

ORIGINAL ARTICLE

ÖZGÜN ARAŞTIRMA

**DEMOGRAPHICS OF YOUNG PATIENTS WITH ISCHEMIC STROKE IN THE CITY OF ÇORUM:
EVALUATION OF RISK FACTORS**

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ABSTRACT

INTRODUCTION: In this study, the risk factors detected in patients aged 18-45 years who were hospitalized for ischemic stroke in the city of Çorum were evaluated.

METHODS: A total of 124 young ischemic strokes (YIS) and 23 transient ischemic attacks (TIA) patients who were hospitalized with a diagnosis of YIS and TIA between January 2013 and January 2023 were included in the study. Risk factors and prognosis in these patients were evaluated.

RESULTS: Among the patients in the YIS group, 79 were male and 45 were female, and the mean age was 39.06±5.96 years. The most commonly identified single risk factor was hypertension (HT), affecting 27 patients, followed by cigarette smoking in 20. The mean homocysteine (HS) and vitamin D (vit D) levels were 21.46±19.63 (5-97) µmol/L and 27.57±17.97 (3-68) ng/ml, respectively. Of the total patients in the YIS group, 52 patients were identified with a lacunar infarct according to the Bamford classification and 39 with a small-vessel occlusion according to the TOAST classification. The Modified Rankin scale was applied to the findings detected at the first-month outpatient clinic visit, and 59 patients had no pathologic symptoms. Recurrent stroke developed in 18 patients over a mean follow-up of one year, in which the classical stroke risk factors were present, while vit D levels were lower and HS levels were higher (p<0.05).

Among the 23 cases diagnosed with TIA, which were followed up at the same time, 16 were male and 7 were female, and the classical risk factors were also present in all of the patients in this group, with HT being the most common.

DISCUSSION AND CONCLUSION: Although the prognosis is better in YIS, the treatment of the risk factors and the detection of the etiology can be important in the prevention of recurrence and the efficient treatment of patients.

Keywords: Young Ischemic stroke, stroke etiology, transient Ischemic attack.

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ÇORUM İLİ GENÇ İSKEMİK İNME HASTALARININ DEMOGRAFİK VERİLERİ, RISK FAKTÖRLERİNİN DEĞERLENDİRİLMESİ

ÖZ

GİRİŞ ve AMAÇ: Bu çalışmada, Çorum ilinde iskemik inme nedeniyle hastaneye yatırılıp yapılan 18-45 yaş arası hastalarda saptanan risk faktörleri gözden geçirilmiştir

YÖNTEM ve GEREÇLER: Ocak 2013 ile Ocak 2023 tarihleri arasında toplam 124 genç iskemik inme (Gİİ) ve 23 geçici iskemik atak (GİA) tanıları ile hastanede yatan hastalar çalışmaya dahil edildi. Bu hastalarda ki risk faktörleri ve prognoz değerlendirildi.

BULGULAR: Gİİ grubunda hastaların 79'u erkek, 45'i kadındı. Yaş ortalaması $39,06 \pm 5,96$ yılı. En sık izlenen tekli risk faktörü hipertansiyon (HT) 27 hastada, ikinci sıklıkta ise hastada sigara içme olarak belirlendi. Ortalama homosistein (HS) düzeyi $21,46 \pm 19,63$ (5-97) $\mu\text{mol/L}$ vitamin D (vit D) düzeyi ise $27,57 \pm 17,97$ (3-68) ng/mlt olarak saptandı. Bamford sınıflamasına göre 52 hastada laküner infarkt, TOAST sınıflamasında 39 hasta küçük damar okluzyonu saptandı. Modifiye rankin skalası taburculuk sonrası birinci ayda poliklinik kontrolü bulguları ile değerlendirildi ve 59 hastada patolojik semptom yoktu. 18 hastada takip eden ortalama bir yıl içinde tekrarlayıcı inme saptandı. Bu grupta klasik risk faktörleri mevcuttu ve tekrarlayıcı inmesi olmayan ile karşılaştırıldığında Vit D düzeyi daha düşük, HS düzeyi ise daha yüksekti ($p < 0,05$). GİA tanısı ile 23 vaka aynı dönemde takip edilmişti. Bu vakaların 16'sı erkek 7'si kadın cinsiyetteydi. Yine bu hasta grubunun tamamında klasik risk faktörleri vardı. HT bu grupta en sık risk faktörüydü.

