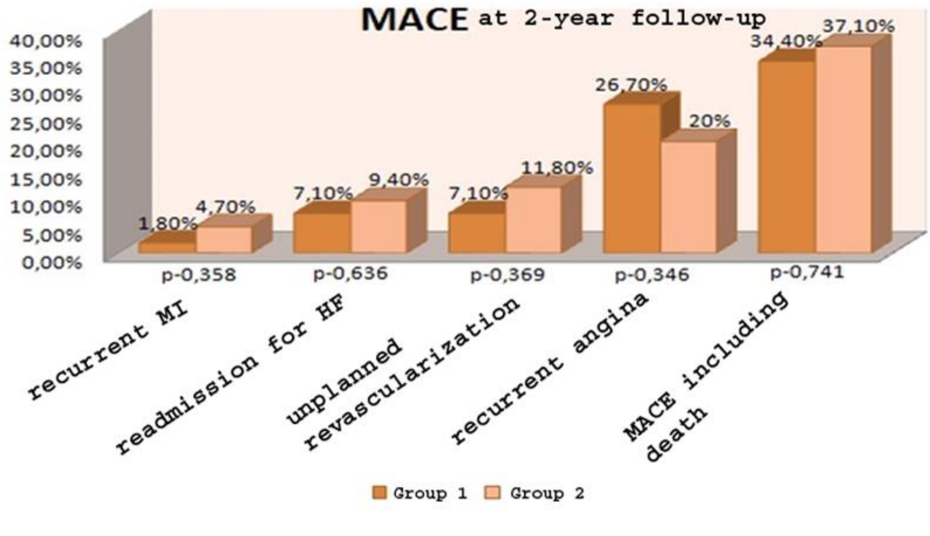


Figure 6. Comparison between groups regarding MACE over the entire study period (2 years).

- After conducting a binary logistic regression for assessing the role of age as a factor in adverse events and choosing for a referent age ≤45 years it becomes evident that advanced age (>45 years) shows a borderline significance (p=0.062; OR 4.282: 95% CI, 0.931-19.706) for being a factor in overall mortality by the end of the first year and a more pronounced effect over the two-year period (p=0.035; OR 5.060: 95% CI, 1.113-22.995). Consequently, younger age is predictive of better prognosis concerning mortality during the follow-up period. However, age does not show predictive value for any of the other events, including the combination of MACE (**Table 35).**

Dependent variable / adverse event	Factor	OR	95% CI		p
One- year all-cause death	Age over 45y	4,282	0,931	19,706	0,062
Recurrent MI	Age over 45y	2,037	0,207	20,094	0,542
Readmission for HF	Age over 45y	0,813	0,208	3,167	0,765
Unplanned revascularization	Age over 45y	2,356	0,618	8,972	0,209
Recurrent angina	Age over 45y	0,818	0,341	1,961	0,653
MACE at 1-year follow-up	Age over 45y	1,140	0,577	2,253	0,706
MACE at 2-year follow-up	Age over 45y	1,208	0,383	3,812	0,747
Two-year all-cause death	Age over 45y	5,060	1,113	22.995	0.035

Table 35. Binary logistic regression. Odds ratio for the occurrence of an event based on age.

OR – odds ratio

95% CI – 95% confidence interval

There is no significant difference between the two groups regarding the number of patients who experienced at least 1 MACE neither in the first nor in the second year **(Figure 7).**

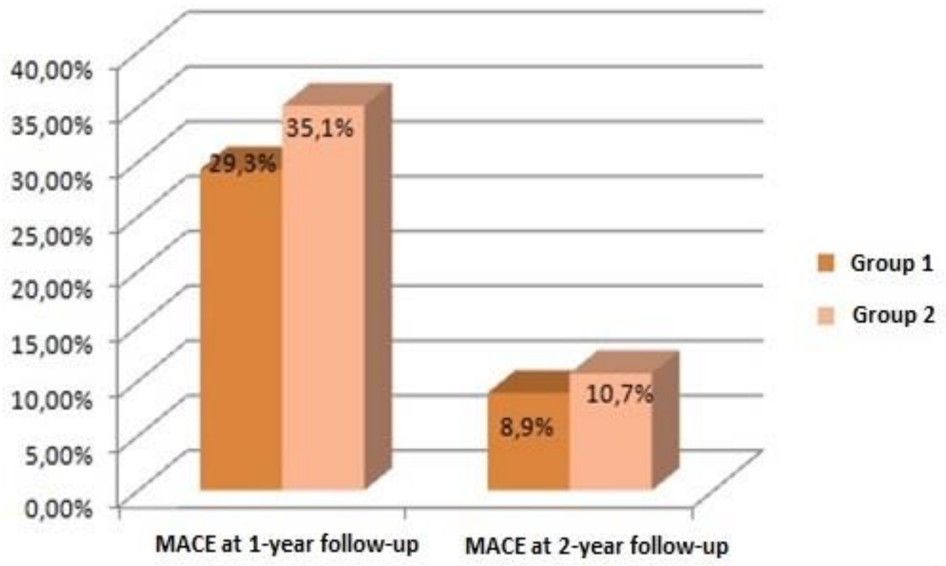
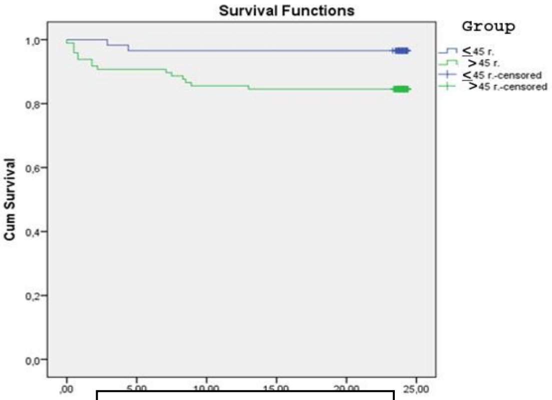


Figure 7. Proportion of patients in each group who experienced at least one MACE.

6.3. Comparative analysis regarding survival and survival without MACE in the first and second year.

Figure 8 represents Kaplan-Meier curves for the cumulative survival rate of the two groups over 24 months. There is an initial divergence in the curves concerning this indicator, and according to the Log-Rank Test, p=0.043, showing a significantly better prognosis for Group 1 in terms of survival.



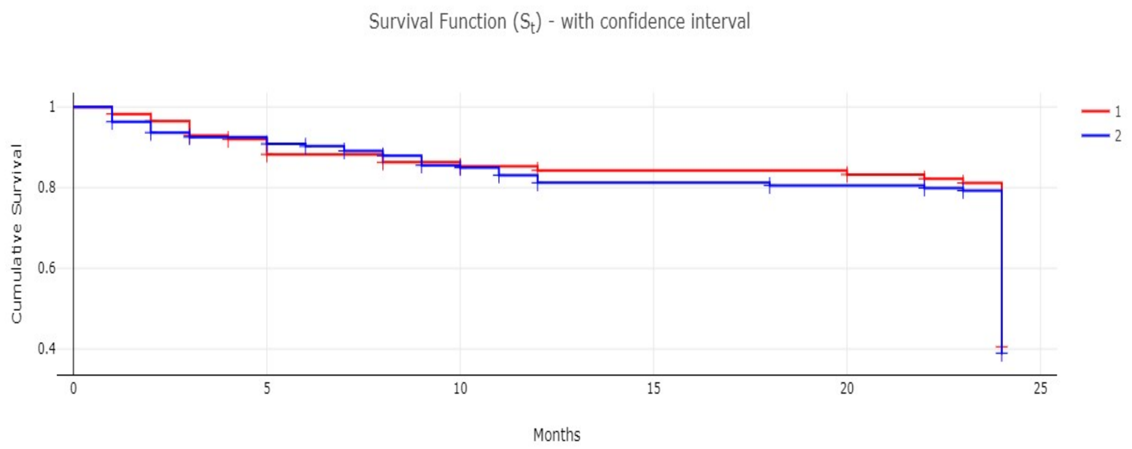
Log RankTest, p=0.043

Figure 8. Kaplan-Meier curves for cumulative survival, stratified by age, for 2-year follow-up.

- Regarding survival, younger patients had a significantly more favorable prognosis at the one-year follow-up, and this trend persisted until the end of the follow-up period **(Table 36).**
- In terms of survival without MACE in the groups by the end of the first year, the proportion is higher in the younger group, but without significance. The same trend persisted until the end of the second year of follow-up (81.1% compared to 79.2%; log-rank test, p = 0.781) (**Table 36 and Figure 9).**

Group	Survival (%)		Survival without MACE (%)	
	1-year follow-up	2-year follow-up	1-year follow-up	2-year follow-up
Age≤ 45	96,6	96,6	84,2	81,1
Age>45	88,6	86,6	81,2	79,2

Table 36. Survival and survival without MACE.



Log RankTest, p=0.781

Figure 9. Kaplan-Meier curves for cumulative survival without MACE.

6.4. Assessment of the impact of various factors such as gender, AH, dyslipidemia, DM, presence of >2 RFs, reduced LVEF, late patient presentation, Killip class >2, infarct localization, presence of MVD and hospital stay duration on all-cause mortality up to two years for each group separately (Univariate analysis).

When evaluating the influence of the listed factors on mortality by the end of the 2-year period from the index event for all studied patients, it is evident that in group 1, none of the factors could be considered to have a negative prognostic value regarding the monitored variable. For group 2, prognostic factors with a negative impact include Killip class >2 upon admission (p - 0.007), the presence of MVD (p-0.019), and a longer hospital stay (p - 0.021). Therefore, patients with these characteristics are more likely to have a fatal outcome by the end of the 2-year period from the index event (Tables 37 and 38).

Group	Variable		All-cause mortality at 2-year follow-up		Total	p
			No	Yes		
Age≤ 45	**Gender**	Male	92,9%(N 52)	100,0%(N 2)	93,1%(N 54)	1,000
		Female	7,1% (N 4)	0,0% (N 0)	6,9% (N 4)	
Age>45	**Gender**	Male	68,2% (N 58)	76,9% (N 10)	69,4% (N 68)	0,517
		Female	31,8% (N 27)	23,1% (N 3)	30,6%(N 30)	
Age≤ 45	**Number of RFs**	≤2 RFs	42,9%(N 24)	50,0%(N 1)	43,1%(N 25)	0,818
		>2 RFs	57,1%(N 32)	50,0%(N 1)	56,9%(N 33)	
Age>45	**Number of RFs**	≤2 RFs	39,8%(N 33)	26,7%(N 4)	37,8%(N 37)	0,340
		>2 RFs	60,2%(N 50)	73,3%(N 11)	62,2%(N 61)	
Age≤ 45	**Time from symptoms onset**	<6 h	71,4%(N 40)	50,0%(N 1)	70,7%(N 41)	0,504
		>6 h	28,6%(N 16)	50,0%(N 1)	29,3%(N 17)	
Age>45	**Time from symptoms onset**	<6 h	61,2%(N 52)	53,8%(N 7)	60,2%(N 59)	0,762
		>6 h	38,8%(N 33)	46,2%(N 6)	39,8%(N 39)	
Age≤ 45	**LVEF%**	<50	33,9%(N 19)	50,0%(N 1)	34,5%(N 20)	0,638
		≥50	66,1%(N 37)	50,0%(N 1)	65,5%(N 38)	
Age>45	**LVEF%**	<50	31,3%(N 26)	53,3%(N 8)	34,7%(N 34)	0,175
		≥50	68,7%(N 57)	46,7%(N 7)	65,3%(N 64)	
Age≤ 45	**Killip class**	1-2	100,0%(N 56)	100,0%(N 2)	100,0%(N 58)	n/a
Age>45	**Killip class**	1-2	98,8%(N 82)	80,0%(N 12)	95,9%(N 94)	0,007
		3-4	1,2%(N 1)	20,0%(N 3)	4,1%(N 4)	
Age≤ 45	**MI localization**	Anterior	44,6%(N 25)	50,0%(N 1)	44,8%(N 26)	0,881
		Other	55,4%(N 31)	50,0%(N 1)	55,2%(N 32)	
Age>45	**MI localization**	Anterior	38,6%(N 32)	53,3%(N 8)	40,8%(N 40)	0,284
		Other	61,4%(N 51)	46,7%(N 7)	59,2%(N 58)	

Age≤ 45	**MVD**	No	87,5%(N 49)	100,0%(N 2)	87,9%(N 51)	1,000
		Yes	12,5%(N 7)	0,0%(N 0)	12,1%(N 7)	
Age>45	**MVD**	No	59,0%(N 49)	26,7%(N 4)	54,1%(N 53)	0,019
		Yes	41,0%(N 34)	73,3%(N 11)	45,9%(N 45)	

Table 37. The analysis of the impact of qualitative variables on mortality by the end of the follow-up period for patients in both groups.

