MEDICAL UNIVERSITY-PLEVEN

FACULTY OF MEDICINE

DEPARTMENT OF NEUROLOGY AND NEUROSURGERY

Dr. Diana Lyubomirova Marinova-Trifonova

EVALUATION OF THE IMPACT OF METABOLIC SYNDROME ON SEVERITY AND CLINICAL OUTCOME IN PATIENTS WITH ACUTE ISCHEMIC STROKE

ABSTRACT

of a dissertation for awarding

of the educational and scientific degree "Doctor"

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Prof. Dr. Maya Penkova Danovska, MD, PhD

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Prof. Dr. Ara Garabed Kaprelian, MD, PhD, MSD

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The scientific jury:

Chairman of the scientific jury:

Assoc. Prof. Dr. Mladen Evtimov Ovcharov, MD, PhD

Members of the scientific jury:

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Prof. Dr. Ara Garabed Kaprelian, MD, PhD, MSD

Assoc. Prof. Dr. Neli Stefanova Petrova, MD, PhD

Assoc. Prof. Dr. Constantin Dimitrov Gospodinov, MD, PhD

Alternate members of the scientific jury:

Prof. Dr. Krasimir Rozenov Genov, MD, PhD, MSD

Assoc. Prof. Dr. Ilia Valkov Valkov, MD, PhD

The materials related to the defense have been published on the website of Medical University - Pleven - www.mu-pleven.bg and are available at the Research Department of the Faculty of Medicine, Medical University - Pleven.

ABBREVIATIONS USED

Abbreviations in Cyrillic:

BP - Blood pressure

AH - Arterial hypertension

AHT - Antihypertensive Therapy

VBVS - Vertebro-basilar vascular system

DBP - Diastolic Blood Pressure

DL - Dyslipidemia

DM - Diabetes Mellitus

CHD - Ischemic heart disease

IVT - Intravenous thrombolysis

ICP - Intracranial pressure

IS - Ischemic stroke

BBB - Blood-brain barrier

CT - Computed tomography

MetS - Metabolic syndrome

CerVD - Cerebrovascular disease

RF - Risk factors

SBP - Systolic blood pressure

WHO - World Health Organization

CVD - Cardiovascular diseases

TIA - Transient ischemic attacks

TT - Thrombolytic therapy

TG - Triglycerides

HVD - Hypertensive vascular disease

Abbreviations in Latin:

ADA - American Diabetes Association

AHA - American Heart Association

ASA - American Stroke Association

BMI - Body mass index

CRP - C-reactive protein

ESO - European Stroke Organization

HDL - High-density lipoprotein

IDF - International Diabetes Federation

LDL - Low-density lipoprotein

mRS - modified Rankin Scale

NCEP - National Cholesterol Education Program

NIHSS - National Institutes of Health Stroke Scale

WHO - World Health Organization

TABLE OF CONTENTS

1. INTRODUCTION

Ischemic stroke is a socially significant disease nowadays that poses numerous daily challenges at both national and global levels. ISs account for up to 88% of all acute cerebrovascular events (Milanov I et al. 2025). According to officially published data from the European Union, every minute one person suffers a stroke, while every six seconds a stroke patient dies somewhere in the world (Milanov I et al. 2025). These alarming statistics focus the attention of multidisciplinary teams and clinicians on the early identification of risk factors, timely primary prevention, rapid diagnosis, and the optimal therapeutic approach for all patients with acute cerebrovascular disorders. Stroke survivors often represent a significant social burden, rather than a newly emerging problem for a particular family or relatives. In the long term, their recovery depends not only on timely treatment during the acute stage but also on subsequent care and rehabilitation, which may continue for months or even years.

Data from the Global Burden of Disease study identify stroke as the second leading cause of death worldwide (Wafa HA et al. 2020, Feigin VL et al. 2023, Pu L et al. 2023, Li XY et al. 2024, Chen X et al. 2025). As the third most common cause of disability, it affects approximately 1.1 million European residents per year, with estimated economic costs reaching €45 billion in 2017. (Wafa HA et al. 2020). In 2023, the Global Burden of Disease study reports IS as the most prevalent subtype, accounting for 63.9% of all acute cerebrovascular events (Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators, 2025). Forecasts suggest that by 2050 the number of stroke survivors worldwide will reach 200 millions, with the majority being elderly individuals (Béjot Y., 2020). The aging of the European population also predicts unfavorable trends on the continent: the population aged over 60 years is expected to increase by 23% at 2030, while the total number of strokes in the European Union is projected to rise by 34% during the period 2015-2035 (Norrving B. et al., 2018). A practically significant objective of the European Stroke Action Plan (SAP-E) is the prevention of every tenth stroke by using effective primary prevention strategies (Norrving B. et al., 2018; Milanov I. et al., 2025).

Current statistical data for Bulgaria reveal unfavorable demographic trends, including high mortality, low life expectancy, and intensive outward migration of young people, summarized by the concept of "demographic crisis". At the end of 2024 the registered Bulgarian population is 6 437 360, of whom 51.9% are women, predominantly of older age, and 48.1% are men mainly in the age group below 55 years. Population aging has been documented through an increasing proportion of individuals over 65 years of age. Bulgaria also

records high crude mortality rate in the European Union - 15.6‰ in 2024 compared with the EU average of 10.8‰ (Annual Report on the Health Status of Citizens in the Republic of Bulgaria, 2024).

IS is a medical emergency and sometimes a life-threatening condition. It represents an acute disturbance of cerebral blood circulation, clinically manifested by persistent neurological deficits as a result of irreversible morphological changes in the affected brain parenchyma. Leading national experts in the therapy of cerebrovascular diseases in Bulgaria report that 80% of strokes are preventable and treatable (Milanov I. et al., 2025). The implementation of strategically important measures, including early identification of risk factors (RFs), treatment of modifiable RFs in at-risk individuals, and effective primary prevention, could positively influence stroke severity and outcome. Priority areas in primary prevention for the period 2022-2030 include personalized risk prediction and the development of accessible programs and national strategies for the management of RFs (Norrving B et al. 2018). Contemporary therapeutic concepts in the acute stage of IS include priority interventions such as intravenous thrombolysis and mechanical thrombectomy.

All these figures represent real patients who expect and rely on our knowledges and professional skills. This has motivated us to investigate in detail one of the most prevalent risk factors - Metabolic Syndrome (MetS) - among Bulgarian IS patients, to analyze and systematize the collected data, and to summarize its impact on stroke severity and outcome. The present dissertation reflects on the clinical experience and professional expertise of generations of neurologists who have dedicated their careers to provide comprehensive care and intensive treatment to acute IS patients admitted to Neurology Clinic of UMHAT “Dr. Georgi Stranski” - Pleven.

2. AIM AND OBJECTIVES

2.1 AIM

The aim of the present dissertation is to investigate the impact of MetS and its individual components on stroke severity and short-term clinical outcome in patients with acute IS by analyzing the prevalence and distribution of the individual MetS components, as well as the clinical and laboratory characteristics, and comorbidities of the studied groups.

2.2 OBJECTIVES

2.2.1 To determine the prevalence and distribution of the individual components of MetS in patients with acute IS.

2.2.2 To determine the prevalence and distribution of some modifiable RFs in IS patients without MetS.

2.2.3 To evaluate the impact of MetS and its individual components on the relative risk of acute IS.

2.2.4 To analyze clinical-laboratory characteristics and comorbidities in IS patients with MetS.

2.2.5 To perform a comparative analysis of the severity of IS in the two studied groups and to evaluate the impact of MetS and its individual components on stroke severity.

2.2.6 To assess the clinical outcome of IS patients with and without MetS by comparing the frequency of unfavorable functional outcome and mortality, and to evaluate the impact of MetS and its individual components on stroke outcome.

3. CLINICAL POPULATION AND METHODS

3.1 CLINICAL POPULATION

A prospective study was conducted involving patients with acute IS, admitted for emergency treatment to Neurology Clinic of UMHAT "Dr. Georgi Stranski" - Pleven, during the period January 2020 - December 2024. A total of 3 510 patients with acute cerebrovascular events were admitted in this period. 2 676 patients of them (76.24%) had acute non-cardioembolic IS, while 567 patients (16.15%) had cardioembolic IS.

The object of observation in this dissertation are patients with acute IS, divided into two groups: IS patients with MetS (group 1) and IS patients without MetS (group 2). Group 1 includes 120 patients who meet the study inclusion criteria and the diagnostic criteria for MetS according to NCEP ATP III definition. Group 2 is represented by 104 patients with acute IS and no concomitant MetS. Patients from the studied groups are comparable by sex and age. The present study includes 224 controls - participants without IS, corresponding to the total number of the investigated cases. The controls without IS are also presented in two groups - group 3, including a total of 92 participants - controls with MetS and group 4 - 132 controls without MetS. All patients meet predefined inclusion criteria. None of the patients meet any of the exclusion criteria of the study.

3.1.1 Inclusion criteria for participation in the study:

Inclusion criteria for IS patients with MetS (group 1):

- age over 18 years;
- presence of an acute-onset persistent neurological deficit lasting more than 24 hours from the onset of IS clinical symptoms;
- presence of combinations of modifiable and/or non-modifiable RFs for IS;
- clinical and laboratory findings for MetS in patients with IS;
- anthropometric measurements supporting the definition of MetS;
- neuroimaging evidence of hypodense lesions of lacunar or larger size;
- written informed consent provided by the patient or his/her relative for voluntary participation in the study.

Inclusion criteria for non-MetS IS patients (group 2):

- age over 18 years;
- presence of an acute-onset persistent neurological deficit lasting more than 24 hours from the onset of IS clinical symptoms;
- presence of combinations of modifiable and/or non-modifiable risk factors for AIS, excluding MetS;
- neuroimaging evidence of hypodense lesions of lacunar or larger size;
- written informed consent provided by the patient or his/her relative for voluntary participation in the study.

Inclusion criteria for controls without IS but with MetS (group 3):

- age over 18 years;
- presence of combinations of modifiable and/or non-modifiable RFs;
- clinical and laboratory findings for MetS;
- anthropometric measurements supporting the definition of MetS;
- written informed consent for voluntary participation in the study.

Including criteria for non-IS and non-MetS controls (group 4):

- age over 18 years old;
- presence of various combinations of modifiable and/or non-modifiable RFs for IS, excluding MetS;
- written informed consent for voluntary participation in the study.

3.1.2 Exclusion criteria for participation in the study:

Exclusion criteria for patients with IS (group 1 and group 2):

- age below 18 years;
- transient neurological deficit within 24 hours of the onset of clinical symptoms of IS;
- residual neurological deficit caused by another neurological disorder or a previous traumatic injury to the central nervous system;
- medical history and clinical evidence of a previous cerebrovascular event;
- medical history and clinical evidence of concomitant cardiovascular pathology - including cardiac rhythm disturbances such as atrial fibrillation/flutter with absolute arrhythmia, left ventricular thrombus, mechanical heart valve, or any other potential cardioembolic source of stroke, as well as other conditions requiring anticoagulant therapy;

- neuroimaging findings explaining the neurological symptoms by other pathological processes, such as intracranial hemorrhage, traumatic hematomas, cerebral venous thrombosis, tumors, or other space-occupying lesions;
- refusal to participate voluntarily in the study.

Exclusion criteria for the non-IS control groups (group 3 and group 4):

- age below 18 years;
- medical history and clinical evidence of a previous cerebrovascular event;
- medical history and clinical evidence of concomitant cardiovascular pathology, including cardiac rhythm disturbances such as atrial fibrillation/flutter with absolute arrhythmia, left ventricular thrombus, mechanical heart valve, or any other potential cardioembolic source of stroke, as well as other conditions requiring anticoagulant therapy;
- refusal to participate voluntarily in the study.

3.1.3 Demographic characteristics of the studied patients

Demographic characteristics of IS patients. The studied acute IS patients (cases) are divided into two groups - group 1 - IS patients with MetS and group 2 - non-MetS IS patients. The group of IS patients with MetS (group 1) includes a total of 120 patients, of whom 56 (47%) are men and 64 (53%) are women. The average age of patients in group 1 is 68.3±10.446 years. In the group of IS patients without MetS (group 2), a total of 104 patients are represented, 53 (51%) of them are men and 51 (49%) are women. The average age of patients in group 2 is 70.1±11.112 years.

Demographic characteristics of non-IS controls. The controls without IS are also presented in two groups - group 3 - controls with MetS and group 4 - controls without MetS. The group of controls with MetS (group 3) includes a total of 92 patients, of whom 44 (47.83%) are men and 48 (52.17%) are women. The average age of controls in group 3 is 69.05±9.782 years. The group of controls without MetS (group 4) consists of 132 patients, of whom 65 (49.24%) are men and 67 (50.76%) are women. The average age of the controls in group 4 is 68.52±11.108 years.

Table 1. *Prevalence of MetS in the studied groups with acute IS and control groups*

Study participants	**Group 1 Cases (n=120)**		**Group 2 Cases (n=104)**		**Group 3 Controls (n=92)**		**Group 4 Controls (n=132)**	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
with MetS	120	**53.6**	N/A	N/A	92	**41.1**	N/A	N/A
without MetS	N/A	N/A	104	46.4	N/A	N/A	132	58.9

Table 1 presents data on the prevalence of MetS among patients with acute IS and in control groups. Group 1 includes IS patients with MetS, with the prevalence of MetS calculated at 53.6% of all investigated IS patients. Group 3 includes controls with MetS, representing a prevalence of 41.1% in the overall control population.

Table 2. *Demographic characteristics of all studied cases/controls*

Characteristics	**Category**	**Frequency of cases (group 1) (n=120)**		**Frequency of cases (group 2) (n=104)**		**Frequency of controls (group 3) (n=92)**		**Frequency of controls (group 4) (n=132)**	
		(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Age groups (decades)	40-49 years	6	5	4	3.85	2	2.17	10	7.58
	50-59 years	20	16.67	13	12.5	13	14.13	21	15.91
	60-69 years	29	24.16	30	28.85	34	36.96	25	18.94
	70-79 years	51	42.50	34	32.69	29	31.52	56	42.42
	80-89 years	11	9.17	21	20.19	14	15.22	19	14.39
	≥90 years	3	2.5	2	1.92	N/A	N/A	1	0.76
Mean age		68.3 ± 10.446		70.1 ± 11.112		69.05 ± 9.782		68.52 ± 11.108	
Gender	male	56	46.70	53	51	44	47.83	65	49.24
	female	64	53.30	51	49	48	52.17	67	50.76
Residence	urban	73	60.83	67	64.42	56	60.87	95	71.97
	rural	47	39.17	37	35.58	36	39.13	37	28.03

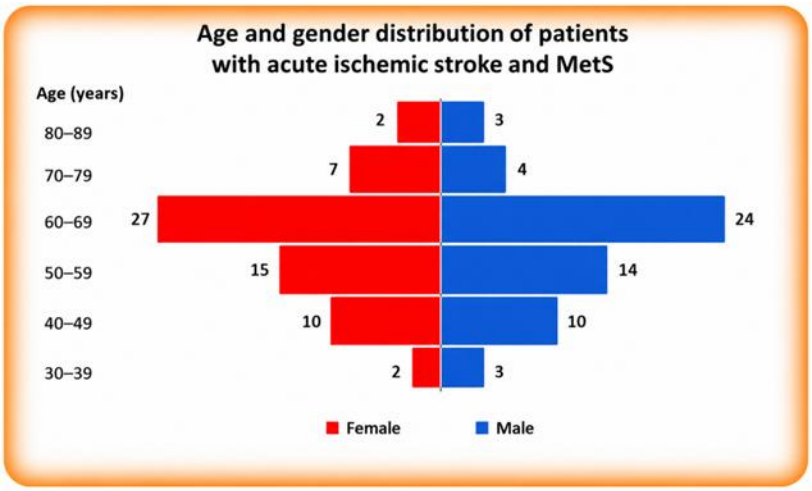

Fig. 2. *Age and gender distribution of IS patients with MetS (group 1)*

Fig. 2 presents the age and gender distribution by decades in group 1. The present study demonstrates that the highest frequency of IS in group 1 is observed in the 70-79-year age group in both sexes. Female patients predominate during the subsequent two age decades. In the younger age groups (50-59 and 60-69 years), a similar number of IS cases with MetS are observed in both sexes. No male patients older than 90 years are registered in group 1.

3.1.4 Treatment in the acute stage of IS - intravenous thrombolysis (IVT)

Among 120 patients in the IS with MetS group (group 1), specific treatment with IVT is administered to 10 patients (8%), while the remaining 110 patients (92%) received non-specific therapy. In group 2 among the 104 IS patients without MetS, thrombolytic therapy is administered to 3 patients (3%), whereas the rest of them - 101 patients (97%) received non-specific treatment (**Fig. 5**).

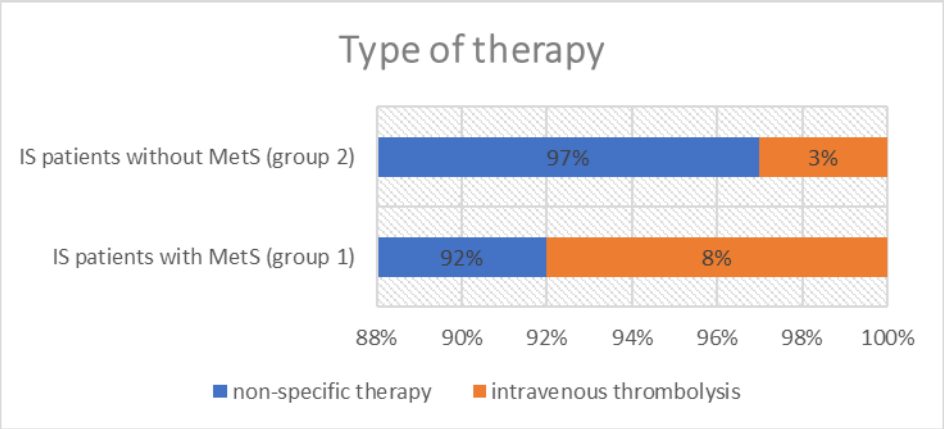

Fig. 5. *Comparative analysis of the percentage distribution of patients in group 1 and group 2 according to the type of therapy administered in the acute stage of IS*

Table 3 presents a comparative analysis of the type therapy-related differences in group 1 and group 2 based on the administered treatment in the acute stage of IS. The data show that IVT is performed in a total of 10 (8%) IS patients with MetS. According to sex distribution, these patients are equally represented, with five male and five female cases. Concerning the distribution in percents, the frequency of thrombolytic therapy in group 1 is similar in both genders - 8.9% in males and 7.8% in females. Data for group 2 indicate that IVT is performed in 3 males (3%). In group 2, no IVT is registered in females.

The frequency of IVT among all studied IS patients is 5.8%.

***Table 3**. Gender-related distribution of patients in group 1 and group 2 according to the type of performed therapy during the acute stage of IS*

Therapy in the acute stage of IS	**IS patients with MetS (Group 1) n = 120**		**IS patients without MetS (Group 2) n = 104**	
	Males n (%)	**Females n (%)**	**Males n (%)**	**Females n (%)**
Specific	5 (8.9%)	5 (7.8%)	3 (5.7%)	0 (0%)
Non-specific	51 (91.1%)	59 (92.2%)	50 (94.3%)	51 (100%)

3.2 METHODS

3.2.1 Clinical and laboratory methods:

- A detailed medical history from the patient or relatives, including anamnesis vitae and anamnesis morbi, onset and progression of neurological symptoms, discussion of preceding complaints and transient neurological symptoms.
- A disscussion of past and concomitant diseases - with particular attention to the comorbidities as arterial hypertension, diabetes mellitus, dyslipidemia (hypercholesterolemia, hypertriglyceridemia or mixed), gout, obesity.
- A registration of previous treatment - including medication classes, dosage regimens, duration of therapy, therapeutic route, and dietary regimens. Medications of the following groups are considered with particular attention: antihypertensive, antidiabetic, statins and fibrates, antiplatelets.
- An assessment of concomitant modifiable and non-modifiable RFs, including their duration and lifestyle-related behavioral changes.

- Use of additional sources of information regarding the patient's health status, including available medical documentation (hospital discharge summaries, outpatient records), information from hospital databases, and records provided by the general practitioner. Information concerning harmful lifestyle habits such as tobacco smoking, alcohol consumption, and illicit substance use was also collected.
- Recording of the general physical examination and systemic clinical assessment.
- Neurological examination performed both on admission and at discharge, including assessment using the NIHSS and Glasgow-Liège Coma Scale (GLCS).
- Laboratory investigations performed according to the clinical pathway and additional physician requests, including complete blood count, biochemical and coagulation parameters (INR, prothrombin time, and when indicated, bleeding and clotting times); blood glucose, follow-up glucose measurements, and glycated hemoglobin (HbA1c) in patients with previously diagnosed or newly diagnosed diabetes mellitus; serial monitoring of carbohydrate metabolism; lipid profile assessment, including total cholesterol, HDL-cholesterol, LDL-cholesterol, and serum triglycerides; serum electrolytes and renal function parameters; fibrinogen and other inflammatory markers when clinically indicated. The results and their deviations are analyzed according to the reference ranges of each laboratory parameter.

3.2.2 Neuroimaging and other instrumental methods:

- Electrocardiography - a standard 12-lead ECG recording is performed in every patient on admission following a mandatory 5-minute resting period before examination.
- Computed tomography of the brain - including detailed assessment of the size and localization of hypodense lesions. Neuroimaging is performed within the first 24 hours of diagnostic evaluation for each patient. In patients undergoing IVT, a control neuroimaging is performed 24 hours after the specific therapy.
- Anthropometric measurements - body weight, height, and waist circumference are recorded. Body Mass Index (BMI) was calculated according to the formula: BMI = Weight (kg)/Height (m^2) via an electronic calculator. Based on BMI, patients are divided into the following groups: normal weight (BMI=18.5-24.9 kg/m^2), overweight (BMI=25.0-29.9 kg/m^2), obesity (BMI≥30 kg/m^2).

3.2.3 Evaluation scales:

- NIHSS (National Institute of Health Stroke Scale) - a standardized scale used routinely in clinical practice to assess the severity of neurological deficits in acute IS patients. The scale comprises 13 evaluated items, with a total score ranging from 0 to 42 points. IS patients are evaluated twice on admission and at discharge. Based on NIHSS scores, mild IS (NIHSS 1-4 sc.), moderate IS (NIHSS 5-15 sc.) and severe IS (NIHSS ≥16 sc.) are distinguished.
- mRS (Modified Rankin Scale) - used to evaluate functional outcome after acute IS and is widely applied for both short-term and long-term outcome assessment. The scale reflects the degree of disability and dependence in IS patients. For the purposes of the present study, patients were classified according to functional outcome as follows: mRS (0-2) - with a favorable outcome, mRS (3-5) - with an unfavorable outcome and mRS (6) - with a fatal outcome.
- GLCS (Glasgow-Liege Coma Scale) - used to assess quantitative disturbances of consciousness and to monitor changes in the level of consciousness, verbal and motor responses, and brainstem reflexes during clinical follow-up. The minimum result is 4 scores, whereas the maximum possible scores are 20. Patients are evaluated twice: the initial assessment is performed on the day of admission, and the final assessment is conducted at discharge.

3.2.4 Statistical methods:

Statistical analysis of the empirical data is performed using IBM SPSS Statistics software (Version 26.0). The initial analysis includes testing the normality of quantitative variables using the Kolmogorov–Smirnov test. Variables with normal distribution are presented as mean ± standard deviation (Mean±SD), whereas non-normally distributed variables are described using the median and interquartile range (Me, IQR). Categorical variables are summarized using frequency analysis and presented as absolute and relative shares (n, %). To evaluate statistical significance and test the study hypotheses, appropriate parametric and non-parametric methods are applied according to data type and distribution characteristics. For normally distributed continuous variables, comparisons between two independent groups are performed using Student's t-test, whereas one-way analysis of variance (ANOVA) is applied for comparisons involving three or more groups. When the assumption of normality is violated, the non-parametric Mann-Whitney U test and Kruskal-Wallis test are used. Associations between categorical variables are analyzed using the chi-square (χ^2) test.

For all statistical analyses, a significance level of $p<0.05$ is considered statistically significant. Microsoft Excel 2019 is used for graphical presentation of the results. Data visualization include bar and pie charts for categorical variables and Box Plots for quantitative variables.

Comparison of the frequency of health events. The present study assesses the strength of the association between MetS and its individual components and the relative risk of developing IS. Relative risk (RR) quantitatively measures the strength of the association between exposure and disease and indicates how many times more likely exposed individuals are to develop IS compared with non-exposed individuals in the control group (Kamburova M. et al., 2024). In cohort studies, RR values greater than 1 indicate a positive association or increased risk for exposed individuals to develop IS, while progressively higher values above 1 suggest a stronger likelihood of a causal relationship (Kamburova M. et al., 2024). The assessment of relative risk was presented using Odds Ratios (ORs) and Confidence Intervals (CIs), calculated with the MedCalc online statistical calculator [Internet].

Correlation analyses are performed to investigate relationships between the individual components of MetS and both stroke severity and clinical outcome in acute IS. They were conducted using Microsoft Excel and visualized through scatter plots.

Regression analyses are performed to evaluate the relationships between the individual components of MetS as independent variables and IS severity and clinical outcome as dependent variables.

