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Ischemic stroke subtypes in subjects with and without diabetes: data from two hospitals in Mongolia

Naranchimeg Gendendagva [1,2 #], Yanjmaa Sankhuu [3,4 #], Anar Bayarmunkh [3], Byambasuren Dagvajantsan [1]*, Altaisaikhan Khasag [3]* and Oyuntugs Byambasukh [3]*

[1] Department of Neurology, Mongolian National University of Medical Sciences, Ulaanbaatar 13270, Mongolia.
[2] Stroke Center, State Central Third Hospital, Ulaanbaatar 14240, Mongolia.
[3] Department of Endocrinology, Mongolian National University of Medical Sciences, Ulaanbaatar 13270, Mongolia.
[4] Department of Diabetes and Endocrinology, First State Central Hospital, Ulaanbaatar 14240, Mongolia.
[#] These authors contributed equally.
* Correspondence: oyuntugs@mnums.edu.mn; byambasuren@mnums.edu.mn; altaisaikhan@mnums.edu.mn; Tel: +976-99017063

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Abstract: According to the World Health Organization report in 2020, the number of stroke deaths in Mongolia has reached 4,401, accounting for 19.84% of the total deaths, ranking as the second leading cause of death in Mongolia. Furthermore, the prevalence of diabetes has been steadily increasing for the last 20 years. In this case-control study (80 diabetic and 160 non-diabetic subjects), we analyzed data from two tertiary stroke centers over the past six months (June-December 2022). Inclusion criteria included patients over 18 years who presented to the emergency department with an acute ischemic stroke (I63 according to ICD 10). We reviewed and compared the data on clinical assessments such as the National Institutes of Health The Stroke Scale (NIHTSS), Glasgow Coma Scale and Modified Rankin Score, laboratory parameters, and TOAST classification of ischemic stroke between diabetic and non-diabetic patients in Mongolia. The mean age was 39.2±15.2, and 33.2% (n = 392) were male. The duration of diabetes in patients ranged from 0 to 23 years, and the median was 5.0. Mean glycated haemoglobin in subjects was 9.75±2.49%, and only 27.5% (n = 22) had HbA1c below 7.5%. Only BMI was significantly different in patients with diabetes compared to patients without diabetes (27.2±4.4 vs. 28.6±5.2). However, for other parameters, no significant difference was observed, but the NIHTSS at discharge was significantly higher in patients with diabetes. According to the TOAST classification, the risk of ischemic stroke caused by microangiopathy (18% vs 33.8%, p=0.142) and macroangiopathy (44.4% vs 57.5%, p=0.192) was 13-15% higher in people with diabetes than in people without diabetes. In regression analysis, patients with diabetes had a six times greater risk of ischemic stroke caused by atherosclerosis than non-diabetic patients. Most subtypes of stroke that occur in people with diabetes are caused by atherosclerosis, both large and small vessels.

Keywords: diabetes; stroke; TOAST; atherosclerosis

1.0 INTRODUCTION

Stroke is a leading cause of morbidity and mortality worldwide (GBD 2019 Stroke Collaborators, 2021). All types of stroke ranked cause of death (13-15%) as the third and surpassed only by heart disease and cancer. Each year, 15,000,000 people suffer from stroke worldwide, of which 5,000,000 result in mortality, and the remaining 10,000,000 result in profound disability (Lindsay et al., 2019). According to the latest data released by the World Health Organization in 2020, the number of stroke deaths in Mongolia has reached 4,401, accounting for 19.84% of the total deaths, ranking as the second leading cause of death in Mongolia (Chimed-Ochir et al., 2022). Mongolia ranks third worldwide in stroke-related deaths (World Life Expectancy, 2020). Furthermore, the prevalence of diabetes has been steadily increasing for the last 20 years. The prevalence of diabetes increased from 3.2% in 1999 to 8.3% in 2020 (Suvd et al., 2002; WHO, 2020). The increasing prevalence of diabetes is one of the most serious health problems in Mongolia, and it is increasingly important to study its impact on macro-vascular complications such as stroke. In a study by Stegmayr et al. (1997), who followed an age-matched population (35-74 years) for eight years, the incidence of acute stroke in diabetic patients was three times higher than in non-diabetic patients. Compared to the non-diabetic population, stroke mortality (both initial and recurrent) in the diabetic population was 4.4 times higher in men and 5.1 times higher in women (Stegmayr et al., 1997). Coronary artery disease increases the risk of ischemic stroke at all ages, with the highest risk among African-Americans under 55 and whites under 65, according to a study by Kissela et al. (2005). In a large case-control study adjusted for multiple risk factors, the risk of stroke was 2.3 to 2.47-fold higher in patients with diabetes (Hu et al., 2022; Kissela et al., 2005).

