Exploring Prevalence and Determinants of Early Acute Coronary Syndrome in Kosovo: A Population Snapshot with Sex Differences

Keywords
Early-onset ACS, Kosovo, cardiovascular risk factors, biochemical indices, cross-sectional, retrospective study

Abstract

Introduction
Acute coronary syndrome (ACS) in young adults represents an important growing clinical challenge worldwide. This study aimed to evaluate the clinical characteristics and predictors of premature ACS, with particular emphasis on sex differences and cardiovascular risk factors.

Material and methods
We retrospectively analyzed 2,909 patients with ACS treated at the University Clinical Centre of Kosovo. Of these, 587 had premature ACS (men <55 years; women <65 years). Data on CV risk factors, electrocardiographic, echocardiographic, angiographic findings and medications, were collected from medical records.

Results
Patients with premature ACS had a higher prevalence of hypercholesterolemia (35.2 vs. 25.1%; p<0.001), uncontrolled hypercholesterolemia (40.4 vs. 26.9%; p<0.001), current smoking (41.1 vs. 22.9%; p<0.001) and family history of CAD (46.2 vs. 32.4%; p<0.001), but a lower prevalence of diabetes, hypertension, and uncontrolled diabetes (all p<0.001) compared with older patients. Among premature ACS patients, women had lower smoking, alcohol use, and uncontrolled hypercholesterolemia, but higher diabetes and hypertension than men. In multivariable analysis, smoking (OR 1.59), uncontrolled hypercholesterolemia (OR 1.71), and family history (OR 1.66) independently predicted premature ACS (all p<0.001). These associations were consistent across sexes: in women, uncontrolled diabetes (OR 1.51) and hypertension (OR 1.49) were additional predictors, whereas in men, smoking (OR 1.63) and uncontrolled hypercholesterolemia (OR 1.73) predominated.

Conclusions
Premature ACS, diagnosed in every 5th patients in Kosovo, is mainly associated with uncontrolled hypercholesterolemia and smoking, while diabetes, hypertension, and hyperglycemia are less common than in older patients. Clear sex differences observed, with a more cardiometabolic profile in women and lifestyle-related risk factors in men.

Exploring Prevalence and Determinants of Early Acute Coronary Syndrome in Kosovo: A Population Snapshot with Sex Differences

Running title: Epidemiology of premature acute coronary syndrome in Kosovo: determinants and sex differences

Correspondence: Prof. Rozafa Koliqi, PharmD, PhD
Department of Clinical Pharmacy and Biopharmacy, Faculty of Medicine, University of Prishtina, Prishtina, Kosovo.
E-mail address: rozafa.koliqi@uni-pr.edu

Words:
Abstract: 340
Manuscript: 2582
References: 929

Abbreviations and Acronyms

ACS	Acute coronary syndrome
ASCVD	Atherosclerotic cardiovascular disease
ACEI	Angiotensin-converting enzyme inhibitors
ARBI	Angiotensin receptor blockers
AF	Atrial fibrillation
AH	Arterial hypertension
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CRF	Chronic renal failure
CLD	Chronic liver disease
COPD	Chronic obstructive pulmonary disease;
CRP	C-reactive protein
CV	Cardiovascular
DM	Diabetes mellitus
FH	Familial Hypercholesterolemia
FPG	Fasting plasma glucose
HDL-C	High-density lipoprotein cholesterol
HbA1c	Glycated hemoglobin
LA	Left atrium
LV	Left ventricle
LDL-C	Low-density lipoprotein cholesterol
LLT	Lipid-lowering therapy
LVEDD	Left ventricle end diastolic dimension
LVESD	Left ventricle end systolic dimension
LVEF	Left ventricle ejection fraction
MRA	Mineralocorticoid receptor antagonist
NOAC	New oral anticoagulation
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
RA	Right atrium
RV	Right ventricle
RBC	Right Blood Cell
TSH	Thyroid stimulus hormone
VT	Ventricular tachycardia
VKA	Vitamin K antagonists
WBC	White blood cell

ABSTRACT

Background and aim: Acute coronary syndrome (ACS) in young adults represents an important and growing clinical challenge, and is associated with substantial long-term morbidity. This study aimed to evaluate the clinical characteristics and predictors of premature ACS, with particular emphasis on sex differences and cardiovascular (CV) risk factors.

Methods: We retrospectively analyzed 2,909 patients with ACS treated at the University Clinical Centre of Kosovo. Of these, 587 (20.2%) had premature ACS (men <55 years; women <65 years). Data on CV risk factors, electrocardiographic, echocardiographic, and angiographic findings, as well as medications, were collected from medical records.

Results: Patients with premature ACS (mean age 49.5±5.4 years, men: 72.9%) had a higher prevalence of hypercholesterolemia (35.2 vs. 25.1%; p<0.001), uncontrolled hypercholesterolemia (40.4 vs. 26.9%; p<0.001), current smoking (41.1 vs. 22.9%; p<0.001) and family history of coronary artery disease (46.2 vs. 32.4%; p<0.001), but a lower prevalence of diabetes, hypertension, and uncontrolled diabetes (all p<0.001) compared with older patients. Among patients with premature ACS, women had lower rates of current smoking (35.2 vs. 46.9%; p=0.01), use of alcohol (2.9 vs. 14.7%; p<0.001) and uncontrolled hypercholesterolemia (32.7 vs. 45.5%) but a higher prevalence of diabetes, uncontrolled diabetes, and hypertension compared with premature men. In multivariable analysis, current smoking (OR 1.59; p<0.001), uncontrolled hypercholesterolemia (OR 1.71; p<0.001), and family history (OR 1.66; p<0.001) were independently associated with premature ACS, irrespective of sex. In women, a more pronounced cardiometabolic profile was observed, with uncontrolled diabetes (OR 1.51; p<0.001) and hypertension (OR 1.49; p<0.001) as independent predictors. However, in men, premature ACS was mainly driven by smoking (OR 1.63; p<0.001) and uncontrolled hypercholesterolemia (OR 1.73; p<0.001).

