

**HOSPITAL BASED STUDY OF CORRELATION BETWEEN MICROALBUMINURIA
AND ISCHEMIC STROKE IN WESTERN MAHARASHTRA**¹Roy Swetabh S., ^{*2}Kulkarni Sandhya S., ³Yadav Subhash L., ⁴Rode Vikram V., ^{*5}Kondewar Mayur K.^{1,3,4,5}Resident, Department of Medicine, Krishna Institute of Medical Sciences, Karad.²Professor, Department of Medicine, Krishna Institute of Medical Sciences, Karad.***Corresponding Author: Kulkarni Sandhya S.**

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ABSTRACT

Introduction: Ischemic stroke is defined as the acute onset in neurological deficit following sudden occlusion of blood supply to the brain tissue due to any cause. Microalbuminuria has been associated with clinical risk factors for stroke like diabetes, hypertension, aging, history of myocardial infarction, obesity, smoking and left ventricular hypertrophy and it predicts poor outcome. **Materials And Methods:** It was an observational Case-Control Study done during Dec 2015 to May 2017 among patients (118 cases and 118 controls) who were admitted with diagnosis of acute ischemic stroke irrespective of age and sex and confirmed by CT scan / MRI brain, within 24 hours after the onset of symptoms in department of General Medicine of a tertiary care hospital. **Results:** Among the 118 cases, 44 patients had presence of Microalbuminuria (MA positive) and 74 patients had no Microalbuminuria (MA negative), whereas among the 118 controls, only 5 had microalbuminuria and 113 had no microalbuminuria. Patients with acute ischemic stroke are 2.26 times more likely to have microalbuminuria thus depicting significant association between ischemic stroke and microalbuminuria (P value: < 0.0001 & Chi-square value: 39.174). **Conclusions:** Microalbuminuria as an independent risk factor in acute ischemic stroke has been extensively studied in the western countries, and has successfully established its association with the acute ischemic stroke. This study supports the already prevailing work done to prove the relationship between microalbuminuria and acute ischemic stroke.

KEYWORDS: microalbuminuria, acute ischemic stroke, neurological deficit, Non communicable diseases, Cardiovascular disorders.

INTRODUCTION

Ischemic stroke is defined as the acute onset in neurological deficit following sudden occlusion of blood supply to the brain tissue due to any cause.

Overtime, numerous risk factors have been found to be associated with increased occurrence of stroke. The most important modifiable risk factors for stroke are hypertension, diabetes mellitus, cigarette smoking and hypercholesterolemia. Other risk factors include heavy alcohol consumption and illicit drug use.^[1]

Atherosclerosis of the arteries supplying the central nervous system is believed to be the main aetiology in ischemic stroke. The realization that atherosclerosis as an inflammatory disease has led to a search for new stroke risk factors such as microalbuminuria (Albumin concentration 30-300mg/day in a 24-hour urine collection).^[2]

Microalbuminuria (MA) has been associated with many disease entities like diabetic nephropathy, hypertension with left ventricular hypertrophy and renal insufficiency,

etc. Microalbuminuria has been associated with clinical risk factors for stroke like diabetes, hypertension, aging, history of myocardial infarction, obesity, smoking and left ventricular hypertrophy and it predicts poor outcome.

The proposed mechanism of microalbuminuria leading to clinical vascular disease is the intimate relationship between low-level albumin excretion and vascular permeability that makes urinary albumin excretion highly sensitive to the presence of any inflammatory process including cerebrovascular disease. The kidney is ideally placed to amplify any small changes in the systemic vascular permeability.

Many studies have been published in the past demonstrating the interaction between the urine microalbumin excretion and the small vessel damage involving the heart, the kidneys and the brain. This cerebro-renal interaction has been implicated with small vessel damage; the cerebral and glomerular small vessels might have a common soil of pathogenesis, as these organs are closely connected to each other through anatomic and vaso-regulatory similarities since small

vessel disorder is a systemic disorder. Information about damage in one organ may be provided by damage through another organ.

