

Risk Factors and Etiological Classification of Ischemic Stroke Subtypes in Southwest Iran

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Abstract- Precise categorization of the causes of ischemic stroke (IS) is crucial for optimizing stroke treatment and assessing the prognosis of patients. This cross-sectional study aimed to determine the risk factors and various subcategories of IS in Iranian patients. The study included all patients with IS referred to Golestan Hospital (Ahvaz, Iran) for one year. Their demographics and clinical data were collected. The etiology of IS was classified based on the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria. A total of 1100 patients with IS were evaluated, 658 were male and 442 were female. They had an average age of 66 years (ranging between 20 and 99 years). The majority of them were in the 61-80 age group. The prevalence of risk factors for IS included hypertension (HTN) (71.4%), diabetes (50.4%), smoking (42.4%), history of previous stroke (28%), dyslipidemia (15.4%), and cardiovascular disease (22.5%). Three months after admission, the mortality rate was 10.7% and the majority of patients exhibited a lower level of disability based on the modified Rankin Score (mRS) compared to the time of admission. The frequency of all risk factors, except for HTN, differed significantly between genders ($P<0.05$). Furthermore, the prevalence of risk factors varied significantly among different stroke etiologic subgroups ($P<0.05$). The most common etiologic factors identified by TOAST classification were associated with large artery atherosclerosis (LAA) and small artery occlusion (SAO). Significant variations were observed in the prevalence of different etiologic subtypes of stroke among genders and across different age groups.

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Keywords: Ischemic stroke; Trial of ORG 10172 in acute stroke treatment (TOAST); Stroke etiology; Ahvaz; Risk factors

Introduction

A stroke is a sudden, focal neurological deficit caused by vascular damage to the central nervous system, usually resulting from infarction or hemorrhage (1). It is the second most prevalent cause of global mortality and morbidity (1). Stroke-related complications have emerged as a significant global health concern, contributing to 81.0% of disability-adjusted life years lost and 75.2% of deaths in developing countries (2). It may arise from a variety of diseases, risk factors, and mechanisms (1,3). Hypertension (HTN) is the primary modifiable risk factor for stroke, with varying degrees of impact on different subtypes. The majority (85%) of strokes are ischemic (1). The most significant causes of

ischemic stroke (IS) include larger-artery atherosclerosis (LAA), cardioembolism (CE), and intracranial small-artery disease, which are considered the most prominent etiologies (4). Stroke rates in Iran are significantly higher than those in many Western nations and often occur at younger ages (5). The primary risk factors for stroke in Iran include HTN, ischemic heart disease, diabetes mellitus (DM), being 65 years of age or older, and being male (6).

The multi-center study known as the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) has developed a classification system primarily used by medical professionals to classify IS (7). The TOAST categorizes patients with IS into five distinct subgroups based on the presumed etiological mechanism (8). The

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classification of etiological subtypes depends on geographical location (9). The distribution of subtypes may vary over time due to advancements in industry and medical interventions (10). It is crucial to analyze the development of subtypes to evaluate the effectiveness of preventive measures and provide direction for future actions (10). Stroke is a highly diverse disorder (4) and various subtypes of IS may exhibit distinct risk factors, clinical manifestations, and prognostic outcomes (4). A precise etiological classification system is essential for managing and predicting outcomes for IS (11). This study aimed to determine the risk factors and various subcategories of IS as defined by TOAST criteria in Iranian patients in Ahvaz, Iran.

Materials and Methods

This cross-sectional study analyzed the medical records of all patients over 18 years old with IS who were hospitalized at Golestan Hospital in Ahvaz (Iran), from October 2022 to October 2023. The cases of subarachnoid or intracranial hemorrhage, and cerebral venous thrombosis were excluded. The study protocol was approved by the Medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.HGOLESTAN.REC.1401.212).

The patients underwent cerebral imaging, either through cranial magnetic resonance imaging (MRI) or cerebral computed tomography (CT), Doppler sonography, and angiographic assessment of brain-supplying arteries, as well as basic blood tests and additional necessary laboratory investigations. Moreover, most patients underwent transthoracic or transesophageal echocardiography. The stroke subtypes were determined based on the available data upon admission using the TOAST criteria. The TOAST classification system includes five distinct categories: 1) large artery atherosclerosis (LAA), 2) small artery occlusion (SAO) (e.g., lacunar infarction), 3) cardioembolism (CE), 4) stroke of other determined cause (SOC), and 5) stroke of undetermined cause (SUC) (7).