TARTIŞMA ve SONUÇ: Genel olarak Gİİ hastalarda prognoz daha iyi seyretmekle birlikte risk faktörlerinin tedavi edilmesi ile etiyojinin belirlenmesi, rekürrensi önlemek ve etkin tedavi açısından önemlidir.

Anahtar Sözcükler: Genç iskemik inme, inme etiyojisi, geçici iskemik atak.

INTRODUCTION

Cerebrovascular diseases (CVD) are among the main causes of death and disability worldwide. The determination of the etiology of stroke is important in the management of the disease, and thus the determination of prognosis. The incidence of CVD in young adults is increasing around the globe, with 2 million young people being affected by stroke and its consequences every year. Young ischemic stroke (YIS) accounts for the majority of patients with cerebrovascular disease in this age group (1,2). A detailed evaluation of YIS is important for the selection of the most appropriate treatment method and for protection and prognosis. YIS is more common and is associated with higher mortality in countries with a low socioeconomic status, and strokes in developing countries are thought to account for more than two-thirds of the global stroke load (3,4), although the significant burden of palliative care and rehabilitation on the economies of countries should be taken into account. A wide range of etiology for YIS that needs to be evaluated, comprehensive diagnostic studies may therefore be required. Idiopathic or rarely seen risk factors in the young age group should be taken into account, although there are many risk factors that are known to be associated with the development of ischemic stroke. The traditional

risk factors for stroke in the older adult population have been identified also in studies of the YIS group (5,6).

METHODS

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki and the study was approved by Clinical Research Ethics Committee of Hitit University (Date: 11.04.2023, No: 2023-34). A total of 124 YIS and 23 Transient ischemic attack (TIA) patients who were hospitalized in the Hospital of Hitit University, Faculty of Medicine with a diagnosis of YIS and TIA between January 2013 and January 2023 were included in the study. The patient files were evaluated retrospectively to identify any of the risk factors listed in the stroke protection guidelines of the World Health Organization and the American Association of Cardiology /American Society of Stroke.

The patient demographics, risk factors, vitamin D levels (Vit D) and homocysteine (HS), etiology subgroups, modified Rankin scores (mRS) at post-discharge month 1 outpatient clinic follow-up and duration of hospital stay were analyzed and Trial of ORG 10172 In Acute Stroke Treatment Classification (TOAST) and Bamford classification was performed.

Statistical Analysis: IBM SPSS Statistics (Version 22.0, SPSS Inc. Chicago, IL, USA Hitit University Licensed) was used for the statistical analysis. Sociodemographic data were expressed as numbers and percentages, mean±standard deviation and median values. Categorical variables were evaluated with Pearson's Chi-Square and Fisher's Exact Tests, and the normality of the distribution of numeric variables was evaluated with a Shapiro-Wilk test. A Student's T-test and a Mann-Whitney U test were used for the evaluation of continuous variables between the groups and non-normal variables, consecutively. Pearson's correlation test was applied to determine any correlations between the numerical variables, and Spearman's correlation test was used for non-normally distributed variables. $p < 0.05$ was accepted as significant.