The relationship between microalbuminuria and incident stroke has been investigated in a number of cross-sectional and prospective studies with a documented positive correlation between the level of microalbuminuria and severity of stroke³.

Since microalbuminuria is strongly linked to stroke risk, the morbidity and mortality can be curbed in patients with elevated urinary albumin excretion by providing early pharmacological intervention to this group of patients. Hence, this study is being planned to study the role of microalbuminuria as a risk factor as well as a potential prognostic marker in acute ischemic stroke.

MATERIALS AND METHODS

It was an observational Case-Control Study done during Dec 2015 to May 2017 among patients (118 cases and 118 controls) who were admitted with diagnosis of acute ischemic stroke irrespective of age and sex and confirmed by CT scan / MRI brain, within 24 hours after the onset of symptoms in department of General Medicine of a tertiary care hospital. The study subjects were enrolled after taking informed consent from the patients/ relatives in their vernacular language.

The patients with history of acute ischemic stroke presenting within 24 hours of the onset of symptoms and the diagnosis being confirmed by CT/MRI Brain were included in the study while patients with Kidney disease with both acquired and congenital etiology, Liver disorders, Chronic inflammatory gastrointestinal disorder, Neoplasm, Those on NSAIDs or other immunosuppressant and other nephro-toxic drugs, Fever or any other focus of infection, Inflammatory Rheumatic disease were excluded from the study. All the patients were screened for the presence of symptoms that gave a possible clue of Cerebro-vascular accident (CVA) or stroke. All subjects (cases and controls) included in the study were IPD (In-patient department) patients. Controls were selected from age and sex matched non-stroke population. The patients were interviewed about their past medical and personal history. General physical examination was done as a routine. A detailed neurological examination was done to assess the extent of the neurological deficits in the patients. Every patient underwent computed tomography of brain/MRI brain on admission as per stroke protocol and the patients with ischemic changes were included in the study. Baseline investigations like Serum glucose levels, blood urea, serum creatinine and lipid profile were estimated. Electrocardiogram (ECG), chest x-ray was done to assess the cardiac status. Ultrasonography (USG) of abdomen was done in few patients to rule out anatomical defect in kidney/liver.

RESULTS

The present Case-Control Study was conducted among patients admitted with diagnosis of acute ischemic stroke in a tertiary healthcare institute. Clinical, systemic assessment along with diagnostic workup was done in all the patients. All the findings were recorded and analyzed. The mean age of case study group patients was 67.35 years and mean age of control group patients was 67.00. Majority of cases were in the age group of 61- 80 years. There was no significant difference observed in the mean age of case and control study group patients. The Case study group was age wise and gender wise matched with control group where number of male subjects are 61 and number of female subjects are 57 with the male to female ratio as 1.07 (Table 1).

Among the 118 cases, 44 patients had presence of Microalbuminuria (MA positive) and 74 patients had no Microalbuminuria (MA negative), whereas among the 118 controls, only 5 had microalbuminuria and 113 had no microalbuminuria. Patients with acute ischemic stroke are 2.26 times more likely to have microalbuminuria thus depicting significant association between ischemic stroke and microalbuminuria (P value: < 0.0001 & Chi-square value: 39.174) (Figure 1). Majority of patients in both MA positive and MA negative group falls in the age range of 61-80 years, Mean age of MA positive patients in control group was 67.09 years. and no significant association was found between various age groups and between gender (P value>0.05) in cases and control groups too (Table 2).

The study participants were asked about their personal history. Out of 118 cases, 61 were tobacco chewers and 57 were not. Of 44 MA positive cases, 25 gave history of tobacco chewing and 23 had history of alcohol intake. Thus, showing no significant correlation between tobacco chewing as well as alcohol intake and Microalbuminuria (Analysed using Chi-Square test) (Table 3).

