Original Article

Evaluation of Metabolic Dysfunction–Associated Steatohepatitisas Risk Factor in Management of Non-Diabetic Patients Presenting with Acute Ischemic Stroke

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Abstract

Background: Metabolic dysfunction–associated steatohepatitis (MASH) is linked to an increased risk of cardiovascular diseases, including acute ischemic strokes and diabetes. However, data on MASH as independent risk factor for ischemic stroke severity and functional outcomes remain limited. To evaluate whether Metabolic dysfunction–associated steatohepatitisserves as an independent risk factor and a marker of increased stroke severity at onset as well as its impact on functional recovery in non-diabetic patients.

Objective: To evaluate whether Metabolic dysfunction–associated steatohepatitisacts as an independent risk factor contributing to the severity of acute ischemic stroke at presentation and affecting functional recovery outcomes in non-diabetic patients.

Methods: This prospective observational cohort, hospital-based study was conducted at Sir Ganga Ram Hospital Lahore, enrolling 54 non-diabetic patients who consented and met inclusion criteria. Patients underwent abdominal ultrasound for MASH screening, with the FIB-4 score calculated from blood samples (age, AST, ALT, and platelet count).27 patients with MASH (GROUP A) were compared to 27 without MASH (GROUP B). The CT scan assessed ischemic stroke at admission, and NIHSS score was recorded. Follow-ups at three and six months involved repeat CT scans and Modified Rankin Score to evaluate disability.

Results: The MASH group had significantly higher mean Body Mass Index (BMI) of 38 kg/m² compared to 28.6 kg/m² in the non-MASH group (p=0.001). NIHSS scores were also higher in the MASH group (26.2 vs. 15.5, p=0.001). At three months, the Modified Rankin score averaged 3.52 in the MASH group versus 2.81 in the non-MASH group (p=0.04). Additionally, more MASH patients presented with reduced consciousness (29.6% vs. 7.4%, p=0.03).

Conclusion: this study highlights the adverse impact of MASH on ischemic stroke severity and functional outcomes in non-diabetic patients, underscoring the need for tailored management strategies.

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Introduction

Metabolic dysfunction–associated steatohepatitis (MASH) causes liver dysfunction and cancer, starting with fat buildup (steatosis) that progresses to inflammation, cell death, and fibrosis, ultimately redu-

cing liver function.[1]

Non-alcoholic fatty liver disease (NAFLD) and Metabolic dysfunction–associated steatohepatitis (MASH) have surged by nearly 50% since the 1990s, with a global prevalence of about 30%. In South Asia, the prevalence is estimated at 33.8%.[2] In Pakistan, it has been found to be around 15% prevalent with an association with metabolic syndrome and contrary to the popular belief, lean fatty liver disease is scarce in Pakistan.[3]

NAFLD can progress to MASH, leading to liver damage, fibrosis, and impaired function. Lazarus JV et al. found that MASH is linked to various diseases, many of which increase mortality risk.[4]

Although NAFLD affects roughly 25-35% of the population, only a small fraction, around 1.5-2%, of those with fatty liver progress to develop MASH.[5] NAFLD is best diagnosed by pathological assessment i.e. tissue diagnosis for fibrosis. However, the guidelines differ in how frequently this should be done.[6] Different radiological techniques including ultrasound and MRI can help in establishing diagnosis of steatohepatitis.[7] The FIB-4 score can be another useful tool, its formula based on age, platelet count and liver enzymes.[8] A score greater than 1.5 indicates liver fibrosis, hence making diagnosis of MASH more likely than NAFLD. MASH is diagnosed, besides imaging, by excluding other possible causes of liver derangements: ethanol consumption, hepato-cellular toxins, congenital disorders, accumulation diseases such as repeated blood transfusions and haemochromatosis.[9]

