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# Cognitive performance in Mongolian patients after transient ischemic attack and the impact of vascular risk factors: a case-controlled study

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**Abstract:** Cognitive impairment is a prevalent occurrence after a transient ischemic attack (TIA), but there is currently insufficient evidence to understand the impact of vascular risk factors (VRFs) on this event. We aimed to determine the occurrence of cognitive impairment following a TIA and to explore whether VRFs correlate with cognitive impairment. This hospital-based case-controlled study recruited patients with TIA aged 45 to 65 years without prior stroke or cognitive decline who underwent the Mini Mental State Examination (MMSE) within 3 months at the Mongolia-Japan Hospital between May and December 2023. Age (±1 year) and sex-matched controls were selected from outpatient departments. One hundred thirty-four patients (N=134) with TIA (61.2% women, mean age, 56.4±6.5 years) were included and compared with 134 controls (61.2% women, mean age, 56.1±6.4 years). Significant differences in MMSE scores were noted between the study groups, with mean scores of 26.32±2.23 for TIA patients and 27.99±1.94 for non-TIA subjects ($p<0.0001$). In the crude model, the presence of hypertension, a family history of myocardial infarction, hypercholesterinaemia, atrial fibrillation, and having three or more VRFs were all significantly associated with global cognitive performance on the MMSE (all $p<0.05$). When age, gender and education are controlled for, performance on the MMSE is uniquely accounted for by the presence of atrial fibrillation and having three or more VRFs (all $p<0.05$). Our results suggest that global cognitive impairment following a TIA may be linked to the number of VRFs in these individuals. This emphasises the importance of sustained management of VRFs beyond the recovery period to mitigate the risk of cognitive impairment.

**Keywords:** Cognition; Ischemic attack; Vascular risk factors

## 1.0 INTRODUCTION

Transient ischemic attack (TIA) is a reversible neurologic dysfunction caused by focal cerebral ischemia and is defined as no evidence of acute infarction in brain tissue (Easton et al., 2009). However, the time-limited (24 hours) diagnostic criteria for TIA are still used in clinical practice in many parts of the world. Focal symptoms of TIA vary depending on the territory of carotid and vertebrobasilar artery insufficiency. However, they are transient, and in most cases, no visible lesions are found in the brain, but cognitive impairment following TIA has been reported (Fens et al., 2013; Pendlebury et al., 2011; Rao et al., 1999; Rowley, 2013; Turner et al., 2016). The prevalence of cognitive decline associated with TIA ranges from 2 to 100%, depending on the study sample size, the cognitive test used, the cut-off score for cognitive impairment, and the period assessed (Hammant et al., 2023; Van Rooij et al., 2016). Nevertheless, the relationship between TIA and cognitive impairment is not fully established (Ganesh & Barber, 2022). Overall, while there is evidence suggesting an association between TIA and cognitive impairment, the exact nature of this relationship remains uncertain due to the complexities involved and the need for further research.

Vascular risk factors (VRFs) such as hypertension and diabetes mellitus impair cerebral microcirculation and lead to large artery stiffness and a higher risk of white matter damage, often identified as leukoaraiosis (Jolly et al., 2013; Triantafyllidi et al., 2009). TIA patients have a greater prevalence of VRFs than healthy controls (Clarey et al., 2014; Guyomard et al., 2011) and a greater rate of neural atrophy over 3 years (Munir et al., 2019). Therefore, cognitive impairment associated with TIA may arise from more chronic vascular disease processes preceding or following the focal ischemic damage caused by the event itself.

In this study, we investigated the cognitive performance of patients within 3 months after TIA in a single-centre case-controlled study of Mongolia. The objectives of this study were twofold: (i) to assess the presence of global cognitive impairment in individuals experiencing their initial transient ischemic attack (TIA) and ascertain whether the occurrence of impairment exceeded anticipated levels when compared to age- and sex-matched control groups without vascular risk factors (VRFs), and (ii) to explore the VRFs that contribute to cognitive impairment associated with TIA. We hypothesized that global cognitive function after TIA would be impaired and associated with the number of VRFs present. The findings of this study will contribute to the early diagnosis of cognitive impairment following TIA and the prompt initiation of treatment to prevent further progression.

