MEDICAL UNIVERSITY OF PLEVEN

FACULTY OF MEDICINE

DEPARTMENT OF NEUROLOGY AND NEUROSURGERY

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CLINICAL CHARACTERISTICS AND ASSESSMENT OF CERTAIN RISK FACTORS IN PATIENTS WITH ISCHEMIC CEREBRAL STROKE IN YOUNG AND MIDDLE-AGED ADULTS

ABSTRACT

To Dissertation For the award of the degree of "Doctor of Education and Science"

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The dissertation consists of 150 pages and is illustrated with 26 tables and 46 figures. The bibliography includes 259 sources, of which 12 are in Cyrillic and 247 in Latin script.

The dissertation has been approved and directed for public defense at the extended department council of the Department of Neurology and Neurosurgery at the Medical University – Pleven, held on February 4, 2025.

The official defense of the dissertation will take place on May 21, 2025, at 12:00 o'clock in the №6 hall at "UMHAT – Dr. Georgi Stranski" EAD, "Georgi Kotchev" street №8A, Pleven.

The materials for the defense are available at the Research Department and have been published on the website of the Medical University – Pleven – www.mu-pleven.bg.

Brief information about the author:

Dr. Georgi Tsvetanov Dimitrov graduated in Medicine from the Medical University - Pleven in 2015. Initially, he began working as a resident physician and later as a specialist trainee at the Neurology Clinic of UMBAL "Dr. Georgi Stranski" EAD, Pleven. In June 2020, Dr. Georgi Tsvetanov Dimitrov obtained a specialization in Neurology. Since 2018, he has been appointed as an assistant at the Department of Neurology and Neurosurgery, Neurology Sector, Medical University – Pleven, and conducts exercises in the specialty "Neurology" for medical students. In March 2019, Dr. Georgi Tsvetanov Dimitrov was enrolled as a PhD student in the regular education format, and in March 2024, he was granted the right to defend his dissertation.

On the topic of his dissertation, Dr. Georgi Tsvetanov Dimitrov has published 3 articles: 1 in the Journal of Biomedical and Clinical Research (JBCR) of MU Pleven and 2 in the Journal of International Medical Association Bulgaria (IMAB).

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ABBREVIATIONS

ACA- The anterior cerebral artery

AF- Atrial fibrillation

AH- Arterial hypertension

AHA- American Heart Association

ASA- American Stroke Association

BMI- Body mass index

BP- Blood pressure

CI - Confidence Interval

CRP - C-reactive protein

CT- Computed tomography

DBP- Diastolic blood pressure

df - degree of freedom

DM- Diabetes mellitus

ECG- Electrocardiography

GBD - Global Burden of Disease

HDL - High – density lipoprotein

HR- Hazard Ratio

IS- Ischemic stroke

LDL - Low – density lipoprotein

Max - Maximum

MCA- Middle cerebral artery

Min - Minimum

MRI- Magnetic resonance imaging

mRs - modifiable Rankin scale

N/A- Noun Available

NIHSS - National Institutes of Health Stroke Scale

OCSP - Oxfordshire Community Stroke Project

OR - Odds Ratio

PAR- Population attributable risk

RFs- Risk factors

RR- Risk Ratio

SBP- Systolic blood pressure

SD - Standard deviation

TIA- Transient ischemic attack

TOAST - Trial of ORG 10172 in Acute Stroke Treatment

WHO- World Health Organization

Contents

1. INTRODUCTION

Ischemic stroke (IS) is a socially significant disease characterized by high morbidity and mortality, leading to long-term physical, mental, and social consequences (Tityanova E et al., 2015).

Every year, approximately 11.6 million people have a stroke, resulting in global costs that exceed 891 billion dollars (Donkor ES 2018, GBD 2019). According to data from the World Health Organization (WHO), the global incidence of IS is 98 per 100,000, and it is expected to increase over the next 10 years, affecting all age groups and both genders (Feigin VL et al., 2022, Pu L et al., 2023).

Undoubtedly, stroke affects not only the elderly population. Over the past twenty years, epidemiological studies have reported an alarming trend of increasing IS incidence among the so-called "young patients" (typically defined as individuals aged between 18 and 55). Between 10% and 20% of all IS cases occur in this age range, with approximately two million young individuals being affected each year (Ekker MS et al., 2018). Recently published data indicate that the incidence of IS in young people in Europe ranges from 5 to 17.4 per 100,000 (Béjot Y et al., 2016, Ekker MS et al., 2019, Amaya Pascasio L et al., 2023). Far more unfavorable data comes from the United States (USA), where the incidence of IS reaches 28 per 100,000 (Yahya T et al., 2020), while in some countries in Africa and Iran, it is ≥ 40 per 100,000 (Boot E et al., 2020). According to the latest published epidemiological data, men are more frequently affected by IS (30.6 per 100,000) compared to women (19.1 per 100,000) (Norman K et al., 2022).

Epidemiological data indicate that Bulgaria ranks among the top countries in the world in terms of morbidity and mortality from stroke. Currently, the incidence of stroke among the Bulgarian population is 185.5 per 100,000, and is expected to increase by 14.0% over the next 10 years. Every year, approximately 22,000 deaths due to stroke occur, and the costs associated with stroke care amount to 47.6 million euros (The Burden of Stroke in Bulgaria – 2017, Stroke Alliance for Europe, 2017). The incidence of IS in Bulgaria exceeds 151 per 100,000 (GBD, 2019). According to the National Center for Public Health and Analyses (NCPHA), in 2022, 43,434 Bulgarians had an IS, of which 3,478 (8.0%) were in the younger age group (under 55 years). Men were more frequently affected than women (1.53:1) (NCPHA, 2022).

The increasing incidence of IS among young and middle-aged patients presents a significant health and socio-economic issue due to the longer life expectancy of these patients with motor and cognitive impairments, epilepsy, depression, and pain (Putaala J, 2020). Moreover, IS significantly increases the risk of clinically manifested dementia, which impacts the activity and functional independence of patients (Petrova N, 2016). On the other hand, IS in young adults carries a disproportionately larger economic burden compared to older individuals, as it affects people in their active working years. The costs related to hospital treatment, outpatient rehabilitation, and social services for young patients with stroke are estimated at approximately 2.0 billion dollars (Tan E et al., 2022).

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The analysis of the published literature to date undoubtedly highlights a global trend of increasing incidence of IS in the age group between 18-55 years. According to most epidemiological studies, this concerning trend is directly linked to the increasing frequency of certain modifiable risk factors (RFs) in these patients. However, the question as to what extent do these modifiable RFs contribute to the occurrence of IS remains debatable. The discussion is highly relevant and concerns both health-related RFs (such as hypertension, diabetes, dyslipidemia, and obesity) as well as lifestyle-related RF (such as smoking, alcohol abuse, low physical activity, obesity, insufficient sleep, and psycho-social stress).

The epidemiological data shows a higher incidence of IS in men compared to women. This is likely consequence of the fact that that men in young and middle adulthood years have a higher prevalence of certain modifiable RFs compared to women. Additionally, an unresolved question remains as to whether and to what extent men are more prone to a combination of certain modifiable RFs related to health status and lifestyle, in comparison to women.

These unfavorable epidemiological trends underline the need for in-depth research and better knowledge and strict control of potential RFs for IS, which will aid in the development of effective interdisciplinary preventive strategies aimed at limiting the adverse effects of RFs, with the goal of reducing the incidence and severity of IS, especially among at-risk populations in young and middle-aged groups (Trivedi MM et al., 2015).

2. GOAL and OBJECTIVES

2.1 Goal

The goal of this dissertation is to investigate the prevalence of certain modifiable RFs related to health status and lifestyle in young and middle-aged patients with acute IS, as well as to assess the clinical characteristics and outcomes of stroke in the studied cohort.

2.2 Objectives

2.2.1. To determine the number and frequency of modifiable RFs in the group of patients with acute IS and in the control group.

2.2.2. To evaluate the strength of the association between modifiable RFs and the risk of IS through a case-control study.

2.2.3. To perform a comparative analysis of the prevalence of modifiable RFs for IS by age and sex.

2.2.4. To conduct a comparative analysis of the prevalence of etiological subtypes of IS by age and sex.

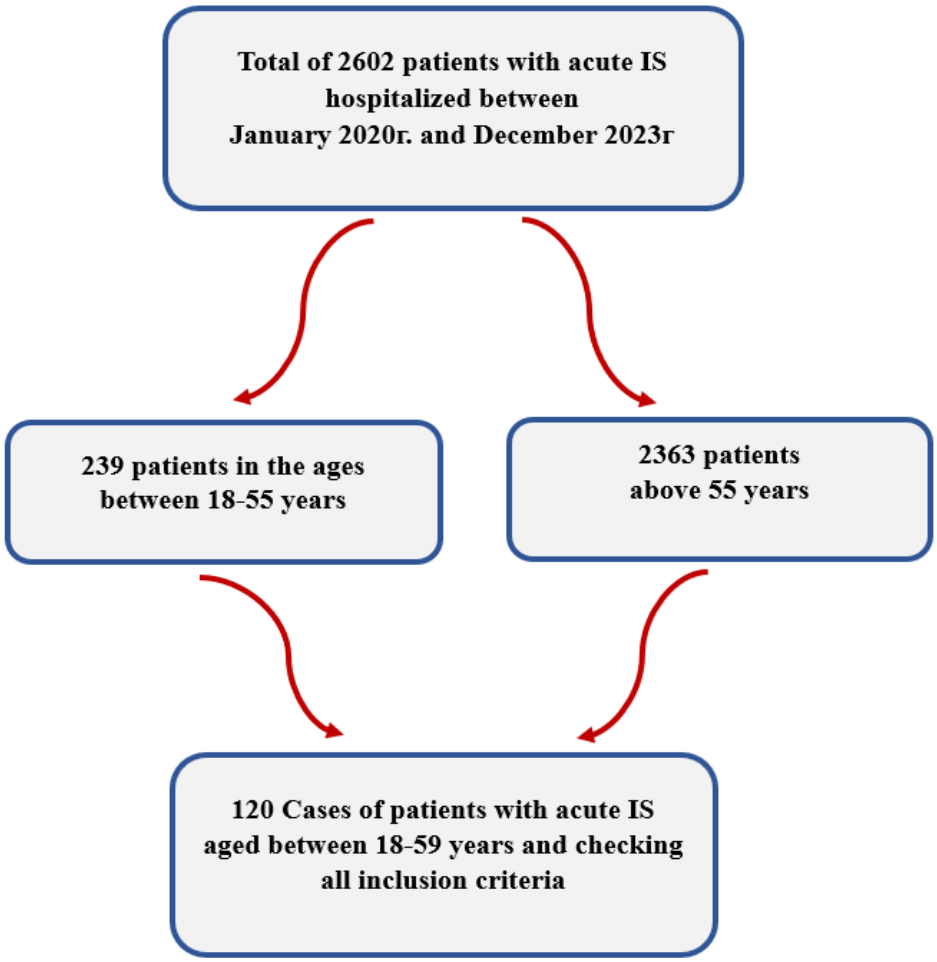
2.2.5. To assess the severity of IS at the time of hospital admission and at discharge.

2.2.6. To evaluate the clinical outcome of IS and identify predictors associated with unfavourble functional outcomes in both age groups.

3. MATERIALS and METHODS

3.1 Materials

This prospective study was conducted at the Neurology Clinic of the University Hospital (UMHAT) "Dr. Georgi Stranski" EAD, Pleven, from January 2020 to December 2023. During this period, a total of 2,602 patients with acute IS were hospitalized at the clinic, of which 239 were aged between 18 and 55 years, and 2,363 were over 55 years old (**Scheme 1**). Out of these patients, a total of 120 cases of acute IS in ages between 18 and 59 years, were included in the study. A second group of 120 individuals was also selected, which included patients (controls) with modifiable RFs for IS, but who have not yet experienced a stroke. The control group was matched in age and sex with the stroke case group. The patients with acute IS were divided into two age groups: the young age group (18-44 years) and the middle-aged group (45-59 years), according to the criteria set by the World Health Organization (WHO).



Inclusion and exclusion criteria for cases and controls

Inclusion criteria for cases:

- Patients aged between 18 and 59 years;
- Acute IS confirmed by clinical examination, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain;
- Written informed consent for participation in the study by the patient and/or their legal representative (family member or guardian).

Inclusion criteria for controls:

- Patients aged between 18 and 59 years;
- Patients without acute IS
- Modifiable RFs
- Written informed consent for participation in the study by the patient and/or their legal representative (family member or guardian).

Exclusion criteria for cases:

- Patients aged below 18 and above 59 years;
- The presence of cerebral venous thrombosis, brain hemorrhage, and/or brain tumor, confirmed through clinical evaluation and neuroimaging (CT or MRI);
- Transient neurological deficit;
- Refusal of participation by the patients or their legal representatives.

Exclusion criteria for controls:

- Patients aged below 18 and above 59 years;
- Previous cerebrovascular incident;
- Refusal of participation by the patients or their legal representatives.

The study was approved by the decision of the Committee on Ethics of Scientific Research at the Medical University of Pleven with protocol №45/ 03.05.2018.

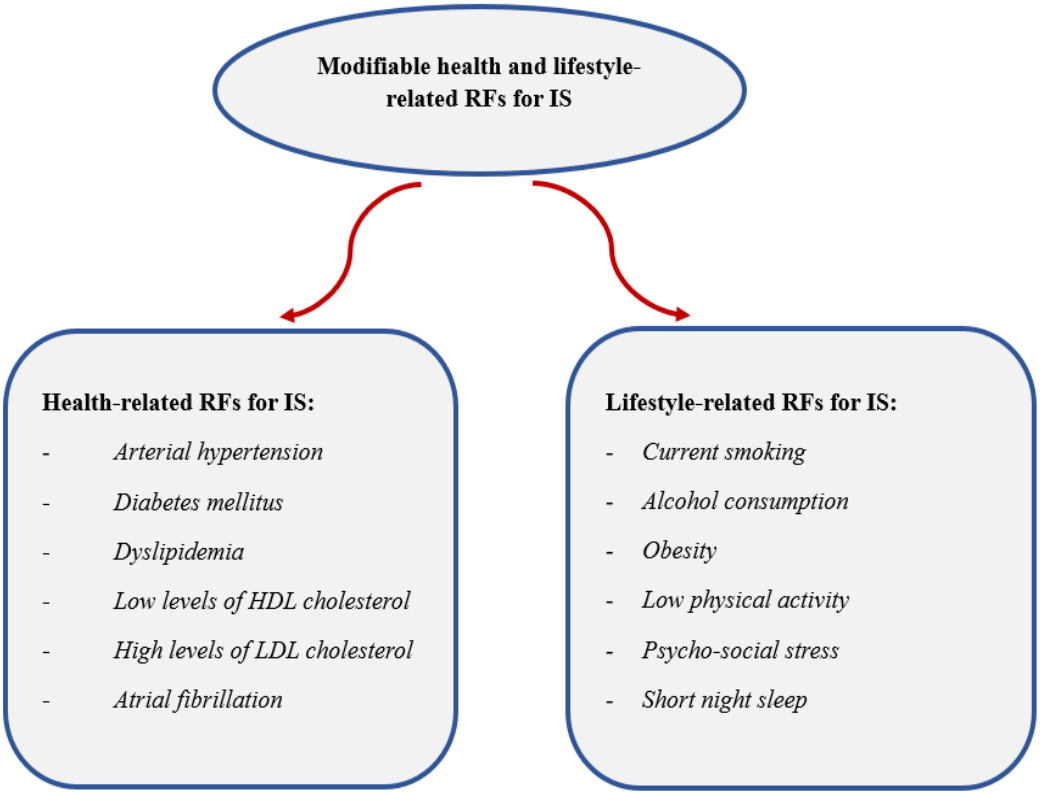
3.2 Methods

3.2.1 Clinical and documentation methods

- The information regarding the current health status, comorbidities, lifestyle-related RFs, and family history of the patients was collected from the patient, their family members (in cases where the patient was unable to provide full medical history) and medical documentation (discharge summaries from other hospitals or departments or outpatient medical records).

- Complete somatic and neurological status.
- Determination of modifiable RFs.

Schema 2 shows the modifiable RFs for IS that were investigated in both the case and control groups of our study.



3.2.2 Laboratory methods

Laboratory tests performed on all patients included in the current study:

- Complete blood count, blood sugar leves, ionogram
- Laboratory tests for kidney function assessment (urea and creatinine);
- Laboratory tests for liver function assessment (ALAT, ASAT, GGTP);
- Laboratory tests for coagulation status assessment (bleeding time, coagulation time, INR, PT);
- Lipid profile (cholesterol, triglycerides, LDL и HDL – cholesterol);

3.2.3 Instrumental methods

- Measurement of Blood Pressure (BP) on both arms using a mechanical sphygmomanometer. The values of BP were assessed at the time of hospitalization, during the hospital stay and at discharge. The assessment of arterial hypertension was categorized according to the criteria of the European Society of Hypertension.

- Electrocardiography (ECG) – all patients included in the study received 12-lead ECG.

3.2.4 Neuroimaging:

- CT of the brain was performed on all patients with acute IS included in our study. Patients who underwent intravenous thrombolysis for acute IS were required to undergo a repeat CT scan of the brain within 24 hours after treatment.
- MRI of the brain was applied to a limited number of patients in our study, specifically those for whom it was necessary to exclude other conditions that could mimic IS.
- Duplex ultrasound examination of the carotid (both extracranial and intracranial) and vertebral brain vessels was performed on all patients included in the study.

3.2.5 Assessment scales

3.2.5.1. Scale for assessment of psycho-social stress - the assessment of psycho-social stress was carried out using a standardized questionnaire, which included questions related to stress at home and at the workplace over the past year, as well as prior to the onset of the acute IS. The psycho-social stress was classified as lack of psycho-social stress, acute and chronic psycho-social stress.

3.2.5.2. Alcohol consumption assessment scale - patients were assessed according to the World Health Organization (WHO) criteria for alcohol consumption, based on the quantity of alcohol consumed daily. The classification is as follows: light alcohol consumption (up to 40 grams of alcohol daily or up to 3 alcoholic drinks), moderate (Between 40 and 60 grams of alcohol daily or 4 to 5 alcoholic drinks) and heavy alcohol consuption (more than 60 grams of alcohol daily or more than 5 alcoholic drinks).

3.2.5.3. Body mass index (BMI) assessment – Overweight in patients was determined based on Body Mass Index (BMI). The following formula was used: $\mathbf{BMI = W/h^2}$, where **W** (weight) is measured in kilograms, **h** (height) is measured in meters. According to the WHO criteria, overweight is defined as a BMI > 25.0.

3.2.5.4. Scales for assessment of severity and functional outcome from stroke

- **National Institutes of Health Stroke Scale (NIHSS)**

  This is the most commonly used scale for assessing the severity of neurological deficits in patients with acute stroke. According to the total score, IS is categorized as follows: mild stroke (1-4 points), moderate stroke (5-15 points), severe stroke (16-20 points), very severe stroke (> 21 points).

- **Modified Rankin Scale (mRs)**

  The Modified Rankin Scale (mRS) is a 7-point scale used to assess the functional outcome of patients after an acute stroke. The scale includes the following grades: 0 (no symptoms); 1 – no significant disability; 2 – slight disability; 3 – moderate disability; 4 – moderate to severe disability; 5 – severe disability; 6 – death. The functional outcome of acute IS is typically categorized into two groups based on the mRS score: favourable outcome (mRs 0-2) (patient is largely independent and able to perform daily activities) and unfavourable outcome (mRs 3-5) (patient requires assistance for daily activities).

Stroke classification based on etiology

In this dissertation, the subtype of IS is classified according to the criteria of the following two classifications:

TOAST Classification (Trial of Org 10172 in Acute Stroke Treatment):

- Large artery atherosclerosis;
- Small vessel disease
- Cardiooembolism
- Other determined causes;
- Undetermined cause.

Oxfordshire Community Stroke Project (OCSP) classification:

The OCSP classification (Oxford Community Stroke Project) categorizes IS into four subtypes:

- Total Anterior Circulation Infarct
- Partial Anterior Circulation Infarct
- Lacunar Infarct
- Posterior Circulation Infarct

The OCSP classification helps neurologists predict the severity of neurological deficit and the clinical outcome of patients with acute IS.

3.2.6 Statistical methods

The statistical analysis of the data was performed using the software products IBM SPSS (Statistical Package for Social Sciences), version 25.0, and MS Excel 2019. The results are described through numerical indicators such as structure, frequency, mean values, correlation coefficients, etc. Parametric, non-parametric statistical tests, and regression analysis were applied. A p-value of < 0.05 was considered statistically significant.

Following statistical methods were applied:

3.2.6.1 Descriptive Statistics

- **Frequency analysis of qualitative variables –** the results are presented using absolute and relative frequencies (number and %).
- **Analysis of variance of quantitative variables –** the results were presented using the mean ($\bar{x}$) and standard deviation (SD) for data that follow a normal distribution. When the data do not follow a normal distribution, the results were presented using the median (Me), interquartile range (IQR), and minimum and maximum values (Min and Max).

3.2.6.2. Non-Parametric Tests

- Pearson's chi-square χ^2 test; Phi and Cramer`s V.
- Point Biserial Correlation Coefficients.
- Mann-Whitney U test.
- Friedman test.
- Wilcoxon Signed Ranks Test.
- Kolmogorov-Smirnov Test.

3.2.6.3. Parametric tests

- Independent samples t-test.
- ANOVA (Analysis of variance).

3.2.6.4.Regression analysis

Regression analysis was used to investigate the relationship between one dependent and one independent variable. In this dissertation, regression analysis was applied to examine the relationship between individual RFs (independent variable) and stroke

(dependent variable). When measuring relative risk, the Odds Ratio (OR) and its Confidence Intervals (CI) were used.

3.2.6.5.Graphical Analysis – visualizing of the obtained results was done by the following graphs: bar chart, line graph, pie chart, radar chart, forest plot, box plot.

4. RESULTS

4.1 Social and demographic characteristics of patients with acute ischemic stroke

Out of the 120 studied patients with acute IS, 41 (34.2%) belong to the young age group (Group A), while 79 (65.8%) are in the middle-aged group (Group B). It was found that 72 (60.0%) are men and 48 (40.0%) are women. The mean age of stroke patients is 48.99 ± 7.58 years. **Figure 1** displays the percentage distribution of patients in the two age groups. The mean age of patients in Group A is 40.46 ± 4.53 years, while the mean age of those in Group B is 53.56 ± 4.23 years.

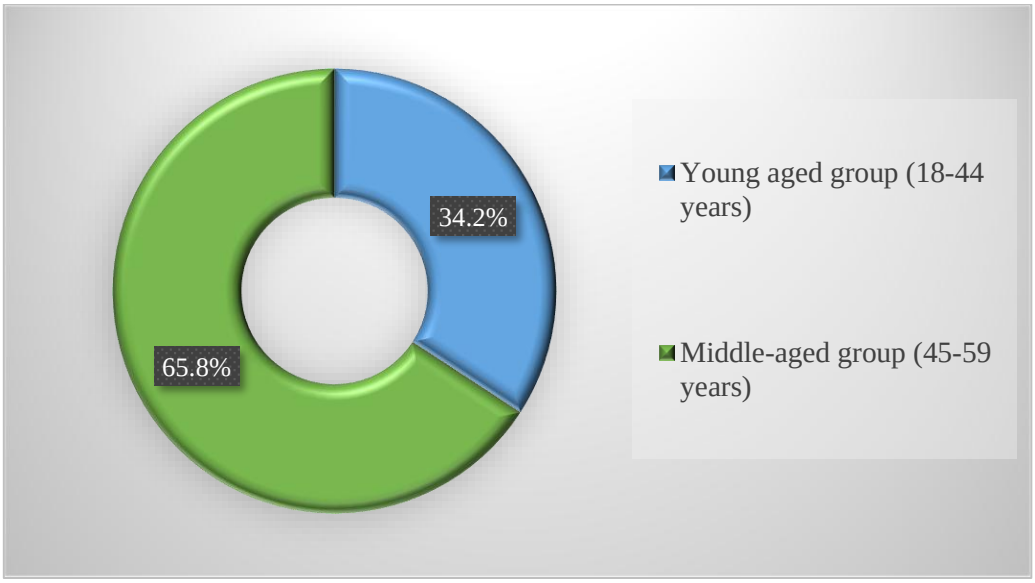


Figure 1 *Percentage distribution of patients in the two age groups*

Figure 2 illustrates the percentage distribution by gender of male and female patients with acute IS across the different age groups. In this study, the frequency of acute stroke among female patients is higher in the age intervals of 30-34 years (8.3%), 35-39 years (16.7%), and 45-49 years (20.8%), while the frequency of AIS among male patients is higher in the age intervals of 40-44 years (29.2%), 50-54 years (23.6%), and 55-59 years (27.8%).