RESULTS

Among the 124 patients with YIS, 79 (63.7%) were male and 45 (36.3%) were female, with mean ages of 39.91 ± 5.35 and 37.57 ± 6.7 years, respectively. The youngest patient was 21 years old. The duration of hospital stay was 10.52 ± 7.94 days. The most common single risk factor in the patient group with detectable risk factors was hypertension (HT) in 27 (25.47%), followed by cigarette smoking in 20 (18.86%), while hyperlipidemia was the only risk factor in 11 (10.37%) patients, and no etiologic factor was identified in 18 (14.51%). Diabetes mellitus (DM), HT and HL were present concomitantly in seven cases and DM and HT concomitantly in five patients. Of the eight patients with cardiac valve disease, three had mitral valve disease and five had aortic valve disease. Furthermore, three patients were identified with patent foramen ovale (PFO) on transesophageal echocardiography. Of the total, 44 patients (35.48%) had a history of cigarette smoking, with a higher ratio identified among the male patients ($n=30$, 68.18%). Alcohol consumption was present in 10 (8.06%) patients, all of whom were male. Genetic susceptibility was determined in six patients, with the factor V Leiden mutation identified in two patients and homozygous MTHFRA1298C and MTHFRC677 T gene mutations in four. Simultaneous morbid obesity and sleep apnea were present in two patients. Paraneoplastic stroke was diagnosed in three patients, all of whom were being followed-up

by the oncology department with diagnoses of acute lymphoblastic leukemia, and breast and lung cancer. Symptomatic carotid stenosis was identified in one patient, and vertebral and carotid system dissection in two patients. Anemia was detected as a risk factor in etiology in five patients with an average hemoglobin level of 7.92 ± 0.92 and thrombocytosis was found to have developed secondary to anemia in one patient in this group (platelet level = $468.600/\mu\text{L}$). Behçet's disease (BD) and systemic lupus erythematosus (SLE) were detected in two and three patients, respectively. According to the medical files, only seven patients had reported symptoms of TIA prior to their stroke. A history of migraine was reported in four female patients, among which, two had anemia and the remaining two had HT and HL as risk factors.

Lacunar infarcts (LACI), partial anterior circulation infarcts (PACI), posterior circulation infarcts (POCI) and total anterior circulation infarcts (TACI) were identified in 52 (41.9%), 43 (34.7%), 18 (14.5%) and 11 (8.9%) cases, respectively, according to the Bamford classification. According to the TOAST classification, small artery occlusion (SAO), major arterial atherosclerosis (MAA), cardioembolism (CE), stroke of other determined cause (SOC) and stroke of undetermined cause (SUC) were recorded in 39 (31.5%), 24 (19.4%), 19 (15.3%), 24 (19.4%) and 18 (14.5%) of the patients, respectively. The patients underwent an mRS evaluation 1 month after discharge, with mRS scores of 0, 1, 2, 3, 4, 5 and 6 recorded in 59 (47.6%), 21 (16.9%), 18 (14.5%), 15 (12%), seven (5.6%), zero (0%) and four (3.2%) cases, respectively. Paraneoplastic stroke, symptomatic carotid stenosis and mitral valve disease were detected in the etiology of the four patients who died. The HS level was less than $15 \mu\text{mol/L}$ (47.58%), $15-30 \mu\text{mol/L}$ (9.67%) and $30-100 \mu\text{mol/L}$ (42.74%) in 59, 12 and 53 of the cases, respectively, and the mean HS level was calculated at 21.46 ± 19.63 (5-97), among which, levels of $15 \mu\text{mol/L}$ and above were accepted as hyperhomocysteinemia (HHS). Vit D deficiency, vit D insufficiency, adequate vit D level and required vit D level were defined as less than 20 ng/ml, 21-29 ng/ml, above 30 ng/ml and 40-60 ng/ml, respectively. Vit D level was less than 20 ng/ml and 21-29 ng/ml, and above 30 ng/ml and 40-60

ng/ml in 52 (41.93%), 14 (11.29%) 21 (16.93%) and 37 (29.83%) of the cases, respectively, and the mean vit D level was 27.57±17.97 (3-68) ng/ml. Hyperlipidemia was defined in patients with a fasting low-density lipoprotein (LDL) of 100 mg/dl and above, and/or in patients diagnosed with hypercholesterolemia. Of the total, three patients were found to have familial dyslipidemia, while the mean LDL of the other patients was 123.98±84.60.