## 2.0 MATERIALS AND METHODS

This study was carried out using a hospital-based, 1:1 age (±1 year) and sex-matched case-controlled research design from March to September 2023, assessing the neurology, emergency care and outpatient departments of the Mongolia-Japan Hospital of Mongolian National University of Medical Sciences. With 80% power at the 5% significance level, the formula was applied:

$$N = \left(\frac{r+1}{r}\right)\frac{p(1-p)\left(Z_\beta + Z^{\propto}/_2\right)2}{(p1-p2)^2} = 135$$

Therefore, 135 pairs of subjects were needed in this study and we recruited 134 cases, 134 controls and 2 subjects were excluded. Cases were determined as those patients with first ever TIA defined as a focal neurological deficit of <24 h duration of presumed vascular origin (Special Report from the National Institute of Neurological Disorders and Stroke Classification of Cerebrovascular Diseases III, 1990), aged 45 – 65 years, who fulfilled the study inclusion criteria, i.e., no history of stroke and have evidence of cognitive impairment. The control group was matched to the case group by age (+/-1 year) and sex, and people without VRFs and diagnosis of TIA were selected for the study. VRFs were defined as hypertension, hyper-cholesterinemia, diabetes mellitus, atrial fibrillation, current smoker, previous history of myocardial infarction (MI) and a positive family history of cerebrovascular disease (TIA/stroke).

Global cognitive functioning was assessed with MMSE as a brief screening for global cognitive functioning. This test consists of questions on orientation to time and place, registration, attention and calculation, recall, language, and visual construction to measure global cognitive functioning. The MMSE consists of 20 questions, and the maximum score to achieve is 30 points, with a higher score indicating a better cognitive performance. A score of 26 – 30 indicates "normal cognitive functioning"; a score of 24 or 25 as "borderline normal cognitive functioning"; a score below 24 as "cognitive impairment", and a score below 18 as "severe cognitive impairment" (Folstein et al., 1975).

All data were collected and statistically analyzed using IBM SPSS 26.0 for Windows (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as mean ± SD and median range according to the data type. The qualitative data were expressed as a number or percentage. Difference and association of qualitative variables (sex, vascular risk factor presence) were statistically tested for significance using the chi-square test, Fisher exact test, and quantitative variables with normal distribution using Student-t test and skewed distribution using the nonparametric test, including the Mann-Whitney U-test of significance. The Shapiro–Wilk test was used to test normality. Linear regression models were used to examine crude main effects of each VRF on MMSE. Adjusted models were created to examine whether any significant main effect of VRFs after adjusting for potential confounders. All statistical tests were two-sided, and p-values of <0.05 were considered statistically significant.

The permission to conduct the study was obtained from the Ethical Review Committee of Mongolian National University of Medical Sciences (MNUMS) (#2023/3-06). The study was carried out with the consent of the participants through an identification sheet. The researchers maintained the confidentiality of the participants.

## 3.0 RESULTS

### 3.1 General characteristics of the study participants

A total of 268 participants were included in the study, including 134 patients in the case group (61.2% female, mean age 56.7±6.6, median 58.0, IQR 11.0) and 134 participants in the control group (61.2% female, mean age 56.1±6.1, median 58.0, IQR 10.0) was analyzed in comparison with the indicators. **Table 1** shows the general characteristics of the study participants. According to the study inclusion criteria, hypertension predominated in the case group, but smoking (28.4% vs 6.0%, p<0.0001), hypercholesterinemia (41.0% vs 8.2%, p<0.0001) were significantly higher than the age- and sex-matched control group. Still, the two groups had no difference in educational level (**Table 1**).

### 3.2 Mini Mental State Examination Scores (MMSE) and cognitive impairment in TIA and non-TIA groups

**Figure 1** illustrates the distribution of MMSE total scores. The distribution displayed a relatively normal pattern in individuals without TIA, with a decreasing frequency of participants corresponding to lower MMSE scores. The majority of non-TIA subjects scored above 24 on the MMSE. Conversely, no similar trend was observed in individuals with TIA. Significant differences in MMSE scores were noted between the study groups, with mean scores of 26.32±2.23 for TIA patients and 27.99±1.94 for non-TIA subjects (p<0.0001). Twenty-four (17.9%) patients in the TIA group had global cognitive impairment (MMSE≤24), which was significantly different from the control group (p<0.0001) (**Table 2**). Examining the MMSE domains revealed noteworthy distinctions in specific cognitive functions among TIA patients compared to non-TIA subjects. TIA patients exhibited significantly lower scores in orientation, attention, working memory, and visual construction, as shown in **Table 2.**