Group	**Variable**		N	**Hospital stay**				p
				Mean	SD	Min	Max	
Age≤ 45	All-cause mortality at 2-year follow-up	No	56	3,86	1,38	2,00	9,00	n/a
		Yes	2	4,50	2,12	3,00	6,00	
Age> 45	All-cause mortality at 2-year follow-up	No	83	3,58	1,45	1,00	10,00	0,021
		Yes	15	5,62	3,28	3,00	12,00	

Table 38. Analysis of the impact of the length of hospital stay on mortality until the end of the follow-up period among patients in both groups.

After conducting binary logistic regression for a quantitative assessment of the factors' impact on mortality, the odds ratios (OR) for the factors with significant prognostic value were determined **(Table 39).**

Group	Factor	OR	95% CI		p
Age> 45	Killip > 2	20,500	1,969	213,430	0,011
	MVD	4,762	1,221	18,564	0,025

Table 39. Odds ratio for factors with negative prognostic value regarding the two-year mortality in Group 2.

6.5. Assesement the influence of factors like gender, AH, dyslipidemia, DM, presence of >2 RFs, reduced LVEF, late patient presentation, Killip class >2, anterior localization of the MI, presence of MVD and duration of hospital stay on the probability of occurrence of MACE at 2-year follow-up for each group separately (Univariate analysis).

- When assessing the influence of the listed factors on the probability of occurrence of a MACE at the end of the 2-year follow-up period from the index event in all patients, it was found that for Group 1, a reduced LVEF < 50% (p - 0.027), anterior localization of the MI (p - 0.025), and the presence of >2 RFs (0.021) had negative prognostic value. For Group 2, the predictors for MACE were a reduced LVEF (p- 0.003), anterior localization of the MI (p - 0.006), and, with borderline significance, the presence of MVD (p - 0.090). Thus, patients with these characteristics are more likely to experience at least one adverse event by the end of the 2-year follow-up. No significant relationship was established between the duration of hospital stay and the likelihood of MACE in either of the two groups **(Tables 40 and 41)**.

Group	**Variable**			MACE at 2-year follow-up		Total	p
				No	Yes		
Age≤ 45	**Gender**	Male	%(N)	94,7%(N 36)	90,0%(N 18)	93,1%(N 54)	0,602
		Female	%(N)	5,3%(N 2)	10,0%(N 2)	6,9%(N 4)	
Age>45	**Gender**	Male	%(N)	65,0%(N 39)	77,8%(N 28)	69,8%(N 67)	0,252
		Female	%(N)	35,0%(N 21)	22,2%(N 8)	30,2%(N 29)	
Age≤ 45	**Number of RFs**	≤ 2RFs	%(N)	55,3%(N 21)	20,0%(N 4)	43,1%(N 25)	0,021
		>2RFs	%(N)	44,7%(N 17)	80,0%(N 16)	56,9%(N 33)	
Age>45	**Number of RFs**	≤ 2RFs	%(N)	35,0%(N 21)	47,2%(N 17)	39,6%(N 38)	0,237
		>2RFs	%(N)	65,0%(N 39)	52,8%(N 19)	60,4%(N 58)	
Age≤ 45	**Time from symptoms onset**	< 6 h	%(N)	68,4%(N 26)	75,0%(N 15)	70,7%(N 41)	0,764
		> 6 h	%(N)	31,6%(N 12)	25,0%(N 5)	29,3%(N 17)	
Age> 45	**Time from symptoms onset**	< 6 h	%(N)	58,3%(N 35)	61,1%(N 22)	59,4%(N 57)	0,833
		> 6 h	%(N)	41,7%(N 25)	38,9%(N 14)	40,6%(N 39)	
Age≤ 45	**LVEF%**	<50%	%(N)	23,7%(N 9)	55,0%(N 11)	34,5%(N 20)	0,017
		≥50	%(N)	76,3%(N 29)	45,0%(N 9)	65,5%(N 38)	
Age> 45	**LVEF%**	<50%	%(N)	23,3%(N 14)	52,8%(N 19)	34,4%(N 33)	0,003
		≥50	%(N)	76,7%(N 46)	47,2%(N 17)	65,6%(N 63)	
Age≤ 45	**Killip class**	1-2	%(N)	100,0%(N 38)	100,0%(N 20)	100,0%(N 58)	n/a

Age>45	**Killip class**	1-2	%(N)	98,3%(N 59)	91,7%(N 33)	95,8%(N 92)	0,147
		3-4	%(N)	1,7%(N 1)	8,3%(N 3)	4,2%(N 4)	
Age≤ 45	**MI-localization**	Anterior	%(N)	34,2%(N 13)	65,0%(N 13)	44,8%(N 26)	0,025
		Other	%(N)	65,8%(N 25)	35,0%(N 7)	55,2%(N 32)	
Age> 45	**MI localization**	Anterior	%(N)	30,0%(N 18)	58,3%(N 21)	40,6%(N 39)	0,006
		Other	%(N)	70,0%(N 42)	41,7%(N 15)	59,4%(N 57)	
Age ≤45	**MVD**	No	%(N)	89,5%(N 34)	85,0%(N 17)	87,9%(N 51)	0,683
		Yes	%(N)	10,5%(N 4)	15,0%(N 3)	12,1%(N 7)	
Age> 45	**MVD**	No	%(N)	61,7%(N 37)	41,7%(N 15)	54,2%(N 52)	0,090
		Yes	%(N)	38,3%(N 23)	58,3%(N 21)	45,8%(N 44)	

Table 40. Analysis of the impact of qualitative variables on MACE until the end of the follow-up in patients in both groups.

Group	Variable		N	Hospital stay				p
				Mean	SD	Min	Max	
Age≤45	MACE at 2-year follow-up	No	38	3,79	1,45	2,00	9,00	0,406
		Yes	20	4,05	1,28	3,00	7,00	
Age>45	MACE at 2-year follow-up	No	60	3,53	1,28	2,00	8,00	0,107
		Yes	36	4,42	2,56	2,00	12,00	

Table 41. Analysis of the influence of hospital stay length on MACE until the end of follow-up in patients in both groups.

In order to quantitatively assess the degree of impact of factors on mortality via binary logistic regression, the odds ratio (OR) for significant influencing factors in Group 1 and Group 2 were determined **(Tables 42 and 43).**

Group	**Factor**	OR	95% CI		p
Age< 45	LVEF < 50%	3,938	1,240	12,507	0,020
	Anterior localization of MI	3,571	1,145	11,137	0,028
	> 2 RFs	4.941	1.389	17.570	0.013

Table 42. Odds ratio for factors with a negative prognostic value regarding the probalility of MACE for 2 years in Group 1.

Group	**Factor**	OR	95% CI		p
Age> 45	LVEF < 50%	3,672	1,513	8,912	0,004
	Anterior localization of MI	3,266	1,378	7,739	0,007
	MVD	2,252	0,970	5,230	0,059

Table 43. Odds ratio for factors with a negative prognostic value regarding the probalility of MACE for 2 years in Group 2.

VI. DISCUSSION

AMI in young individuals is relatively rare. Its frequency varies between 2 and 10% (Zimmerman et al., 1995; Doughty et al., 2002; Fournier et al., 2004). However, McGill et al. (2000) reported an unexpectedly high incidence of coronary artery disease found in autopsy series in men under 35, with advanced coronary lesions described in 20% of cases. The majority of authors define the prognosis for young patients with AMI as relatively favorable compared to that for older individuals, with in-hospital mortality ranging between 0.7 and 7% (Barbash et al., 1995; Rosengren et al., 2006; Chua et al., 2010; AzinAlizadehasl et al., 2010). Still during long-term follow-ups, a decrease in survival is observed among young individuals who have survived MI, with mortality reaching 15% at seven years of follow-up (Zimmerman et al., 1995) and 25-29% at 15 years (Awad-Elkarim et al., 2003; Fournier et al., 2004).

Despite the reported relatively low frequency and benign prognosis of MI, interest in this disease among young patients is increasing due to the fact that the condition can lead to disability, incapacity to work, and death during the prime of life, as well as devastating socio-economic and psychological consequences for the patient, their family, and economic repercussions on the gouvernment.

Young patients with MI exhibit different demographic, clinical, risk, and angiographic profiles, as well as different prognosis compared to older patients. Defining their characteristics would likely benefit in better understanding this patient group, aiming for improved primary and secondary prevention, developing programs to enhance public awareness, early diagnosis, and more prompt and effective treatment.

Southeastern Europe is a region with high morbidity and mortality due to cardiovascular diseases. However, there is a lack of sufficient data in the literature regarding the characteristics of young patients with MI.

The aim of the current retrospective study is to determine the peculiarities of young patients with MI by comparing them with an older group. All patients underwent selective coronary angiography, and the results are derived from routine practice at a high-volume reference center in Bulgaria.

1. Demographic characteristics

Our results show that the mean age of patients in Group 1 is 39.74±4.97 years (ranging from 18 to 45 years according to the inclusion criteria), while in Group 2, the mean age is 67.21±10.18 years (without an upper limit). After a review of the literature, large studies defining the same age cut-off for both groups demonstrate significant similarities to our results. Morillas et al. (2002) reported a mean age of 40.06 years for young patients and 67.3 years for older patients. Lv et al. (2021) reported 39.95 years and 65.06 years, respectively, while Chen et al. (1995) reported 39 years and 66 years, respectively. We do not observe a trend toward earlier presentation among the patients we studied compared to the data reported thus far.

Regarding gender distribution, we observe an absolute predominance of males in Group 1 - 91.8% males compared to 8.2% females (p= 0.001). These findings are consistent with the literature, where Lei and Bin (2019) reported frequencies ranging from 67.5% to 94.8% in favor of males among patients with MI under the age of 45. In Group 2, the male gender also significantly predominates, but with a decreasing ratio-male:female, compared to Group 1 (70.3% versus 29.7%). In the majority of studies with a similar design, the percentage ratio in favor of the male gender is higher among younger patient groups (Hoit et al., 1986; Morillas et al., 2002; Jing et al., 2016). This trend is clearly demonstrated in the Euroheart Acute Coronary Syndrome Survey, where it becomes evident that with each decade, the proportion of women with AMI gradually increases from 17.5% in the under 55 age group to 56.2% in the over 85 age group (Rosengren et al., 2006). This trend is likely explained largely by the known protective role of estrogen before menopause. According to Alshahrani et al. (2013), the predominance of males among young patients with AMI is one of the probable reasons for delays in the treatment of young women presenting with AMI.