Conclusion: Premature ACS, diagnosed in every fifth patient in Kosovo, is mainly associated with uncontrolled hypercholesterolemia and smoking, while diabetes, hypertension, and hyperglycemia are less common than in older patients. Clear sex differences were observed, with a more cardiometabolic profile in women and predominantly lifestyle-related risk factors in men. These findings highlight the distinct risk factor patterns in premature ACS and emphasize the importance of targeted prevention and early risk factor control in this population.

Keywords: Early-onset ACS, Kosovo, cardiovascular risk factors, biochemical indices, cross-sectional, retrospective study

Highlights

- Premature ACS affects one in five patients in Kosovo and is mainly associated with uncontrolled hypercholesterolemia and smoking, while diabetes, hypertension, and hyperglycemia are less common than in older ACS.
- Clear sex differences exist, with a more pronounced cardiometabolic profile in women and predominantly lifestyle-related risk factors in men.
- These findings support targeted prevention strategies and early risk factor control in patients with premature ACS.

INTRODUCTION

Coronary artery disease (CAD) represents the most common form of cardiovascular (CV) disease. It remains a leading cause of death, disability, and reduced quality of life which is largely driven by atherosclerotic processes, plaque instability, and thrombotic events leading to myocardial ischemia and infarction [1]. The overall burden of CAD is expected to increase further, because of the rising prevalence of cardiometabolic conditions, particularly obesity, diabetes, and metabolic syndrome, as well as demographic aging, reflected by an increasing proportion of older individuals who are at higher CV risk, along with urbanization and lifestyle changes [2]. Nevertheless, beyond the effects of aging, the occurrence of acute coronary syndrome (ACS) at a younger age has emerged as an important and distinct clinical entity, with significant implications for both individuals and healthcare systems [3]. Premature ACS defined as onset before 55 years in men and 65 years in women, is associated with substantial clinical and socioeconomic consequences [4, 5]. Elucidating the underlying mechanisms and identifying key determinants are essential for the development of effective prevention and early intervention strategies [6, 7].

The prevalence and impact of CV risk factors are not uniform across populations but vary widely depending on regional characteristics, lifestyle patterns, cultural influences, and socioeconomic conditions [8]. Differences in dietary habits, physical activity levels, use of tobacco, and access to healthcare services contribute to considerable heterogeneity in CV risk profiles, influencing both disease onset and progression [9, 10].

In addition, important sex-related differences exist in the presentation and determinants of CV disease [11]. Women often exhibit distinct behavioral and psychosocial risk profiles, including higher levels of stress, depression, and other psychosocial factors, which may adversely affect clinical outcomes [12]. These disparities are further amplified by socioeconomic inequalities, including unequal access to healthcare, education, and preventive resources that can influence disease recognition, management, and long-term prognosis [13]. Such factors contribute to persistent sex-related differences in CV outcomes and disproportionately affect vulnerable populations [14].

Therefore, the aim of this study was to comprehensively evaluate CV risk factors and sex-related differences in patients with premature acute coronary syndrome.

METHODS

Study design and patients

This retrospective study included 2,909 patients presenting with typical ACS from our cardiac center in Kosovo. Participants were categorized according to age into premature ACS (men <55 years and women <65 years; n=587) and remaining ACS patients (men ≥55 years and women ≥65 years; n=2,322). Patient's enrollment and data collection were performed at the Clinic of Cardiology, University Clinical Centre of Kosovo, between January 2024 and August 2025. Individuals with normal coronary angiograms, trauma-related conditions, acute organ injury, or hemorrhagic shock requiring surgical management were excluded. The study was conducted in accordance with national and institutional regulations and the principles of the revised Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of the University Clinical Centre of Kosovo and the Faculty of Medicine, University of Prishtina **(No. 1489/2025).** Patient confidentiality was strictly maintained, and all data were used solely for research purposes.

Cardiovascular risk factor assessment

Cardiovascular risk factors were assessed using clinical records obtained at the Clinic of Cardiology, University Clinical Centre of Kosovo. Variables included demographic characteristics (age and sex), smoking status (categorized as current or former), arterial hypertension (defined as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80

mmHg on at least two separate measurements, or a prior diagnosis or use of antihypertensive therapy) [15], diabetes mellitus (fasting plasma glucose ≥126 mg/dL, HbA1c ≥6.5%, or previously diagnosed or treated with glucose-lowering medications or insulin) [16], hypercholesterolemia (total cholesterol ≥200 mg/dL [5.2 mmol/L] and or LDL-C ≥130mg/dL [3.4mmol/L]or ongoing lipid-lowering therapy), and uncontrolled hypercholesterolemia (total cholesterol ≥200 mg/dL or LDL-C ≥116 mg/dL despite lipid-lowering treatment) [17], family history of coronary artery disease (presence of the disease in a first- or second-degree relative, irrespective of age at diagnosis) and alcohol intake. Poor glycemic control was defined as fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or HbA1c ≥7.0% despite ongoing therapy [18,19].

Laboratory and imaging assessment

Laboratory assessments included a comprehensive panel of routine biochemical and hematological parameters, such as complete blood count, fasting plasma glucose, and a detailed lipid profile, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. Additional collected data comprised serum albumin, total protein, and indicators of renal and hepatic function. Routine biochemical parameters were measured from blood samples collected in the morning, according to standard clinical practice. Cardiac structure and function were evaluated using standard transthoracic echocardiography performed by experienced cardiologists at the Clinic of Cardiology, University Clinical Centre of Kosovo. Key parameters included left ventricular end-diastolic and end-systolic dimensions (LVEDD and LVESD), left ventricular ejection fraction (LVEF), and atrial dimensions [20].