All patients or their relatives have provided informed consent for the transfer of their data to the data management center. Data collection was conducted prospectively using a standardized questionnaire. The questionnaire included demographic information, details on the onset of ischemia, hospital admission, vascular risk factors, prior medical history, complications, and the

severity of the clinical deficit. The modified Rankin Scale (mRS) was used for assessment upon admission and after three months. The mRS is a tool used to assess the level of disability or dependence in the daily functioning of individuals who have experienced a stroke or other neurological impairments (12). This ranking scale, which evaluates a patient's level of disability from 0 (no symptoms) to 6 (death) (12). Trained personnel then entered the data into the database twice to ensure accuracy.

Statistical analysis

Statistical analysis was employed applying SPSS version 24. The Kolmogorov-Smirnov test assessed the normal distribution of the data. Continuous variables were presented as mean±standard deviation (SD). In addition, categorical variables were explored as percentages and analyzed using the chi-square or Fisher's exact test. Statistical significance was determined at a *P* of less than 0.05.

Results

This study assessed a total of 1100 patients with IS including 658 males and 442 females. They had an average age of 66.10±13.76 years (mean±SD), ranging from 20 to 99 years. The majority of patients were in the age group of 61-80 years. The prevalence of risk factors for IS comprised HTN (71.4%), diabetes (50.4%), smoking (42.4%), prior stroke history (28%), dyslipidemia (15.4%), and cardiovascular disease (22.5%) (Table 1). Three months post-admission, the mortality rate was 10.7%, and the majority of patients had reduced levels of disability based on mRS compared to their initial admission status. The most common types of strokes according to the TOAST classification were related to LAA (n=338, 30.7%), followed by SAO (n=291, 26.5%), and CE (n=228, 20.7%) (Table 1).

The frequency of all risk factors, except for HTN, differed significantly between the two genders (*P*<0.05) (Table 2). The prevalence of risk factors varied significantly among different stroke etiologic subgroups (*P*<0.05) (Table 3). Furthermore, there were notable variations in the prevalence of different etiological subtypes of stroke between the two genders and among different age groups (Tables 4 and 5). The frequency of LAA and CE were higher among patients in the age group of 61-80 years (Table 5).

Table 1. Demographics and clinical characteristics of patients with ischemic stroke(n=1100)

Demographics and clinical characteristics		Patients with IS
		Mean±SD
Age (years)		66.10±13.76
Gender	Male	658 (59.8)
	Female	442 (40.2)
Age group	20-40	61 (5.5)
	41-60	318(29)
	61-80	528 (48)
BMI	≥81	193 (17.5)
	<24.9	36(3.3)
	25-29.9	831(75.5)
Risk Factors	>30	233(21.2)
	Hypertension	785 (71.4)
	Diabetes Mellitus	554 (50.4)
	Hyperlipidemia	169 (15.4)
	Smoking	64 (42.4)
	Cardiovascular Disease	247 (22.5)
mRS at admission	Prior stroke	308 (28)
	0-2	518(47.1)
	3	274(24.9)
mRS after 3 months	4-5	308(28)
	0-2	747(67.9)
	3	187(17)
Deceased	4-5	48(4.4)
		118(10.7)
TOAST subtype	Large artery atherosclerosis (LAA)	338 (30.7)
	Cardioembolism (CE)	228 (20.7)
	Small artery occlusion (SAO)	291(26.5)
	Stroke of other determined cause (SOC)	78 (7.1)
	Stroke of undetermined cause (SUC)	165 (15)

mRS: modified Rankin Score; IS: Ischemic stroke

Table 2. Risk factors according to gender of patients with ischemic stroke (n=1100)

Risk factors	Mele (n=658)		Female (n=442)	P
	n (%)			
Hypertension	Yes	461(70.1)	324 (73.3)	>0.05
	No	197 (29.9)	118 (26.7)	
Diabetes Mellitus	Yes	298 (45.3)	256 (57.9)	<0.05*
	No	360 (54.7)	186 (42.1)	
Hyperlipidemia	Yes	76 (11.6)	93(21)	<0.05*
	No	582 (88.4)	349 (79)	
Smoking	Yes	247 (37.5)	69 (15.6)	<0.05*
	No	411 (65.2)	373 (84.4)	
Cardiovascular Disease	Yes	122 (18.5)	125 (28.3)	<0.05*
	No	536 (81.5)	317 (71.7)	
Previous stroke	Yes	167 (25.4)	141 (31.9)	<0.05*
	No	491 (74.6)	301 (68.1)	

Analysis method: Chi-square test; *significant at < 0.05

Table 3. Risk factors in patients with various etiologies of ischemic stroke (n=1100)

