

Research Article

A prospective study of age-related differences in modifiable risk factors, stroke subtype, and functional outcome in young and middle-aged patients with first-ever ischemic stroke

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Summary

The objective of our study was to compare the age-related differences in the prevalence of modifiable risk factors (RF), stroke subtype and functional outcome at hospital discharge in young and middle-aged patients with first-ever ischemic stroke (IS). The study included 120 patients with acute first-ever IS, aged 18–59 years, admitted to the Neurology Clinic of Dr. Georgi Stranski University Hospital, Pleven. Of these, 41 (34.2%) were in the young-age group and 79 (65.8%) were middle-aged. The middle-aged patients had higher rates of arterial hypertension (81.0%), diabetes mellitus (45.6%), dyslipidemia (83.5%), low levels of HDL cholesterol (68.4%), high levels of LDL cholesterol (72.2%) and arterial fibrillation (7.6%). The most common subtype of IS in middle-aged patients was large artery atherosclerosis (40.5%), small vessel occlusion (29.1%) and cardioembolism (6.3%). In comparison, we found a higher incidence of IS in the young patients with other determined (34.1%) and undetermined aetiology (34.1%). Our data on functional outcomes at hospital discharge confirm age-related differences in the prevalence of modifiable RFs and stroke subtype in young and middle-aged patients with first-ever IS. These findings highlight the need to develop specific therapeutic approaches for early identification and effective control of health- and lifestyle-related RFs to reduce the incidence of the most common subtypes of IS.

Key words: functional outcome, ischemic stroke, lifestyle-related risk factors, middle-aged patients, young patients

Introduction

Ischemic stroke (IS) is a socially significant disease characterized by long-term physical and mental disability worldwide (Titianova et al. 2015). For the last 20 years, the incidence of IS in young adults (defined as individuals aged 18–55 years) has increased notably and varies from 5–15/100 000 person-years in most European countries (Li et al. 2002; Béjot et al. 2021).

The risk of acute cerebrovascular incidents increases proportionally with the number of modifiable risk factors (RFs) (Boot et al. 2020). Although young and middle-aged IS patients share the same health- and lifestyle-related RFs



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(Putala 2020), the number of these RFs prevails in the older ones (Smajlović 2015). Recently published studies show that the number of modifiable RFs increases with age, and patients over 35 have approximately twice as many modifiable RFs as younger ones (Boot et al. 2020). This trend highlights the need for a better understanding of age-related differences in modifiable RFs, which are significant determinants of the IS subtype and outcome in young adult patients, particularly (Hathidara et al. 2019).

Although the generally accepted consensus is that young adult IS patients have a favourable clinical outcome at hospital discharge compared to the older ones, around 30% of the patients younger than 50 years have an unfavourable outcome at hospital discharge (Leys et al. 2002; Maaijwee et al. 2014). Stroke survivors may have a variety of physical and mental disabilities that impair their quality of active social life (Lutski et al. 2017). Therefore, the option to predict stroke severity and clinical outcome, especially in young IS patients, is of paramount importance for a successful therapeutic approach.

The objective of this study was to compare the age-related differences in the prevalence of modifiable RFs, stroke subtype, and functional outcome at discharge of young and middle-aged patients with acute first-ever IS.

Materials and methods

A prospective study of 120 patients aged 18–59 years with acute first-ever IS, admitted to the Neurology Clinic of Dr. Georgi Stranski University Hospital, Pleven from January 2021 to January 2023, was conducted. The study's inclusion criteria were: patients aged 18–59 years; acute IS - confirmed by clinical examination and CT or MRI imaging. The study's exclusion criteria were: clinical and neuroimaging data of cerebral venous thrombosis, brain haemorrhage and/or tumour; transient neurological deficit. All patients underwent the following tests on admission: standard blood tests (serum glucose, cholesterol, triglycerides, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, liver function, kidney function, coagulation assessment and homocysteine); neuroimaging (brain CT and/or MRI); 12-channel ECG (electrocardiography); duplex ultrasound of the carotid arteries. The cohort was divided into two age groups: young-aged group (18–44 years) and middle-aged group (45–59 years), according to the World Health Organization (WHO) criteria.

The following health- and lifestyle-related RFs were analyzed: arterial hypertension (AH), diabetes mellitus (DM), dyslipidemia, low HDL cholesterol levels, high LDL cholesterol levels, atrial fibrillation (AF), current smoking (>20 cigarettes per day), alcohol consumption (>5 alcoholic drinks per day), low physical activity (< 30 min, 1 day/ week), body overweight and short night sleep (<6 hours per night). The aetiology of IS was determined according to the TOAST classification into large artery atherosclerosis (LAA), small vessel occlusion (SVO), cardiac embolism (CE), IS with other determined aetiology and IS with undetermined aetiology (Adams and Biller 2015).