2. Risk Factors

Despite the different risk profile among young patients with AMI, it turns out that they exhibit the same traditional cardiovascular RFs as older patients with ischemic heart disease. A meta-analysis of 8 RCT indicated that, compared to older patients, young patients with AMI have a higher frequency of smoking, obesity, and a family history of CVD. On the other hand, they have a lower frequency of AH and DM, while regarding dyslipidemia, there is no significant difference (Lei and Bin, 2019). In their literature review, Shah et al. (2016) reported a greater incidence of MI, especially among young patients, who also had nontraditional atherogenic RFs and etiologies such as cocaine use, spontaneous coronary artery dissection, Kawasaki disease, factor V Leiden mutation, low estrogen levels, and oral contraceptive use in young women.

The results of the current study have presented data regarding traditional RFs, including illicit drug abuse, as there is no evidence of any patient having any of the other rarer RFs.

There is a notably high frequency of patients in both groups having a combination of ≥ 2 RFs—specifically, 83.6% in Group 1 and 92.8% in Group 2, with no significant difference between the groups. Notably, more than half (57.4%) of the young studied patients had 3 or more RFs. There are significant differences between the two groups concerning three RFs—smoking, AH, and obesity—and borderline significance for DM. The predominant RFs in the entire studied patient population include male gender (77.9%), AH (84.3%), and dyslipidemia (88.3%). Exept male gender, discussed above as the predominant RF in Group 1, dyslipidemia holds the highest percentage in the younger group (in 88.5% of patients), followed by AH (70.5%), smoking (55.7%), and family history (27.9%). In Group 2, AH has the highest frequency (91.9%), followed by dyslipidemia (88.3%) and obesity (31.5%).

According to the INTERHEART study, smoking, AH, abnormal lipid profile, and DM have the highest relative impact on the risk of MI, calculated through OR (odds ratio) and PAR (population attributable risks), with this risk being more pronounced in patients under 40 years of age compared to older individuals. The combination of nine risk factors leads to a significantly higher PAR ($p<0.0001$) for MI among younger individuals compared to older ones (Yusuf et al., 2004).

Although no significant difference in the frequency of dyslipidemia is found between the two groups ($p=0.963$), the exceptionally high frequency of this risk factor in both groups is notable. In fact, this frequency is higher than reported in similar studies (Chua et al., 2010; Yandrapalli et al., 2019; Lv et al., 2021). Possible reasons for this discrepancy could include variations in the definitions of "dyslipidemia", genetic factors, unhealthy behaviors, and underestimation of primary prevention in our country. Despite contradictory data regarding the role of dyslipidemia as a RF, especially in young patients, Lei and Bin (2019) defined it as a primary RF in a meta-analysis of randomized controlled trials, particularly highlighting high levels of LDL cholesterol. Consistent with the results obtained in our study population, no statistical difference regarding this RF was demonstrated between age groups. However, they observed that young patients with MI have higher levels of serum triglycerides, LDL, and total cholesterol and lower levels of serum HDL compared to older patients with MI. These findings support the necessity for early identification of dyslipidemia at a younger age, correction of lipid profiles, and increased attention given to serum HDL cholesterol levels. The recorded high frequency of dyslipidemia in the studied population is in accordance with the findings reported by Chan et al. (2006), who reported an 86% frequency of dyslipidemia in their population of young patients with MI. It's noteworthy that this frequency was significantly greater than that observed in patients older than 45 years. The authors emphasize the need for early diagnosis and treatment of dyslipidemia through lifestyle changes and pharmacological therapy. They highlighted that modifying this RF has been proven to reduce the risk of CVD, particularly in the young population, which is initially perceived as having low risk, leading to an underestimation of primary prevention efforts in this entity.

AH has high proportion in both groups in the current analysis, reaching levels of 70.5% in Group 1 and 91.9% in Group 2 ($p <0.001$). Consistent with our results, most authors have prioritized AH and DM for older patients (Zimmerman et al., 1995;

Doughty et al., 2002; Chen et al., 2014). However, according to Anderson et al. (2008), the adjusted relative risk for this RF is greater in young patients with respect to clinical outcomes. Therefore, early diagnosis and treatment of AH in young individuals are crucial for reducing the frequency of MI among them.

Regarding the presence of diabetes, similar to the findings of the previously mentioned studies, a higher frequency of diabetes was observed in Group 2, with borderline significance.

Other RFs for which a significant difference is observed between the groups are smoking, more prevalent among young patients (55.7% vs. 28.8%; p=0.001), and obesity (16.4% vs. 31.5%; p=0.031), which conversely is less represented among them.

Smoking deserves particular attention, as the literature suggests that smoking is the predominant modifiable RF with statistical significance in young patients with MI in comparative analyses (Zimmerman et al., 1995; Lei et al., 2019; Yandrapalli et al., 2019; Lv et al., 2021). More than half of the patients in Group 1 are defined as smokers (55.7%), closely corresponding with findings from a retrospective cohort analysis of young myocardial infarction patients conducted in the United States, where 56.8% presented with this RF (Yandrapalli et al., 2019). The majority of studies indicate an even greater proportion of smoking among young individuals with acute coronary syndrome, ranging from 62 to 90% (Uhl & Farrell, 1983; Wolfe & Vacek, 1988; Zimmerman et al., 1995; Chan et al., 2006; Alizadehasl et al., 2010).

Smoking, as a traditional RF, may act by plural mechanisms in the development of coronary artery disease: it plays a role not only in atherogenesis, increasing the risk of early coronary incidents but also in thrombogenesis and a pronounced tendency for coronary vasospasm. Furthermore, smoking causes endothelial dysfunction by enhancing platelet aggregation and blood viscosity. These mechanisms could partially explain the high frequency of NOCD found in young smokers with AMI (Morillas et al., 2002).

The importance of reducing smoking rates among young individuals is highlighted by observations in the VALIANT study by Anderson et al. (2008). They found a significant correlation between age and smoking and age and hypertension concerning prognosis. The adjusted relative risk attributed to these factors is most pronounced in young patients. Among them, only smoking predominates in young individuals and is associated with a greater risk of post-MI events compared to older persons. The smoking-related risk diminishes with age.

Another risk factor for which a significant difference observed between the two groups is obesity, but in contrast with the literature data, Group 1 had a significantly smaller proportion of obese patients compared to Group 2 (16.4% versus 31.5%). Lei and Bin (2019) reported frequencies of 36.21% and 31.95%, respectively, defining a significant difference with higher frequencies among younger patients. It is evident that actually the proportion of obese patients in the older groups is similar, meaning that the differences arise from a significantly lower percentage of obese patients in the investigated Group 1. We note much lower prevalence of obesity in the younger age group, compared to the 48.2% reported by Chua et al. (2010). In contrast, Lv et al. (2021) reported lower frequencies of this RF (18.3%) in the younger population but with a defined BMI threshold of ≥28 kg/m2.

Anderson et al. (2008) defined obesity as one of the risk factors with predictive value for a worsened prognosis in young patients with MI during a two-year follow-up.

Only two patients in group 1 reported illicit substance abuse. However, since the center does not employ drug tests, the actual number of these patients could potentially be higher.

Gulati et al. (2020) categorize MI in young individuals due to the intake of prohibited substances as a separate category and define it as non-traditional cardiovascular RF. According to the NHANES-3 survey, cocaine use was attributed as the cause for 25% of non-fatal MI in individuals between 18 and 45 years old (Qureshi et al., 2001). Potential illicit substances abuse should be considered in all young patients with AMI, particularly when traditional RFs are absent, and documented coronary vasospasm is observed via angiography, in order to guide subsequent treatment.

In a gender sub-analysis examinating the differences in the presence of RFs, no such differences were found regarding any of them in either of the two age groups.

This result contradicts the findings from the VIRGO Study Analysis, where young women were burdened more by cardiovascular RFs, while men had a higher frequency of hypercholesterolemia and smoking ($p<0.01$); there were no differences in the frequency of AH, previous coronary artery disease, or cocaine use between the genders (all $p>0.1$) (Bucholz et al., 2017). The small proportion of women in Group 1 could mask hidden differences in the risk profile between genders. Another potential reason for the discrepancy in the results could be the higher age cut-off defining "young" in the VIRGO Study.

We find alarming the result concerning the presence of prior RFs in both groups, with 96.7% of young individuals and 99.1% of older individuals having at least one RF, and no significant difference was detected. These findings in young patients are consistent with those of Chan et al. (2006). However, they presented a considerably lower percentage of individuals with ≥ 2 RFs, 83.6% in Group 1 of the present study and 92.8% in Group 2, without a significant difference noted. Lower proportions were also indicated by Yandrapalli et al. (2019) in a study involving 1,462,168 patients (67.2% compared to 70.7%).

The presence of a greater number of RFs in an individual is directly related to the extent of atherosclerosis. In an autopsy series involving individuals between 2 and 39 years old, it was demonstrated that the prevalence of lipid streaks in the coronary arteries increased from 1.3% to 11.0% with 0 and 4 risk factors, respectively. This evidence shows that as the number of risk factors increases, so does the severity of asymptomatic coronary and aortic atherosclerosis (Berenson et al., 1998).

The presence of modifiable RFs, particularly a combination of multiple factors among young individuals, as observed in the present study, has been proven to significantly increase the risk of MI to a much greater extent in younger individuals than in older individuals, as per the INTERHEART study (Yusuf et al., 2004). This outcome emphasizes the urgent need for effective primary prevention measures, not only in older patients but also in the younger population, where modifying these RFs could prevent a portion of premature MIs.

As a weakness of the current study we note the lack of analysis addressing non-traditional RFs, such as hypercoagulable states, autoimmune conditions, and familial hypercholesterolemia, stemming from its retrospective nature. Thrombophilia should be considered in young patients with MI in the absence of traditional RFs and with a positive family history.

In our study, the proportion of patients with history of previous MI in group 1 is half of that in group 2 (6.7% compared to 13.5%), but without a significant difference. The incidence of previous MI in group 1 is consistent with that reported in a study based on the PRIMVAC registry (6.9%); however, Morillas et al. (2002) indicated a significant difference regarding this indicator, pointing to a higher frequency in adult patients. The rates for both groups are higher than those reported by Lv et al. (2021) at 4.5% compared to 7.9%. According to their univariate analysis, the authors did not identify prior MI as a predictor of in-hospital or two-year mortality in patients ≤45 years old, unlike in those older than 45 years.

There is a significant difference between the groups regarding the frequency of prior revascularization, with 3.3% in group 1 and 24.3% in group 2 ($p<0.001$). Lv et al. (2021) reported similar frequencies in the younger group - 3.2% - and lower in the older group - 5.1%, specifically focusing only on the frequency of prior PCI. It is expected that including surgical revascularization might increase the percentage of patients, especially in the >45 years age group, presuming that younger patients less frequently have a history of previous bypass surgery. The authors did not identify a history of previous PCI as a predictor of increased 2-year mortality in the younger patient group but found it significant in the >45 age group.

