

Relation of Non-Alcoholic Fatty Liver Disease with Acute Ischemic Stroke and Its Impact on Stroke Severity

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Abstract:

Background: Stroke is one of the leading causes of death and disability worldwide. Several modifiable and non-modifiable factors are established as risk factors for stroke. Non-alcoholic fatty liver disease (NAFLD) is a risk factor for cardiovascular disease but little is known about **Objective:** Its relationship with ischemic stroke. Considering this, it is important to identify the relation between non-alcoholic fatty liver disease and ischemic stroke, which would be helpful to stratify the risk of stroke. **Methods:** The current cross-sectional analytical study was conducted at the Department of Neurology and Medicine, Mymensingh Medical College Hospital. One hundred and twenty patients with first ever acute ischemic stroke and equal number of apparently healthy controls were included in the study. Non-alcoholic fatty liver disease was diagnosed by abdominal ultrasonography by a consultant radiologist. National Institute of Health Stroke Scale (NIHSS) was used to assess stroke severity at admission. **Results:** In this study mean ($\pm$ SD) age of the stroke patients was 59.94($\pm$ 11.41) years and 62.50% were male. Non-alcoholic fatty liver disease (NAFLD) was found in 50 (41.7%) of stroke patients and in 31 (25.8%) of the control group and difference was statistically significant ($p < 0.05$). Non-alcoholic fatty liver disease (NAFLD) was found as a predictor of poor outcome of ischemic stroke with OR: 2.051; 95% CI (1.187-3.542), $p = 0.010$. Mean NIHSS score was 11.76 $\pm$ 5.96 in patients with NAFLD and 8.31 $\pm$ 5.57 in patients without NAFLD (p value was < 0.05). It was revealed that NAFLD and the NIHSS score had a statistically significant positive relation. **Conclusion:** The study revealed that non-alcoholic fatty liver disease related with severe acute ischemic stroke and patients with NAFLD have more severe stroke.

Keywords: Ischemic Stroke, National Institute of Health Stroke Scale (NIHSS), Non-alcoholic Fatty Liver Disease (NAFLD), Stroke Severity

Background

Ischemic strokes caused by sudden occlusion of arteries supplying the brain, either due to a thrombus at the site of occlusion or emboli from another part of the circulation.¹ Worldwide stroke is the second leading cause of death and third

leading cause of disability accounting for 11% of total deaths.² Well established modifiable risk factors for ischemic stroke include dyslipidemia, hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation, valvular heart disease, carotid stenosis, cigarette smoking, and obesity.³

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The identification and treatment of stroke risk factors has important consequences on the prognosis of stroke. Along with traditional risk factors, some new modifiable risk factors like environmental, occupational, behavioral, physiological and metabolic risk factors are contributing for development of stroke. More than 90% of stroke burden is due to modifiable risk factors.⁴

Non-alcoholic fatty liver disease (NAFLD) plays an important role in the development of stroke.^{5,6} Non-alcoholic fatty liver disease (NAFLD) is characterized by the presence of significant lipid accumulation in the liver parenchyma without excessive alcohol ingestion (<20gm/day) and any other liver diseases. In recent years, NAFLD has already become a familial clinical diagnosis and in general population, its incidence and prevalence have been steadily rising.⁷

The pathophysiology related to NAFLD to stroke have not been fully understood. In NAFLD, inflammatory response is increased and thus it activates pro-inflammatory signaling pathway. Inflammatory cytokines play a role in development of atherosclerosis and ischemic stroke.^{8,9} Moreover, NAFLD fibrosis causes cerebral microangiopathy, systemic and vascular inflammation and also causes mixed coagulopathy that increases the risk of ischemic and hemorrhagic stroke.¹⁰ NAFLD has been associated to increased carotid arterial stiffness, as well as an increase in arterial wall thickness and intima-media index thickness of the internal carotid artery, which may raise the risk of a subsequent stroke.^{11,12} Some studies have also shown NAFLD is associated with more severe stroke and a poorer result in people who have had an acute ischemic stroke.^{6,13} Moreover, carotid intima media thickness (CIMT) levels were higher in patients with NAFLD compared to healthy control.¹⁴ Additionally, a Japanese study also demonstrates that NAFLD is significantly and independently associated with high risk CIMT that may cause ischemic stroke.¹⁵

There is no documented study in Bangladesh investigating the relation of NAFLD with ischemic stroke. So, the aim of this study is to evaluate the

relation of NAFLD in patients admitted with acute ischemic stroke and its impact on severity of neurological disability in our country.

