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Risk Factors, Vascular Lesion Distribution and Outcome of Strokes Due to Intracranial Atherosclerosis in rural south India

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Abstract
Background: *Intracranial atherosclerotic stenosis (ICAS) is a common cause of ischemic stroke worldwide and probably in India.. The common risk factors for development of intracranial atherosclerosis include hypertension, diabetes, tobacco use and hyperlipidemia. The morbidity and mortality associated with ischemic stroke makes it essential that individuals with risk factors must be identified and appropriate interventions must be done to prevent stroke.*
Aim: *The aim of this study was to describe the risk factors, distribution of vascular lesions and outcome of stroke due to ICAS.*
Methodology: *All consecutive patients of ischemic stroke due to ICAS were enrolled prospectively on the basis of a predefined inclusion and exclusion criteria. Demographic details and history of systemic illnesses particularly diabetes and hypertension was noted in all the cases. Vascular territory involved was determined on the basis of imaging (computerized tomography, Magnetic resonance imaging and MR angiography. Details about, risk factors, vascular lesions and outcome were noted. Data was examined using SSPE 16.0 software. For statistical purposes p value less than 0.05 was taken as statistically significant.*
Result: *Out of 455 patients there were 328 (72.09%) males and 127 (27.91%) females with a M:F ratio of 1:0.38. The most common age group affected in males and females was 61-70 years (M-29.45%, F-11.42%) followed by 51-60 years (25.93%) in males and more than 70 years (9.89%) in females. The difference in mean age of males and females was found to be statistically 'highly significant'. The most common risk factors associated with stroke was hypertension (54.29%) followed by diabetes mellitus (51.43%).Middle cerebral artery was involved in majority of the cases (n-299, 65.71%). Mean duration of hospital stay was found to be 9.81 +/- 7.17 days. Mortality rate was found to be 11.65%.*
Conclusion: *Intracranial atherosclerotic stenosis (ICAS) is a common cause of ischemic stroke Identification of risk factors and their management remains the best strategy for preventing recurrence.*
Keywords: *Intracranial atherosclerosis, Ischemic stroke, Middle cerebral artery, Risk Factors.*

Introduction

Intracranial atherosclerosis is one of the important causes of ischemic stroke leading to significant amount of morbidity and mortality worldwide. Intracranial atherosclerosis involving one of the major intracranial arteries may present as recurrent ischemic strokes. The common risk factors for development of intracranial atherosclerosis include hypertension, diabetes, tobacco use and hyperlipidemia. The risk of intracranial atherosclerotic stenosis (ICAS) is higher in Indian patients and it accounts for about 33%-50% of ischemic strokes and >50%of transient ischemic attacks (TIAs) in these populations. This susceptibility may be due to genetic factors and life style or dietary habits. The main mechanisms by which intracranial atherosclerosis causes ischemic infarcts include hypo-perfusion, embolism and plaques extension. In many cases combinations of these 3 mechanisms may occur simultaneously[1].

Ischemic stroke is a clinical syndrome caused by various mechanisms of cerebrovascular disease. Intracranial atherosclerotic stenosis (ICAS) is the most common vascular lesion in stroke patients worldwide[2]. Large vessel ICAS which includes intracranial internal carotid artery, middle cerebral artery, posterior cerebral artery (PCA), vertebral artery (VA), and basilar artery (BA) represents a more advanced stage of intracranial atherosclerotic disease, in which the vessel lumen has narrowed. In clinical practice as well as for research purpose, a diameter stenosis of 50-99% is taken to qualify for symptomatic ICAS[3]. The estimated prevalence of symptomatic ICAS in more recent literature ranges from 20% to 53%, depending on the study population, race and imaging method. High rates of recurrent ischemic stroke in symptomatic ICAS mandate early diagnosis and treatment.

The diagnosis of intracranial atherosclerosis can be diagnosed reliably by imaging modalities such as doppler studies, MR angiography and CT angiography. These are safe and relatively affordable imaging modalities for the diagnosis of intracranial atherosclerosis. Conventional cerebral angiography is not used commonly because of its invasive nature but it has been reported to be gold standard test for diagnosis and estimation of intracranial arterial stenosis[4].