**Table 1:** General characteristics of TIA and non-TIA subjects

| Characteristics | TIA (n=134) | Non-TIA (n=134) | P-value |
|---|---|---|---|
| Age (mean ± SD) | 56.7 ± 6.6 | 56.1 ± 6.1 | 0.480 |
| Sex | | | |
| Male, n (%) | 52 (38.8%) | 52 (38.8%) | 1.000 |
| Female, n (%) | 82 (61.2%) | 82 (61.2%) | |
| Education level | | | |
| Low | 44 (32.8%) | 41 (30.6%) | 0.362 |
| Medium | 69 (51.5%) | 64 (47.8%) | |
| High | 21 (15.7%) | 29 (21.6%) | |
| Hypertension (yes) (%) | 128 (95.5%) | - | |
| Hypercholesterinaemia (yes) (%) | 55 (41.0%) | 11 (8.2%) | <0.0001*** |
| Diabetes (yes) (%) | 28 (20.9%) | - | |
| Atrial fibrillation (yes) (%) | 15 (11.2%) | - | |
| Family history of stroke (yes) (%) | 37 (27.6%) | 28 (20.9%) | 0.254 |
| Family history of MI (yes) (%) | 15 (11.2%) | 6 (4.5%) | 0.067 |
| Smoking (yes) (%) | 38 (28.4%) | 8 (6.0%) | <0.0001*** |

*Unless otherwise indicated, values are presented as means ± SD or percentages, ***P-value≤0.0001.*

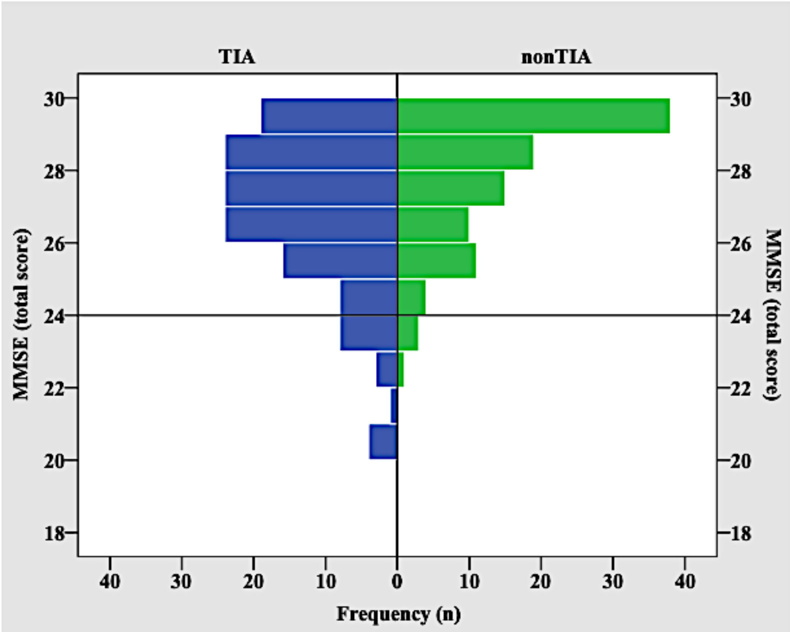


**Figure 1:** Distribution of MMSE total score according to study groups. The distribution of MMSE is shown in patients with TIA and non-TIA subjects. Blue bars indicate MMSE in people with TIA, while green bars indicate MMSE in non-TIA participants. The distribution displayed a relatively normal pattern in non-TIA subjects, with a decreasing frequency of participants corresponding to lower MMSE scores. Majority of the non-TIA subjects scored above 24 on the MMSE. Conversely, no similar trend was observed in individuals with TIA.