RESULTS

4.1 MetS and modifiable RFs in patients with acute IS

4.1.1 MetS, components of MetS and their prevalence in IS patients with MetS (group 1)

Table 6. *Prevalence of MetS components in IS patients with MetS (group 1)*

Components of MetS (Group 1)	**IS patients with MetS**	
	n=120	**%**
Elevated BP >130/85 mmHg or antihypertensive therapy	119	99.2
Fasting blood glucose >5.6 mmol/L or diagnosed diabetes mellitus type II	115	95.8
Overweight and obesity (BMI≥25 kg/m²)	114	95
Elevated TG> 1.7mmol/L or therapy against elevated TG	72	60
Lower HDL-cholesterol (<1.03mmol/L in males and < 1.3mmol/L in females)	48	40

Table 6 presents the prevalence of the individual components of MetS among IS patients with MetS. The results indicate that the most prevalent MetS components among the studied patients are elevated BP (99.2%) and DM (95.8%). According to anthropometric measurements and calculated BMI, 114 patients (95%) are classified as overweight or obese (BMI≥25 kg/m²). Lipid profile abnormalities include hypertriglyceridemia in 72 patients (60%) and lower HDL cholesterol levels in 48 patients (40%).

4.1.2 Modifiable RFs for IS patients and their prevalence in IS patients without MetS (group 2)

Table 7. *Prevalence of modifiable RFs in IS patients without MetS (group 2)*

Modifable RFs (Group 2)	**IS patients without MetS**	
	n=104	**%**
Arterial hypertension	82	78.8
Overweight and obesity (BMI≥25 kg/m²)	81	77.9
Lower HDL-cholesterol (<1.03mmol/L in males and <1.3mmol/L in females)	33	31.7
Elevated TG> 1.7 mmol/L	20	19.2
Diabetes mellitus	4	3.8

Table 7 presents data on the prevalence of the most common modifiable RFs in group 2. Among IS patients without MetS, arterial hypertension shows the highest prevalence (78.8%). Lipid profile analysis demonstrates reduced HDL cholesterol in 33 patients (31.7%) and hypertriglyceridemia in 20 patients (19.2%). According to anthropometric measurements and calculated BMI, 81 patients (77.9%) are diagnosed as overweight or obese (BMI≥25 kg/m²). The prevalence of DM is substantially lower, affecting only 4 patients (3.8%).

4.1.3 Comparative analysis of the prevalence of some pre-stroke modifiable RFs

Table 8. *Prevalence of some pre-stroke modifiable RFs in group 1 and group 2*

Pre-stroke modifiable RFs	IS patients with MetS n=120 (%)	IS patients without MetS n=104 (%)	P value
Arterial hypertension	119 (99.2)	82 (78.8)	0.009
Diabetes mellitus	115 (95.8)	4 (3.8)	0.000
Dyslipidemia	80 (66.7)	10 (9.6)	0.000
CHD	37 (30.8)	9 (8.7)	0.000
Smoking	61 (50.8)	62 (59.6)	0.928

Table 8 presents the prevalence of some pre-stroke modifiable RFs in the studied groups. Our findings demonstrate a significantly higher prevalence of RFs in group 1, particularly AH (99.2%), DM (95.8%), and dyslipidemia (66.7%). In group 2, arterial hypertension has the highest prevalence (78.8%), followed by active smoking (59.6%) and dyslipidemia (9.6%). Statistical analysis using Pearson's chi-square test shows significant differences between the studied groups regarding AH ($\chi^2 = 6.811$, df = 1, $p = 0.009$), DM ($\chi^2 = 103.538$, df = 1, $p < 0.001$), dyslipidemia ($\chi^2 = 54.444$, df = 1, $p < 0.001$), and CHD ($\chi^2 = 17.043$, df = 1, $p < 0.001$). No statistically significant difference is observed regarding active smoking as a behavioral risk factor ($\chi^2 = 0.008$, df = 1, $p = 0.928$). Notably, the proportion of smokers is high in both groups, ranging from 50.8% to 59.6%.

4.1.4 Comparative analysis of the prevalence and number of some modifiable RFs in all studied groups. Assessment of the relative risk for IS.

Table 9. *Prevalence of some modifiable RFs in all studied groups*

Prevalence of some modifiable RFs in the studied groups								
RF	**Cases IS and MetS (group 1) (n=120)**		**Cases IS without MetS (group 2) (n=104)**		**Controls MetS without IS (group 3) (n=92)**		**Controls without MetS and IS (group 4) (n=132)**	
	n	(%)	n	(%)	n	(%)	n	(%)
Arterial hypertension	119	99.2	82	78.8	84	91.3	67	50.7
Diabetes mellitus	115	95.8	4	3.8	43	52.4	9	6.8
Obesity	114	95	81	77.9	87	94.6	66	50
Hypertrigliceridemia	72	60	20	19.2	33	35.9	6	4.5
Lower HDL-cholesterol	48	40	33	31.7	25	30.5	15	11.4
MetS	120	100	N/A	N/A	92	100	N/A	N/A

***Table 10**. Evaluation of the impact of MetS and its individual components on the relative risk for IS*

MetS	Patients with IS n = 224 (%)	Controls without IS n = 224 (%)	Odds Ratio (OR)	95% Confidence Intervals (Cl)	P value
Metabolic syndrome	120 (53.6)	92 (41.1)	**1.656**	1.139-2.406	**0.008**
Components of MetS					
Arterial hypertension	201 (89.7)	151 (67.4)	**4.225**	2.527-7.064	< **0.001**
Diabetes mellitus	119 (53.1)	52 (23.2)	**3.749**	2.497-5.628	< **0.001**
Hypertriglyceridemia	92 (41.1)	39 (17.4)	**3.306**	2.138-5.113	< **0.001**
Overweight and obesity (BMI ≥25 kg/m²)	195 (87)	153 (68.3)	**3.120**	1.929-5.048	< **0.001**
Lower HDL-cholesterol	81 (36.2)	40 (17.9)	**2.606**	1.683-4.035	< **0.001**

The evaluation of the impact of MetS and its individual components on the relative risk for IS shows that AH is associated with the highest statistically significant relative risk of IS (OR: 4.225; 95% CI: 2.527-7.064; p<0.001). Statistically significant relative risks (p<0.001) are also observed for DM (OR: 3.749; 95% CI: 2.497-5.628), hypertriglyceridemia (OR: 3.306; 95% CI: 2.138-5.113), overweight/obesity (OR: 3.120; 95% CI: 1.929-5.048), and lower HDL-cholesterol (OR: 2.606; 95% CI: 1.683-4.035).

These findings demonstrate that MetS is associated with a 1.6-fold increased relative risk of IS (**Table 10**).

***Table 11.** Evaluation of the relative risk for IS in MetS groups (group 1 and group 3)*

Components of MetS	IS patients with MetS (group 1) n = 120 (%)	Controls with MetS (group 3) n = 92 (%)	Odds Ratio	95% Confidence Intervals (Cl)	P value
Arterial hypertension	119 (99.2)	84 (91.3)	**11.333**	1.391-92.326	**0.023**
Diabetes mellitus	115 (95.8)	43 (46.7)	**26.209**	9.791-70.157	< **0.001**
Hipertrigliceridemia	72 (60.0)	33 (35.9)	**2.682**	1.530-4.701	< **0.001**
Overweight and obesity (BMI≥25 kg/m²)	114 (95.0)	87 (94.6)	1.092	0.323-3.696	0.888
Lower HDL-cholesterol	48 (40.0)	25 (27.2)	1.787	0.994-3.213	0.053

A comparative assessment of the relative risk of IS associated with individual MetS components is performed between IS patients with MetS (group 1) and MetS controls without IS (group 3) (**Table 11**). Analysis of the presented data demonstrates that individual MetS components are associated with a higher risk of IS within the metabolic syndrome groups compared to the MetS controls without IS. Our study confirms that DM shows the strongest statistically significant association with IS risk (OR: 26.209; 95% CI: 9.791-70.157; p<0.001). Statistically significant associations are also observed for other components of MetS - AH (OR: 11.333; 95% CI: 1.391-92.326; p=0.023) and hypertriglyceridemia (OR: 2.682; 95% CI: 1.530-4.701; p<0.001). No statistically significant differences are found regarding the increased stroke risk associated with overweight/obesity (OR: 1.092; 95% CI: 0.323-3.696; p=0.888) or lower HDL-cholesterol (OR: 1.787; 95% CI: 0.994-3.213; p=0.053).

Table 12. *Evaluation of the relative risk for IS in the non-MetS groups (group 2 and group 4)*

Modifiable RFs	**IS patients without MetS (group 2) n = 104 (%)**	**Controls without MetS (group 4) n = 132 (%)**	**Odds Ratio**	**95% Confidence Intervals (Cl)**	**P value**
Arterial hypertension	82 (78.8)	67 (50.8)	**3.616**	2.022-6.467	< **0.001**
Diabetes mellitus	4 (3.8)	9 (6.8)	0.547	0.164-1.828	0.327
Hypertriglyceridemia	20 (19.2)	6 (4.5)	**5.000**	1.928-12.970	< **0.001**
Overweight and obesity (BMI≥25 kg/m²)	81 (77.9)	66 (50.0)	**3.522**	1.981-6.260	< **0.001**
Low HDL-cholesterol	33 (31.7)	15 (11.4)	**3.625**	1.841-7.141	< **0.001**

We also analyze several modifiable risk factors in the non-MetS groups (group 2 and group 4). Our findings confirm that hypertriglyceridemia is associated with the highest statistically significant relative risk of IS (OR: 5.000, 95% CI: 1.928-12.970, p<0.001). Statistically significant relative risks (p<0.001) are also observed for lower HDL-cholesterol - (OR: 3.625, 95% CI: 1.841-7.141), AH (OR: 3.616, 95% CI: 2.022-6.467), and obesity (OR: 3.522, 95% CI: 1.981-6.260). Only DM (OR: 0.547, 95% CI: 0.164-1.828, p=0.327) does not show a statistically significant difference between the two non-MetS groups (**Table 12**).

Table 13. *Evaluation of the relative risk for IS according to the number of MetS components in the studied case and control groups*

Mets Combinations	IS patients n=224 (%)	Controls without IS n=224 (%)	Odds Ratio	95% Confidence intervals (CI)	P value
3 components of MetS	51 (22.8)	52 (23.2)	0.975	0.628-1.514	0.911
4 components of MetS	45 (20.1)	21 (9.4)	**2.430**	1.394-4.236	**0.002**
5 components of MetS	20 (8.9)	6 (2.7)	**3.562**	1.402-9.047	**0.008**

The results presented in **Table 13** demonstrate the impact of different combinations of MetS components on the relative risk of acute IS. The data indicate that the combination of three MetS components does not increase the relative risk of IS (OR: 0.975, 95% CI: 0.628-1.514, p=0.911). In contrast, the combination of four MetS components significantly increases the relative risk of IS (OR: 2.430, 95% CI: 1.394-4.236, p=0.002). The presence of all five MetS components also significantly affects stroke risk, being associated with a 3.6-fold increased risk of acute IS (OR: 3.562, 95% CI: 1.402-9.047, p=0.008).

4.2 Clinical and laboratory results

4.2.1 Elevated blood pressure - an analysis of data and a comparative evaluation of the results

Table 14. *Distribution of the studied patients in group 1 and group 2 according to SBP and DBP values*

Blood pressure	IS patients with MetS (group 1) n = 120 (%)	IS patients without MetS (group 2) n = 104 (%)
SBP		
≤ 130 mmHg	38 (31.7)	42 (40.4)
> 130 mmHg	82 (68.3)	62 (59.6)
DBP		
≤ 85 mmHg	78 (65.0)	67 (64.4)
> 85 mmHg	42 (35.0)	37 (35.6)

Table 14 presents the percentage distribution of IS patients according to BP values recorded on admission. Based on one of the diagnostic criteria for MetS - elevated BP > 130/85 mmHg the enrolled patients are classified according to the measured values of SBP and DBP. In group 1, SBP>130 mmHg is recorded in 82 patients (68.3%), while in group 2 it is observed in 62 patients (59.6%). DBP>85 mmHg is documented in 42 IS patients (35.0%) with MetS and in 37 IS patients (35.6%) without MetS.

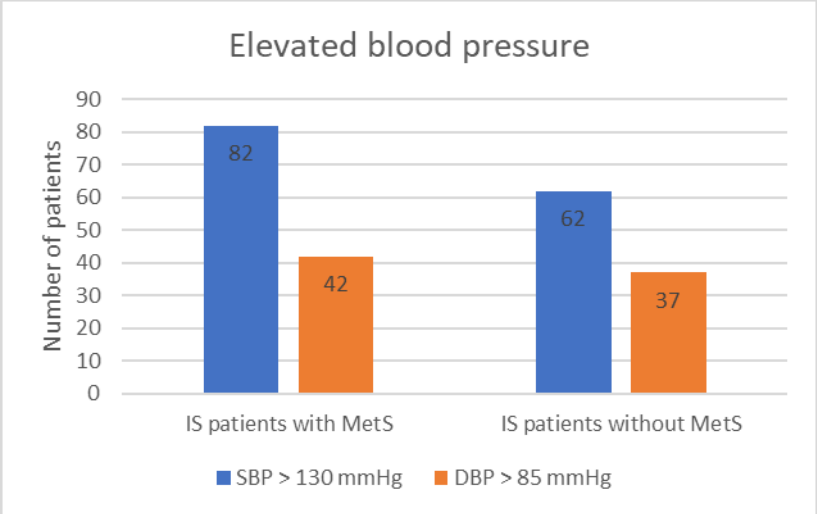

Fig. 10. *Comparative assessment of the elevated SBP and DBP in the studied patients from group 1 and group 2*

The mean SBP in group 1 is 142.6±22.508 mmHg, which is higher than the mean SBP in group 2 (138.6±17.456 mmHg); however, the difference is not statistically significant (t = –1.491, df = 222, p = 0.137). The mean DBP in group 1 is 83.4±11.986 mmHg compared with 81.8±9.293 mmHg in group 2. The difference between the mean DBP values is also not statistically significant (t = –1.136, df = 222, p = 0.257).

4.2.2 Hyperglycemia - an analysis of data and a comparative evaluation of the results

Table 15. *Distribution of the studied patients in group 1 and group 2 according to hyperglycemia on admission*

Hyperglycemia on admission	**IS patients with MetS (group 1) n = 120 (%)**	**IS patients without MetS (group 2) n = 104 (%)**
< 5.6 mmol/L	10 (8.3)	79 (76)
≥ 5.6 mmol/L	110 (91.7)	25 (24)

Table 15 presents the distribution of patients in the studied groups according to the presence of hyperglycemia on admission. In group 1, hyperglycemia on admission ≥ 5.6 mmol/L is recorded in 110 patients (91.7%), whereas in group 2 it is observed in 25 patients (24.0%). A comparative evaluation of admission hyperglycemia is illustrated in **Figure 12**. Statistical analysis of laboratory results shows that median glucose levels in the IS group with MetS are 9.4 mmol/L (IQR: 7.4–12.5), compared with 5.7 mmol/L (IQR: 5.1–6.2) in the IS group without MetS. A statistically significant difference is found between both groups (U = 1113.000, z = –10.599, p < 0.001).

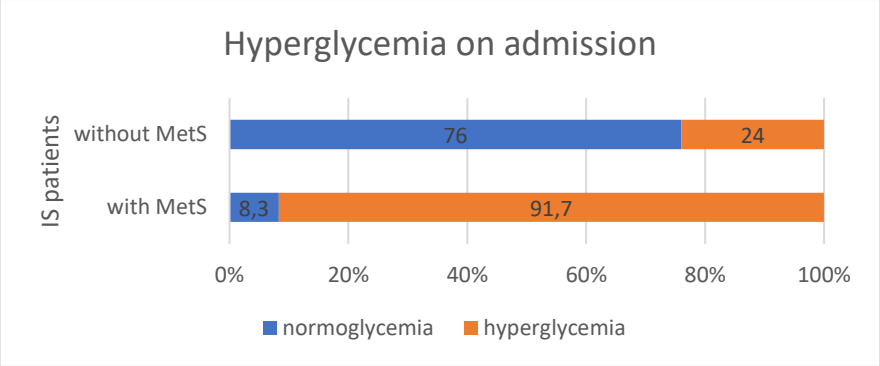

Fig. 12. *Comparative assessment of hyperglycemia on admission in patients from group 1 and group 2*

4.2.3 Dyslipidemia - an analysis of data and a comparative evaluation of the results

Table 16. *Distribution of the studied patients in group 1 and group 2 according to the lipid profile*

Lipid profile	**IS patients with MetS (group 1) n = 120 (%)**	**IS patients without MetS (group 2) n = 104 (%)**
Total cholesterol		
<5.2 mmol/L	61 (50.8)	62 (59.6)
≥5.2 mmol/L	59 (49.2)	42 (40.4)
HDL - cholesterol		
≥1.03 mmol/L in men and ≥1.3 mmol/L in women	69 (57.5)	70 (32.7)
<1.03 mmol/L in men and < 1.3 mmol/L in women	**51 (42.5)**	**34 (32.7)**
LDL - cholesterol		
<3.3 mmol/L	102 (85)	95 (91.3)
≥3.3 mmol/L	18 (15)	9 (8.7)
Triglycerides		
≤ 1.7 mmol/L	45 (37.5)	84 (80.8)
> 1.7 mmol/L	**75 (62.5)**	**20 (19.2)**

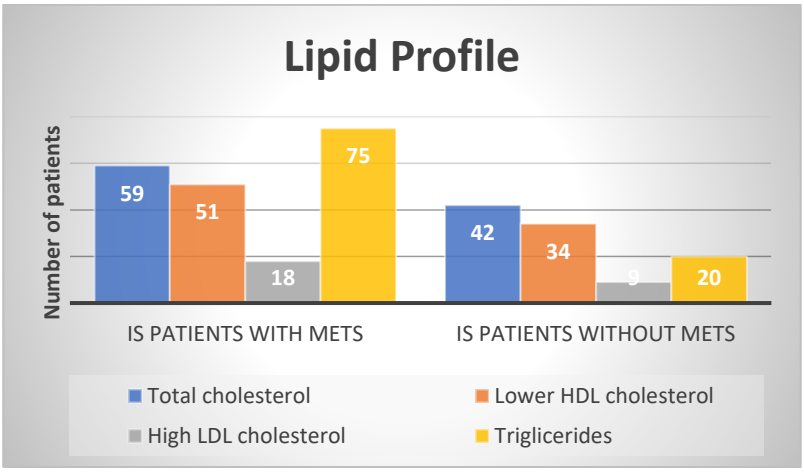

Fig. 13. *Comparative analysis of the lipid profile in patients from group 1 and group 2.*

The lipid profile of the investigated patients is presented in **Table 16** and **Fig. 13**. In group 1, hypertriglyceridemia is identified in 75 patients (62.5%), whereas elevated triglyceride levels are measured in 20 patients (19.2%) in group 2. Comparison of mean triglyceride levels reveals a statistically significant difference between the two groups ($U = 3124.000$, $z = –6.442$, $p < 0.001$). The analysis of LDL cholesterol levels shows elevated LDL cholesterol in 18 patients (15.0%) from group 1 and in 9 patients (8.7%) from group 2. A statistically significant difference is observed when comparing mean LDL cholesterol levels between the groups ($U = 4797.500$, $z = –2.986$, $p = 0.003$). No statistically significant difference is found between the groups regarding mean HDL cholesterol levels ($U = 5413.500$, $z = –1.715$, $p = 0.086$). Similarly, comparison of mean total serum cholesterol levels between both groups does not reveal a statistically significant difference ($t = –1.041$, $df = 221.988$, $p = 0.299$).

Table 17. *Comparative assessment of the mean lipid profile parameters in the studied patients from group 1 and group 2.*

Mean lipid profile parameters	**IS patients with MetS (group 1) n = 120**	**IS patients without MetS (group 2) n = 104**	**P value**
Total cholesterol (mmol/L)	5.2 ±1.398	5.1 ± 1.220	0.299
HDL - cholesterol (mmol/L)	1.4 (1.0, 1.6)	1.4 (1.1, 1.6)	0.086
LDL - cholesterol (mmol/L)	2.6 (2.1, 3.0)	2.3 (2.0, 2.6)	0.003
Triglycerides (mmol/L)	1.9 (1.3, 3.1)	1.3 (1.0, 1.6)	0.000

Table 17 presents a comparative assessment of the mean lipid profile parameters in the studied patients. Analysis of the results shows no statistically significant difference in total cholesterol ($t = -1.041$, $df = 221.988$, $p = 0.299$) or HDL cholesterol ($U = 5413.500$, $z = -1.715$, $p = 0.086$) between the compared groups. Statistical analysis confirms higher mean values of LDL cholesterol, 2.6 (2.1, 3.0), and triglycerides, 1.9 (1.3, 3.1), in the group of IS patients with MetS compared with group 2, whose values are LDL cholesterol 2.3 (2.0, 2.6) and triglycerides 1.3 (1.0, 1.6), respectively. A statistically significant difference is found regarding the mean triglyceride levels ($U = 3124.000$, $z = -6.442$, $p = 0.000$) and LDL cholesterol levels ($U = 4797.500$, $z = -2.986$, $p = 0.003$) between the studied IS patient's groups.

4.2.4 Overweight and obesity - an analysis of data and a comparative evalution of the results

Table 18. *Distribution of the studied patients in group 1 and group 2 according to BMI*

BMI (kg/m²)	**IS patients with MetS (group 1) n = 120 (%)**	**IS patients without MetS (group 2) n = 104 (%)**
BMI (18.5-24.9)	6 (5)	23 (22.1)
BMI (25.0-29.9)	47 (39.2)	65 (62.5)
BMI (30.0-34.9)	42 (35)	15 (14.4)
BMI (35.0-39.9)	19 (15.8)	1 (1)
BMI (≥40.0)	6 (5)	0 (0)

The RF obesity is analyzed using the distribution of patients in groups 1 and 2 according to calculated BMI. **Table 18** summarizes obese patients predominate in group 1, which includes 47 patients (39.2%) who were overweight and a total of 67 patients (55.8%) with different degrees of obesity. In group 2, 65 patients (62.5%) are overweight, while 16 patients (15.4%) had varying degrees of obesity. The analyzed results demonstrate that higher-risk patients with IS and obesity predominate in the MetS group, which is also visualized on **Fig. 14**.

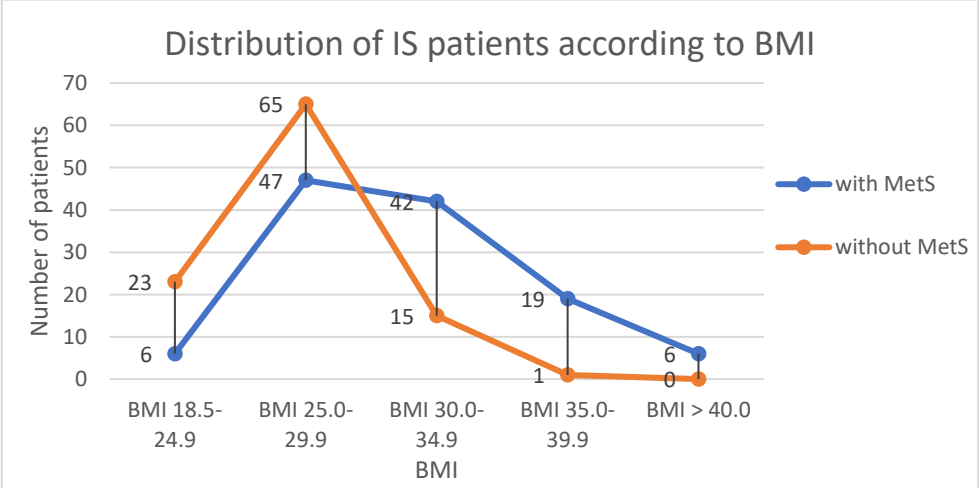

Fig. 14. *Comparative evaluation of the distribution of patients from group 1 and group 2 according to BMI*

Statistical analysis shows that the median BMI values in IS patients with MetS are 30 (27, 33), whereas in group 2 (IS without MetS) they are 27 (25, 29), demonstrating a statistically significant difference (U = 2879.500, z = 6.971, p = 0.000) between both groups.