Electrocardiographic (ECG) recordings were systematically reviewed to assess cardiac rhythm and detect ischemic changes, including ST-segment deviations and T-wave inversions. All measurements were performed in accordance with current international guidelines to ensure accuracy and reproducibility. Information on CV medications, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, antiplatelet agents, and lipid-lowering therapies, was obtained from patients' medical records.

Statistical analysis

Descriptive statistics were used to summarize the data, with categorical variables reported as frequencies and percentages, and continuous variables expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR) when appropriate. Differences between groups were evaluated using the independent samples t-test for continuous variables and the chi-square test for categorical variables. Relationships between variables were further examined using appropriate correlation analyses, including point-biserial correlation, where applicable.

To identify factors associated with premature ACS, univariate analyses were initially performed, followed by multivariable modeling to adjust for potential co-founders. These analyses were conducted both in the overall population and separately according to sex. Statistical significance was defined as a two-sided p value <0.05 [21]. All statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic and clinical indices in premature compared to older ACS patients

Patients with premature ACS (n=587, 20.2%; men: 72.9%) had a mean age of 49.5±5.4 years, compared with 70.6±4.2 years in those with older ACS (men: 70.9%). Compared with older patients, individuals with premature ACS more frequently exhibited hypercholesterolemia (35.2% vs 25.1%; p<0.001), uncontrolled hypercholesterolemia (40.4% vs 26.9%; p<0.001), active smoking (41.1% vs 22.9%; p<0.001), and a family history of coronary artery disease (46.2% vs 32.4%; p<0.001). In contrast, cardiometabolic conditions were less prevalent among younger patients, including diabetes (31.6% vs 48.6%), hypertension (46.6% vs 68.6%), and hyperglycemia (43.7% vs 62.1%) (all p<0.001). Similarly, the burden of non-CV comorbidities was lower in the premature ACS group. Overall, these findings suggest a distinct risk profile in premature ACS, characterized by a higher prevalence of lifestyle-related and lipid abnormalities, but a lower burden of traditional age-related comorbidities.

Regarding treatment patterns, prasugrel use was more frequently taken by patients with premature ACS (64.1 vs 27.7%; p<0.001). Conversely, older patients were more likely receiving ACE inhibitors or angiotensin receptor blockers, diuretics, and oral anticoagulants (NOAC/VKA) (all p<0.05), while the use of lipid-lowering therapy did not differ significantly between groups (p=0.66). Electrocardiographic findings demonstrated that ST-segment changes were more

prevalent in patients with premature ACS compared with older patients (74.1% vs 61.1%; p<0.001), whereas T-wave inversion was observed less frequently in the premature group. These patterns suggest a more acute ischemic presentation among younger patients. Additionally, cardiac arrest and atrial fibrillation were less common in younger patients (all p<0.05; **Table 1**).

Laboratory and cardiac imaging data in premature compared to older ACS patients

At presentation, patients with premature ACS had higher total cholesterol levels (5.9 vs 3.7 mmol/L; p=0.03) and LDL-C (3.61 ± 1.3 vs 2.73 ± 1.6 mmol/L; p=0.04), while HDL-C and triglyceride levels were comparable between groups (1.1 ± 0.7 vs 1.1 ± 0.9 mmol/L; p=0.65, and 1.9 ± 1.4 vs 2.2 ± 1.7 mmol/L; p=0.62, respectively). In contrast, older patients demonstrated less favorable laboratory profiles, including higher fasting glucose, impaired renal function, and increased inflammatory markers (all p<0.05; **Table 2**). Coronary angiographic findings also differed between groups. Premature ACS was more frequently associated with single-vessel disease, compared to older patients who frequently had multivessel disease (38.2 vs 30.9%; p<0.001). Echocardiographic assessment revealed differences in cardiac structure and function. Older patients had larger left ventricular dimensions, increased left atrial size, and enlarged right ventricle and right atrium, along with a modest reduction in left ventricular ejection fraction (p<0.05 for all; **Tables 1 and 2**).

Sex differences in premature ACS patients

In the premature ACS cohort, women were less likely than men to smoke (35.2% vs 46.9%; p=0.01), consume alcohol (2.9% vs 14.7%; p<0.001), or have uncontrolled hypercholesterolemia (32.7% vs 45.5%). In contrast, cardiometabolic conditions, including diabetes, hyperglycemia, and hypertension, were more prevalent in women. Among non-CV comorbidities, thyroid disorders and anemia were also more common in women (both p<0.05). Electrocardiographic patterns differed by sex, with T-wave inversion more frequent in women, whereas ST-segment changes were less common. The prevalence of prior cardiac events did not differ between sexes. (**Table 3**).

Predictors of premature ACS patients

In multivariable analysis, current smoking (OR 1.59, 95% CI 1.40 to 1.81; p<0.001), uncontrolled hypercholesterolemia (OR 1.71, 95% CI 1.32 to 2.15; p<0.001) and family history (OR 1.66, 95% CI 1.34–2.06; p<0.001) were independently associated with increased risk of premature ACS. In contrast, age ≤45 years (OR 0.61, 95% CI 0.11–0.88; p<0.001) was associated with a lower likelihood of premature ACS.

These associations were observed in both sexes, although distinct risk patterns emerged. Among women, a more pronounced cardiometabolic profile was evident, with uncontrolled diabetes (OR 1.51; p<0.001) and arterial hypertension (OR 1.49; p<0.001) identified as significant predictors. In men, premature ACS was more strongly associated with lifestyle and lipid-related factors, particularly current smoking (OR 1.63; p<0.001) and uncontrolled hypercholesterolemia (OR 1.73; p<0.001; **Table 4**).