TOAST subtype	LAA	CE	SAO	SOC	SUC	P
Risk factors			n (%)			
Hypertension	223(66)	190 (83.3)	226 (77.7)	57 (73.1)	89 (53.9)	<0.05*
Diabetes Mellitus	88 (26)	202 (88.6)	183 (62.9)	30 (38.5)	51 (30.9)	<0.05*
Hyperlipidemia	24 (7.1)	79 (34.6)	49 (16.8)	17(21.8)	-	<0.05*
Smoking	122 (36.1)	137 (60.1)	36 (12.4)	21 (26.9)	-	<0.05*
Cardiovascular Disease	247(73.1)	-	-	-	-	<0.05*
Previous stroke	87(25.7)	77 (33.8)	82 (28.2)	12(15.4)	50(30.3)	<0.05*

Analysis method: Chi-square test; *significant at < 0.05

Table 4. TOAST classification according to gender of patients with ischemic stroke (n=1100)

Toast subtype	Mele (n=658)	Female (n=442)	P
	n (%)		
Large artery atherosclerosis (LAA)	213 (32.4)	125 (28.3)	
Cardioembolism (CE)	189 (28.7)	39 (8.8)	
Small artery occlusion (SAO)	135 (20.5)	156 (35.3)	<0.05*
Stroke of other determined cause (SOC)	66 (10)	12 (2.7)	
Stroke of undetermined cause (SUC)	55 (8.4)	110 (24.9)	

Analysis method: Chi-square test; *significant at < 0.05

Table 5. TOAST classification according to age group of patients with ischemic stroke (n=1100)

TOAST subtype	Age group				P
	20-40	41-60	61-80	≥81	
	n (%)				
Large artery atherosclerosis (LAA)	28(45.9)	72(22.6)	156(29.5)	82(42.5)	
Cardioembolism (CE)	2 (3.3)	66(20.8)	160 (30.3)	-	
Small artery occlusion (SAO)	31 (50.8)	88(27.7)	138(26.1)	34 (17.6)	<0.05*
Stroke of other determined cause (SOC)	-	14(4.4)	34 (6.4)	30(15.5)	
Stroke of undetermined cause (SUC)	-	78(24.5)	40 (7.6)	47(24.4)	

Analysis method: Chi-square or Fisher's exact test; *significant at < 0.05

Discussion

This study assessed a total of 1100 patients with IS, including 658 males and 442 females. They had a mean age of 66 years (ranging from 20 to 99 years). The majority of patients were in the age group of 61-80 years. In a study of 100 patients with IS in Tabriz (Iran), 58% were men and 42% were women. This finding was consistent with the higher frequency of men in the present study (13). The average age of the patients in their study (13) and another similar study (14) in Iran was 62 and 61 years old, respectively. In other comparable studies (15,16), the average age of patients with IS was higher than that in this study, indicating a younger age range for IS patients in Iran. The relationship between gender and subtypes of IS remains unclear (17). Various studies have reported conflicting findings(17). Some studies indicate a significant association between gender and specific subtypes of IS (18,19), while others have found no significant correlation (17,20-22).

In the current study, the prevalence of risk factors for IS included HTN (71.4%), DM (50.4%), smoking (42.4%), history of previous stroke (28%), dyslipidemia (15.4%), and cardiovascular disease (22.5%). The most frequent risk factor in this study was HTN, which was consistent with findings from other studies (5,9,23-25). The frequency of all risk factors, except HTN, differed significantly between the two genders. Furthermore, the prevalence of risk factors varied significantly among different stroke etiologic subgroups. The frequency of all risk factors, except dyslipidemia, was significantly higher in men than in women. It was reported that HTN is a major risk factor for IS (26). A study (27) indicated that physical inactivity, smoking, and obesity are significant lifestyle risk factors related with the occurrence of IS. The incidence of stroke is strongly correlated with certain risk factors (e.g., HTN, DM, dyslipidemia, smoking, and age) (28).

In this study, it was observed that three months post-admission, the mortality rate was 10.7%, and the majority

of patients had reduced levels of disability based on mRS in comparison to their initial admission status. The mRS score at three months post-admission for patients with IS was linked to the long-term prognosis, providing insight into the patient's risk factors and stroke features (29). In a comparable study conducted in China involving 530 patients with IS, the mortality was 7.4% upon completion of the 3-month follow-up (4).

This study revealed that LAA (37%) was the most frequent cause of stroke among IS patients in Ahvaz (Iran), followed by SAO (26.5%) and CE (20.7%). Significant differences were found between the two genders and among different age groups in terms of the frequency of various causes of stroke. Furthermore, patients aged 61-80 with IS had higher rates of LAA and CE. One study found that among 2634 patients with IS, SUC was the most prevalent type of stroke (57%), followed by SOC (17.3%) (9). Another study reported that CE-related strokes accounted for 25.2% of all strokes, making them the most common type, followed by strokes due to large artery atherosclerosis (LAA) at 12.6% (30). In addition, the prevalence of SOC was 11.2% (30). A study in Isfahan (Iran), revealed that among 1910 patients with IS, SUC was the most frequent type of stroke (43%) (31). Furthermore, the frequency of CE was 21.5%, LAA was 8.4%, SAO was 25%, and 1.2% was SOC (31).