3. Clinical presentation

3.1. Presence of prior angina

Few studies have compared age differences in terms of the presence of prior angina. This indicator is subjective and lacks a precise temporal definition. The recruited retrospective data indicates no significant difference in the presence of prior angina symptoms between the two groups (41% versus 46.8%, respectively; $p=0.459$), with a relatively high percentage of young patients reporting preceding angina symptoms. In the literature, the prevailing opinion is that MI in young individuals is less frequently associated with prior angina. In an observational study of 266 patients under the age of 35 with their first MI, 88 patients (33.1%) had symptoms preceding the MI. Among them, 52 reported nonspecific chest pain, while only 36 had a history typical of angina (Malik et al., 2016). According to the Euroheart acute coronary syndrome survey, the frequency of prior angina significantly increases with advancing age (Rosengren et al., 2006). Sinha et al. (2017) suggested that MIs without prodromal symptoms are more common in young individuals with CAD. They explain this fact at a histopathological level, stating that young patients tend to have atherosclerotic plaques richer in lipid core and poorer in connective tissue, prone to rupture before the development of angina symptoms compared to older patients. This could also explain the higher frequency of STEMI among younger individuals.

3.2. *Symptoms at presentation*

The majority of patients in both groups presented with typical chest pain upon admission, the proportion of which decreased with advancing age; however, there was no significant difference between the groups, namely, 90.16% compared to 85.6% ($p = 0.534$). In group 1, the most commonly reported symptoms after typical chest pain are shortness of breath (16.4%) and sweating (14.7%), while in group 2, they are shortness of breath (14.4%) and nausea/vomiting (8.1%). Most authors present a high percentage of patients in the young cohort reporting typical chest pain, exceeding 90%, corresponding to the obtained results, even noting a significant difference between age groups. Schoenenberger et al. (2011), in a large prospective cohort study that divided MI patients into groups under and over 35 years old, reported that chest pain was the most common symptom in both groups. However, it significantly prevailed in the younger group - 91.6% compared to 83.7% (9 out of 10 young patients presented with chest pain) ($P = 0.003$); shortness of breath and signs of heart failure were significantly lower in younger patients.

Given the findings from Canto et al. (2012) in an observational study using data from the National Registry of Myocardial Infarction of an existing significant bidirectional relationship (gender and age) in MI presentation without chest pain ($P < 0.001$) (the younger the women, the more likely they were to present without chest pain compared to men), we conducted a gender subanalysis in both groups. It revealed no significant difference between the sexes in either Group 1 or Group 2. The authors highlighted significantly higher in-hospital mortality among young women presenting without chest pain, with this association decreasing with age.

3.3. Time from symptom onset to hospital presentation

The mean time of presentation for young patients with AMI is nearly 4 hours shorter (7.76 hours) than that in Group 2 (11.67 hours), leading to a statistically significant difference when comparing this variable (p= 0.004). These results are concordant with data from previous studies, where a tendency toward earlier presentation in younger groups was observed.

Morillas et al. (2002) noted shorter times from symptom onset to presentation at a healthcare facility—120 minutes and 160 minutes—for the age groups respectively. However, the time to admission to a coronary care unit for the younger group somewhat approximated that of Group 1 (215 minutes), while for Group 2, it was once again shorter (260 minutes). The authors reported a significant difference between the groups for both indicators.

When defining a time interval of 6 hours from the onset of symptoms, dividing patients in two time subgroups a significant trend persists for younger individuals to present earlier at a healthcare facility (p=0.047). We should not underestimate the fact that nearly 28% of young patients presented at the hospital after 6 hours from the beginning of symptoms. Lv et al. (2021) noted an even higher frequency of delays beyond 6 hours from the symptoms onset in the younger group, close to 50%, without defining the upper limit of infarction onset. Given the small number of asymptomatic patients in the study, according to the authors, this phenomenon might mainly be explained by insufficient awareness of acute coronary events in young adults with cardiovascular risk factors. These findings, along with ours, emphasize the need for effective educational programs aimed at reducing hospital delays and thereby improving treatment effectiveness.

An analysis based on data from the VIRGO study was conducted in order to determine the reasons for the poorer long-term prognosis in young women with MI compared to men. Women experienced significantly longer delays from symptom onset to presentation (>6 hours) ($p<0.01$), leading to more severe MI (Killip class and Grace score) and delayed reperfusion (beyond recommended time frames). According to Bucholz et al. (2017), this delay is one of the reasons for the worsened prognosis.

When conducting a gender-based subgroup analysis in the current study, no statistical difference was observed regarding delays >6 hours between the sexes. Nevertheless, only in group 1 the proportion of women presenting late exced that of men ($p=0.612$). The lack of concordance with the findings of other studies and the significant difference in this parameter might be explained to some extent by the small number of women in group 1. In contrast, the VIRGO study focused on the specificities of the female gender, with a selection ratio of 2:1 in favor of women. Additionally, the defined age cut-off was greater than that specified in the current analysis. With a larger number of women in the young population with MI, a masked tendency toward delayed presentation could potentially be revealed.

3.4. Acute HF at presentation

Killip and Kimball (1967) defined the role of heart failure accompanying MI concerning in-hospital mortality before the reperfusion era.

More patients in group 2 present with acute HF Killip class >2 (14.4%) compared to those in group 1 (4.9%), with borderline significance ($p= 0.057$), supporting data from previous studies (Rosengren et al., 2006; Lv et al., 2021). Despite the similarities in group differences, Lv et al. (2021) reported lower proportions of patients with a high Killip class in both groups than we did in our study. Chua et al. (2010) reported higher frequencies, reaching 20.2% and 31.5% for Killip classes III and IV in the younger and older groups, respectively, and again observed a significant difference. Rosengren et al. (2006) reported an increasing proportion of patients with HF (Killip class 3-4) with advancing age, dividing the study group into 5 age decades. The multivariate analysis shows that Killip class 3 or 4 upon hospitalization can be an independent predictor for in-hospital morbidity (OR: 31.15, 95% CI: 7.22–137.06, $P <0.001$), as well as for the combination of in-hospital morbidity and mortality (OR: 42.15, 95% CI: 8.13–218.57, $P <0.001$) in young patients (Chua et al., 2010). In fact, all young patients in our study who presented with Killip class >2 died during the index hospitalization, supporting the aforementioned statement.

3.5. Relation STEMI/NSTEMI in the groups

In both groups, ST-elevation STEMI tends to be more prevalent, but no significant difference in this parameter is observed when comparing the two groups. There are controversal data regarding the exact STEMI/NSTEMI ratio in young individuals, but the prevailing opinion suggests that, compared to older populations, STEMI is more frequent than NSTEMI among younger patients (Schoenenberger et al., 2011; Puricel et al., 2013; Zasada et al., 2021).

In the PRIAMHO II study, a Spanish prospective investigation involving 6210 MI patients divided into 2 groups, under and over 45 years old, STEMI occurred in 78.8% of patients in the first group and in 65.4% of patients in the second group, while the frequency of NSTEMI and LBBB was significantly lower in younger individuals than in older individuals (Morillas et al., 2007). The frequency of STEMI in group 1 in our study is consistent with that reported by the authors but is greater in group 2.

In the present study, patients with NSTEMI and low risk who were subjected to a selective invasive strategy were not included, which could have partially reduced the actual proportion of patients with NSTEMI in both groups.

3.6. Localization of the myocardial infarction

The majority of patients in both Group 1 and Group 2 present with myocardial infarctions of the anterior wall of the left ventricle (over 40% in both groups), followed by infarctions of the inferior wall. There is no significant difference observed in the predominance of any specific localization between the groups.

The incidence of anterior wall MI is higher in the younger population compared to older adults according to previous studies (Anderson et al., 2008; Christus et al., 2011; Lv et al., 2021). In the VALIANT study, it was observed in 69.7% of patients aged between 18 and 45 years and in 56.4% of patients over 65 years old (Anderson et al., 2008). Our findings support the prevalence of this type of infarction, but a significant difference was not established between the two age groups ($p = 0.822$).

A study conducted at the University of Michigan Medical Center (UMMC), categorizing patients with myocardial infarction into three age groups—those under 46, between 46 and 54, and over 54 years old—also revealed a significant difference in the localization of the MI (anterior, posterior, inferior, apical, lateral, right ventricular, etc.) among the three groups; however, in contrast with the widely accepted opinion, the authors noted inferior infarctions as the most common, according to ECG data within each age category (Doughty et al., 2002).

4. Echocardiographic and laboratory parameters

4.1. Left ventricular ejection fraction

Considering the results from comparing the proportion of patients with acute HF, it is surprising that there's no significant difference in the LVEF during hospitalization between the groups. The comparison was not made with the mean value; instead, the measure was categorized into three groups—preserved LVEF, mildly reduced LVEF, and reduced LVEF.

These findings contrast with the hypothesis that the LVEF is higher in younger individuals compared to older ones with MI (Lv et al., 2021). In our analysis, the majority of patients in both groups have preserved LVEF (≥ 50%)—62.3% versus 59.5%, corresponding to Lv et al.'s data for both groups above 50%; moreover, they found a statistically significant difference. However, in our study, these differences did not reach statistical significance when the patients were categorized into three larger groups. Nonetheless, a meta-analysis presented by Lei and Bin (2019) regarding LVEF between the two age groups revealed no significant differences ($p= 0.07$), aligning with the results obtained in our study. Nearly a quarter of the young population in our study had a reduced LVEF, which should not be neglected, as Lv et al. (2021) identified the LVEF, along with a high Killip class, as an independent predictor of in-hospital mortality in patients aged ≤ 45 years with MI.

4.2. Mitral regurgitation

In terms of the severity of mitral regurgitation, significant differences were observed. A higher proportion of patients in Group 1 presented with mild mitral regurgitation (<2 degree) compared to Group 2 (98.4% versus 73.0%; $p < 0.001$). Only one patient in Group 1 (1.6%) had mitral regurgitation ≥2 degree and she had a fatal outcome during the index event.

However, comparative analyses regarding this parameter are limited. Presumably, adult patients tend to have an initially higher degree of MR due to various overlapping etiological factors, including ischemic and degenerative causes. Alizadehasl et al. (2010) reported a significant difference in this parameter, with 6% of young patients (≤35 years old) and 14% of those older than 35 years having moderate or severe MR. Sinha et al. (2017), in their study focusing on even younger MI patients (≤30 years old), reported a greater frequency of severe mitral regurgitation compared to the findings in the current study, specifically 3.3%. However, without specifying age differences, Lamas et al. (1997) identified the presence of moderate MR as an independent predictor of cardiovascular mortality following MI during a 3.5-year follow-up.

4.3. Laboratory parameters

The average peak values of the cardiac biomarkers were compared for each group. There is no significant difference in any of the three tracked parameters between the two groups. Considering that these markers could indicate the degree of myocardial damage, the results correspond to those showing no significant difference in the left LVEF mentioned earlier. Nevertheless, we found that the peak values of the biomarkers are higher in group 1. These results partially correspond to those indicated by Chua et al. (2010), who showed significantly higher values only for CPK in the younger group but not for the CPK-MB fraction.

Shiraishi et al. (2005) compared only CPK and similarly did not find a significant difference between the groups. One year later, in determining predictors of MACE, Shiraishi et al. (2006) did not identify a correlation between peak CPK values and the likelihood of MACE in either of the age groups.

5. Angiographic characteristics and procedural features

Radial access is very frequent in both groups (95.1% versus 85.6%). There is a borderline significance favoring its preference in Group 1 (p-0.057). Similar results were reported by Lv et al. (2021) with an even more significant difference. In recent years, several studies have demonstrated the benefits of radial access in patients with ACS undergoing PCI by experienced radial operators, leading to its recommendation in current guidelines. The radial approach is associated with a lower bleeding risk at the puncture site, vascular complications, and the need for blood transfusions, as observed in the MATRIX trial (Valgimigli et al., 2015). There was also a benefit observed in terms of mortality when radial access was used, which was supported by previous findings in the RIVAL trial (Jolly et al., 2011).