DISCUSSION

The present cohort analysis highlights three main observations. The present cohort analysis highlights three main observations. Premature ACS was associated with a higher prevalence of smoking, hypercholesterolemia, family history of coronary artery disease, and alcohol use, whereas diabetes and arterial hypertension were less frequent compared with older patients. These findings may reflect differences in underlying pathophysiological mechanisms, with premature ACS more strongly driven by lifestyle-related and genetic factors, while age-related comorbidities accumulate over time [4, 17, 18]. Distinct sex-related patterns were also observed, with men more commonly presenting with smoking and uncontrolled hypercholesterolemia, while women showed a greater burden of diabetes and hypertension. Current smoking and uncontrolled hypercholesterolemia emerged as the most powerful predictors of premature ACS, and these associations persisted after sex stratification, with a particularly strong effect among women.

Premature ACS has gained increasing attention as a distinct clinical condition due to its rising occurrence and growing burden on healthcare systems. Clarifying its pathophysiological mechanisms and identifying key risk factors are essential steps toward improving prevention and enabling earlier and more effective management [5, 6, 7]. Smoking and hypercholesterolemia were more frequent observed in premature ACS, highlighting their important contribution to

early-onset coronary artery disease. These findings underscore the key role of modifiable lifestyle and lipid-related risk factors in younger individuals, in contrast to the greater influence of cardiometabolic conditions in older patients. In this context, evidence from 52 countries reported by Yusuf et al. highlights the role of income level in shaping the distribution of conventional CV risk factors. Notably, smoking and uncontrolled hypercholesterolemia appear to be more prevalent in low- and middle-income countries, likely reflecting limited access to screening, lipid-lowering therapies, and suboptimal risk factor management [4, 22]. Despite the generally higher prevalence of alcohol consumption among younger populations, the rate observed in this study was relatively low, consistent with reports indicating a declining burden of alcohol use in Balkan countries [23]. Genetic susceptibility has been widely recognized as an important determinant of ACS, particularly in its premature form [24, 25]. In our cohort, a positive family history was more frequently observed among younger patients, supporting the notion that inherited factors, together with shared environmental influences, play a key role in the development of early-onset disease and may account for a substantial proportion of cases [26]. Given that atherosclerosis often begins early and progresses sub-clinically over time, familial aggregation may accelerate disease development even in the absence of other major CV risk factors. This may partly explain the more pronounced influence of genetic predisposition in younger individuals [27].

The present findings show an important feature of premature ACS patients in whom risk factors profile differs significantly according to sex. While both sexes are exposed to common CV risk factors, their distribution and clinical impact differ. In women, premature ACS appears to be more closely linked to cardiometabolic disturbances, including diabetes, hyperglycemia, and hypertension, whereas behavioral and lipid-related factors play a more prominent role in men. While smoking, alcohol consumption, and uncontrolled hypercholesterolemia were consistently less frequent in women, non-cardiovascular conditions such as thyroid disease and anemia were more commonly observed. These sex-specific differences suggest distinct underlying pathways contributing to premature ACS [28]. In women, the predominance of metabolic factors may influence disease expression, whereas in men, lifestyle-related exposures appear to be more relevant drivers [29]. Finally, our results identify smoking, uncontrolled hypercholesterolemia, and family history as the most prominent independent determinants of premature ACS. These associations were evident irrespective of sex, although distinct patterns emerged. In women, premature ACS was more strongly associated with uncontrolled diabetes and arterial

hypertension. In contrast, in men, the condition appeared to be driven predominantly by smoking and uncontrolled hypercholesterolemia [30].

This study highlights specific clinical features of patients with premature ACS, including family history and other conventional risk factors for atherosclerosis. These risk factors show clear sex-related patterns, with men more commonly presenting with smoking and uncontrolled hypercholesterolemia, while women have a greater burden of diabetes and hypertension. Accordingly, these findings emphasize the need for targeted preventive strategies, including lifestyle modification in men and stricter control of diabetes and hypertension in women. Although these associations are not exclusive, they warrant particular clinical attention.

Study strengths: This is the first study to investigate premature ASCVD in patients from Kosovo. Because the university hospital is a tertiary high-referral centre, its catchment area also includes patients from neighboring regions. Variations in therapy availability and healthcare systems may help explain the differences between our findings and those reported in other European countries, including those within the Greater Western Balkans. Finally, to the best of our knowledge, this is also the largest real-world evidence analysis on this topic from the region.

Study limitations: The findings of this study should be interpreted in light of several limitations. The retrospective design, without longitudinal follow-up, precluded evaluation of LDL-C target achievement and treatment optimization over time. In addition, LDL-C measurements were unavailable in a notable proportion of patients, limiting assessment of individualized lipid-lowering strategies. Information on menopausal status was not available, which may have influenced the interpretation of sex-related differences in lipid profiles and CV risk. Data on MASLD/MASH and metabolic syndrome were also unavailable, limiting a more comprehensive assessment of cardiometabolic risk. Finally, although this single-center study reflects national practice, it may still limit generalizability.

Conclusion: Premature ACS in Kosovo is predominantly driven by modifiable risk factors, particularly uncontrolled hypercholesterolemia and smoking, while traditional age-related comorbidities such as diabetes, hypertension, and hyperglycemia are less prevalent than in older

patients. Genetic susceptibility may further contribute to early disease onset. Notably, sex-specific patterns were observed, with a higher cardiometabolic burden in women and a predominance of lifestyle-related risk factors in men. These findings highlight the need for early, targeted prevention strategies and more aggressive lipid management to reduce the burden of premature ACS.