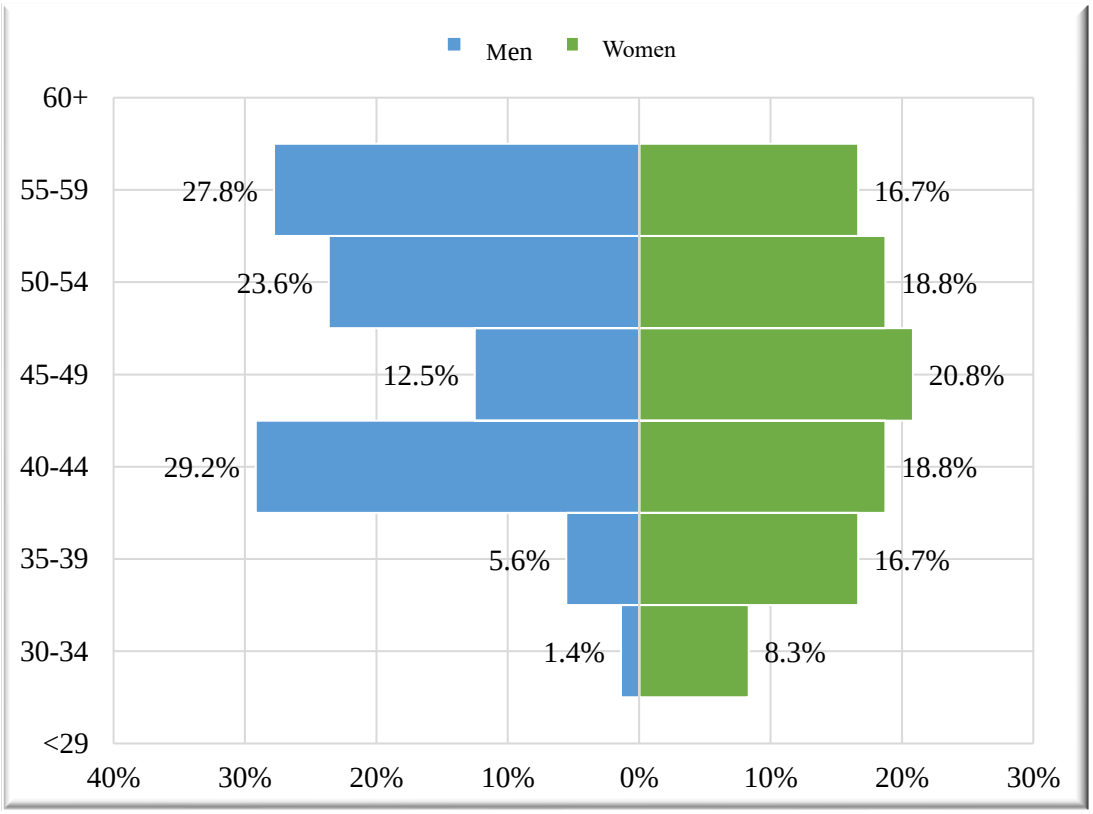


Figure 2 *Percentage distribution by gender across the different age groups*

4.2 Modifiable RFs of acute IS

Table 1 presents the frequency of distribution of all modifiable RFs among the studied patients with IS. The most common RFs associated with health conditions for IS are arterial hypertension (AH) and dyslipidemia (72.5%), followed by low HDL cholesterol (63.3%), high LDL cholesterol (59.2%), diabetes mellitus (DM) (35.8%), and atrial fibrillation (5.0%). Among all the patients with IS, 80 (66.7%) are current smokers, and 40 (33.3%) consume alcohol. More than 50% of patients have low physical activity, and 36.7% are overweight (BMI > 25.0). Additionally, we found that 59 (49.2%) of the patients experience psycho-social stress (either acute or chronic), and 34 (28.3%) report having short night sleep (less than 6 hours per night).

Table 1 Percentage distribution of health and lifestyle-related RFs for IS

Modifiable RFs for IS	**N=120 (100%)**
Health-related RFs	
Arterial hypertension	87 (72.5%)
Dyslipidemia	87 (72.5%)
Low levels of HDL (<1,5mmol/l)	76 (63.3%)
High levels of LDL (>2,59mmol/l)	71 (59.2%)
Diabetes mellitus	43 (35.8%)
Atrial fibrillation	6 (5.0%)
Lifestyle-related RFs for IS	
Smoking	80 (66.7%)
Low physical activity (<30 min walking daily)	68 (56.7%)
Psycho-social stress	59 (49.2%)
Body overweight (BMI>25.0)	44 (36.7%)
Alcohol consumption	40 (33.3%)
Short night sleep (< 6 hours daily)	34 (28.3%)

4.2.1 Odds Ratio assessment of modifiable RFs

Table 2 compares the frequency distribution of health-related RFs between patients with acute IS and the control group. The patients with IS showed a significantly higher frequency of AH, dyslipidemia, low HDL cholesterol, high LDL cholesterol, and DM compared to the control group.

Table 2/ *Percentage distribution of health-related RFs of cases and controls*

Modifiable health-related RFs	Patients with IS (cases) N=120	Patients without IS (controls) N=120	p-value
Arterial hypertension	87 (72.5%)	25 (20.8%)	**< 0.001**
Dyslipidemia	87 (75.2%)	31 (25.8%)	**< 0.001**
Low HDL cholesterol	76 (63.3%)	30 (25.0%)	**< 0.001**
High LDL cholesterol	71 (59.2%)	29 (24.2%)	**< 0.001**
Diabetes mellitus	43 (35.8%)	10 (8.3%)	**< 0.001**
Atrial fibrillation	6 (5.0%)	3 (2.5%)	0.317

Table 3 and **Figure 3** present the results of the conducted regression analysis, which provides information on the relative risk of acute IS associated with individual modifiable health-related RFs in the patients. We found that AH is the most significant RF, associated with the highest risk of IS (OR: 10.018, 95% CI: 5.523-18.173). Other modifiable RFs that significantly increase the risk of IS include: Dyslipidemia (OR: 7.569, 95% CI: 4.270 – 13.416), DM (OR: 6.143, 95% CI: 2.910-12.968), low HDL cholesterol (OR: 5.182, 95% CI: 2.973-9.031), high LDL cholesterol (OR: 4.547, 95% CI: 2.612-7.914).

Table 3/ *Relative risk assessment for IS (OR u 95% CI)*

Modifiable health-related RFs	Odds Ratio (OR)	95% Confidence intervals (CI)	p-value
Arterial hypertension	10.018	5.523 – 18.173	**<0.001**
Dyslipidemia	7.569	4.270 – 13.416	**<0.001**
Low HDL cholesterol	5.182	2.973 – 9.031	**<0.001**
High LDL cholesterol	4.547	2.612 – 7.914	**<0.001**
Diabetes mellitus	6.143	2.910 – 12.968	**<0.001**
Atrial fibrillation	2.053	0.501 – 8.405	0.317

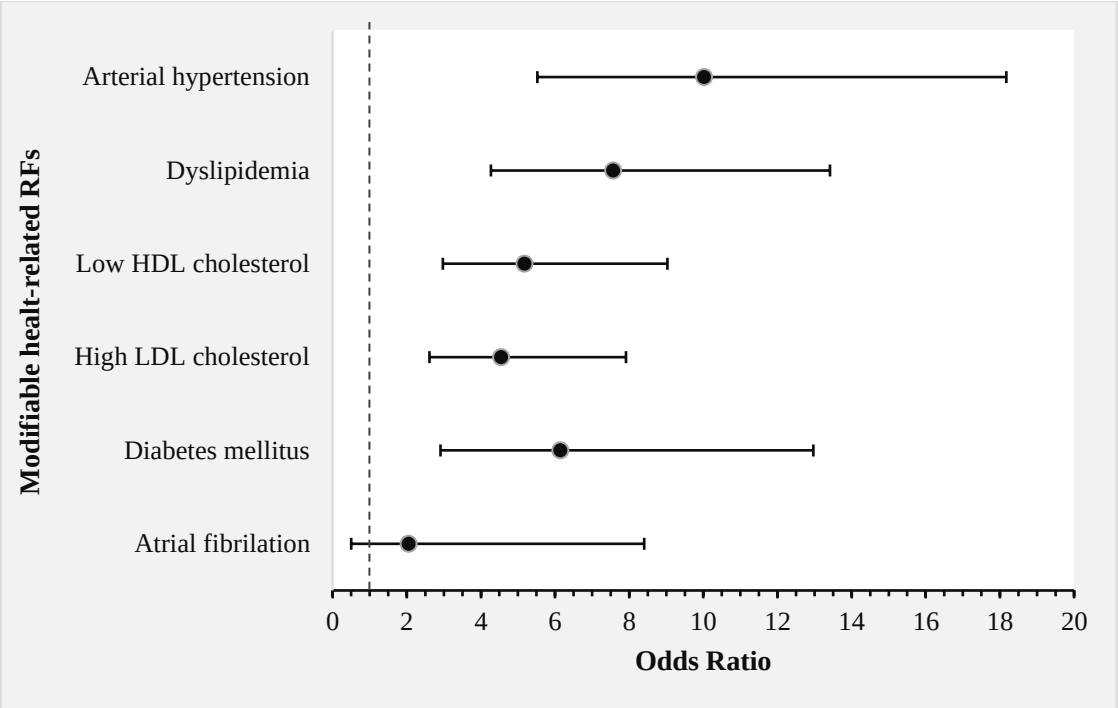


Figure 3*/ Relative risk assessment for IS (OR u 95% CI)*

In **Table 4**, the frequency of distribution of lifestyle-related modifiable RFs between patients with acute IS and the control group is compared. Patients with acute IS exhibited significantly higher frequencies of all modifiable RFs related to lifestyle compared to the control group.

Table 4/ *Percentage Distribution of Health-Related RFs in patients with Ischemic Stroke and Controls*

Modifiable lifestyle-related RFs	**Patients with IS (cases) N=120**	**Patients without IS (controls) N=120**	**p-value**
Smoking	80 (66.7%)	38 (31.7%)	< **0.001**
Smoking more than 20 cigarettes daily	60 (50.0%)	12 (10.0%)	< **0.001**
Alcohol abuse	34 (28.3%)	10 (8.3%)	< **0.001**
Low physical activity	68 (56.7%)	23 (19.2%)	< **0.001**
Overweight	44 (36.7%)	25 (20.8%)	**0.007**
Psycho-social stress	59 (49.2%)	38 (31.7%)	**0.006**
Short night sleep	34 (28.3%)	20 (16.7%)	**0.030**

Table 5 and **Figure 4** show results of the regression analysis on relative risk of acute IS associated with lifestyle-related RFs in the studied patients.

Of all lifestyle-related RFs smoking >20 cigarettes daily is associated with the highest risk for IS (OR: 9.00, 95% CI: 4.489-18.043). Other RF which significantly increase the risk of IS are as follows: low physical activity (OR: 5.515, 95% CI: 3.086 - 9.855), alcohol abuse (OR: 4.349, 95% CI: 2.035 - 9.294), obesity (OR: 2.200, 95% CI: 1.237-3.941), psycho-social stress (OR: 2.087, 95% CI: 1.234 - 3.530) short duration of night sleep (OR:1.977, 95% CI: 1.060 - 3.686).

|***Table 5/*** *Relative risk assessment for IS (OR and 95% confidence intervals)*

Modifiable lifestyle-related RFs	**Odds Ratio (OR)**	**95% Confidence intervals (CI)**	**p-value**
Smoking more than 20 cigarettes daily	9.000	4.489 – 18.043	**<0.001**
Alcohol abuse	4.349	2.035 – 9.294	**<0.001**
Low physical activity	5.515	3.086 – 9.855	**<0.001**
Body overweight	2.200	1.237 – 3.914	**0.007**
Psycho-social stress	2.087	1.234 – 3.530	**0.006**
Short night sleep	1.977	1.060 – 3.686	**0.030**

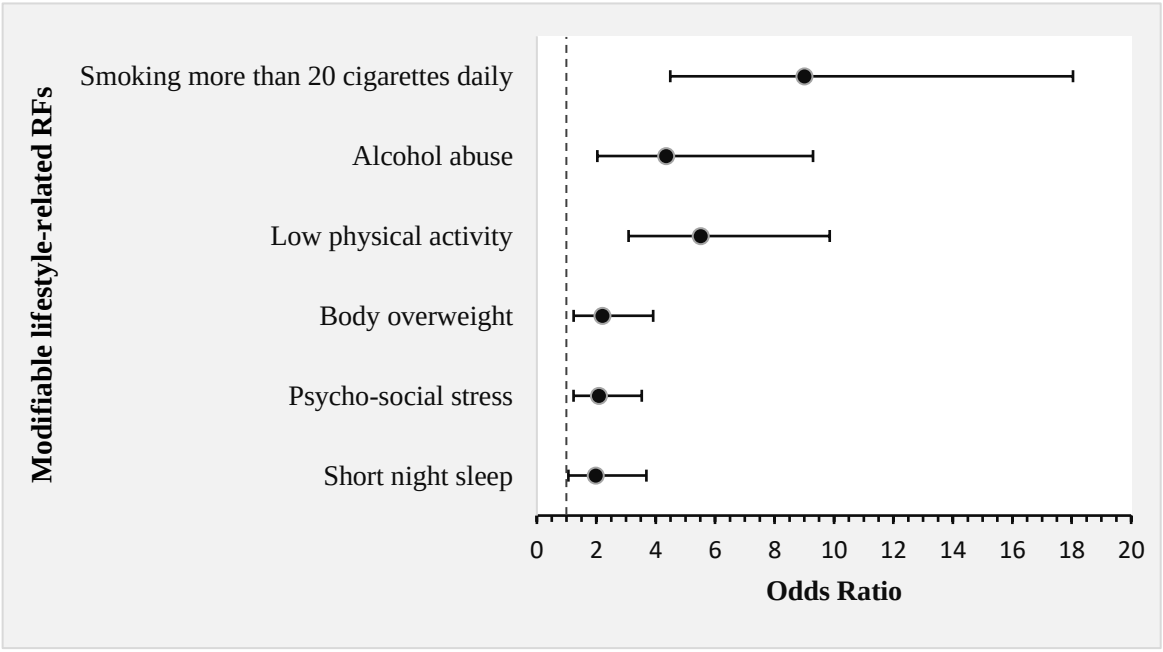


Figure 4/ *Relative risk assessment for IS (OR and 95% confidence intervals)*

4.2.2 Age differences in the prevalence of health-related and lifestyle-related risk factors for IS among patients of young and middle age.

Table 6 presents the distribution of health-related RFss for IS across two age groups. Among middle-aged patients with IS, the prevalence rates of all RFs are in the following order: dyslipidemia (83.5%), AH (81.0%), reduced HDL cholesterol (68.4%), elevated LDL cholesterol (72.2%), DM (44.3%) and atrial fibrillation (7.6%). Younger patients exhibited a slightly higher incidence of hyperhomocysteinemia (19.5%) compared to their middle-aged counterparts (11.4%) Statistically significant differences between the two age groups were observed concerning AH (χ^2=8.404, df=1, p=0.004), DM (χ^2=7.892, df=1, p=0.007), dyslipidemia (χ^2=14.146, df=1, p<0.001), and elevated LDL cholesterol (χ^2=16.137, df=1, p<0.001).

Table 6/ *Distribution of health-related risk factors (RFs) based on age groups*

Modifiable health-related RFs	**Young age group n = 41 (34.2%)**	**Middle-aged group n = 79 (65.8%)**	**p – value**
Arterial hypertension	23 (56.1%)	64 (81.0%)	**0.004**
Atrial fibrillation	0 (0.0%)	6 (7.6%)	0.070
Diabetes mellitus	8 (19.5%)	35 (44.3%)	**0.007**
Dyslipidemia	21 (51.2%)	66 (83.5%)	**<0.001**
Low HDL levels (<1,5mmol/l)	22 (53.7%)	54 (68.4%)	0.113
High LDL levels (>2,59mmol/l)	14 (34.1%)	57 (72.2%)	**< 0.001**
Hyperhomocysteinemia (>15.0µmol/l)	8 (19.5%)	9 (11.4%)	>0.05

Figure 5 presents the prevalence rates of AH, DM, and dyslipidemia across different age intervals. As age increases, there is an exponential rise in the frequency of these risk factors.

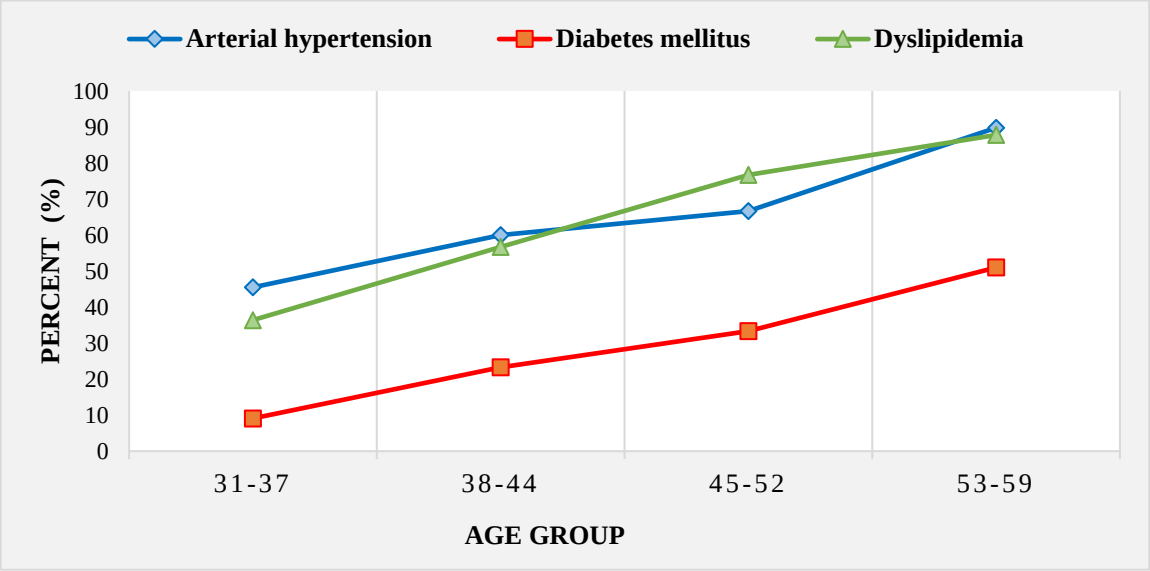


Figure 5/ *Distribution of health-related risk factors (RFs) based on age groups*

Table 7 presents the distribution of lifestyle-related RFs for IS across two age groups. In younger patients, higher frequencies were observed for current tobacco use (75.6%), psycho-social stress (51.2%), and short night sleep (34.1%). Conversely, middle-aged patients exhibited higher rates of low physical activity (57.0%) and overweight (39.2%). However, these differences between the age groups were not statistically significant (p>0.05).

Table 7/ *Distribution of lifestyle-related RFs across age groups*

Modifiable lifestyle-related RF	**Young age group n = 41 (34.2%)**	**Middle-aged group n = 79 (65.8%)**	**p – value**
Current smoking	31 (75.6%)	49 (62.0%)	0.134
Alcohol consumption	10 (24.4%)	30 (38.0%)	0.134
Low physical activity	23 (56.1%)	45 (57.0%)	0.928
Body overweight	13 (31.7%)	31 (39.2%)	0.417
Psycho-social stress	21 (51.2%)	38 (48.1%)	0.746
Short night sleep (less than 6 hours per night)	14 (34.1%)	20 (25.3%)	0.309

Figure 6 illustrates the age-related differences in the number of cigarettes smoked per day. It shows that 56.1% of younger patients and 46.8% of middle-aged patients smoke more than 20 cigarettes daily. Smoking fewer than 20 cigarettes per day are 19.5% of younger patients and 15.2% of middle-aged patients. However, these differences between the two age groups are not statistically significant (p>0.05).

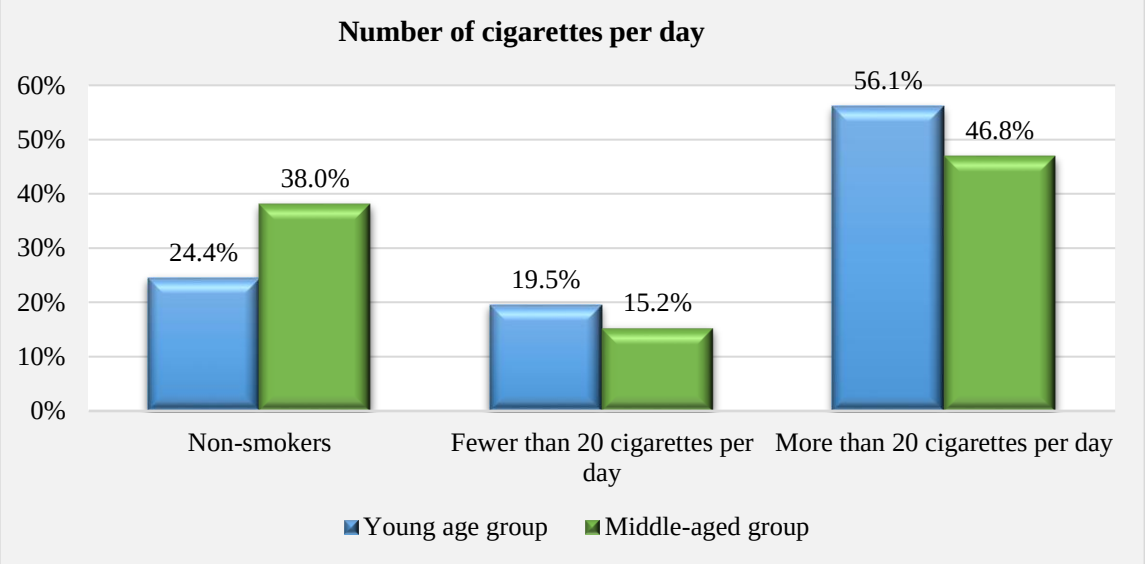


***Figure 6**/ Comparing between number of cigarettes per day across two age groups of patients with IS*

Figure 7 presents the differences in the severity of alcohol consumption between two age groups. Middle-aged patients show a higher frequency of heavy alcohol consumption (31.6%) compared to younger patients (22.2%).

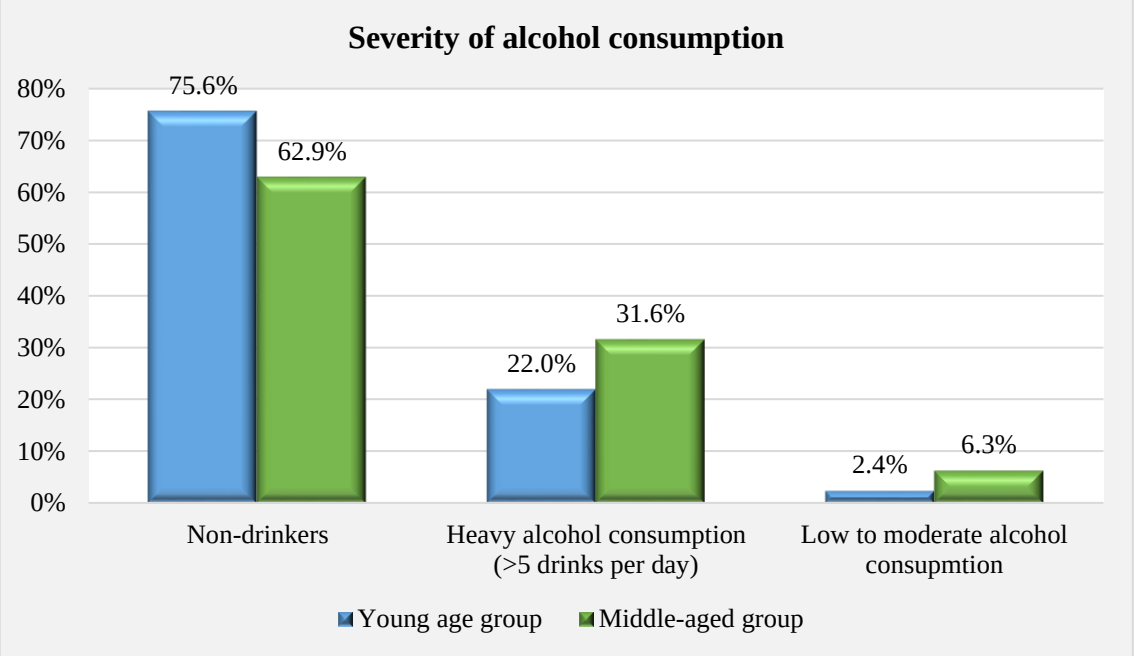


***Figure 7**/ Age differences in alcohol consumption*

Figure 8 shows a relative analysis in the distribution of all modifiable RF between the two age groups.

