



GENDER-RELATED DIFFERENCES IN MODIFIABLE RISK FACTORS AND ISCHEMIC STROKE SUBTYPE IN YOUNG AND MIDDLE-AGED PATIENTS – A PROSPECTIVE STUDY

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ABSTRACT

Background: Male and female patients differ in their risk factors (RFs) and ischemic stroke (IS) subtype. A better understanding of the gender-related differences an important approach to successful prevention strategies for reducing the impact and burden of IS in young adults.

Objective: To compare the gender-related differences in the prevalence of modifiable RFs and IS subtypes in young and middle-aged patients.

Material and Methods: In the study were included 80 patients with acute IS, aged 18 – 59 years, admitted to the Neurology Clinic of UMHAT “Dr Georgi Stranski” Pleven. The following RFs were analyzed: arterial hypertension (AH), diabetes mellitus (DM), dyslipidemia, atrial fibrillation (AF), current smoking, number of cigarettes smoked per day, alcohol abuse, low physical activity, body overweight and chronic psychosocial stress. IS subtype was identified according to the Org 10172 Trial of Acute Stroke (TOAST). The statistical analysis was performed with the Statistical Package for Social Sciences, version 26.0 (SPSS).

Results: Of all the 80 patients, 46 (57,5%) were males with a mean age 48,15±7,42 years, and 34 (42,5%) were females with a mean age 47,38±8,56. Male patients had higher rates of AH (80,4%), DM (47,8%), AF (4,3%), current smoking (73,9%), number of cigarettes smoked per day (60,9%), alcohol abuse (41,3%) and chronic psychosocial stress (52,2%), while the female ones showed higher rates of low physical activity (61,8%) and body overweight (38,2%). A statistical significance was found only for AH (p=0,004), DM (p=0,026), current smoking (p=0,007), number of cigarettes smoked per day (p=0,025) and alcohol abuse (p=0,031). The most common subtype of IS in males was large artery atherosclerosis (47,8%) and small vessel occlusion (28,3%). The female patients demonstrated a higher frequency of IS with other determined etiology (38,2%) and undetermined etiology (26,5%).

Conclusion: Our data contribute to a better understanding of the gender-related differences of modifiable RFs and IS subtype in young and middle-aged patients with acute IS. The above findings definitely imply the necessity of developing additional specific therapeutic strategies for the effective control of modifiable RFs and lifestyle improvement in order to reduce the incidence of the most common subtypes of IS.

Keywords: Ischemic stroke, risk factors, gender-related differences, subtype ischemic stroke, young and middle – age patients.

INTRODUCTION:

Stroke is a leading cause of long-term disability and the second cause of death worldwide [1]. More than 11 million people suffer from IS each year. Half of these cerebrovascular events occur in low and middle-income countries. About 10%-20% of IS occur in young adult patients (usually defined as 18-55 years) [2, 3]. Bulgaria ranks third in the incidence of stroke and 9,2% of all strokes occur in young and middle-aged patients with a predominance of males [4].

In the general population IS are more common in males, than in females. According to recently published data, the incidence of IS in young adult males is 30,6 per 100 000, while in females it is 19,1 per 100 000 [5]. Nowadays, the increasing incidence of IS in young adults is associated with a higher prevalence of modifiable RFs. [6].

The INTERSTROKE study proves the major role of the following RFs for IS: AH, DM, dyslipidemia, cardiac disease, current smoking, alcohol abuse, low physical activity and others [7].

Male and female patients differ in their RFs for IS. Some modifiable RFs, such as oral contraceptive use, pregnancy, postpartum period, migraine with aura, and postmenopausal hormone replacement therapy, are female-specific [8]. On the other hand, most of the modifiable RFs are shared and occur in both male and female patients, but have a higher incidence in one of the sexes. This trend emphasizes the need for a better understanding of sex-related differences in modifiable RFs, which are important determinants of the incidence and IS etiologic subtype in young and middle-aged patients [9].

Early identification and control of potentially modifiable RFs for IS are important approaches for primary and secondary prevention strategies in reducing the impact and burden of IS in young adults. [1, 2, 3, 7].

In the present study, we aimed to compare the gender-related differences in the prevalence of modifiable RFs and IS subtypes in young and middle-aged patients.