Recurrent stroke developed in 18 patients within a mean follow-up of 1 year. The classical stroke risk factors (HT, DM, HL) were present in all patients with recurrent stroke, while Vit D levels were lower and HS levels were higher ($p < 0.05$). The mean HS level at the time of the first stroke event was 18.38±10.83 in the group with no recurrent stroke, and 39.60±19.73 in the recurrent stroke group. The mean vit D level was in the recurrent stroke group, being 18.04±15.03 and in the non-recurrent stroke group 29.19±17.40. When comparing the two groups with and without stroke recurrence, no significant difference was detected in LDL values. Table 1 summarizes the BAMFORD, TOAST and mRS findings in YIS. Table 2 summarizes the average LDL, HS and vitamin D levels in the subgroups (recurrent and non-recurrent stroke).

Table 1. TOAST BAMFORD and mRS classification of patients.

TOAST	BAMFORD	mRS
MAA 19 (15.3%)	TACI 11 (8.9%)	0 59 (47.6%)
CE 24 (19.4%)	PACI 43 (34.7%)	1 21 (16.9%)
SAO 39 (31.5%)	LACI 52 (41.9%)	2 18 (14.5%)
SOC 24 (19.4%)	POCI 18 (14.5%)	3 15 (12%)
SUC 18 (14.5%)		4 7 (5.6%)
		5 0 (0%)
		6 4 (3.2%)
N= 124 (100%)	N=124 (100%)	N= 124 (100%)

Acute stroke treatment classification (TOAST), Modified rankin Scores (mRS), Major arterial atherosclerosis (MAA), Cardioembolism (CE), Small artery occlusion (SAO), stroke of other determined cause (SOC), stroke of undetermined cause (SUC), Total anterior circulation infarcts (TACI), Partial anterior circulation infarcts (PACI), Lacunar infarcts (LACI), Posterior circulation infarcts (POCI).

In the same period, 23 cases diagnosed with TIA were followed-up for a mean duration of 6.4±4.2 days. The mean age in this group was 39.9±8.9 years, and 16 of the patients were male (69.6%) and seven were female (30.4%) Classical risk factors were present in all patients in the group, while HT, DM and HL were found in 12 (52.2%), eight (34.8%) and three (13%) patients,

Table 2. Mean vitamin D, LDL, and homocysteine levels in subgroups (recurrent and non-recurrent stroke)

Group	Mean vitamin D level ng/ml (min/max)	Mean homocysteine level μ mol/L (min/max)	Mean LDL level (mg/dl) (min/max)
Recurrent ischemic stroke	18.04±15.03 (3.03/43.9)	39.60±19.73 (20.87/80.33)	133,0±39,0 (95.9/272.8)
Non-Recurrent ischemic stroke	29.19±17.40 (11.80/56.60)	18.38±10.83 (7.56/49.22)	130.7±41.6 (87.2/270.1)
P value	0.035	0.025	0.424

Low-density lipoprotein (LDL).

respectively. The mean LDL, vit D and HS levels in the group with hyperlipidemia were 168±48.7, 25.6±9.07 ng/ml and 9.4±5.5 μ mol/L, respectively. Of these patients, 10 had hemihypoesthesia and hemiparesis, 10 had speech impairment (aphasia and/or dysphasia), and 3 had dysarthria, ataxia, and dizziness symptoms. No recurrent stroke occurred in this group during follow-up. Tables 3 and 4 summarize the average HS, vit D and LDL levels in the YIS and TIA patient groups, respectively, and the risk factors detected in these two groups.

No significant difference was found in the risk groups or the results of the classifications of the different sexes other than alcohol consumption and cigarette smoking.

Table 3. Risk factors in young ischemic stroke and transient ischemic attack patients, number of patients.