MA positive and MA negative case subjects were compared with respect to blood pressure, renal parameters (Blood urea and Serum Creatinine), lipid profile status (Cholesterol: HDL ratio), blood sugar levels (random), duration of hospital stay and no significant relation was established between these parameters and microalbuminuria by student's t test and P value >0.05. Mean Systolic BP was 142.73 mm Hg in MA positive patients and 137.08 mm Hg in MA negative. Mean Diastolic BP was 85.45 mm Hg in MA positive patients and 82.11 in MA negative. Mean value of serum creatinine was 1.16 mg/dl and blood urea – 29.18 mg/dl in MA positive patients while serum creatinine mean value was 1.12 mg/dl with blood urea 28.99 mg/dl in MA negative patients. The Cholesterol to HDL ratio was found to be 4.39 in MA positive and 4.12 in MA negative patients. Mean Blood sugar value (random) was calculated as 144.16 mg/dl in MA positive patients and 129.93 mg/dl in MA negative patients. The mean duration of hospital stay was 7.89 days in MA positive patients and 7.45 days in MA negative patients. The difference

between findings of all of the above parameters in both the groups was not found statistically significant (Table 4).

Neurological evaluation was done using Glasgow coma scale (GCS) in all 118 acute ischemic stroke patients on admission and discharge. The mean GCS on discharge of MA positive patients was 12.34 and MA negative patients was 14.63. By applying t test significant association was established between GCS on admission and discharge and MA where GCS was significantly lower in patients with MA when compared to patients without MA (Table 5). In the present study, 44 MA positive patients, 28 showed unchanged outcome, 11 died and only 5 showed improved condition on discharge. Among 74 total MA negative cases, 68 showed improved health condition on discharge, only 5 showed unchanged prognosis and 1 died (Table 5). We found a significant association found between patient outcome and MA (Value of $\chi^2 = 6.874$, $p=0.00471$, significant). More number of cases with unchanged or deteriorated outcome belonged to the MA positive group while MA negative group patients were mostly having improved outcome. Among all the patients participated in the study, 29 were diabetic and of these 29, 13 showed microalbuminuria and 16 were MA negative. Blood pressure was taken of all acute ischemic stroke patients on admission and staging of hypertension was done as per Joint National Committee (JNC) -7. Patients were

categorised as having normal BP, Pre- hypertension, Stage 1 Hypertension and stage -2 hypertension. Most MA positive patients were having stage 1 and 2 Hypertension in comparison to MA negative patients who were mostly normotensive. Significant association was seen between hypertension and MA. Of 118 cases, 25 total patients had Left ventricular hypertrophy (LVH) findings on ECG. Of 44 MA positive patients only 11 had positive findings of LVH on ECG.

Of 118 patients, 84 were diagnosed on MRI brain scan and 34 were diagnosed on CT scan. Type of infarct was classified as small vessel infarct (lacunar infarct), Large vessel infarct (involving major vessel like Anterior cerebral artery (ACA), Middle cerebral artery (MCA), Posterior cerebral artery (PCA)) and combined infarct (Table 5). Most MA positive and negative cases had small vessel infarct. Of 44 MA positive cases- 26 patients had small vessel infarct, 14 had large vessel infarct (all involving MCA territory) and 4 had combined infarct.

Of 74 MA negative patients, 36 had Small vessel infarct, 32 had large vessel infarct (most involving MCA territory> PCA territory > ACA territory) and only 6 had combined infarct. The association between Small vessel infarct, Large vessel infarct, combined infarct and MA was not found significant (P value: 0.2210 & Chi-square value: 1.49).

Table 1: Age and Sex wise distribution of patients.

Age (in years)	Case (n=118)		Control (n=118)	
	Male	Female	Male	Female
21-40	2	2	2	2
41-60	13	13	13	13
61-80	37	38	37	38
>81+	9	4	9	4
Total	61(51.69%)	57(48.31%)	61(51.69%)	57(48.31%)
Mean ± SD	67.35 ± 10.17		67.00 ± 12.56	

Table 2: Age and Sex wise distribution of MA positive and negative patients in Case group (n=118).

Age (in years)	MA Positive		MA Negative	
	Male (No %)	Female (No %)	Male (No %)	Female (No %)
21-40	1	0	1	2
41-60	2	6	11	7
61-80	13	18	24	20
>81+	3	1	6	3
Total	19(31.14%)	25(43.86%)	42(68.85%)	32 (56.15%)
Mean ± SD	67.22 ± 9.87		67.47 ± 11.02	

Table 3: Comparison of different parameters between MA positive and Negative case patients.