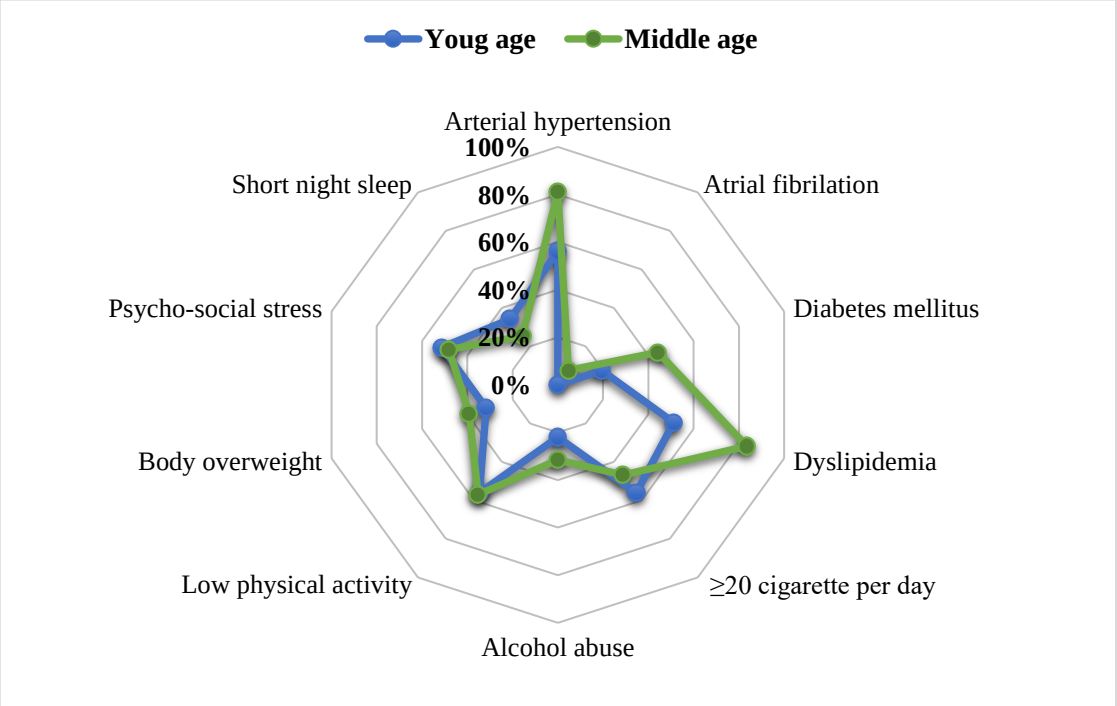


***Figure 8**/ Distribution of all modifiable RFs between the two age groups*

Table 8 and **Figure 9** compare the number of modifiable RFs between two age groups. We found that 77.2% of middle-aged patients had a combination of ≥4 modifiable RFs compared to 46.3% of younger patients. Additionally, the middle-aged group demonstrated a higher mean number of modifiable RFs per person (4.5 ± 1.4) compared to the younger group (3.9 ± 1.6). The differences between the two groups are statistically significant ($p < 0.01$).

Table 8/ Comparison of the number of modifiable RFs across age groups and their mean values

Number of modifiable RF	**Young age group n=41 (34.2%)**	**Middle age group n=79 (65.8%)**	**p - value**
Modifiable RFs ≤ 3	22 (53.7%)	18 (22.8%)	**0.001**
Modifiable RFs ≥ 4	19 (46.3%)	61 (77.2%)	
Mean number of modifiable RFs	3.9±1.6	4.5±1.4	**<0.001**

Figure 9 presents the percentage distributions of patients with 1 to ≥6 modifiable RFs across two age groups. Young patients exhibited higher frequencies of having 1 RF (2.4%), 2 RFs (12.2%), and 3 RFs (41.5%). In contrast, middle-aged patients demonstrated a higher frequency of having 4 RFs (19.0%), 5 RFs (34.2%) and ≥ 6 RFs (22.7%).

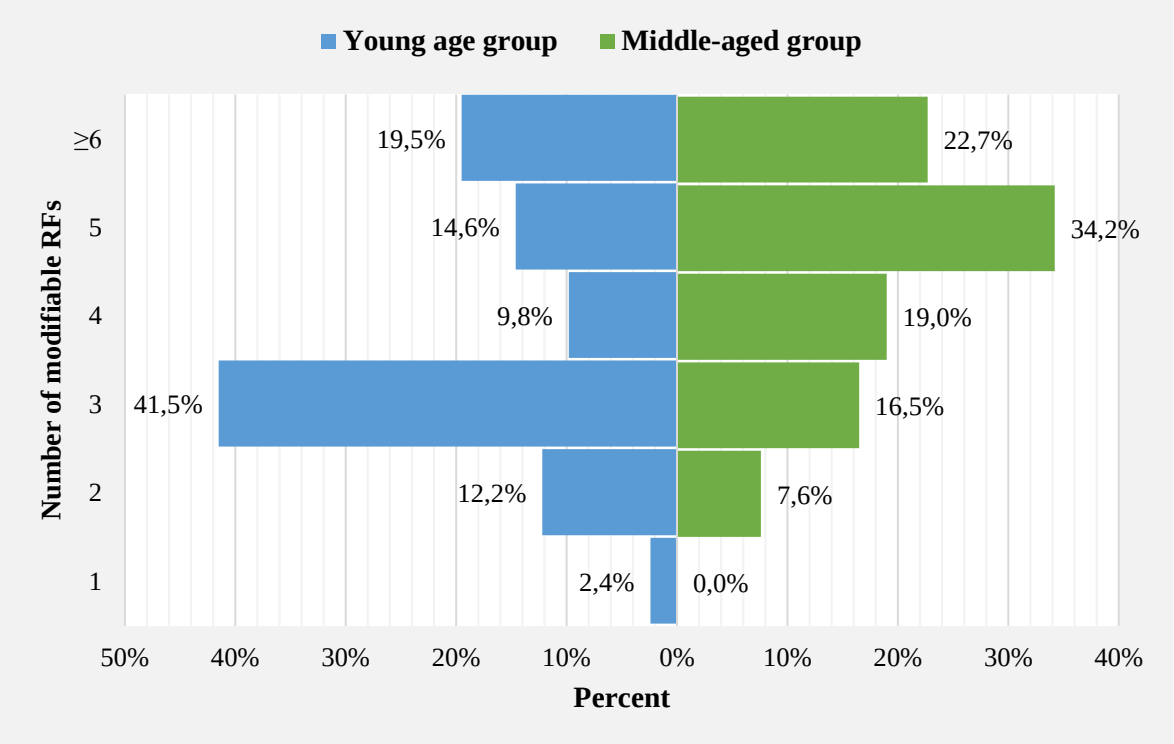


***Figure 9**/ Percentage distributions of patients in the two age groups based on the number of modifiable RFs*

Figure 10 illustrates the age-related differences in the mean, maximum, and minimum values of certain modifiable RFs associated with the health status of patients with acute IS. Statistical analysis revealed that middle-aged patients had higher mean levels of total serum cholesterol (5.83 ± 1.36 mmol/L), LDL cholesterol (3.25 ± 1.24 mmol/L), triglycerides (2.36 ± 1.51 mmol/L), and glucose (8.10 ± 4.19 mmol/L) compared to younger patients. Significant differences were found in LDL cholesterol ($p = 0.025$) and serum glucose ($p = 0.017$). Additionally, during hospitalization, significantly higher mean values of systolic blood pressure (SBP) were recorded in middle-aged patients (143.10 ± 21.34 mmHg) compared to younger patients (135.73 ± 20.84 mmHg). Diastolic blood pressure (DBP) values were slightly higher in the middle-aged group (83.86 ± 10.12 mmHg) than in the younger group (82.56 ± 10.37 mmHg), but no statistically significant differences were observed ($p > 0.05$).

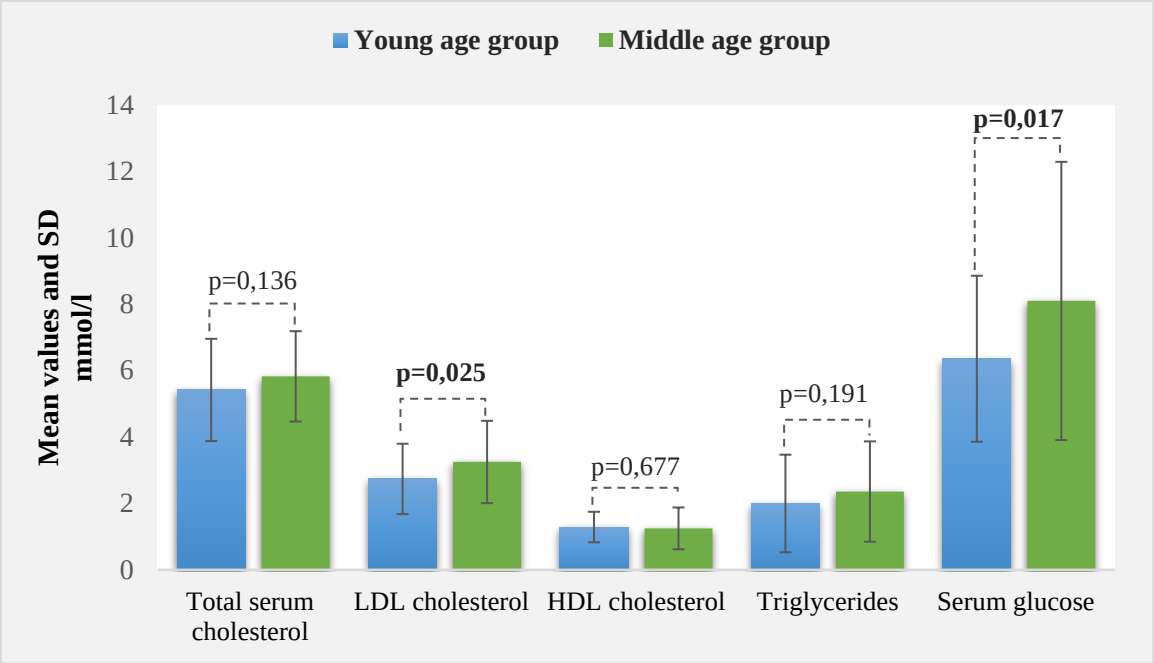


Figure 10/ *Difference between the mean values of some modifiable RFs in the two age groups*

Figure 11 shows the age differences in the mean values of SBP and DBP during hospitalization.

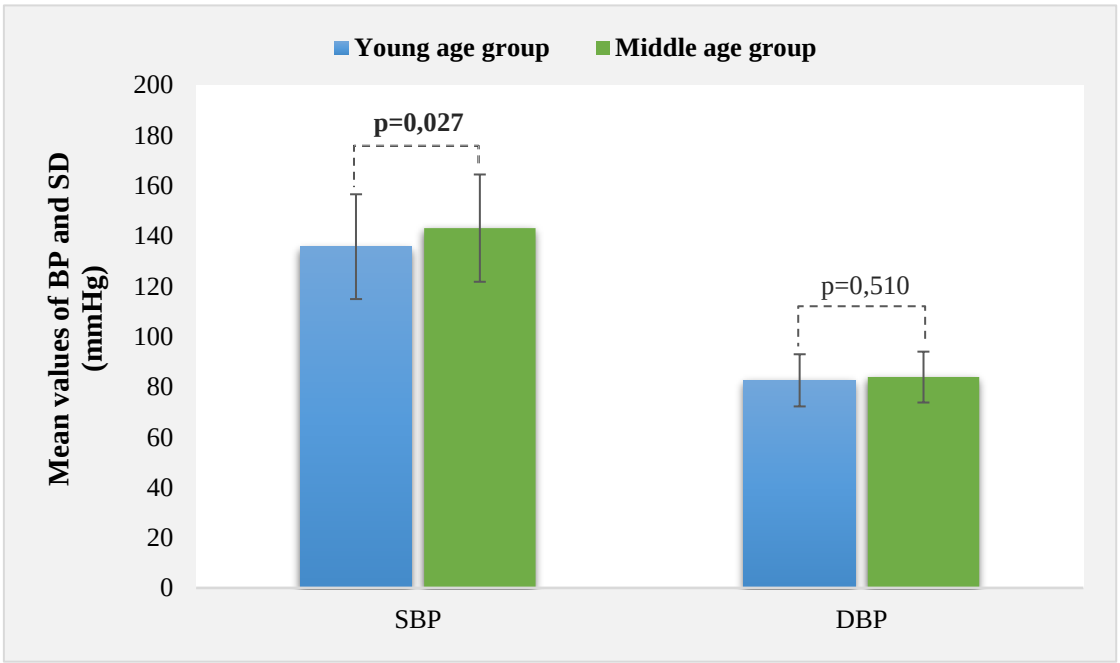


Figure 11/ *Difference between mean values of SBP and DBP in the two age groups*

4.2.3 Gender differences in the prevalence of health- and lifestyle-related RFs for IS in young and middle-aged patients

Table 9 presents data on gender differences in the prevalence of health-related RFs. Overall, men are more frequently affected by all the examined RFs in the following order: AH (80.6%), dyslipidemia (73.6%), low HDL cholesterol levels (66.7%), high LDL cholesterol levels (62.5%), DM (44.4%), and atrial fibrillation (5.6%). Hyperhomocysteinemia is found in 16.7% of women and 12.5% of men. Statistically significant differences in the prevalence of RFs between the two sexes are observed for AH (χ^2=5.859, df=1, p=0.016) and DM (χ^2=5.805, df=1, p=0.016).

Table 9/ Prevalence of health-related RFs by gender.

Health-related RFs	**Men n = 72 (60.0%)**	**Women n = 48 (40.0%)**	**p – value**
Arterial hypertension	58 (80.6%)	29 (60.4%)	**0.016**
Atrial fibrillation	4 (5.6%)	2 (4.2%)	0.732
Diabetes mellitus	32 (44.4%)	11 (22.9%)	**0.016**
Dyslipidemia	53 (73.6%)	34 (70.8%)	0.738
Low HDL levels (<1,5mmol/l)	48 (66.7%)	28 (58.3%)	0.353
High LDL levels (>2,59mmol/l	45 (62.5%)	26 (54.2%)	0.363
Hyperhomocysteinemia (>15.0µmol/l)	9 (12.5%)	8 (16.7%)	>0.05

Table 10 presents data on gender differences in the prevalence of lifestyle-related RFs. More common lifestyle-related RFs among men include current smoking (75.0%), alcohol consumption (47.2%), and psychosocial stress (50.0%). Among women, a higher prevalence was observed for low physical activity (66.7%), overweight (45.8%), and reduced night sleep (29.2%). Statistically significant differences were found for smoking (χ^2=5.625, df=1, p=0.018) and alcohol consumption (χ^2=15.625, df=1, p<0.001).

***Table 10**/ Prevalence of life style-related RFs by gender*

Life style-related RFs	Men n = 72 (60.0%)	Women n = 48 (40.0%)	p – value
Current smoking	54 (75.0%)	26 (54.2%)	**0.018**
Alcohol consumption	34 (47.2%)	6 (12.5%)	**<0.001**
Low physical activity	36 (50.0%)	32 (66.7%)	0.071
Overweight	22 (30.6%)	22 (45.8%)	0.089
Psycho-social stres	36 (50.0%)	23 (47.9%)	0.823
Short night sleep (less than 6 hours per night)	20 (27.8%)	14 (29.2%)	0.869

Figure 12 presents data on gender differences in the number of cigarettes smoked per day among patients with acute IS. Statistical analysis showed that the proportion of men who smoke more than 20 cigarettes per day is twice as high (62.5%) compared to women (31.3%). On the other hand, a higher proportion of women were found to smoke fewer than 20 cigarettes per day (22.9%) or not smoke at all (45.8%). The differences between the two sexes are statistically significant (χ^2=11.250, df=2, p<0.01).

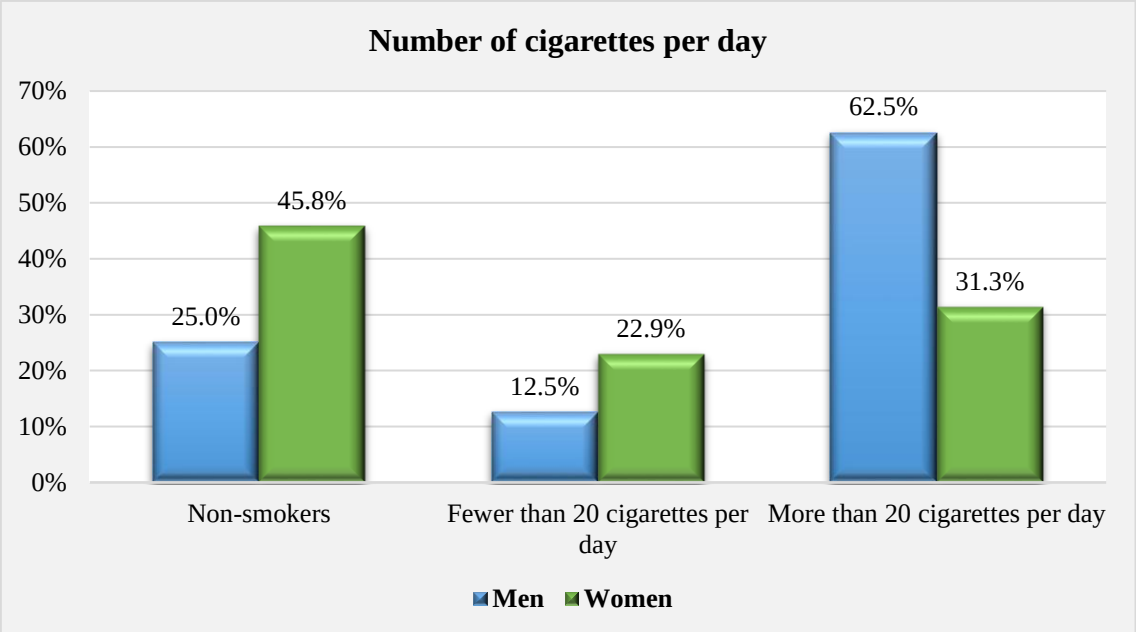


***Figure 12**/ Number of cigarettes per day by gender*

Figure 13 presents data on gender differences based on the duration of smoking. Our results show that 73.6% of men and 45.8% of women have been smoking for more than 10 years. In the category of smoking for less than 10 years, women show a slightly higher

prevalence (8.3%) compared to men (1.4%). The differences between the two sexes are statistically significant (χ^2=10.639), df=2, p=0.005).

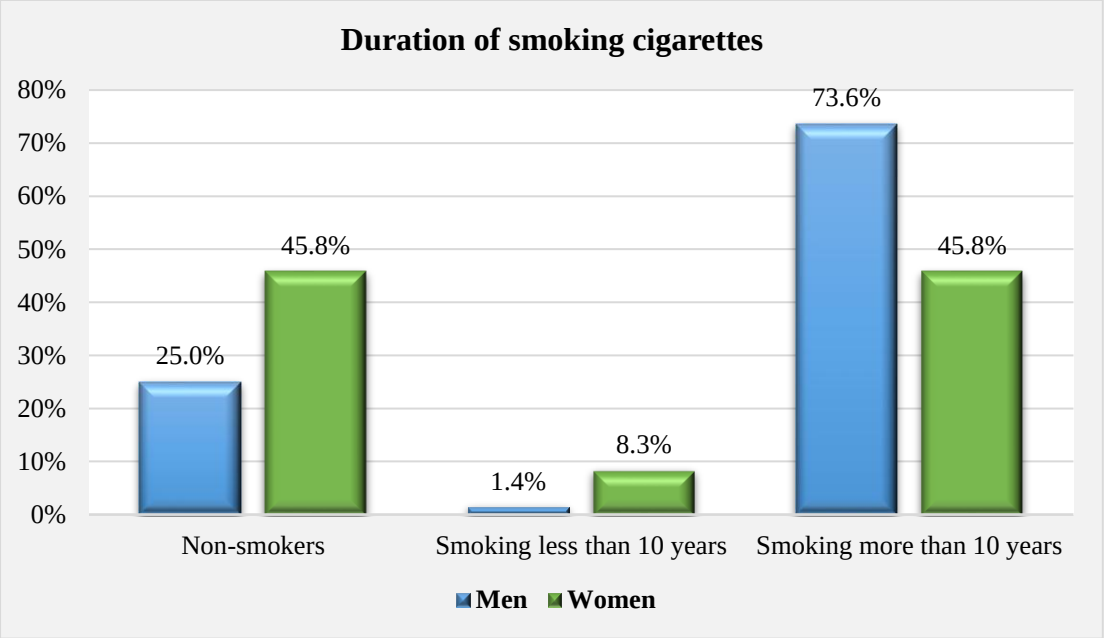


***Figure 13**/ Gender differences based on duration of smoking*

Figure 14 presents data on the severity of alcohol consumption among men and women. In men with acute IS, heavy alcohol consumption is more commonly observed (40.3%) compared to women (6.9%). The differences are statistically significant (χ^2=15.633, df=2, p<0.001).

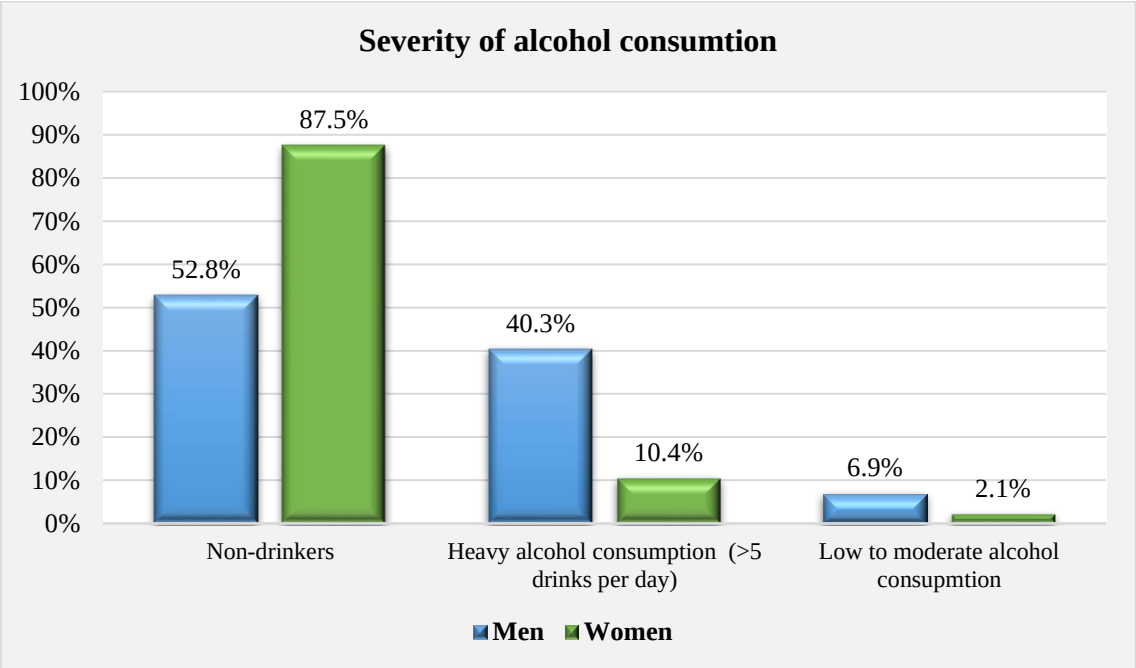


***Figure 14**/ Differences by gender of alcohol consumption*

Figure 15 presents a comparative assessment of the prevalence of all modifiable RFs between the two sexes.