Ischemic stroke can occur in patients without diabetes. In Pakistan, the prevalence of stroke in non-diabetics was 0.7% while, in diabetic patients its prevalence was 1.2% as diabetes is an independent risk factor for stroke.[10] A review by Alkagiet S and colleagues reported that incidence for stroke patients who were found to have MASH, ranged from 7.7% to 42.5% with the observation that stroke was twice more likely to occur in patients with MASH.[11] Another study found that MASH was found in nearly 41% of patients who were admitted for an ischemic stroke for the first time showing a high incidence in this patient sub-group.[12] Li H et al. found that patients with MASH had higher NIHSS scores, greater stroke progression (25.4% vs. 13.6%), and more severe CVA compared to those without MASH.[13] A study showed that stroke outcomes were worse in patients with MASH. The NIHSS score at admission was higher in MASH patients (8.7 ± 7.4 vs. 5.5 ± 6.5), and the Modified Rankin score at discharge was also worse (3.6 ± 2.3 vs. 1.8 ± 2.4).[14] However, there is a study which shows that MASH does not impact outcomes after stroke, presenting a gray area in the literature.[15]

There is limited research on MASH as an independent stroke risk factor in non-diabetic patients. This study aims to explore the association of Metabolic dysfunction-associated steatohepatitis with acute ischemic stroke outcomes in non-diabetics, providing valuable clinical insights and guiding management strategies.

Methods

This prospective observational cohort hospital-based study was conducted in the Department of Medicine Unit I at Sir Ganga Ram Hospital, affiliated with Fatima Jinnah Medical University in Lahore, Pakistan from June 30, 2023, to December 30, 2023. Ethical approval was obtained and informed consent was taken from all participants. A total of 54 non-diabetic patients with acute ischemic stroke were enrolled using non-probability consecutive sampling. The sample size was calculated using OpenEpi statistical software based on differences in Modified Rankin Score at six months between patients with and without Metabolic dysfunction– associated steatohepatitis (MASH), ensuring a 95% confidence interval and 80% statistical power, resulting in 27 patients in each group. Inclusion criteria consisted of patients aged 65 to 90 years, of any gender, with a confirmed diagnosis of acute ischemic stroke on CT scan, a history of hypertension, and no evidence of diabetes in the past three months. Patients with prediabetes defined as HbA1c between 5.7%–6.4% or fasting glucose between 100–125 mg/dL, were also excluded to ensure a strictly non-diabetic cohort. Additional exclusion criteria included patients with diabetes, structural heart disease, sepsis, active Hepatitis B or C infection, chronic liver disease of other causes, history of significant alcohol intake, multiple blood transfusions, hemolytic disorders, hemorrhagic stroke, stress hyperglycemia during hospitalization, pregnancy, or known hypercoagulable conditions. All patients underwent abdominal ultrasonography to evaluate hepatic steatosis, and MASH diagnosis was further supported by calculating the FIB-4 score using AST, ALT, platelet count, and age. The formula used was FIB-4 = (Age × AST) / (Platelet count × $\sqrt{}$ ALT), with scores >1.3 indicating significant fibrosis : >1.3 (<65 yrs), >2.0 (≥ 65 yrs), >2.67 high. Stroke severity at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS), and non-contrast CT scans of the brain were performed at baseline to confirm ischemic stroke and exclude hemorrhage. Follow-up assessments were conducted at three and six months, during which repeat

CT scans were performed to monitor radiological changes, and functional recovery was evaluated using the Modified Rankin Score. Data were analyzed using SPSS version 25. Continuous variables were presented as mean ± standard deviation and analyzed using independent t-tests, while categorical variables were compared using chi-square or Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

Results

In Group A, the mean age of participants was 56.9 ± 11.0 years, with a gender distribution of 44.4% females (n=12) and 55.6% males (n=15). The mean BMI was 38.0 ± 7.15 kg/m². In addition to imaging, relevant laboratory investigations were performed for all patients at baseline. Blood samples were collected to assess liver enzymes including AST and ALT, platelet count, and viral markers. PCR tests for Hepatitis B and C were conducted to exclude underlying viral hepatitis. These laboratory parameters were also used to calculate the FIB-4 score for evaluating hepatic fibrosis. Patients' clinical history was taken to confirm the absence of alcohol use, blood transfusions, and pregnancy as per the study's exclusion criteria. The mean FIB-4 score was 2.23 ± 0.53, with liver size averaging 18.84 ± 2.5 cm on ultrasound. At admission, the mean NIHSS score was 26.2 ± 8.33, while the Modified Rankin Scores were 3.52 ± 1.22 at three months and 1.22 ± 1.18 at six months. Neurological deficits were present in all patients upon admission, with 14.8% (n=4) experiencing seizures and 29.6% (n=8) being unconscious. At the three-month follow-up, 96.3% (n=26) had neurological deficits, with some residual effects noted at six months, including speech impairment in 14.8% (n=4) and restricted activity in 29.6% (n=8). One patient in this group died after six months due to intractable seizures.