The patients who have been diagnosed to be having significant intracranial atherosclerosis remain at high risk of stroke. The risk increases if concomitant systemic illnesses such as hypertension and diabetes are present. One of the important part of managing patients with significant intracranial atherosclerosis is risk modification such as blood pressure control and maintenance of blood sugar levels in patients with hypertension and diabetes respectively. All patients with significant intracranial atherosclerosis must be advised anticoagulation therapy such as aspirin or warfarin. Many studies have reported the benefit of dual anti platelet therapy such as aspirin and clopidogrel in lowering the risk of stroke risk in patients with intracranial atherosclerosis. Surgical management of critical intracranial atherosclerosis may consist of measures such as extra-cranial to intracranial bye-pass grafting, endovascular treatment such as percutaneous trans-luminal angioplasty and stenting[5].

In patients with any degree of intracranial atherosclerosis the essence of management lies in the early diagnosis, identification of risk factors and their modification and drug therapy in patients diagnosed to be having significant atherosclerosis on the basis of imaging. We conducted this study to analyze risk factors, distribution of vascular lesions and outcome of patients with stroke due to intracranial atherosclerosis in rural south India.

Materials and Methods

This was a prospective study conducted in the department of neurology in which consecutive patients of stroke due to intracranial stenosis who were admitted in a tertiary care institute situated rural area of south India were included on the basis of a predefined inclusion and exclusion criteria. Informed consent was obtained from the

patient or the caregiver. The diagnosis of ischemic stroke due to large artery intracranial atherosclerosis was made as per the Trial of ORG 10172 in acute stroke treatment (TOAST classification). Stenosis of internal carotid artery is a common cause of ischemic stroke so patients detailed history of present and preceding (if any) illness with a special emphasis on vascular risk factors, findings of physical as well as neurological examination details, disease duration laboratory characteristics, presence of any complications and treatment received were noted. The data was recorded in a predesigned case record forms. Magnetic resonance angiography (MRA) was done in all patients. Proximal middle cerebral arteries, proximal anterior cerebral arteries, intracranial internal carotid arteries, proximal posterior cerebral arteries, vertebral arteries and basilar arteries were evaluated for presence of stenosis (segmental flow gap or luminal stenosis or occlusion (non-visualized vessel segment with absent distal flow). For study purpose arterial lesions corresponding to the location or territory of the recent infarct on diffusion weighted imaging were considered symptomatic. Asymptomatic lesion was defined as stenosis or occlusion not related to the current neurologic signs and with no old infarction visible on neuroimaging in its respective vascular territory. The distribution of stenotic and occlusive lesions was noted. Patients were put on treatment with anti-platelet drugs in addition to other required medications. Outcome of the treated cases was measured at the time of discharge. All data were entered into the Microsoft Excel file, and the analysis was performed. Mean, standard deviation, and Student's t test was performed for quantitative variables. Frequency, percentage, and Chi square tests were performed for qualitative variables. The statistical analysis was done using SSPE 16.0 software. P value less than 0.05 was taken as statistically significant.

Diagnostic criteria for risk factors

1. **S**ystolic blood pressure (SBP) 140 and or diastolic blood pressure >90 mm of hg.
2. Diagnosed cases of diabetes or fasting glucose level of more than 126 mg/dl or 2-hour postprandial blood glucose level of >200 mg/dl or HBA1C level of more than 6.
3. Hyperlipidemia history of dyslipidemia, cholesterol > 200 mg/dl, Low-density lipoprotein >100 mg/dl (or) triglycerides >150 mg/dl.
4. Smoking if the patient was a current smoker or had quit smoking in the past 6 months.
5. History of alcohol consumption.

Inclusion criteria

1. Patient or caregiver given informed consent for the study.
2. Patient presenting with Stroke (stroke was defined as focal/global symptoms lasting >24 h and associated with imaging evidence of acute ischemia in the distribution of the stenotic vessel on computed tomography or magnet resonance imaging)
3. Intracranial atherosclerotic disease comprised the involvement of the intracranial Carotid, middle cerebral, posterior cerebral, intracranial vertebral arteries and basilar artery.