Variables	MA Positive	MA Negative	Significance	
Smoking	Smokers	7(63.63%)	4(36.37%)	p=0.9469
	Non-Smokers	67(56.98%)	40(43.02%)	
Tobacco chewing	Yes	36(59.02%)	25(40.98%)	p=0.5039
	No	38(66.67%)	19(33.33%)	
Alcohol Intake	Yes	9(39.13%)	14(60.87%)	p=0.0680
	No	65(68.42%)	30(31.58%)	

Table 4: Relationship between various clinical parameters and presence of MA.

	MA Negative	MA Positive	Significance (Student's t-test) and P value	Inference / Significance
	Mean ± SD	Mean ± SD		
Systolic BP (mm Hg)	137.08 ± 16.6	142.73 ± 14.8	T value: 1.81 P value: 0.071	Not significant
Diastolic BP (mm Hg)	82.11 ± 8.33	85.45 ± 6.97	T value: 0.76 P value: 0.44	Not significant
Sr. Creatinine (mg/dl)	1.12 ± 0.208	1.16 ± 0.252	T value: 0.932 P value: 0.353	Not significant
Blood Urea (mg/dl)	28.99 ± 7.35	29.18 ± 7.34	T value: 1.723 P value: 0.087	Not significant
Cholesterol HDL ratio	4.12 ± 0.98	4.39 ± 1.12	T value: 1.314 P value: 0.191	Not significant
Blood sugar level (mg/dl)	129.93 ± 49.07	144.16 ± 49.72	T value: 1.723 P value: 0.087	Not significant
Hospital stay (in days)	7.45 ± 1.52	7.89 ± 2.05	T value: 1.32 P value: 0.18	Not significant

Table 5: Relationships between various clinical conditions and presence of MA.

Variables		MA Positive	MA Negative	P-value
GCS	on admission	12.22±2.57	14.33±2.44	0.0321
	on discharge	12.34±3.02	14.63±2.58	
Outcome at discharge	Improved	5 (5.12)	68(57.63)	0.00471
	Unchanged	28(23.73)	5 (4.24)	
	Deteriorated	11(9.32)	1 (0.85)	
Diabetes mellitus	DM	16(55.17%)	13(44.83%)	0.45 59
	No DM	58(66.67%)	31(33.33%)	
Hypertension	Normal BP	4 (3.39)	35(29.66)	< 0.001
	Pre-HTN	4(3.39)	12(10.17)	
	Stage 1 HTN	19(16.10)	14(11.87)	
	Stage 2 HTN	17(14.41)	13(11.01)	
ECG	Left ventricular hypertrophy (LVH)	14(56%)	11(44%)	0.5832
	No Abnormality detected (NAD)	60(64.52%)	33(35.48%)	
Type of Infarct	Small vessel /Lacunar infarct	26 (22.03%)	36 (30.5%)	0.2210
	ACA	00	01 (0.8%)	
	MCA	14 (15.25%)	27 (22.88%)	
	PCA	00	04 (3.38%)	

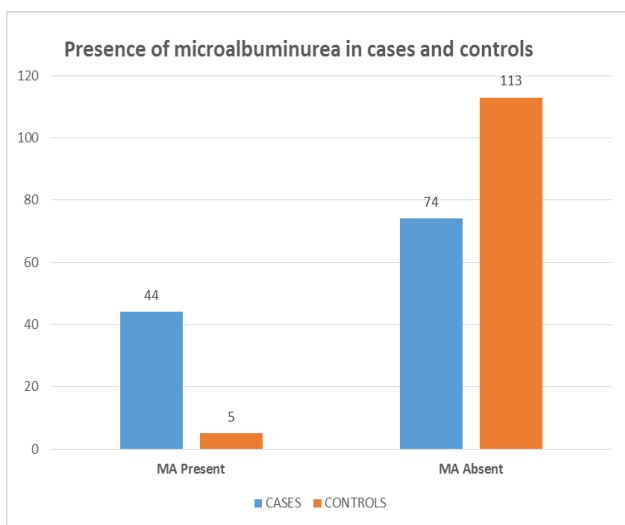


Figure 1: Distribution of study subjects according to presence of microalbuminurea P value: < 0.0001.