Upon reviewing the groups, it appears that the tendency of using femoral access is observed in patients with initially higher Killip class and hemodynamic instability. This aligns with the significant difference found in acute HF between groups and might somewhat explain the lower frequency of radial access use in Group 2 and its association with better prognosis in terms of mortality.

Two of the three patients in Group 1 who had femoral access died during the index event, both of whom were in cardiogenic shock.

5.1. IRA-infarct related artery

In most young patients, the LAD is the Infarct-Related Artery (IRA) (40.9%), followed by the RCA (27.9%). For Group 2, RCA and LAD have nearly the same frequency, at 37.8% and 36.9%, respectively. There wasn't a significant difference observed in the predominance of a specific IRA between the two groups.

The dominance of the LAD as the “culprit” artery in young individuals with AMI has been previously reported in the literature (Zimmerman et al., 1995; Shiraishi et al., 2005; Chua et al., 2010; Lv et al., 2021). Zasada et al. (2021) even noted a significant difference in the predominance of the LAD as the culprit artery in a younger age group (<40 years old) (p<0.001).

In our study, only one patient from the younger age group had the LMA as the target artery; however, this difference lacked significance. Lei and Bin's meta-analysis (2019) also did not reveal a significant difference in the location of the target lesion between young and older individuals: LAD (p = 0.22), RCA (p = 0.36), and LCX (p = 0.11).

5.2. Number of arteries involved (SVD, DVD, MVD, NOCD)

In our study, single-vessel coronary artery disease (SVD) is the most common angiographic finding among patients in Group 1 (49.2%), followed by DVD - 27.9% and MVD - 11.5%. For Group 2, MVD is most prevalent (46.8%), while SVD is only observed in 22.5%. Significant differences are noted between the groups for SVD and MVD ($p < 0.001$) but not for DVD. Non-obstructive coronary disease (NOCD) is observed in 11.5% of younger patients and 1.8% of older patients ($p = 0.006$).

Our data are consistent with previous reports indicating that SVD is significantly more common among younger MI patients than among older patients (Wolfe and Vacek, 1988; Zimmerman et al., 1995; Rosengren et al., 2006; Colkesen et al., 2008; Lei and Bin, 2019).

MVD and LMA engagement are rare finding in Group 1, suggesting that younger patients exhibit less pronounced coronary atherosclerotic involvement.

Chen et al. (1995) argue that the weaker atherosclerotic involvement of the coronary arteries and the fact that myocardial infarctions in young patients often occur without preceding symptoms support the hypothesis that premature coronary artery disease is more strongly associated with rapid disease progression (plaque rupture and/or erosion) rather than a gradual development. They support this view via histopathological findings revealing that atherosclerotic plaques in young patients with coronary artery disease are characterized by lipid-rich cores and a relative lack of fibrous caps.

It seems there are similarities between our results and those reported by Zasada et al. (2021) in a study of young patients with MI (< 40 years old) in the Polish population. Specifically, in the group of patients under 40 years old, significantly more frequent outcome from angiography was normal coronary arteries (19.97% vs. 1.85%) and nonsignificant coronary atherosclerosis (14.44% vs. 6.75%) - MINOCA - $P < 0.001$. When significant coronary atherosclerosis was present, SVD was the most common finding in the younger group (47.99% vs. 35.41%), whereas MVD was found in 15.82% of younger patients compared to 46.02% of older patients - (P <0.001). The incidence of left main stenosis was found to be 0.40% in patients in group 1 and 0.30% in those in group 2. Regarding the IRA, it was most commonly the LAD in both groups, but the authors highlighted a statistically significant difference in the frequency between the two groups (51.26% vs. 36.32%, P <0.001), followed by the RCA (25.05% vs. 32.28%, P <0.001), the LCX (14.08% vs. 19.31%, P <0.001), and the LMA (1.84% vs. 3.23%, P <0.001).

Based on these data, the authors suggest that patients with non-significant coronary atherosclerosis and those without evidence of atherosclerosis but diagnosed with a MI (MINOCA, nearly 35% of younger patients and only 9% of older patients) are potential candidates for an expanded diagnostic evaluation of the coronary arteries, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) (Zasada et al., 2021).

The AMI-Kyoto Multi-Center Risk Study - a multicenter, retrospective analysis that included 1651 patients with AMI in Japan between January 2000 and June 2004. The study compared two groups: a younger group (<40 years old, consisting of 27 patients) and an older group (60 to 70 years old, consisting of 338 patients). The aim was to determine differences in clinical profiles, risk factors, angiographic findings, immediate outcomes of PCI, and in-hospital prognosis between these age groups. Shiraishi et al. (2005) defined the age threshold for the second group in order to exclude the negative impact of advanced age on the outcomes of PCI and hospital outcomes. The presence of SVD was significantly more common in the younger group (76.9% versus 56.6%, $p < 0.05$), while MVD was more common in older patients, although the difference was not statistically significant. Normal coronary arteries were a more frequent angiographic finding in Group 1 (3.8% versus 0.6%), yet again lacking statistical significance. The frequency of total occlusion (TIMI 0) at presentation in the younger group was relatively higher compared to the older group, which, according to the authors, might suggest acute thrombosis at a single lesion as a cause of MI in young patients. This fact together with the prevalence of SVD in young patients and the high frequency of smoking as a risk factor, suggests a more thrombotic and spasmogenic coronary obstruction rather than atherosclerotic obstruction in this population. According to Shiraishi et al. (2005), this theory might influence the choice of interventional procedure.

Shiraishi et al. (2006) identified MVD as a predictor for MACE in the mid-term among young patients with MI.

The frequency of MVD in Group 1 aligns roughly with that reported in large studies: Zimerman et al. (1995) indicated levels around 14%; Zasada et al. (2021) reported a level of 15.82%, while Chen et al. (1995) even report rates as high as 42% in patients under 45, although encompassing the entire spectrum of coronary syndromes.

We noted a significant difference concerning LMA involvement between the two groups (1.6% vs. 14.4%; p 0.007), where in Group 1, the only patient with LMA involvement had it as the target artery. Several studies have highlighted the prevalence of LMA involvement in older individuals. Zasada et al. (2021) reported an LMA involvement rate of 1.84% in the younger population, while Rosengren et al. (2006) reported higher rates of 6%, but specifically among men under 55 years of age.

We noted that there is a significant prevalence of NOCD in the younger group compared to the older group (11.5% vs. 1.8%; $p = 0.006$). Among the young patients with NOCD, one had documented coronary arterial vasospasm, another had Takotsubo cardiomyopathy, and in the remaining 5 cases, the cause remained unclear. In Group 2, one patient with NOCD had Takotsubo cardiomyopathy, and for the other, the cause remained unclear. Patients with unclear reasons for MI in the context of non-obstructive coronary artery disease or normal coronary arteries fall under the group termed MINOCA (Myocardial Infarction with Non-Obstructive Coronary Arteries). MINOCA is found in approximately 6% of patients with AMI (Pasupathy et al., 2015). However, the literature reports a wide range of frequencies between 3.5% and 15%, likely due to variations in studied populations and the heterogeneity of definitions (Tamis-Holland and Jneid, 2018). In the latest **2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation** the criteria for MINOCA exclude by a consensus the myocarditis and the Takotsubo cardiomyopathy from this group of patients (Collet et al., 2021). In our study, these patients are grouped under the definition of non-obstructive coronary artery disease.

There are data indicating that MINOCA is more common in young patients than in older patients and predominantly affects women (Safdar et al., 2018).

We find similarities in the reported frequencies of non-obstructive coronary disease and differences between age groups in the current study with those reported in previous studies. Safdar et al. (2018) in VIRGO reported 11.1%, primarily in a female population, aged <55 years; Malik et al. (2016) described angiographic findings in very young patients (<35 years) and reported a frequency of 9.57%; Kanitz et al. (1996) in a retrospective cross-sectional study reported a frequency of 13.8% of normal coronary arteries in patients with MI under 40 years; Zasada et al. (2021) described normal coronary arteries in 19.97% and non-significant coronary atherosclerosis in 14.44% of patients; in the Euroheart acute coronary syndrome survey, 5.6% of men under 55 and 13.3% of women in this group had these findings (Rosengren et al., 2006). Sinha et al. (2006) reported 12.2%. Kanitz et al. (1996) reported 16.5%.

A higher frequency is described in an analysis based on the Coronary Artery Surgery Study Registry (CASS): a total of 22% of young men and 34% of young women had 0-vessel coronary disease (normal coronary arteries and non-obstructive coronary atherosclerosis), while in older age groups, these patients comprised 5% of men and 18% of women, respectively ($p < 0.0001$). Sub-analysis revealed that normal, without visible atherosclerotic changes, coronary arteries were found in 37% of young patients of both genders and in 13% of adult patients of both genders, with the percentage being higher in women in both age groups (Zimmerman et al.,1995).

According to Safdar et al. (2018), in VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients), out of 2690 patients under 55 years old, 88.4% were diagnosed with AMI due to CAD, 11.1% were classified as having MINOCA, and 0.6% remained unclassified. Of those with MINOCA, 25.1% demonstrated a clear mechanism (class IV), such as coronary artery vasospasm (n=11), spontaneous coronary artery dissection (n=61), or coronary artery embolism (n=3), while the majority (n=224 in class III) did not have an identified cause. Compared with men, women had a fivefold greater frequency of MINOCA.

In the current analysis, there were no patients with spontaneous coronary artery dissection or coronary anomalies.

In comparison to MI with obstructive coronary artery disease, the prevalence of conventional cardiovascular RFs such as smoking, AH, DM, dyslipidemia, obesity, family history of heart disease, and previous MI or peripheral artery disease is significantly lower in patients with MINOCA (Kilic, 2020; Merlo et al., 2022).

It is presumed that patients with MINOCA might have a more favorable prognosis compared to those with MI and obstructive CAD (Patel et al., 2006; Larsen et al., 2013; Pasupathy et al., 2015). However, conflicting findings have been reported in various studies, some indicating a similar or even worse prognosis (Kang et al., 2011; Planer et al., 2013). Pasupathy et al. (2015) reported a 0.9% in-hospital mortality and a 4.7% one-year mortality rate among MINOCA patients. Tamis-Holland and Jneid (2018) noted that the mortality rates among MINOCA patients in the VIRGO registry were twice as high as those reported in a healthy population of young women.

In the present study, one patient in the young age group with MI and NOCD died during the index hospitalisation, accounting for 14.3% of the patients with NOCD in this small cohort.

5.3. PCI strategy and average number of implanted stents

The majority of patients in both groups underwent stent implantation (Group 1 - 94.44%, Group 2 - 93.6%), with no significant difference between the groups (p=0.82). All implanted stents were drug-eluting stents. The choice is in line with contemporary recommendations and based on studies indicating the advantage of stent implantation over balloon angioplasty and the superiority of the latest generation DES compared to BMS in AMI, regardless of age. According to the COMFORTABLE AMI and EXAMINATION trials, the new generations of DES outperform BMS in patients with MI, particularly concerning the need for reintervention (Raber et al., 2012; Sabate et al., 2012). Additionally, a reduction in all-cause mortality has been reported over a 5-year follow-up with DES compared to BMS (Sabate et al., 2016).

Stent implantation is recommended over balloon angioplasty (Ibánez et al., 2017; Byrne et al., 2023), although recent small-scale studies have not shown a difference in FFR results at nine months post-revascularization, comparing patients with MI treated DES or drug-eluting balloons (DEB) - the REVELATION trial (Vos et al., 2019). Further evidence with larger patient groups is needed.