In Group B, the mean age of participants was 59.1 ± 9.53 years, with 40.7% females (n=11) and 59.3% males (n=16). The mean BMI was 28.6 ± 4.40 kg/m². Among these patients, 25.9% (n=7) had a history of hypertension or ischemic heart disease, while 7.4% (n=2) had a history of treated Hepatitis B/C and were PCR negative at enrollment. Only one patient (3.7%, n=1) reported occasional alcohol intake, with no recent consumption. Laboratory results indicated a mean AST of 20.0 ± 5.30 u/L, ALT of 22.3 ± 4.63 u/L, and a platelet count of 251.9 ± 32.1 x 10^9. The mean FIB-4 score was 0.98 ± 0.20, and liver size averaged 13.5 ± 0.92 cm on ultrasound. At admission, the mean NIHSS score was 15.5 ± 6.30, while the Modified Rankin Scores were 2.81 ± 1.00 at three months and 0.70 ± 0.72 at six months. All patients presented with neurological deficits, and 11.1% (n=3) experienced seizures. By the three-month follow-up, 74.1% (n=20) retained neurological deficits, but no patients were unconscious or had seizures. At six months, 55.6% (n=15) exhibited residual deficits, including speech impairment, restricted activity, and intellectual changes, with no reported mortality in this group.

Table 1: *Comparison of patient demographics between the two groups.*

Variable	Coef	OR	95% CI Lower–Upper	p-value
Group	7.47	1748.20	0.44 – 6,993,116	0.078
Age	0.13	1.14	0.98 – 1.33	0.098
Gender	0.28	1.32	0.04 – 43.10	0.876
BMI	-0.11	0.89	0.71 – 1.11	0.311
NIHSS	0.76	2.14	1.16 – 3.98	0.016

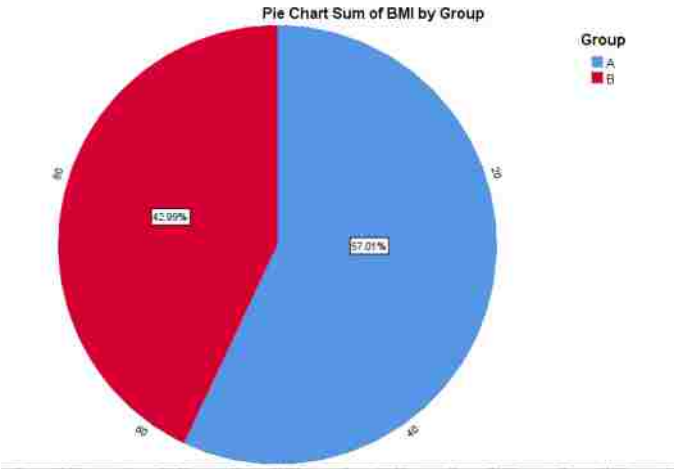

Figure 1: *Regression analysis of predictors of poor functional outcome (mRS >2 at 3 months) in non-diabetic patients with acute ischemic stroke*

Table 2 *Comparison of the NIHSS score using student t-test and the Modified Rankin Score using Mann-Whitney U-test for both groups p-value less than 0.05 as significant.*

Variable	Group A		Group B		P-Value
	Mean	±	Mean	±	
NIHSS Score	26.2	8.33	15.5	6.30	0.001*
Modified Rankin Score 3 Months	3.52	1.22	2.81	1.00	0.04*
Modified Rankin Score 6 Months	1.22	1.18	0.70	0.72	0.06

There was a significant difference in NIHSS scores at admission and Modified Rankin Score at 3 months between the two groups. However, no significant difference was found at 6 months follow-up for Modified Rankin Score. Figure 2 Modified Ranking Score at 3 month.