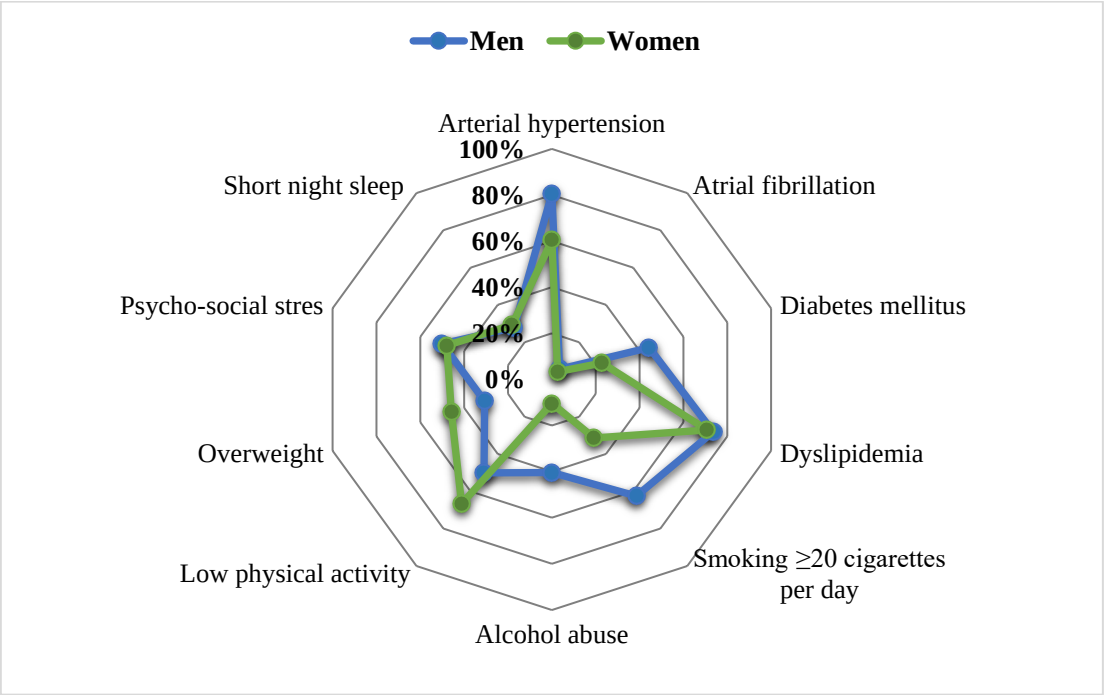


***Figure 15**/ Comperative analysis in the prevalence of all modifiable RFs between the genders*

Table 11 presents a comparison of the number of modifiable RFs between the two sexes. Over 50% of both men and women with acute IS have a combination of ≥ 4 modifiable RFs, with a higher proportion observed in men (70.8%) compared to women (60.4%). However, these differences are not statistically significant ($p > 0.05$). The analysis of the mean number of modifiable RFs shows that men have an mean of 4.6 RFs per person, while women have an mean of 3.9 RFs per person. These differences are statistically significant ($p = 0.022$).

***Table 11**/ Comparison of the number of RF by gender*

Number of modifiable RFs	**Men n = 72 (60.0%)**	**Women n = 48 (40.0%)**	**p - value**
Modifiable RFs ≤ 3	21 (29.2%)	19 (39.6%)	0.236
Modifiable RFs ≥ 4	51 (70.8%)	29 (60.4%)	
Mean number of modifiable RFs	4.6±1.5	3.9±1.5	**0.022**

Figure 16 presents the percentage distribution of patients from both sexes with between 1 and ≥6 RFs. All women had at least 1 RF, while men had a combination of at least 2 RFs. We found that men more frequently had combinations of 3 RFs (26.4%), 5 RFs (34.7%), and ≥6 RFs (23.7%), whereas women more often had combinations of 2 RFs (16.7%) and 4 RFs (22.9%).

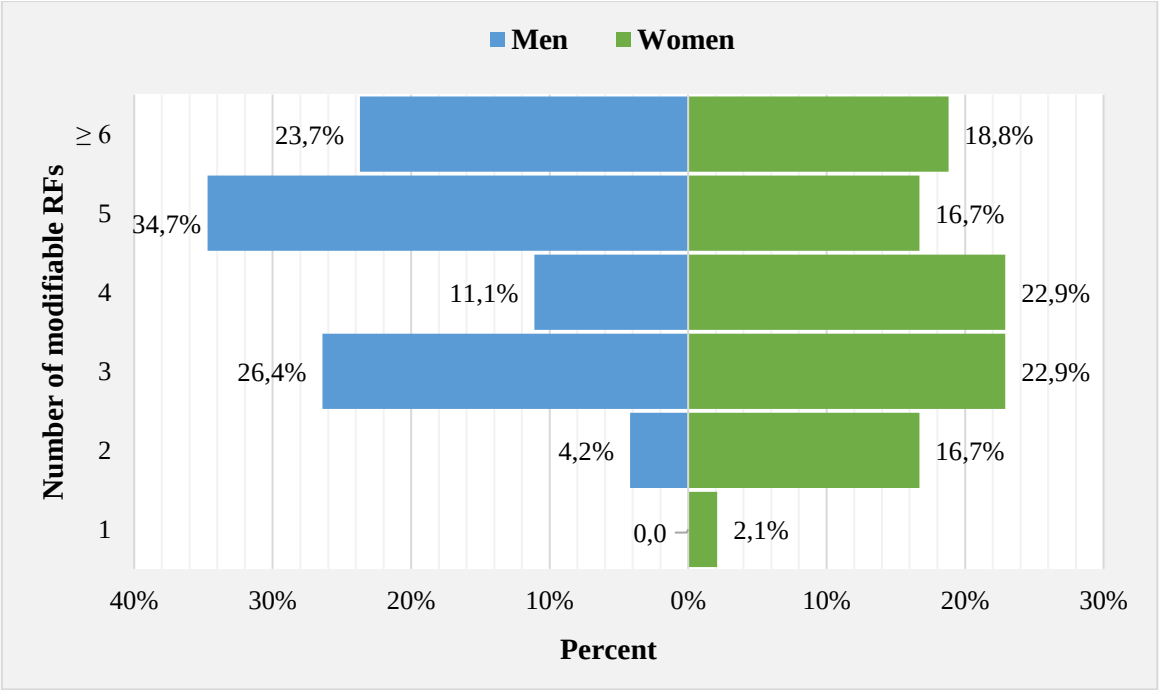


Figure 16/ *Distribution of patinets by gender with 1 to ≥ 6 RF*

Figure 17 presents gender differences in the mean, maximum, and minimum values of certain modifiable health-related RFs. Statistical analysis shows that men have higher mean levels of total serum cholesterol (5.78±1.30), LDL cholesterol (3.12±1.17), triglycerides (2.53±1.62), and glucose (7.68±3.50). Statistically significant differences between the sexes were found only in triglyceride levels ($p < 0.01$).

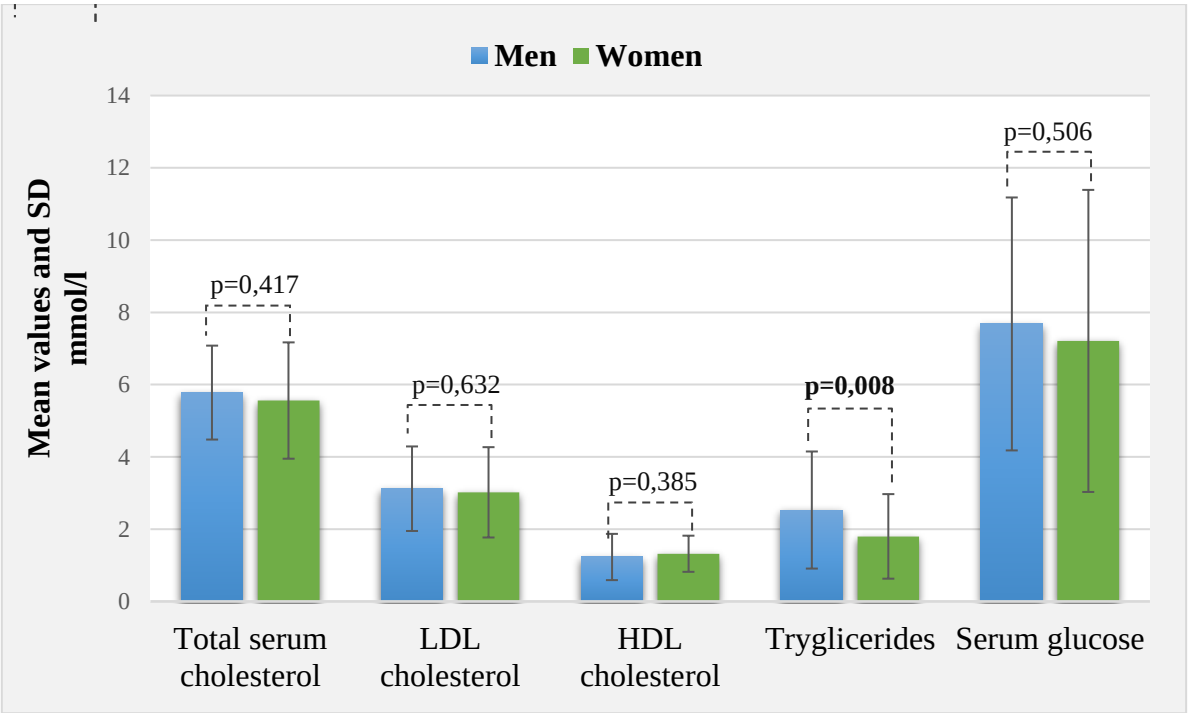


Figure 17/ *Assessment of mean values and SD of serum lipids and glucose leves between the genders*

Figure 18 presents the mean values of SBP and diastolic arterial pressure DBP. Male patients showed significantly higher mean values of SBP (144.02±21.02) and DBP (86.18±9.6) compared to female patients.

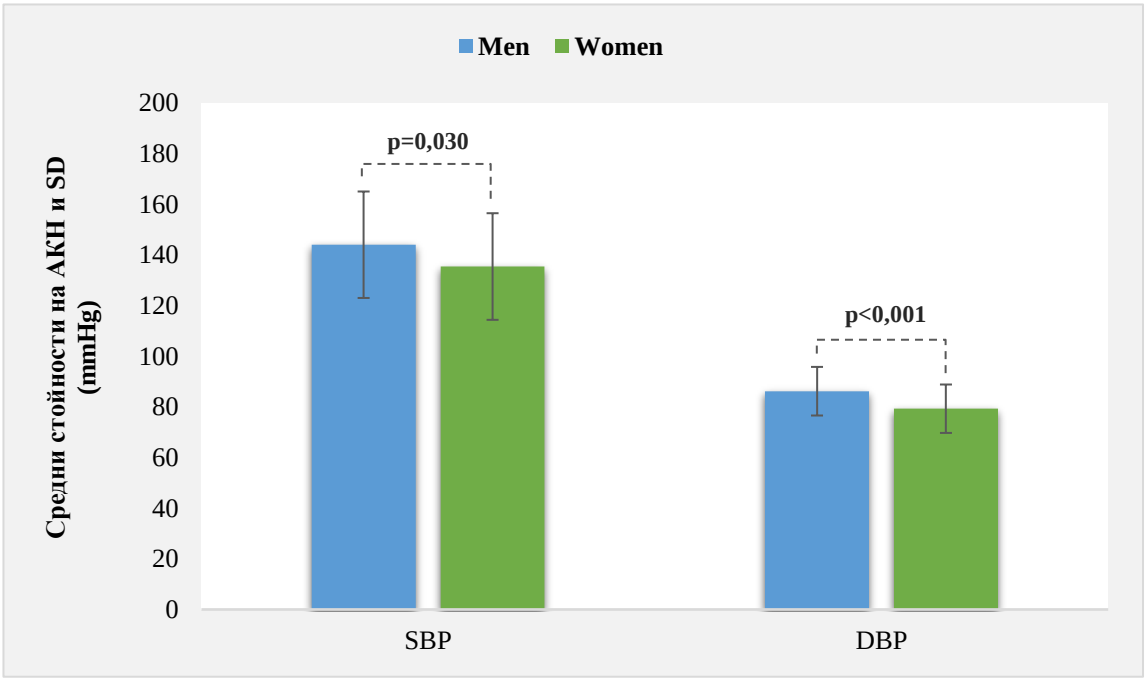


Figure 18/ *Comperative analysis of the mean values of SBP and DBP between the genders*

4.2.4 Differences in the prevalence of health-related and lifestyle-related RFs between men and women across the two age groups

Table 12 presents the distribution of health-related RFs among men and women across two age groups. Men in the younger age group demonstrated a higher prevalence of all health-related RFs. A statistically significant difference was observed only for AH (χ^2=4.977, df=1, p=0.026). In the middle-aged group, men showed a higher prevalence of AH (87.0%), DM (56.5%), low HDL cholesterol levels (73.9%), high LDL cholesterol levels (73.9%), while women showed a slightly higher prevalence of dyslipidemia (84.8%). A statistically significant difference was observed for DM (χ^2=6.662, df=1, p=0.010).

Table 12/ *Differences in the distribution of health related RFs in men and women of the two age groups*

Modifiable health-related RFs	**Young age group n=41 (34.2%)**		**p-value**	**Middle-aged group n = 79 (65.8%)**		**p-value**
	Men n=26 (63.4%)	**Women n=15 (36.6%)**		**Men n=46 (58.2%)**	**Women n=33 (41.8%)**	
Arterial hypertension	18 (69.2%)	5 (33.3%)	**0.026**	40 (87.0%)	24 (72.7%)	0.112
Diabetes mellitus	6 (23.1%)	2 (13.3%)	0.448	26 (56.5%)	9 (27.3%)	**0.010**
Dyslipidemia	15 (57.7%)	6 (40.0%)	0.275	38 (82.6%)	28 (84.8%)	0.791
|Low HDL cholesterol levels (<1,5mmol/l)	14 (53.8%)	8 (53.3%)	0.975	34 (73.9%)	20 (60.6%)	0.210
High LDL cholesterol levels (>2,59mmol/l	11 (42.3%)	3 (20.0%)	0.147	34 (73.9%)	23 (69.7%)	0.680

Table 13 presents the distribution of lifestyle-related RFs among men and women in the two age groups. Among the younger age group men showed higher frequencies of smoking more than 20 cigarettes per day (65.4%), alcohol abuse (26.9%), psychosocial stress (53.8%), while women had higher frequencies of low physical activity (73.3%), obesity (40.0%), short night sleep (30.8%). No statistically significant differences were found in this age group ($p > 0.05$). Among the middle-aged group men demonstrated higher rates of

smoking more than 20 cigarettes per day (60.9%), alcohol abuse (47.8%), short night sleep (26.1%), while women had higher rates of low physical activity (63.6%), obesity (48.5%), psychosocial stress (48.5%).

The differences in the prevalence of smoking more than 20 cigarettes per day (χ^2 = 8.711, df = 1, p = 0.003) and alcohol abuse (χ^2 = 13.328, df = 1, p < 0.001) were found to be statistically significant.

Table 13/ *Differences in distribution of health and life style-related RFs in men and women in the two age groups .*

Modifiable lifestyle-related RFs	**Young age group n=41 (34.2%)**		**p-value**	**Middle-aged group n = 79 (65.8%)**		**p-value**
	Men n=26 (63.4%)	**Women n=15 (36.6%)**		**Men n=46 (58.2%)**	**Women n=33 (41.8%)**	
Smoking (>20 cigarettes per day)	17 (65.4%)	6 (40.0%)	0.115	28 (60.9%)	9 (27.3%)	**0.003**
Alcohol abuse	7 (26.9%)	2 (13.3%)	0.311	22 (47.8%)	3 (9.1%)	**<0.001**
Low physical activity	12 (46.2%)	11 (73.3%)	0.091	24 (52.2%)	21 (63.6%)	0.310
Overweight	7 (26.9%)	6 (40.0%)	0.386	15 (32.6%)	16 (48.5%)	0.154
Psychosocial stress	14 (53.8%)	7 (46.7%)	0.658	22 (47.8%)	16 (48.5%)	0.954
Short night sleep (<6 hours daily)	8 (30.8%)	6 (40.0%)	0.548	12 (26.1%)	8 (24.2%)	0.852

Figures 19 and **20** present a comparative assessment of the prevalence of all modifiable RFs among men and women in the two age groups.

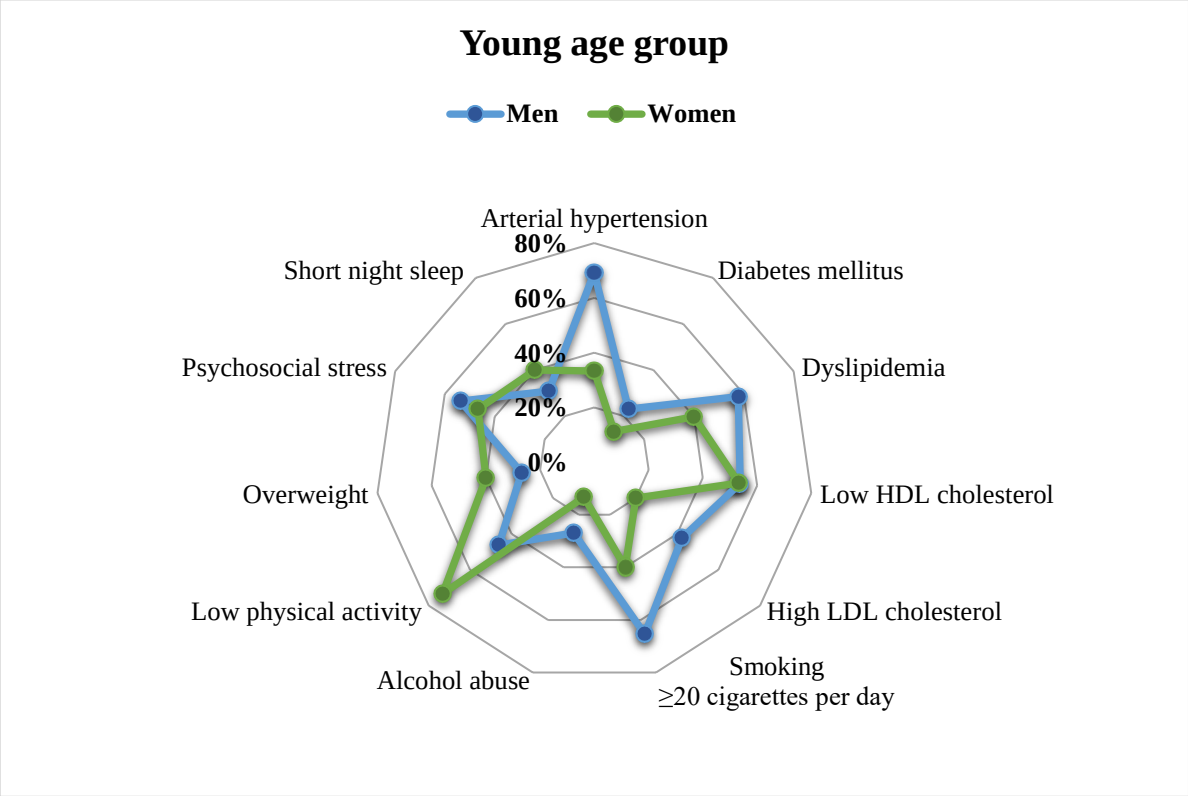


***Figure 19**/ Comparative analysis in the prevalence of all modifiable RFs among men and women in young age*

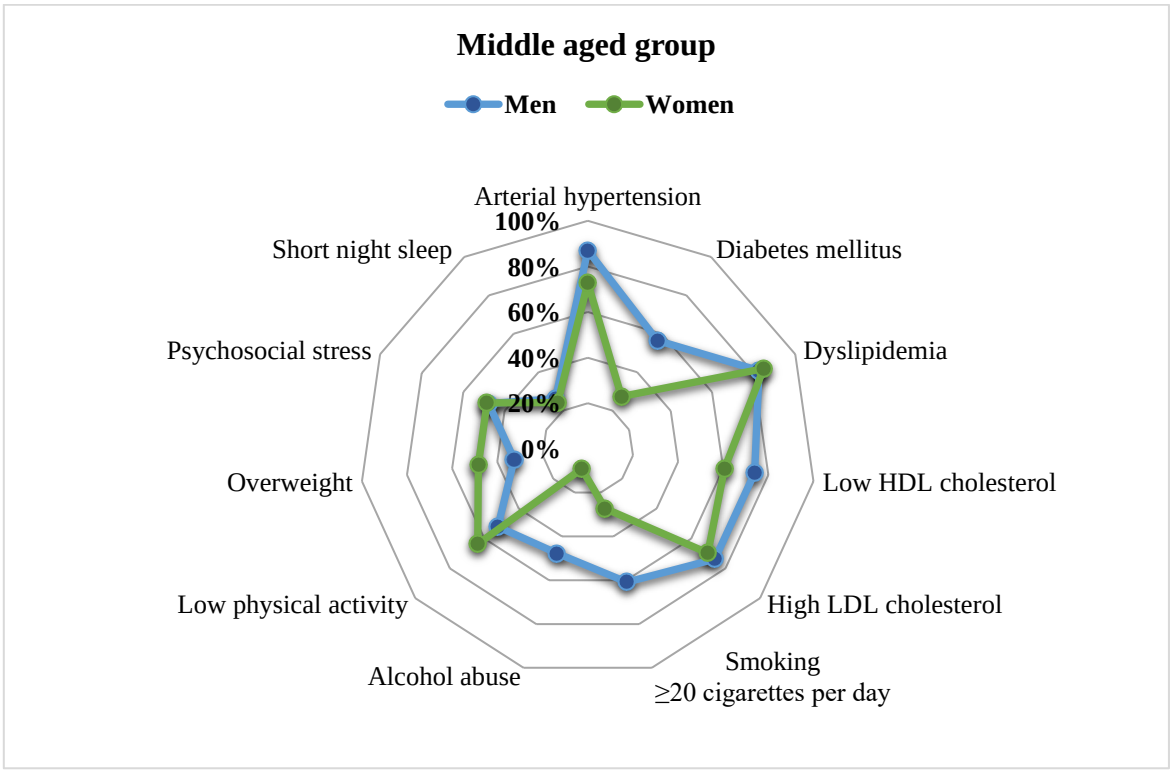


***Figure 20**/ Comparative analysis in the prevalence of all modifiable RFs among men and women in middle-aged*

4.3 Follow-up of the patients and assessment of the clinical characteristics of IS

In all patients included in the study, the following clinical characteristics of IS were monitored and assessed during hospitalization and at discharge: stroke localization, etiological subtype, severity, and outcome of the IS.

4.3.1 General data of the IS localization. Differences by age and gender.

Figure 21 presents data on the distribution of patients according to the localization of IS. We found that in 93 patients (77.0%), the IS was localized in the anterior cerebral circulation (including the middle and anterior cerebral arteries), while in 27 patients (23.0%), the IS was localized in the posterior cerebral circulation.

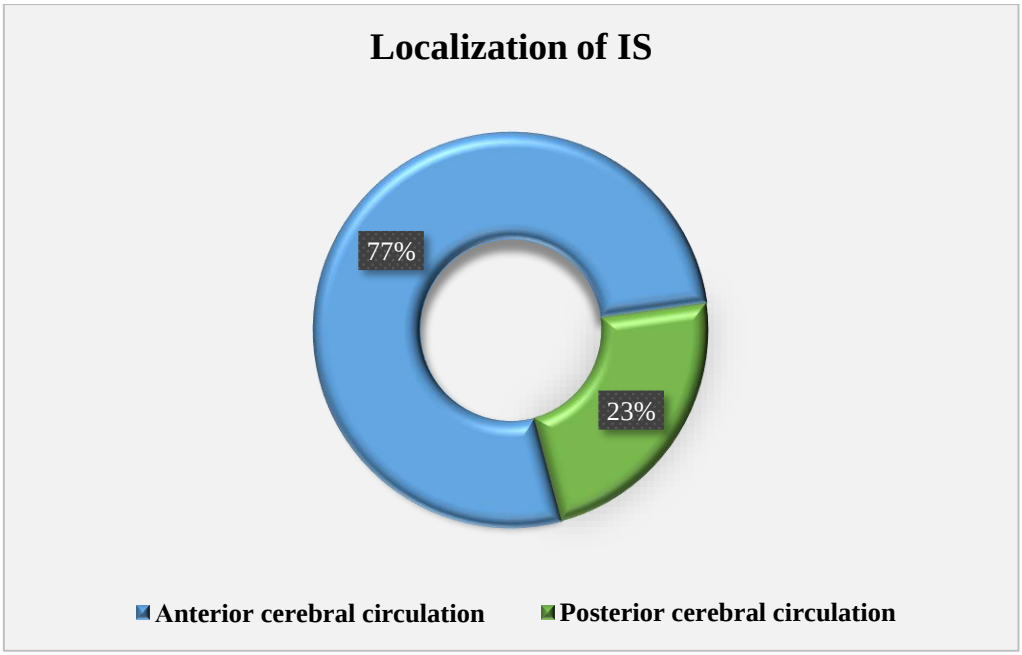


Figure 21/ *Distribution of patients by IS localization*

Figure 22 presents data on the distribution of patients according to the affected vascular territory. The most common localization of IS was in the middle cerebral artery (MCA) territory (72.0%), followed by the anterior cerebral artery (ACA) territory (23.0%) and the vertebrobasilar vascular system (5.0%).