MATERIAL AND METHODS:

A prospective analysis of 80 patients with acute IS, admitted to the Neurology Clinic of UMHAT "Dr. Georgi Stranski" Pleven from January 2021 to January 2022 was done. The inclusion criteria of the study were: 1. Patients aged between 18 – 59 years; 2. Acute onset of neurological deficit lasting more than 24 hours; 3. IS confirmed by CT or MRI. The exclusion criteria of the study were: 1. Cerebral venous thrombosis; 2. Neuroimaging of brain hemorrhage; 3. Transient ischemic attack (TIA). The following investigations were performed on admission at the clinic: standard blood tests (serum glucose, cholesterol, triglycerides, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, homocysteine), 12 channel ECG (electrocardiography), brain CT and/ or MRI and duplex ultrasound of the carotid arteries.

The modifiable RFs for IS were classified into: 1. Health-related RFs—AH, DM, AF, hypercholesterolemia (>5,1mmol/l), hypertriglyceridemia (>2,3mmol/l), high low-density lipoprotein cholesterol (high LDL-C), low high-density lipoprotein cholesterol (low HDL-C), systolic blood pressure (>140mmHg) and diastolic blood pressure (>90mmHg) on admission. 2. Lifestyle-related RFs - current smoking, number of cigarettes (≥ 20 cigarettes per day), alcohol abuse (>5 alcoholic drinks per day), low physical activity (<30 min, 1 day/ week), body overweight and chronic psychosocial stress. According to the number of modifiable RFs, the IS patients were divided into two groups. The first group included patients with ≤ 3 modifiable RFs, and the second group included patients with ≥ 4 modifiable RFs. The etiological subtype of IS was determined according to the TOAST criteria in: 1. Large artery

atherosclerosis (LAA), including patients with intracranial or extracranial stenosis >50% detected by duplex ultrasound and CT/ MRI cerebellar or subcortical hemispheric infarct lesion greater than 1,5cm; 2. Small vessels occlusion (SVO), including patients with CT/ MRI data for subcortical hemispheric infarction lesion with a diameter of less than 1,5cm; 3. Cardioembolism (CE) including patients with at least one possible cardiac source for embolism; 4. IS with other determined etiology (patients with identified rare causes of stroke such as thrombophilia antiphospholipid syndrome, hyperhomocysteinemia, hematological disorders and others); 5. IS with undetermined etiology.

The categorical variables (AH, DM, current smoking, number of cigarettes per day, alcohol consumption, low physical activity, body overweight and chronic psychosocial stress) were defined by their absolute and relative frequency. The quantitative variables (Cholesterol, Triglycerides, LDL, HDL, blood pressure) were presented by mean, minimal and maximal values (Min \div Max). The statistical analysis was performed with the Statistical Package for Social Sciences, version 26.0 (SPSS). Pearson's chi-squared test (χ^2), Independent sample t-test and Mann – Whitney U test were also used. A value of $p \leq 0.005$ was considered statistically significant.

RESULTS:

Of all the 80 patients, included in the study, 46 (57,5%) were males with a mean age $48,15 \pm 7,42$ years and 34 (42,5%) were females with a mean age $47,38 \pm 8,56$.

The modifiable RFs in patients of both gender with acute IS are presented in table 1.

Table 1. Distribution of the modifiable RFs for IS, total and by gender.

Modifiable Risk factors (RFs)	Total n=80 (100%)	Males n=46 (57,5%)	Females n=34 (42,5%)	P – value
Arterial Hypertension (AH) Yes, present	54 (67,5)	37 (80,4)	17 (50,0)	0,004*
Diabetes mellitus (DM) Yes, present	30 (37,5)	22 (47,8)	8 (23,5)	0,026*
Atrial fibrillation (AF) Yes, present	3 (3,8)	2 (4,3)	1 (2,9)	0,743*
Current smoking (smokers)	49 (61,3)	34 (73,9)	15 (44,1)	0,007*
Number cigarettes (≥ 20 cigarettes per day)	38 (47,5)	28 (60,9)	10 (29,4)	0,025*
Alcohol abuse (>5 alcoholic drinks per day)	24 (30,0)	19 (41,3)	5 (14,7)	0,031*
Low physical activity (<30 min 1 day/week)	48 (60,0)	27 (58,7)	21 (61,8)	0,242*
Body overweight	28 (35,0)	15 (32,6)	13 (38,2)	0,602*
Chronic psychosocial stress	39 (48,8)	24 (52,2)	15 (44,1)	0,476*