The TOAST classification system of the stroke subtype is easy to use and includes good observer agreement with experts. It represents five subtypes of ischemic stroke: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, a stroke of other identified etiology, and a stroke of unknown etiology (Adams et al., 1993; Koennecke et al., 2011; Mima et al., 2016; Mishra et al., 2010). Several studies have reported that the TOAST classification is suitable for assessing ischemic stroke in populations with and without diabetes mellitus (DM) and is effective for treatment (Koennecke et al., 2011; Mima et al., 2016; Mishra et al., 2010). Furthermore, stroke patients are vulnerable to a broad range of complications, especially during the acute phase. These complications frequently impede neurological recovery and can significantly impact functional outcomes, lengthening hospital stays and delaying successful rehabilitation (Adams et al., 1993; Simonsen et al., 2022). The National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Score (mRS) are the most frequently employed primary outcome measures in the management of ischemic stroke. These measures assess the functional and neurological status of patients, respectively, and are widely utilized to evaluate 90-day outcomes. The NIHSS in 1 week satisfies the requirements for a surrogate endpoint and may be used as a primary outcome measure in acute treatment trials for ischemic stroke, particularly in diabetic patients. But it could also reduce stroke outcome assessment to its essential elements (eg: neurological deficit) and reduce the trial duration and cost (Adams et al., 1993; Koennecke et al., 2011; Mima et al., 2016; Mishra et al., 2010). This study aimed to compare the clinical assessment, laboratory parameters, and TOAST classification of ischemic stroke between diabetic and non-diabetic patients in Mongolia.

2.0 MATERIALS AND METHODS

2.1 Data source and study population

In this case-control cross-sectional study, we analyzed data from two tertiary stroke centers (First State Central Hospital and State Central Third Hospital) over the past six months (June-December 2022). Inclusion criteria included patients over 18 years of age who presented to the emergency department with an acute ischemic stroke (I63 according to ICD 10). Patients with hemorrhagic stroke, recurrent ischemic stroke and transient ischemic attacks were excluded. Sample size calculation was based on the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines for reporting case-control studies (von Elm et al., 2007). The calculated sample size was 80 in the case group (patients with diabetes) using a significance level of 5% and a power of 80%. The control group consisted of non-diabetic patients who were specifically chosen to match the patient group experiencing acute ischemic stroke in terms of age and gender, with a 1:2 ratio. We selected these control patients from our hospital's medical records, and they did not have a history of stroke or other neurological disorders. The study was conducted according to the Helsinki Declaration, and it was approved by the medical ethical committee of the Mongolian National University of Medical Sciences (METc 2022/3-05).

2.2 Variables and measurements

The TOAST classification system includes five categories: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-artery occlusion (lacune), 4) stroke of other determined etiology, and 5) stroke of undetermined etiology (Adams et al., 1993). Diagnoses were based on clinical features and data collected by tests such as brain imaging [computed tomography (CT) / magnetic resonance imaging (MRI)], cardiac imaging (echocardiography, etc.), duplex imaging of extracranial arteries, arteriography, and laboratory assessments for a pro-thrombotic state.

The NIHSS was used in this study, which is a graded neurological examination that assesses speech, language cognition, inattention, visual field abnormalities, motor and sensory impairments, and ataxia (Meyer et al., 2002). In addition, we used the modified Ranking scales (a descriptive categorization of functional recovery) which are the grades of stroke severity ranging from "no significant disability" to "severe disability" (Banks & Marotta, 2007). Furthermore, the Glasgow Coma Scale (GCS) was calculated at the time of admission and discharge of patients (Teasdale et al., 2014). GCS and NIHSS are scoring systems used to assess a patient's level of consciousness and neurological deficit, respectively. The GCS is a simple and widely used scoring system that evaluates three components: eye-opening, motor response, and verbal response. Each component is scored on a scale from 1 to 4 or 6, with higher scores indicating a better level of consciousness. The maximum score on the GCS is 15, with scores ranging from 3 (indicating deep unconsciousness) to 15 (indicating full consciousness). The NIHSS, on the other hand, is a more comprehensive scoring system that evaluates a patient's neurological deficit caused by a stroke. The NIHSS consists of 11 items, with scores ranging from 0 to 42. Each item evaluates a different neurological function, such as level of consciousness, gaze, visual fields, facial palsy, motor function of the limbs, and language. Higher scores on the NIHSS indicate more severe neurological deficits (Mahdy et al. 2019).