Exclusion criteria

1. Patient or caregiver refused consent.
2. Other cause of stroke other than atherosclerosis such as atrial fibrillation, myocardial infarction, mitral stenosis, mechanical valve, intra-cardiac vegetations, dilated cardiomyopathy or ejection fraction <30% and other clear causes of stroke.

Results

In this study 455 consecutive patients with ischemic stroke were included on the basis of a predefined inclusion and exclusion criteria. Out of 455 patients there were 328 (72.09%) males and 127 (27.91%) females with a M:F ratio of 1:0.38.
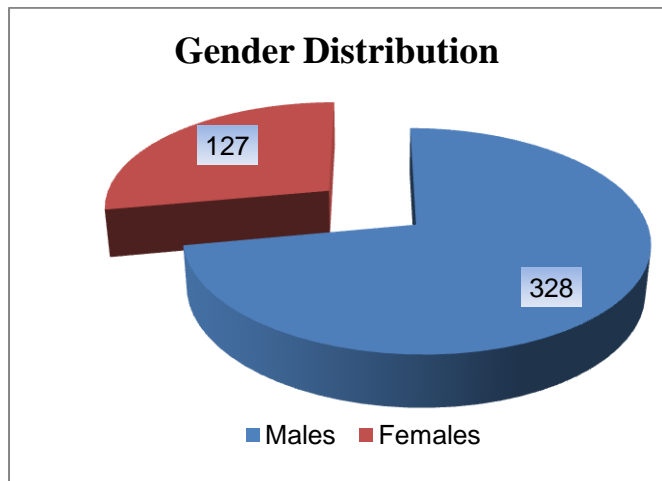
Gender Distribution

Figure 1: Gender Distribution of the affected cases.

The analysis of the age groups of the affected cases showed that the most common age group affected in males and females was 61-70 years (M-29.45%, F-11.42%) followed by 51-60 years (25.93%) in males and more than 70 years (9.89%) in females. The mean age of patients in males and females was found to be 60.06 +/- 8.65 years and 63.95 +/- 9.30 years respectively. The difference in mean age of males and females was found to be statistically 'highly significant'. Females were found to be affected at relatively older age as compared to males.

Table 1: Gender wise age distribution of the studied cases

Age Group	Males		Females	
	No of cases	Percentage	No of cases	Percentage
Less Than 50 yrs	34	7.47%	12	2.64%
51-60 yrs	118	25.93%	18	3.96%
61-70 yrs	134	29.45%	52	11.42%
>70 yrs	42	9.23%	45	9.89%
Total	328	72.09%	127	27.91
Mean Age	60.06 +/- 8.65 yrs		63.95 +/- 9.30 yrs	
95% CI- 2.0753 to 5.7047 P = < 0.0001 (Highly Significant)				

The analysis of risk factors present in the studied cases showed that the most common risk factors associated with stroke was hypertension (54.29%) followed by diabetes mellitus (51.43%). The other risk factors seen in studied cases were hyperlipidemia (37.14%), alcoholism (29.01%) and smoking (21.32%). (16.04%) patients were found to have a co-existing coronary artery disease.
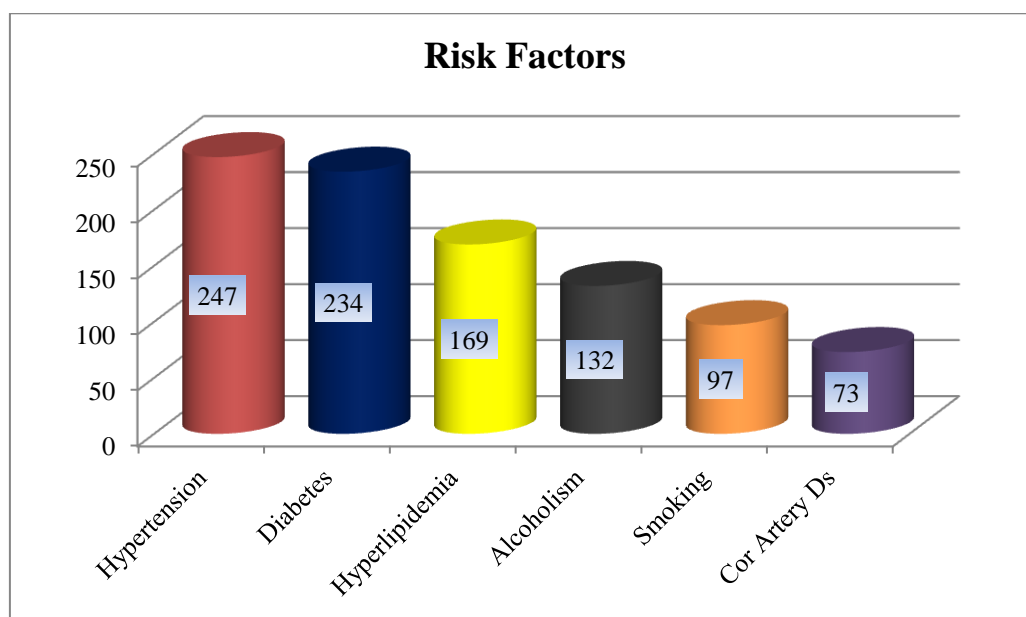