4.3 Evaluation of severity of IS

4.3.1 Evaluation of the severity of IS on patient's admission

4.3.1.1 Evaluation of the severity of IS on admission of patients from the studied groups (group 1 and group 2) - distribution and comparative assessment according to NIHSS

Table 20. *Distribution of severity of IS on admission of the studied IS patients according to NIHSS*

Severity of IS on patient's admission	**IS patients with MetS (group 1) n = 120 (%)**	**IS patients without MetS (group 2) n = 104 (%)**
NIHSS: 1-4 sc.	20 (16.7)	30 (28.9)
NIHSS: 5-15 sc.	76 (63.3)	56 (53.8)
NIHSS: ≥ 16 sc.	24 (20.0)	18 (17.3)

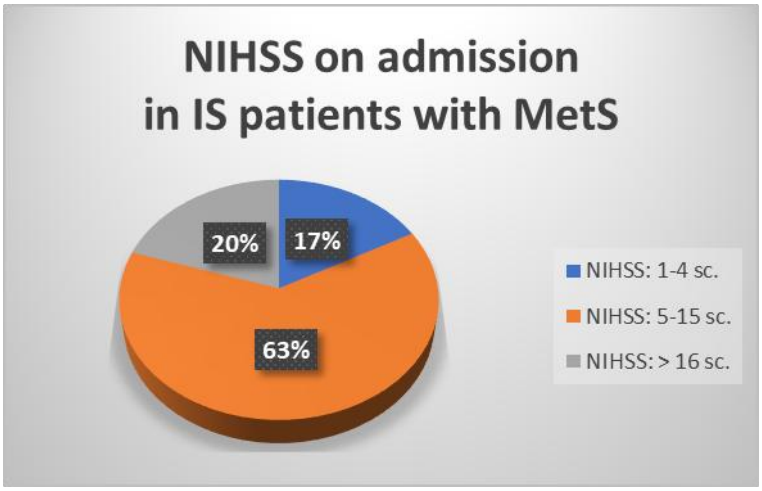

Fig. 16. *Distribution of the severity of neurological deficit on admission in IS patients with MetS (group 1) according to NIHSS*

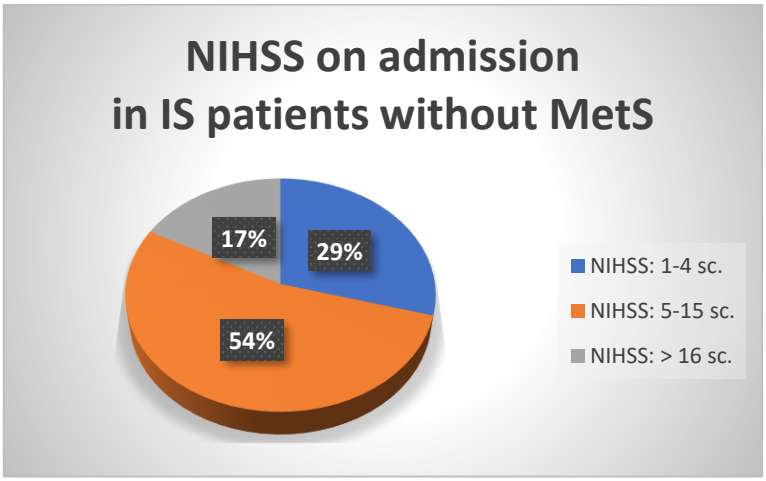

Fig. 17. *Distribution of the severity of neurological deficit on admission in IS patients without MetS (group 2) according to NIHSS.*

Table 20, Fig. 16 and Fig. 17 present the distribution of severity of neurological deficit according to NIHSS in patients from group 1 and group 2. We find that on admission the highest proportion of patients in group 1 has moderate strokes with NIHSS 5-15 sc., representing 63.3% of all patients. Mild strokes (NIHSS 1–4 sc.) are registered in 16.7% of patients, while moderate-to-severe strokes (NIHSS≥16 sc.) are observed in 20%. In group 2, the highest proportion of patients on admission also has moderate strokes with NIHSS 5-15 sc., accounting for 53.8% of patients. Mild strokes (NIHSS 1–4 sc.) are diagnosed in 28.9%, while moderate-to-severe strokes (NIHSS≥16 sc.) are found in 17.3%. Our results show median NIHSS scores on admission of 7 (5, 14) in group 1 and 7 (4, 12) in group 2, with no statistically significant difference (U = 5655.500, z = -1.212, p = 0.226) between both groups.

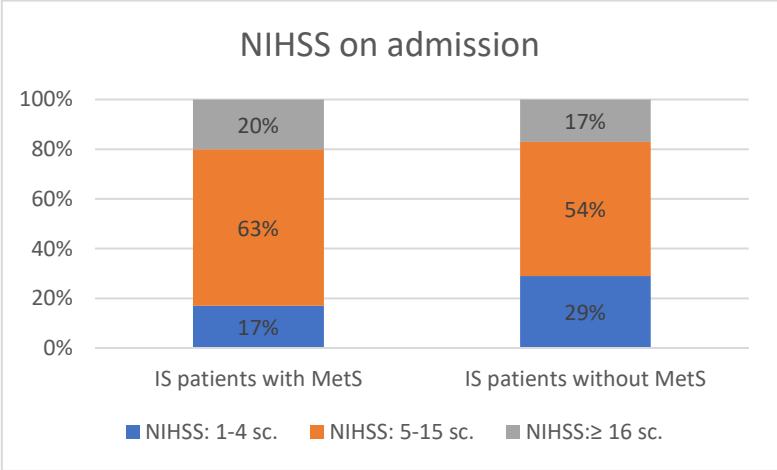

Fig. 18. *Comparative analysis according to NIHSS on admission - distribution of patients in the studied group 1 and group 2*

4.3.1.2 Evaluation of the impact of MetS on the relative risk for mild (NIHSS 1-4 sc.), moderate (NIHSS 5-15 sc.) and moderate to severe (NIHSS≥16 sc.) stroke according to NIHSS on admission

Table 21. *Evaluation of the impact of MetS on the risk of IS according to severity of IS on admission*

Severity of IS	IS patients with MetS (group 1) n = 120	IS patients without MetS (group 2) n = 104	Odds Ratio	95% Confidence Intervals (CI)	P value
Mild (NIHSS 1-4 sc.)	20	30	**0.493**	0.260-0.936	**0.031**
Moderate (NIHSS 5-15 sc.)	76	56	1.480	0.867-2.528	0.151
Moderate to severe and severe (NIHSS ≥16 sc.)	24	18	1.194	0.607-2.350	0.607

According to the results of the analysis (**Table 21**), MetS does not significantly increase the risk (p=0.151) of developing a moderate IS (NIHSS 5-15 sc.) (OR: 1.480, 95% CI 0.867-2.528), nor does it significantly affect (p=0.607) the risk of a moderate-to-severe IS (NIHSS≥16 sc.) (OR: 1.194, 95% CI 0.607-2.350). However, MetS negatively influences the relative risk of developing a mild IS (NIHSS 1-4 sc.) (OR: 0.493, 95% CI 0.260-0.936), with a statistically significant difference (p=0.031).

4.3.1.3 Evaluation of the impact of individual components of MetS/RF on the relative risk of moderate (NIHSS 5-15 sc.) and moderate to severe (NIHSS≥16 sc.) strokes according to NIHSS on admission

Table 22. *Evaluation of the severity of IS according to NIHSS on admission and components of MetS/RF factors at hospitalization - a distribution in group 1 and group 2*

	Severity of IS according to NIHSS on admission					
Component of MetS/ RF	**Mild (NIHSS 1-4) (group 1) n = 120**	**Mild (NIHSS 1-4) (group 2) n = 104**	**Moderate (NIHSS 5-15) (group 1) n = 120**	**Moderate (NIHSS 5-15) (group 2) n = 104**	**Moderate to severe and severe (NIHSS ≥16) (group 1) n = 120**	**Moderate to severe and severe (NIHSS ≥16) (group 2) n = 104**
AH, n (%)	19 (15.8)	22 (21.2)	76 (63.3)	46 (44.2)	24 (20.0)	14 (13.5)
Hyper glycemia, n (%)	17 (14.2)	8 (6.7)	69 (57.5)	9 (8.6)	24 (20.0)	8 (7.7)
Obesity (BMI≥25), n (%)	19 (15.8)	19 (18.3)	72 (60.0)	48 (46.1)	23 (19.2)	14 (13.5)
Hypertrigly ceridemia, n (%)	15 (12.5)	8 (7.7)	43 (35.8)	10 (9.6)	14 (11.7)	2 (1.9)
Low HDL-cholesterol, n (%)	8 (6.7)	12 (11.5)	33 (27.5)	16 (15.4)	7 (5.8)	5 (4.8)

Table 22 presents the distribution of patients in group 1 and group 2 according to the severity of IS and the individual components of MetS/RFs at hospitalization. Analyzing the results in the studied groups, it can be summarized that in group 1 the number of patients with each individual RF exceeds that in group 2.

Table 23. *Evaluation of the relative risk for moderate IS (NIHSS 5-15sc.) according to NIHSS on admission and components of MetS/RFs at hospitalization.*

Variables	Moderate (NIHSS 5-15 sc.) (group 1) n = 120	Moderate (NIHSS 5-15 sc.) (group 2) n = 104	Odds Ratio	95% Confidence Intervals (Cl)	P value
Arterial hypertension, n	76	46	**2.178**	1.274-3.723	**0.004**
Hyperglycemia (on admission), n	69	9	**14.281**	6.589-30.951	**< 0.0001**
Overweight and obesity (BMI ≥25 kg/m²), n	72	48	**1.750**	1.029-2.976	**0.039**
Hypertriglyceridemia, n	43	10	**5.249**	2.477-11.126	**< 0.0001**
Lower HDL-cholesterol, n	33	16	**2.086**	1.071-4.063	**0.031**

The results of our study (**Table 23**) confirm that all components of MetS increase the relative risk for moderate IS (NIHSS 5-15 sc.) - hyperglycemia on admission ($p<0.0001$), hypertriglyceridemia ($p<0.0001$), elevated blood pressure ($p=0.004$), overweight and obesity (BMI≥25 kg/m²) ($p=0.039$) and lower HDL-cholesterol ($p=0.031$). Among IS patients, hyperglycemia on admission increases the relative risk of moderate stroke 14.2-fold, hypertriglyceridemia 5.2-fold, AH 2.1-fold, low HDL cholesterol 2-fold, and overweight/obesity (BMI≥25 kg/m²) 1.7-fold according to NIHSS.

Table 24. *Evaluation of the relative risk for moderate to severe and severe IS (NIHSS≥16 sc.) according to NIHSS on admission and components of MetS/RF factors at hospitalization.*

Variables	Moderate to severe and severe (NIHSS≥16sc.) (group 1) n = 120	Moderate to severe and severe (NIHSS≥16sc.) (group 2) n = 104	Odds Ratio	95% Confidence Intervals (Cl)	P value
Arterial hypertension, n	24	14	1.607	0.783-3.299	0.196
Diabetes mellitus, n	22	2	**11.449**	2.622-49.987	**0.001**
Hyperglycemia (on admission), n	24	8	**3.000**	1.284-7.010	**0.011**
Obesity (BMI≥25 kg/m²) , n	23	14	1.524	0.739-3.143	0.254
Hypertriglyceridemia, n	14	2	**6.736**	1.493-30.380	**0.013**
Lower HDL-cholesterol, n	7	5	1.226	0.377-3.987	0.734

Analyzing the relative risk of moderate to severe and severe stroke (NIHSS≥16 sc.) we find that DM ($p=0.001$) is associated with almost 11.4-fold higher risk, hypertriglyceridemia increases 6.7-fold ($p=0.013$) and hyperglycemia on admission ($p=0.011$) is associated with a 3-fold increased risk of IS with NIHSS≥16 sc. (**Table 24**).

4.3.1.4 Correlations between the individual components of MetS and severity of neurological deficit assessed by NIHSS at hospital admission

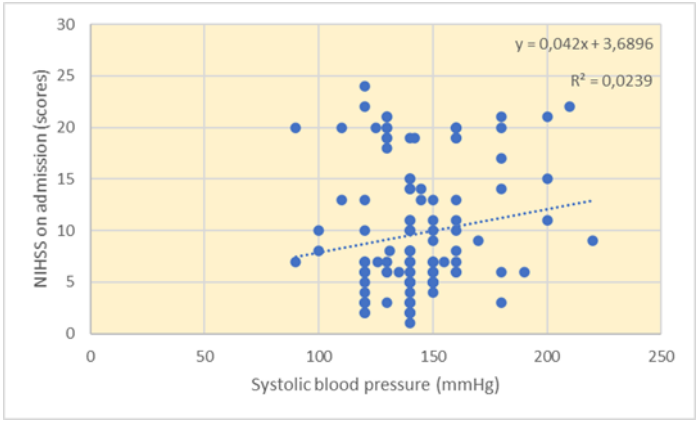

Fig. 19. *Correlation between SBP and severity of neurological deficit assessed by NIHSS at hospital admission*

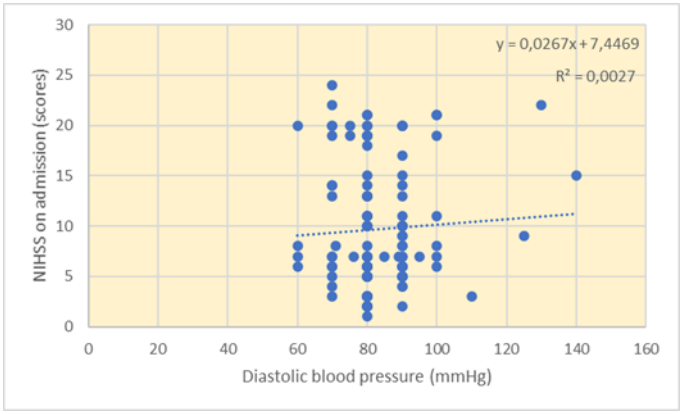

Fig. 20. *Correlation between DBP and severity of neurological deficit assessed by NIHSS at hospital admission*

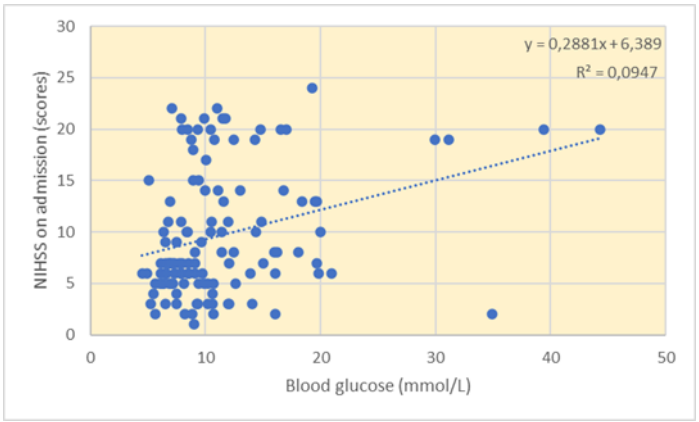

Fig. 21*. Correlation between hyperglycemia on admission and severity of neurological deficit assessed by NIHSS at hospital admission*

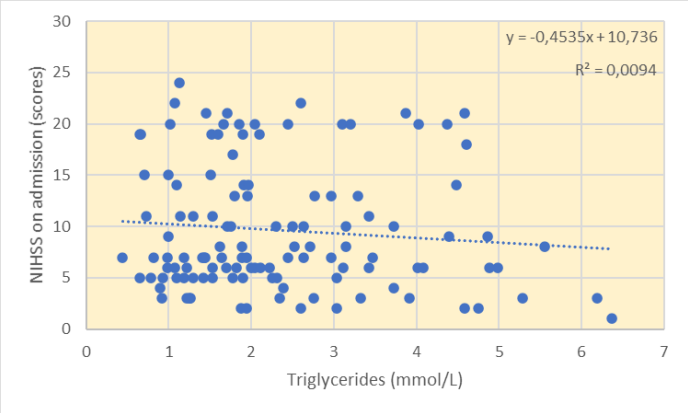

Fig. 22. *Correlation between TG and severity of neurological deficit assessed by NIHSS at hospital admission*

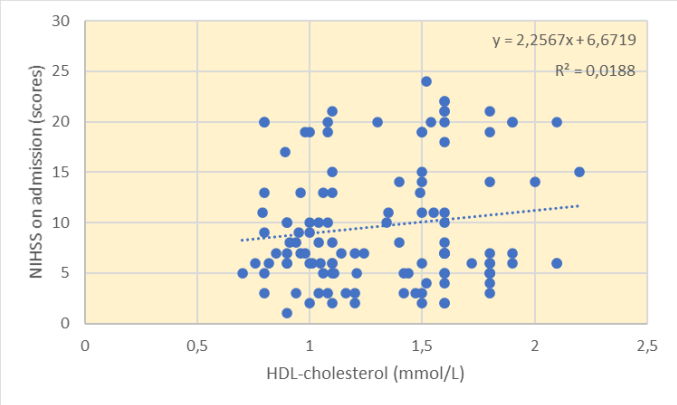

Fig. 23. *Correlation between HDL-cholesterol and severity of neurological deficit assessed by NIHSS at hospital admission*

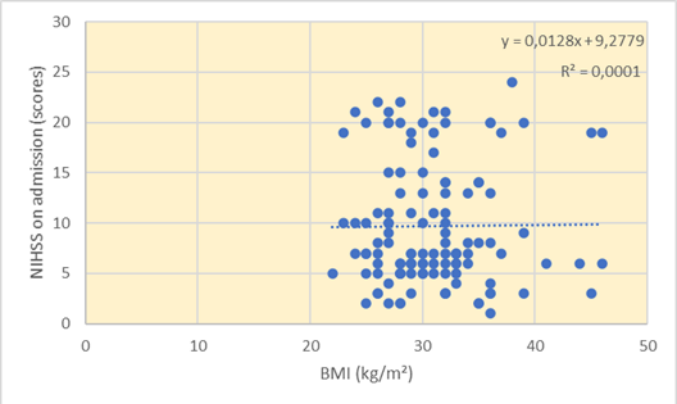

Fig. 24. *Correlation between BMI and severity of neurological deficit assessed by NIHSS at hospital admission*

Table 25. *Correlation analysis, strength of association between MetS components and severity of neurological deficits assessed on the NIHSS scale at hospitalization*

Variables	**NIHSS at hospitalization R^2-Coefficient of determination**	**NIHSS at hospitalization r-Correlation coefficient**	**Positive correlation/ strength of association**
SBP	0.0239	0.1545	Weak (0≤r<0.3)
DBP	0.0027	0.0519	Weak (0≤r<0.3)
Hyperglycemia	0.0947	0.3077	**Moderate (0.3≤r<0.5)**
TG	0.0094	0.0969	Weak (0≤r<0.3)
HDL cholesterol	0.0188	0.1371	Weak (0≤r<0.3)
BMI	0.0001	0.01	Weak (0≤r<0.3)

Table 25 and **Fig. 19-24** show the correlation between the individual components of MetS in group 1 and the severity of neurological deficits assessed on the NIHSS scale at hospitalization. For each MetS component, a correlation coefficient (r) is calculated to determine the strength of its association with the severity of neurological deficit according to NIHSS. The results demonstrate a positive correlation between all investigated MetS components and the severity of neurological deficit on admission (**Table 25**). However, based on the specific r values, these associations are generally weak. The only exception is hyperglycemia on admission, which shows a moderate positive correlation with the severity of neurological deficit on admission of IS patients with MetS.

Table 26*. Regression analysis of the severity of neurological deficit according to NIHSS on admission*

SUMMARY OUTPUT								
Regression Statistics								
Multiple R	0,441245532							
R Square	0,194697619							
Adjusted R Square	0,151938201							
Standard Error	11,854696							
Observations	120							
ANOVA								
	df	*SS*	*MS*	*F*	*Significance F*			
Regression	6	3839,378643	639,89644	4,55332711	0,000357617			
Residual	113	15880,32136	140,533817					
Total	119	19719,7						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95,0%*	*Upper 95,0%*
Intercept	-5,724965296	12,59427625	-0,4545688	0,6502915	-30,6764981	19,22656746	-30,67649805	19,22656746
САН	0,118771909	0,077766596	1,52728698	0,12948397	-0,03529774	0,272841562	-0,035297743	0,272841562
ДАН	-0,189891976	0,145910556	-1,3014273	0,19575938	-0,4789671	0,099183152	-0,478967105	0,099183152
Глюкоза	0,627048027	0,174102066	3,60161164	0,00047132	0,282120433	0,971975621	0,282120433	0,971975621
ТГ	0,698266389	0,871005732	0,80167829	0,42442169	-1,02735306	2,423885839	-1,02735306	2,423885839
HDL-холестерол	9,142034279	3,121081153	2,92912418	0,00411272	2,958609598	15,32545896	2,958609598	15,32545896
BMI	-0,173572393	0,227797136	-0,7619604	0,44767109	-0,62487961	0,27773482	-0,624879605	0,27773482

The regression analysis demonstrates that hyperglycemia on admission and HDL-cholesterol are significant predictors of the severity of neurological deficit at hospital admission (**Table 26**). In summary, among all MetS components, only admission

hyperglycemia shows a statistically significant moderate positive correlation with the severity of neurological deficit (p=0.0004).

4.3.2 Evaluation of the severity of IS at patient's discharge

4.3.2.1 Evaluation of the severity of IS at discharge of patients from the studied groups (group 1 and group 2) - distribution and comparative analysis according to NIHSS

Table 27. *Distribution of severity of IS at discharge of the studied IS patients according to NIHSS*

Severity of IS according to NIHSS at discharge	**IS patients with MetS (group 1) n = 120 (%)**	**IS patients without MetS (group 2) n = 104 (%)**
NIHSS: 1-4 sc.	48 (40.0)	48 (46.1)
NIHSS: 5-15 sc.	49 (40.8)	40 (38.5)
NIHSS: over 16 sc.	23 (19.2)	16 (15.4)

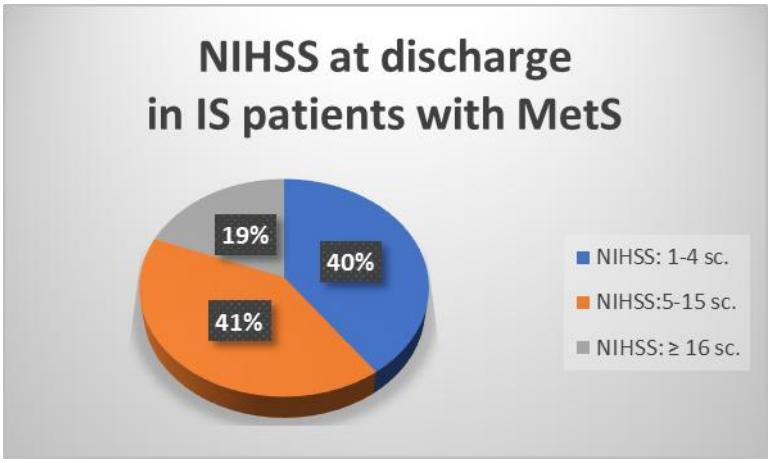

Fig. 25. *Distribution of IS severity at discharge of IS patients with MetS (group 1) according to NIHSS*

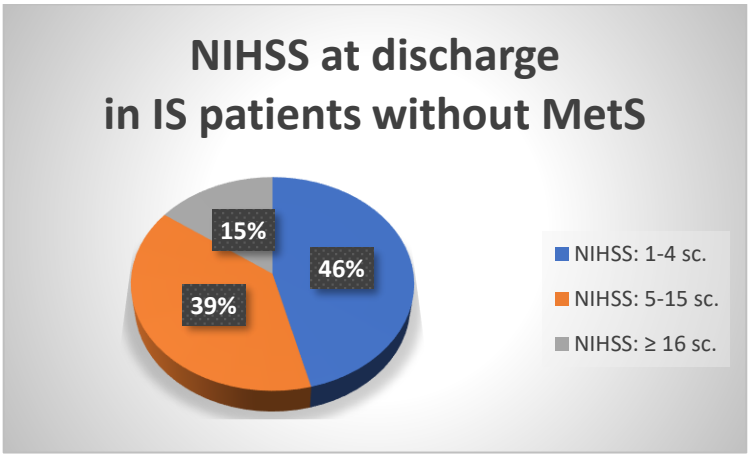

Fig. 26. *Distribution of IS severity at discharge of IS patients without MetS (group 2) according to NIHSS*

Table 27, **Fig. 25** and **Fig. 26** illustrate the distribution of stroke severity in IS patients from group 1 and group 2 at discharge according to NIHSS. We find that, among patients in group 1, the proportions of patients with mild (NIHSS 1-4 sc.) and moderate stroke (NIHSS 5-15 sc.) are similar at discharge, accounting for 40% and 41%, respectively. Among patients in group 1, the lowest proportion is observed in those with moderate-to-severe stroke (NIHSS ≥16 sc.), representing 19% of cases. The results for group 2 show that, at discharge, the highest proportion of patients has mild stroke (NIHSS 1-4 sc.), accounting for 46%. Moderate strokes (NIHSS 5-15 sc.) are recorded in 38.5%, while moderate-to-severe strokes (NIHSS≥16 sc.) are observed in 15% of patients. Our results demonstrate median NIHSS scores at discharge of 5 (3, 12) in group 1 and 5 (3, 9.75) in group 2, with no statistically significant difference between the two groups ($U = 5874.500$, $z = -0.759$, $p = 0.448$).

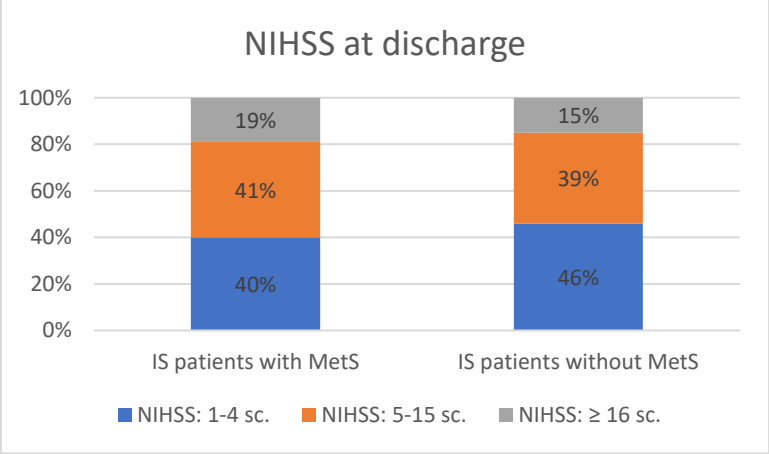

Fig. 27. *Comparative analysis according to NIHSS at discharge - distribution of patients in group 1 and group 2*

4.3.2.2 Evaluation of the impact of MetS on the relative risk for mild (NIHSS 1-4 sc.), moderate (NIHSS 5-15 sc.) and moderate to severe (NIHSS≥16 sc.) stroke according to NIHSS at discharge

Table 28. *Evaluation of the impact of MetS on the severity of IS according to NIHSS at discharge*

Severity of IS according to NIHSS at discharge	IS patients with MetS (group 1) n = 120	IS patients without MetS (group 2) n = 104	Odds Ratio	95% confidence intervals (CI)	P value
Mild (NIHSS 1-4 sc.)	48	48	0.778	0.457-1.323	0.354
Moderate (NIHSS 5-15 sc.)	49	40	1.104	0.645-1.889	0.717
Moderate to severe and severe (NIHSS ≥16 sc.)	23	16	1.304	0.647-2.627	0.457

According to the analysis, MetS does not significantly affect the risk of mild IS (NIHSS 1-4 sc.) at discharge (OR: 0.778, 95% CI 0.457-1.323, p=0.354). MetS is also not associated with moderate IS (NIHSS 5-15 sc.) (OR: 1.104, 95% CI 0.645-1.889, p=0.717) or moderate-to-severe IS (NIHSS≥16 sc.) (OR: 1.304, 95% CI 0.647-2.627, p=0.457) at discharge (**Table 28**).