ACKNOWLEDGMENT:

Funding: This research received no external funding.

Institutional review board statement: Ethical approval was obtained from the Institutional Ethics Committee of the Doctors Chamber of Kosovo and the Medical Faculty, University of Prishtina (*1489/2025*).

Conflicts of Interest: The authors have no conflict of interest to declare.

Data Availability Statement: Due to patient confidentiality and institutional regulations, the data are not publicly available but can be provided by the corresponding author upon reasonable request.

Author contributions: I.B., and R.K.: Conceptualization, study design, methodology and project administration; I.B., R.K., E.M., N.S., and V.H.: data analysis and writing the first draft of manuscript. I.B., M.Y.H., and M.B.: Review manuscript. All authors have read and agreed to the published version of the manuscript.

TABLE LEGENDS:

Table 1. Baseline demographic and clinical characteristics of patients with premature ACS compared with those with older ACS, including cardiovascular risk factors and comorbidities.

Table 2. Echocardiographic parameters and laboratory indices in patients with premature ACS versus older ACS, reflecting cardiac function and biochemical profiles.

Table 3. Sex-stratified comparison of demographic and clinical characteristics between patients with premature and older ACS.

Table 4. Multivariable predictors independently associated with premature ACS

FIGURE LEGENDS:

Figure 1. Graphical abstract illustrating the prevalence, risk factor profile, and sex-related differences in premature acute coronary syndrome in Kosovo.

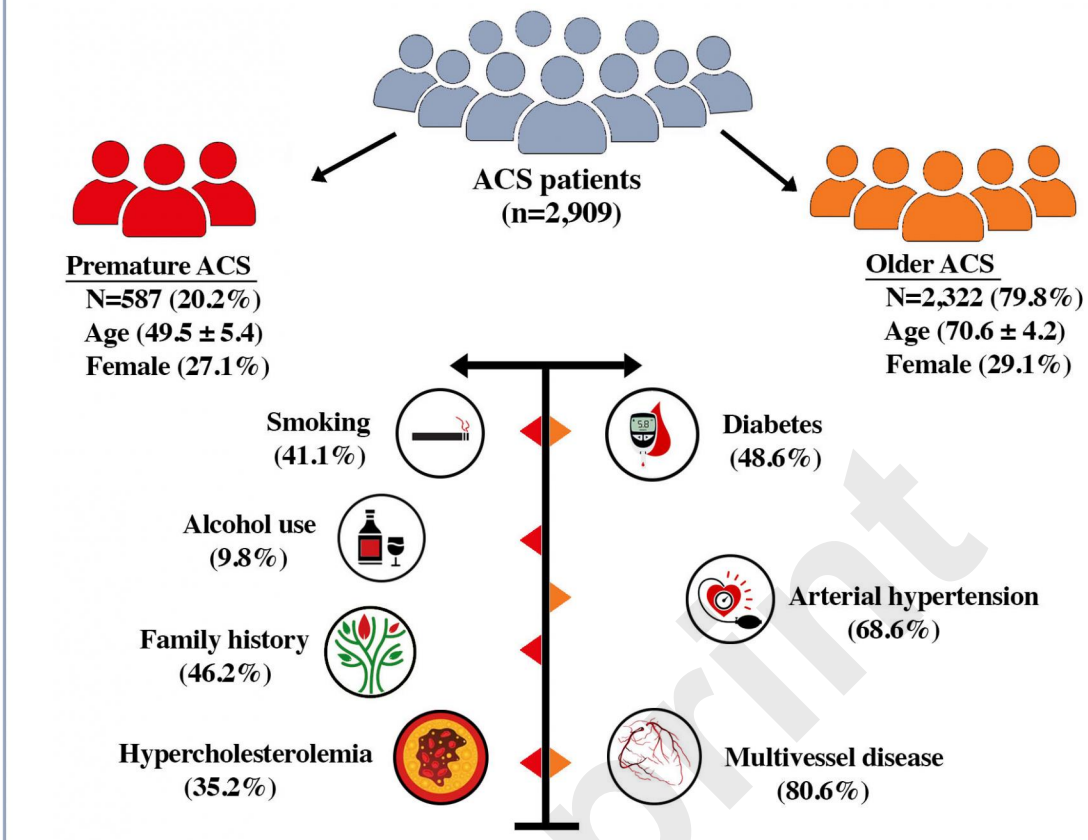
References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. J Am Coll Cardiol. 2020;76(25):2982–3021.
2. Xu S, Zhang Y, Jiang W, Liu J, Li W, Sun L, et al. Global burden of atherosclerotic cardiovascular disease attributed to lifestyle and metabolic risks. Sci China Life Sci. 2025.
3. Hoxha V, Dragusha E, Morina S, Dragusha E, Thaqi S, Henein MY et al. Sex-Related Differences in Predictors of Acute Coronary Syndrome in Kosovo: A Cross-Sectional Study. J Clin Med. 2025 Nov 11;14(22):8002.
4. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study). Lancet. 2004; 364 (9438): 937-952.
5. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *Circulation.* 2019; 140: e596–e646
6. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. Circulation. 2021;143(8):e254–e743.
7. Bredehorst M, Müller OJ, Katus HA, Sliwa K, Schulz-Menger J, Thiele H, et al. Recommendations for the primary prevention of atherosclerotic cardiovascular disease: a systematic guideline review. Front Med (Lausanne). 2024;11:1494234.
8. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA. 2003;290(7):898–904.
9. Banach M, Surma S. Monitoring of traditional atherosclerosis cardiovascular disease risk factors - is it enough to prevent premature acute coronary syndrome? Lancet Reg Health Eur. 2024 Feb 13;38:100866.
10. Bytyci I, Toth P, Bytyqi S, Henein M, Banach M. Worldwide patterns for premature atherosclerotic cardiovascular disease: a meta-analysis. Circulation. 2025;152(25).
11. Vogel B, Acevedo M, Appelman Y, Merz CNB, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. Lancet. 2021;397(10292):2385–2438.
12. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerdts E, Foryst-Ludwig A, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. Nat Rev Cardiol. 2016;13(9):516–528.
13. Stringhini S, Carmeli C, Jokela M, Avendaño M, Muennig P, Guida F, et al. Socioeconomic status and the 25×25 risk factors as determinants of premature mortality: a multicohort study. Lancet. 2017;389(10075):1229–1237.
14. Ebong IA, Goff DC, Rodriguez CJ, Chen H, Bertoni AG. The role of psychosocial stress in cardiovascular disease: implications for women. J Am Coll Cardiol. 2024.

15. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycaemia in type 2 diabetes, 2022. *Diabetologia*. 2022;65(12):1925–1966.
16. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J*. 2024;45(38):3912–4018.
17. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227–3337.
18. Dagenais GR, Leong DP, Rangarajan S, Lanas F, Lopez-Jaramillo P, Gupta R, et al.Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE study): a prospective cohort study. *Lancet*. 2020;395:785–794.
19. Meng X, Yuan J, Li W, Chen J, Wang H, Liu Z, et al. Predictive value of fasting plasma glucose for short-term prognosis in patients with type 2 diabetes mellitus after acute decompensated heart failure. Front Endocrinol (Lausanne). 2023; 14:1171583.
20. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2019;32(1):1–64.
21. Kirkwood BR, Sterne JAC. *Essential Medical Statistics*. 2nd ed. Oxford: Blackwell Science; 2003.
22. Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, et al. Reducing the global burden of cardiovascular disease, part 1: the epidemiology and risk factors. Circ Res. 2017;121(6):677–694.
23. Todorovic J, Santric Milicevic MM, Terzic Z, Stevanovic A, Terzic-Supic Z, Stamenkovic Z, et al. Burden of alcohol use disorder in Balkan countries. Eur J Public Health. 2022;32: ckac130.190.
24. Khera AV, Won HH, Peloso GM, O'Dushlaine C, Liu D, Stitziel NO, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol. 2016;67(22):2578–2589.
25. Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. Nat Rev Cardiol. 2018;15(4):230–240.
26. Banach M, Fras Z, Gaita D, Pecin I, Bajraktari G, Bjelakovic B, et al. The European Program for Prevention (EPP) – implementing proven preventing measures now! *Global Heart*. 2025;20(1):103.
27. Banach M, Mazidi M, Mikhailidis DP, Toth PP, Jozwiak J, Rysz J et al. Association between phenotypic familial hypercholesterolaemia and telomere length in US adults: results from a multi-ethnic survey. Eur Heart J. 2018 Oct 21;39(40):3635-3640.
28. Maas AHEM, Appelman YEA. Gender differences in coronary heart disease. Neth Heart J. 2010;18(12):598–603.

29. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, Franconi F, Gerdts E, Foryst-Ludwig A, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. Nat Rev Cardiol. 2016;13(9):516–528.
30. Baigent C, Keech A, Kearny PM, Blackwell L, Buck G, Pollicino C, et al. Cholesterol Treatment Trialists collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90.056 participants in 14 randomised trials of statins. Lancet. 2005; 366: 1267-78.

Early ACS in Kosovo: Prevalence, determinants, and sex differences



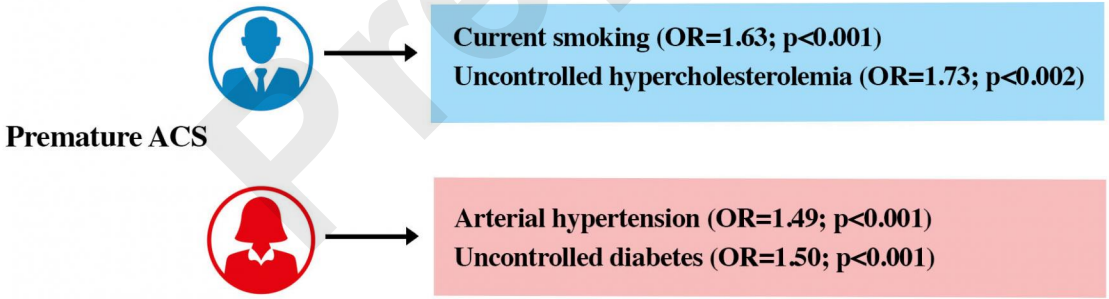


Table 1. Demographic and clinical characteristics of patients with premature ACS in comparison with those with older ACS.