Materials and Methods

This is a cross sectional comparative study done in Department of Neurology, Mymensingh Medical College Hospital, Mymensingh from February, 2022 to January, 2024. Patients who were admitted to the Department of Neurology and Department of Medicine, Mymensingh Medical College Hospital fulfilling the criteria of acute ischemic stroke age more than or equal to 18 years and both sexes, presented within 48 hours of acute stroke onset and evident by neuroimaging study are included in the case group. Age and sex-matched apparently healthy patient attendants and hospital staff were included in the control group. It was a purposive type of non-probability sampling.

NAFLD was diagnosed by abdominal ultrasonography showing excessive fat deposition along with no history of drinking alcohol or alcohol consumption less than 20 gm/day and no causes for secondary hepatic fat accumulation such as chronic viral hepatitis (Hepatitis B and C virus) or any history of hepatotoxic drugs. Grade I NAFLD: Fatty infiltration occurs when the echogenicity is merely elevated. Grade II NAFLD: Fatty infiltration occurs when the liver's echogenic walls are obscured. Grade III NAFLD: Fatty infiltration occurs when the echogenic liver obscures the diaphragmatic outline. Stroke severity was defined according to the National Institute of Health Stroke Scale (NIHSS) on admission. Normal Examination (0-1), Minor stroke (1-4), Moderate stroke (5-15), Moderate to severe stroke (16-20), Severe stroke (>20).

Results

This cross-sectional analytical study was done in MMCH including 120 patients of acute ischemic stroke from the Department of Neurology and Department of Medicine as a case and 120 age and sex matched apparently healthy individual were included as control group. In our study, both groups' majority respondents were above 60 years [40.8% in case and 37.5% in control]. There was male preponderance in both case and control group,

[62.5% in case and 65.8% in control]. More than half of the stroke cases (51.7%) hailed from rural areas in the study but in control group majority of respondents (49.2%) were from urban areas. The mean level of BMI was 23.52 ± 3.57 and 22.08 ± 2.71 respectively, in stroke patient and control group. There was no significant difference in case and control group.

In this study, NAFLD was present in 50 (41.7%) and 31 (25.8%) subjects respectively, in stroke patients and control group. The difference was statistically significant ($p < 0.05$). Grade II and Grade III NAFLD were higher in acute ischemic stroke patients than control, whereas Grade I NAFLD was higher in control group. This difference was statistically significant ($P < 0.05$) (Figure 1). The mean level of NIHSS score was 11.76 ± 5.96 and 8.31 ± 5.57 respectively, in stroke patients with and without NAFLD. The difference was statistically significant ($p < 0.05$) (Figure 2).

In our study it was revealed that, increasing grade of non-alcoholic fatty liver disease (NAFLD) was related with greater stroke severity as assessed by NIHSS scale. Majority of patients with grade I NAFLD were confined to minor or moderate stroke severity at admission. On the other hand, patients with grade II and III were consisted with moderate to severe or severe strokes category by NIHSS. Here, P value was < 0.001 , which was statistically significant ($p < 0.05$).

Multivariate binary logistic regression was used to see the independent predictors of ischemic stroke. Age, sex, smoking, hypertension, diabetes mellitus, ischemic heart disease, dyslipidemia and NAFLD were analyzed. After performing the binary logistic regression analysis, NAFLD emerged as an independent predictor of ischemic stroke with odds ratio (OR) 2.05; (95% CI = 1.187-3.542) and p value 0.010 ($p < 0.05$). Other independent predictors of stroke in the analysis male sex, smoking, diabetes mellitus, hypertension and dyslipidemia.

Table-I
Distribution of the study subjects by demographic profile (n=120)

Demographic profile		Case N (%)	Control N (%)
Age (years)	<40	6(5.0)	8(6.7)
	41-50	25(20.8)	25(20.8)
	51-60	40(33.3)	42(35.0)
	>60	49(40.8)	45(37.5)
	Mean $\pm$ SD	59.94 $\pm$ 11.41	55.04 $\pm$ 8.29
Residence	Male	75(62.5)	79(65.8)
	Female	45(37.5)	41(34.2)
	Rural	62(51.7)	50(41.7)
	Urban	42(35.0)	59(49.2)
	Sub-urban	16(13.3)	11(9.2)
BMI (Mean $\pm$ SD)		23.52 $\pm$ 3.57	22.08 $\pm$ 2.71