The mean number of implanted stents is significantly lower in group 1 (p=0.045), consistent with the findings of previous studies (Rathod et al., 2016). This is likely associated with the demonstrated predominance of SVD and a less generalized atherosclerotic process in the younger group.

Procedural success, defined by achieving TIMI III blood flow in the IRA, is above 90% in both groups, with no significant difference (p=0.754). These findings align with findings reported in large studies (Lv et al., 2021).

6. In-Hospital complications

The widely accepted view is that hospital complications are more common in adult patients with AMI, and the risk of these complications increases with age (Avezum et al., 2005; Rosengren et al., 2006). In line with previous studies, we find a significantly lower proportion of in-hospital complications in patients in group 1 (21%) compared to group 2 (42%; p = 0.009) (Doughty et al., 2002; Chua et al., 2010). Focusing solely on the young group with AMI, a correlating similarity is observed with the data reported by Malik et al. (2016), who found 29% in-hospital events in the studied young population. It's worth noting that only post-infarction angina during hospital stay is a more frequent complication in Group 1 compared to Group 2. The most common complications in Group 1, each occurring at the same frequency, included ventricular tachycardia or fibrillation (VT/VF) at 4.9%, cardiogenic shock at 4.9%, resuscitated cardiac arrest at 4.9%, and post-infarction angina at 4.9% of the patients.

Morillas et al. (2002) presented results on short-term prognosis and complications during the stay in the intensive cardiac care unit (ICCU). A small percentage of patients in Group A experienced malignant ventricular arrhythmias: 9.1% had ventricular tachycardia (VT), and 8.8% had ventricular fibrillation (VF). In

Group B, these were significantly less common - 6.4% and 4.9%, respectively. The authors explain this as a result earlier presentation from symptoms onset of younger patients. On the other hand, atrial fibrillation and third-degree atrioventricular (AV) block were more common in the older population of patients. Mechanical complications, such as free wall rupture of the left ventricle, were observed in 0.1% of Group A and 1.5% of Group B (P = 0.002); interventricular communication was found in 0.1% of patients in Group A and 0.7% in Group B (NS).

No mechanical complications were observed in Group 1 in the present study, whereas they occurred in 2.7% of patients in Group 2.

We did not observe a significant difference in the average length of hospital stay (4.16 versus 4.48 days). In a retrospective study by Shiraishi et al. (2006), they also did not find a difference but identified it as a predictor of MACE in the older group. Surprisingly, the length of hospital stay in our patient population turned out to be shorter compared to what was reported in some previous studies (Shiraishi et al., 2006; Lv et al., 2021), with the latter reporting a significantly longer stay for patients over 45 years old.

7. In-hospital mortality

7.1. Frequency

The majority of the data in literature reviews indicate a more favorable prognosis, including in-hospital outcomes, for young patients with AMI compared to older ones. Despite nearly half the mortality rate in group 1 compared to that in group 2 (4.9% versus 10.8%), no significant difference was observed in this parameter ($p = 0.190$). Conducting binary logistic regression with patients aged ≤ 45 years as a referent, the OR for in-hospital mortality is 2.343, with a 95% confidence interval of 0.635–8.651, $p = 0.201$.

The in-hospital mortality rate in group 1 is higher than the most commonly reported rates in previous analyses, which typically range between 2 and 3%.

For example, in a large contemporary prospective observational study involving 24,125 patients based on the China Acute Myocardial Infarction Registry, the in-hospital mortality rate (2.0% versus 7.0%; $p < 0.0001$) was significantly lower in the younger patient group (Lv et al., 2021).

According to the results of the Young MI Registry study, in-hospital mortality was slightly higher among men (2.2%) compared to women (1.2%), but this difference was not statistically significant ($p = 0.20$) (DeFilippis et al., 2020).

Additionally, Chua et al. (2010) reported hospital mortality rates among patients under and over 45 years old (3.0% versus 12.3%, $P = 0.002$), with the majority of patients being treated with primary PCI.

Avezum et al. (2005) according to data from the GRACE study, reported an even lower hospital mortality rate (1.3%) among patients under 45 years old with ACS, especially considering that not all of them underwent an invasive strategy. According to the Euroheart Acute Coronary Syndrome survey, the frequency was 1.4%, even with a wider age range < 55 years (Rosengren et al., 2006).

Shiraishi et al. (2005), in the AMI-Kyoto Multi-Center Risk Study, similar to our findings, did not observe a significant difference in in-hospital mortality between young and older patients with AMI. This study was notable as the first to demonstrate that immediate outcomes from primary PCI and hospital outcomes in young patients with AMI were comparable to those in older patients.

Rarely a higher frequency of hospital mortality compared to our published results is reported concerning in studies in the Southeastern European region. Rumboldt et al. (1995) indicate a 6.2% hospital mortality rate among patients under 45 years old and higher in those above 45 years - 22.1%, but these authors reported a significant difference.

Alizadehasl et al. (2010) reported a 7% hospital mortality rate among individuals ≤ 35 years old with AMI treated interventionally.

Canto et al. (2012), in a gender subanalysis and considering the clinical presentation, reported frequencies reaching 10.2% for men and 15.3% for women under 45 years old presenting without chest pain. They identified painless presentation as one of the strongest predictors of in-hospital mortality among young women.

7.2. Influence of qualitative variables on the likelihood of a fatal outcome during the index hospitalization

- Group 1

When using Fisher's Exact Test, it appears that there is a statistical dependency between reduced LVEF<50% and presenting with high Killip class HF, and hospital mortality in group 1.

It turns out that the risk of a fatal outcome in young patients increases by 13 times with reduced and moderately reduced LVEF compared to young patients with preserved LVEF.

All patients in the young group who presented with Killip class 3-4 died during the index hospitalization, constituting all deceased patients. Consequently, a high Killip class upon presentation is a strong predictor of a fatal outcome in young individuals, likely exerting a more pronounced negative influence than in adults.

It becomes evident that young age alone is not a predictor of a better prognosis in terms of mortality. According to our binary logistic regression, with referent patients ≤ 45 years old, the OR for in-hospital mortality is 2.343, with a 95% CI of 0.635 to 8.651 ($p = 0.201$).

There is no statistical dependence found between gender, presence of AH, DM, dyslipidemia, combination of CV RFs, delayed presentation, anterior localization of MI, duration of hospital stay, and the presence MVD and the risk of a fatal outcome during the index hospitalization.

- Group 2

For group 2, there is statistical significance between the following variables: LVEF < 50%, high Killip class at presentation, presence of >2 CV RFs, and a fatal outcome during the index hospitalization.

Upon reviewing the literature data, we find some similarities in factors related to a fatal outcome during the index hospitalization coincident with our findings. Lv et al. (2021), in a study involving 24,125 patients with MI from the China Acute Myocardial Infarction registry, after univariate and subsequent multivariate analysis, identified LVEF, along with gender, Killip class, and cardiac arrest upon admission as independent predictors of in-hospital mortality among patients ≤45 years old. According to Chua et al. (2010), only Killip class 3 and 4 could be factors with influence on hospital mortality in younger individuals, whereas in adults, these include gender, non-smoking status, CKD, and Killip class 3 and 4. In the current analysis, the presence of CKD was not tracked, in order to determinate it as a prognostic factor in the studied population.

There is no statistical dependence found between gender and the lethal outcome during the hospital stay in group 1.

The female gender is associated with a worse prognosis among young patients with MI in most available reports. DeFilippis et al. (2020) suggested that even after correcting for differences in RFs and treatment in the Young MI registry study, young women had a higher frequency of death from any cause. Several studies indicate a nearly twofold higher mortality in females (Mehta et al., 2016; Chandrasekhar et al., 2018). The Partners YOUNG-MI Registry (DeFilippis et al., 2020) does not find a difference in in-hospital mortality between genders, with even higher rates among men. However, the adjusted long-term all-cause mortality among young women was 1.63 times greater than that among young men. The Partners YOUNG-MI Registry study demonstrated that young women with MI are less frequently subjected to coronary angiography and revascularization and are less likely to be treated according to the guidelines compared to men. These patients less frequently present with STEMI and more often have NOCD, SVD and less pronounced atherosclerotic involvement. According to GENESIS PRAXY (Khan et al., 2013), young women significantly more often present without chest pain compared to men, which is one of the determinants of higher hospital mortality among them. According to the VIRGO study, young women with myocardial infarction also have a more severe risk factor profile compared to men (Bucholz et al., 2017). All these characteristics could contribute to a worse prognosis for women in the young age group. However, regarding hospital mortality in the VIRGO study, being female was not a predictor of higher mortality.

In the present study, the small number of women in group 1 could be one of the reasons for the underestimation of female sex as a factor associated with a poorer hospital outcome.

8. One- and two-year follow-up

The prevailing opinion is that young patients with IHD represent a relatively low risk population in terms of prognosis compared to older patients.

Even before the widespread establishment of interventional reperfusion strategies in the treatment of ACS, studies from the 1980s and 1990s suggested that outcomes were more favorable for young patients with IHD compared to any group of older patients up to 7 years after hospitalization (Klein et al., 1987; Chen et al., 1995; Zimmerman et al., 1995). Young age has been identified as an independent prognostic factor for favorable clinical outcomes following MI across all age ranges (Goldberg et al., 1998).

Several factors have been highlighted by Schoenenberger et al. (2011) as potential reasons for a more favorable prognosis in younger individuals. First - the typical clinical symptoms allowing for faster presentation and treatment; second - more frequent application of guideline-based therapy in younger patients; third - a less pronounced coronary atherosclerotic involvement, which in turn could partly explain the similar, or even better, prognosis in young patients with STEMI compared to NSTEMI; and fourth - less pronounced comorbidities.

However, "alarming" long-term outcomes for individuals with IHD under 40 years old have been reported by Cole et al. (2003): the 15-year overall mortality is 30%, increasing to 45% for those with a prior MI. Considering the potential danger of premature death, long-term disability, and socio-economic damages in young MI patients on the one hand and the significantly higher risk of long-term mortality reported by Jing et al. (2016) in young MI patients compared to an age-matched background population on the other, it might be suggested that the prognosis for young individuals isn't as benign, and they carry residual risks unrecognized when comparing solely between age groups.

In the current study, all-cause mortality and the composite of major adverse cardiovascular events (MACE) at 1 and 2 years were analyzed.

At the end of the first year, the mortality in group 1 is significantly lower compared to group 2 (3.4% versus 13.3%; p=0.044). Considering the absence of fatalities in the second year of follow-up, the difference becomes more significant for the entire period (3.4% versus 15.5%; p=0.021). The results regarding this parameter are worse than those reported by Chen et al. (2014), who compared the prognosis in three age groups of patients with MI (<45 years; 45-60 years; and >60 years), where the one-year mortality rates were 0%, 0.43% [95% CI: 0–0.91%], and 2.26% [95% CI: 1.65–2.87%] ($p < 0.001$), respectively. Lv et al. (2021) also indicated 1.5% versus 7.9% for all-cause mortality at the 2-year follow-up in groups of MI patients under and over 45 years, respectively ($p < 0.0001$), with a statistically significant difference in midterm prognosis (mean follow-up period of 3.0 years). Rathod et al. (2016) also reported lower levels of all-cause mortality compared to the current analysis: significantly lower mortality rates among young patients compared to those above 45 years old (2.7% versus 12.5%; $p < 0.0001$). Young age has been identified as a predictor of a better prognosis regarding all-cause mortality. In the patient population examined in the present study, binary logistic regression showed that young age is a predictor of lower one-year all-cause mortality, with borderline significance (p=0.062; OR 4.282: 95% CI, 0.931-19.706); for the two-year period, the impact is even more pronounced (p=0.035; OR 5.060: 95% CI, 1.113-22.995). Therefore, young age is a predictor of better prognosis concerning mortality during the follow-up period and does not emerge as a factor for any of the individual or combined MACE at the two-year follow-up (p=0.747; OR 1.208: 95% CI, 0.383-3.812).