**Table 2:** Mini mental state examination (MMSE) total and individual domain scores in TIA and non-TIA subjects

| MMSE Subtest/ maximum score | Subtest details | TIA (mean ± SD) | non-TIA (mean ± SD) | P-value |
|---|---|---|---|---|
| Orientation/10 | Orientation to place and time | 9.39 ± 0.98 | 9.81 ± 0.39 | <0.0001*** |
| Attention and calculation/5 | Serial 7 subtraction/WORLD backwards | 3.85 ± 0.88 | 4.32 ± 0.76 | <0.0001*** |
| Working memory/6 | | 4.54 ± 0.73 | 5.16 ± 0.82 | <0.0001*** |
| Registration/3 | Repeat "apple, table, penny" | 2.99 ± 0.08 | 3.00 ± 0.00 | 0.318 |
| Recall/3 | Recall "apple, table, penny" | 1.54 ± 0.72 | 2.16 ± 0.82 | <0.0001*** |
| Language/8 | | 7.63 ± 0.61 | 7.67 ± 0.62 | 0.552 |
| Naming/2 | Naming a pencil and watch | 2.00 ± 0.00 | 2.00 ± 0.00 | 1.000 |
| Repetition/1 | repeat "no ifs, ands or buts" | 0.99 ± 0.09 | 1.00 ± 0.00 | 0.318 |
| Comprehension /3 | Perform 3 step command | 2.73 ± 0.49 | 2.74 ± 0.54 | 0.975 |
| Reading/1 | Read and obey written instruction "close your eyes" | 0.95 ± 0.22 | 0.98 ± 0.26 | 0.313 |
| Writing/1 | Write a sentence | 0.91 ± 0.29 | 0.97 ± 0.17 | 0.039* |
| Visual construction/1 | | | | |
| Copying/1 | Intersecting pentagons | 0.89 ± 0.31 | 0.98 ± 0.13 | 0.002* |
| **Overall score** | | **26.32 ± 2.23** | **27.99 ± 1.94** | **<0.0001*** ** |
| **MMSE≤24** | | **24 (17.9%)** | **8 (6.0%)** | **0.004*** |

*Unless otherwise indicated, values are presented as means ± SD or percentages, *P-value<0.05, ***P-value≤0.0001.*

### 3.3 Vascular risk factors (VRFs) on cognitive performance in the TIA group

**Table 3** shows that MMSE scores were significantly lower in the presence of most individual VRFs. The strongest predictor was hypertension, followed in decreasing order by a family history of myocardial infarction, hypercholesterinaemia, and atrial fibrillation. Patients with three or more VRFs had a worse MMSE score than those without VRFs (p=0.006). Controlling for age, gender and education reduced the strength of the effect of each VRF on MMSE. As shown in **Table 3**, when controlling for age, gender, and education, only atrial fibrillation and having three or more VRFs remained as unique predictors of MMSE.

**Table 3:** Effects of vascular risk factors on MMSE in TIA group

| Outcome | Cognitive measures by vascular risk factors | | | | | |
|---|---|---|---|---|---|---|
| | Crude model | | | Adjusted model | | |
| | β | 95% CI | P-value | β | 95% CI | P-value |
| Hypertension | -2.09 | -3.91 to -0.028 | 0.024* | -1.49 | -3.37 to 0.376 | 0.116 |
| Hypercholesterinaemia | -0.77 | -1.54 to -0.01 | 0.048* | -0.64 | -1.40 to 0.12 | 0.097 |
| Diabetes | -0.28 | -1.22 to 0.66 | 0.557 | -0.31 | -1.24 to 0.623 | 0.515 |
| Atrial fibrillation | -1.19 | -2.39 to 0.00 | 0.050* | -1.31 | -2.49 to -0.13 | 0.030* |
| Family history of stroke | 0.03 | -0.82 to 0.89 | 0.942 | 0.11 | -0.73 to 0.95 | 0.795 |
| Family history of MI | -1.27 | -2.46 to -0.08 | 0.037* | -0.90 | -2.13 to 0.32 | 0.147 |
| Smoking | 0.06 | -0.79 to 0.91 | 0.896 | -0.01 | -0.86 to 0.84 | 0.980 |
| Vascular risk factors >3 | -1.05 | -1.80 to -0.31 | 0.006* | -0.98 | -1.73 to -0.22 | 0.012* |

*Adjusted model = after controlling the age, gender and education. *P-value <0.05*

## 4.0 DISCUSSION

The present study used a cognitive screening test (MMSE) to evaluate global cognitive ability within 3 months after TIA. We sought to identify whether vascular risk factors differently impacted cognitive ability. As a result of our study, patients with VRFs within 3 months after TIA between the ages of 45 and 65 had global cognitive decline compared to age- and sex-matched control groups without VRFs and not affected by TIA. The previous studies on cognitive function after TIA are scarce, and findings were heterogeneous (Van Rooij et al., 2016). The characteristics of the patients studied, the definition of cognitive decline, the tests used, and the time since TIA occurred differ among the results of the studies (Ganesh & Barber, 2022). The reported prevalence of cognitive decline after TIA ranges from 2% to 100% (Hammant et al., 2023).