Table-II
Comparison of presence of NAFLD between case and control

NAFLD	Case (n=120)	Control (n=120)	P value
Present	50 (41.7)	31 (25.8)	0.009*
Absent	70 (58.3)	89 (74.2)	

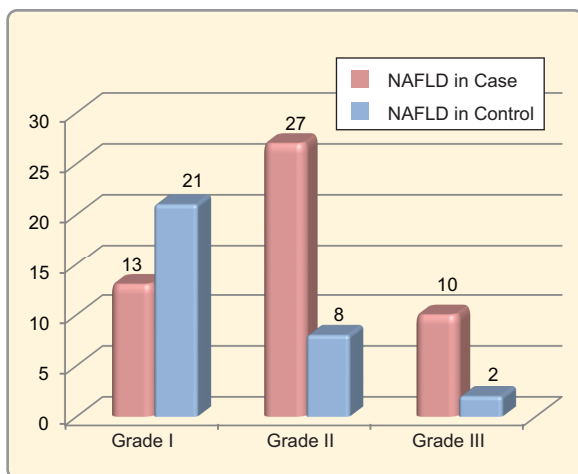


Figure 1: Bar diagram showing frequency different of NAFLD grade between case and control.

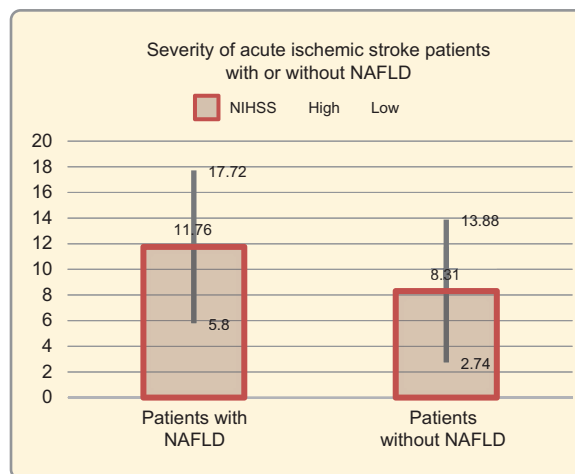


Figure 2: Bar diagram showing severity of acute ischemic stroke patients with or without non-alcoholic fatty liver disease.

Table-III
Relation between grade of NAFLD with stroke severity (by NIHSS)

Stroke severity	NAFLD Grade			P value
	Grade I	Grade II	Grade III	
	(13)	(27)	(10)	<0.001
Minor	6(46.2)	2(7.4)	0(0)	
Moderate	5(38.4)	11(40.7)	3(30)	
Moderate to severe	2(15.4)	12(44.4)	3(30)	
Severe	0(0)	2(7.4)	4(40)	

*significant

Table-IV
Multivariate binary logistic regression analysis of predictors of ischemic stroke

Variables	OR	95%CI for OR		P value
		Lower	Upper	
Age, years	0.939	0.901	0.978	0.075
Male sex	1.972	1.072	3.510	<0.001
Smoker	3.224	2.741	9.040	<0.001
Hypertension	2.434	3.248	7.160	<0.001
Diabetes mellitus	3.723	1.456	9.520	0.006
Ischemic heart disease	2.997	0.746	10.404	0.106
Dyslipidemia	2.125	1.578	7.580	<0.001
NAFLD	2.051	1.187	3.542	0.010

OR: Odds ratio; CI: Confidence interval.

Discussion

In this study, the mean age of the patients with acute ischemic stroke was 59.94 ± 11.41 years and participants were more frequent among the patients

above 60 years with frequency (40.8% in case and 37.5% in control group) and about 33.3% of them were aged between 51-60 years. A hospital-based study in Dhaka medical college hospital observed

that majority of the stroke happened among the patients aged more than 45 years old.¹⁶ Another relevant study showed mean age $56.30 \pm (13.88)$ years which matches with current study.¹⁷ Male dominance was noted among the stroke patients with 62.5% male with a male to female ratio of 1.7:1. Similar observation was also reported by with a male-female ratio of 2:1 in a previous study.¹⁸

Our current study revealed, more than half of the stroke cases (51.7%) hailing from rural areas. As Mymensingh Medical College Hospital is a govt. hospital, most of the patients come from rural areas, so this study proportion of rural population were higher. Similar result also found in study conducted in 2021.¹⁹

In this study, majority of the participants in both groups were from lower class (43.30% and 37.50% respectively case and control group then lower middle, then upper middle, then upper lower and lower respectively. Regarding pre-existing risk factors, 42.5% of acute ischemic stroke patients were found to 42.5% have hypertension, 35.8% had diabetes mellitus and 11.7% had IHD, 40.8% had dyslipidemia and 23.3% had obesity. The etiology of stroke is multifactorial, and apart from non-modifiable risk factors for stroke (like age, sex, ethnicity, low weight at birth, inherited diseases) hypertension, diabetes mellitus, heart diseases, smoking, dyslipidemia, alcohol abuse, obesity were widely accepted as modifiable risk factors.²⁰ In the present study, smoking, hypertension, diabetes mellitus and dyslipidemia were significantly frequent among patients with acute ischemic stroke than control.