Variable	Premature ACS (n = 587)	Older ACS (n=2322)	P Value
Cardiac risk factors			
Age (years)	49.5 ± 5.4	70.6 ± 4.2	<0.001
Male gender (n, %)	428 (72.9)	1646 (70.9)	0.34
AH (n, %)	273 (46.6)	1593 (68.6)	<0.001
DM (n, %)	185 (31.6)	1128 (48.6)	<0.001
Uncontrolled DM (n, %)	257 (43.7)	1142 (62.1)	<0.001
Hypercholesterolemia (n, %)	207 (35.2)	583 (25.1)	<0.001
Uncontrolled hypercholesterolemia (n, %)	237 (40.4)	625 (26.9)	<0.001
Current smokers (n, %)	241 (41.1)	532 (22.9)	<0.001
Former smokers (n, %)	135 (23.1)	367 (15.8)	<0.001
Alcohol use (%)	57 (9.80)	121 (5.21)	0.02
Family History (n, %)	271 (46.2)	752 (32.4)	<0.001
Number of cardiac risk factors			
0 risk factor (%)	107 (18.2)	186 (8.0)	<0.001
1-2 risk factor (%)	406 (69.1)	1695 (73)	0.17
≥ 3 risk factors (%)	70 (12)	485 (20.9)	0.02
Other risk factors			
CRF (%)	64 (11)	787 (33.9)	<0.001
Thyroid disorders (%)	42 (7.1)	67 (2.9)	0.02
CLD (%)	95 (16.2)	559 (24.1)	0.01
COPD (%)	8 (1.3)	167 (7.2)	0.02
Anaemia (%)	64 (11.1)	399 (17.2)	0.03
Drugs			
LLT (%)	575 (97.9)	2233 (96.2)	0.76
Aspirin (%)	551 (93.9)	2048 (88.2)	0.04
Clopidogrel (%)	168 (28.7)	348 (59.3)	<0.001
Prasugrel (%)	376 (64.1)	643 (27.7)	<0.001
NOAC/VKA (%)	8 (1.3)	204 (8.8)	<0.001
ACEI/ARBI (%)	273 (46.6)	1593 (68.6)	<0.001
MRA (%)	53 (9.1)	341 (14.7)	0.32
Diuretic	122 (20.8)	938 (40.4)	<0.001
Number of coronaries included			
1 vessel (n, %)	204 (34.7)	202 (8.15)	<0.001
2 vessels (n, %)	265 (45.2)	168 (7.25)	<0.001
≥3 vessels (n, %)	118 (20.1)	1871 (80.6)	<0.001
ECG changes			
T inversion (%)	118 (20.2)	778 (33.5)	<0.001
ST depression/elevation (%)	435 (74.1)	1430 (61.1)	<0.001
Previously cardiac events			
Myocardial infarction (%)	25 (4.2)	130 (22.1)	<0.001
PCI/CABG (%)	24 (4.1)	113 (19.3)	<0.001
Stroke (%)	5 (0.9)	142 (6.1)	<0.001
PAD (%)	6 (1.1)	114 (4.9)	0.04
Complication			
AF (%)	10 (1.7)	144 (6.2)	0.01

VT (%)	16 (2.7)	26 (1.1)	0.31
Cardiac arrest (%)	13 (2.2)	128 (5.5)	0.02

Abbreviations: AH: arterial hypertension; ACEI; Angiotensin-converting enzyme inhibitors; ARBI: Angiotensin receptor blockers: AF: Arterial Fibrillation; CABG: Coronary artery bypass grafting; CRF: Chronic renal failure; CLD: Chronic liver disease; COPD: Chronic obstructive pulmonary disease; DM: diabetes mellitus; MRA: Mineralocorticoid receptor antagonist; NOAC: New oral anticoagulation; PAD: Peripheral artery disease; PCI; Percutaneous coronary intervention LLT: Lipid lowering therapy; VT: Ventricular tachycardia; VKA: Vitamin K antagonists

Table 2. Echocardiographic and laboratory indices of patients with premature ACS in comparison with those with older ACS.

Variable	Premature ACS (n = 587)	Older ACS (n=2322)	P Value
Echocardiographic indices			
LV EDD (mm)	49.2 ± 5.4	54.2 ± 6.4	<0.001
LV ESD (mm)	20.1 ± 5.1	32.3 ± 6.1	<0.001
EF (%)	54.4 ± 8.3	48.1 ± 9.3	0.007
RV (mm)	30.2 ± 5.1	33.8 ± 5.1	0.02
RA transversal (mm)	36.4 ± 5.3	39.3 ± 4.1	0.02
RA longitudinal (mm)	40.8 ± 5.1	45.6 ± 6.1	0.01
LA transversal (mm)	38.1± 5.1	41.1 ± 8.1	0.01
LA longitudinal (mm)	41.1± 6.3	47.9 ± 7.3	<0.001
Laboratory indices			
WBC ($10x^3$/uL)	10 ± 3.3	10.1 ± 3.3	0.34
RBC (10x6/uL)	4.6± 4.3	4.2 ± 1.2	0.57
Hgb (g/dL	15.4 ± 4.3	12.1 ± 3.3	0.04
Hematocrit (%)	42.3 ± 6.1	37.1 ± 6.3	0.01
Platelet ($10x^3$/uL)	228 ± 67	221 ± 73	0.23
FPG (mmol/L)	7.3 ± 4.7	10.6 ± 6.7	<0.001
CRP (mg/L)	20.4 ± 39	59.5 ± 41	<0.001
Urea (mmol/L)	6.48 ± 8.3	10.7 ± 20	0.02
Creatinine (µmol/L)	98.1 ± 49	125 ± 83	0.02
TSH (ml/UL)	2.3 ± 1.4	3.6 ± 2.3	0.27
Total cholesterol (mmol/L)	5.9 ± 1.2	4.7 ± 3.1	0.03
Triglycerides (mmol/L)	1.9 ± 1.4	2.2 ± 1.7	0.62
LDL-C (mmol/L)	3.61 ± 1.3	2.73 ± 1.6	0.041
HDL-C (mmol/L)	1.1 ± 0.7	1.1 ± 0.9	0.65

Abbreviations: AH: arterial hypertension; AF: Arterial Fibrillation; CHD: Coronary heart disease; CRP; C-reactive protein; DM: diabetes mellitus; FPG: Fasting plasma glucose; LV: Left ventricle; EDD: End diastolic volume; ESV: End systolic volume; RV: Right ventricle; RA: Right atrium; LA: left atrium; TSH: Thyroid stimulus hormone; LDL-C: Low density lipoprotein; HDL-C: High density lipoprotein; Hgb: Hemoglobin; RBC: Right Blood Cell; WBC: White Blood Cell