4.3.2.3 Evaluation of the impact of individual components of MetS/RF on the relative risk of moderate (NIHSS 5-15 sc.) and moderate to severe (NIHSS≥16 sc.) strokes according to NIHSS at discharge

Table 29. *Evaluation of the severity of IS according to NIHSS at discharge and components of MetS/RFs at discharge - distribution in group 1 and group 2*

	Severity of IS according to NIHSS at discharge					
Components of MetS/RF	**Mild (NIHSS 1-4sc.) (group 1) n = 120**	**Mild (NIHSS 1-4sc.) (group 2) n = 104**	**Moderate (NIHSS 5-15 sc.) (group 1) n = 120**	**Moderate (NIHSS 5-15 sc.) (group 2) n = 104**	**Moderate to severe and severe (NIHSS ≥16sc.) (group 1) n = 120**	**Moderate to severe and severe (NIHSS ≥16sc.) (group 2) n = 104**
AH, n (%)	49 (40.8)	41 (39.4)	47 (39.2)	28 (26.9)	23 (19.2)	13 (12.5)
Hyperglycemia, n (%)	41 (34.2)	10 (9.6)	46 (38.3)	9 (8.6)	23 (19.2)	6 (5.8)
Obesity (BMI≥25kg/m²), n (%)	45 (37.5)	34 (32.7)	47 (39.2)	35 (33.6)	22 (18.3)	12 (11.5)
Hyper triglyceridemia, n (%)	31 (25.8)	13 (12.5)	25 (20.8)	5 (4.8)	16 (13.3)	2 (1.9)
Lower HDL-cholesterol, n (%)	22 (18.3)	20 (19.2)	23 (19.2)	10 (9.6)	3 (2.5)	3 (2.9)

Table 29 presents the distribution of patients from group 1 and group 2 according to IS severity and the individual MetS components/RFs at discharge. Analysis of the data shows that the number of patients with a RF is higher in the MetS IS group compared to group 2.

Table 30. *Evaluation of the relative risk for moderate IS (NIHSS 5-15 sc.) according to NIHSS and components of MetS/RFs at discharge*

Variables	Moderate (NIHSS 5-15 sc.) (group 1) n = 120	Moderate (NIHSS 5-15 sc.) (group 2) n = 104	Odds Ratio	95% Confidence intervals (Cl)	P value
Arterial hypertension, n	47	28	1.748	0.991-3.083	0.054
Hyperglycemia (on admission), n	46	9	**6.562**	3.019-14.262	**< 0.0001**
Obesity (BMI≥25 kg/m²) , n	47	35	0.393	0.734-2.195	0.393
Hypertriglyceridemia, n	25	5	**5.210**	1.916-14.172	**0.001**
Lower HDL-cholesterol, n	23	10	2.229	1.007-4.935	0.048

The results of this study (**Table 30**) confirm that hyperglycemia on admission ($p<0.0001$) and hypertriglyceridemia ($p=0.001$) affect the risk for moderate stroke at discharge. We find that admission hyperglycemia significantly increases the relative risk of moderate stroke 6.5-fold, while hypertriglyceridemia increases the risk 5.2-fold according to NIHSS at discharge.

Table 31. *Evaluation of the relative risk for moderate to severe and severe IS (NIHSS≥16 sc.) according to NIHSS and components of MetS/RFs at discharge*

Variables	Moderate to severe and severe (NIHSS≥16sc.) (group 1) n = 120	Moderate to severe and severe (NIHSS≥16sc.) (group 2) n = 104	Odds Ratio	95% Confidence Intervals (Cl)	P value
Arterial hypertension, n	23	13	1.660	0.794-3.471	0.178
Diabetes mellitus, n	21	5	**4.200**	1.523-11.581	**0.006**
Hyperglycemia (on admission), n	23	6	**3.913**	1.526-10.033	**0.004**
Obesity (BMI≥25 kg/m²), n	22	12	1.721	0.806-3.676	0.161
Hypertriglyceridemia, n	16	2	**7.846**	1.759-34.994	**0.007**
Lower HDL-cholesterol, n	3	3	0.863	0.170-4.372	0.859

Data from the present study concerning moderate to severe and severe strokes (NIHSS ≥16 sc.) indicate that DM ($p=0.006$), hyperglycemia on admission ($p=0.004$), and hypertriglyceridemia ($p=0.007$) increase the risk of severe strokes at discharge (**Table 31**). Analysis of the relative risk for moderate to severe and severe stroke shows that hypertriglyceridemia is associated with a 7.8-fold higher risk, DM increases the risk 4.2-fold, and hyperglycemia on admission is associated with a 3.9-fold higher risk of IS with NIHSS ≥16 sc. at discharge. MetS itself does not affect the severity of acute IS in patients with NIHSS 5-15 sc. and NIHSS ≥16 sc., neither on admission nor at discharge.

4.3.2.4 Correlation between individual components of MetS and severity of neurological deficit assessed by NIHSS at discharge.

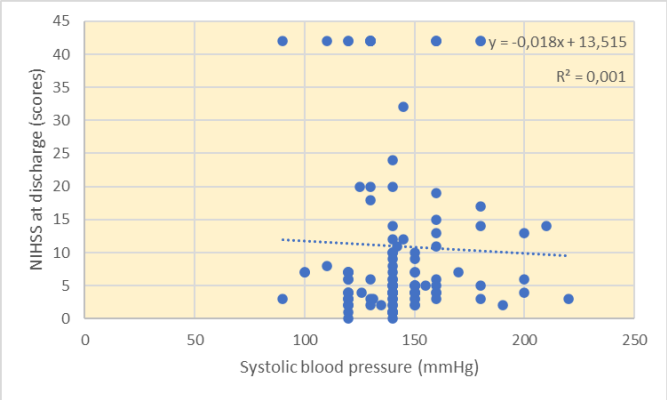

Fig. 28. *Correlation between SBP and severity of neurological deficit assessed by NIHSS at discharge*

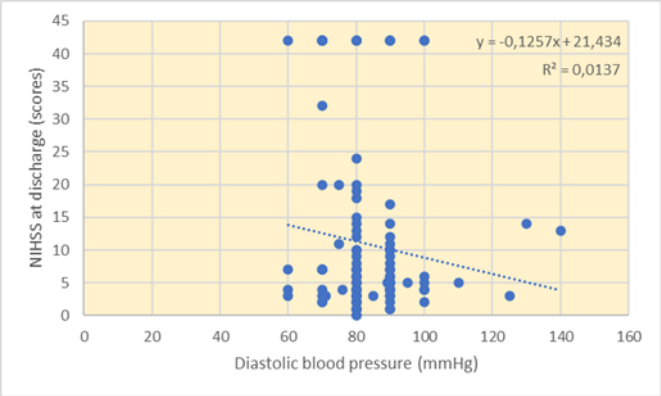

Fig. 29. *Correlation between DBP and severity of neurological deficit assessed by NIHSS at discharge*

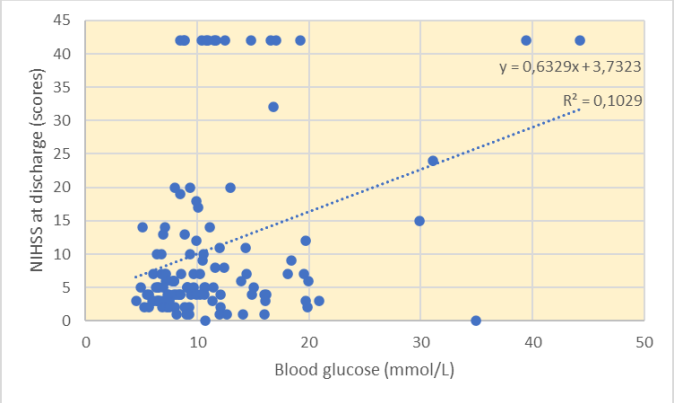

Fig. 30. *Correlation between hyperglycemia on admission and severity of neurological deficit assessed by NIHSS at discharge*

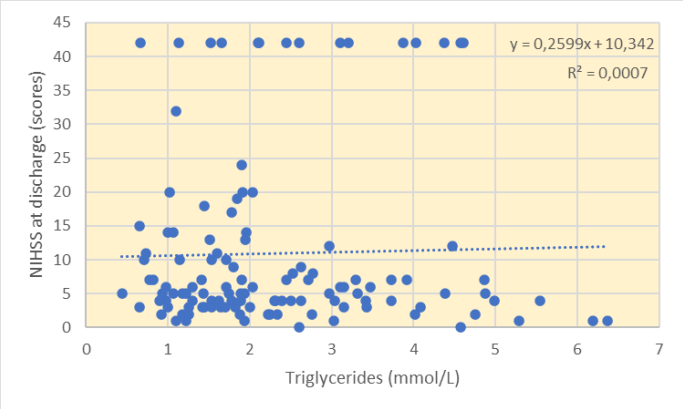

Fig. 31. *Correlation between TG and severity of neurological deficit assessed by NIHSS at discharge*

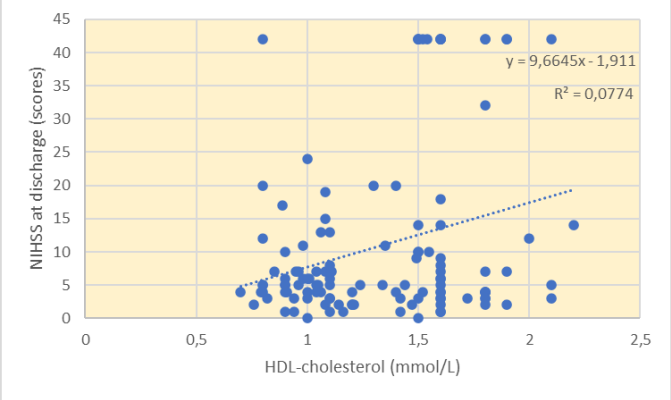

Fig. 32. *Correlation between HDL-cholesterol and severity of neurological deficit assessed by NIHSS at discharge*

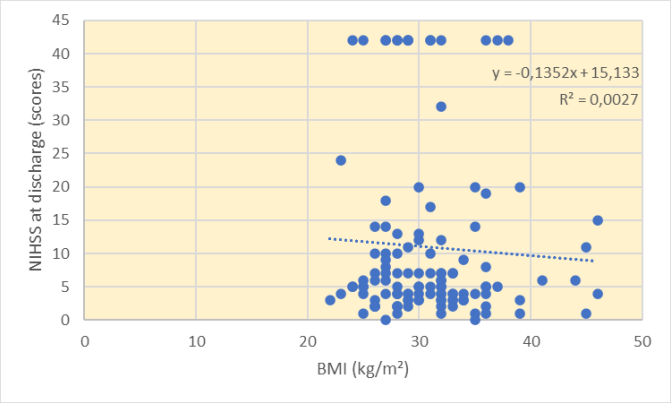

Fig. 33. *Correlation between BMI and severity of neurological deficit assessed by NIHSS at discharge*

Table 32. *Correlation analysis, strength of association between MetS components and severity of neurological deficit assessed by NIHSS scale at discharge*

Variables	NIHSS at discharge R^2-Coefficient of determination	NIHSS at discharge r-correlation coefficient	Positive correlation/ strength of association
SBP	0.001	0.0316	Weak (0≤r<0.3)
DBP	0.0137	0.1170	Weak (0≤r<0.3)
Hyperglycemia	0.1029	0.3207	**Moderate (0.3≤r<0.5)**
TG	0.0007	0.0264	Weak (0≤r<0.3)
HDL cholesterol	0.0774	0.2782	Weak (0≤r<0.3)
BMI	0.0027	0.0519	Weak (0≤r<0.3)

Table 32 and **Fig. 28–33** show the correlations between individual MetS components in group 1 and the severity of neurological deficit assessed by NIHSS at discharge. A correlation coefficient (r) is calculated separately for each MetS component to determine the strength of association between the respective component and the severity of neurological deficit according to NIHSS at discharge. The results presented in **Table 32** demonstrate a positive correlation between all investigated MetS components and severity of neurological deficit at discharge. However, based on the specific r-values, these relationships are generally weak positive correlations. The only exception is hyperglycemia on admission, demonstrated a moderate positive correlation with the severity of neurological deficit at discharge in IS patients with MetS.

Table 33. *Regression analysis of the severity of neurological deficit according to NIHSS at discharge*

SUMMARY OUTPUT								
Regression Statistics								
Multiple R	0,425725							
R Square	0,181242							
Adjusted R Squa	0,137768							
Standard Error	5,672127							
Observations	120							
ANOVA								
	df	*SS*	*MS*	*F*	*Significance F*			
Regression	6	804,7728908	134,1288151	4,16898332	**0,000800785**			
Residual	113	3635,552109	32,17302752					
Total	119	4440,325						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*ower 95,0%*	*Upper 95,0%*
Intercept	-1,99987	6,025994888	-0,331873435	0,74059959	-13,93845034	9,938715	-13,9385	9,938715
САН	0,094339	0,037209054	2,535373818	**0,01259972**	0,020621014	0,168057	0,020621	0,168057
ДАН	-0,07073	0,069813957	-1,013055795	0,31319777	-0,209039475	0,067589	-0,20904	0,067589
Глюкоза	0,339856	0,083302775	4,079767881	**8,4298E-05**	0,174818164	0,504894	0,174818	0,504894
ТГ	-0,44328	0,41675091	-1,063651295	0,2897544	-1,268936363	0,382381	-1,26894	0,382381
HDL-холестерс	1,692452	1,493346556	1,133328133	0,2594753	-1,266137203	4,651041	-1,26614	4,651041
BMI	-0,03135	0,108994304	-0,287636883	0,77415156	-0,247288157	0,184587	-0,24729	0,184587

The regression analysis shows that hyperglycemia on admission and SBP are significant components of MetS influencing the severity of neurological deficit at discharge (**Table 33**). In conclusion, among all MetS components, only hyperglycemia on admission demonstrates a statistically significant moderate positive correlation with the severity of neurological deficit ($p<0.05$).

4.4 Analysis of the short-term clinical outcome in IS patients at discharge

Table 34. *Comparative analysis of the clinical outcome in the studied group 1 and group 2 patients according to mRS at discharge*

mRS (scores)	**IS patients with MetS (group 1) n = 120 (%)**	**IS patients without MetS (group 2) n = 104 (%)**	**P Value**
1	2 (1.7)	1 (1.0)	**0.001**
2	13 (10.8)	34 (32.7)	
3	27 (22.5)	27 (26.0)	
4	34 (28.3)	17 (16.3)	
5	21 (17.5)	17 (16.3)	
6	23 (19.2)	8 (7.7)	

Table 34 illustrates in detail the possible functional outcomes according to mRS, visualizing the distribution of patients and their percentages for mRS scores ranging from 1 to 6. No patients with an mRS score of 0 were recorded at discharge.

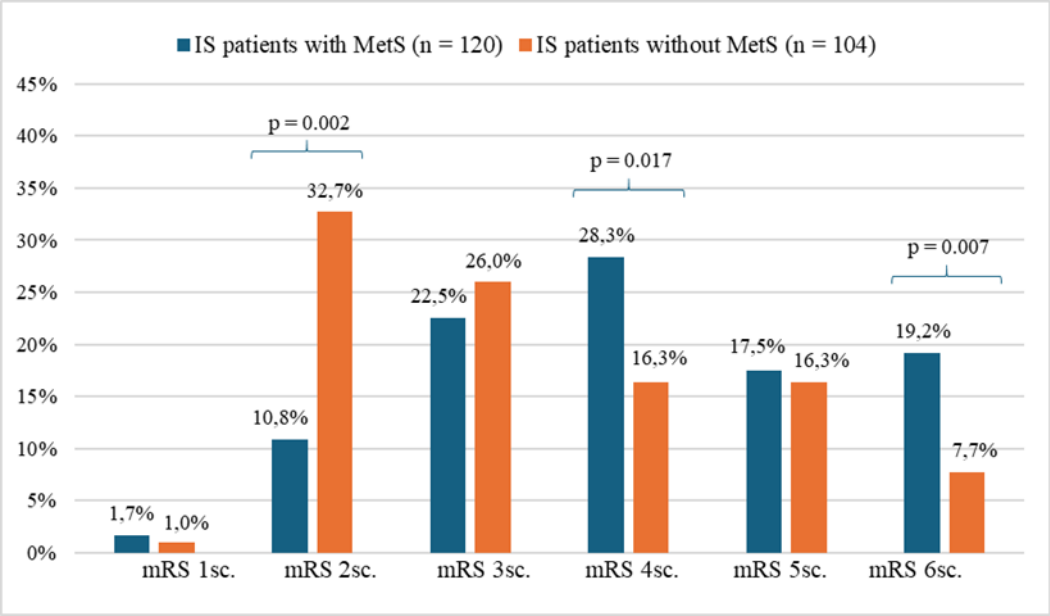

Fig. 35*. Comparative analysis of functional outcome at discharge in the two studied groups of cases according to mRS*

An unfavorable functional outcome characterized by moderately severe disability and mortality is observed at a considerably higher rate in group 1 - 28.3% for mRS 4 and 19.2% for mRS 6, respectively (**Table 34 and Fig. 35**). In group 2, the highest proportion of cases has

slight disability, accounting for 32.7% with mRS 2. The results of functional outcome assessment according to mRS demonstrate statistically significant differences for: mRS 2 sc. ($\chi 2 = 9.383$, df = 1, p = 0.002), mRS 4 sc. ($\chi 2 = 5.667$, df = 1, p = 0.017) and mRS 6 sc. ($\chi 2 = 7.258$, df = 1, p = 0.007) between both studied groups.

Table 35. *Evaluation of the short-term stroke outcome in the studied groups - distribution according to mRS at discharge*

Short-term stroke outcome according to mRS (0-6)	**IS patients with MetS (group 1) n = 120 (%)**	**IS patients without MetS (group 2) n = 104 (%)**	**P value**
Favorable functional outcome mRS (0-2)	15 (12.5)	35 (33.7)	**0.001**
Unfavorable functional outcome mRS (3-5)	82 (68.3)	61 (58.6)	
Unfavorable fatal outcome mRS (6)	23 (19.2)	8 (7.7)	

Evaluation of the short-term stroke outcome is presented in **Table 35** and **Fig. 36**. In group 1, the following distribution is observed: favorable functional outcome in 15 patients (12.5%); unfavorable functional outcome - in 82 patients (68.3%) and unfavorable fatal outcome in 23 patients (19.2%). In group 2, a favorable functional outcome is observed in 35 patients (33.7%); unfavorable functional outcome - in 61 (58.6%) and unfavorable fatal outcome in 8 (7.7%). A statistically significant difference in functional stroke outcome is identified between the studied groups ($\chi^2 = 22.032$, df = 5, p = 0.001).

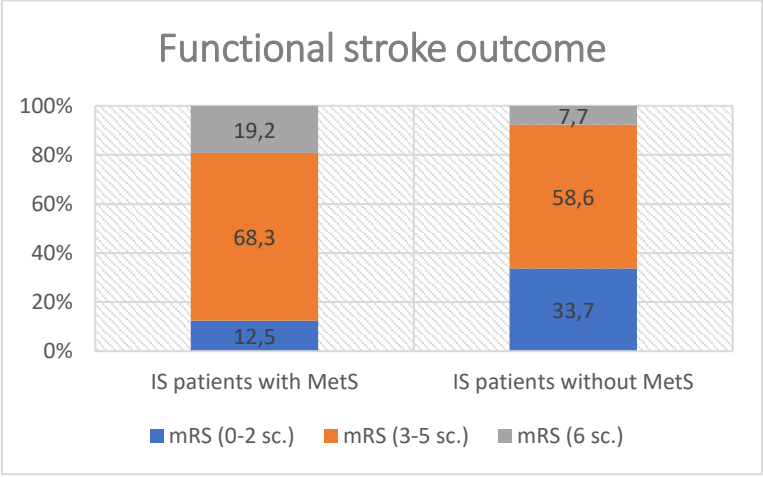

Fig. 36*. Comparative analysis of functional stroke outcome according to mRS at discharge - percentage distribution in group 1 and group 2*

4.4.1 Evaluation of the impact of MetS on the relative risk of unfavorable functional and fatal outcome in IS patients

Table 37. *Evaluation of the relative risk for unfavorable functional (mRS 3-5) and fatal outcome (mRS 6) according to mRS and MetS at discharge*

Variables	IS patients with MetS (group 1) n = 120	IS patients without MetS (group 2) n = 104	Odds Ratio	95% Confidence intervals (Cl)	P value
Unfavorable outcome (mRS 3-5) (group 1 and group 2) n = 224	82	61	1.521	0.879-2.631	0.133
Lethal outcome (mRS 6) (group 1 and group 2) n = 224	23	8	**2.845**	1.213-6.674	**0.016**

According to the presented data, MetS does not significantly increase the relative risk of an unfavorable outcome (mRS 3-5) at discharge (p=0.133). However, the results of our study confirm that MetS is associated with a 2.8-fold higher risk of short-term mortality (mRS 6) in IS patients (p=0.016) (**Table 37**).

4.4.2 Evaluation of the impact of the individual components of MetS/RF on the relative risk of unfavorable functional and fatal outcome in IS patients

Table 38*. Evaluation of the short-term clinical outcome in IS patients according to mRS and components of MetS/RFs at discharge - percentage distribution in group 1 and group 2*

	Clinical outcome at discharge					
Components of MetS/RF	**Favorable (mRS 0-2) (group 1) n = 120**	**Favorable (mRS 0-2) (group 2) n = 104**	**Unfavorable (mRS 3-5) (group 1) n = 120**	**Unfavorable (mRS 3-5) (group 2) n = 104**	**Fatal (mRS 6) (group 1) n = 120**	**Fatal (mRS 6) (group 2) n = 104**
Arterial hypertension, n (%)	15 (12.5)	27 (25.9)	81 (67.5)	49 (47.1)	23 (19.2)	6 (5.8)
Diabetes mellitus, n (%)	16 (13.3)	2 (1.9)	77 (64.2)	0 (0)	22 (18.3)	2 (1.9)
Obesity (BMI≥25), n (%)	14 (11.7)	26 (25.0)	79 (65.8)	48 (46.1)	21 (17.5)	7 (6.7)
Hyper triglyceridemia, n (%)	10 (8.3)	11 (10.6)	47 (39.2)	8 (7.7)	15 (12.5)	1 (1.0)
Lower HDL-cholesterol, n (%)	15 (12.5)	13 (12.5)	29 (24.2)	18 (17.3)	4 (3.3)	2 (1.9)

Table 38 presents the percentage distribution of patients in group 1 and group 2 according to their short-term clinical outcome and the individual components of MetS/RF at discharge. Data analysis demonstrates that the number of patients with RFs is higher in the higher-risk group 1 compared with group 2.

Table 39. *Evaluation of the relative risk for unfavorable clinical outcome (mRS 3-5) according to mRS and components of MetS/RFs at discharge*

Variables	**Unfavorable clinical outcome (mRS 3-5) (group 1) n = 120**	**Unfavorable clinical outcome (mRS 3-5) (group 2) n = 104**	**Odds Ratio**	**95% Confidence intervals (Cl)**	**P value**
Arterial hypertension, n	81	49	**2.331**	1.355-4.010	**0.002**
Hyperglycemia (on admission), n	73	16	**8.543**	4.475-16.308	< **0.0001**
Obesity (BMI≥25 kg/m²) , n	79	48	**2.248**	1.311-3.855	**0.003**
Hypertriglyceridemia, n	47	8	**7.726**	3.440-17.351	< **0.0001**
Lower HDL-cholesterol, n	29	18	1.523	0.789-2.940	0.210

Based on our results, hyperglycemia on admission (p<0.0001), hypertriglyceridemia (p<0.0001), overweight/obesity (p=0.003), and AH (p=0.002) significantly affect the relative risk of an unfavorable stroke outcome (mRS 3-5) (**Table 39**). Among IS patients: hyperglycemia on admission increases the relative risk for unfavorable outcome by 8.5-fold; hypertriglyceridemia increases the risk by 7.7-fold; overweight and obesity (BMI≥25 kg/m²) are associated with a 2.2-fold higher risk; AH increases the risk by 2.3-fold. Of all MetS components, lower HDL-cholesterol is the only factor that does not significantly affect the risk of an unfavorable outcome (p=0.210).

Another factor found to significantly increase the risk for unfavorable functional outcome (mRS 3-5) after IS is moderate stroke severity at admission (NIHSS 5-15 sc.) (OR: 2.375, 95% CI 1.314-4.292, p=0.004).