DISCUSSION

Microalbuminuria signifies abnormal vascular permeability and its presence may be considered as kidney's notice for markedly enhanced cerebrovascular risk. 118 acute ischemic stroke patients were selected as case study subjects. Equal number of age and sex matched patients who did not have past or present history of stroke were selected as control subjects. Demographical characteristics of the study participants were studied. No significant correlation was found between the age and microalbuminuria. Most patients both MA positive and MA negative belonged to age group 61-80 years. This is similar to the study done by Maskey et al and Singh et al where most patients belonged to >60 years of age.^[5,6] No predominance of either gender was found in MA positive and MA negative patients in Case study group in our study where number of males were 31.14% and number of females were 43.86% in MA positive group and 68.85% were males and 56.15% were females in MA negative group. It is also similar to a study done by Pattanaik et al in 60 cases of acute ischemic stroke, among cases with microalbuminuria positives, 55.2% were males and

44.8% were females and in microalbuminuria negatives males are 61.3% and 38.7% females. In both groups microalbuminuria is more common in males but not statistically significant.^[7] This was consistent with study by Turaj *et al.* where male patients were more with no statistical significance.^[8]

In our study the prevalence of microalbuminuria was 44 among the 118 patients, which is 37.29%. This was compared to some previous studies which also took into account case and controls and is depicted in the following table.

Study	Sample size	Year of study	Microalbumuria in case	Microalbuminuria in controls
Pattanaik <i>et al</i> ^[7]	60	2016	29 (48.3%)	3(10%)
Singh S <i>et al</i> ^[9]	60	2015	30 (50%)	10 (33.33%)
Slowik <i>et al</i> ^[10]	60	2002	46.7%	16.7%
Turaj <i>et al</i> ^[8]	52	2001	46.1%	13.5%
Beamer <i>et al</i> ^[11]	97	1999	29%	10%
Muralidhara N <i>et al</i> ^[16]	116	2015	47.92	----
PC Mathur <i>et al</i> ^[12]	50	2005	68	----
Yoko <i>et al</i> ^[13]	166	2011	37.06	----
Muhammad Ahsan <i>et al</i> ^[14]	195	2013	48.2	----
AnupaThampy <i>et al</i> ^[15]	70	2013	60	----
Dr Anand Singh ^[6]	60	2017	68.33	----
Present study	118	2016	37.29%	4.24%

Assessment of the Glasgow coma scale has been taken to estimate the prognosis of the patients in our study. Many of the well-known studies in the west have considered Scandinavian Stroke scale and the NIHSS (National Institute of Health Stroke Scale) to correlate between ischemic stroke and Microalbuminuria and hence no study was found in literature for comparison with our study which took into account the Glasgow coma scale for neurological assessment. In the present study the mean GCS was 12.22±2.57 among the MA positive patients, and it was 14.33±2.44 among MA negative patients. This clearly states that the GCS was significantly lower in patients with MA when compared to patients without MA (p value of 0.0321, significant p value < 0.05). Our study points out that MA positive patient had poorer prognosis as depicted by their unchanged outcome on discharge. Hence presence of microalbuminuria proves to be an important marker for prognosis in ischemic stroke. It may serve as an assessment marker in case of patients requiring aggressive medical intervention. The prevalence of microalbuminuria in hypertensive stroke patients in this study was 57% as compared to 18.18% in non-hypertensive stroke patients and a statistically significant relation was found between hypertension and MA in our study with p value < 0.001. The prevalence value was similar to the findings of other studies as shown in table below.