Total serum cholesterol (mmol/l) (Mean ± SD, Min ÷ Max)	5,70±1,46 (3,22 ÷ 11,20)	5,72±1,35 (3,22 ÷ 10,57)	5,67±1,62 (3,35 ÷ 11,20)	0,879**
Low density lipoprotein cholesterol (mmol/l) (Mean ± SD, Min ÷ Max)	3,15±1,24 (1,28 ÷ 7,76)	3,25±1,18 (1,30 ÷ 5,68)	3,03±1,33 (1,28 ÷ 7,76)	0,436**
High density lipoprotein cholesterol (mmol/l) (Mean ± SD, Min ÷ Max)	1,32±0,55 (0,52 ÷ 4,49)	1,17±0,44 (0,52 ÷ 2,10)	1,51±0,63 (0,84 ÷ 4,49)	0,006**
Triglycerides (mmol/l) (Mean ± SD, Min ÷ Max)	2,25±1,52 (0,62÷8,40)	2,55±1,60 (0,62÷8,40)	1,83±1,32 (0,73÷7,02)	0,036**
Systolic arterial pressure at admission (Mean ± SD, Min ÷ Max)	140,25±23,27 (100,00÷240,00)	145,32±21,19 (110,00÷200,00)	133,38±24,48 (100,00÷240,00)	0,022**
Diastolic arterial pressure at admission (Mean ± SD, Min ÷ Max)	82,87±10,14 (60,00÷120,00)	85,97±9,81 (70,00÷120,00)	78,67±9,15 (60,00÷100,00)	0,001**

* Chi-squared test (χ^2 test);

** Independents sample t-test and ANOVA – table test.

AH was found the major risk factor in 67,5% of acute IS patients. Males had a higher incidence of AH (80,4%) compared to females (50,0%). The difference was found statistically significant ($\chi^2=8.255$, $df=1$, $p=0,004$). DM was found in 37.5% of the patients. The frequency of DM was 2 times higher in males (47.8%) than in females (23.5%). The difference was statistically significant ($\chi^2=4.924$, $df=1$, $p=0,026$). AF was found in 4,3% of male patients and in 2,9% of female ones. That difference was not statistically significant ($p=0,743$). Males demonstrated higher rates of current smoking (73,9%), a number of cigarettes smoked per day (60,9%), alcohol abuse (41,3%) and chronic psychosocial stress (52,2%). A statistical significance was found only for current smoking ($\chi^2=7.313$, $df=1$, $p=0,007$), number of cigarettes smoked

per day ($\chi^2=9.383$, $df=3$, $p=0,025$) and alcohol abuse ($\chi^2=8.862$, $df=3$, $p=0,031$). The female patients showed higher rates of low physical activity (61,8%) and body overweight (38,2%), but they were not statistically significant ($p>0,05$). Higher mean values of total serum cholesterol (5,72±1,35), LDL cholesterol (3,25±1,18) and serum triglycerides (2,55±1,60) were found in males. HDL cholesterol demonstrated significantly lower mean values (1,17±0,44) in males, compared to females ($p=0,006$). On admission to the clinic, male patients had higher mean values of systolic (145,32±21,19) and diastolic (85,97±9,81) blood pressure, ($p<0,05$).

The comparison in the number of modifiable RFs in patients with acute IS of both gender is presented in table 2 and figure 1.