On admission, the severity of IS was assessed using the National Institutes of Health Stroke Scale (NIHSS). Functional outcome at discharge was evaluated by the modified Rankin scale (mRs) as favourable (score 0–2) or unfavourable (score 3–6).

The statistical analysis was performed using the statistical package for Social Science (SPSS) version 26.0. Differences between categorical variables were expressed with Pearson's chi-square (χ^2) test. Continuous variables (mean and median values) were compared with independent samples of the T-test and the Mann-Whitney U test. A value of $p \leq 0.05$ was considered statistically significant.

Results

Of the 120 patients with first-ever acute IS included in the study, 41 (34.2%) were in the young-aged group (mean age 40.2 ± 3.939 years) and 79 (65.8%) in the middle-aged one (mean age 53.6 ± 4.236 years).

The health-related RFs in IS patients of both age groups are presented in Table 1. The middle-aged patients demonstrated higher rates of AH (81.0%), DM (45.6%), dyslipidemia (83.5%), low levels of HDL cholesterol (68.4%), high levels of LDL cholesterol (72.2%) and AF (7.6%). A statistical significance was found for AH ($\chi^2 = 8.404$, $df = 1$, $p = 0.004$), DM ($\chi^2 = 7.892$, $df = 1$, $p = 0.005$), dyslipidemia ($\chi^2 = 14.146$, $df = 1$, $p < 0.001$) and high level of LDL cholesterol ($\chi^2 = 16.137$, $df = 1$, $p < 0.001$).

Table 1. Distribution of the health-related RFs for IS, total and by age group.

Health-related risk factors (RFs)	Total n = 120 (100%)	Young age group n = 41 (34.2%)	Middle-aged group n = 79 (65.8%)	p-value
Arterial Hypertension (AH)	87 (72.5)	23 (56.1)	64 (81.0)	0.004*
Diabetes mellitus (DM)	44 (36.7)	8 (19.5)	36 (45.6)	0.005*
Dyslipidemia	87 (72.5)	21 (51.2)	66 (83.5)	< 0.001*
Low levels of HDL cholesterol (<1.5 mmol/l)	76 (63.3)	22 (53.7)	54 (68.4)	0.113*
High levels of LDL cholesterol (>2.59 mmol/l)	71 (59.2)	14 (34.1)	57 (72.2)	< 0.001*
Atrial fibrillation (AF)	6 (5.0)	0 (0.0)	6 (7.6)	0.070*

*Chi-squared test (χ^2 test).

Data concerning the prevalence of lifestyle-related RFs in both age groups with acute first-ever IS are given in Table 2. Although middle-aged IS patients were found to have a higher frequency of alcohol abuse (31.6%), low physical activity (57.0%) and obesity (39.2%), compared to the young-aged patients, the differences were not statistically significant ($p > 0.05$).

Table 2. Distribution of the lifestyle-related RFs for IS, total and by age group.

Lifestyle-related risk factors (RFs)	Total n = 120 (100%)	Young age group n = 41 (34.2%)	Middle-aged group n = 79 (65.8%)	p-value
Current smoking (≥ 20 cigarettes per day)	60 (50.0)	23 (56.1)	37 (46.8)	0.323*
Alcohol consumption (>5 alcoholic drinks per day)	34 (28.3)	9 (22.0)	25 (31.6)	0.292*
Low physical activity (<30 min 1 day week)	68 (56.7)	23 (56.1)	45 (57.0)	0.928*
Body overweight (obesity)	44 (36.7)	13 (31.7)	31 (39.2)	0.417*
Short night sleep (<6 hours per night)	34 (28.3)	14 (34.1)	20 (25.3)	0.507*

*Chi-squared test (χ^2 test).

A comparative assessment of the distribution of all modifiable RFs between the two age groups is presented in Fig. 1.

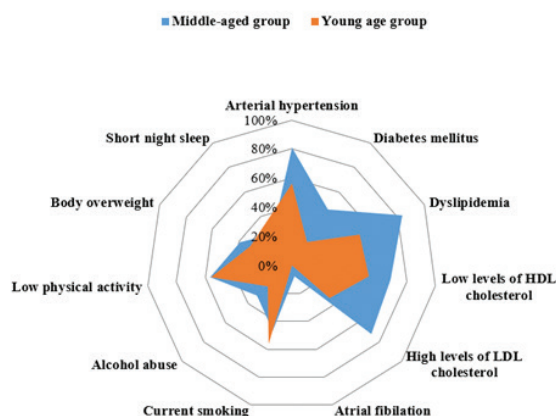


Figure 1. Comparative assessment of the distribution of all modifiable RFs between the two age groups.