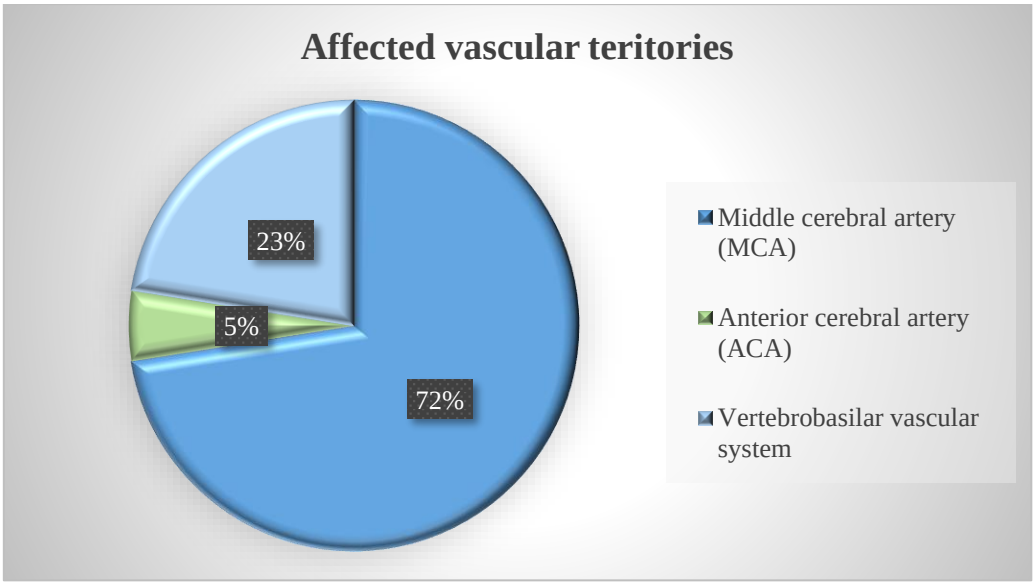


Figure 22/ *distribution of patients according to the affected vascular territory*

4.3.2 Etiological subtype of IS according to TOAST and OCSP. Distribution of modifiable RFs by stroke subtype.

Figure 23 presents the percentage distribution of the etiological subtypes of IS according to the TOAST classification. The most common subtype was large artery atherosclerosis – 32.52%, followed by lacunar infarction – 24.20%, stroke of undetermined etiology – 23.31%, stroke of other determined etiology – 15.87%, cardioembolic stroke – 4.21%.

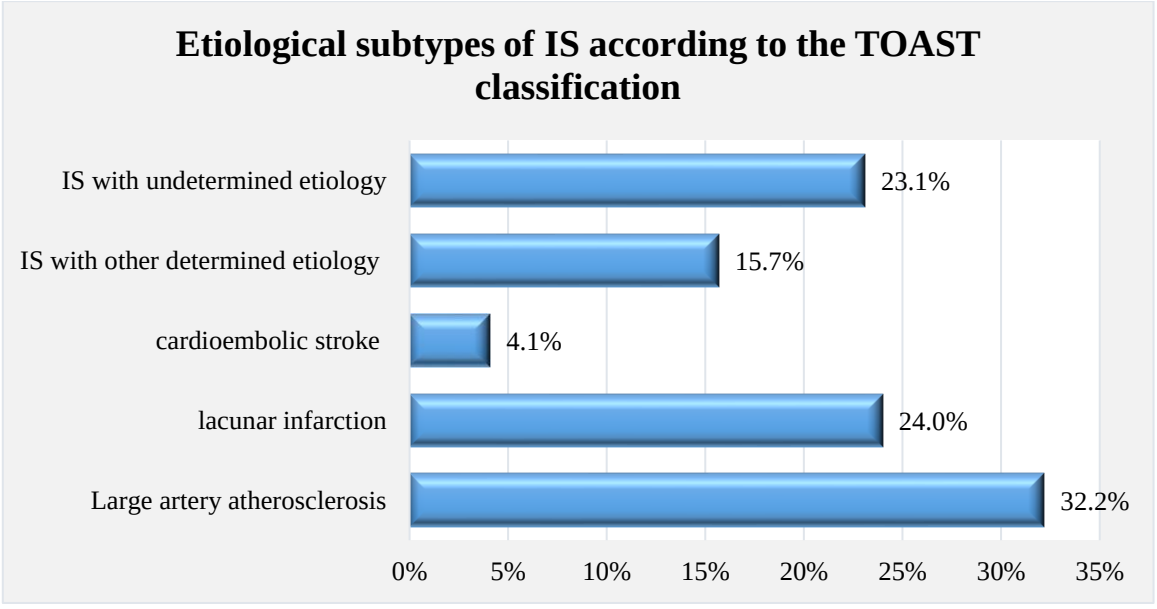


Figure 23/ *Percentage distribution of the etiological subtypes of IS according to the TOAST classification*

Table 14 presents data from the regression analysis of modifiable RFs that were significantly associated with large artery atherosclerosis. Statistical analysis revealed that large artery atherosclerosis was significantly associated with: AH, DM and Dyslipidemia. Cases of small vessel disease (lacunar stroke) showed a significant association only with AH. Cardioembolic stroke demonstrated a strong correlation exclusively with atrial fibrillation.

***Table 14**/ Regression analysis of modifiable risk factors associated with large artery atherosclerosis*

Modifiable RF	B	S.E.	Wald	d.f.	Sig.	Exp (B)	95% CI	
							Low limit	High limit
Arterial hypertension	1.954	0.643	9.224	1	**0.002**	7.059	2.000	24.915
Diabetes mellitus	0.976	0.404	5.834	1	**0.016**	2.654	1.202	5.861
Dyslipidemia	1.279	0.533	5.759	1	**0.016**	3.592	1.264	10.210

Figure 24 illustrates the differences in the distribution of etiological subtypes of IS between the two age groups. Our findings show that middle-aged patients were more frequently affected by large artery atherosclerosis (40.5%) and small vessel disease (29.1%). Younger patients with IS exhibited a higher frequency of stroke of undetermined etiology (34.1%) and stroke of other determined etiology (34.1%). Cardioembolism was observed only among middle-aged patients, with a prevalence of 6.3%. The differences between the two age groups were statistically significant ($p < 0.001$).

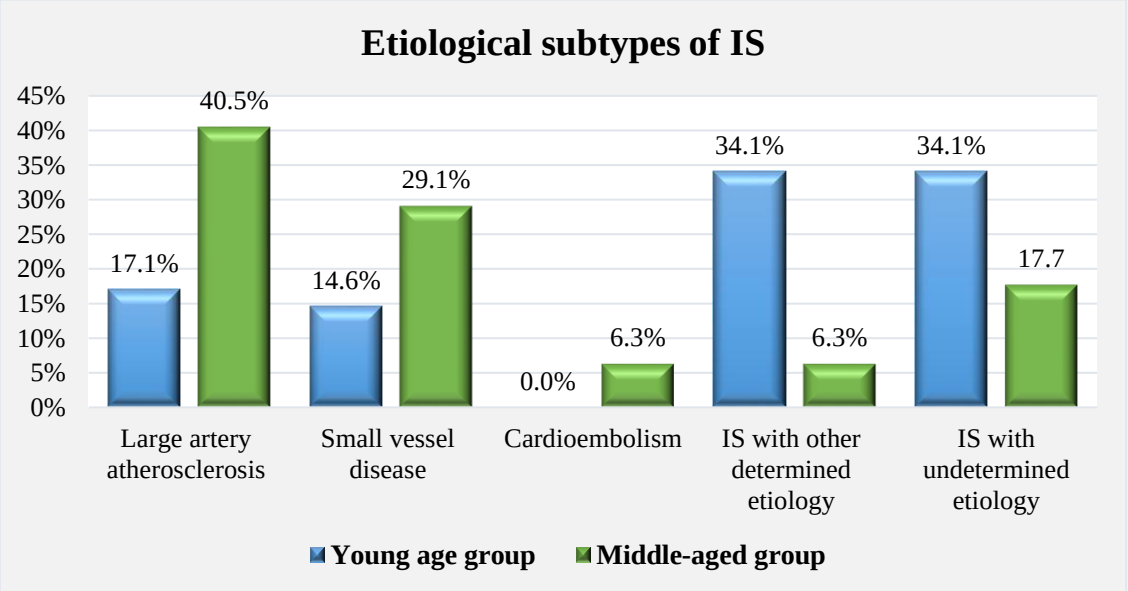


***Figure 24**/ Distribution of stroke subtype in the two age groups*

Figure 25 presents the differences in the distribution of IS etiological subtypes between the two genders. Our results show that men had a higher frequency of large artery atherosclerosis – 43.1% and small vessel disease – 26.4%, while women showed a higher frequency of stroke of undetermined etiology – 31.3% and stroke of other determined etiology – 27.1%. The differences between the two groups were statistically significant (p=0.05).

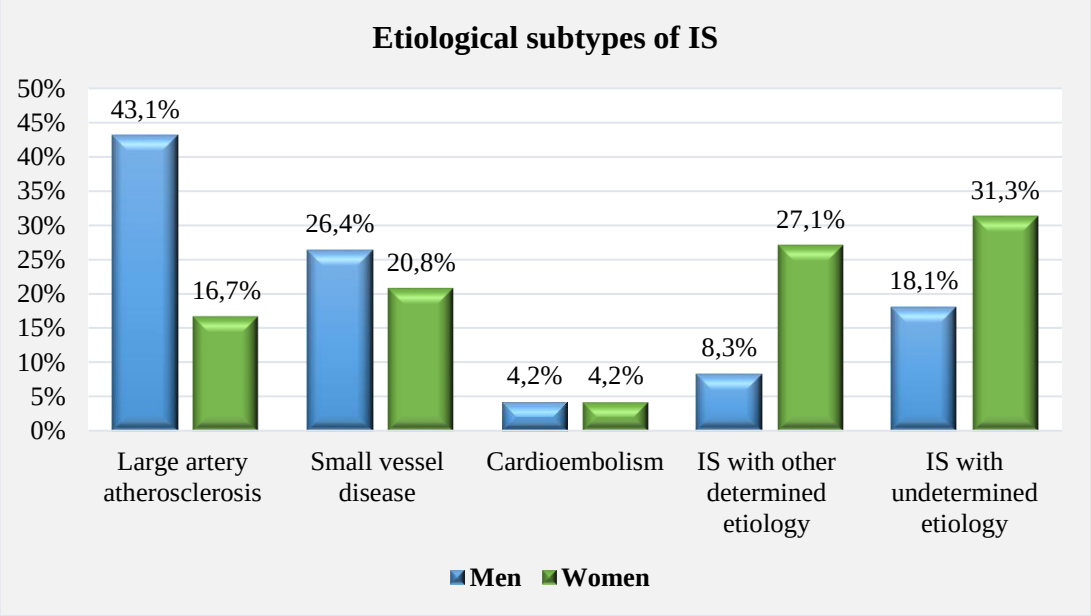


***Figure 25**/ Distribution of stroke subtypes among the genders*

Figure 26 presents the subtypes of IS according to the OCSP classification. Among all patients with acute IS 29 patients (24.2%) had a lacunar infarct, 25 patients (20.8%) had a total anterior circulation infarct, 41 patients (34.2%) had a partial anterior circulation infarct and 25 patients (20.8%) had a posterior circulation infarct.

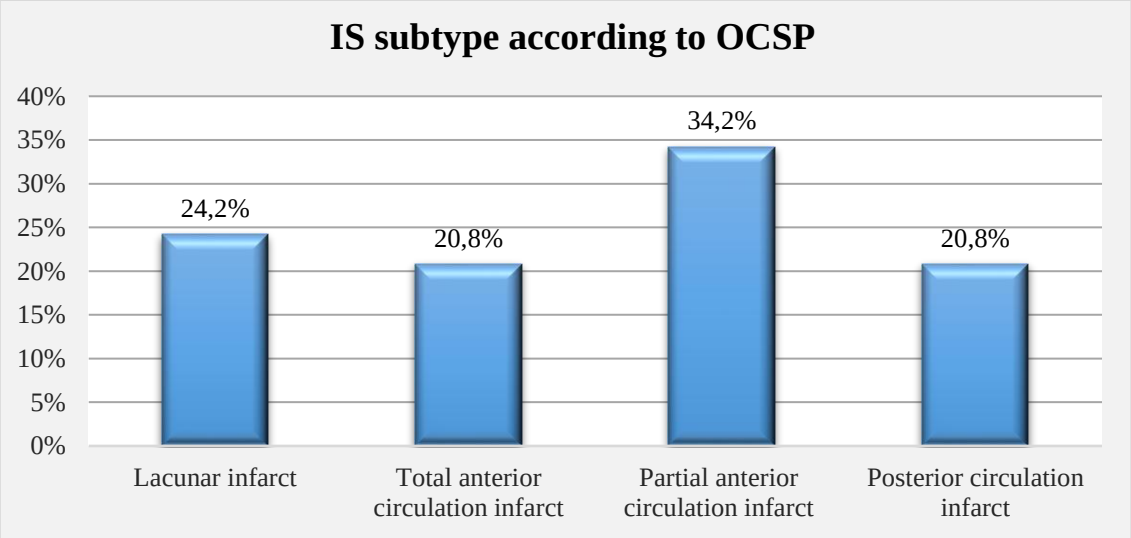


***Figure 26**/ Percentage prevslence of stroke subtype according to OCSP*

Figure 27 illustrates the differences in the distribution of IS subtypes by age group, according to the OCSP classification. We determined that middle-aged patients were more frequently affected by posterior circulation infarcts – 24.1% and lacunar infarcts – 25.3%. In contrast, younger patients more often presented with partial anterior circulation infarcts – 36.6% and total anterior circulation infarcts – 26.8%. The differences between the age groups were not statistically significant ($p > 0.05$). (26.8%).

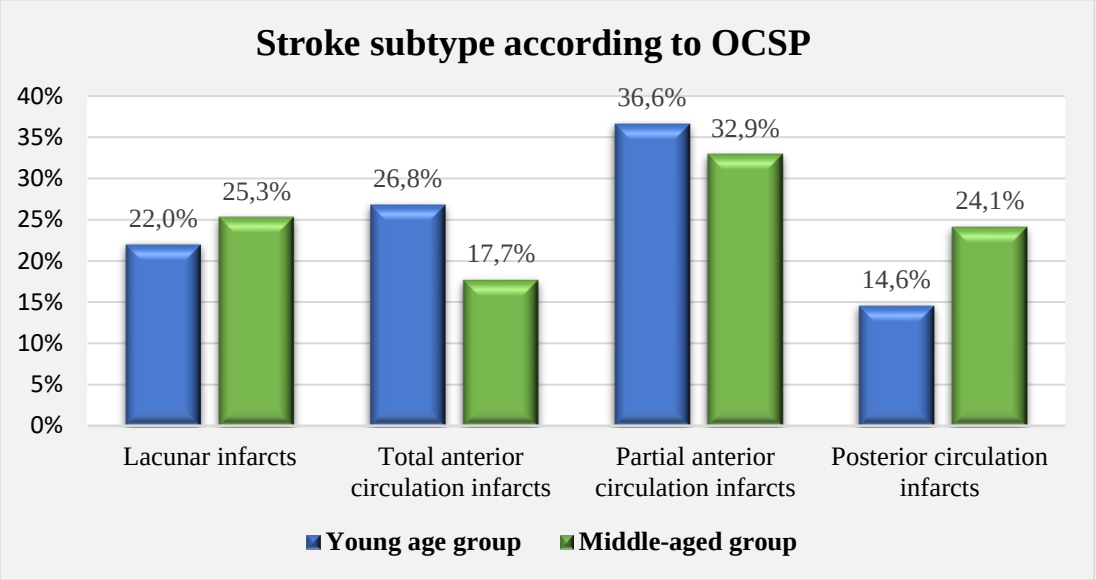


Figure 27/ *Percentage distribution of patients by age groups according to OCSP*

Figure 28 illustrates the differences in the distribution of ischemic stroke (IS) subtypes by gender, based on the OCSP classification. Our findings indicate that men had a slightly higher frequency of lacunar infarcts – 25.0% and total anterior circulation infarcts – 22.2%. In contrast, women showed a higher frequency of partial anterior circulation infarcts – 35.4% and posterior circulation infarcts – 22.9%

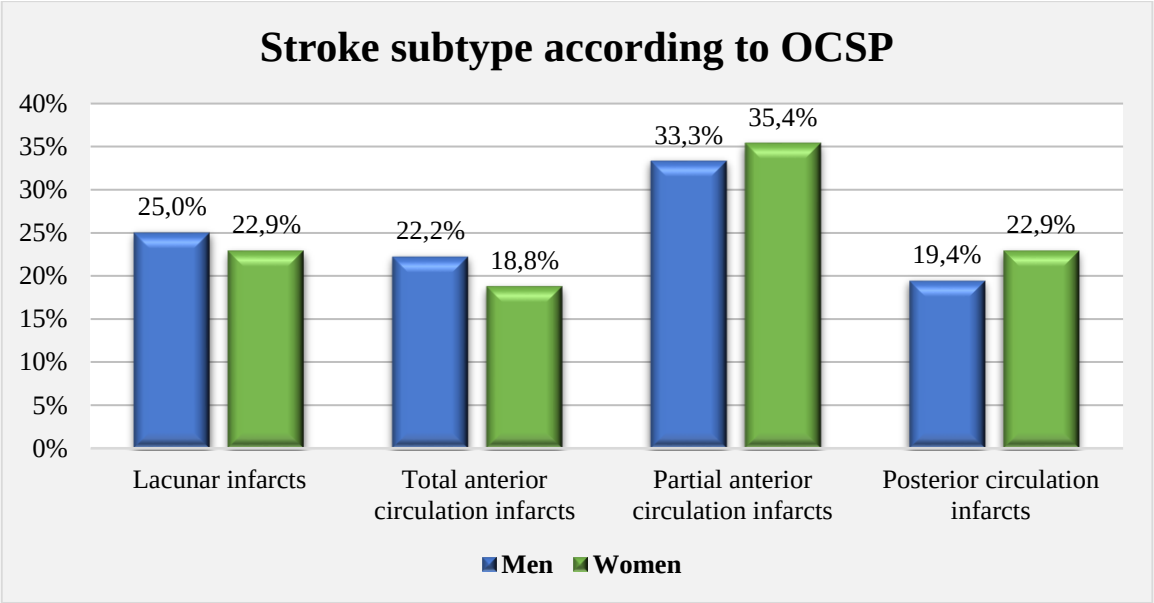


***Figure 28**/ Percentage distribution of patients by gender according to the OCSP classification*

4.4 Analysis of the treatment of patients with acute IS.

In 13 patients (11.0%) with acute IS, intravenous thrombolysis was performed, while the remaining 107 patients (89.0%) received non-specific (conservative) treatment. **Figure 29** presents the percentage distribution of patients based on the type of treatment administered for acute IS.

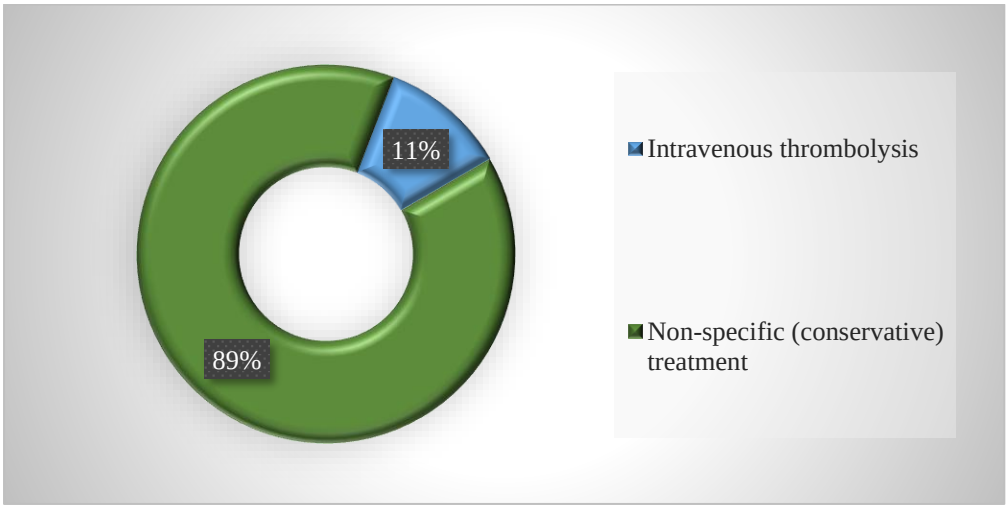


***Figure 29**/ Percentage distribution of patients according to treatment of acute IS*

Table 15 presents the distribution of patients by age group and gender according to the type of treatment administered for acute IS. Intravenous thrombolysis was performed in 8 patients (19.5%) from the younger age group and 5 patients (6.3%) from the middle-aged group. The frequency of intravenous thrombolysis was slightly higher among women (12.5%) compared to men (9.7%).

***Table 15**/ Distribution of patients according to treatment*

Treatment of acute IS	Young age group N (%)	Middle-aged group N (%)	Men N (%)	Women N (%)
Intravenous thrombolysis	8 (19.5%)	5 (6.3%)	7 (9.7%)	6 (12.5%)
Non-specific treatment	33 (80.5%)	74 (93.7%)	65 (90.3%)	42 (87.5%)

4.5 Assessment of IS severity and functional outcome. Predictors of unfavourable clinical outcome.

Figure 30 presents the percentage distribution of patients according to the severity of IS, assessed using the NIHS scale at the time of hospital admission. The mean NIHSS score was 6.73 ± 4.04. According to NIHSS results at admission 44 patients (36.7%) had a mild IS, 69 patients (57.5%) had a moderate IS, 7 patients (5.8%) had a moderate to severe IS.

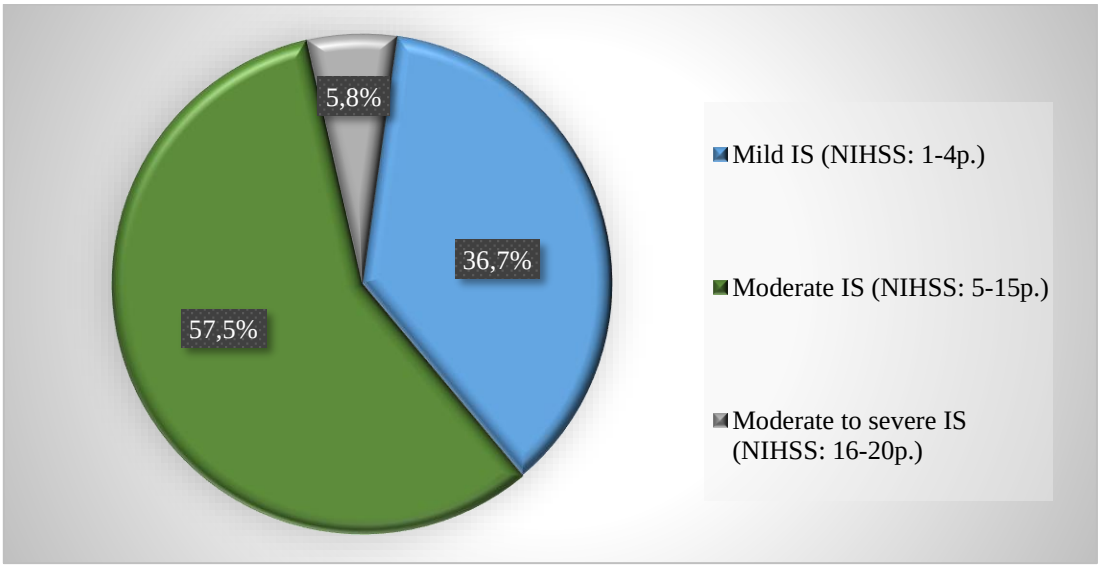


***Figure 30**/ Distribution of patients based on IS severity*

Figure 31 presents the age-related differences in the severity of IS assessed by the NIHS scale at hospitalization. Our data shows that younger patients more frequently had moderate (68.3%) and moderate-to-severe (9.8%) IS compared to middle-aged patients.