For other parameters, body mass index (BMI) is calculated based on weight and height. In addition, information on blood pressure, laboratory parameters (fasting glucose, triglycerides, low-density lipoproteins, high-density lipoproteins, cholesterol, and glycated hemoglobin), diabetes treatment, and duration of illness was obtained through medical records.

2.3 Statistical analysis

In descriptive statistics, data were expressed as means with a standard deviation (SD) and as numbers with percentages. The differences between groups were compared using the Student's T-test and Pearson Chi-Square test. Binary logistic regression analysis was performed to explore the association between diabetes status and stroke subtypes, and non-diabetes group was considered as the reference group for the regression analysis. Statistical analyses were performed using IBM SPSS V.27.0. A two-sided statistical significance was set at $p<0.05$ for all tests.

3.0 RESULTS

3.1 General characteristics of the study population

The mean age of the study participants was 39.2 ± 15.2 and 33.2% (n=392) were male. There were no statistically significant differences in age and gender. The duration of diabetes in patients ranged from 0 to 23 years, and the median was 5.0. Of these, 3.8% (n=9) were newly diagnosed with diabetes, while 12.5% (n=30), 7.9% (n=19), 4.6% (n=11), 0.8% (n=2) and 2.9% (n=7) were diagnosed with diabetes for 0 – 5, 6 – 10, 11 – 15, 16 – 20 and over 21 years. Mean glycated haemoglobin in subjects was 9.75 ± 2.49%, only 27.5% (n=22) had HbA1c below 7.5%, and the remainder had HbA1c above 7.5%. Among subjects with diabetes, 26.2% (n=21) used insulin, while others received oral antidiabetic drugs.

3.2 Clinical parameters and risk factors

As shown in **Table 1**, only BMI was significantly different in patients with diabetes compared to patients without diabetes (27.2 ± 4.4 vs 28.6 ± 5.2). However, for other parameters, no significant difference was observed, but NIHSS at discharge was significantly higher in patients with diabetes (**Table 1**). Moreover, blood pressure and triglyceride levels were slightly higher among patients with diabetes. There was no significant difference in the length of hospital stay or intrahospital mortality between those with and without diabetes. In terms of stroke risk factors, there were significant differences between the two groups in the incidence of hypertension (88.8% of patients with diabetes and 77.5% of those without diabetes). The next risk factor involved dyslipidemia. However, no significant differences were found between the two groups for dyslipidemia (52.2%), smoking (39.1%), and myocardial infarction (5.8%).

Table 1. General characteristics of the study population.

Findings	Diabetes		*P* value
	Without (n=160)	With (n=80)	
Age (year)	57.1 ± 9.1	59.0 ± 8.6	Matched
Male gender, n (%)	50 (31.3)	22 (27.5)	Matched
Systolic blood pressure (mm Hg)	140.1 ± 26.6	142.2 ± 21.7	0.662
Diastolic blood pressure (mm Hg)	89.7 ± 15.9	89.5 ± 14.6	0.357
CGS, admission	14.0 ± 2.3	13.7 ± 2.7	0.478
CGS, discharge	14.5 ± 1.4	14.3 ± 2.0	0.497
NIHSS, admission	6.36 (5, 0-31)	6.29 (5, 0-32)	0.581
NIHSS, discharge	4.60 (2, 0-20)	5.21 (3, 0-32)	0.425
mRS	1.54 (1, 0-5)	1.92(1, 0-5)	0.167
Hospital duration (days)	8.34 ± 2.62	8.54 ± 3.17	0.606
Intrahospital mortality, n (%)	6 (3.8)	2 (2.5)	0.466
Body mass index (kg/m^2)	27.2 ± 4.4	28.6 ± 5.2	**0.030**
Obesity, n (%)	35 (21.9)	29 (36.3)	**0.014**
Total cholesterol (mmol/L)	5.01 ± 1.11	5.11 ± 1.15	0.974
LDL-C (mmol/L)	3.18 ± 0.95	3.17 ± 0.97	0.950
HDL-C (mmol/L)	1.17 ± 0.41	1.15 ± 0.35	0.754
Triglycerides (mmol/L)	1.87 ± 0.96	2.06 ± 0.95	0.249
HbA1c (%)	-	9.72 ± 2.4	NA
Diabetes duration (years)	-	7.36 (0-23)	NA

Data are presented as mean ± SD and number (percentages, %).