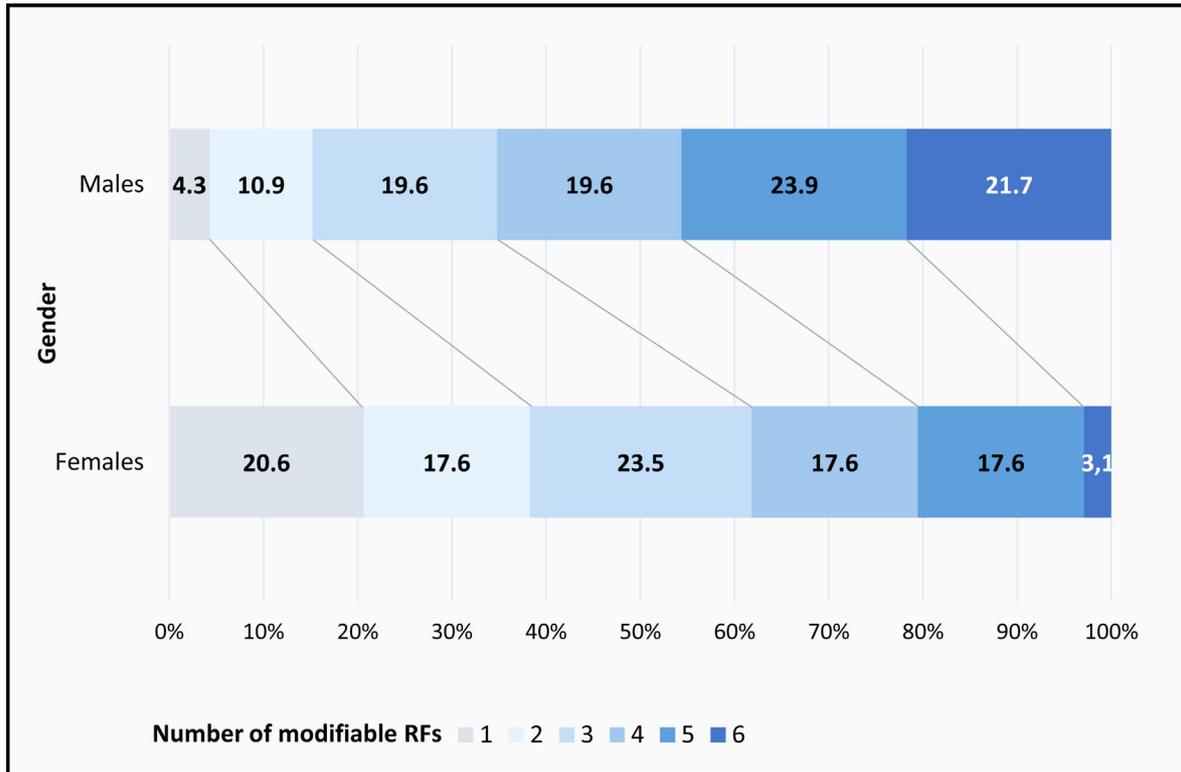
Table 2. Comparison of the number modifiable RFs by groups and median values for both gender.

Number of modifiable RFs	Males N=46 (57,5%)	Females N=34 (42,5%)	p - value
Modifiable RFs ≤ 3	16 (34,8)	21 (61,8)	0,017*
Modifiable RFs ≥ 4	30 (65,2)	13 (38,2)	
Median value of Modifiable RFs (Min ÷ Max)	4 (1,0÷6,0)	3 (1,0÷6,0)	0,001**

* Chi-squared test (χ^2 test);

** Independents sample t – test and ANOVA – table test.

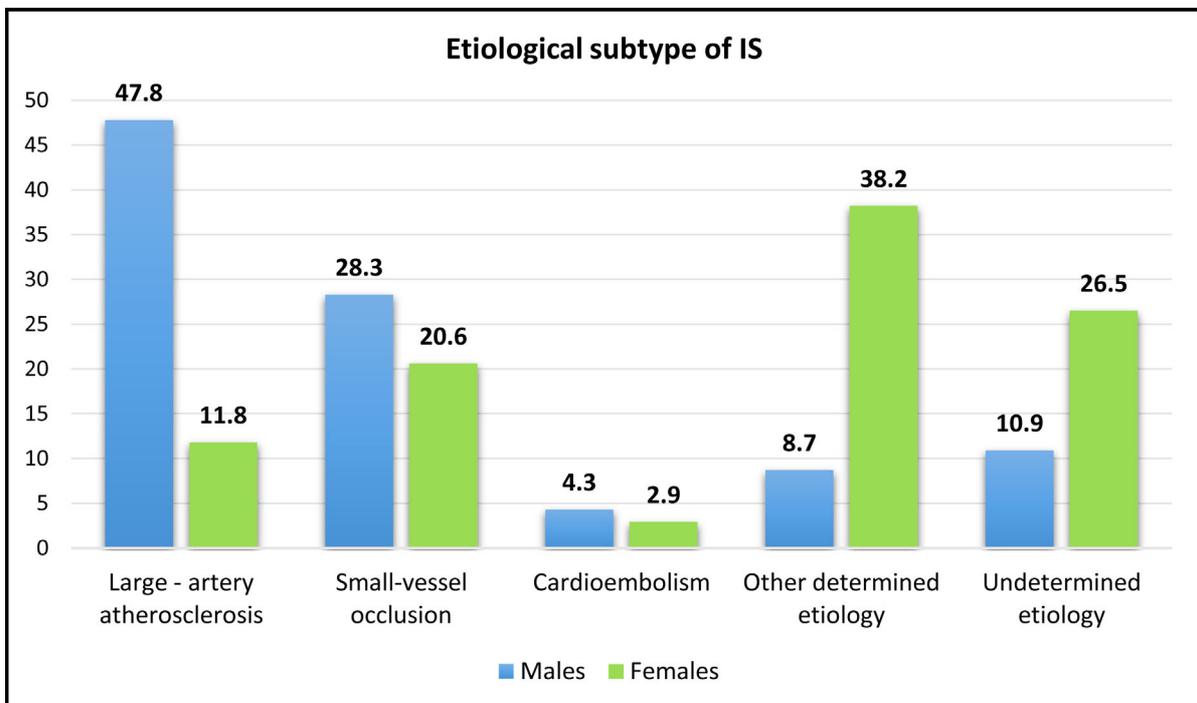
Fig. 1. Proportion of the patients by gender with 1 to 6 modifiable RFs.