Study	Prevalence % (MA with HTN)
Sabharwal R K <i>et al</i> ^[16]	33.3%
Bigazzi <i>et al</i> ^[18]	40%
R.Habbal <i>et al</i> ^[19]	67.8%
Muhammad Ahsan Farooq <i>et al</i> ^[14]	57%
Present study	57%

The prevalence of microalbuminuria in Diabetic stroke patients in present study was 44.8% as compared to

33.33% in non-diabetic stroke patients which is less than similar studies and no significant statistical correlation was found between Diabetes Mellitus and microalbuminuria in the present study. Our study was found to be similar to a study done by Farooq *et al* in which among the diabetic subjects studied, MA was present in 54.45% with P value 0.204 – statistically non-significant.^[14]

3.39% MA positive cases where smokers while 5.93% MA negative patients were smokers. Our study could not establish a statistical significance between smoking and MA as the p value was not significant (0.9469) in our study. Of 11 patients who had history of smoking, 4(36.7%) was MA positive and 7(63.63%) were MA negative. R k Gupta *et al* (2014) showed smokers had 4 fold prevalence for MA.^[20] Maskey A *et al* (2007) identified smoking as second most common modifiable risk factor of stroke.^[6] Our study could not establish a statistical correlation between tobacco chewing and MA with p value being 0.5039 and also between alcohol consumption and MA with p value being 0.0680.

In Our study, 25 patients (21.18%) had LVH on ECG which is correlating with above studies but no relationship could be established between MA and ECG findings of LVH. Maskey A *et al* found left ventricular hypertrophy (LVH) in 27.5% of cases of stroke.^[6] There is no significant association between ECG findings and MA positive and negative cases in case study group.

There is no significant association between Small vessel infarct, Large vessel infarct, combined infarct and MA (p=0.128) with most i.e. 59.09% of MA positive and 48.65% of MA negative cases being small vessel infarcts. 38.13% patients had MCA territory infarct. 7.27% had combined infarcts. CT scan results in study done by Singh A *et al* revealed that middle cerebral artery infarct

predominated the study population (right and left 78.33%) which co-relates with our study in which most large vessel infarcts were of MCA territory.^[6]

Pattanaik et al concluded that prevalence of microalbuminuria in different subtypes of infarction were 50% in MCA infarct, 16.7% in ACA infarct, 3.3% in PCA infarct, lacunar infarcts in 16.6% and combination of territories in 13.3%.^[7] Here microalbuminuria did not differ among major sub types of stroke. According to Beamer prevalence of microalbuminuria did not differ among major sub types of strokes.^[50] Our study also established the same findings.

As in our study serum urea serum creatinine serum lipid profiles were found similar in cases and controls and not statistically significant and is similar to study done by Pattanaik et al.

CONCLUSIONS

Microalbuminuria was present in 37.29 % of the patients out of the 118 patients studied and presence of MA significantly correlated to the Glasgow coma scale for assessing the prognostic significance. Lower the GCS, the prevalence and the values of the MA were more. Prevalence of MA was high in hypertensive patients and statistical significant equation was found between MA and presence of hypertension.

There was no significant correlation between DM and presence of MA in our study. This could be because presence of MA in DM is multifactorial and it depends on duration of the disease, glycemic control of the patient. There was no significant correlation between the Age and the presence of MA, even among the subdivided age groups. No significant gender discrepancy with the presence of MA was found. Also, there was no significance between smoking history, tobacco chewing or alcohol consumption and the presence of MA. The study did not find a significant correlation between the lipid parameters and MA.

Microalbuminuria as an independent risk factor in acute ischemic stroke has been extensively studied in the western countries, and has successfully established its association with the acute ischemic stroke. This study may serve to add the data that is already available pertaining to the significant risk factors and other parameters. The importance of microalbuminuria in other systemic diseases and its behavior has to be further studied so that its prognostic significance can be established.

We could also infer that the presence of MA may in addition serve as an important prognostic indicator for the neurological outcomes of the disease.

The presence of MA appears to independently predict poor clinical outcome following acute stroke. Since screening for MA is relatively easy and inexpensive, it

could be effective in identifying stroke patients at risk for unfavourable outcomes.

More studies are to be encouraged to in order to find the relationships between the MA and its significance in other systemic involvement, and its pathological alterations as a risk factor for Ischemic stroke.

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