3.3 Subtypes of stroke

According to the TOAST classification, the risk of ischemic stroke caused by microangiopathy (18% non-DM vs. 33.8% DM, p=0.142) and macroangiopathy (44.4% non-DM vs 57.5% DM, p=0.192) was 13-15% higher in people with diabetes than in people without diabetes (**Figure 1**). Atherosclerotic causes (91.3%) were more common than other causes of ischemic stroke in diabetes patients (p=0.001). In addition, there was a significant difference in cardioembolism between those with and without diabetes (3.8% vs 11.9%, p=0.029). In regression analysis, patients with diabetes had a six times greater risk of ischemic stroke caused by atherosclerosis than non-diabetic patients (**Table 2**).

Table 2. Association between diabetes status and stroke subtypes.

Findings	Logistic regression		*P* value
	OR	95% CI	
Large vessel atherosclerosis	1.44	0.80-2.60	0.221
Small vessel disease	1.32	0.77-2.28	0.313
Cardioembolism	0.29	0.08-1.01	0.051
Other determined ethiology	0.07	0.01-0.54	**0.011**
Undetermined ethiology	1.26	0.56-2.81	0.576
Atherosclerotic causes (large and small vessel diseases)	6.09	2.63-14.1	**<0.001**

Binary logistic regression analysis. The reference group refers to the "patients without diabetes". Data are expressed as ORs and 95% confidence intervals (95% CI). OR, odds ratio; CI, confidence interval.

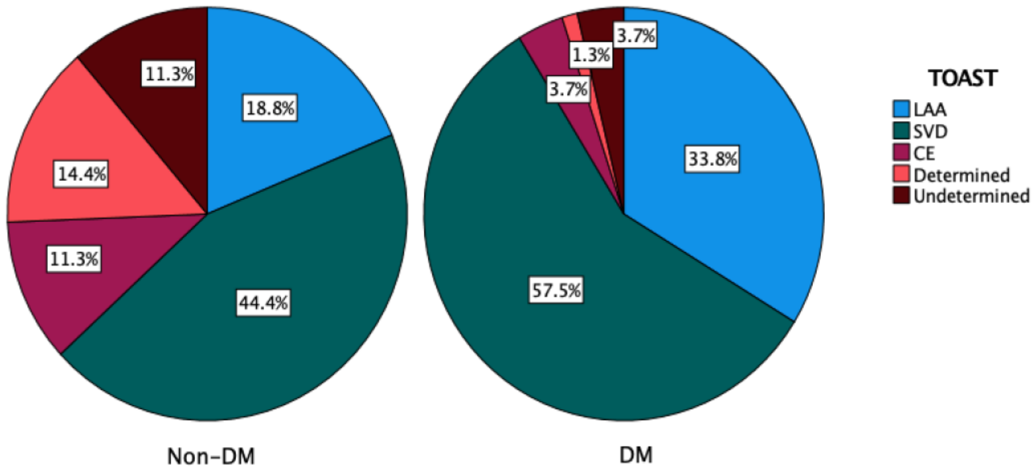

Figure 1: Ischemic stroke subtypes in subjects with and without diabetes. DM - Diabetes Mellitus, LAA - Large Artery Atheroslerosis, SVD - Small Vessel Disease, CE - Cardioembolic Disease

4.0 DISCUSSION

Many factors can cause strokes and are usually of vascular origin. The increasing prevalence of diabetes is one of the most severe health problems in Mongolia, and it is increasingly important to study its impact on macro-vascular complications such as stroke. We found that patients with diabetes had a six times greater risk of ischemic stroke caused by atherosclerosis than non-diabetic patients. This might be associated with poor diabetic control. In particular, the disease duration was relatively short and glycated hemoglobin was relatively high in diabetic patients who participated in this study.