***Table 40**. Evaluation of the relative risk for fatal outcome (mRS 6) according to mRS and components of MetS/RFs at discharge.*

Variables	Fatal outcome (mRS 6) (group 1) n = 120	Fatal outcome (mRS 6) (group 2) n = 104	Odds Ratio	95% confidence intervals (Cl)	P value
Arterial hypertension, n	23	6	**3.873**	1.511-9.928	**0.005**
Hyperglycemia (on admission), n	22	3	**7.558**	2.192-26.062	**0.001**
Overweight and obesity (BMI ≥25 kg/m²) , n	21	7	**2.939**	1.195-7.230	**0.019**
Hypertriglyceridemia, n	15	1	**14.714**	1.909-113.439	**0.010**
Lower HDL-cholesterol, n	4	2	1.759	0.315-9.803	0.520

When investigating the influence of individual MetS components on the risk of fatal outcome, the following results are obtained: hypertriglyceridemia had the strongest impact, increasing the relative risk by 14.7-fold; hyperglycemia on admission increases the risk by 7.5-fold; AH increases the risk by 3.8-fold; and overweight/obesity (BMI≥25 kg/m²) is associated with a 2.9-fold higher risk of early mortality after IS. Data from our clinical population confirm a significant increase in the risk of fatal outcome at discharge associated with: hyperglycemia on admission (p=0.001), AH (p=0.005), hypertriglyceridemia (p=0.010) and overweight/obesity (BMI≥25 kg/m²) (p=0.019). Of all MetS components, only reduced HDL-cholesterol does not significantly affect the risk of fatal outcome (p=0.520) (**Table 40**).

4.4.3 Evaluation of the impact of the number of MetS components on the relative risk for unfavorable functional outcome in IS patients

***Table 41.** Evaluation of the relative risk for unfavorable functional stroke outcome (mRS 3-5) according to the number of MetS components*

Components of MetS - number	Odds Ratio (OR)	95% Confidence Intervals (Cl)	P value
Three components	5.205	2.066-13.116	0.0005
Four components	5.444	2.165 – 13.690	0.0003
Five components	3.873	1.511 – 9.928	0.0048

Table 41 demonstrates that different combinations of MetS components increase the relative risk of an unfavorable functional stroke outcome. Our study shows that the combination of four MetS components in IS patients is associated with the highest risk of an unfavorable functional outcome (OR: 5.444, 95% CI 2.165-13.690, p=0.0005). The next statistically significant combination (p=0.0003) associated with an increased risk of poor stroke outcome is the presence of three MetS components (OR: 5.205, 95% CI 2.066-13.116). The

combination of five MetS components is associated with an almost 3.9-fold increased risk of an unfavorable outcome after IS (OR: 3.873, 95% CI 1.511-9.928), with statistical significance (p=0.0048).

4.4.4 Correlation between individual components of MetS and clinical outcome of stroke according to mRS

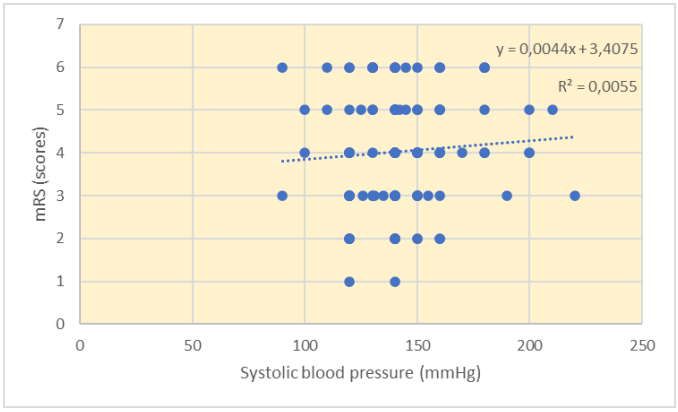

Fig. 38. *Correlation between SBP and clinical outcome of stroke according to mRS*

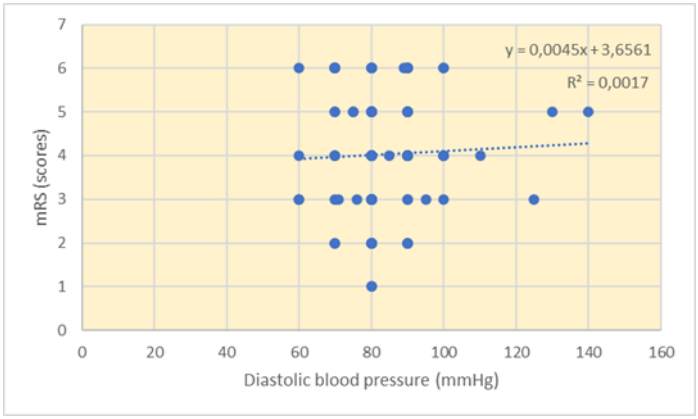

Fig. 39. *Correlation between DBP and clinical outcome of stroke according to mRS*

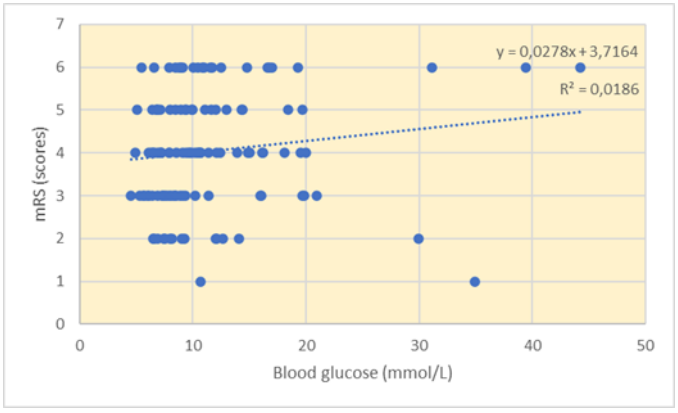

Fig. 40. *Correlation between hyperglycaemia on admission and clinical outcome of stroke according to mRS*

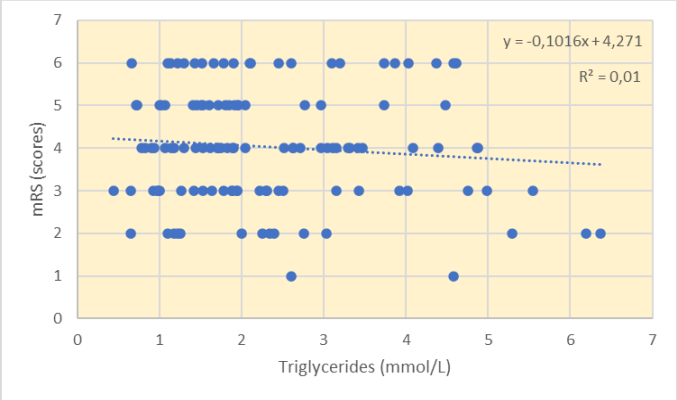

Fig. 41. *Correlation between TG and clinical outcome of stroke according to mRS*

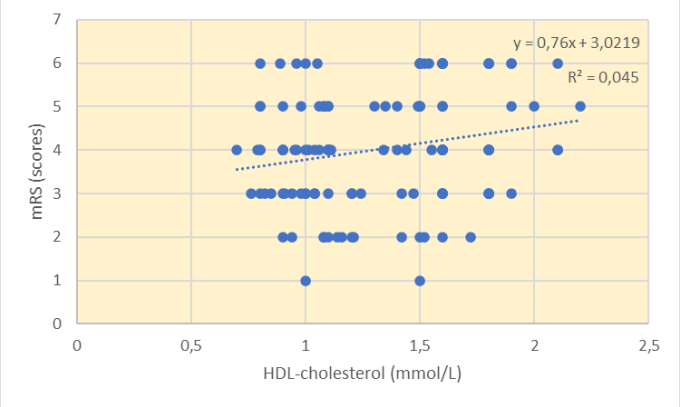

Fig. 42. *Correlation between HDL-cholesterol and clinical outcome of stroke according to mRS*

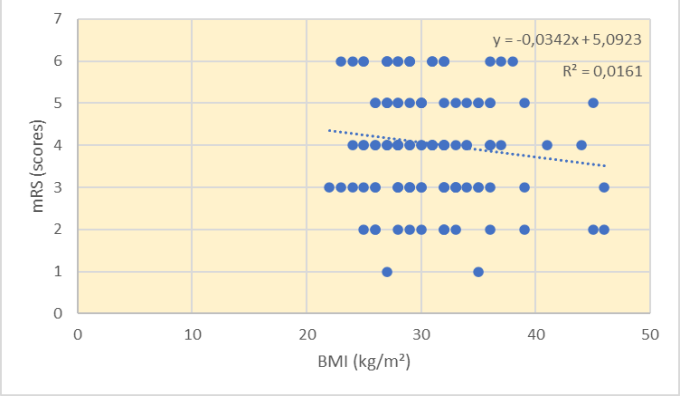

Fig. 43. *Correlation between BMI and clinical outcome of stroke according to mRS*

Table 42. *Correlation analysis, strength of association between MetS components and clinical outcome of stroke according to mRS*

Variables	mRS R^2-Coefficient of determination	mRS r-correlation coefficient	Positive correlation/ strength of association
SBP	0.0055	0.0741	Weak (0≤r<0.3)
DBP	0.0017	0.0412	Weak (0≤r<0.3)
Hyperglycemia	0.0186	0.1363	Weak (0≤r<0.3)
TG	0.01	0.1	Weak (0≤r<0.3)
HDL cholesterol	0.045	0.2121	Weak (0≤r<0.3)
BMI	0.0161	0.1268	Weak (0≤r<0.3)

Table 42 and **Fig. 38-43** illustrate the correlations between individual MetS components in group 1 and stroke clinical outcome assessed by mRS. A separate correlation coefficient (r) is calculated for each MetS component to determine the strength of its association with stroke clinical outcome. The results of the correlation analysis present in **Table 42** demonstrate a positive but weak correlation between all investigated MetS components and stroke clinical outcome as assessed by mRS. Thus, all examined MetS components show a positive association with stroke outcome; however, based on the presented correlation coefficients, these relationships are weak.

Table 43. *Regression analysis for the short-term clinical outcome of stroke*

SUMMARY OUTPUT								
Regression Statistics								
Multiple R	0,304885							
R Square	0,092955							
Adjusted R	0,044793							
Standard E	1,297917							
Observatic	120							
ANOVA								
	df	*SS*	*MS*	*F*	*Significance F*			
Regressior	6	19,50807	3,251346	1,930052311	0,08189683			
Residual	113	190,3586	1,684589					
Total	119	209,8667						
	Coefficients	*tandard Erı*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95,0%*	*Upper 95,0%*
Intercept	2,810083	1,378891	2,037931	0,043892129	0,078252431	5,541914439	0,078252431	5,541914439
САН	0,008355	0,008514	0,981265	0,328558192	-0,008513591	0,025223194	-0,008513591	0,025223194
ДАН	-0,00129	0,015975	-0,08056	0,93593162	-0,032936543	0,030362526	-0,032936543	0,030362526
Глюкоза	0,036081	0,019062	1,892884	0,060931604	-0,00168308	0,073846059	-0,00168308	0,073846059
ТГ	-0,05208	0,095362	-0,54618	0,586020903	-0,241015124	0,136845488	-0,241015124	0,136845488
HDL-холес	0,645243	0,341713	1,88826	0,061555473	-0,031752125	1,322238543	-0,031752125	1,322238543
BMI	-0,03261	0,02494	-1,30744	0,193717607	-0,082019757	0,016803433	-0,082019757	0,016803433

The regression analysis does not identify any statistically significant component of MetS influencing the short-term clinical outcome of stroke (**Table 43**).

The present study established that the severity of neurological deficit on admission influences the clinical outcome at the time of hospital discharge.

Our study finds that the severity of neurological deficit on admission affects the clinical outcome of IS at discharge.

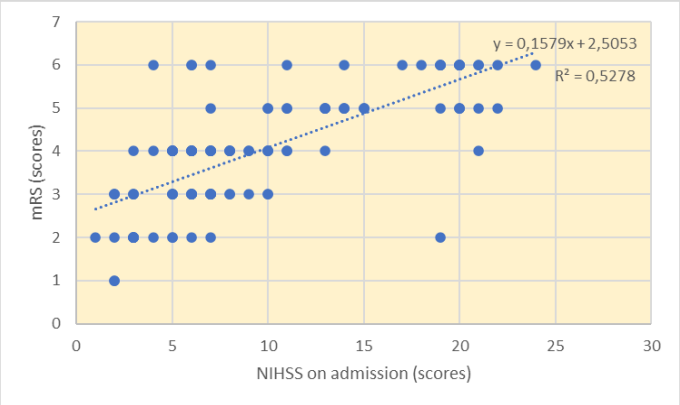

Fig. 44. *Correlation between the severity of neurological deficit according to NIHSS on admission and the clinical outcome of stroke assessed by mRS*

Using correlation analysis and the demonstrated relationship between stroke severity according to the NIHSS on admission and stroke clinical outcome, we calculate a correlation coefficient (r=0.726), indicating a strong positive correlation between stroke severity on admission and short-term clinical outcome (**Fig. 44**). Our findings are further confirmed by the regression analysis performed (**Table 44**).

Table 44. *Regression analysis for the short-term clinical outcome of stroke*

SUMMARY OUTPUT								
Regression Statistics								
Multiple R	0,726481781							
R Square	0,527775778							
Adjusted R Square	0,523773878							
Standard Error	0,916441734							
Observations	120							
ANOVA								
	df	*SS*	*MS*	*F*	*Significance F*			
Regression	1	110,7625433	110,7625433	131,8812948	5,96239E-21			
Residual	118	99,10412338	0,839865452					
Total	119	209,8666667						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95,0%*	*Upper 95,0%*
Intercept	2,505274576	0,157174802	15,9394161	3,31726E-31	2,194025677	2,816523476	2,194025677	2,816523476
NIHSS 1	0,15793889	0,013753001	11,48395815	5,96E-21	0,130704203	0,185173576	0,130704203	0,185173576

5. DISCUSSION

5.1 Analysis of modifiable RFs in IS patients

The results of our study show that the most prevalent modifiable RF among the studied IS patients is AH. In group 1 AH is diagnosed in 119 patients (99.2%) and in group 2 it is found in 82 patients (78.8%). Overall, AH is diagnosed in 201 patients (89.7%) of all IS patients, making it the most common modifiable RF. The findings demonstrate that the prevalence of AH in group 1 was substantially higher than in group 2 (99.2% vs. 78.8%), which can be explained by the diagnostic criteria for MetS IS patients.

DM is another frequently observed modifiable RF among IS patients. In group 1, where DM constituted one of the principal components of MetS, it is diagnosed in 115 patients (95.8%), whereas in group 2 it is present in a significantly smaller number of cases - only 4 patients (3.8%). Overall, DM is identified in 119 patients (53.1%) with acute IS. A statistically significant difference is observed in the studied groups regarding the prevalence of this RF ($\chi^2 = 103.538$, df = 1, p = 0.000).

Based on anthropometric measurements and calculated BMI, we find that overweight and obesity (BMI≥25 kg/m²) occur in 114 patients (95%) in group 1 and in 81 patients in group 2 (77.9%). In group 1 we report that 47 patients (39.2%) are overweight and 67 patients (55.8%) are with varying degrees of obesity. Group 2 includes 65 patients (62.5%) who are overweight and 16 patients (15.4%) with different degrees of obesity. From the presented results, it is evident that higher-risk patients with IS and obesity predominate in the IS group with MetS.

Another widespread modifiable RF is dyslipidemia. In IS patients with MetS, it is found in 80 patients (66.7%), and in group 2 - in 10 patients (9.6%). The diagnosed patients with dyslipidemia are a total of 90 (40.2%) with a statistically significant difference ($\chi 2 = 54.444$, df = 1, p = 0.000) between both groups. According to WHO data, Bulgaria belongs to the high-risk category of countries, and according to AHA recommendations, high-risk individuals with LDL-C levels ≥190 mg/dL require intensive lipid-lowering therapy aimed to achieve a ≥50% reduction in LDL-C levels (Aygun S et al. 2022). The AHA recommendations for patients with DM include moderate-intensity statin therapy, whereas high-risk diabetic patients with multiple concomitant RFs and advanced age require high-intensity lipid-lowering therapy to achieve target lipid values (Aygun S et al. 2022). In patients with DM but without established CVDs, it is necessary to maintain LDL-C levels <2.6 mmol/L (Kristensen FPB et al. 2023). According to the recommendations of the European Society of Cardiology and ADA, in high-

risk patients with TG>2.3 mmol/L (>200 mg/dL), behavioral modifications should accompany first-line statin therapy and if the target values for LDL-C and hypertriglyceridemia above 2.3 mmol/L (>200 mg/dL) are achieved, additional fibrate therapy is recommended (Grundy SM et al. 2019, Aygun S et al. 2022, Kristensen FPB et al. 2023). According to a population-based study by Kristensen FPB et al. (2023) in Denmark, 22% of newly diagnosed DM patients in the general population have a TG of 2.3 mmol/L, and the risk of stroke increases significantly at TG values between 1-2.0 mmol/L (Kristensen FPB et al. 2023). Our study documents that hypertriglyceridemia occurs in 72 patients (60%) from the higher-risk group 1 and in 20 patients (19.2%) from group 2 with a statistically significant difference in their averages ($U = 3124.000$, $z = -6.442$, $p = 0.000$). As a part of the metabolic components, we report lower HDL-cholesterol in 48 patients (40%) of group 1. Comparing it with 33 patients (31.7%) in group 2 and calculating average HDL cholesterol values ($U = 5413.500$, $z = -1.715$, $p = 0.086$), we find no statistically significant difference between the studied groups.

When investigating CHD as a concomitant cardiovascular condition among IS patients, a statistically significant difference is identified between the studied groups ($\chi^2 = 17.043$, $df = 1$, $p = 0.000$). The prevalence of this cardiovascular pathology is documented in 37 patients (30.8%) in group 1 and in 9 patients (8.7%) in group 2. A total of 46 patients (20.5%) are diagnosed with CHD as concomitant CVD in our study.

Nowadays active smoking is a significant behavioral RF, but the current study does not show a statistically significant difference ($\chi2 = 0.008$, $df = 1$, $p=0.928$) between the studied groups with a high overall percentage of smokers - 54.9%.

The present study confirms that the most prevalent modifiable RFs associated with the health status of Bulgarian patients with acute IS are AH (89.7%), overweight and obesity (87.0%), DM (53.1%), hypertriglyceridemia (41.1%), and lower HDL-cholesterol (36.2%).

An analysis of published data by Bulgarian researchers regarding the prevalence of modifiable RF in IS patients reveals variations in findings and generally lower frequencies than those observed in our patient's cohort. A study by Dimitrov G. (2025), involving 120 IS patients with mean age of 48.99±7.58 years, reports as the most common RFs - AH (72.5%), dyslipidemia (72.5%), DM (35.8%) and smoking (66.7%). A study by Dimitrova D. (2024) in 351 IS patients at average age of 55.8±7.092 years documents as the most common RFs - AH (93.4%), dyslipidemia (83.2%) and DM (27.1%). Our findings regarding the prevalence of AH are similar to those reported by Tsalta M. (2021), who investigated 150 Bulgarian patients with

acute IS and found AH to be the most prevalent RF, affecting 98.7% of patients. Compared to our results differences are observed regarding other modifiable RFs reported by the author, including dyslipidemia (74.7%), DM (24.7%), and smoking (63.3%) (Tsalta M., 2021). In another publication, Tsalta-Mladenov ME and colleagues presents the following vascular RFs as the most prevalent in the Bulgarian patients - AH (98.7%), dyslipidemia (74.7%), heart failure (49.3%), CHD (39.3%), atrial fibrillation (32.0%) and DM (24.7%) (Tsalta-Mladenov ME et al. 2021). A possible explanation for the higher prevalence of RFs observed in our study may be the advanced age of the cases and the predominance of MetS as the leading clinical constellation in the patient's group 1.

International studies have also reported findings that differ from our results regarding the prevalence of certain RFs. A retrospective multicenter study based on a Swiss Stroke Registry in patients aged between 18-55 years reports as the most prevalent RFs dyslipidemia (55%), smoking (38%) and AH (37%) (Dittrich TD et al. 2024). A study by Rahman H et al. (2023) among 120 IS patients aged 41-80 years in Pakistan shows a prevalence of AH (65%), DM (36.3%), dyslipidemia (32.7%) and smoking (32%). A high-risk vascular profile in 244 Indian patients with IS is reported by Renjen PN et al. (2015) with the most common RFs - AH (56.9%), DM (34.8%), smoking (38.9%), hyperlipidemia (23.7%) and CHD (18.0%). In a study of 2054 IS patients in Catalonia at average age of 76 years, the authors find that among patients older than 80 years, the most prevalent RFs are AH (38.82%) and dyslipidemia (25.06%), with a predominance of females (60.33%) (Reverté-Villarroya S et al. 2022). Patients aged 55–80 years demonstrate the highest proportion of individuals presenting with 3-4 vascular RFs (42.76%), with prevalence rates of AH (34.31%) and dyslipidemia (26.33%), and a predominance of males (Reverté-Villarroya S et al. 2022). Regarding sex-related differences, the authors report that women aged 55-80 years have the highest number of RFs (3-4), while among women older than 65 years the most prevalent RFs are DM, atrial fibrillation, and AH (Reverté-Villarroya S et al. 2022). A hospital-based study conducted in Indonesia reports 300 IS patients with the prevalence of the studied RF reported as follows: AH (89.3%), DM (25%), DL (57.7%), smoking (19.3%), age over 60 years (36%), and as the most common three-component combination of RFs (35.3%) (Juli C et al. 2022). Savic M et al. (2018) conducted a case-control study in 120 IS patients at average age of 71.32±6.92 years. In the studied cohort, the authors find as the most common RFs - AH (46.67%), DM (40.83%), DL (71.67%), BMI (29.14±7.18) (Savic M et al. 2018). Nacu A et al. (2016) investigate 2484 IS patients at average age of 70.8±14.9 years and summarize as the most prevalent RF-AH in all age groups

and among the etiological subtypes - IS due to occlusion of small vessels and atherosclerosis of large vessels in the age group of 50-74 years (Nacu A et al. 2016). In patients over 75 years, 54.7% are found to be women, with the highest prevalence of AH (61.6%), atrial fibrillation (43.1%) and DM (15.3%) (Nacu A et al. 2016). Data from the GCNKSS (Greater Cincinnati-Northern Kentucky Stroke Study) study confirm a higher prevalence of AH in diabetic patients (79%), compared with a non-diabetic group of patients (57%) (Air EL et al. 2007). The SHET (Systolic Hypertension in Europe Trial) study reports a 73% reduction in the incidence of strokes in concomitant DM and optimal AHT (Air EL et al. 2007).

Table 45 presents a comparative analysis of the prevalence of the most prevalent RFs in IS patients between the present and other studies conducted in Bulgaria and abroad.

Table 45. *A comparative analysis of the prevalence of the most prevalent RFs in IS parients between our study and others conducted in and outside the country.*

Authors' team, year of Pulbishing	**Country**	**Number of patients (n)**	**Average age of patients**	**Risk factors for IS (%)**				
				AH	**DM**	**DL**	**Smoking**	**AF**
Current Study, 2026	Bulgaria	224	69.2±10.773	89.7	53.1	40.2	54.9	N/A
Dimitrov G., 2025	Bulgaria	120	48.99± 7.58	72.5	35.8	72.5	66.7	5.0
Popovska T. et al., 2024	Bulgaria	118	72.73±10.08	97.5	30.5	54.2	22.9	N/A
Tsalta M., 2021	Bulgaria	150	68.76±11.36	98.7	24.7	74.7	63.3	32.9
Andonova S., 2015	Bulgaria	1698	70.18±8.6	92.8	24.3	13.7	15.5	28.3
Tarwoto P.R. et al., 2025	Indonesia	201	85% over 59	71.3	63	46.2	31.5	N/A
Raharinavalona S.A. et al., 2025	Madagascar	68	64.7% over 60	83.8	10.3	58.8	44.1	N/A
Brewer P.C. et al., 2024	USA	4142	67.73±14.69	78.8	36.7	41.77±13.91	39.4	17.2
Alawneh K.Z. et al., 2022	Jordania	359	67.8±12.2	80.5	52.1	91.1	N/A	8.4
Ambawatte S.B. et al., 2021	Sri Lanka	343	62.0±11.6	66.5	46.4	43.1	32.4	19.6
Tsivgoulis G. et al., 2018	Greece	568	75±11.7	81.1	26.3	67	22.5	34.3
Mi D. et al., 2012	China	519	61.1±11.9	78.6	31.2	74.6	40.1	N/A
Biswas M. et al., 2009	USA	378	71+13	79.3	35.2	30.6	28.2	22.5

5.2 Analysis of the components of MetS in IS patients

MetS, as a clinical constellation of interrelated RFs, includes three or more mandatory components such as elevated BP, DM, hypertriglyceridemia, lower HDL-cholesterol and obesity. Worldwide, many research teams have investigated its prevalence both in the general population and among IS patients. Our study aims to evaluate the impact of this RF on the severity and short-term outcome in Bulgarian patients with acute IS. Group 1 in our study comprises 120 IS patients with MetS out of a total of 224 IS patients. We find that the prevalence of MetS is 53.6% at average age of all studied patients 69.2±10.773 years. Our results are similar to those of Liu L et al. (2015), who analyze 530 patients with acute IS at mean age of 69.3±11.2 years and find that 58.3% of patients met the diagnostic criteria for MetS (Liu L et al. 2015). A comparable prevalence of MetS (55%) is reported by another research group in 2023, examining 120 IS patients at average age of 58.8±9.8 years (Rahman H et al. 2023). A study conducted in neighboring Turkey reports a 60% prevalence of MetS among 80 IS patients (Varol S. 2024). Our results differ from those of a study published in 2013 among patients with first-ever stroke in Cameroon, where the authors report a MetS prevalence of 79% (Balti E et al. 2013). According to Wang GS et al. (2016), the prevalence of MetS among patients with mild IS is 40.2%.