All the patients with IS had at least one modifiable RF. Over 60% of the male patients had ≥ 4 modifiable RFs compared to the female ones (38.2%). The median number of modifiable RFs in males was 4, while in females it was 3. The differences between both genders were statistically significant ($p < 0.05$).

Gender differences in IS subtype are presented in figure 2.

Fig. 2. Distribution of IS subtype in both gender



Of all the 80 IS patients according to the TOAST classification, 32,5% (n=26) had LAA; 25,0% (n=20) had SVO; 3,8% (n=3) had cardioembolism; 21,3% (n=17) had other determined etiology as thrombophilia, antiphospholipid syndrome, hyperhomocysteinemia, and hematologic disorders, and in 17,5% (n=14) IS had undetermined etiology. The most common subtypes of IS in males were LAA (47,8%) and SVO (28,3%). The female patients demonstrated a higher incidence of IS with other determined etiology (38,2%) and undetermined etiology (26,5%). The differences between the two gender groups were statistically significant ($p=0,001$).

DISCUSSION:

In the present study, a comparative analysis of gender differences in RFs and the etiological subtype of IS in young and middle-aged patients was conducted. A case-control study of 2125 patients with acute first stroke shows high population attributable risks (PARs) of AH, DM, current smoking and alcohol consumption in male patients for all stroke subtypes, while females have higher PARs of low physical activity and overweight/ obesity [10].

AH and smoking are conventional vascular RFs in young stroke patients [11]. In general, AH is the most significant modifiable RF for IS, more common in males [12]. Smoking is an independent RF for IS with a strong dose – dependent relationship between the number of cigarettes smoked per day and the risk of IS especially in young male patients [2]. In our study AH and current smoking (≥ 20 cigarettes per day) are leading vascular RFs in males, compared to females. Similar are the results of a single-center cohort study in China in young adults with IS. In this study, males have a statistically higher rate of AH (43.0%) and smoking (41.1%) in comparison to females [13]. Another Chinese retrospective study of 444 young adult patients with acute IS reveals that 53.2% of the male patients were smokers and 45.0% of them had a history of AH [14].

Diabetes mellitus is also an independent RF for IS. The risk of IS in diabetics is ten times higher than in non – diabetics [12]. DM is strongly associated with the risk of IS in females compared to males [15]. According to the Framingham study females with DM have a 3,6 times higher risk for stroke, while males with DM have only $\approx 2,5$ times higher risk for stroke compared with non-diabetics [16]. According to our study results DM was 2 times more common in males, than in females. Similar findings with a significantly higher rate of DM in males with IS than in females are presented by other studies [5, 13, 14].

Daniel Šanák and al. have found that 10.2% of patients under the age of 50 have paroxysmal AF with a male predominance [17]. In our results, 3.8% of the patients have established AF. The number of IS males with AF is higher than the number of females with AF, but the difference is not statistically significant.

High alcohol consumption is less-well documented lifestyle RF for IS. According to Putaala, alcohol abuse is two times higher in males (42,0%), than in females (20,0%) [6]. Our data confirm these gender differences. We found a three times higher frequency of alcohol abuse in males with

IS than in females.

Low physical activity and abdominal obesity are associated with an increased risk of IS in young adult patients. They are more common in females than in males [5]. The SIFAP (Stroke in Young Fabry Patients) study has found that females with IS are more likely to be overweight (73,0%) with low physical activity (50,4%) than males [18]. In our study, 60,6% of the female IS patients had low physical activity, and 36,4% had body overweight, but the gender related differences were not statistically significant.

Psychosocial stress is a poorly documented risk factor for IS. A case-control study demonstrates that moderate to severe work-related stress is significantly associated with stroke risk [19]. Both acute and chronic psychosocial stress increase the risk of cerebrovascular accident in populations of all ages, but more frequently in males [20, 21]. Our data reveal higher rates of males with chronic psychosocial stress compared to females, but the differences were not statistically significant.