A study among 235 patients with IS in Indonesia revealed that the most common stroke subtype was LAA at 59.6%, followed by SAO at 26.7%, SUC at 9.8%, CE at 2.1%, and stroke of SOC at 0.9% (17). Hypertension emerged as the predominant vascular risk factor, with significant associations observed specifically in the SVD and SUC subtypes (17). The LAA subtype was found to be the most prevalent among various studies conducted in French (32), Brazil (33), and the Persian Gulf Countries (34), consistent with the findings of the present study. In various Asian nations, SAO emerged as the predominant subtype of IS (35). A study in Taiwan revealed that the most prevalent IS subtype was SAO, accounting for 37.7% of cases, followed by LAA (27.7%) (35). Small artery occlusion (SAO) also represented the most common stroke subtype in Japan (54.1%) (21), Jordan (36%) (36), Kuwait (69.8%) (22), and Saudi Arabia (23). Conversely, a substantial multicenter study in Germany (18) and a cohort study (37) identified CE as the predominant subtype.

It was reported that patients with cryptogenic IS or SUC had lower rates of HTN, DM, peripheral vascular disease, hypercholesterolemia, and a history of smoking compared to patients with LAA (38). However, a study in

Iran indicated that patients with cryptogenic IS had a significantly higher mortality rate compared to patients with other subtypes of IS (39). The incidence of cryptogenic stroke ranges from 17% to 39%, depending on the classification system, age, and diagnostic evaluation (40). Stroke caused by CE accounts for 20 to 30% of IS with a higher incidence in elderly patients (41). The cryptogenic stroke category within the TOAST classification includes strokes with multiple possible causes and strokes that have not been classified or evaluated despite extensive diagnostic evaluation (42). It was suggested that an incomplete assessment of the causes of SUC in patients could worsen the outcome (31). The TOAST classification system is widely used for the etiological classification of IS and is widely recognized for its simplicity, logic, and practicality. However, a significant limitation is that the categorization of 'undetermined' causes of stroke is as high as approximately 40% (43).

This study identified a significantly higher proportion of modifiable risk factors for IS among patients in Ahvaz, Iran. In addition, HTN and DM were the most common risk factors. These observations emphasize the importance of implementing effective primary and secondary prevention strategies that target modifiable risk factors (9). A study revealed that adults with both high triglycerides (TG) and low high-density lipoprotein (HDL) cholesterol or low-density lipoprotein (LDL) cholesterol levels of ≥ 130 mg/dL, mostly those with DM, have an increased risk of stroke (44).

The findings of the study in Gorgan (Iran) (25) revealed that individuals over the age of 70 are at a higher risk of stroke, which is consistent with other studies involving Iranian patients with IS (6). Identifying the cause of a stroke is a primary objective in the assessment of stroke patients in clinical settings (45). Nevertheless, ischemic stroke is a complex condition with multiple underlying disorders contributing to its pathogenesis (45). Patients with IS living in urban areas faced a 1.5 times higher risk of stroke compared to their rural counterparts. This variation may be linked to unhealthy lifestyle habits, such as insufficient physical activity levels and an unhealthy diet (46).

This study had several limitations, notably its single-center design. The medical records revealed deficiencies in certain parameters, and some diagnoses were not thoroughly documented. It is recommended that future studies include a longer duration, a larger sample size, and multiple centers to improve the quality of findings. A prospective study is suggested to focus on categorizing patients with IS from the time of admission. Identifying

stroke risk factors among Iranian patients with ischemic stroke is crucial for developing prevention strategies and effectively managing these risk factors (25).

The study findings indicate that a history of DM, heart failure, HTN, hyperlipidemia, and smoking were significant risk factors for IS among the evaluated patients. The highest incidence of IS was observed in males and individuals aged over 50 years. The most common causal factors, according to the TOAST classification, were linked to LAA and SAO. Accurate categorization of ischemic stroke is crucial for developing treatment strategies and evaluating the patients. Given the widespread presence of these risk factors, it is crucial to prioritize accurate management, raise public awareness, and make lifestyle changes to effectively prevent and address the complications associated with both primary and secondary strokes. These findings can help healthcare organizations identify key priorities and ameliorate the quality of care for patients with IS in hospital settings.

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SM and SR developed the study concept and protocol. SHM conducted data analysis and prepared the initial draft of the manuscript. All authors reviewed the manuscript draft and provided their approval for the final version.

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