Regarding the included components of MetS, there are also differences in the literature sources we have found. The present study demonstrates that the most prevalent components of MetS are elevated BP (99.2%), DM (95.8%) and overweight and obesity with BMI≥25 kg/m² (95%), followed by hypertriglyceridemia (60%) and lower HDL cholesterol (40%). In contrast, the prevalence of individual vascular RFs is substantially lower in group 2, in which MetS is not identified as a modifiable RF. In the group of IS patients without MetS, we observe the highest prevalence of AH (78.8%), overweight and obesity with BMI≥25 kg/m² (77.9%), followed by lower HDL-cholesterol (31.7%), hypertriglyceridemia (19.2%) and the lowest one of DM (3.8%).

A recent study by Tarwoto PR et al. (2025), with a design similar to ours, divides participants into 81 stroke patients and 120 non-stroke controls. The authors identify AH, obesity, dyslipidemia, smoking, and low physical activity as the most prevalent RFs in Indonesia. They document a prevalence of AH of 71.3% among stroke patients compared to 28.7% in the control group (Tarwoto PR et al., 2025). Concomitant DM is present in 63% of patients and 37% of controls, while smoking is recorded in 46 patients (57.5%), a proportion similar to that observed in our study (Tarwoto PR et al., 2025).

Miti NJ et al. (2022) publish results from a hospital-based case-control study in Bangladesh including 132 participants, divided into two groups - with and without IS with a mean age of cases 54.36±9.94 years (Miti NJ et al. 2022). MetS is diagnosed in 50.0% of cases and 26.2% of controls and is statistically significant for stroke ($p<0.05$) (Miti NJ et al. 2022). Elevated BP is reported in 75.8% of cases and in 39.4% of controls with a statistically significant association between AH and IS ($p<0.05$) (Miti NJ et al. 2022). The results of the study confirm non-statistically significant hyperglycemic values ($p>0.05$) in 37.9% of cases compared to 25.8% in controls (Miti N J et al. 2022). Regarding lipid profile of patients, statistically significant differences ($p<0.05$) are found for lower HDL-cholesterol (65.2% of cases vs. 45.5% of controls) and elevated TG levels (65.2% of cases vs. 37.9% of controls) (Miti NJ et al., 2022). Abdominal obesity is reported in 22.7% of cases and in 30.3% of controls (Miti NJ et al. 2022). Similar to our findings, Miti NJ et al. (2022) confirm that AH is significantly more prevalent among stroke patients group compared to the controls ($\chi2 = 17.87$, $p<0.05$) (Miti NJ et al. 2022). The authors also find a significant association for lower HDL-cholesterol ($p<0.05$), even specifying its 2.4-fold prevalence in the case group (Miti NJ et al. 2022). The study does not confirm a statistically significant difference for hyperglycemia on admission and abdominal obesity (Miti NJ et al. 2022). Clinicians' opinions remain divergent on whether BMI or waist circumference are more informative measure of obesity. The clinical experience clearly confirms that obesity is an independent predictor of stroke occurrence (Tian Y et al. 2024). Ambawatte SB et al. (2021) conduct a study in 343 IS patients at average age of 62.0±11.6 years and document that AH (66.5%), DM (46.4%) and dyslipidemia (43.1%) are the most common RF predominantly in males (59.2%). Our results for group 2 differ regarding AH, which we diagnose in a substantially higher proportion of patients (89.1%). Another large population-based study from Southeast Europe, Greece by Tsivgoulis G et al. (2018) examines 568 IS patients with a mean age of 75±11.7 years, of whom 52.8% are men and reports the following prevalence rates of RFs - AH (81.1%), DM (26.3%), DL (67%), smoking (22.5%) (Tsivgoulis G et al. 2018).

Our results are similar to a case-control study by Ciobanu N et al. (2017) in Moldova, who examine 125 IS patients with MetS at average age of 66 years and find a prevalence of MetS - 54.4% among the studied patients and the following prevalence rates of MetS components: AH (90%), obesity (82%), hyperglycemia (57%), reduced HDL-cholesterol (40%) and hypertriglyceridemia (28%) (Ciobanu N et al. 2017). Another study similar to our is published in 2016 by Zhang X et al. The included patients are with first-ever mild IS with a

mean age of 66.3±9.2 years and 41% of them meet the diagnostic criteria for MetS (Zhang X et al. 2016). Analysis of MetS components shows that the most common of them is elevated BP (96.5%), while the other metabolic abnormalities are distributed as follows: obesity (80.4%), hyperglycemia (80.4%), hypertriglyceridemia (48.3%) and low HDL-cholesterol (18.4%) (Zhang X et al. 2016). A study by Kala SN et al. (2013) in IS patients includes 112 cases with a mean age of 61.8 years and 112 controls at average age of 58.5 years. Analysis of RF in the studied patients shows that the prevalence of AH is significantly higher in the case group (68.8%) than in the controls (29.5%), which confirms the strength of the association between AH and IS (Kala SN et al. 2013). The mean SBP in the cases is 164.4 mmHg and in the control group - 141.8 mmHg (Kala SN et et al. 2013). In comparison, we record lower SBP values: 142.6 22.508 mmHg in IS patients with MetS and 138.6±17.456 mmHg in non-MetS IS patients. In the study of Kala SN et al. (2013), the mean DBP in the case group is 98.6 mmHg, and in the control group the mean DBP is 87.2 mmHg. Comparing with our results, the mean DBP values are 83.4±11.986 mmHg in group 1 and 81.8±9.293 mmHg in group 2. The prevalence of DM is 32.1% among cases and 19.6% in controls which confirms a significant association between DM and IS (OR=1.94) (Kala SN et al. 2013). Fasting hyperglycemia is found in the case group in 76.8% and in the controls - 73.2% (Kala SN et al. 2013). We report 110 patients (91.7%) with hyperglycemia on admission in group 1 and 25 patients (24%) in group 2. The lipid profile of the patients from the study by Kala SN et al. (2013) shows TG> 150 mg% in 15.2% in the case group and in 20.5% in the controls, and reduced HDL cholesterol≤40 mg% is measured in 38.4% of cases and 36.6% of controls. No significant association between hyperlipidemia and IS is identified. Compared to our findings, the authors' results differ in the recorded prevalence of hypertriglyceridemia and lower HDL-cholesterol. In our group 1, hypertriglyceridemia is identified in 60.0% of patients, compared to 19.2% in the controls. Regarding obesity, Kala SN et al. (2013) report a significant association between BMI and IS (OR=3.13), with BMI≥30 kg/m² observe in 37.5% of cases and 16.1% of controls. In our study, 67 patients (55.8%) in group 1 present with different degrees of obesity (BMI≥30 kg/m²), compared with 16 patients (15.4%) in the control group. In summary, all MetS components examined in details among the studied IS patients, Kala SN et al. conclude that there is a strong association (OR=2.87) between MetS and IS and report a prevalence of MetS among their cases - 82.1% and in the controls - 61.6% (Kala S N et al. 2013). A comparative analysis of the prevalence of MetS and its individual components among IS patients in the present study and in similar studies conducted in other countries is presented in **Table 46.**

Table 46. *A comparative analysis of the prevalence of MetS and its components between the present study and similar ones conducted in other countries*

Authors' team, year of publication	**Country**	**Number of patients (n)**	**Mean age of patients**	**MetS prevalence (%)**	**Components of MetS**				
					AH (%)	**Hyperglycemia (%)**	**TG (%)**	**Low HDL-cholesterol (%)**	**Obesitas (%)**
Current Study, 2026	Bulgaria	120	68.3±10.446	53.6	99.2	95.8	60	40	55.8
Raharinavalona S.A. et al., 2025	Madagascar	239	67.8 % over 60 years old.	77.9	94.8	61.6	43.0	64.8	64.8
Varol S., 2024	Turkey	80	64.76±11.31	60	76.3	41.3	35	71.3	70
Miti N. J. et al., 2022	Bangladesh	66	54.36±9.94	50.0	75.8	37.9	65.2	65.2	22.7
Ciobanu N. et al., 2017	Moldova	125	66	54.4	90	57	28	40	82
Zhang X. et al., 2016	China	208	66.3±9.2	41	96.5	80.4	48.3	18.4	80.4
Kala S.N. et al., 2013	India	224	61.8	71.4	99.1	76.8	15.2	38.4	37.5
Ashtari F., 2012	Iran	200	62.24±9.9	62	68	57	169.7 mean	50	85
Mi D. et al., 2012	China	182	62.2±10.9	26	81.3	52.8	39.1	53.4	58.8

In the present study of IS patients we identify several metabolic clusters comprising the following combinations: of three components - in 51 patients (22.8%), four components - 45 patients (20.1%) and five components - 20 patients (8.9%). Analysis of the results shows that, within group 1, the largest subgroup consists of patients with a combination of three MetS components (22.8%), followed by those with four components (20.1%), and finally those with all five components (8.9%). The most prevalent three-component combination in group 1 is arterial hypertension - diabetes mellitus - hypertriglyceridemia. The most prevalent four component MetS combination that we identify is the combination of AH-DM-hypertriglyceridemia-overweight/obesity. All five MetS components are found in 20 patients (8.9%) with gender-related differences - males predominate and are 2.33 times more numerous than females.

In controls without IS (group 3), we specify that there are different combinations of three components of MetS - in 52 patients (23.2%), four components - 21 patients (9.4%) and five components - 3 patients (2.7%). The distribution of these combinations differs from that observed in IS patients. In the control group, the most prevalent pattern is the combination of three MetS components (23.2%), whereas the prevalence of four-component (9.4%) and five-component (2.7%) combinations is considerably lower.

Analyzing the most common combinations of MetS components, we find that the presence of more components affects the relative risk of IS. The present study confirms that the combination of three components of MetS does not increase the relative risk for IS (OR: 0.975, 95% Cl 0.628-1.514, p=0.911). The combination of four components of MetS increases the relative risk of IS (OR: 2.430, 95% Cl 1.394-4.236) with a statistically significant difference found between the two groups (p=0.002). The combination of five components of MetS also affects the risk and is associated with a 3.6-fold increased risk of acute IS (OR: 3.562, 95% Cl 1.402-9.047) with a statistically significant difference between the studied groups (p=0.008). These findings demonstrate that the relative risk of acute IS increases proportionally with the number of MetS components. Our case-control study confirms that the combination of four components of MetS increases 2.4 times and that of five components increases the relative risk of IS by 3.6 times.

A review of international literature sources presents some similar results to our findings on the impact of individual components of MetS on the relative risk of IS. Based on their own results from patients with coronary artery disease, Koren-Morag N et al. (2005) postulate that

each individual component of MetS is a predictor of IS, with elevated BP and impaired glucose tolerance being the most significant of them (Koren-Morag N et al. 2005). Ninomiya JK et al. (2004) report that individual MetS components, with the exception of abdominal obesity, are significantly associated with an increased risk of myocardial infarction and stroke, indicating that this risk is the highest for hypertriglyceridemia (OR: 1.66, 95% Cl 1.20-2.30, p=0.003). Our results show that all MetS components are individually associated with an increased risk of IS, the most significant among them is the elevated BP. In group 2, AH as a modifiable RF is also associated with a significantly increased risk for IS. According to Koren-Morag N et al. (2005), MetS is associated with a 1.5-fold higher risk of IS. Our results confirm that MetS increases the relative risk of IS by 1.6 times. MetS patients with DM, especially females, are considered to be the highest risk group for cerebrovascular accidents, and the calculated relative risk of stroke in them increases up to 2 times (Koren-Morag N et al. 2005). An increase in the IS risk is observed with the increase in the number of MetS components - in monitored patients with atherosclerotic disease, the risk increases more than 5-fold in patients with four or more components of MetS (Koren-Morag N et al. 2005). Results from our case-control study confirm that the combination of four components of MetS increases 2.4-fold and that of five-components increases the relative risk of IS by 3.6 times. Regarding gender-related differences, Koren-Morag et al. (2005) report that the risk of IS is highest among men with four or five MetS components, whereas among women the highest risk is associated with the five-component MetS combination (Chen H-J et al., 2006). Other authors also support the concept of a proportional increase in stroke risk with an increasing number of MetS components, reporting for three components (HR: 2.61; 95% CI 2.09-3.25) and for four components (HR: 3.18; 95% CI 2.54-3.98) (Park SK et al., 2021). Of all MetS components, the authors find that elevated BP (HR: 2.13; 95% Cl 1.66-2.73) and fasting hyperglycemia (HR: 1.56; 95% Cl 1.14-2.13) are associated with the highest relative risk for IS (Park SK et al. 2021).

Iso H et al. (2007) report that in a long-term follow-up Asian cohort of five Japanese communities, including 256 IS patients and 116 cases with CHD, the number of components of MetS affects the risk of IS, but a plateau is reported in the presence of three or more components. The authors find that the risk of IS is 8 times higher and the incidence of IS is 2-3 times higher than that of CHD (Iso H et al. 2007). Their results confirm that MetS is associated with a 1.5-2.5-fold higher risk for CHD and IS in a Japanese population aged 40-69 years (Iso H et al. 2007) and the impact of MetS on the risk of IS reported by the authors is similar to that of our study. Motillo et al. claim that MetS is associated with a two-fold

increased risk of stroke (Moghadam-Ahmadi A et al. 2023). Other authors suggest that MetS increases the risk of clinically overt stroke, silent cerebral infarctions, and post-stroke cognitive impairments by two- to four-fold (Li P et al. 2016). Results similar to ours confirm that individual components of MetS such as elevated BP (OR=3.8), hyperglycemia (OR=4.1) and hypertriglycedemia (OR=3.7) separately also increase the risk of stroke (Jamee AS et al. 2019).

A study of the individual components of MetS confirms that the prevalence of MetS increases with age in both sexes (Scuteri A et al. 2010). AH, as a component of MetS, has been established as a significant RF for stroke occurrence without significant gender-related differences (Suh S et al. 2014). In MetS patients in southern European countries, the most common component is elevated BP (>90%) (Scuteri A et al. 2015). These values correspond to the very high prevalence of AH in all studied IS patients (89.7%), as well as only in the IS group with MetS (99.2%). An analysis of the individual components of MetS according to their geographical distribution shows that dyslipidemia is reported mainly in Northern Europe and America, and abdominal obesity is prevalent in women from Southern Europe, the United Kingdom and America (Scuteri A et al. 2015). The authors also report substantial differences in the prevalence of specific metabolic combinations across countries - elevated BP-hypertriglyceridemia-abdominal obesity occurs in the United Kingdom (32.3%), Sardinia (19.6%) and Germany - 18.5% (Scuteri A et al. 2015). Another possible combination of metabolic components - hyperglycemia-elevated BP-abdominal obesity is recorded in Italy (31.4%), Belgium (20.4%) and Spain (18.4%) (Scuteri A et al. 2015). Based on the analysis, our study documents that in Bulgarian IS patients with diagnosed MetS, the most common combinations of different components of MetS are AH-DM-hypertriglyceridemia-obesity and the three-component combination AH-DM-hypertriglyceridemia.

The results of the CHANCE (Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular events) study in 5170 patients with mild IS or TIA in 114 Chinese clinical centers show that MetS patients with DM have more vascular RF and higher NIHSS (Chen W et al. 2017). Among the MetS components, AH is the most prevalent (99.1%), followed by dyslipidemia (89.9%) and obesity (88.2%) (Chen W et al., 2017). Similarly, our study identifies AH (99.2%), DM (95.8%), and overweight/obesity (95.0%) as the most prevalent MetS components. The Northern Manhattan Study confirms an increased risk of stroke among women with MetS, while the Framingham Offspring Study demonstrates that MetS, even in the absence of DM, is represented as a significant RF among women (Takahashi K et al., 2007).

Our results differ from those of the ARIC (Atherosclerosis Risk In Communities) study, which reports the following prevalence of the individual components of MetS: abdominal obesity (53%), hyperglycemia (49%), elevated BP (43%), lower HDL-cholesterol (39%) and hypertriglyceridemia (28%). Abdominal obesity is more prevalent among women (66%), whereas hyperglycemia (56%), lower HDL-cholesterol (43%) and hypertriglyceridemia (33%) predominate among men (Rodriguez-Colon S et al., 2009). The ARIC study also confirms that the number of MetS components increases the relative risk of stroke, reporting hazard ratios of 2.82 (95% CI 1.57-5.07) for three components, 4.16 (95% CI 2.35-7.38) for four components, and 4.92 (95% CI 2.73-8.87) for five components (Rodriguez-Colon S et al., 2009).

The data presented in this analysis reinforce the multicomponent nature of MetS and the variability in the prevalence of its individual components across different populations. By characterizing specific metabolic combinations among IS patients, our study supports the view that there is no single mandatory component of MetS; however, MetS itself, its individual components, and particularly the combinations of four and five components significantly increase the relative risk of stroke among Bulgarian patients with acute IS (Kassi E et al., 2011).

5.3 Evaluation of the impact of MetS on the relative risk for IS

In the present study, we find that MetS was a highly prevalent modifiable RF among the 224 IS patients at average age of 69.2±10.773 years, affecting 53.6% of the study cohort. By investigating the strength of the association between MetS and IS, we demonstrate that MetS is associated with a 1.65-fold higher relative risk of IS among the studied Bulgarian patients (OR: 1.656, 95% CI 1.139-2.406, p = 0.008). Our findings are supported by a meta-analysis evaluating the impact of MetS on stroke risk, which summarizes data from 11 studies and confirms that MetS patients have a significantly higher risk of stroke (RR: 1.435, 95% CI 1.131-1.820, p = 0.000) (Li X et al., 2021). MetS has been shown to be a significant RF for increasing the relative risk of stroke among 10357 participants in the NHANES III (The Third National Health and Nutrition Survey) (OR: 2.16, 95% Cl 1.48-3.16, p=0.0002) (Ninomiya JK et al. 2004).

We investigate and confirm the impact of individual components of MetS on increasing the relative risk for IS. The analysis of our results shows that the most prevalent component of MetS is AH (89.7%). Examining the strength of the association between AH and IS, we found that AH increases the risk of IS by 4.22 times (OR: 4.225, 95% CI 2.527-7.064, p<0.0001). Our results differ from those of Tsalta M. (2021), who in another similar aged clinical

contingent reports a higher relative risk of 28.778 for IS associated with AH (OR: 28.778, 95% Cl 6.670-124.155). Our results also differ from those of Dimitrov G (2025), who reports 10.018 relative risk of IS, associated with AH (OR: 10.018, 95% Cl 5.523-18.173) in patients at average age of 48.99±7.58 years. Likewise, our results differ from those of the case-control study by Mallmann AB et al. (2012), which includes 133 IS patients and 272 controls and reports an 11.2-fold higher relative risk of IS associated with AH (OR: 11.2, 95% CI 5.4-23.3) and PAR=84.9%; 95% Cl (72.5-93.5).

Evaluating the impact of individual RFs on the risk of IS, it has been shown that AH is the most significant component that increases the risk of stroke (O'Donnell MJ et al. 2012, Kjeldsen SE et al. 2017, Peters SAE et al. 2020, Horn JW et al. 2021), confirmed by the present study. Comparison with the available literature demonstrates results comparable to those reported by other international authors. Our data on the impact of AH on stroke risk are similar to those of the famous INTERSTROKE case-control study, which includes data from 32 countries and concludes that a combination of ten modifiable risk factors accounted for 90% of the population-attributable risk (PAR) for stroke (O'Donnell MJ et al., 2012; Peters SAE et al., 2020). INTERSTROKE results show that AH increases 2.98 stroke risk (OR: 2.98, 99% Cl 2.72-3.28) and PAR=47.9%; 99% CI (45.1-50.6) and confirm that AH is the most significant modifiable RF (O'Donnell MJ et al. 2012, Kjeldsen SE et al. 2017, Peters SAE et al. 2020), responsible for over 80% of the global risk of strokes (Pacinella G et al. 2024). In patients with IS participants in the Northeast China Rural Cardiovascular Health Study, the combination of AH and obesity is found to be associated with the highest risk of IS, especially in women (Chen MQ et al. 2021). Patients with MetS are a high-risk group for IS and elevated BP is one of the main components of the syndrome as defined (Schilliaci G et al. 2004). The results of a prospective Italian study PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) indicate that patients with MetS are older, with a longer duration of AH and higher SBP (Schilliaci G et al. 2004).

DM as a modifiable RF, is associated with an increased risk of stroke and a more unfavorable functional outcome (Larsson SC et al. 2017). There is a correlation between the duration of DM and the risk of cerebrovascular event, and diabetics have a significantly higher probability of developing lacunar strokes (Maida CD et al. 2024). In young IS patients under 55 years of age and concomitant DM, a 10-fold higher risk of stroke has been reported (Maida CD et al. 2024). Data from the population-based study REGARDS (REasons for Geographic And Racial Differences in Stroke) present 1405 IS patients and identify AH, DM, smoking,

and atrial fibrillation as the most prevalent RFs (Howard G et al. 2023). The authors investigate age-related differences in the prevalence of these RFs and find that DM has a greater impact on stroke risk in young patients at the age under 65 years (Howard G et al. 2023).

According to the hospital-based Fukuoka Stroke Registry, involving 10245 IS patients with a mean age of 72.7±12.5 years, diabetics more frequently exhibit AH (86.6%), dyslipidemia (62.8%), smoking (58.1%), chronic kidney disease (39.8%), and coronary artery disease (20.7%), with a predominance of males (66.9%) (Kuroda J et al. 2019). Posterior circulation strokes are more frequently observed among diabetic patients (38.5%), and DM is associated with an increased risk of posterior circulation IS (OR: 1.41, 95% CI 1.25-1.60) and thrombotic posterior circulation stroke (OR: 1.61, 95% CI 1.42-1.82) (Kuroda J et al., 2019). Another group of authors reports that DM is associated with an increased risk of IS overall (OR: 1.12, 95% CI 1.07-1.17), large-artery atherosclerotic stroke (OR: 1.28, 95% CI 1.16-1.40), and small-vessel occlusion stroke (OR: 1.21, 95% CI 1.10-1.33), but not cardioembolic stroke (OR: 1.06, 95% CI 0.97-1.15, p=0.17) (Larsson SC et al. 2017). A meta-analysis of 64 prospective studies in IS patients with DM confirms the increased risk of stroke in women (OR: 2.28; 95% CI 1.93-2.69) and in men (OR: 1.83; 95% CI 1.60-2.08) (Larsson SC et al. 2017).

Examining the strength of the association between DM and IS, the present study finds that DM increases the risk of IS by 3.7 times (OR: 3.749, 95% Cl 2.497-5.628). Patients with MetS have a five-fold higher risk of developing DM type II compared to healthy individuals (Grundy SM et al. 2008, Kaur J et al. 2014, Jamee AS et al. 2019). A postulate of the risk of CVD and DM is that it increases with the number of MetS components (Jamee AS et al. 2019). Approximately 35 times the risk of DM is higher in patients with four or more components of MetS (Klein BE et al. 2002). Compared to our results, Dimitrov G (2025) reports a 6-fold higher risk of IS in younger patients (OR: 6.143, 95% Cl 2.910-12.968). In a study of Tsalta M (2021), DM increases the relative risk of stroke by 2.6-fold (OR: 2.649, 95% Cl 1.279-5.487).

Hyperglycemia is recorded in 66% of patients in acute IS and is a proven predictor of increased stroke mortality and lack of effect from undergoing IVT (Maida CD et al. 2024). Stress hyperglycemia is determined in patients without concomitant DM, in whom blood glucose is measured ≥7.8 mmol/l or HbA1c>6.5% and is recorded in 8-35% of stroke patients at hospitalization (Yaneva ZA et al. 2018). A Bulgarian retrospective study in 555 IS patients in 2016-2017 shows that stress hyperglycemia is reported in 20.9% of the studied cohort, and

fatal outcome occurs in 25.8% of patients, of whom with stress hyperglycemia (32.76%), DM type 2 (33.80%) and normoglycemia (19.05%) (Yaneva JA et al. 2018). The authors find a higher level of stress hyperglycemia in patients with moderate non-fatal stroke compared to others with mild stroke (p=0.033) and do not establish a correlation between blood glucose levels on admission and the severity of non-fatal IS (Yaneva JA et al. 2018). A study in 2007-2013 among Bulgarian patients divided in two groups of 129 patients with a mean age of 71 years, of whom 41% are diagnosed with DM, finds that hyperglycemia during hospitalization is more common in men, and levels of blood glucose ≥ 14.3 mg/mL are an independent predictor of fatal outcome in the first three days of stroke, especially in patients without DM (Arabadzhieva D et al. 2015). Hyperglycemia significantly affects the outcome of stroke, especially in lacunar strokes and is a predictor of an unfavorable outcome in the three months after stroke (Weir CJ et al. 1997).

According to another European investigator team, hyperglycemia is found in over 33% of patients in the acute stage of IS (Tsivgoulis G et al. 2019). Our results show that in the group of IS patients with MetS, hyperglycemia on admission is registered in 110 patients (91.7%) and in group 2 - IS patients without MetS - in 25 patients (24%) or in total for all IS patients it is observed in 60.3%.