Hoit et al. (1986) compared one-year morbidity and mortality in a study involving three groups of patients, with the youngest group being <45 years old. They also observed lower rates among the young patients (2.6%) compared to 10.3% and 24.4% in the other two age groups, respectively.

Cocequently, the results regarding survival (96.6%) and survival without MACE (70.7%) in the studied young Bulgarian population are less favorable compared to previous analyses. Fournier et al. (2004) reported a survival rate of around 99% and survival without MACE at 88% during one-year follow-up.

Shiraishi et al. (2006) reported higher mortality rates for young MI patient groups during a two-year follow-up, along with the absence of significant differences between the two age groups (the second group being limited between 60 and 70 years old), specifically 4.8% versus 6.8%, respectively. In their report, they demonstrated for the first time that the midterm prognosis for young MI patients is comparable to that of patients aged between 60 and 70 years in Japan. However, survival curves and event-free survival showed some, albeit statistically insignificant, divergence around the two-year mark. The authors hypothesized that the follow-up period might be too short to manifest significant differences.

As expected, Anderson et al. (2008) presented poorer outcomes concerning all-cause mortality (6.9%) when following a young population after MI for a period of 24 months, focusing on selected high-risk patients with LVEF $\leq$ 35%.

Rarely do we encounter contrasting views when comparing short- and midterm prognoses in the literature. For instance, Vedin et al. (1975), during their follow-up of 440 patients, found no difference in one-year mortality between patients younger and older than 55 years. Conversely, Zukel et al. (1969) noted even higher one-year mortality among patients under 40 years old in their study. Notably, young MI survivors had a better long-term prognosis compared to older individuals.

In the ARIC Community Surveillance Study, Arora et al. (2019) compared gender differences in the prognosis of young patients with MI (aged 35-54 years). They reported one-year all-cause mortality rates for women and men of 9% versus 7% and cardiovascular mortality rates of 5% versus 3%, respectively (p=0.08). These values exceed those observed in the Bulgarian population studied in the present research. After adjusting for race, hospital geographic location, and year of admission, the risk of one-year all-cause mortality was comparable between women and men (HR = 1.10; 95% CI: 0.83 - 1.45).

Our results showed that gender as a variable does not show statistical significance concerning the one- and two-year all-cause mortality rates (p=1.000 for Group 1).

A high frequency of MACE is observed during the follow-up period. The percentage of patients experiencing at least 1 MACE in the first year is 29.3% for Group 1 and 35.1% for Group 2 (p=0.461), and for the second year, it is 8.9% compared to 10.7%, with no significant difference found. For any of the adverse events separately, as well as for the combination of MACE for 2 years, no significant difference was observed between the groups, except for all-cause mortality. The latter result aligns with data from the AMI-Kyoto Multi-Center Risk Study, where Shiraishi et al. (2006) reported no difference in the mid-term prognosis of patients with AMI treated interventionally across two age groups, without any variation in any MACE, even concerning mortality.

Similarly, but over a longer follow-up period of 53.4 ± 44.2 months for the younger group and 45.5 ± 43.4 months for the older group, Chua et al. (2010) did not observe a significant difference in the frequency of repeated PCI or recurrent myocardial infarction between the two groups. However, the mortality rate over the follow-up period was significantly lower in the younger group.

A significant portion of adverse events for Group 1 comprises recurrent angina (19.6%), followed by readmission for HF (7.1%) and unplanned revascularization in 5.4% of patients at the one-year follow-up; recurrent angina was most common in Group 1, occurring in 7.1% of patients in the second year, while other events had very low frequencies. Recurrent angina occurred more frequently in younger patients compared to older ones over the entire follow-up period, although this adverse event also represented a substantial portion in Group 2.

The frequency of adverse events is higher compared to what has been reported thus far in the literature. In a large prospective observational study from the China Acute Myocardial Infarction registry, Lv et al. (2021) reported a much lower frequency of MACE - 2.2% compared to 8.1% over a 2-year period for the same age groups, revealing a significant difference. The considered MACE included all-cause mortality, recurrent MI and stroke, which may explain the significant difference in frequency. However, even concerning all-cause mortality and recurrent heart attacks, the authors reported lower frequencies, specifically 2% and 0.1%, respectively, for the younger patient group. There were no cases of stroke during follow-up in the entire population tracked in our study. Without being a MACE, the authors noted a frequency of rehospitalization due to heart failure at 3.0% compared to 8.1% ($p < 0.0001$), and regarding younger patients, the frequency was lower than that in Group 1 from the current analysis.

Regarding the occurrence of recurrent angina after 1 year following MI in young patients, Incalcaterra et al. (2013) also reported relatively high frequencies, somewhat consistent with our results, defining recurrent ischemic events as a combination of new episodes of angina or MI requiring hospitalization - at 13.5%.

High levels of MACE, defined as all-cause death from recurrent MI, stroke, and target vessel revascularization (TVR), were reported by Rathod et al. (2016) in an observational cohort study involving 3618 STEMI patients treated with primary PCI over an average follow-up period of 3.0 years - 12.8% versus 22.9%; $p<0.0001$ for groups ≤ 45 years and > 45 years. Considering the differences in MACE definitions, there appears to be relative alignment with the data from our study, and in terms of recurrent MI, our results also show a similar trend.

Zimmerman et al. (1995) supported the hypothesis that better survival among younger patients is likely linked to less severe coronary atherosclerosis. They base this on a high percentage of angiographically normal coronary arteries and SVD in their study population. These patients showed improved survival even after adjusting for variables such as coronary anatomy, LVEF, and treatment. The study was initiated before the introduction of thrombolytic therapy as a treatment method. However, after a 5-year period, there was a worrisome decrease in survival rates, with reported mortality exceeding 15% by the seventh year (Zimmerman et al., 1995) and reaching 25-29% at 15 years (Fournier et al., 2004; Awad-Elkarim et al., 2009).

The recurrence of angina is subjective, heightened by the retrospective analysis of the study and was assessed entirely based on medical history. The assessment did not include inducing ischemia to validate the credibility of the complaints. One limitation noted is the absence of grading according to existing scores.

Including recurrent angina as an adverse event is important, especially for the young population of patients following MI. According to the TRANSLATE-ACS Study, 29.3% of MI patients reported experiencing angina symptoms within 6 weeks post-PCI, and 38.9% reported experiencing symptoms within 12 months, with younger age being a significant predictor in both cases. Surprisingly, incomplete revascularization after PCI was not a factor in the occurrence of angina (Fanaroff et al., 2017). According to the PREMIER and TRIUMPH studies, the frequency of angina following MI is approximately 20%, and a higher occurrence has also been observed among younger patients (Maddox et al., 2008; Doll et al., 2016).

A high frequency of angina post-MI is reported even in patients without obstructive CAD and is more common in younger patient populations, as indicated by the results of the current analysis. According to multicenter studies, one out of four patients reported angina within 1 year after MI, and the frequency was at least as high as that in patients with obstructive CAD. Consequently, the rate of rehospitalization did not significantly differ. Considering the lack of favorable effects of interventional procedures on these patients, more aggressive guideline-based medical therapy is necessary, along with programs to improve patient compliance (Grodzinsky et al., 2015).

The high rate of recurrent angina in the studied young patient population, regardless of its subjective nature, could be a factor from a psychosocial perspective. Patients with persistent angina significantly more often report difficulties performing daily activities and are more prone to moderate to severe anxiety and depression, consequently leading to impaired quality of life (Fanaroff et al., 2017). On the other hand, a reverse correlation has been found—patients with symptoms of depression are more likely to exhibit angina symptoms within one year following a myocardial infarction. This is crucial in ensuring optimal outpatient care for post-MI patients. Patients with depressive symptoms are at an increased risk of various adverse cardiac events, including cardiac death and subsequent hospitalization (Maddox et al., 2008). Shah et al. (2016a) considered that identifying and treating depression following a MI in young patients is of crucial importance.

Early identification of stress disorders following a MI is particularly crucial in young patients, whose conditions are not only more prevalent but also result in social, psychological, and economic implications due to decreased work capacity during their prime years. Moreover, they serve as factors contributing to subsequent adverse cardiovascular events. The mental health of these patients should be a focal point in post-myocardial infarction rehabilitation programs (Grodzinsky et al., 2015).

In the current serie, a multifactorial analysis was conducted to determine the prognostic influence of qualitative and quantitative variables on all-cause mortality and MACE over a 24-month period following the index hospitalization.

Younger age alone serves as a predictor of better prognosis concerning mortality over a 2-year period but not specifically for MACE during that same period.

For Group 1, none of the factors shows a clear predictive influence on mortality. One possible reason for this could be the small number of deceased young patients during this period. For Group 2, predictors of an increased risk of all-cause mortality include a higher Killip class upon admission (>2), the presence of MVD, and a longer hospital stay.

Regarding MACE during the follow-up period, factors that increase the risk of adverse events in Group 1 include: LVEF < 50%, anterior localization of the MI, and the presence of more than two RFs. For Group 2, these factors comprise LVEF < 50%, anterior localization of MI, and the presence of MVD.

The literature review of studies with a similar design and a comparable follow-up period has defined predictors for worsened short-term and medium-term prognosis in young patients following MI. This stands in contrast to the obtained results.

For example, back in 1987, Klein et al., (1987), before the introduction of reperfusion therapy to the routine use, identified the number of affected arteries and LVEF as the most significant predictors for an increased risk of mortality in both adult and young patients.

Lv et al. (2021) identified LVEF, creatinine level, and education level as variables associated with 2-year mortality in young patients. The cumulative rates of all-cause mortality and major adverse cardiac and cerebrovascular events (MACCE) are comparable between young women and older men.

Trzeciak et al. (2017) identified the strongest independent predictors associated with increased 12-month risk of MACE in patients under 40 years old as class 3 or 4 on the Killip scale at presentation ([HR] 6.82; 95% CI, 3.44–13.52; P <0.0001) and every 5% decrease in LVEF (HR, 1.29; 95% CI, 1.16–1.43; P <0.0001), assessed during hospitalization for AMI.

Incalcatera et al. (2013), in a one-year follow-up of patients under 45 years of age after an AMI, indicated that AH and obesity, as well with a borderline significance for DM, were associated with a higher frequency of new episodes of angina or MI. During longer-term follow-up (4.9±1.6 years), none of the cardiovascular RFs were significantly associated with new events. The authors concluded that although the RFs most commonly associated with coronary artery disease in adult patients, namely, AH and DM, were less prevalent in younger individuals, they still play a prognostic role.

Anderson et al. (2008) highlighted the significance of RFs concerning the prognosis of young patients following a MI in the VALIANT trial. The authors pointed out a significant correlation between age and smoking, as well as age and AH, concerning the prognosis over a 24-month period. They observed that, in younger patients, the risk attributed to these RFs was greater than that in older individuals. Among these RFs, only smoking was more common among young patients. After adjusting for important covariates, smoking was associated with a greater risk of post-MI events in younger patients compared to older ones. Additionally, the risk attributed to smoking decreased as age progressed: for those under 45 years, the hazard ratio was 1.6 [95% CI; 1.1-2.5], while for those 45 years and older, it was 0.9 [95% CI; 0.9-1.1]; P = 0.014.