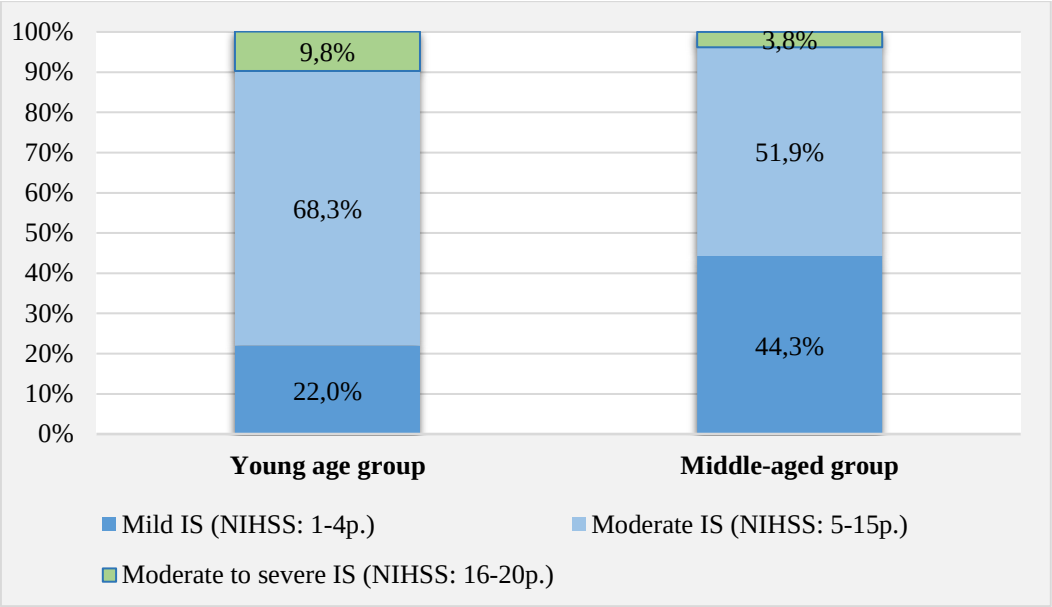


Figure 31/ *Age-related differences in the severity of IS*

Figure 32 illustrates the age-related differences in the maximum, minimum, and mean NIHSS scores at admission. Younger patients showed a higher mean score (6 points) compared to middle-aged patients (5 points). The differences between the two age groups are statistically significant (p = 0.029).

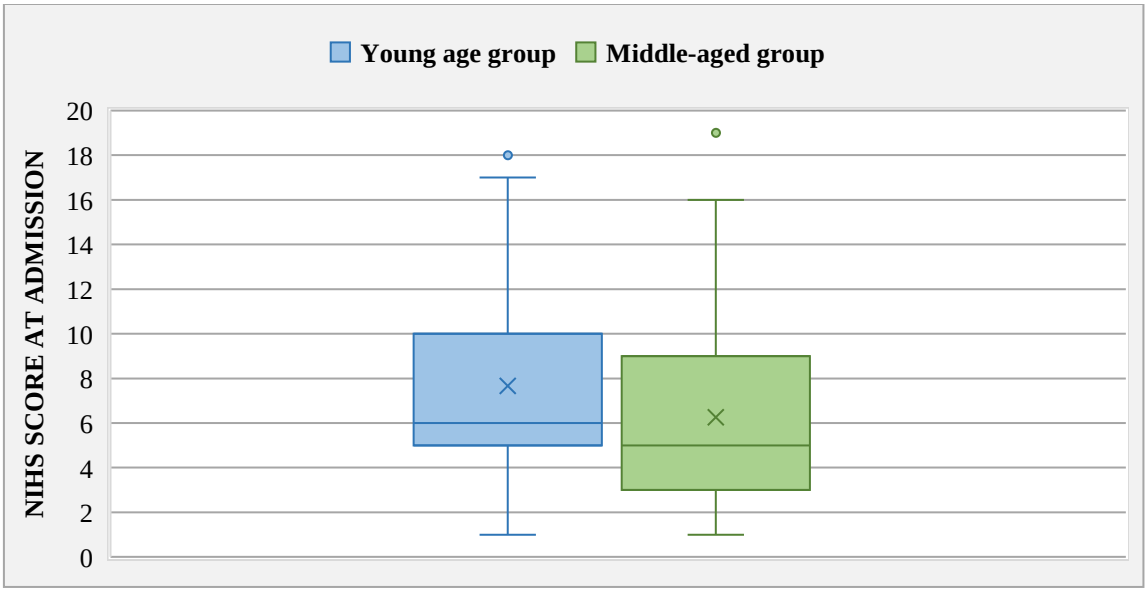


Figure 32/ *Comparison of NIHSS results at admission in both age groups*

Figure 33 presents data on the severity of neurological deficit, assessed using the NIHSS scale, across the different subtypes of IS according to the OCSP classification. The mean NIHSS scores for the various IS subtypes are as follows: total anterior circulation infarct – 12.08 ± 3.91 points (range: 6–19), partial anterior circulation infarct – 6.98 ± 2.17

points (range: 3–12), lacunar infarct – 3.59 ± 1.59 points (range: 1–9), and posterior circulation infarct – 4.64 ± 2.92 points (range: 1–13). We found that cases with total and partial anterior circulation infarcts had significantly higher mean NIHSS scores compared to lacunar and posterior circulation infarcts ($p < 0.001$).

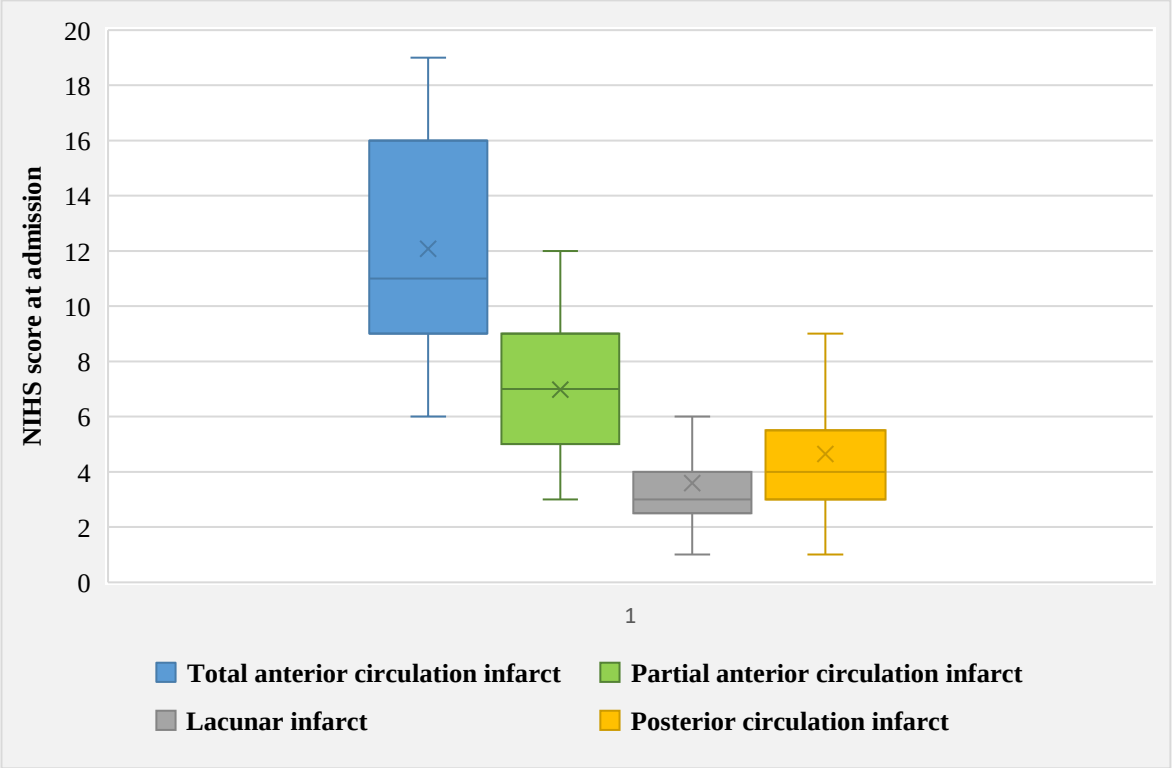


Figure 33/ *Assessment of the severity of neurological deficit across the different subtypes of IS according to the OCSP classification*

Table 16 and **Figure 34** present a comparative assessment of the clinical outcome between the two age groups at discharge. An unfavourable clinical outcome was observed in 24 (58.5%) of the younger patients and in 17 (41.8%) of the middle-aged patients. The differences were not statistically significant ($p > 0.05$).

***Table 16**/ Comparative assessment of the functional outcome between the two age groups at discharge based on mRs.*

Functional outcome at discharge	Young age group n=41 (34.2%)	Middle age group n = 79 (65.8%)	p-value
Favourable outcome (mRs 0-2p.)	17 (41.5)	46 (58.2)	0.081
Unfavourable outcome (mRs 3-5p.)	24 (58.5)	33 (41.8)	

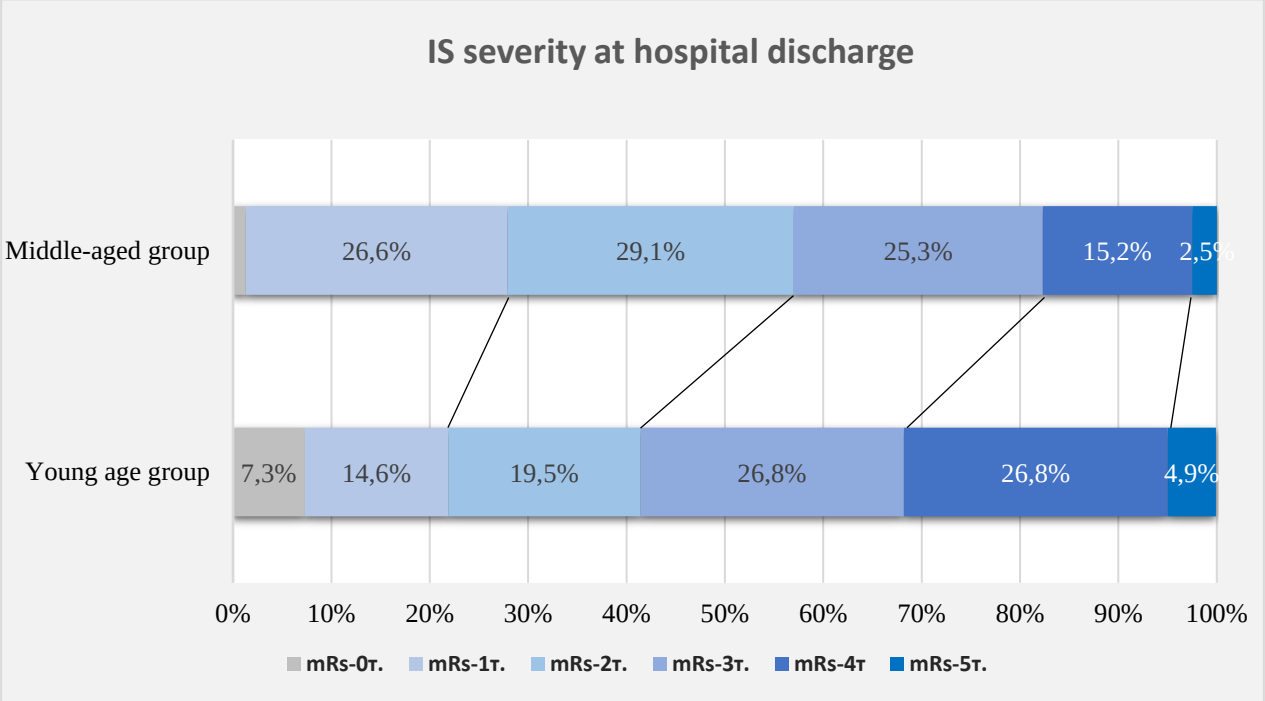
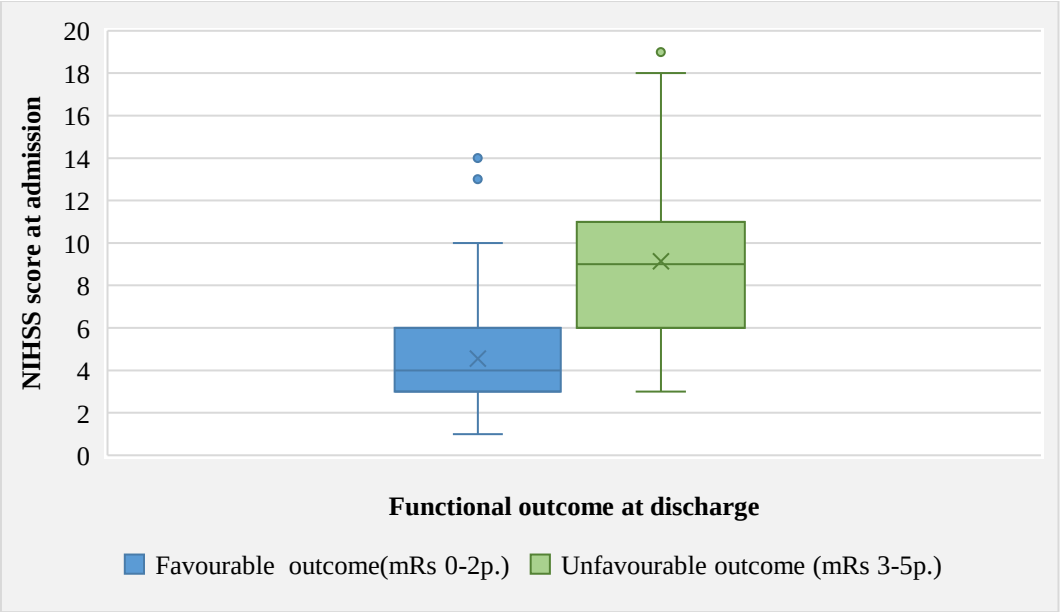


***Figure 34/** Percentage distribution of patients according to severity of IS based on mRS*

Figure 35 presents data on the differences in NIHSS scores (mean values and median) at admission between patients with favourable and unfavourable functional outcomes at discharge. Patients with an unfavourable functional outcome at discharge (mRS = 3–5 points) demonstrated higher mean NIHSS scores (9 points) compared to those with a favourable outcome (NIHSS – 4 points). The differences were statistically significant ($p < 0.001$).



Figyure 35/ *Comparison of mean points on NIHSS between groups with rfavourable and unfavourable outcome at discharge*

According to the data from the multivariate regression model, significant predictors of unfavourable outcome at discharge (mRS = 3–5 points) include a higher NIHSS score (>5 points) at hospital admission and total anterior circulation infarct (OR: 12.571, 95% CI: 3.508–45.047). A higher NIHSS score at admission (>5 points) is associated with a 10-fold increased risk (OR: 10.147, 95% CI: 4.356–23.635) of an unfavourable clinical outcome at discharge. Total anterior circulation infarct is associated with a 12-fold higher risk of unfavourable clinical outcome at discharge.

Table 17/ *Predictor assessment for unfavourable outcome (mRs =3-5p.) at discharge*

Predictors for unfavourable outcome based on mRs (3-5т.)	**Odds Ratio (OR)**	**Confidence interval (95%CI)**		**p - value**
		Low limit	**High limit**	
More than 5 pointss on NIHSS at admission	10.147	4.356	23.635	**<0.001**
Total anterior circulation infarct	12.571	3.508	45.047	**<0.001**
Partial anterior circulation infarct	1.456	0.682	3.105	0.312

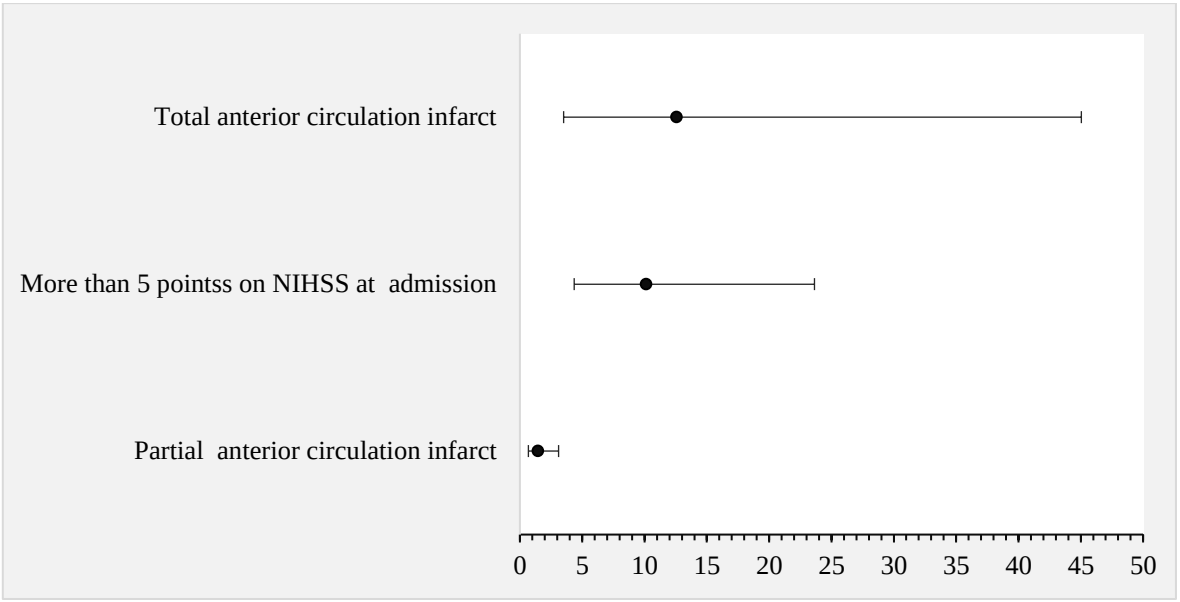


Figure 36/ *Predictor assessment for unfavourable outcome (mRs=3-5m.) at discharge*

5. DISCUSSION

5.1 Modifiable RFs for IS

In the present study, we found that the most common modifiable health-related RFs among young and middle-aged patients with acute IS were: AH (72.5%), dyslipidemia (72.5%), low levels of HDL cholesterol (63.3%), high levels of LDL cholesterol (59.2%), DM (35.8%), and atrial fibrillation (5.0%). Among the lifestyle-related modifiable RFs, the most prevalent were current smoking (66.7%), low physical activity (56.7%), psychosocial stress (49.2%), overweight (36.7%), alcohol abuse (28.3%), and short night sleep (28.3%). We conducted a comparative analysis of our findings with data from studies by Bulgarian and international authors. According to a prospective study conducted on 101 young Bulgarians (<50 years old) with acute IS, the most frequently observed modifiable RFs were hyperlipidemia (71.4%), AH (62.2%), smoking (24.5%), DM (12.2%), and alcohol abuse (4.1%) (Cholakova M., 2019). Our data are similar to the results of this study, although we report a higher prevalence of the modifiable RFs we examined. According to a study by Tsalta (2021) conducted on 150 Bulgarian patients with acute IS, AH was the most common modifiable RF (98.7%), followed by dyslipidemia (74.7%), smoking (63.3%), heart rhythm disorders (32.9%), DM (24.7%), and alcohol abuse (8.7%). In comparison we observed a lower prevalence of AH, dyslipidemia, and atrial fibrilation, but a higher prevalence of current smoking (66.7%) and alcohol abuse (28.3%).

In 2013, the results of the SIFAP (Stroke in Young Fabry Patients) study were published, which included 4,467 young patients (aged 18–55 years) with acute IS and TIA from 15 European countries. This study demonstrated a higher prevalence of smoking (56.0%), low physical activity (48.0%), AH (47.0%), dyslipidemia (35.0%), elevated LDL cholesterol levels (42.0%), reduced HDL cholesterol levels (28.0%), overweight (38.0%), DM (10.0%), and atrial fibrillation (2.0%). Alcohol abuse (33.0%) and short night sleep (18.0%) were reported as underdocumented RFs (Von Sarnowski B et al., 2013).

Table 18 presents a comparative assessment of the prevalence of certain modifiable RFs for IS between our study and previously conducted similar studies. We report a higher prevalence of AH, dyslipidemia, and DM compared to the results presented by other authors. In most studies, the prevalence of atrial fibrilation in young patients with IS is low (under 5.0%). Only Shihmanter R et al. reported a higher prevalence of atrial fibrilation (8.0%). Compared to the results of other authors, we observed a higher prevalence of behavioral risk factors such as current smoking, low physical activity, and obesity.

Table 18/ Comparative assessment of the prevalence of certain modifiable RF for IS between our study and previously conducted similar studies.

Study author	Year	Country	Mean age (participants)	AH (%)	Dyslipidemia (%)	DM (%)	AF (%)	Smoking (%)	Alcohol abuse (%)	Low physical activity (%)	Obesity (%)
Current study	**2024**	Bulgaria	48.9	72.5	72.5	35.8	5.0	66.7	28.3	56.7	36.7
Ekker MS и съавт.	**2023**	Netherland	44.2	37.7	65.4	10.4	N/A	49.6	7.0	N/A	N/A
Amaya Pascasio L и съавт.	**2023**	Spain	43.5	29.9	26.4	10.5	3.8	48.0	9.4	N/A	12.1
Norman K и съавт.	**2022**	Sweden	49.0	28.9	N/A	15.4	5.0	30.4	N/A	N/A	N/A
Vibo R и съавт.	**2021**	Estonia	44.7	51.7	64.6	12.4	7.6	56.4	15.6	N/A	33.2
Shihmanter R и съавт.	**2021**	Israel	46.5	52.0	60.0	28.0	8.0	41.0	3.0	N/A	18.0
Kono Y и съавт.	**2020**	Japan	48.0	55.0	47.0	21.0	3.0	42.0	24.0	N/A	14.0
Tang M и съавт.	**2020**	China	38.2	43.0	37.2	17.1	1.2	41.1	N/A	N/A	N/A
Aigner A и съавт.	**2017**	Germany	44.8	44.2	31.0	10.3	N/A	48.0	32.7	49.2	21.6
B von Sarnowski и съавт.	**2013**	15 European countries	47.0	46.6	34.9	10.3	2.4	55.5	33.0	48.2	22.3

5.2 Assessment of odds ratio (OR) for IS in patients of young and middle-age

Arterial hypertension is a RF that leads to damage and dysfunction of the vascular endothelium, thereby inducing the process of atherosclerosis in the cerebral arteries and arterioles. Furthermore, AH causes lipohyalinosis of the penetrating arterioles that supply blood to the white matter of the brain. These two mechanisms through which AH affects the vessel wall play a key role in the development of atherothrombotic and lacunar ischemic strokes (Yu JG et al., 2011).

According to the INTERSTROKE study, the strength of the association between AH and the risk of IS increases with age, and patients aged 35–45 years have a population-attributable risk (PAR) of 50.7%. According to this study, AH increases the risk of IS by five times (OR: 5.41, 95% CI: 3.40–8.58) in young patients (Khan M et al., 2023). In comparison, we present a two-fold higher relative risk for IS associated with AH (OR: 10.018, 95% CI: 5.523 – 18.173). A possible explanation for the higher OR observed in our study is the older average age of the patients included in our research (48.99±7.58). A similar trend is observed in the study by Tsalta (2021), according to which the mean age of their studied patients is 68.76±11.36, and those with AH have a 28 times higher risk of IS (OR: 28.778, 95% CI: 6.670 – 124.155). Based on these findings, we can assert that with increasing age, the strength of the association between AH and the risk of IS increases.

The relationship between dyslipidemia and the risk of IS is complex and multifaceted. It is accepted that dyslipidemia plays an important role in the atherosclerosis of large arteries and demonstrates a positive correlation with IS in adult patients [Kloska A et al., 2020]. According to recent studies, there is a negative relationship between dyslipidemia and the risk of IS in young patients (OR<1) (Aigner A et al., 2017, Kivioja R et al., 2018, Ramírez-Moreno JM et al., 2022, Khan M et al., 2023). Our results are in contradiction with these findings, as we establish a positive correlation between the RF dyslipidemia and the risk of IS (OR: 7.569, 95% CI: 4.270 – 13.416).

High LDL and low HDL cholesterol are traditional lipid markers that clearly increase the risk of IS in adult patients, but the strength of this relationship in young patients is still a topic of debate (Kloska A et al., 2020).

It has been proven that HDL plays an important role in the reverse transport of excess cholesterol from the peripheral vessels to the liver, where it is excreted. Additionally, HDL has other beneficial biological properties such as: anti-atherogenic, anti-apoptotic, anti-thrombotic, antioxidant effects, as well as vasodilatory and cytoprotective functions (Kosmas CE et al., 2018). Low levels of HDL cholesterol induce the atherosclerotic process in the

carotid vessels and increase the risk of IS (Demarin V et al., 2010). Two independent studies found a positive relationship between low HDL cholesterol and the risk of IS in young patients. The existence of this relationship defines low HDL cholesterol as a significant marker for IS in young and middle-aged patients. According to the study by Ramírez-Moreno et al. (2022), low HDL cholesterol is associated with a 5.20 times higher risk of IS (OR: 5.20, 95% CI: 3.29 – 8.21), while in the study by Reetta Kivioja et al. (2018), young patients with low HDL cholesterol have a 2.31 times higher risk of IS (OR: 2.31, 95% CI: 1.35 – 3.95). The data from this dissertation supports these results. We found that low HDL cholesterol increases the risk of IS by 5.18 times, emphasizing the need for effective control of low HDL cholesterol, especially in young and middle-aged patients.

It has been established that LDL cholesterol penetrates the endothelial layer of arterial vessels and induces the process of atherosclerosis (Wadhera RK et al., 2016). Recent studies in young patients showed a negative relationship between elevated LDL cholesterol levels and the risk of IS (OR<1) (Kivioja R et al., 2018, Ramírez-Moreno JM et al., 2022). In contrast, we found a clear positive relationship between high LDL cholesterol and the risk of IS (OR: 4.547, 95% CI: 2.612 – 7.914).