Patients of the middle-aged group with first-ever acute IS were found to have a greater number of modifiable RF than young-aged ones (Fig. 2).

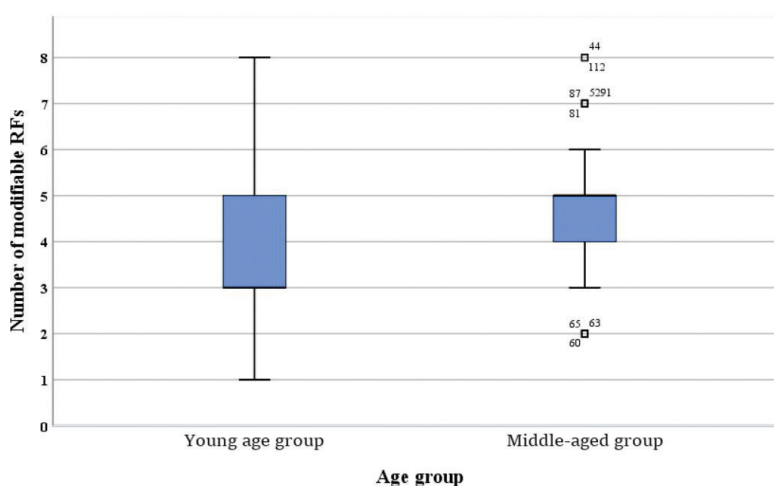


Figure 2. Comparison of the number of modifiable RFs by age group.

The median number of all modifiable RFs in the young-aged group was 3 (1 ÷ 8), and in the middle-aged group was 5 (2 ÷ 8). The Mann-Whitney U test results showed statistically significant differences: $U = 1119.5, p < 0.001$.

The distribution by IS subtype in both age groups is presented in Table 3. The most common IS subtype among all patients was LAA (32.5%), followed by SVO (24.2%), IS with undetermined aetiology (23.3%) and IS with other determined aetiology (15.8%) such as thrombophilia, antiphospholipid syndrome, hyperhomocysteinemia, and cardiac embolism (4.2%). The middle-aged patients had much more frequent LAA (40.5%) and SVO (29.1%). The young-aged IS patients demonstrated a higher incidence of stroke with other determined aetiology (34.1%) and undetermined aetiology (34.1%). Cardioembolic IS was present only in the middle-aged patients (6.3%). The differences between the two age groups were statistically significant ($p < 0.001$).

Table 3. Distribution by IS subtype according to the TOAST classification, total and by age group.

Ischemic stroke subtype according to the TOAST classification	Total n = 120 (100%)	Young age group n = 41 (34.2%)	Middle-aged group n = 79 (65.8%)
Large-artery atherosclerosis (LAA)	39 (32.5)	7 (17.1)	32 (40.5)
Small vessel occlusion (SVO)	29 (24.2)	6 (14.6)	23 (29.1)
Cardioembolism	5 (4.2)	0 (0.0)	5 (6.3)
IS with other determined etiology	19 (15.8)	14 (34.1)	5 (6.3)
IS with undetermined etiology	28 (23.3)	14 (34.1)	14 (17.7)

The comparison of functional outcomes in patients with acute IS of both age groups is presented in Table 4.

Table 4. Comparison of functional outcome by age groups at discharge.

Functional outcome at hospital discharge	Young age group n = 41 (34.2%)	Middle-aged group n = 79 (65.8%)	p-value
Favorable outcome (mRs 0–2)	17 (41.5)	46 (58.2)	0.081*
Unfavorable outcome (mRs 3–5)	24 (58.5)	33 (41.8)	

*Chi-squared test (χ^2 test).

Unfavourable outcomes at discharge were registered in 58.5% of young IS patients and 41.8% of middle-aged ones. The differences were not statistically significant ($p > 0.05$). Patients of the young-aged group with first-ever acute IS had a higher median NIHSS score on admission than the middle-aged ones (Fig. 3). The median NIHSS score on hospital admission was 6 (1 ÷ 18) in the young and 5 (1 ÷ 19) in the middle-aged group. Stroke severity on admission was found statistically significant for the unfavourable functional outcome at discharge ($p < 0.001$).