Fournier et al,. (2004) defined the long-term prognosis and functional status in young patients with MI as less favorable, especially when a reduced LVEF and peripheral arterial disease were present.

According to Shiraishi et al. (2005), young patients with MACE, compared to those without MACE have significantly higher rates of MVD. However, among older patients, those experiencing MACE were more likely to have MVD, prior MI, and significantly longer hospital stays compared to patients without MACE. LVEF was not a predictor for MACE in either group during mid-term follow-up.

The lack of a definitive predictor for a worsened prognosis concerning mortality among young patients likely stems from several factors: a small sample size of young patients, a shorter follow-up period, and the exclusion of certain variables such as CKD, prior MI, prior PCI, PCI without stent placement, family history of IHD, education level, and so on. These omissions have been recognized as limitations in the current analysis.

Data from a retrospective cohort study by Yagel et al. (2021) involving long-term follow-up of young patients with ACS treated with PCI also deserve attention. The mean follow-up period was 9.1 ± 4.6 years. The strongest predictors for MACCE and/or mortality were identified as PCI without stent insertion, involvement of the LAD and AH. According to the linear multivariate regression model, the strongest predictor of recurrent events was AH ($P = 0.004$). The authors emphasize that contrary to expectations regarding long-term prognosis following PCI strategy for more favorable outcomes was not confirmed in the conducted study. They explain this result by suggesting that the invasive approach primarily affects short-term prognosis, up to one year, after which factors such as lifestyle modification and compliance play a more significant role in the long-term prognosis.

According to the data from our analysis, the fact that young patients with more RFs had a higher likelihood of experiencing MACE within the first two years reinforces the critical need for early identification and modification of RFs in young patients. This finding also underscores the importance of promoting adherence to effective secondary prevention measures.

The high frequency of MACE in patients with left ventricular dysfunction highlights the necessity for stricter monitoring of this high-risk group, optimal adherence to both medication-based and non-medication-based therapies, in line with contemporary guidelines, becomes crucial. These approaches aim to reduce rehospitalizations, mortality rates and enhance the overall quality of life of these individuals.

Limitations

Several limitations exist and need to be mentioned: : 1) This study represents a relatively small sample size, and a larger study needs to be performed in the future to confirm our findings. With a larger cohort, potential gender differences in the tracked parameters could become more evident. Additionally, a longer follow-up duration could aid in identifying definitive predictors for a worsened prognosis. 2) There is a lack of data regarding the presence of hypercoagulable states or familial hypercholesterolemia in young AMI patients. 3) The COVID-19 pandemic may partially affect the morbidity and mortality rate in unrecognized individuals, as some patients are treated during this period. 4) IVUS or OCT was not used and could be a subject of future research.

Summary

Bulgaria belongs to a region with high rates of cardiovascular morbidity and mortality. However, data regarding the characteristics of young patients with acute AMI are scarce. Despite the low frequency of acute coronary events in young individuals, they can lead to considerable social, psychological, and economic consequences when they occur at a working age in patients considered to have a long life expectancy.

In the studied young Bulgarian population, an exceptionally widespread presence of traditional atherosclerotic RFs is established, primarily smoking, AH, dyslipidemia. These factors not only are associated with the risk of MI but also impact patient prognosis. The tracked patients exhibit a high-risk profile concerning in-hospital mortality and are characterized by a high frequency of subsequent adverse events.

An emphasis is placed on the necessity of early identification of modifiable RFs, improving primary and secondary prevention, initiating educational programs to reduce patient presentation time, enhancing access to medical care, and ensuring high awareness among clinicians for toward early disease recognition and consequently more effective treatment. These measures intend to reduce the incidence, disability, and mortality among this initially categorized low-risk patient group.

VII. CONCLUSIONS

Based on the conducted literature review and the results of the statistical analysis, which included a comparison between the two age groups of patients with MI, the following conclusions can be drawn in response to the established objectives:

1. AMI is relatively rare among young individuals. Consequently, patients experiencing premature AMI are often neglected in many clinical studies. The high risk of disability and mortality due to CVD, including in young patients, demands a focus on this insufficiently investigated population. It differs in terms of demographic, risk, clinical profile, angiographic characteristics, and prognosis compared to older patients. Data on the characteristics of these patients are scarce in regions such as Southeastern Europe, particularly in Bulgaria, which is characterized by some of the highest age-standardized levels of Disability-Adjusted Life Years (DALYs) attributable to IHD.

2. The tracked patients in the young age group (mean age - 39.74±4.97 years) did not show a trend for earlier presentation compared to the reported data thus far. There is a significant male predominance observed in Group 1 ($p= 0.001$). In Group 2, although males are still predominant, their proportion is significantly smaller compared to Group 1. These results align with existing data from large studies.

The studied patient population in both age groups initially presented higher-risk profiles than did similar populations described in previous studies. Young patients with MI exhibit the same traditional RFs for IHD but differ in a specific risk profile. Significant differences are observed between the two groups regarding three RFs - smoking, AH and obesity, with borderline significance for DM. Younger patients demonstrate a significantly higher frequency of RFs such as male gender and smoking, and a lower occurrence of AH, obesity, and DM.

A significant difference is observed between the groups regarding the frequency of prior revascularization - 3.3% in Group 1 and 24.3% in Group 2 - $p<0.001$.

3. The young population of MI patients has a significantly shorter time delay from the onset of symptoms compared to older individuals. No differences are found

between the two genders concerning this parameter in the young age group. These results align with those from published registries and studies.

However, nearly one-third of premature MI patients present themselves after the sixth hour from the symptoms onset.

4. Patients under 45 years old present with a lower Killip class compared to those above this age, with a prevalence of STEMI over NSTEMI among them. The low Killip class is a factor predicting a more favorable prognosis.

5. The majority of patients with premature MI have preserved left LVEF, and no significant difference is detected regarding this parameter during hospital stay between the two age groups.

There is no significant difference concerning the mean values of the markers for myocardial necrosis between the groups. If the hypothesis is considered that these markers could indicate the extent of myocardial damage, they correspond to the results showing no significant difference in LVEF.

6. Young patients with MI exhibit a particular angiographic profile. They most commonly present with SVD, lesser atherosclerotic coronary involvement compared to older patients, rarely involvement of the LMA, the most frequent IRA is the LAD, and they have a significantly higher frequency of NOCD compared to older patients. Consequently, the mean number of stents implanted per patient in the young group is significantly smaller.

7. Regarding the invasive strategy in the management of ACS in the studied Bulgarian patient population, full adherence to the established current European guidelines for the treatment of ACS patients is noted. A high procedural success rate of more than 90% is observed, defined by the degree of post-procedural TIMI blood flow.

8. The in-hospital prognosis for young MI patients is relatively benign compared to that for older individuals, with a significant difference observed only concerning complications but not mortality. The latter is higher than reported in previous studies with a similar design.

The factors contributing to a higher risk of fatal outcome during the index hospitalization in Group 1 are reduced LVEF < 50% and Killip class on admission > 2, while in Group 2, they include reduced LVEF < 50%, Killip class at admission > 2, and the presence of >2 RFs.

Despite the extremely rare frequency of MI in young women, they are considered to constitute a high-risk group with high mortality rates. Likely due to the small number of women in our studied young group, female gender was not defined as a predictor for increased in-hospital mortality.

9. The prognosis for young patients following MI is relatively favorable regarding all-cause mortality but not concerning MACE over a two-year period. We observe a high frequency of adverse events in the young population. A comparison with healthy individuals from the general population, matched by gender and age, is necessary for an accurate prognostic assessment.

10. The recurrence of angina is highly frequent in the stidied young population. Given the established bidirectional relationship between post-MI angina and depressive states, particularly in young individuals, and the consequent increased risk of adverse cardiac events, including cardiac death and subsequent hospitalization, as well as deteriorated quality of life, it underscores the need to enhance rehabilitation programs and focus on mental health.

11. Young patients with a more severe baseline risk profile, low LVEF, and anterior localization of MI likely have a worsened prognosis concerning major MACE at a two-year follow-up.

12. The emphasis is on the need for early recognition of modifiable risk RFs, improving primary and secondary prevention, initiating educational programs for young individuals to shorten the time to first medical contact, enhancing clinicians' awareness for early recognition of this condition, and providing more effective treatment for this specific population initially considered low risk to reduce disability and premature cardiovascular mortality.

VIII. CONTRIBUTIONS

1. For the first time, in Bulgaria, an assessment of the baseline characteristics, risk profile, clinical presentation, angiographic findings, in-hospital and two-year outcomes was conducted for young patients aged ≤45 years with AMI, and the data obtained were compared to those of patients >45 years with AMI (original contribution; scientific and applied contribution).

2. For the first time, in Bulgaria and as one of the few similar studies in the available literature, this research presents a comparative analysis between two age groups (≤45 years old and patients >45 years old with AMI) regarding angiographic findings, in-hospital complications, and mortality, based entirely on the results of interventionally treated patients following contemporary procedural guidelines. The majority of existing data until now have involved comparisons of mixed patient populations subjected to optimal medical therapy, thrombolysis, pharmacoinvasive strategy, PCI, and CABG (original contribution).

3. For the first time, in Bulgaria, this study defines a particular risk profile for young patients with AMI. The findings reveal an absolutele male predominance, higher prevalence of smoking compared to older patients, particularly high rates of AH and dyslipidemia, and a significant proportion of patients with ≥2 RFs in the observed young Bulgarian population. These findings confirm the role of smoking as a primary RF for AMI in young individuals. These data could delineate future directions for primary and secondary prevention strategies aimed at reducing morbidity and mortality (original contribution; scientific and practical contribution).

4. The study presents a specific angiographic profile for young patients with AMI: less severe atherosclerotic involvement, a prevalence of SVD, most frequent engagement of the LAD as the IRA, less frequent engagement of the LMA, and significantly higher rates of MI in the setting of non-obstructive coronary arteries (confirmatory contribution).

5. Defining the studied young Bulgarian population with AMI as a high-risk group approaching the risk level seen in older patients (original contribution; scientific-applied contribution).

6. Identification of a high-risk cohort among patients under 45 years old through an analysis of factors influencing the risk of mortality during hospitalization (reduced LVEF <50% and Killip class at admission >2). Patients exhibiting these characteristics require increased attention during hospital stays and adherence to existing treatment guidelines (confirmed contribution; scientific-applied contribution).

7. Establishment of a relatively favorable prognosis among young patients post-MI in terms of all-cause mortality but not regarding MACE and survival without MACE over a two-year period. Identification of a high frequency of adverse events in the young population. Conducting an analysis of factors potentially influencing these indicators (scientific-applied contribution).

8. Significant evidence of a high rate of readmission for HF, recurrence of angina, and unplanned revascularization over a two-year period, similar to that seen in older adults, with negative socio-economic aspect. Given the established high frequency of recurrent angina in young MI patients and the identified mutual relationship between post-MI angina and depressive states, there's emphasis on improving rehabilitation programs and focusing on mental health to enhance overall quality of life (original contribution; scientific-applied contribution).

IX. PUBLICATIONS RELATED TO THE THESIS

1. **Dimitrova IN**. Acute myocardial infarction in young individuals: Demographic and risk factor profile, clinical features, angiographic findings and in-hospital outcome. Cureus 15(9): e45803. doi:10.7759/cureus.45803
2. **Dimitrova IN**, Trendafilova D. Pregnancy-associated myocardial infarction. Cardiovascular diseases, 2023, 54(2): 35-41.
3. **Dimitrova IN**, Trendafilova D. Myocardial infarction with non-obstructive coronary arteries (MINOCA). Cardiovascular diseases, 2023, 54(2): 3-11.