Compared to our study, these studies included significantly older patients, cognitive assessment was performed much later after TIA, and patients with previous stroke were not excluded from the study. Instead, we aimed to investigate the effects of cognitive decline by performing a cognitive assessment within 3 months of TIA without including patients over 65 years of age with a history of stroke. In our study, global cognitive impairment was found in patients with TIA with a frequency of 17.9%, which is consistent with other studies.

We found that patients with TIA with VRFs had poorer cognitive function compared to controls without VRFs, and we found that an increase in the number of VRFs was associated with the likelihood of cognitive decline. Consistent with many previous studies, the presence of VRFs was associated with reduced performance on cognitive functioning (Faraco & Iadecola, 2013; Goette & Braun-Dullaeus, 2008; Guyomard et al., 2011; Munkhsukh et al., 2021). Based on examining the effects of each VRF, the cognitive screening test performance was significantly reduced in association with heart failure, heart attack, and hypertension, and executive function scores were significantly associated with hypertension (Aam et al., 2021). Stroke-free individuals with atrial fibrillation performed significantly worse in tasks of learning and memory (ß ¼ 20.115, P, 0.01) as well as attention and executive functions (ß ¼ 20.105, P, 0.01) compared with subjects without atrial fibrillation, which highlighted that atrial fibrillation is a risk factor for cognitive impairment and hippocampal atrophy (Goette & Braun-Dullaeus, 2008).

Our research found that atrial fibrillation remained correlated with a lower MMSE score, even after adjusting for age, gender, and education. This observation aligns with the findings of the previously mentioned study. When we examined the unique contribution of each VRF and controlled the age, gender and education, performance on the cognitive screening test was significantly impaired, global cognitive function scores were significantly impacted by atrial fibrillation and having three or more VRFs. While it is well established that VRFs affect cognition, this finding provides evidence that the reported cognitive dysfunction after TIA may be attributed to the increased prevalence of VRFs in such patients. Though it is widely acknowledged that VRFs influence cognitive function, this discovery supports the idea that the observed cognitive impairment following TIA could be linked to the higher occurrence of VRFs in these individuals.

Our study's limitation was that we used MMSE for global cognitive performance after TIA which may have been underestimated because of its lower sensitivity compared to the Montreal Cognitive Assessment (MoCA) (Pendlebury et al., 2010).

The causes of cognitive decline and the associated risk factors in TIA remain unclear. Future research endeavours should incorporate advanced brain imaging methods to delineate cerebral vascular microstructure and functional damage. Moreover, future studies are needed to focus on domain-specific cognitive impairment after TIA and utilise more sensitive screening tools. This would involve incorporating the validated Mongolian version of the MoCA and Addenbrooke's Cognitive Examination Revised (ACE-R), providing a more thorough assessment of cognitive function in this population. Additionally, long-term evaluation and follow-up of cognitive function after TIA are essential to discern whether cognitive decline is temporary, stable, or progressive.

## 5.0 CONCLUSIONS

TIA patients with VRFs exhibited diminished global cognitive function in comparison to controls of similar age and sex who did not have VRFs. The extent of cognitive impairment in individuals experiencing a TIA seems to be linked to the quantity of VRFs present. The findings of this study hold significant implications for understanding the relationship between TIA and impaired cognitive functions. The identification of a potential association between TIA and impaired cognitive functions underscores the importance of proactive screening and management of cognitive health in individuals who have experienced TIA. Early detection of cognitive impairments in this population could lead to timely interventions to mitigate further decline and improve overall quality of life. Moreover, these findings shed light on the need for integrated care approaches considering both cerebrovascular health and cognitive function. Healthcare providers can use this knowledge to develop comprehensive treatment plans tailored to the unique needs of patients with TIA, incorporating strategies to address cognitive deficits alongside traditional vascular risk factor management.

**Author Contributions:** D.T. and A.E. conceived the study, collected and interpreted the data, designed the tables, drafted and edited the manuscript. D.T. was involved in the study design, performed the statistical analyses, generated the figures, reviewed and edited the manuscript. T.G. were involved in the study design, reviewing and editing of the manuscript, and providing guidance for the entire manuscript. All authors equally contributed to the study and worked as a team.

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

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