Etiology	YIS(n)	TIA(n)
HT	27	12
DM	-	8
HL	11	3
Smoking	44	-
Undetermined	18	-
DM+HT+HL	7	-
DM+HT	5	-
HVD	8	-
PFO	3	-
Alcohol	10	-
Genetic	6	-
Morbid obesity/sleep apnea	2	-
Paraneoplastic	3	-
Symptomatic carotid stenosis	1	-
Dissection	2	-
Anemia	5	-
BD	2	-
SLE	3	-
TIA	7	-
Migraine	4	-

Hypertension (HT), Diabetes Mellitus (DM), Hyperlipidemia (HL), Heart valve disease (HVD), Patent foramen ovale (PFO), Behçet disease (BD), Systemic lupus erythematosus (SLE), Transient ischemic attack (TIA).

Table 4. Mean vitamin D, LDL, and homocysteine levels in YIS and TIA groups.

	Mean vitamin D level ng/ml (min/max)	Mean homocysteine level μ mol/L (min/max)	Mean LDL level (mg/dl) (min/max)
YIS	27.57 \pm 17.97 (3/68)	21.46 \pm 19.63 (5/97)	123.98 \pm 84.60 (43/390)
TIA	25.6 \pm 9.07 (3/64)	9.4 \pm 5.5 (5/15)	168 \pm 48.7 (50/400)

Young ischemic stroke (YIS), Transient ischemic attack (TIA), Low-density lipoprotein (LDL).

DISCUSSION AND CONCLUSION

Formerly rare causes of CVD have been gradually increasingly, identified as a result of advances in the diagnostic tests and neuroimaging used to identify the etiology of stroke. The incidence of YIS has been reported in a range of 2.5–40/100,000, but is increased in those over the age of 35 years (7,8). Although modifiable risk factors affecting youth and older adults are similar, their prevalence differs. Rare etiologies in such cases should be considered, although the known classical risk factors such as DM, HT, HL and atrial fibrillation (AF) are also detected in young age groups. The risk factors and etiology of YIS have been investigated in many studies (9,10), although this study is the first to investigate the risk factors and causes of YIS among the population of Çorum.

The most common risk factors between the ages of 15 and 44 years are reported to be dyslipidemia, cigarette smoking and HT in studies (11). Preventable factors are more common in YIS than in the older adult age group, and the detection and treatment of modifiable risk factors should be considered important for the prevention of both primary and secondary stroke. A higher rate of plasticity of the brain in YIS may explain the better prognosis in YIS when compared to older adult patients. YIS is a major disadvantage individually and also in terms of the society, although the prognosis in YIS is good. Hence, the detection of the etiologic factors in young patients is important for the prevention of recurrent stroke and other complications (12). Although it is usually more common in men, different ratios of men and women have been reported in YIS studies. The majority of men in this study support the findings of previous studies (13–15). The classical risk factors that are often observed in YIS are HT, DM, HL and cigarette smoking (16), and the high incidence of these factors may be explained by the sociocultural structure, the way

of life and traditional nutritional habits.

The TOAST classification has been used for the evaluation of YIS subgroups in many studies, among which SUC is the most frequently encountered, followed by SOC and CE. The most frequently encountered subgroup in this study group was SAO which was thought to be compatible with the widespread incidence of classical risk factors in the present patient group.

Renna et al reported PFO to be a main risk factor for YIS, accounting for 39.3%, followed by oral contraceptive (OC) use, cigarette smoking, hyperlipidemia and HHS (11). HHS was identified in 65 cases in this study, and the HHS rate in the recurrent stroke group was higher than in the non-recurrent stroke group. No increase in HS levels was noted in the TIA group, and no recurrent stroke was recorded in this group. This supports the use of HS level as a preliminary marker for recurrent stroke (17). Harris et al. determined dyslipidemia as the most frequent risk factor in SUC among the TOAST subgroups, and HT in the other subgroups. Isolated dyslipidemia was identified in 11 patients in this study and was found to be an additional risk factor in 16 cases (18). The results of this study suggest that different risk factors are common in YIS, while classical risk factors are increased among older adults. Revascularization is recommended in patients with symptomatic carotid stenosis of 70–90% is detected in studies of interventional neurology (19). A single patient in this group was diagnosed with symptomatic carotid stenosis and referred to the interventional neurology clinic. Cases of stroke developing secondary to dissection have been reported in case reports or case series, although the reported incidence of dissection is varied. Two male patients who had a stroke secondary to dissection as a result of trauma were followed up in the cardiovascular surgery department (20). Factor V Leiden, prothrombin, proteins C and S, and antithrombin are known to be significantly associated with an increased stroke risk (21). Araj et al. identified an MTHFR mutation in 94% of 35 cases of YIS, and MTHFR 1298 and MTHFR 677 mutations in 47% and 53%, respectively, in those with a positive MTHFR mutation (22). In this study, two patients had MTHFR 1298 gene mutation and 677 gene mutations among four patients.