Diabetes mellitus is a significant risk factor for IS, as it induces inflammatory processes in the vascular wall, accelerates atherosclerosis of the carotid arteries, and increases the risk of thrombosis (Zhu J and Jiang Y, 2023). Several case-control studies reported that the relative risk for IS associated with DM in young patients ranges between 1.76 - 2.76 (Kivioja R et al., 2018, Ramírez-Moreno JM et al., 2022, Khan M et al., 2023). The data from our study confirm this relationship, showing that DM increases the risk of acute IS by 6 times in young and middle-aged patients (OR: 6.143, 95% CI: 2.910 – 12.968).

Table 19/ *Comparative assessment of odds ratio (OR) for stroke according to our study and several other studies.*

Study author	Year	Country	Age	Odds Ratio					
				AH	Dyslipidemia	Low HDL cholesterol	High LDL cholesterol	DM	AF
Current study	**2024**	Bulgaria	18-59	10.18	7.56	5.18	4.54	6.14	2.05
Maria Khan et al.	**2023**	Multicentric study in 32 countries	18-45	5.41	N/A	N/A	N/A	N/A	8.42
Ramírez-Moreno et al.	**2022**	Spain	18-55	2.36	0.75	5.20	0.23	1.76	4.77
Reetta Kivioja et al.	**2018**	Finland	25-49	1.76	N/A	2.16	0.68	2.76	10.43
Annette Aigner et al.	**2017**	Germany	18-55	2.3	0.9	N/A	N/A	1.9	N/A

Smoking causes oxidative stress, damages the vascular endothelium, and accelerates carotid atherosclerosis. These harmful effects make smoking a leading behavioral RF for IS (Parmar MP et al., 2023). According to the large-scale INTERSTROKE study, each increase in the number of cigarettes smoked per day is associated with a higher risk of IS, both in men and women. Young individuals (<50 years) who smoke more than 20 cigarettes a day have a higher risk of developing acute IS (OR: 2.49, 95% CI: 1.78–3.47) compared to those who smoke fewer (Smyth A et al., 2023). In our study, smoking more than 20 cigarettes per day increases the risk of acute IS by 9 times, which is consistent with the results of the aforementioned study.

Alcohol consumption varies depending on age, gender, and regional population affiliation. It has been established that high alcohol consumption is more strongly associated with the risk of hemorrhagic stroke than with IS (Smyth A et al., 2023). In the study by Maria Khan et al. (2023), excessive alcohol consumption was assessed as one of the most important behavioral RFs for IS in young individuals. According to the data from this study, alcohol abuse is associated with a 5.41 times higher risk of IS. Recently published data from Martinez-Majander N et al. (2024) indicate that alcohol abuse is an independent RF for cryptogenic IS in young men (OR: 2.72, 95% CI: 1.25–5.92). Our results are similar to those from these studies. We found that alcohol abuse (>5 alcoholic drinks per day) increases the risk of IS by 4 times (OR: 4.349, 95% CI: 2.035–9.294). The higher risk of IS in patients with

alcohol abuse can be explained by the synergistic effect between alcohol and hypertension. This explanation is confirmed in the study by Kiyohara Y et al. (1995), according to which the relative risk of IS is higher in patients with AH who abuse alcohol than in patients with HT who do not abuse alcohol. Alcohol abuse leads to higher sympathetic nervous system activity and subsequent increases in blood pressure values during the morning hours (Metoki H et al., 2006). In our study, we evaluated the mean values of SBP and DBP between IS patients who abuse alcohol and those who do not. Our results show that IS patients who abuse alcohol have higher average systolic and diastolic blood pressure values compared to those who do not abuse alcohol. However, these differences were not statistically significant.

According to ASA, physical activity and exercise improve endothelial and vasomotor function, leading to vasodilation and lowering of blood pressure. Furthermore, regular physical activity reduces insulin resistance and improves lipid metabolism, resulting in weight loss (Kernan WN et al., 2014). In addition, it should be emphasized that regular moderate to vigorous physical activity has an antithrombotic effect by reducing blood viscosity, fibrinogen levels, and platelet aggregation (Lee CD et al., 2003). It has been proven that there is an inverse relationship between the level of physical activity and the risk of stroke (Ghozy S et al., 2022). According to Annette Aigner et al. (2017), low physical activity is the most important behavioral RF for IS in young patients (OR: 5.9, 95% CI: 5.1–6.7). Our results are consistent with the data from that study. We found a 5.15-fold increased risk of IS associated with low physical activity. These findings are biologically plausible, as physical inactivity is a RF for most metabolic RFs such as AH, DM, and overweight, and it is commonly associated with an unhealthy cardiovascular diet and alcohol consumption (Aigner A et al., 2017).

Overweight leads to increased BP, blood glucose and serum lipid levels. In addition, it causes hypercoagulability and increased platelet aggregation, which accelerate the atherosclerotic process and increase the risk of acute IS (Kernan WN et al., 2013). According to Mitchell AB et al. (2015), overweight (BMI >30 kg/m^2) increases the risk of IS by 1.57 times in young patients (<49 years). We also found a positive association between overweight (BMI >25.0) and IS (OR: 2.200, 95% CI: 1.237–3.914).

Several hypothetical mechanisms are being discussed to explain the relationship between psychosocial stress and IS. Acute psychosocial stress activates the sympathetic nervous system, thereby causing vasoconstriction or rupture of atherosclerotic plaques in predisposed individuals (Mittleman MA and Mostofsky E, 2011). On the other hand, chronic psychosocial stress leads to dysregulation of the sympathetic nervous system, endothelial dysfunction, and atherosclerosis of the carotid arteries (Kershaw KN et al., 2017). The

INTERSTROKE study identifies psychosocial stress as one of the important behavioral RFs for IS. According to the data from this study, psychosocial stress is associated with a 2.33-fold increased risk of acute IS in individuals under 45 years of age (Khan M et al., 2023). Our study also found a positive correlation between psychosocial stress and IS in our patient population (OR: 2.087, 95% CI: 1.234–3.530).

Short sleep duration (<6 hours per night) impacts the body through various pathophysiological mechanisms, including elevated cortisol levels via activation of the hypothalamic-pituitary-adrenal axis, fluctuations in blood pressure with increased systolic and diastolic values, impaired endothelial function, elevated CRP levels, and hypercoagulability. Collectively, these effects promote atherosclerosis and increase the risk of acute IS (Chiang JK, 2014; Ji A et al., 2020). In our study, we found that short night sleep increases the risk of acute IS by 1.977 times. Our findings are consistent with the results of a large case-control study, which reported that sleep duration of less than 6 hours per night is associated with a 2.64-fold higher risk of IS (OR: 2.64, 95% CI: 1.69–4.12) (McCarthy CE et al., 2023).

5.3 Age-related differences in prevalence of modifiable RFs in young and middle-aged patients with acute IS

The data from the present study demonstrate that AH and dyslipidemia are the most common modifiable health-related RFs in patients with acute ischemic stroke (AIS). We found that 72.5% of all patients studied had AH, with its prevalence being significantly higher in the middle-aged group (81.0%) compared to the younger group (56.1%). Likewise, dyslipidemia was observed in 83.5% of middle-aged patients and 51.2% of younger patients. Supporting our findings are the results published by KS Tan et al., who reported that AIS patients over 35 years of age had a significantly higher prevalence of AH (53.7%) and dyslipidemia (48.6%) than their younger counterparts (KS Tan et al., 2014). On the other hand, a retrospective study conducted in Estonia confirmed that approximately 50.0% of AIS patients over 44 years of age were affected by AH and dyslipidemia (Schneider S et al., 2017).

According to the results of a large prospective cohort study, middle-aged AIS patients had twice the prevalence of DM (39.0%) compared to younger patients (15.5%), with a higher proportion of low HDL cholesterol also found in the middle-aged group (Jo YJ et al., 2022). In comparison, we found DM in 44.3% of middle-aged patients and 19.5% of younger patients. Furthermore, our results show that 68.4% of middle-aged patients had low HDL

cholesterol levels, compared to 53.7% in younger patients. In summary, the data we present confirm age-related differences in the prevalence of DM and low HDL cholesterol.

Kono et al. (2020) reported a relatively low proportion of atrial fibrillation in both age groups, with middle-aged acute IS patients showing a slightly higher prevalence (5.0%) compared to the younger group (2.0%). In our study, we found the presence of AF only among middle-aged patients, with a reported frequency slightly higher (7.6%) than that presented in the aforementioned study.

According to data from Yao et al. (2012), smoking and alcohol abuse are more frequently observed behavioral RFs in younger IS patients. They reported that 55.1% of these patients were current smokers, and 32.7% consumed excessive amounts of alcohol. Our data show that 75.6% of young IS patients are current smokers, but heavy alcohol consumption is more frequently observed among middle-aged patients (31.6%).

Aguilera Peña et al. (2021) reported that obesity is a more common risk factor among IS patients over 45 years of age (10.0%) compared to younger patients (2.9%). We found a high prevalence of overweight/obesity in both age groups, with middle-aged patients showing a slightly higher frequency (39.2%) compared to younger ones (31.7%). Contradictory to our findings, a prospective study reported a higher frequency of obesity in young IS patients (under 44 years) compared to middle-aged patients; however, these differences were not statistically significant (Kono Y et al., 2020).

According to Von Sarnowski et al. (2013), 19.2% of middle-aged patients and 15.9% of younger patients diagnosed with acute IS had short night sleep duration (less than 6 hours per night). These results contradict our findings, which indicate a higher proportion of short sleep duration among the younger age group (34.1%) than the middle-aged group (25.3%). However, the differences we observed were not statistically significant.

According to Kes VB et al. (2016), young IS patients (<45 years) have higher mean levels of total serum cholesterol, triglycerides, and elevated LDL cholesterol, while older patients (>45 years) show higher mean values of serum glucose and CRP. The results from that study contradict our findings regarding serum lipid levels. We found higher mean levels of total cholesterol, triglycerides, and LDL cholesterol in the middle-aged group. In addition, the middle-aged patients in our study also demonstrated higher mean levels of serum glucose and CRP, which is consistent with the findings of the previously mentioned study..

In their publication, Yea Jin Jo et al. (2022) state that young patients with acute IS have a significantly higher prevalence of obesity, smoking, and excessive alcohol consumption compared to older patients. On the other hand, middle-aged IS patients have a

higher prevalence of AH, DM, dyslipidemia, and atrial fibrillation compared to the younger group. The data from our study confirm the differences in the distribution of health-related RFs, but reveal contradictory findings regarding the prevalence of lifestyle-related RFs for IS.

Renata Shihmanter et al. (2021) reported that middle-aged IS patients (aged 46–55) have a higher mean number of RFs per person (mean 3.5±1.6), compared to their younger counterparts (mean 2.9±1.8). Data from the same study showed that young IS patients more frequently had 0–1 RF (33.0%) and a combination of 2–3 RFs (40.0%), whereas middle-aged patients more commonly presented with ≥4 RFs (52.0%). In comparison with this study, we found an average of 4.5±1.4 modifiable RFs per person in the middle-aged group and 3.9±1.6 in the younger group, with the differences between the two groups being statistically significant. Moreover, over 70.0% of middle-aged patients in our study had a combination of ≥4 modifiable RFs, while 53.7% of young patients had a combination of ≤3 modifiable RFs. The results we present are consistent with the findings of the aforementioned study.

5.4 Gender-related differences in the prevalence of modifiable RFs in young and middle aged patients with acute IS.

Men and women differ in the distribution of (RFs for acute IS. Some modifiable RFs, such as pregnancy, the postpartum period, use of oral contraceptives, migraine with aura, and postmenopausal hormone replacement therapy, are specific to the female sex (Chang BP et al., 2018). On the other hand, most modifiable RFs are shared between men and women, but have a higher prevalence in one of the two sexes. Additionally, differences in the distribution of modifiable RFs between men and women vary across age groups and decades. These differences highlight the need for a better understanding of sex-related disparities in the prevalence of modifiable RFs, which are important determinants of the etiological subtype of IS in young and middle-aged patients (Roy-O'Reilly M and McCullough LD, 2018).

Tang M. et al. (2020) reported a higher prevalence of AH (43.0%) and smoking (41.1%) in men with acute IS. The data from our study confirm these findings. We observed that both AH and current smoking have a significantly higher prevalence among men compared to women. According to a retrospective study conducted on 444 young and middle-aged patients with acute IS, 53.2% of men were current smokers, and 45.0% had AH (Wu X et al., 2022).

Several recent studies have found that DM has a higher prevalence among men with acute IS compared to women (Tang M et al., 2020; Norman K et al., 2022; Wu X et al., 2022). Our results are consistent with these findings. We observed a twofold higher prevalence of

DM in men than in women. In contrast, the study by Khan et al. reported a higher prevalence of DM (85.0%) in women with acute IS compared to men (59.9%) (Khan Fahmi Yousef and Ibrahim Abdulsalam Saif, 2018).

In the study by Šaňák D et al. (2015), 10.2% of IS patients under 50 years of age had paroxysmal atrial fibrillation, with a predominance in men. Differences in the prevalence of atrial fibrillation between sexes were also reported by Tang et al., who found AF in 1.4% of men, while the rate in women was under 1.0% (Tang M et al., 2020). Our data are similar to those findings. We recorded AF in 5.6% of men and 4.2% of women. However, the differences between the sexes were not statistically significant. In contrast to these findings, a prospective study conducted on 3,412 young IS patients reported atrial fibrillation as a more frequent modifiable RF in women (14.8%) than in men (5.4%) (Geng C et al., 2018).

According to Putaala (2020), alcohol abuse is twice as common among men (42.0%) than women (20.0%). Our study results are consistent with this: we observed a fourfold higher rate of alcohol abuse among men (40.3%) compared to women (10.4%). These differences were statistically significant.

The SIFAP study demonstrated that women with acute IS had a higher prevalence of overweight (73.0%) and low physical activity (50.4%) than men (Von Sarnowski B et al., 2013). We report similar results, with 45.8% of women being overweight and 66.7% having low physical activity levels. However, the sex-related differences in our study were not statistically significant.

Psychosocial stress remains a poorly documented behavioral RF for IS. A case-control study confirmed that moderate to severe stress is significantly associated with stroke risk (Ramírez-Moreno JM et al., 2020). Both acute and chronic psychosocial stress may act as triggering factors for the onset of acute cerebrovascular events across all age groups and more frequently among men (Kotlęga D et al., 2016; Graber M et al., 2019). Our data show a slightly higher frequency of psychosocial stress in men (50.0%) compared to women (47.9%).

According to the SIFAP study, reduced night sleep duration (<6 hours per night) was significantly more prevalent among men (20.6%) than women (13.9%) (Von Sarnowski B et al., 2013). Our findings on this risk factor are contradictory, as we observed a slightly higher prevalence of reduced nighttime sleep among women (29.2%) compared to men (27.8%). The differences we reported were not statistically significant.

Several studies conducted on young and middle-aged patients with acute IS have found that men have a higher prevalence of dyslipidemia, low HDL, and high LDL cholesterol compared to women (Von Sarnowski B et al., 2013; Tang M et al., 2020; Putaala J,

2020). We also observed a similar trend. Over 70.0% of both men and women in our study had dyslipidemia, with a slightly higher prevalence among men. Additionally, we found higher mean levels of total serum cholesterol, triglycerides, and LDL cholesterol in men compared to women. Our findings are consistent with those of Cong Geng et al. (2018), who also reported higher mean cholesterol and triglyceride levels in men than in women. In both studies, statistically significant differences were found only for mean triglyceride levels.

According to data from Cong Geng et al. (2018), men had higher mean SBP and DBP upon hospital admission compared to women. Our data clearly confirm the presence of sex-related differences in blood pressure values. We observed significantly higher mean SBP and DBP values in men than in women. Notably, contradictory findings were reported in a prospective cohort study conducted by Wang Y et al. (2019), where women had significantly higher mean SBP values than men.

Modifiable RFs for IS tend to be more frequently grouped in men than in women (Putaala J, 2010). According to Rina Vibo et al. (2021), the frequency of well-documented RFs for IS is higher in men. More than 50.0% of men in their study had a combination of ≥3 modifiable RFs compared to women (Vibo R, 2021). Sarnovski et al. (2013) reported that 29.2% of men and 20.3% of women over the age of 45 had a combination of ≥4 well-documented modifiable RFs. The results of our study demonstrate that the proportion of men with ≥4 modifiable RFs is 70.8%, while for women it is 60.4%. These differences were not statistically significant. Renata Shihmanter et al. (2021) reported that men in their study had an mean of 3.5±1.8 modifiable RFs per person, while women had an mean of 2.8±1.5 modifiable RFs per person. Similarly, we found that men have an mean of 4.6±1.5 modifiable RFs per person, while women have an average of 3.9±1.5 modifiable RFs per person.

Regarding the distribution of RFs between men and women in each age group, we observed the following differences: in the younger age group, AH is twice as high in men (69.2%) as in women (33.3%). In middle-aged patients, the prevalence of DM is 56.5% in men and 27.3% in women. Regarding lifestyle-related RFs, we found that middle-aged men have approximately twice the prevalence of smoking >20 cigarettes per day (60.9%) and four times the prevalence of alcohol abuse (47.8%) compared to women. In comparison, women in both age groups have a higher frequency of overweight and lower physical activity compared to men.

Our results are similar to those from earlier studies. Amaya Pascasio et al. (2023) reveal that men under the age of 50 have a significantly higher prevalence of AH, DM, dyslipidemia, and smoking, while women have a higher frequency of obesity. Similar results are reported by

Yao XY et al. (2012). According to their study, men under 50 years of age with acute IS have a higher prevalence of AH, DM, smoking, and alcohol abuse compared to women.

According to data from a large study conducted in Denmark, AH is a more frequent RF in men with their first IS under the age of 50, with the frequency of AH equalizing between the sexes after this age. The authors of this study report that men in both the younger and middle-aged groups have a higher prevalence of DM compared to women. Regarding lifestyle-related RF, this study highlights the following trends:

- The prevalence of alcohol abuse increases with age, and this RF has a higher frequency in men across all age groups. The most significant difference is observed in the 50-60 age group, where alcohol abuse reaches 20.0% in men and 7.0% in women;
- Smoking has a higher prevalence in men up to 50 years of age and reaches 60.0% in both sexes;
- Obesity is a more common RF in young women under 50 years of age compared to men (Andersen KK et al., 2010)..

In 2017, Maslarov D. published data on the prevalence of multiple health and lifestyle-related RFs in patients with suspected TIA. This study presents some interesting trends:

- Young women have a lower prevalence of hypertension compared to young men. As they approach their fifth decade, this difference visibly diminishes;
- Diabetes mellitus is observed in 22% of women and 18% of men. Women under 45 years of age have twice the prevalence of diabetes compared to men;
- The prevalence of dyslipidemia is significantly higher in men from both age groups compared to women;
- Smoking is approximately twice as common among young men (48%) compared to women (26%). Similar gender differences are observed in patients over 55 years of age, with 29% of women and around 38% of men being current smokers.
- Alcohol abuse has a significantly higher prevalence among men, both in the young and middle-aged groups. The highest prevalence of alcohol abuse is observed in young men, but as age increases, the prevalence of this RF decreases in both genders.

5.5 Characteristics of IS – localization and etiological subtype according to TOAST and OCSP classifications

5.5.1 Stroke localization

Tsalta et al. (2021) reported that 50.6% of patients had IS localized in the anterior circulation, while 49.4% had it in the posterior cerebral circulation. According to another study on 104 young patients with acute IS, 67.3% of them had localization of the IS in the anterior cerebral circulation, and 25.0% in the posterior cerebral circulation (Chatzikonstantinou et al., 2012). According to Bettina von Sarnowski et al. (2017), young patients have a higher frequency of ischemic stroke in the anterior cerebral circulation (70.0%) than in the posterior cerebral circulation (30.0%). Overall, our data are consistent with those from these studies and confirm the widely accepted trend that IS in the anterior cerebral circulation is more common than in the posterior cerebral circulation. Of all the reported patients with IS in the anterior cerebral circulation, we found that the middle cerebral artery (MCA) is more frequently affected (72.9%) than the posterior cerebral artery (PCA) (23.0%).

5.5.2 Etiological stroke subtype according to TOAST classification. Age and gender differences in the prevalence of different etiological stroke subtypes.

The etiological subtype of IS depends on age, sex, and geographic location. Atherosclerosis of large arteries and small vessel disease are the most common subtypes of IS in patients over 35 years of age. The frequency of these subtypes increases proportionally with age and the number of modifiable RFs (Yahya T et al., 2020). In our study, we found that according to the TOAST classification criteria, the most commonly observed etiological subtype of IS is atherosclerosis of large arteries (32.5%), followed by lacunar IS (24.2%), IS of undetermined etiology (23.3%), IS of another determined etiology (15.8%), and cardioembolic IS (4.2%).

Table 20 presents data on the frequency of different IS subtypes in our study and in the studies of some foreign authors.

Table 20/ *Comparison in the prevalence of etiological stroke subtypes in our study and studies of some foreign authors*

Study author	Year	Country	Mean age (participants)	Large artery atherosclerosis (%)	Cardioembolic IS (%)	Small vessel disease (%)	IS with other determined etiology (%)	IS with undetermined etiology (%)
Настоящо изследване	**2024**	България	48.9	32.5	4.2	24.2	15.8	23.3
Gökçimen G и Kozak HH	**2024**	Турция	44.2	14.6	9.0	9.0	9.0	58.4
BETAŞ, S и съавт.	**2023**	Турция	37.8	13.4	16.7	19.8	11.5	38.6
Ekker MS и съавт.	**2023**	Нидерландия	44.2	4.5	17.1	12.5	21.7	25.2
Kõrv L и съавт.	**2021**	Естония	44.3	16.0	15.0	6.0	8.0	55.0
Shihmanter R и съавт.	**2021**	Израел	46.5	8.0	10.0	37.0	20.0	25.0
Kono Y и съавт.	**2020**	Япония	48.0	15.0	8.0	28.0	23.0	16.0
Tang M и съавт.	**2020**	Китай	38.2	39.4	6.8	7.8	29.0	17.0
Ge JJ и съавт.	**2020**	Китай	45.0	43.7	5.1	39.0	6.3	5.9
Goeggel Simonetti B и съавт.	**2015**	Швейцария	46.0	11.0	32.0	9.0	24.0	16.0
Yesilot Barlas N и съавт.	**2013**	15 Европейски страни	42.0	9.3	17.3	12.2	21.6	39.6

Based on the comparative analysis of the presented data, the following conclusions can be made:

1. Our data demonstrate a higher frequency of IS due to atherosclerosis of large arteries and small vessel disease compared to results from other studies conducted in Europe. Similar results could be attributed to the higher mean age of the participants in our study and the higher prevalence of modifiable (RFs among them. On the other hand, the frequency of atherosclerotic IS increases with age and the number of modifiable RFs. Only the studies by Tang et al. (2020) and Ge JJ et al. (2020) report a higher frequency of atherosclerosis of large arteries, which might also be explained by the influence of ethnic background on the IS subtype, as it has been found that Asians are more frequently affected by atherosclerosis of large arteries compared to the white population (Ornello R et al. 2018).

2. From the comparative analysis of other etiological subtypes, we observe a lower frequency of IS of undetermined and other defined etiology compared to studies conducted in Europe. Yesilot Barlas N et al. (2013) confirm the generally accepted trend that around 40.0% of IS remain with unclear etiology. In our study, the frequency of this etiological subtype is approximately 2 times lower (23.3%). Regarding cases with other defined etiology, the most common causes of IS are carotid artery dissection, vasculitis, systemic lupus, thrombophilia, antiphospholipid syndrome, and migraine with aura (Yesilot Barlas N et al. 2013). The results from our study allow us to conclude that the most common causes for IS with other defined etiology are thrombophilia, antiphospholipid syndrome, and hyperhomocysteinemia.

3. In comparison with other studies, we present the lowest frequency of cardioembolic IS. According to our results, atrial fibrillation (AF) is the only cause of cardioembolism in the patients included in this study. By contrast, other studies report various causes for cardioembolic IS, such as patent foramen ovale (PFO), infectious endocarditis, and mechanical valve prosthesis.

It has been established that the prevalence of modifiable RFs varies among different etiological subtypes of IS (Jaffre A et al., 2014). Alawneh KZ et al. (2020) report that AH, DM, and hyperlipidemia are more frequently observed modifiable RFs in thrombotic IS, while overweight and atrial fibrillation are more common RFs in small vessel disease. We find that DM, dyslipidemia, and smoking (>20 cigarettes daily) have a higher prevalence in cases with atherosclerosis of large vessels. For lacunar IS, we observe a higher prevalence of AH and overweight, while cardioembolic IS shows a higher prevalence of AF, alcohol abuse, and low physical activity.