The current study showed, NAFLD was present in 50 (41.7%) and 31 (25.8%) of the subjects, respectively, in stroke patients and the control group. It showed that the frequency of NAFLD was significantly higher in ischemic stroke patients and the difference was significant statistically ($p < 0.05$). After performing the binary logistic regression analysis, NAFLD emerged as an independent predictor of ischemic stroke (OR: 2.051, 95% CI = 1.187-3.542) and p value was 0.01, which was statistically significant. Present study results agreed with other previous studies.^{21,22,23} In the study

of Moshayedi, NAFLD was significantly higher in acute ischemic stroke (42.7% compared with 22.7% in control subjects).²¹

In the present study, number of Grade II and Grade III NAFLD were higher in acute ischemic stroke patients than control, whereas Grade I NAFLD was higher in control group. This difference was statistically significant ($p \text{ value} < 0.05$). This result was similar to the findings of studies.^{22,24} Rasool and his associates showed that the level of carotid intima-media thickness was more in cases than in controls and it was progressively raised with increasing the grade of fatty liver and which was statistically significant.²² Xu and his associates showed in their study that, the severity of NAFLD was associated with a higher risk of ischemic stroke and the odds ratios for patients with mild, moderate and severe NAFLD were 1.15 (95% CI, 1.05-1.25), 1.19 (95% CI, 1.06-1.34) and 1.21 (95% CI, 1.08-1.50), respectively.²⁴

In this present study, mean BMI in acute ischemic stroke and control group were 23.52 ± 3.57 and 22.08 ± 2.71 , respectively and this difference was statistically significant ($p < 0.05$). It was related to a previous study, where mean BMI was 28.11 ± 4.38 in case and 25.14 ± 3.04 in control group and p value was < 0.001 which statistically significant.²⁵ Another study showed mean BMI was 26.67 ± 2.70 in acute ischemic stroke with NAFLD and where 25.51 ± 3.21 was in patients without NAFLD. BMI level was higher in NAFLD comparing without NAFLD and it was statistically highly significant ($p < 0.001$).¹³ But another study revealed mean BMI was 26.71 ± 3.02 in cases and 25.34 ± 2.65 was in control group which was non-significant statistically.²¹

The study demonstrated NIHSS score was 11.76 ± 5.96 in acute ischemic stroke with NAFLD and 8.31 ± 5.57 in patients without NAFLD. That is mean NIHSS score was significantly higher in patients with NAFLD comparing without NAFLD ($p \text{ value} < 0.001$). Similar finding was found in a previous study, where mean NIHSS score in patients with or without NAFLD were 8.7 ± 7.4 and 5.5 ± 6.5 . Another study also showed mean NIHSS score was 6.2 ± 3.2 in patients with NAFLD and 5.5 ± 3.7 in patients without NAFLD.¹³

Other findings of this study showed increasing grade of non-alcoholic fatty liver disease (NAFLD) was associated with greater stroke severity as assessed by NIHSS scale. Majority of patients with grade I NAFLD were confined to minor or moderate stroke severity at admission. On the other hand, patients with grade II and III were consisted with moderate to severe or severe strokes category by NIHSS. Here, P value is <0.001, which is highly statistically significant. This study demonstrates a relation between non-alcoholic fatty liver disease (NAFLD) and acute ischemic stroke in a group of Bangladeshi population.

The present study demonstrated a significant relation between NAFLD and ischemic stroke. NAFLD was found significantly higher in stroke patients compared to control and prevalence of increasing grade of NAFLD was also higher in stroke patients compared to control group. The present study results agreed to a recent meta-analysis where NAFLD was significantly higher in ischemic stroke patients than control.²⁶

Conclusion

From this study it was found that NAFLD was significantly higher in acute ischemic stroke patients than in healthy control. Patients with NAFLD experienced more severe stroke as compared to non-NAFLD patients. Higher grading of NAFLD was also related with more severe stroke. NAFLD was also an independent predictor of ischemic stroke.

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