Dyslipidemia is a modifiable RF for IS, occurring slightly more frequently in men [22]. TC, LDL-C, and triglycerides are significantly associated with IS risk [23]. Elevated LDL cholesterol levels correlate with large vessel atherothrombosis and slightly increase the risk of IS in both sexes. Recently published data show a significant association between low levels of HDL cholesterol and the risk of stroke in males, while in females such a relationship has not been established. On the other hand, elevated triglyceride levels are associated with an increased risk of IS in both sexes, but the risk is significantly higher in males [24]. Our study results demonstrated high mean values of total serum cholesterol and LDL cholesterol in both sexes with a slight male predominance. We also found a significantly lower mean HDL cholesterol value and high mean triglycerides in males with IS compared with females, which is in contradiction with the results of Wang et al. about significantly higher mean values of total serum cholesterol, triglycerides and LDL cholesterol in females with IS [25]. Only data concerning the low mean values of HDL cholesterol in men were confirmed by our study results.

According to the American Heart Association (AHA), AH is defined as systolic blood pressure (SBP) >140 mmHg and diastolic blood pressure (DBP) > 90 mmHg [26]. Approximately 77% of the patients with an acute cerebrovascular accident have arterial blood pressure values above 140/90 mmHg, with males more often affected. [2]. In a study by Cong Geng et al, young adult males with IS have significantly higher SBP and DBP on admission compared with female ones [27]. Our results definitely confirm such gender-related differences. We found significantly higher values of SBP and DBP in IS males compared to females. On the contrary, a prospective cohort study has published data for significantly higher values of SBP in females compared to males [25].

The combination of ≥ 4 well-documented modifiable RFs is independently associated with a higher risk for IS and a composite of arterial events. Apparently, most of the modifiable RFs for IS cluster in males than in females [6, 28]. According to an Estonian prospective study, the over-

all incidence of well-documented RF is higher in male patients. More than 50% of males in the Estonian study have a clustering of ≥ 3 modifiable RFs as compared to the females [29]. Sarnovski et al. have found that 29.2% of males aged 45 years and older have ≥ 4 well-documented modifiable RFs, while the proportion of female patients is 20.3% [18]. In comparison, the proportion of males with ≥ 4 modifiable RFs in our study was 65.2% compared with 38.2% in females.

The etiology of IS in young adults depends on age, gender and geographical location. Male young adults after 40 years of age are more likely to suffer from LAA and SVO. A significant contributor to this trend is the increasing prevalence of modifiable RFs among males [2, 30]. According to a Japanese multicenter prospective study, young adult males have a slightly higher proportion of LAA (15,0%) than females (14,0%) [31]. We found a four times higher incidence of LAA in male patients (47,8%), compared to females (11,8%). Vibo and al. revealed a higher incidence of LAA in males. On the other hand, 12.2% of female patients with IS had small vessel disease, compared to 10.6% in male patients [29]. Such results are in conflict with our results. We found a higher incidence of SVO in males (28.3%) compared to 20.6% in females. Similar are the data of Tang et al. with SVO in 9.9% of males and only 3.1% in females [13]. Our study results demonstrate that LAA and SVO are the most common subtypes of IS among young adult patients.

According to a multicenter observational cohort study, IS with another defined etiology is more common in females and younger patients, but in 39.6% of the cases, the etiology remains undetermined [32]. A retrospective study of 2634 young adults in India demonstrates a higher incidence of IS with other defined etiology in females (26.0%) compared to males (15,5%) [33].

We found IS with other defined etiology in 38,2% of the females and only in 8,7% of the males.

Our data confirm that females are more often affected by IS with another determined etiology, compared to male ones.

CONCLUSION:

Our study results undoubtedly confirm the existence of gender – related differences of the modifiable RFs and IS subtype in young and middle-aged patients with acute IS. Male patients have a significantly higher proportion of modifiable RFs, such as AH, DM, current smoking and alcohol abuse, compared to female ones. Concerning gender-related differences in the IS subtype it has been found that males are mostly affected by LAA and SVO, while females suffer more commonly by IS of other definite etiology and undetermined etiology.

Our findings definitely imply the necessity of developing additional specific therapeutic strategies for the effective control of the modifiable RFs and lifestyle improvement in order to reduce the incidence of the most common subtypes of IS in young and middle-aged patients.

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