Our data are similar to those of other researchers who report hyperglycemia at hospitalization in 2/3 of IS patients, explaining it with diagnosed or newly diagnosed DM, or stress hyperglycemia (Lindsberg PJ et al. 2004). A study in seven European countries examines the impact of DM on the clinical outcome of stroke and documents that among diabetics, AH (p=0.001) and lacunar strokes are more common (Megherbi SE et al. 2003, Maida CD et al. 2024). Hyperglycemia on admission has been reported in up to 40% of IS cases without a prior diagnosis of DM (Maida CD et al. 2024). A meta-analysis involving data from 64 cohort studies reports that DM is associated with higher risk of stroke in women (adjusted RR: 2.28, 95% CI 1.93-2.69) than in men (adjusted RR: 1.83, 95% CI 1.60-2.08), identifying DM as a more prevalent RF among females (Martin et al. 2025).

Obesity is a well-documented modifiable RF for cardiovascular accidents and strokes (Miwa K et al. 2024). The relative risk estimates based on BMI indicate a 1.4-fold increased risk of stroke (OR: 1.40; 95% CI 1.29-1.52), a 1.38-fold increased risk of IS (OR: 1.38; 95% CI 1.20-1.59) in both sexes, and a markedly increased risk of DM type II, particularly among women (OR: 3.18; 95% CI 2.97-3.39) (Censin JC et al. 2019). Overweight (HR: 1.06;

95% CI 1.03-1.11) and obesity (HR: 1.14; 95% CI 1.06-1.27) in men, as well as obesity (HR: 1.13; 95% CI 1.01-1.19) in women are associated with a higher risk of IS compared to normal weight individuals (Shiozawa M et al. 2021). The results of population-based studies SAHS (San Antonio Heart Study) and IRAS (The Insulin Resistance Atherosclerosis Study) confirm that BMI is an predictive indicator for the development of MetS, and patients with a BMI> 30 kg/m² are three to eight times more prone to the syndrome (Palaniappan LP et al. 2011). In the present study, we find that the combination of overweight (BMI≥25 kg/m²) and obesity (BMI≥30 kg/m²) increased the relative risk of IS (OR: 3.120, 95% Cl 1.929-5.048) with a statistically significant difference between the studied IS groups (p<0.001). According to Dimitrov G. (2025), excess body weight increases the risk of IS 2.2 times (OR: 2.200, 95% Cl 1.929-5.048). A study, analyzing the impact of 12 modifiable RFs on stroke risk, finds that genetically determined higher BMI is significantly associated with an increased risk of IS (OR: 1.14, 95% Cl 1.06-1.22) as well as stroke due to occlusion of the large arteries (OR 1.32, 95% Cl 1.12-1.57) (Harshfield EL et al. 2021). A meta-analysis of six cohort studies from Europe, the United States, and Australia confirms that stroke risk increases by 22% for every 5 kg/m² increase in BMI (Larsson SC et al. 2017). Kurth T et al. (2002) find a significant increase in the relative risk for IS with an increase in BMI, regardless of the impact of other RFs. Among the men studied, BMI does not affect stroke severity, but higher BMI is associated with a greater prevalence of AH and DM (Kurth T et al. 2002).

Investigating dyslipidemia as a RF, we find that in the studied patients it does not increase the relative risk of stroke (OR: 0.721, 95% Cl 0.496-1.049, p=0.087), but lower HDL-cholesterol increases it 2.6-fold (OR: 2.606, 95% Cl 1.683-4.035) with a statistically significant difference (p<0.001). Hypertriglyceridemia is also significant RF in IS patients. The present study demonstrates that elevated TG>1.7 mmol/L are associated with a 3.3-fold higher relative risk of IS (OR: 3.306, 95% Cl 2.138-5.113) with a statistically significant difference between the studied groups (p<0.001). Comparing our results to those of other Bulgarian researchers who investigate modifiable RF in stroke, differences are found. According to Dimitrov G (2025), lower HDL-cholesterol increases almost 5.2-fold the relative risk of IS (OR: 5.182, 95% Cl 2.973–9.031). Our results are similar to those of Tsalta M. (2021), who reports that dyslipidemia increases the relative risk of IS by 0.561 times (OR: 0.561, 95% Cl 0.293-1.074). A population-based study finds that lower HDL-cholesterol is associated with an increased risk of stroke (HR=1.23, 95% CI 1.18-1.28) and myocardial infarction (HR=1.47, 95% CI1.41-1.54) (Han BH et al. 2020). Based on data from a Chinese prospective study Kailuan Study

involving 96 258 participants with a mean age of 51.5 years and a predominance of men (79.6%) Li H et al. (2022) reports a 31% increased risk of stroke at HDL-C levels ≤1.06 mmol/L and an 85% increased risk at HDL-C levels ≥2.05 mmol/L. The authors conclude that higher HDL-cholesterol is associated with a higher incidence of stroke (Li H et al. 2022). A meta-analysis associated with LDL-C-lowering therapy indicates that each 1 mmol/L reduction in LDL-cholesterol is associated with a 20% reduction in IS risk (RR: 0.80, 95% CI 0.76-0.84) (Martin SS et al. 2025). Another meta-analysis from 62 prospective studies shows that an increase of 1 mmol/L in HDL-cholesterol lead to a decrease in the relative risk of IS (RR: 0.75, 95% CI 0.69-0.82) (Martin SS et al. 2025). A study in 632 IS patients, evaluating the impact of lipids and their predictive value for stroke, confirms that hypertriglyceridemia is significantly associated with a higher risk of IS, respectively in women (HR: 1.12, 95% CI 1.01-1.23) and in men (HR: 1.07, 95% CI 1.02-1.13) (Liu X et al. 2019).

After examining each RF individually, we further investigate the strength of association between the individual components of MetS in IS patients with MetS, comparing them with a control group of individuals with MetS but without IS. The results not only confirm the importance of each MetS component in relation to stroke risk but also identify the most significant contributors. In MetS patients, AH as a component of MetS, increases the risk of stroke 11.3-fold (OR: 11.333, 95% Cl 1.391-92.326) with a statistically significant difference (p=0.023), DM - 26.2 times (OR: 26.209, 95% Cl 9.791-70.157) with a statistically significant difference (p<0.001), hypertriglyceridemia significantly increases the risk of stroke by 2.6 times (OR: 2.682, 95% Cl 1.530-4.701).

For comparison, we also evaluate the association between individual modifiable RFs in IS patients without MetS and a control group without IS and without MetS. Considerable differences are observed regarding their influence on stroke risk compared with the MetS group described above. In patients without MetS, we find that hypertriglyceridemia increases the risk of stroke 5 times (OR: 5.000, 95% Cl 1.928-12.970), AH - 3.6 times (OR: 3.616, 95% Cl 2.022-6.467), lower HDL-cholesterol - 3.6 times (OR: 3.625, 95% Cl 1.841-7.141), and overweight and obesity with BMI≥25 kg/m² - 3.5 times (OR: 3.522, 95% Cl 1.981-6.260) with a statistically significant difference (p<0.001) between the studied groups. The only RF that has no a significant impact on stroke risk among patients without MetS is DM (OR: 0.547, 95% CI 0.164-1.828; p=0.327).

In conclusion, we can summarize that as the most significant components of MetS, increasing the relative risk of IS in patients with metabolic disorders, we prove to be DM (OR: 26.209), AH (OR: 11.333) and hypertriglyceridemia (OR: 2.682).

5.7 Analysis of the impact of MetS on the severity of IS

MetS patients are a high-risk clinical contingent who are at a significantly higher risk of having first-ever IS (Liu L et al. 2015). The metabolic profile of patients, and especially the number of MetS components, correlates with the risk of having a cerebrovascular disease (Liu L et al. 2015), which is age-related, increases with age, and is highest in patients over 65 years (Jermakow N et al. 2022). Therefore, considering the mean age of the patients included in the present study, they belong to this high-risk age group. Based on the age distribution of the studied IS patients, most of them are in the eighth decade, and the mean age in the IS group with MetS is 68.3±10.446 years. These participants are at advanced age, characterized by an increased risk of stroke regardless of the presence or absence of metabolic disturbances. Some individual MetS components, such as AH and DM, are present in more than 95% of our MetS cohort. Considering the metabolic status of the investigated cases, we find that most of the patients in group 1 present with three or four MetS components. Furthermore, 8.9% of all studied patients are cases with both acute IS and MetS in whom all five components of MetS are identified. Some of these patients have been insufficiently monitored and treated, resulting in clinical evidence of suboptimal BP control and laboratory findings of decompensated carbohydrate metabolism at hospital admission. Global trends indicating epidemic, and even pandemic, proportions of obesity among European populations are also confirmed in our cohort, particularly in the MetS group, where obesity represents a significant and highly prevalent modifiable RF. The lipid-lowering therapy documented in our patients is likely insufficiently effective, as dyslipidemia remains a common RF. Particular attention should also be paid to the suboptimal fibrate therapy, as evidenced by the elevated TG observed on admission in high-risk IS patients. Another meta-analysis, incorporating data from 13 cohort studies, concludes that stroke occurs 1.6 times more frequently in patients with MetS than in those without MetS (Liu L et al., 2015). The authors' study does not establish a significant correlation between MetS and short-term stroke outcomes and does not confirm a relationship between the number of MetS components and the short-term prognosis of IS (Liu L et al. 2015). Chen W et al. (2017) report that transient ischemic attacks and mild IS, accounting for approximately 65% of all strokes, are associated with a 10-15% increased risk of recurrent stroke within the subsequent three months. Patients with mild ISs are predominantly younger

than 65 years with mild neurological deficits and a favorable long-term stroke outcomes (Marsh E et al. 2023). The statistically analyzed data in the present study provide a real opportunity to evaluate the impact of individual MetS components on the risk of unfavorable clinical outcomes following IS and to identify optimal therapeutic approaches for high-risk patients. Such interventions may reduce post-stroke disability and improve long-term prognosis. Regarding post-stroke mortality, it has been documented that cardiovascular mortality occurs earlier in MetS patients and the five-year mortality rates are significantly higher (Balti E et al., 2013).

The present study, enrolling a proportion (53.6%) of high-risk patients with MetS, provides data on stroke severity both on admission and at discharge among patients with acute IS. The evaluation of the neurological deficit is performed on the NIHSS scale, which is an established, reliable tool for assessing stroke severity, routinely used in clinical practice and is a numerical expression of the neurological deficit that has occurred in patients with acute IS based on 15 items (Kwah LK et al. 2014, Juli C et al. 2022, Glimmerveen A et al. 2023). The scores on the NIHSS scale range from 0 to 42 points, with higher scores indicating more severe neurological impairment (Kwah LK et al. 2014, Glimmerveen A et al. 2023). On admission we find the following distribution of patients according to the stroke severity: in the IS group with MetS, patients with mild IS (NIHSS: 1-4 sc.) are 16.7%, moderate IS (NIHSS: 5-15 sc.) are 63.3% and with severe IS (NIHSS: ≥16 sc.) are 20%. In group 2, the distribution according to NIHSS is: 28.9% patients with mild IS (NIHSS: 1-4 sc.), 53.8% with moderate IS (NIHSS: 5-15 sc.) and 17.3% with severe IS (NIHSS: ≥16 sc.). Comparing the studied groups, the highest proportion of patients in them has moderate IS. However, mild ISs are more common in group 2 than in the MetS IS group (28.9% vs. 16.7%). Severe strokes account for one-fifth of all IS patients with MetS and are more frequent than in IS patients without MetS.

Comparison of our findings with those reported by Dimitrov (2025) reveals similar proportions of mild and moderate IS among patients corresponding to our group 2: mild IS (36.7%), moderate IS (57.5%), and severe IS (5.8%), with a mean NIHSS score of 6.73±4.04 on admission. The median NIHSS score among all patients in our study is 7 (5, 13). Our high-risk patients in the IS group with MetS differ substantially regarding the prevalence of mild IS (16.7%) and severe IS (20.0%), a finding that cannot be explained only with the advanced age. Our data demonstrate a considerably higher frequency of severe IS, and this tendency persists at discharge. Similar to our results are those of Liu et al. (2015), who study 530 IS patients, 58.3% of whom meet the diagnostic criteria for MetS with a mean age of 69.3±11.2 years. The

authors conclude that MetS can worsen the patient's condition and prognosis, but it is not an independent predictor of short-term outcome (Liu L et al. 2015). They do not establish a significant correlation between MetS and short-term stroke outcomes and do not confirm a relationship between the number of MetS components and the short-term prognosis of IS (Liu L et al. 2015). Another research group of Zhang X et al. (2016) publishes results from 208 patients with first-ever IS with a mean age of 66.3±9.2 years and a mean NIHSS score of 3 points on admission. Among the studied patients, 41% have MetS, and 23.5% experience early neurological deterioration. This deterioration occurs predominantly in older patients (p=0.040), as well as in those diagnosed with MetS (p=0.005) and DM (p=0.005) (Zhang X et al., 2016).

Evaluating the impact of MetS on stroke severity, we analyze the recorded NIHSS scores. The distribution of patients on admission shows that patients with moderate strokes (NIHSS 5-15 sc.) predominate - 63.3% in group 1 and 53.8% in group 2. Through our analysis, we establish that MetS does not significantly increase the risk (p=0.151) of developing a moderate IS (NIHSS 5-15 sc.) (OR: 1.480, 95% CI 0.867-2.528), nor does it significantly affect (p=0.607) the risk of developing a moderate-to-severe IS (NIHSS≥16 sc.) (OR: 1.194, 95% CI 0.607-2.350). MetS negatively affects the risk of mild IS (NIHSS 1-4 sc.) (OR: 0.493, 95% Cl 0.260-0.936) with a statistically significant difference (p=0.031). We also examine its individual components, proving that during hospitalization, all components of MetS increase the relative risk of moderate IS (NIHSS 5-15 sc.) with a statistically significant difference between the studied groups. In IS patients we find that hyperglycemia on admission increases 14.2-fold (OR: 14.281, 95% Cl 6.589-30.951, p<0.0001), hypertriglyceridemia increases 5.2-fold (OR: 5.249, 95% Cl 2.477-11.126, p<0.0001), AH increases 2.1-fold (OR: 2.178, 95% Cl 1.274-3.723, p=0.004), lower HDL-cholesterol increases 2-fold (OR: 2.086, 95% Cl 1.071-4.063, p=0.031) and overweight and obesity (BMI≥25 kg/m²) (OR: 1.750, 95% Cl 1.029-2.976, p=0.039) increases 1.7 times the relative risk of moderate stroke (NIHSS 5-15 sc.). An analysis of moderate to severe and severe strokes (NIHSS≥16 sc.) at hospitalization shows that among all MetS components DM (OR: 11.449, 95% Cl 2.622-49.987, p=0.001) and hypertriglyceridemia (OR: 6.736, 95% Cl 1.493-30.380, p=0.013) significantly increase the risk of moderate to severe stroke. Hyperglycemia on admission (OR: 3.000, 95% Cl 1.284-7.010, p=0.011) also positively influences the relative risk of stroke with an NIHSS≥16 scores. As a result of the treatment administered during the acute stage of IS, we observed changes in NIHSS scores at discharge. The percentage distribution of patients at discharge shows that in group 1 the percentage of patients with NIHSS 5-15 sc. decreases to

40.8% and in group 2 - to 38.5%. Our results on stroke severity are similar to those of a published hospital-based study in Indonesia in 300 IS patients who has moderate IS - 62% at admission and 53% at discharge (Juli C et al. 2022). Our analysis proves that MetS does not significantly affect (p=0.354) the risk of mild IS (NIHSS 1-4 sc.) at discharge (OR: 0.778, 95% Cl 0.457-1.323). MetS is not associated with moderate IS (NIHSS 5-15 sc.) (OR: 1.104, 95% Cl 0.645-1.889) as well as moderate to severe IS (NIHSS≥16 sc.) (OR: 1.304, 95% Cl 0.647-2.627) at discharge. Evaluation of the impact of individual MetS components confirms that, at discharge, admission hyperglycemia (OR: 6.562, 95% CI 3.019-14.262, p<0.0001) significantly increases the risk of a moderate stroke by 6.5-fold, while hypertriglyceridemia (OR: 5.210, 95% CI 1.916-14.172, p=0.001) increases the relative risk by 5.2-fold according to NIHSS assessment.

An analysis of severe strokes (NIHSS≥16 sc.) at discharge shows that the same components are statistically significant - hypertriglyceridemia (OR: 7.846, 95% Cl 1.759-34.994, p=0.007), hyperglycemia on admission (OR: 3.913, 95% Cl 1.526-10.033, p=0.004) and DM (OR: 4.200, 95% Cl 1.523-11.581, p=0.006). As a summary of the impact of the individual components of MetS, we can point out that hyperglycemia on admission affects the risk of moderate and severe strokes. Our results contradict those of another Bulgarian study, which does not establish a correlation between the blood glucose level at hospitalization and the severity of non-fatal IS (Yaneva ZHA et al. 2018).

The performed correlation analyses confirm a moderate correlation between hyperglycemia on admission and the severity of neurological deficit both at admission and at discharge in IS patients with MetS. Regression analyses demonstrate that admission hyperglycemia and HDL cholesterol are significant predictors of the severity of neurological deficit at hospitalization, whereas admission hyperglycemia and SBP are significant MetS components influencing the severity of neurological deficit at discharge.

5.8 Analysis of the impact of MetS on the clinical outcome of IS

In the present dissertation, MetS is diagnosed in 53.6% of the studied patients, comprising group 1. According to data from different publications, the prevalence of MetS among IS patients ranges from 33.4% to 58.3% (Renjen PN et al. 2025; Sharma J Sr et al. 2025). The risk of stroke in MetS patients is defined as 70% higher compared to that of non-MetS patients (Sharma J Sr et al. 2025). Data from epidemiological studies confirm that MetS increases the risk of stroke by 1.5-1.6 times (Chen W et al. 2025, Renjen PN et al. 2025). MetS

is considered as an independent predictor of unfavorable functional outcome following a cerebrovascular event, demonstrating a dose-dependent correlation with the number of MetS components present (Chen W et al. 2025; Sharma J Sr et al. 2025).

According to a review by Sharma J Sr et al. (2025), MetS affects not only the short-term outcome after stroke but also has a significant impact on long-term prognosis. High-risk IS patients with MetS are at higher risk for an unfavorable functional outcome, poor prognosis and recurrent stroke (Sharma J Sr et al. 2025). Theoretically, effective management of the metabolic components of the syndrome could reduce the risk of IS by approximately 30% (Sharma J Sr et al. 2025). Sharma J Sr et al. (2025) further suggest that stroke risk and subsequent unfavorable outcomes are specifically associated with certain MetS components, including elevated BP, abdominal obesity and hyperglycemia. Other authors consider dyslipidemia to be associated with poorer short-term stroke outcomes (Renjen PN et al. 2025) These components have been extensively studied in our patients as well, and our results support the authors' conclusions above.

Liu L et al. (2015) do not establish a significant correlation between MetS and short-term stroke outcomes and do not confirm an association between the number of MetS components and short-term IS prognosis. The authors conclude that MetS alone is not a predictor of short-term prognosis, but hyperglycemia is a significant predictor of poor functional outcome (Liu L et al. 2015, Renjen PN et al. 2025). Tarwoto PR et al. (2025) demonstrate a significantly higher risk of IS in diabetics, a worse functional outcome in mild stroke due to occlusion of small arteries, and a higher recurrence of stroke within a year. DM is a predictor of recurrent stroke and stroke occurring after TIA, increasing the risk of recurrent stroke by 2.1 to 5.6 times compared with patients without diagnosed diabetes (Air EL et al. 2007). De Silva DA et al. (2022) find that DM is a predictor of poor long-term functional outcome in patients younger than 65 years. The authors also document a statistically significant increase in the risk of unfavorable functional outcome six months after stroke among patients older than 65 years, regardless of the presence of concomitant DM (De Silva DA et al. 2022).

The results of our study show the following percentage distribution according to the functional outcome by mRS. In the group of IS patients with MetS, we find a favorable functional outcome (mRS 1-2) in 15 cases (12.5%); unfavorable functional outcome (mRS 3-5) - in 82 cases (68.3%) and unfavorable fatal outcome (mRS 6) - in 23 cases (19.2%). In group 2, we register a favorable functional outcome (mRS 1-2) in 35 patients (33.7%);

unfavorable functional outcome (mRS 3-5) - in 61 (58.6%) and fatal outcome (mRS 6) in 8 cases (7.7%). We find a statistically significant difference in the functional stroke outcome ($\chi 2 = 22.032$, df = 5, p = 0.001) between the studied groups. The correlation analysis confirms a weak positive correlation between all investigated MetS components and clinical stroke outcome. Regression analysis does not identify any individual MetS component as a significant determinant of short-term clinical stroke outcome. However, the present study demonstrates that the severity of neurological deficit on admission significantly influences clinical outcome at discharge. This finding is further supported by the correlation analysis, which reveals a strong positive correlation (r=0.726) between stroke severity at admission and short-term clinical outcome.

Another Bulgarian study among patients with young and middle-aged IS by Dimitrov G (2025) reports an early unfavorable functional outcome (mRS 3-5) in 58.5% of the young and 41.8% of the middle age group (mRS 3-5). No fatal outcomes are registered at discharge in the studied cohort (Dimitrov G. 2025). The author's results concerning the unfavorable functional outcome (mRS 3-5) are similar to ours for group 2 (58.6%). In contrast, our group 1 patients exhibits a higher proportion of unfavorable functional outcomes (68.3%) as well as a high mortality rate (19.2%). A possible explanation for these differences may lie in the older average age of our participants and the high-risk vascular profile associated with MetS, which likely influenced stroke outcome.

According to another Bulgarian researcher, Tsalta M. (2021), the patients included in his study have a mean mRS score of 2.63±1.46 at hospitalization, which improves to 2.02±1.53 three months after stroke (p = 0.022). The author reports that 52.7% of patients are functionally independent (mRS≤2) at discharge, increasing to 69.9% by the third month after stroke (Tsalta M., 2021).

The conclusions of international investigators regarding the relationship between MetS and short-term functional outcome after IS are inconsistent. A study by Chen W et al. (2025) evaluates the association between MetS and clinical outcome in 699 IS patients treated with intravenous thrombolysis, among whom the prevalence of MetS is 31%. Its results confirm a significant association between MetS and poor functional outcome in thrombolyzed patients, a lower incidence of favorable functional outcome (mRS 0-2), higher mortality, and a higher incidence of complications such as spontaneous intracerebral bleeding in the third month of stroke compared to non-MetS patients (Chen W et al. 2025). Another study, published in 2025,

compares two groups of 146 patients with and without MetS and confirms that the number of MetS components correlated with all-cause mortality, and the relationship is dose-dependent (Chen W et al. 2025). The authors document that with three components of MetS present, the relative risk of all-cause mortality is 2.49 times higher (95% CI: 1.38-3.78; p<0.01), and with 4-5 components, it increases to 3.27 times (95% CI: 1.79-6.23; p<0.01) (Chen W et al. 2025). A possible favorable outcome at the third month of stroke is documented in 32.2% of MetS patients compared to 50.7% of the control group (adjusted OR=0.47, 95% CI: 0.28-0.77; p<0.01), confirming that MetS is associated with unfavorable functional outcome and is an independent predictor of thrombolysis complicated by intracerebral hemorrhage (adjusted OR=2.40, 95% CI: 1.17-4.92; p=0.02) (Chen W et al., 2025).

In a study by Raharinavalona SA et al. (2025) in 701 IS patients, of whom 77.9% with diagnosed MetS, no significant association is found between MetS and stroke mortality (Raharinavalona SA et al. 2025). Imam Y et al. (2024) conduct a study in 1571 patients with posterior circulation stroke with a mean age of 54.9±12.7 years. The authors report an unfavorable functional outcome (mRS>2) in 39.5% at discharge, significantly associated with advanced age, proximal, and multiple stroke localization (p<0.05) (Imam Y et al. 2024). An unfavorable functional outcome is recorded at the third month of stroke in 27.4% of patients, significantly associated with advanced age, male sex, and the selected MENA cohort (p<0.05) (Imam Y et al. 2024). Zhang X-G et al. (2022) study patients treated with mechanical thrombectomy at average age of 72.9±12.41 years in the period 2018-2021. The analysis of the clinical outcome in the studied 258 patients shows that 58.9% of them have an unfavorable outcome on the third month after stroke (mRS 3-6). (Zhang X-G et al. 2022). Mortality (mRS 6) is observed in 22.87% of patients; among them, 43 deaths were due to vascular causes, 14 to non-vascular causes, and 2 resulted from recurrent fatal stroke (Zhang X-G et al., 2022). Chen Z et al. (2020) study 248 patients at average age of 66.7 years with anterior circulation stroke treated with endovascular thrombectomy, of whom 46% are with MetS. The authors report that MetS patients are more likely to have DM, be older, and be female (Chen Z et al., 2020). An unfavorable functional outcome (mRS 3-6) occurs in 52.8%, and at the third month, a fatal outcome is recorded in 19% (Chen Z et al. 2020). The authors conclude that an unfavorable functional outcome from stroke affecting the large vessels in the anterior circulation is more common in patients with MetS at the third month after endovascular thrombectomy (Chen Z et al. 2020). Mi D et al. (2012) study 701 Chinese patients with symptomatic intracranial stenosis, 26% of whom are diagnosed with MetS. The authors find a

non-significally increased incidence of recurrent strokes (7.1%; p=0.07) in the MetS group and a similar one-year mortality rate in MetS patients (3.3%) compared to the rest (3.5%; p=0.91) (Mi D et al. 2012). The presented results do not confirm that MetS is associated with an increased risk of mortality within a year of stroke and do not associate MetS with a significantly increased risk of all-cause mortality (Mi D et al. 2012). Arteaga DF et al. (2022) analize 57 patients, participating in the SHINE study, with anterior circulation IS due to occlusion of large arteries. They find that collateral circulation status do not modify the relationship between glycemic control and stroke outcome; however, good collateral status (38% of patients) is associated with a favorable functional outcome (OR 5.02; 95% CI 1.37-16.0). Intensive glycemic control does not improve stroke outcome (Arteaga DF et al., 2022).