Table 3. Demographic and clinical characteristics of premature ACS, by sex

Variable	Premature ACS (Male; n=428)	Premature ACS (Female; n=159)	P
Cardiac risk factors			
Age (years)	68.4 ± 3.3	70.4 ± 3.3	0.09
AH (%)	178 (41.5)	82 (51.7)	<0.001
DM (n, %)	111 (25.9)	59 (37.2)	0.01
Uncontrolled DM	165 (38.6)	77 (48.8)	<0.001
Hypercholesterolemia (%)	157 (36.7)	54 (33.8)	0.09
Uncontrolled hypercholesterolemia	195 (45.5)	52 (32.7)	<0.001
Current smoking (%)	201 (46.9)	56 (35.2)	<0.001
Former smoking (n, %)	103 (24.1)	35 (22.2)	0.22
Alcohol (%)	63 (14.7)	5 (2.9)	<0.001
Family History (%)	189 (44.2)	75 (47.2)	0.61
Number of cardiac risk factors			
0 risk factor (%)	82 (19.1)	28 (17.6)	0.22
1-2 risk factor (%)	292 (68.2)	111 (69.9)	0.29
≥ 3 risk factors (%)	48 (11.2)	21 (13.2)	0.33
Other risk factors			
CRF	42 (9.9)	20 (12.5)	0.12
Thyroid disorders	35 (8.1)	23 (14.7)	0.01
CLD	67 (15.6)	27 (16.9)	0.31
COPD	8 (1.9)	4 (2.6)	0.16
Anaemia	37 (8.7)	22 (13.9)	0.01
Drugs			
LLT (%)	415 (97.1)	156 (98.2)	0.47
Aspirin (%)	399 (93.2)	150 (94.4)	0.52
Clopidogrel (%)	105 (24.5)	52 (32.9)	<0.001
Prasugrel (%)	299 (69.8)	92 (58.2)	<0.001
NOAC/VKA	5 (1.2)	3 (1.8)	0.14
ACE/ARBI (%)	205 (47.9)	70 (44.3)	0.34
MRA (%)	36 (8.5)	16 (9.9)	0.22
Diuretic	73 (17.1)	39 (24.6)	0.01
Number of coronaries included			
1 vessel (n, %)	163 (38.2)	49 (30.9)	0.001
2 vessels (n, %)	193 (45.1)	71 (44.9)	0.19
≥3 vessels (n, %)	73 (17.1)	38 (24.1)	0.001
ECG changes			
T inversion	74 (17.2)	38 (24.1)	0.01
ST depression/elevation	330 (77.2)	112 (70.8)	0.01
Previously cardiac events			
Myocardial infarction (%)	21 (4.9)	6 (3.9)	0.14
PCI/CABG (%)	22 (5.1)	5 (3.5)	0.22
Stroke (%)	3 (0.7)	2 (1.3)	0.34
PAD (%)	5 (1.2)	2 (1.1)	0.18
Complication			
AF	6 (1.4)	3 (2.1)	0.11
VT	12 (2.9)	4 (2.5)	0.29
Cardiac arrest	6 (1.5)	5 (2.9)	0.18

Abbreviations: AH: arterial hypertension; ACEI; Angiotensin-converting enzyme inhibitors; ARBI: Angiotensin receptor blockers: AF: Arterial Fibrillation; CABG: Coronary artery bypass grafting; CRF: Chronic renal failure; CLD: Chronic liver disease; COPD: Chronic obstructive pulmonary disease; DM: diabetes mellitus; MRA: Mineralocorticoid receptor antagonist; NOAC: New oral anticoagulation; PAD:

Peripheral artery disease; PCI; Percutaneous coronary intervention LLT: Lipid lowering therapy; VT: Ventricular tachycardia; VKA: Vitamin K antagonists

Table 4. Predictors of premature ACS overall and by sex.

Variable	Univariate predictors OR (95% CI)	P value	Multivariate predictors OR (95% CI)	P value
	All patients			
Age ≤45 years	0.499 (0.356 to 0.505)	<0.001	0.661 (0.119 to 0.881)	<0.001
Male gender	1.104 (1.008 to 1.352)	0.039	1.071 (0.832 to 1.292)	0.361
Uncontrolled diabetes	0.806 (0.682 to 0.981)	<0.001	0.819 (0.104 to 0.902)	0.023
Arterial hypertension	0.446 (0.341 to 0.557)	<0.001	0.827 (0.219 to 0.941)	0.011
Uncontrolled hypercholesterolemia	1.846 (1.482 to 2.298)	<0.001	1.710 (1.328 to 2.125)	<0.001
Current smoking	1.757 (1.585 to 1.949)	<0.001	1.596 (1.403 to 1.816)	<0.001
Alcohol use	1.454 (1.130 to 2.138)	0.007	1.016 (0.303 to 1.316)	0.311
Family history	1.753 (1.476 to 2.083)	<0.001	1.663 (1.346 to 2.064)	<0.001
	Multivariate analysis			
	Males	**P**	**Females**	**P**
Current smoking	1.633 (1.118 to 2.461)	<0.001	0.611 (0.421 to 0.901)	<0.001
Uncontrolled hypercholesterolemia	1.732 (1.181 to 2.641)	<0.001	0.682 (0.492 to 0.911)	<0.001
Arterial hypertension	0.680 (0.461 to 0.975)	<0.001	1.491 (1.031 to 2.192)	<0.001
Uncontrolled DM	0.673 (0.408 to 0.969)	<0.001	1.501 (1.031 to 2.191)	<0.001
Family history	0.893 (0.628 to 1.289)	0.561	1.121 (0.781 to 1.691)	0.344