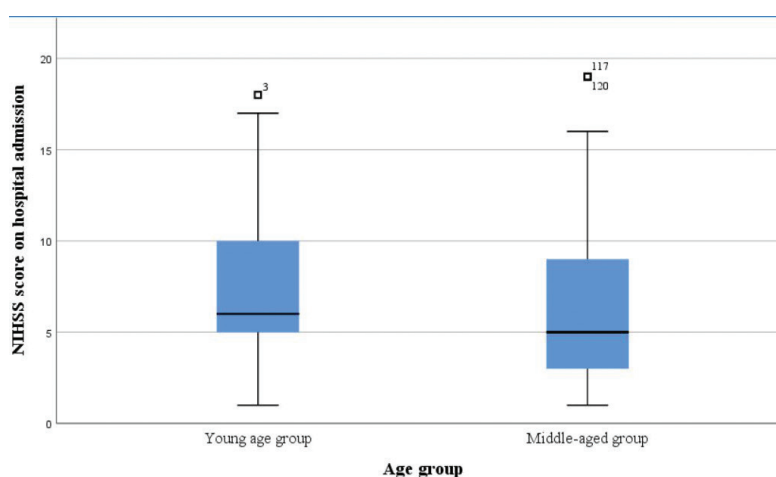


Figure 3. Comparison of NIHSS on admission in both age groups.

Discussion

We compared age-related differences in modifiable RFs, stroke subtype according to the TOAST classification, and functional outcome at discharge in young and middle-aged patients with acute first-ever IS.

Currently, well-documented health-related RFs for IS are AH, dyslipidemia, DM and cardiovascular diseases, including atrial fibrillation (Smajlović 2015; Putaala 2020). A retrospective Estonian study demonstrated that IS patients over 44 years suffered more often from AH, dyslipidemia, DM, coronary heart disease and AF. About 50.0% of the middle-aged patients in this study had AH and dyslipidemia (Schneider et al. 2017). Another prospective study found significantly higher rates of AH (53.7%) and dyslipidemia (48.6%) in IS patients over 35 years (Tan et al. 2014). Our results are similar to the data cited by these studies. We found a significantly higher rate of AH (81.0%) and dyslipidemia (83.5%) in the middle-aged patients compared to the young-aged ones.

According to the Stroke in Young Fabry Patients (SIFAP1) study, 1 in 10 patients had DM (Putaala 2016). In a large prospective cohort study, DM was two times higher in middle-aged IS patients (39.0%) than in the young-aged ones (15.5%). The same study also found higher rates of hyperlipidemia and low HDL cholesterol in middle-aged IS patients (Jo et al. 2022). We also found a higher frequency of DM, dyslipidemia, and low HDL cholesterol in the middle-aged than in the young-aged group.

Kono et al. (2020) presented a comparatively low rate of AF in both age groups, but the middle-aged IS patients had a higher rate of AF (5.0%) compared to the younger ones (2.0%). According to our study results AF was present only in middle-aged IS' patients with an incidence slightly higher (7.6%) than in the above study.

Well-documented lifestyle-related RFs, such as smoking, excessive alcohol consumption, low physical activity and drug abuse, significantly contribute to the IS risk in young patients (Polivka et al. 2019). Smoking and alcohol abuse are behavioural RFs that are more common in young IS patients (Putaala 2020; Siriratnam et al. 2020). Yao et al. (2012) also found that in young IS' patients, smoking and alcohol abuse were more common behavioural RFs. They reported that 55.1% of the younger IS' patients were current smokers, while 32.7% had heavy alcohol consumption (Yao et al. 2012). Our data showed that 56.1% of the young IS patients were current smokers, while heavy alcohol consumption was more common in the middle-aged group (31.6%). Low physical activity and obesity are generally accepted as mutually related behavioural RFs. Obesity in young adults is associated with a higher risk of IS (Boot et al. 2020c). Aguilera-Pena et al. (2021) reported that 10.0% of IS patients over 45 had obesity, compared with only 2.9% of the younger ones. Our data demonstrated higher rates of obesity in both age groups, with a slight prevalence in the middle-aged group. In conflict with our results are data from another prospective study that found higher obesity rates in the young-aged group (under 44 years) compared with the middle-aged group. However, these differences were not statistically significant (Kono et al. 2020).