Risk factors for stroke, such as OC, history of migraine and pregnancy, and postpartum period

should be questioned in anamnesis of young female stroke patients. Of the 45 women evaluated in this patient group, four female patients were identified with migraine accompanying classical risk factors, In the patient group I examined, no pregnant, postpartum patients and OC use were found. I believe that the anemia detected in five of patients is actually important in increasing the awareness of all clinicians about the etiopathogenesis of stroke. In addition to articles related to the association of anemia with cardiovascular diseases, which are a risk factor for stroke, there are studies investigating the effect of anemia and stroke etiopathogenesis, anemia and prognosis after stroke (23-26).

Education level has been identified as an effective indicator of prognosis in stroke. In a study not limited to YIS, the mortality rate was reported to be low in the first month after a stroke in single patients, although the rate of recurrent stroke was higher in this group in the first year following the stroke. No effects of marital status or education level were evaluated in this study since no long-term follow-up data of the patients was available (27,28). Because of social concerns, patients do not tend to disclose their alcohol use, so I had difficulty detecting exact alcohol use. Nevertheless, society should be warned about the association between alcohol consumption and stroke. Although there is a proven association between sleep disorders and stroke, patients with a history of obstructive sleep apnea syndrome (OSAS) but who had not been tested were evaluated with advanced tests, and a diagnosis of OSAS was determined in two (29,30). The mean vit D levels in this study indicated insufficiency in both the YIS and TIA groups, and was lower in patients with recurrent stroke. Studies have reported an association between low vit D levels and the incidence of stroke, while high serum concentrations of vit D have been shown to be protective against mortality and the recurrence of cardiovascular diseases, including stroke (31,32). BD and SLE were detected in the etiology of two and three patients, respectively, among the patients followed-up in this study. The prevalence of ischemic stroke was found to be increased in a prospective study of 306 patients with BD in a study by Wu et al. Many studies attention the association of both BD and SLE with CVD (33-36).

Hospital stay durations of stroke patients are affected by many factors, such as the severity of

stroke, comorbid diseases and the etiology of the stroke. Hospitalizations in excess of 7 days have been found to be associated with such complications as sepsis and pressure sores (37). Longer hospital stay durations have been reported in the majority of patients, although the severity of stroke was mild, which may be explained by lengthened laboratory and imaging studies. One month after patients were discharged from the hospital, mRS levels showed a good prognosis, similar to many previous studies (38).

Among the limitations of this study are its single-center design, the absence of an evaluation of body mass index, the lack of an evaluation of some sociodemographic data was performed on the prognosis, and the lack of a calculated physical activity score for the patients, and so these were not analyzed among the risk factors. Detailed tests were performed on all patients for the etiologic evaluation. During the study period, venous embolism patients were excluded from the study. Considering the etiological diversity in young patients with venous embolism, I think that this issue should be evaluated independently.

As a conclusion, risk factors that were detected in a broad spectrum in addition to the findings of this study were compatible with the results of previous studies, although conducted in a single-center. The risk factors, causes, severity and prognosis of stroke differ in YIS compared when to the older adult population. Although the prognosis is better in YIS, the treatment of risk factors and the detection of the etiology are important for the prevention of recurrence and for the efficient treatment of patients.

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- Ethics**
Ethics Committee Approval: The study was approved by Clinical Research Ethics Committee of Hitit University (Date: 11.04.2023, No: 2023-34).
Informed Consent: The author declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.
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