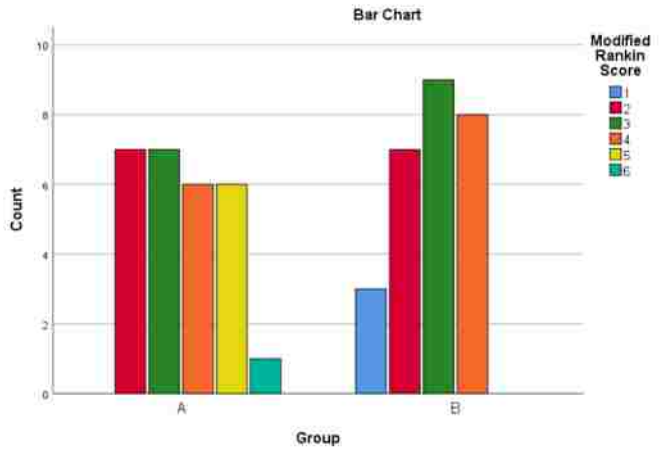

Figure 2: *Modified Ranking Score at 3 month*

Table 3: *Comparison using chi-square test of residual neurological deficits identified at 3 and 6 months follow-up with p-value <0.05 as significant.*

Variable	Group A	Group B	P-Value
Speech Impairment	14.8% (n=4)	14.8% (n=4)	1.00
Restricted Activity or Paresis	29.6% (n=8)	14.8% (n=4)	0.01*
Intellectual Deficits	18.5% (n=5)	14.8% (n=4)	0.71
Neurological Deficits at Admission	100% (n=27)	100% (n=27)	1.00
Seizures at Admission	14.8 (n=4)	11.1% (n=3)	0.68
Unconscious at admission	29.6% (n=8)	7.4% (n=2)	0.03*
Neurological Deficits at 3 months	96.3% (n=26)	74.1% (n=20)	0.02*
Seizures at 3 months	7.4% (n=2)	0% (n=0)	0.15
Unconscious at 3 months	7.4% (n=2)	0% (n=0)	0.15
Neurological Deficits at 6 months	77.8% (n=21)	55.6% (n=15)	0.08
Seizures at 6 months	3.7% (n=1)	0% (n=0)	0.31
Unconscious at 6 months	3.7% (n=1)	0% (n=0)	0.31
Mortality	3.7% (n=1)	0% (n=0)	0.31

A significant difference was found between the two groups for unconsciousness at admission, neurological deficits at 3 months, and restricted activity or paresis at 6 months ($p<0.05$). Patients with MASH had higher rates of these outcomes.

Discussion

Our study found that MASH influences the severity of stroke at onset and its improvement over time. Additionally, MASH was identified as an independent risk factor for various outcomes related to stroke and its severity in non-diabetic patients experiencing acute ischemic stroke. Our results were generally consistent with those of a study conducted by Alkageit et al.[11]

In our study, The average age of patients in both groups was similar, with Group A having a mean age of 56.9 years and Group B 59.1 years, about a decade younger than the global stroke average of 69 years. This aligns with a previous study in Pakistan by Farooq et al.[16] Our participants did not exhibit any significant gender disparity, which is consistent with previous studies showing that strokes affect both genders similarly.[16,17]

However, there was a significant difference in BMI: patients with MASH had a mean BMI of 38.0, compared to a mean BMI of 28.6 in those without the condition ($p=0.001$). The BMI difference suggests that obesity linked to MASH contributes to insulin resistance, atherosclerosis, and inflammation, which can worsen stroke outcomes in non-diabetic patients.[18] In our study, patients had, hepatic parameters—such as AST, ALT, platelet counts, FIB-4 score, and liver size on ultrasound—differed significantly between the two groups. Specifically, ALT and AST levels were elevated, while platelet counts were reduced. FIB-4 scores were higher, and the liver was more likely to be enlarged on ultrasound.[9,19] All off these findings are evident in the current literature. All patients in the MASH group has a FIB-4 score higher than 1.50 while those without any evidence of MASH had a FIB-4 score that was lower than 1.50.