The age of patients is a well-established non-modifiable RF and is considered as one of the principal predictors of clinical IS outcome. According to Murphy SJ et al. stroke incidence doubles with each decade after the age of 55 years (Murphy SJ et al. 2020). The aging of the European population is expected to increase the number of cerebrovascular events, affecting both sexes. According to the latest 2023 data reported by AHA, stroke incidence increases with advancing age in both sexes (Tsao CW et al., 2023). AHA projections estimate that by 2030 an additional 3.4 million American adults will experience a stroke, representing a 20.5% increase compared with 2012 (Tsao CW et al., 2023). In 2010, the incidence of stroke among Americans aged over 85 years was 23%, and is expected this percent to rise to 34% by 2050 (Howard G et al. 2023). A study conducted in neighboring Romania identifies heart failure (OR: 7.170, 95% CI: 1.897-27.092, p=0.004), age (OR: 1.041, 95% CI: 0.985-1.101, p=0.15), and higher NIHSS scores on admission as unfavorable predictors of poor functional outcome at six months after the acute stage of IS, with higher admission NIHSS scores being associated with worse outcomes on the mRS at six months (OR: 1.087, 95% CI: 0.967-1.222, p=0.164) (Bârsan IC et al., 2024).

Age-related prevalence of stroke differs between sexes, with males predominating in younger and middle-aged groups, whereas in older age groups the rates become similar or even higher among females (Tsao CW et al. 2023). With ageing in stroke patients over 85 years of age, the female sex predominates (Tsao CW et al. 2023). A study conducted among 47 Bulgarian IS patients finds that patients with mild to moderate post-stroke cognitive deficit within a one-year follow-up are predominantly elderly, female, diagnosed with DM and with elevated levels of hs-CRP during hospitalization (Alexandrova ML et al. 2016). As significant independent predictors of the development of post-stroke cognitive impairments, the authors

point to age and elevated levels of hs-CRP (Alexandrova ML et al. 2016). A study by Wu CY et al. (2010) analyzes differences in the incidence of stroke RF across age groups, as well as gender-determined differences. The age distribution of patients shows that among 1161 patients, 60.5% are at the age between 50-75 years and over 75 years of age are 26.4% (Wu CY et al. 2010). In the age group of 50-75 years AH (69.7%), DM (34.9%), obesity (21.7%), and male sex (63.3%) predominate as RF (Wu CY et al. 2010). In the elderly over 75 years, the prevalence of RF is as follows: AH (67.3%), DM (32.4%), obesity (12.7%) with a dominant female sex (33.6%) (Wu CY et al. 2010). The authors report that AH and DM are the most common RFs in older participants, with no significant difference between sexes (Wu CY et al. 2010).

Statistical data indicate that stroke incidence doubles with each decade after the age of 55 years, and more than one-third of acute strokes occur in individuals older than 80 years (Héja M et al. 2021). The authors examine 1125 patients at average age of 68.2±12.4 years treated with IVT and their results show that 34.7% of patients aged over 80 years achieved a favorable outcome (mRS 0-2) (Héja M et al. 2021). At the third month after the stroke, a favorable functional outcome (mRS 1-2) is reported at 49.9% of the studied patients, an unfavorable functional outcome (mRS 3-6) at 46.1% and a fatal outcome (mRS 6) one year after the stroke is documented at 26.6% (Héja M et al. 2021). The mortality rate is comparable to our higher-risk group 1. The results of the French prospective study PARADISE (The Prognosis After Revascularization therapy in the Dijon Ischemic Stroke Evaluation) conducted in 2016-2019 with included 300 patients at average age of 86.3±4.6 years, show that in the third month after the revascularization therapy, 58% of patients have unfavourable outcome, of whom 37% had died and a year after the stroke 59% have mRS>3 and 44% have died (Ruel S et al. 2023). Tripathy SS et al. (2025) investigate 56 IS cases and 56 controls, in 67.9% of cases MetS is diagnosed. The authors report that significant RFs for stroke are age ($p<0.0001$), BMI ($p<0.0001$), and MetS ($p=0.001$) (Tripathy SS et al. 2025). Age above 60 years (AOR=5.3; 95% CI: 1.845-15.277) increases stroke risk 5.3-fold, BMI≥25 kg/m² (AOR=4.6; 95% CI: 1.6-13.3) increases risk 4.6-fold, and MetS (AOR=2.8; 95% CI: 1.0-8.0) increases risk 2.8-fold within the studied cohort (Tripathy SS et al. 2025).

The age distribution of 1156 Bulgarian stroke patients at average age of 71±11.6 years shows a predominance of the number of elderly patients above 70 years (56%) (Tsalta-Mladenov M et al. 2019). Our study findings show a similar percentage - 54.5% of IS patients are older than 70 years. However, regarding the influence of advanced age on the risk of

unfavorable functional outcome after stroke, we do not identify a significant association. The distribution of individual RFs also shows some differences in individual age groups - AH is present in 73.7% of patients younger than 45 years and is almost universally prevalent in middle-aged and elderly patients; DM is found in 30% of patients between 45-70 years of age and in 28% in the age group above 70 years; DL has a high prevalence of between 60-70% in the three aged groups (Tsalta-Mladenov M et al. 2019). The increasing number of RF and advanced age correspond to a more severe neurological deficit in the studied patients (Tsalta-Mladenov M et al. 2019).

5.9 Analysis of the impact of MetS on the relative risk for unfavourable functional outcome of IS (mRS 3-6)

In the present study, we prove that MetS does not significantly increase the relative risk (p=0.130) for an unfavorable outcome (mRS 3-5) of stroke at discharge (OR: 1.523, 95% Cl 0.883-2.627). We also find that MetS is associated with an increased relative risk (OR: 2.845, 95% Cl 1.213-6.674, p=0.016) for death (mRS 6) in IS patients with a statistically significant difference found between the studied groups and is associated with a 2.8-fold higher risk of early death.

We also consider the importance of its individual components for an unfavorable functional outcome. Our results confirm that hyperglycemia on admission (p<0.0001), hypertriglyceridemia (p<0.0001), overweight/obesity (p=0.003) and elevated BP (p=0.002) in IS patients with MetS affect the risk of an unfavorable outcome (mRS 3-5) of IS. We report that hyperglycemia on admission is associated with an 8.5-fold increased risk of unfavorable outcome (OR: 8.543, 95% Cl 4.475-16.308, p<0.0001). Hypertriglyceridemia increases 7.7-fold the relative risk of unfavorable outcome (mRS 3-5) of stroke (OR: 7.726, 95% Cl 3.440-17.351, p<0.0001). Overweight and obese patients (BMI≥25 kg/m²) show a 2.2-fold higher risk (OR: 2.248, 95% Cl 1.311-3.855, p=0.003) and in those diagnosed with hypertension, the relative risk of unfavorable outcome (mRS 3-5) increases by 2.3-fold (OR: 2.331, 95% Cl 1.355-4.010, p=0.002). Of all MetS components, only lower HDL-cholesterol does not significantly affect the risk of an unfavorable outcome (p=0.210). Examining the group of IS patients with MetS, we find that moderate stroke (NIHSS 5-15 sc.) on admission (OR: 2.375, 95% Cl 1.314-4.292, p=0.004) significantly increases by almost 2.4-fold the relative risk of unfavorable functional outcome (mRS 3-5), supported by Kwah LK et al. (2014), who present the NIHSS scale as a strong independent predictor of stroke outcome.

Regarding the impact of the individual components of MetS on the risk of fatal outcome, our results confirm that hyperglycemia on admission (p=0.001), AH (p=0.005), hypertriglyceridemia (p=0.010) and overweight/obesity (BMI≥25 kg/m²) (p=0.019) significantly affect the risk of short-term death (mRS 6). Hyperglycemia on admission is associated with a 7.5-fold increased risk of death (OR: 7.558, 95% Cl 4.475-16.308, p=0.001). In patients with diagnosed AH, the relative risk of death (mRS 6) increases by 3.9 times (OR: 3.873, 95% Cl 1.511-9.928, p=0.005), and those with overweight and obesity (BMI≥25 kg/m²) show a 2.9-fold higher risk (OR: 2.939, 95% Cl 1.195-7.230, p=0.019). Of all MetS components, only the lower HDL-cholesterol does not significantly affect the risk of early mortality (p=0.520). Our findings regarding the influence of dyslipidemia on stroke outcome differ from those reported in a Chinese study involving 1 568 IS patients, which finds that HDL-cholesterol (OR: 0.482, 95% CI: 0.245-0.946) and triglycerides (OR: 0.883, 95% CI: 0.391-1.992) are significantly associated with clinical outcome (Xu T et al., 2014).

We also evaluate the impact of the number of components of MetS on the relative risk of unfavorable functional outcome (mRS 3-5) in IS patients. Our study proves that the combination of four components of MetS in IS patients is associated with the highest risk of unfavorable functional outcome (OR: 5.444, 95% Cl 2.165-13.690, p=0.0005). The next statistically significant combination (p=0.0003) increasing the relative risk of poor IS outcome is that of three components of MetS (OR: 5.205, 95% Cl 2.165-13.116). The combination of five components of MetS is associated with an almost 3.9-fold increased risk of unfavorable IS outcome (OR: 3.873, 95% Cl 1.511-9.928) with established statistical significance (p=0.0048). These findings confirm that patients with MetS are not only at high risk for cerebrovascular events, but that, once IS has occurred, the number of MetS components influences stroke outcome.

Our results are also supported by other authors' publications. AH is the most prevalent modifiable RF, statistically significant for IS severity and associated with poorer functional outcome (Rodríguez-Yañez M et al. 2021). A 2016 meta-analysis summarizes that every 10 mmHg reduction in SBP is associated with a 27% reduction in the relative risk of IS (RR: 0.73; 95% CI: 0.68-0.77) and a 13% reduction in all-cause mortality (RR: 0.87; 95% CI: 0.84-0.91) (Rodríguez-Yañez M et al., 2021). Post-stroke elevated BP is associated with a higher risk of clinical deterioration and poorer functional outcomes regardless of antihypertensive therapy during the acute stage (Ishitsuka, K et al., 2014). Persistently elevated SBP after the acute phase is significantly associated with poorer functional recovery, while

elevated SBP and DBP values are predictors of early neurological deterioration and unfavorable functional outcome (mRS≥3) at three months after stroke (Ishitsuka K et al. 2014). Studies evaluating the impact of individual RFs on stroke risk have shown that the risk increases with the number of metabolic abnormalities, with AH being the most important component (Horn JW et al. 2021).

DM as a well-documented modifiable RF, is also associated with an increased risk of poor functional outcome (Larsson SC et al. 2017). Hyperglycemia has been identified as a predictor of increased stroke mortality and reduced benefit from IVT (Maida CD et al. 2024). Regarding age-related differences, DM appears to have a greater impact on stroke risk in younger patients under the age of 65 years (Howard G et al. 2023). Among thrombolyzed patients, every 100 mg/dL increase in admission blood glucose above the reference range is associated with a reduced likelihood of neurological improvement (OR=0.76) and an increased risk of complications such as symptomatic intracerebral hemorrhage (OR=1.75, 95% CI 1.11-2.78, p=0.02) (Lindsberg PJ et al. 2004). In patients undergoing revascularization therapy, a baseline glucose level of 140 mg/dL is identified as an independent predictor of unfavorable outcome at three months (OR=8.4, CI 1.8-40.0) (Lindsberg PJ et al. 2004). In summary, hyperglycemia may be associated with clinical deterioration, hemorrhagic transformation, unfavorable clinical outcome, and reduced efficacy of revascularization therapies (Lindsberg PJ et al. 2004). A study conducted across seven European countries evaluating the impact of DM on stroke outcome finds that AH is more common among diabetic patients (p=0.001), who also exhibit poorer clinical outcomes (mRS 2-5) and a higher risk of death at three months after stroke, particularly among men (Megherbi SE et al. 2003, Maida CD et al. 2024).

Obesity is a well-established modifiable RF for stroke and an independent predictor of mortality in the general population (Miwa K et al. 2024), while the abdominal obesity is a predictor of CVD and DM type II (Jamee AS et al. 2019). A study by Branscheidt M et al. (2016) reports that BMI does not significantly influence functional outcome or mortality in patients treated with IVT. The authors find no significant association between overweight versus normal weight and mortality (OR: 1.341, 95% CI: 0.684-2.629), nor between obesity versus normal weight and mortality (OR: 1.081, 95% CI: 0.400-2.919) (Branscheidt M et al. 2016). In another study, Suzuki T et al. (2014) report a 17% increased risk of mortality among MetS patients and a population-attributable risk of 9.5% for death among White Americans with MetS. Based on Global Burden of Disease 2021 data, another research group reported in 2024 a 1.96-fold increase in IS mortality associated with elevated BMI levels in Eastern and

Central Europe, North Africa, the Middle East, and Central Asia, as well as a higher frequency of fatal outcomes among women aged ≥70 years (Guo X et al. 2024). Considering the expected association between age and unfavorable stroke outcome, we stratified our cohort according to age and sex and found that female sex and age ≥ 65 years increase the risk of fatal stroke outcome (mRS 6) (OR: 1.006, 95% CI: 0.525-1.928).

Supporting the hypothesis of the "obesity paradox" are the data from a study by Wang J et al. (2020) analyzing the relationship between obesity and mortality in patients with first IS in 754 patients at average age of 61.45 years. A more favorable stroke outcome is observed in 33.7% of overweight patients and 10.1% of obese patients compared with patients of normal weight (Wang J et al. 2020). They confirm the paradoxical relationship between overweight and abdominal obesity and lower mortality in the studied Chinese cohort (Wang J et al. 2020). In support of the same hypothesis, Hou Z et al. (2021) report that obesity is associated with lower mortality compared with patients with normal or low BMI. The authors study a cohort of 12 964 non-diabetic IS patients with a mean age of 64.83±12.2 years and demonstrate a correlation between BMI and unfavorable stroke outcome (OR: 0.757; 95% CI: 0.690-0.832), as well as between BMI and stroke mortality (OR: 0.647; 95% CI: 0.562-0.746) at 12 months after stroke (Hou Z et al., 2021). Contrary to the above findings are the results of Miwa K et al. (2024), who investigate the impact of BMI on stroke outcomes in 43668 patients with an average age of 74±12 years. Obesity is more frequently observed among younger patients with a metabolic risk profile, and a BMI≥30.0 kg/m² is associated with an increased risk of unfavorable outcome (OR: 1.44, 95% CI: 1.01-2.17) and early mortality (OR: 2.42, 95% CI: 1.26-4.65) in patients with large-artery atherosclerosis (Miwa K et al. 2024). In contrast, overweight status is not associated with an increased risk of unfavorable outcome (OR: 0.87, 95% CI: 0.78-0.98) and is linked to a lower risk in patients with small-vessel occlusion (OR: 0.59, 95% CI: 0.37-0.95) (Miwa K et al. 2024). The authors report a significantly lower frequency of unfavorable outcomes among obese patients, particularly in those older than 80 years; however, their findings do not support the “obesity paradox” hypothesis in patients with atherosclerotic IS (Miwa K et al. 2024).

6. SUMMARY

The present dissertation is a prospective study of patients with acute IS that evaluates the impact of MetS and its individual components on stroke severity and short-term clinical outcomes. The study identifies significant clinical constellations of RF among stroke patients admitted for urgent treatment to the Neurology Clinic of UMHAT "Dr. Georgi Stranski" - Pleven. Its findings provide evidence-based solutions for therapeutic approaches, prognostic assessment, and preventive strategies in high-risk patients who may be susceptible to early neurological deterioration and short-term mortality.

Our study aims to investigate the prevalence of the individual components of MetS, as well as the number and possible combinations of these components in patients with acute IS. We examine the MetS components in detail and assess their prevalence in our high-risk patient's cohort (group 1). The obtained results are analyzed and compared with those of IS patients without MetS (group 2).

The most prevalent components of MetS in group 1 are arterial hypertension, diabetes mellitus, and obesity. AH, the most common modifiable RF, is also identified as the most predominant RF in group 2. Using a comparative analysis between the studied groups, we demonstrate that each individual RF occurs more frequently in the MetS group. Summarizing the data on the prevalence of the MetS components, we find that AH and obesity exert the strongest influence on the association and contribute most significantly to increase the relative risk of IS. We also clarified the role of the individual MetS components in patients with metabolic abnormalities. Analysis of risk-factor prevalence in the non-MetS groups reveals differences regarding their influence on stroke risk.

We evaluate the impact of each component of MetS, as well as the syndrome itself, on the relative risk of IS. Based on a comparative case-control analysis with equal proportional distribution, our results confirm that MetS increases the risk of IS by 1.6-fold in the studied clinical population. This finding is consistent with reports from other authors. Regarding the individual MetS components, AH is identified as the most significant factor increasing the relative risk of IS. We prove that the next prevalent component is DM, which increases the risk of IS by 3.7 times, while hyperglycemia on admission is detected in 60% of stroke patients. The most common combination of MetS components is the four-component cluster of AH, DM, hypertriglyceridemia and obesity, observed in 16.7% of IS patients with MetS.

In this dissertation, the clinical and laboratory parameters are analyzed and presented as mean values. A relatively low rate of thrombolytic treatment (5.8%) is observed, with IVT

being performed more frequently in male patients from group 1, findings comparable to those reported in other Bulgarian studies. We also conducted a detailed analysis of the non-specific therapies administered (antihypertensive, antidiabetic, and lipid-lowering treatment) in relation to accompanying comorbidities. Among IS patients with MetS, the most commonly prescribed medications are diuretics, beta-blockers, and calcium channel blockers, in accordance with current international therapeutic guidelines.

We establish an association between the individual components of MetS and the severity of neurological deficit on admission. Percentage distributions in the study groups are calculated and compared, correlation analyses are performed, and the influence of the individual MetS components on the degree of disability at discharge is evaluated.

We do not find evidence that MetS influences the risk of an unfavorable functional outcome after stroke; however, our findings indicate that MetS increases the risk of short-term mortality in patients with acute IS. We further clarify the strength of the association between the individual MetS components and stroke outcome, which is characterized by weak positive correlations. Among the MetS components, hyperglycemia on admission demonstrates a moderate correlation with the severity of neurological deficit in IS patients.

In the present study, we demonstrate that the severity of neurological deficit at hospitalization significantly influences stroke outcome, a finding confirmed statistically by regression analysis.

The results obtained enrich both scientific knowledge and clinical practice regarding the comprehensive management of IS patients, providing an additional opportunity for prognostic assessment of stroke outcome. Strict control of individual MetS components, continuous monitoring, and a multidisciplinary, personalized therapeutic approach - particularly in high-risk patients with IS and MetS - could improve short-term prognosis.

Against the background of the ongoing aging of the population, the increasing burden of comorbidities, and the growing prevalence of MetS in the general population, we confirm that MetS patients represent not only a high-risk group for the occurrence of acute IS but also for a more unfavorable short-term clinical outcome. Contemporary clinical challenges require targeted preventive measures, behavioral modifications, and therapeutic strategies that, in the long term, may alter the specific outcomes and correlations described in this dissertation.

In conclusion, the findings of our study provide additional clinically relevant information by documenting and analyzing specific associations and percentage distributions within a Bulgarian cohort of high-risk patients with MetS, despite the relatively limited sample size.

7. CONCLUSIONS

Based on the results presented in this dissertation, the following conclusions can be drawn:

1. The prevalence of MetS and its individual components among patients with acute IS is comparable to that reported by other authors conducting similar studies.
2. The most prevalent MetS components in patients with acute IS are arterial hypertension, diabetes mellitus, obesity, and hypertriglyceridemia.
3. MetS and its individual components are associated with a statistically significant increase in the relative risk of IS. AH, DM, and hypertriglyceridemia show the strongest associations with IS risk. Among IS patients without MetS, hypertriglyceridemia, lower HDL-cholesterol, obesity, and AH significantly increase stroke risk.
4. Admission hyperglycemia is more common in IS patients with MetS and represents a significant predictive factor for the severity of neurological deficit.
5. MetS does not significantly affect the risk of moderate or severe IS. Hyperglycemia on admission, hypertriglyceridemia and AH increase the risk of moderate IS. DM, hypertriglyceridemia and hyperglycemia on admission significantly increase the relative risk of severe stroke. MetS itself does not influence the severity of neurological symptoms. However, individual components such as hyperglycemia on admission and hypertriglyceridemia affect the severity of neurological deficit at discharge. Admission hyperglycemia and HDL cholesterol are predictors of neurological deficit severity at hospitalization, while admission hyperglycemia and systolic blood pressure are significant MetS-related factors influencing neurological deficit severity at discharge.
6. MetS is not a significant predictor of short-term unfavorable stroke outcome but is associated with an increased risk of early mortality. Individual MetS components demonstrate weak positive correlations with stroke outcome.
7. The severity of neurological deficit on admission significantly affects the short-term stroke outcome.

8. CONTRIBUTIONS

1. The prevalence of individual MetS components in patients with acute IS is analyzed and compared with the prevalence of vascular risk factors in IS patients without MetS. The study expands existing knowledge regarding RF distribution among IS patients.
2. The strength of association between MetS, its individual components, and the relative risk of IS was evaluated using a case-control design.
3. The impact of MetS and its components on the risk of moderate and severe IS is investigated, and their relationship with unfavorable functional outcome is assessed. These findings contribute to the limited evidence regarding the impact of MetS on stroke severity and outcome.
4. The study confirms that MetS significantly increases the risk of early mortality, representing a contribution of confirmatory value.
5. Hyperglycemia on admission is identified as a significant prognostic factor for the severity of neurological deficit at stroke onset, which in turn significantly influences early clinical outcome in patients with IS and MetS.
6. Patients with MetS require stricter control of risk factors, multidisciplinary expert evaluation, and optimized therapeutic management because of their increased risk of severe post-stroke disability and mortality during the acute stage of IS. This represents an important contribution with practical clinical applicability.

9. PUBLICATIONS RELATED TO THE DISSERTATION

Full-text publications related to the topic of the dissertation:

1. Marinova-Trifonova D, Danovska-Mladenova M, Yanakieva M, Ovcharova-Dukhlenska E, Vasileva V, Stoev P. Influence of metabolic syndrome on short-term outcome in patients with acute noncardioembolic ischemic stroke. Jubilee Scientific Conference with International Participation "50 Years of Medical Education and Science in Pleven", 01-03 November 2024: Proceedings "50 Years of Medical Education and Science in Pleven", p. 866-871; ISBN: 978-954-756-346-9.

2. Vasileva V, Danovska M, Todorova Y, Dimitrov G, Marinova D. Lipid profile and statin therapy in patients with atrial fibrillation and acute ischemic stroke receiving anticoagulant therapy. J of IMAB. 2026 Apr-Jun; 32(2):6792-6796. ISSN: 1312-773X.

3. Dimitrov, G., Danovska, M., Marinova, D., Stoev, P., Simeonova, Y. Gender-Related Differences in Modifiable Risk Factors and Ischemic Stroke Subtype in Young and Middle-aged Patients–a prospective study. Journal of IMAB, 2023, Jan-Mar, 29(1): 4793-4799; ISSN: 1312-773X.

4. Dimitrov GT, Danovska MP, Simeonova YI, Gencheva II, Stoev PG, Ovcharova EM, Marinova DL. Comparative evaluation of risk factors in young and middle-aged patients with acute ischemic stroke. J of IMAB. 2020 Jan-Mar; 26 (1):2926-2930; ISSN 1312-773X.

10. APPENDICES

10.1 APPENDIX 1. DIAGNOSTIC CRITERIA FOR METABOLIC SYNDROME

Components of the MetS	WHO 1998	NCEP (National Cholesterol Education Program) ATP III 2001	IDF (International Diabetes Federation) 2005	AHA 2004
Blood pressure	>140/90 mmHg	>130/85 mmHg or antihypertensive therapy	>130/85 mmHg or antihypertensive therapy	>130/85 mmHg
Blood glucose	>6.1 mmol/L	>5.6 mmol/L or 100 mg/dl or antidiabetic therapy	>5.6 mmol/L or 100 mg/dl or diagnosed DD	>5.6 mmol/L or 100 mg/dl
HDL-cholesterol in men	<0.9 mmol/L or 35mg/dl	<1.0 mmol/L or 40mg/dl or therapy against low HDL-cholesterol	<1.0 mmol/L or 40mg/dl or therapy against low HDL-cholesterol	<40mg/dl or 1.03 mmol/l
HDL-cholesterol in women	<1.0 mmol/L or 40 mg/dl	<1.3 mmol/L or 50 mg/dl or therapy against low HDL-cholesterol	<1.3 mmol/L or 50 mg/dl or therapy against low HDL-cholesterol	<50 mg/dL или 1.3 mmol/L
Triglycerides	>1.7 mmol/L or 150 mg/dl	>1.7 mmol/L or 150 mg/dl or therapy for elevated TG	>1.7 mmol/L or 150 mg/dl or therapy for elevated TG	> or = 150 mg/dl or 1.7 mmol/L
Waist circumference in men		>102 cm	>94 cm	> or = 102 cm
Waist circumference in women		>88 cm	>80 cm	> or = 88 cm
Waist circumference/hip circumference (men)	>0.9			
Waist circumference/hip circumference (women)	>0.85			
BMI	>30 kg/m²			

10.2 APPENDIX 2. QUESTIONNAIRE FORM

It is developed and used in the present study, and its content is published in the full-text dissertation.

11. ACKNOWLEDGEMENTS

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