According to the results of studies that investigated the subtypes of stroke by TOAST classification, it was similar in terms of the cause of atherosclerosis compared to the results of the study by Tuttolomondo et al. (2008). Tuttolomondo et al. found that the cause of atherosclerosis was 73.0% in non-diabetic subjects, whereas it was 83.2% in diabetic subjects (Tuttolomondo et al., 2008). Our study indicated 62.9% and 91.3% in people with and without diabetes. In another study by Harris et al. (2018) that did not compare those with and without diabetes, but classified all study participants according to the stroke subtypes, large artery atherosclerosis was the most prevalent stroke subtypes at 59.6%, followed by small vessel disease at 26.7%, undetermined etiology at 9.8%, cardioembolism at 2.1%, and other determined etiology at 0.9%. Furthermore, in contrary to the studies of Tuttolomondo and Harris, our study had a relatively high proportion of undetermined and determined etiology stroke. The proportion of strokes classified as undetermined etiology was high at 26.9% in the Pakistani study by Zafar et al. (2018). Our study found that cardioembolism was particularly high among people without diabetes.

A study by Tuttolomondo et al. (2008) reported a ratio of 9.8% to 19.6% among individuals with and without diabetes. Another notable finding from a study conducted in Pakistan was that cardioembolism represented the largest proportion of 10,172 cases of stroke, accounting for 40.0% (Zafar et al., 2018). In contrast to other studies, our study found a significantly higher rate of large vessel atherosclerosis in people with diabetes. This may be due to inadequate diabetes control among Mongolians. Ntaios et al. also reported similar causes of large and small vessel strokes in people with diabetes, with large vessel atherosclerosis associated with peripheral vascular complications and smoking (Ntaios et al., 2016). Our study had a higher percentage of smokers than other studies, although the difference was insignificant between the two groups. Given these findings, future studies should investigate the causes and risks of stroke in detail among Mongolians, particularly those with diabetes.

Our study observed a slightly higher NIHSS discharge score in patients with diabetes, which is consistent with findings from previous studies. For example, Tziomalos et al. reported that while neurological deficits assessed by NIHSS did not differ between patients with and without diabetes during the acute phase, the deficits were more pronounced in the Type 2 diabetes mellitus (T2DM) group at discharge (Tziomalos et al., 2014). However, we did not observe any differences in clinical parameters between people with and without diabetes, in contrast to other studies which did find significant differences. In a study by Jørgensen et al., a variety of serious neurological deficits were identified in patients who had an acute stroke with diabetes (Jørgensen et al., 1994). But most studies compared months or years after the stroke. For instance, it has been found that the motor function capacity of stroke patients with diabetes is worse than those without diabetes, and the risk of memory loss, recurrent stroke, and death was higher in previous studies (Kissela et al., 2005; Stegmayr et al., 1997). Patients with diabetes showed greater residual neuropathological deficits after a stroke and were more likely to be hospitalized for long-term disability (Laing et al., 2003; Lithner et al., 1988; Mishra et al., 2010; Mitsios et al., 2018) . In a large study by Laing et al. (2003), patients diagnosed with diabetes before the age of 30 who were treated with insulin had a significantly higher incidence of death than the general population (Maida et al., 2022). The limitation of the study is that we were unable to thoroughly examine risk factors for stroke due to the limited number of risk factors that clinicians included in their diagnoses. As such, we conducted analyses to compare the identified risk factors between the case and control groups. We could not conduct regression analysis to determine the significance of each risk factor due to the possibility of overlapping causes and risk categories between the stroke subtypes. Future researchers may wish to conduct a more detailed study, including examining factors such as the duration of hypertension, smoking history, and cigarette consumption. Our study was conducted as a preliminary investigation of differences between individuals with and without DM, focusing on subtypes. Consequently, it is necessary to continue this study to explore long-term outcomes Therefore, it is imperative to pursue further investigation in this study to delve into long-term outcomes and determine the primary factors contributing to disability among individuals with diabetes.

5.0 CONCLUSIONS

Most subtypes of stroke that occur in people with diabetes are caused by atherosclerosis, both large and small vessels. In addition, risk factors and long-term consequences should be further explored in people with diabetes in Mongolia.

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Conflicts of Interest: The authors declare no conflict of interest.

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