Patients with MASH had higher NIHSS scores at admission ($p=0.001$), indicating greater stroke severity. MASH is an independent risk factor for stroke severity, though hepatitis B/C history worsened severity further. MASH combined with hepatitis B/C resulted in more severe stroke symptoms. The literature also indicates that the presence of both hepatitis B/C infections and MASH tends to lead to more aggressive and advanced fibrosis, regardless of whether the viral infection is active or inactive.[19] However, since patients with MASH but without hepatitis B/C had a mean NIHSS score of 25, while those without MASH and without hepatitis B/C had a mean score of 15, the significant difference between these groups indicates that MASH itself is an independent risk factor for more severe stroke at onset.

For the second objective of this study, we used the modified Rankin Scale (MRS) at follow-up to evaluate whether outcomes differed between patients with MASH and those without. At the 3-month follow-up, the MRS was significantly higher for patients with MASH, indicating worse outcomes. However, there was no significant difference between the two groups at the 6-month follow-up. We also examined the effects of viral status, hypertension, and ischemic heart disease (IHD) on the

MRS at 3 months, none of these factors modified the effect, but at 6 months, patients without MASH showed significantly better MRS scores if they were non-hypertensive and did not have IHD, compared to those with these comorbidities. Viral status did not influence the MRS at either follow-up point. Previous studies have documented that patients with MASH experienced more severe strokes at presentation and generally have worse outcomes.[11,16,17]

A study found no significant difference in NIHSS and MRS scores between patients with and without MASH, though the cohort included diabetics. MASH patients were generally younger, likely due to obesity and its related effects.[19,20] Interestingly, some evidence in the literature suggests that NAFLD and MASH have a protective effect in acute ischemic strokes with lower severity scores seen and better functional outcomes.[21]

Studies show worse outcomes in MASH patients, with NIHSS scores of 8.7 and MRS of 3.6 at discharge, compared to 5.5 and 1.8 in those without MASH. These differences are linked to comorbidities like diabetes. However, there is limited research comparing NIHSS and MRS scores in MASH patients while accounting for comorbidities. Our study is among the few that has investigated this relationship, particularly in the context of recent research over the past decade, which has established an association between strokes and metabolic-associated fatty liver disease and MASH. Tang et al. (2022) found no significant impact of MASH on ischemic stroke outcomes, suggesting that coexisting metabolic risk factors might play a more significant role than liver pathology alone.

Our results also indicated that patients with MASH were more likely to be intubated or unconscious, and their neurological deficits persisted for a longer duration. These findings highlight the need for further research, particularly in the South Asian population where fatty liver disease is prevalent. Well-designed studies are required to compare stroke severity at admission and improvement over follow-up between patients with and without NAFLD, incorporating stratification for comorbidities. Such research will provide a clearer understanding of the impact of MASH on stroke and its outcomes, potentially leading to more aggressive rehabilitation and management strategies for stroke patients with MASH if a definitive relationship between stroke severity and functional outcomes is established. This study is among the few that exclusively analyzed non-diabetic stroke patients with MASH, using standardized tools like NIHSS and Modified Rankin Score for follow-up. However, it has limitations including a small sample size, single-center design, and lack of advanced imaging or biopsy for definitive MASH diagnosis. The exclusion of pre-diabetics could also limit generalizability.

Conclusion

This study shows that Metabolic dysfunction–associated steatohepatitis (MASH) significantly worsens stroke severity and delays functional recovery in non-diabetic patients with acute ischemic stroke. MASH patients had higher NIHSS scores at admission and poorer functional outcomes at three months, supporting its role as an independent risk factor. These Observations highlight the need for early identification and tailored management of stroke patients with underlying MASH.

Ethical Approval: The Institutional Review Board, Fatima Jinnah Medical University, Lahore approved this study vide No. 58-MD-Medicine/ IRB.

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Authors' Contribution:

AW: Conception & design, acquisition of data, drafting of article

AA: Acquisition of data, analysis & interpretation of data, drafting of article

AJ: Analysis & interpretation of data

MSJ: Drafting of article

BS: Critical revisions for important intellectual content, final approval of the version to be published

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