In the study by Aude Jaffre et al. (2014), it was reported that thrombotic IS in young patients is significantly associated with DM, AH, low HDL cholesterol, and smoking, while lacunar IS is associated with AH and advanced age. Our results are similar to those reported in this study. We find that IS due to atherosclerosis of large arteries is significantly associated with AH, DM, and dyslipidemia, while cases of small vessel disease are significantly associated only with AH. Cardioembolic IS shows a strong correlation with AF.

Nacu A et al. (2016) report that the prevalence of atherosclerosis of large arteries and small vessel disease increases in middle-aged patients, reaching its peak around the age of 50. According to another study by Ge JJ et al. (2020), atherosclerosis of large arteries and small vessel disease are more common subtypes of IS in middle-aged patients compared to younger ones. A large multicenter study in Japan reveals that middle-aged patients have twice the prevalence of atherosclerosis of large arteries (20.0%) compared to younger patients (10.0%). This study also shows that small vessel disease is slightly more common in the middle-aged group (27.0%) compared to the younger group (25.0%) (Kono Y et al., 2020). Our data confirm the results of these studies. We observe a twofold higher prevalence of atherosclerosis of large arteries (40.5%) and small vessel disease (29.1%) in middle-aged patients compared to younger patients. A possible explanation for these results could be the higher mean number of modifiable RFs (an average of 4.5 RFs per person) in middle-aged patients compared to younger patients (an average of 3.9 RFs per person).

Vibo et al. (2021) report a higher prevalence of IS with unspecified etiology and other defined etiology in younger patients (48.5% and 9.7%, respectively) compared to middle-aged patients (39.8% and 7.4%, respectively). According to our results, the main etiology remains unclear in 34.1% of young patients and 17.7% of middle-aged patients. On the other hand, 34.1% of young patients had IS with another specified etiology compared to only 6.3% of middle-aged patients. Our data clearly confirm that young patients are more frequently affected by IS with an unspecified etiology and other etiology compared to middle-aged patients.

Spengos K et al. (2010) observe that young men have twice the frequency of atherosclerosis of large arteries (8.4%) compared to women (4.5%). The same study reports a threefold higher frequency of small vessel disease in men (25.2%) compared to women (7.3%). Our data align with these results. We find that men have three times the frequency of atherosclerosis of large arteries (43.1%) compared to women (16.7%), which contrasts with the findings of Vibo et al. (2021), who report a higher frequency of small vessel disease in

women (12.2%) compared to men (10.6%). According to our results, small vessel disease is observed in 26.4% of men and 20.8% of women.

A retrospective study conducted with 2634 young patients in India shows a higher prevalence of IS with another defined etiology in women (26.0%) compared to men (15.5%) (Dash D et al., 2014). In our study, IS with another defined etiology is found in 27.1% of women and 8.3% of men.

The results we present are also confirmed by data from a large multicenter study conducted in 15 European countries. According to their findings, atherosclerosis of large arteries and small vessel disease are more common subtypes of IS in patients over 40 years old and in men, while IS with another defined etiology and unspecified cause are more frequent in young patients (<40 years) and in women (Yesilot Barlas N et al., 2013).

5.5.3 Etiological stroke subtype according to OCSP classification. Age and gender related differences in the prevalence of the etiological stroke subtypes.

The OCSP classification is commonly used in clinical practice and categorizes IS into four subtypes: total infarction of the anterior cerebral circulation, partial infarction of the anterior cerebral circulation, lacunar infarction, and infarction in the posterior cerebral circulation (Amarenco P et al., 2009). This scale provides an additional opportunity for predicting the severity of neurological deficit and clinical outcome in patients with acute IS (De Andrade JBC et al., 2021).

According to Ojha R et al. (2015), 41.5% of patients have lacunar infarction, followed by partial infarction of the anterior cerebral circulation (36.6%), infarction in the posterior cerebral circulation (16.2%), and total infarction of the anterior cerebral circulation (5.7%). This study did not find statistically significant differences in the distribution of IS subtypes by the OCSP classification across different genders and age groups. However, it highlighted that partial and total infarctions of the anterior cerebral circulation predominate in young patients, while middle-aged patients more frequently experience lacunar infarctions and infarctions in the posterior cerebral circulation. Regarding gender differences, the authors report that women are more frequently affected solely by partial infarction of the anterior cerebral circulation.

In comparison, in our study, the most common subtype of IS according to the OCSP classification is partial infarction of the anterior circulation (34.2%), followed by lacunar infarction (24.2%). Total infarction of the anterior cerebral circulation and infarction in the

posterior circulation have the same distribution frequency (20.8%) and are more commonly seen in younger patients than in middle-aged patients. On the other hand, women in our study are more frequently affected by partial infarction of the anterior circulation (35.4%) and lacunar infarction (22.9%) compared to men. We also did not observe statistically significant differences in the subtypes of IS between different genders and age groups.

5.6 Analysis of stroke treatment

Intravenous thrombolysis (IVT) using recombinant tissue plasminogen activator (rtPA) is one of the approaches for specific treatment of IS. The goal of administering IVT within 4.5 hours of the onset of the first symptoms of IS is to achieve timely reperfusion and limit the ischemic zone. Administering rtPA within a three-hour window from the onset of the stroke significantly improves the outcome for patients with acute IS (Berge E et al., 2021). In recent years, there has been a trend in Bulgaria for an increase in the number of IVT procedures. However, thrombolytic treatment in our country remains at a low frequency compared to other European countries. According to data published in 2019, approximately 2.5% of all patients with acute IS in Bulgaria receive IVT each year. This rate is about 5 times lower than in Western European countries (Aguiar de Sousa D et al., 2019).

Of all the patients with acute IS included in our study, only 13 (11.0%) received IVT. Our results are similar to those of Cholakova (2019), who reported IVT in 12 (12.4%) of the patients in her study. The data from the study by Dodds JA et al. (2019) confirm the hypothesis that IVT is a more commonly used treatment method in young patients with acute IS (under 40 years of age) than in older patients. A similar trend was observed in our study, where the proportion of IVT performed was slightly higher in younger patients compared to middle-aged patients.

In patients treated with IVT, we observed a higher frequency of certain behavioral RFs such as smoking (>20 cigarettes per day) and alcohol abuse, while patients who did not undergo IVT had a higher frequency of AH, DM, and dyslipidemia. Cholakova (2019) also noted a significantly higher rate of smoking in patients who received IVT (58.3%) compared to patients treated with nonspecific conservative treatment.

5.7 Assessment of stroke severity at hospitalization and discharge. Predictors of unfavourable clinical outcome.

Despite the common notion that young patients with IS have a more favourable clinical outcome at hospital discharge compared to older individuals, approximately 30% of

patients under the age of 50 experience an unfavourable outcome at discharge (Leys D et al., 2002; Maaijwee NA et al., 2014). Patients who have suffered an IS often remain with various degrees of physical and mental impairments, which significantly affect the quality of their active social lives (Lutski M et al., 2017). Therefore, the ability to predict the severity and clinical outcome of IS, particularly in younger patients, is of paramount importance for successful therapeutic management.

Data from our study reveal that the mean NIHSS score among patients with IS is 6.73±4.04. This result is twice as high as that reported by Ekker MS et al. (2023), who noted an average NIHSS score of 3 at admission among patients included in their study. Upon analyzing our data regarding stroke severity, we found that 36.7% of patients had a mild IS (NIHSS: 1–4), 57.5% had a moderate IS (NIHSS: 5–15), and 5.8% had a moderate-to-severe IS (NIHSS: >16). In comparison, Yang Si et al. (2020) reported that more than 80.0% of patients in their study had mild IS and only 4.7% had severe IS. Similar results were observed in the study by Fang Li et al. (2017), where over 70.0% of patients were assessed as having mild stroke, 21.0% as moderate, and only 1.6% as severe IS. Compared to these studies, we report a higher frequency of patients with moderate and severe IS. Nedeltchev et al. (2005) reported that total anterior circulation infarct is associated with more severe neurological deficit (mean NIHSS of 13) compared to lacunar infarct (mean NIHSS of 3) and posterior circulation infarct (mean NIHSS of 3.5). Their study also showed that partial anterior circulation infarcts were associated with more severe deficits (mean NIHSS of 5) than lacunar infarcts. Our data are consistent with these findings. We observed that patients with total and partial anterior circulation infarcts had significantly more severe neurological deficits (12.08±3.91 and 6.98±2.17 points on NIHSS, respectively) compared to patients with lacunar and posterior circulation infarcts (3.59±1.59 and 4.64±2.92 points on NIHSS, respectively).

Following regression analysis, we found that a higher NIHSS score at admission (NIHSS >5) and total anterior circulation infarct are independent predictors of an unfavourable functional outcome at discharge (mRS = 3–5). Similar results were reported by Nedeltchev et al. (2005) and Lutski et al. (2017), who also found stroke severity (NIHSS >5) and total anterior circulation infarct to be independent predictors of poor functional outcomes at hospital discharge.

The study by Lutski et al. (2017) also reported that over 50.0% of middle-aged patients (>50 years) had unfavourable functional outcomes (mRS = 2–5) compared to younger patients. In contrast, our findings show a higher proportion of poor outcomes at discharge

among the younger age group (58.5%) compared to the middle-aged group (41.8%). However, this difference was not statistically significant.

6. CONCLUSION

In this prospective study, our aim was to analyze the prevalence of certain modifiable RFs related to health status, lifestyle, and behavior in young and middle-aged patients with a first episode of acute IS. To assess the risk of IS associated with each of the examined modifiable RFs, we employed a case-control study design. We analyzed age- and sex-related differences in the prevalence of modifiable RFs, as well as clinical characteristics of IS such as etiologic subtype, localization, severity, and clinical outcome.

Following a comprehensive analysis, we found that patients with acute IS had a significantly higher prevalence of all studied modifiable RFs compared to patients without IS. The health-, lifestyle-, and behavior-related modifiable RFs examined in our study were found to significantly increase the risk of acute IS. Our results clearly confirmed the existence of age- and sex-related differences in the distribution of modifiable RFs among young and middle-aged patients with acute IS. Among middle-aged patients, there was a significantly higher prevalence of health-related modifiable RFs such as AH, DM, dyslipidemia, and elevated LDL cholesterol compared to younger patients. Moreover, middle-aged patients showed significantly higher mean levels of LDL cholesterol, serum glucose, and SBP than those in the younger group. Notably, younger patients were more frequently affected by lifestyle-related modifiable RFs, such as current smoking, psychosocial stress, and reduced night sleep.

Regarding sex-related differences, we found that men had a significantly higher prevalence of AH, DM, current smoking, and alcohol consumption compared to women. Conversely, the female sex was more frequently affected by overweight, low physical activity, and reduced nocturnal sleep. Male patients also exhibited significantly higher mean levels of triglycerides, SBP, and DBP.

When analyzing the association between modifiable RFs and the etiological subtypes of AIS, the following correlations were identified:

- Atherosclerotic stroke was found to be significantly associated with AH, DM, and dyslipidemia;
- Small vessel disease-related IS was significantly associated only with AH;
- In cases of cardioembolic stroke, a positive correlation was found only with atrial fibrillation.

The findings of our study also confirmed that middle-aged patients and male patients are more frequently affected by large artery atherosclerosis and small vessel disease, whereas younger patients and females more often present with IS of undetermined or other determined etiology.

The analysis of results based on the OCSP classification supports previously presented data indicating that total anterior circulation infarcts (TACI) and posterior circulation infarcts (POCI) are more frequently observed among younger patients, compared to those of middle age. In terms of sex differences, women were more often affected by partial anterior circulation infarcts (PACI) and lacunar infarcts (LACI) compared to men.

We also established that total anterior circulation infarcts and a higher initial NIHSS score upon admission are significant predictors of unfavorable clinical outcomes at discharge. Moreover, our results fully support the hypothesis that total anterior circulation infarct is significantly associated with a higher NIHSS score at admission, compared to lacunar infarcts and posterior circulation infarcts. According to our findings, young patients with IS more frequently have higher NIHSS scores at admission and a worse clinical outcome at discharge compared to middle-aged patients.

Our study highlights the critical need to develop and implement urgent measures aimed at increasing public awareness of the adverse effects of modifiable RFs in raising the risk of IS. It is absolutely essential to establish multidisciplinary strategies for effective primary and secondary prevention of IS, particularly among young and middle-aged individuals. Top priorities should include the timely identification and effective control of modifiable RFs, as well as a conscious shift in lifestyle habits. This approach can serve as a fundamental tool in reducing the incidence of the most common etiological subtypes of acute IS in young and middle-aged patients.

7. DEDUCTIONS

Based on our results and the comparative analysis conducted, the following conclusions can be drawn:

1. The prevalence of the modifiable RFs investigated in patients with acute IS across both age groups is comparable to the prevalence reported in similar studies from Europe and Asia. However, our comparative analysis reveals a higher prevalence of the most common and well-documented health-related RFs, such as AH, dyslipidemia, reduced HDL cholesterol levels, elevated LDL cholesterol levels, and DM. Our findings strongly support the well-established trend that AH, DM, atrial fibrillation, and dyslipidemia increase exponentially with age. AF was identified as a modifiable RF for AIS with a relatively low prevalence among younger patients, though its frequency increases with advancing age.;
2. According to our data, smoking and low physical activity are the most prevalent lifestyle-related modifiable RFs for IS, with a predominance of heavy smokers (≥20 cigarettes per day). We also observed a high prevalence of certain RFs that have been previously defined by other authors as poorly documented, namely: low physical activity, psychosocial stress, overweight, alcohol abuse, and short sleep duration.
3. Each of the modifiable RFs studied—related to health status, lifestyle, and behavioral patterns—significantly increases the risk of acute IS. Each of the modifiable RFs studied—related to health status, lifestyle, and behavioral patterns-significantly increases the risk of acute IS. Compared to data from other studies, we also identified a positive correlation between dyslipidemia and the risk of IS;
4. Modifiable RFs related to health status—such as AH, DM, dyslipidemia, atrial fibrillation, low HDL cholesterol, and high LDL cholesterol-are more prevalent among middle-aged patients and men. Additionally, male patients and those of middle age with acute IS exhibit poorer control of SBP and DBP, total serum cholesterol, HDL, and LDL cholesterol levels;
5. Lifestyle-related modifiable RFs, such as current smoking (more than 20 cigarettes per day), psychosocial stress, and short sleep duration, are more prevalent among younger patients. Among female patients, the most commonly observed risk factors are low physical activity, overweight, and reduced sleep duration. A significantly higher average number of modifiable RFs for IS is found among middle-aged patients and men compared to younger patients and women;

6. In our study, we observe a higher frequency of IS due to atherosclerosis of large arteries and small vessel disease compared to other studies conducted in Europe;
7. We observe the presence of age and gender differences in the distribution of the etiological subtypes of IS, with middle-aged patients and men more frequently experiencing atherosclerosis of large arteries, small vessel disease, and cardioembolism, while young patients and women more commonly have IS of undefined and other defined etiology;
8. According to our data, total infarction in the anterior cerebral circulation and a higher score on the NIHSS scale at admission are significant predictors of unfavourable clinical outcomes upon discharge;
9. The facts we have established, the results obtained, and the discussions made highlight the need for further studies to determine the leading RFs for acute IS, especially in young patients.

8. CONTRIBUTIONS

1. A comparative analysis has been conducted on the prevalence of some modifiable RFs related to health status and lifestyle in patients with acute IS aged between 18-59 years in Bulgaria. When compared with data from similar global studies, this provides an opportunity for critical evaluation and the development of an effective strategy to reduce the risk of IS ;
2. For the first time in Bulgaria, a case-control study has been conducted to investigate the strength of the relationship between modifiable RFs and the risk of IS in young and middle-aged patients. A positive correlation has been presented between each of the studied RFs and the risk of IS. The results obtained complement and clarify poorly documented and scarce data so far regarding the contribution of certain RFs to the risk of IS;
3. For the first time in Bulgaria, age and gender differences in the distribution of modifiable RFs have been thoroughly studied. The obtained data confirm and complement some previously established concepts, according to which middle-aged patients with acute IS are more likely to suffer from AH, DM, dyslipidemia, and elevated LDL cholesterol, while young patients have a higher frequency of current smoking, psychosocial stress, and reduced night sleep. Regarding gender differences in the distribution of modifiable RFs, we unequivocally confirm that men with IS have a significantly higher frequency of AH, DM, current smoking, and alcohol consumption, while women are more often affected by overweight, low physical activity, and reduced night sleep;
4. Age and gender differences in the distribution of etiological subtypes of IS according to the TOAST and OCSP classifications have been studied. The data from the comparative analysis support European and global trends, according to which IS caused by atherosclerosis of large arteries and small vessel disease are more common etiological subtypes in middle-aged patients and males, while young patients and females have a higher frequency of IS with an undefined or other defined etiology;
5. Our data confirm that total infarction of the anterior cerebral circulation and a higher mean score on the NIHSS scale at hospital admission are significant predictors of an unfavourable clinical outcome at discharge.

9. PUBLICATIONS ASSOCIATED WITH THE DISSERTATION WORK

Fulltext publications, associated with the dissertation work:

1. **G. Dimitrov**, M. Danovska, J. Simeonova , I. Gencheva, P. Stoev, E. Ovcharova, D. Marinova, Comparative evaluation of risk factors in young and middle-age patients with acute ischemic stroke; February 2020 Journal of IMAB - Annual Proceeding (Scientific Papers) 26(1):2926-2930. **Web of Science**
2. **G. Dimitrov**, M. Danovska, D. Marinova, P. Stoev, J. Simeonova; Gender-related differences in modifiable risk factors and ischemic stroke subtype in young and middle-aged patients—a prospective study; February 2023 Journal of IMAB - Annual Proceeding (Scientific Papers).- **Web of Science**
3. **G. Dimitrov**, M. Danovska, E. Mineva – Dimitrova; A prospective study of age-related differences in modifiable risk factors, stroke subtype, and functional outcome in young and middle-aged patients with first-ever ischemic stroke; Journal of Biomedical and Clinical Research 17(2): 157–166 (2024). **Web of Science.**

Publications in scientific events with posters and published abstracts from forums in Bulgaria related to the topic of the dissertation:

1. **Г. Димитров**, М. Дановска, П. Божинов, П. Стоев, Й. Младенова, И. Генчева; Серумни нива на хомоцистеин като рисков фактор за атеротромботичен исхемичен мозъчен инсулт; Българска неврология, том 20, май, 2019г.;
2. **G. Dimitrov**, M. Danovska, I. Gencheva; Importance of relationship between serum homocysteine level and other vascular risk factors for acute ischemic stroke; J. Biomed. Clin. Res. Volume 12, Number 1, Suppl. 2, 2019;
3. **Г. Димитров**, М. Дановска, Д. Маринова – Трифонова, Е. Овчарова; Сравнителен анализ на рисковите фактори при пациенти в млада и средна възраст с първи исхемичен инсулт, Българска неврология, том 22, октомври, 2021г.;
4. **G. Dimitrov**, M. Danovska, P. Stoev, D. Marinova – Trifonova, E. Mineva – Dimitrova; Modifiable risk factors for ischemic stroke stroke in young and middle-aged patients: a case-control study. Jubilee scientific conference with international participation "50 Years of medical education and science in Pleven", Abstract Book. J. Biomed. Clin. Res, 2024.

Publications in foreign scientific events with posters and published abstracts from foreign forums related to the topic of the dissertation:

1. **G. Dimitrov**, M. Danovska, J. Simeonova and E. Ovcharova; Acute ischemic stroke severity and outcome in young and middle-age patients; International Journal of Stroke, 2020, Vol. 15(1S) 3–752, The Author(s) 2020;
2. **G. Dimitrov**, M. Danovska, J. Simeonova, E. Ovcharova; Clinical outcome of young and middle-aged patients with first-ever ischemic stroke; October 2021 Journal of the Neurological Sciences 429:119955;
3. **G. Dimitrov**, M. Danovska, D. Marinova 1, J. Simeonova ; Gender Related Differences in Lifestyle Risk Factors of Young and Middle – Aged Patients with Acute Ischemic Stroke; 2022 European Journal of Neurology, 29 (Suppl. 1), 838–918;
4. **G. Dimitrov**, M. Danovska, P. Stoev, D. Marinova - Trifonova; Predictors of Unfavorable Functional Outcome in Young and Middle- Aged Patients with First – Ever Ischemic Stroke; ESOC 2023 Abstract Book. European Stroke Journal. 2023;8(2_suppl):3-669.

10. APPENDIX

10.1 Appendix 1: Assessment scales

- **National Institute of Health Stroke Scale (NIHSS).**

NIHSS (National Institute of Health Stroke) скала

Изследван елемент	Наименование /Област	Отговор/Оценка	Резултат
1A	Съзнание (количествени нарушения)	0 – Буден, с живи реакции 1– Сомнолентен 2– Притъпени реакции 3– Кома/нереагиращ	
1B	Въпроси при нарушение на съзнанието	0 – Отговаря правилно и на двата въпроса 1 – Отговаря правилно на един въпрос 2 – Неправилно отговаря и на двата въпроса	
1C	Команди при нарушение на съзнанието	0 – Изпълнява правилно и двете команди 1 – Изпълнява правилно само една команда 2 – Не изпълнява правилно нито една задача	
2	Очни движения/ погледни парези	0 – Нормални очни движения 1 – Частична погледна пареза 2 – Спрегнато отклонение/тотална погледна пареза	
3	Зрителни полета	0 – Без дефекти в зрителните полета 1 – Частична хемианопсия 2 – Пълна хемианопсия 3 – Билатерална хемианопсия (слепота)	
4	Лицеви движения лезия на VII КН	0 – Нормални симетрични движения 1 – Лека лицева пареза 2 – Частична лицева пареза 3 – Пълна едностранна парализа	
5	Двигателна дейност (ръка)	0 – Няма отпускане (пронация)	
	а. Лява	1 – Отпускане преди 10 секунди	
	б. Дясна	2 – Отпускане преди 5 секунди 3 – Няма съпротива срещу гравитацията (пада) 4 – Липсват активни движения	
6	Двигателна дейност (крак)	0 – Няма отпускане (пронация)	
	а. Ляв	1 – Отпускане преди 10 секунди	
	б. Десен	2 – Отпускане преди 5 секунди 3 – Няма съпротива срещу гравитацията (пада) 4 – Липсват активни движения	
7	Атаксия на крайниците	0 – Липса на атаксия 1 – Атаксия в един крайник 2 – Атаксия в два крайника	
8	Сетивност	0 – Нормални сетивни функции 1 – Лека загуба на сетивност (хемихипестезия) 2 – Тежка или тотална загуба на сетивност	
9	Реч	0 – Нормални езикови способности/няма афазия 1 – Лека до умерена афазия 2 – Тежка афазия 3 – Мутизъм или глобална афазия	
10	Артикулация/ дизартрия	0 – нормална артикулация 1 – Лека дизартрия 2 – Тежка дизартрия до анартрия	
11	Изчерпване и невнимание (неглект)	0 – Няма 1 – Лека (загуба на една сензорна модалност) 2 – Тежка (загуба на две и повече сензорни модалности)	
Обща NIHSS оценка:_____(0–42)			

- **Modified Rankin scale**

Точки	Описание
0	Няма симптоми
1	Без значими
2	Незначителни увреждания: невъзможност да извършва всички предишни дейности; но е в състояние да се грижи за себе си без асистент
3	Умерено увреждане: изискващо някаква помощ, но може да се движи без асистент
4	Умерено-тежка инвалидност: не може да ходи без асистент и не може да се грижи за собствените си телесни нужди без асистент
5	Тежка инвалидност: прикован на легло, невъздържден и изискващ постоянна сестринска грижа и внимание
6	Смърт

- **Medical Research Council (MRC) scale**

Степен	Описание
0	Пълна парализа
1	Минимална мускулна контракция
2	Наличие на активно движения само ако се елиминира ефектът на гравитацията
3	Слаба мускулна контракция срещу гравитацията
4	Активно движение срещу гравитация и съпротивление
5	Нормална мускулна сила

10.2 Appendix 2: Questionnaire

Questionnaire for conducting a scientific study on the topic: "Clinical characteristics and assessment of certain risk factors in patients with ischemic cerebral stroke in young and middle-aged adults."

The questionnaire is divided into four sections. The first section aims to identify the risk factors (RF) in patients with ischemic cerebral stroke (ICS). The second section presents the results of laboratory, imaging, and instrumental tests performed. The third section provides information on some characteristics of ICS (etiological subtype, localization, and severity of the stroke). The final, fourth section is related to the treatment provided. The results from the study will be used for scientific purposes.

The full content of the questionnaire used can be found in the "Appendices" section of the dissertation as well as with the author, Dr. Dimitrov.