A multicenter prospective cohort study reported short sleep (less than 6 hours per night) as associated with an increased risk of IS (Zhao et al. 2021). Von Sarnowski et al. (2013) found that 19.2% of the middle-aged patients with IS had shorter night sleep (less than 6 hours per night) compared to 15.9% in the young-aged group. These results conflict with our results because we found a higher rate of short night sleep in young patients (34.1%) than in middle-aged patients (25.3%). However, these differences were not statistically significant.

Jo et al. (2022) concluded that young IS patients had a significantly higher rate of obesity, smoking, and heavy alcohol consumption than older IS patients. On the other hand, older IS patients had more frequent AH, DM, dyslipidemia and AF compared with the younger ones. Overall, our findings confirmed the differences in the prevalence of health-related RFs but conflicting results concerning the prevalence of lifestyle-related RFs.

According to the study of Shihmanter et al. (2021), middle-aged IS patients (range 46–55 years) had a significantly greater number of RFs per individual (mean 3.5 ± 1.6) compared to the young-aged patients (mean 2.9 ± 1.8). Our results also revealed a higher median number of modifiable RFs (median 5) in the middle-aged group compared to the young-aged one (median 3). The differences we found were statistically significant.

Literary data available indicate that LAA and SVO are the most common subtypes of IS in young patients over 35 years. The incidence of these IS subtypes increases proportionally with age and the number of modifiable RFs. (Yesilot Barlas et al. 2013; Yahya et al. 2020). Jaffre et al. (2014) found that atherothrombosis was significantly associated with smoking, DM, AH and low HDL cholesterol, while SVO was associated with age and AH only. According to a Japanese multicenter prospective study, the frequency of LAA was two times higher (20.0%) in middle-aged IS patients than in the young-aged (10.0%). This study also found that the frequency of SVO was slightly higher in the middle-aged group (27.0%) than in the young-aged group (25.0%) (Kono et al. 2020). Our data are in line with these study results. We found a frequency of LAA twice as high (40.5%) and SVO (29.1%) in the middle-aged group compared to the young-aged one. A possible explanation for this trend could be the higher median number of modifiable RFs in middle-aged IS patients (median 5) compared to young patients (median 3).

Vibo et al. (2021) demonstrated a higher incidence of IS with undetermined aetiology and other determined aetiology in young-aged patients: 48.5% and 9.7%, respectively, than in middle-aged patients, 39.8% and 7.4%, respectively. In comparison, we found that the underlying aetiology of IS remained unclear in 34.1% of the young and 17.7% of the middle-aged patients. On the other hand, 34.1% of the younger patients had IS with other determined aetiology versus only 6.3% of the middle-aged patients. Our data confirmed that young-aged patients are more often affected by IS with undetermined aetiology and other determined aetiology than middle-aged patients.

According to Lutski et al. (2017), the IS severity (NIHSS > 5) on admission was significantly associated with unfavourable outcomes (mRs > 3) at discharge. This study also presented that above 50.0% of the older patients (>50 years) had unfavourable outcomes at discharge (mRs 2–5) compared with the younger patients (27.5%). Our study results do not agree with these results. We found a higher rate of unfavourable outcomes at discharge in the young-aged group (58.5%) compared with the middle-aged group (41.8%). However, the differences were not statistically significant. A possible explanation for our results could be the significantly higher NIHSS score on admission (median 6) in the young-aged group, compared with the middle-aged one (median 5). Our data agrees with such data in the study of Nedeltchev et al. (2005). They revealed that a higher NIHSS score (median > 5) at hospital admission was one of the independent predictors of unfavourable outcomes of IS young adults at discharge.

Conclusion

In summary, the present study emphatically confirmed the existence of age-related differences in the prevalence of modifiable RFs and stroke subtypes in young- and middle-aged patients with acute first-ever IS. Middle-aged IS patients had a significantly higher proportion of health-related RFs, such as AH, DM, dyslipidemia and high levels of LDL cholesterol, than the young-aged ones. A higher prevalence of lifestyle-related RFs, such as heavy alcohol consumption, low physical activity and overweight, was registered in the middle-aged IS patients compared to the young-aged ones.

Our findings also confirmed that middle-aged patients more often had LAA and SVO, while young-aged patients suffered more commonly from IS with other determined and undetermined aetiology.

Concerning functional outcomes, we found that young-aged patients with acute first-ever IS had more often unfavourable outcomes at discharge than middle-aged ones with a higher median NIHSS score on admission.

Our findings emphasize the urgent need to improve patient awareness of the crucial significance of lifestyle RFs and the effective implementation of more effective preventive strategies for early identification and control of health-related modifiable RFs, which are essential for reducing the incidence of IS in young adult patients.

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