Figure 2: Risk Factors in the studied cases.

The analysis of the cases on the basis of part of part of circulation involved showed that in anterior circulation middle cerebral artery was involved in majority of the cases (n-299, 65.71%) followed by anterior cerebral artery (n-24, 5.27%) and internal carotid artery (n-6, 1.32%). In posterior circulation basilar artery was affected in 35 (7.69%) patients whereas posterior cerebral artery was involved in 33 (7.25 %) patients. Mixed arterial lesions were noted in 58 (12.75%) patients.
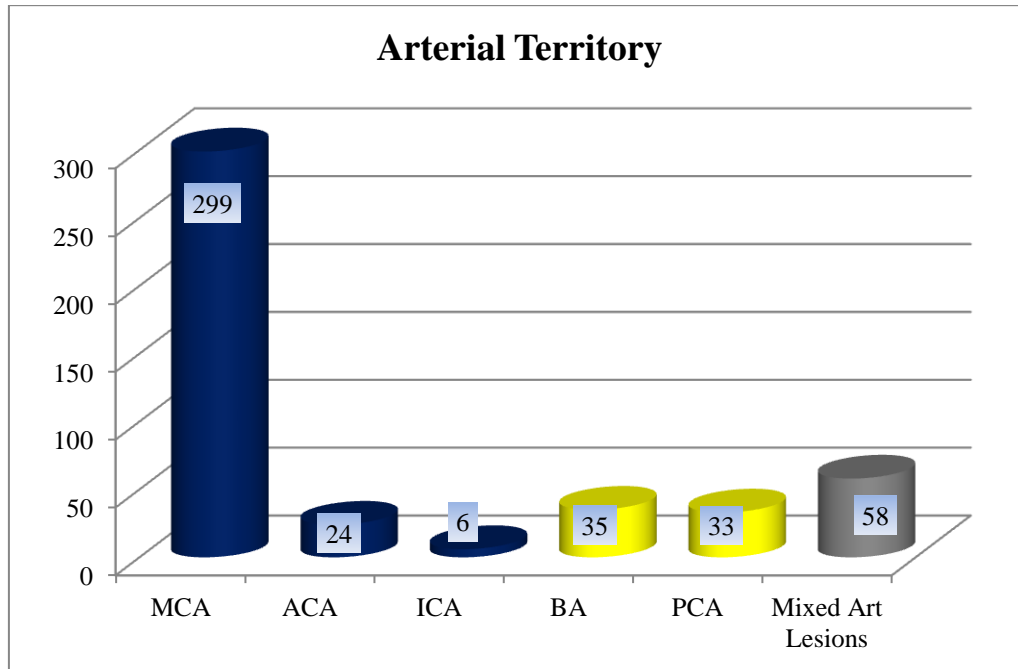
Arterial Territory

MCA: 299, ACA: 24, ICA: 6, BA: 35, PCA: 33, Mixed Art Lesions: 58

Figure 3: Arterial Territory involved in studied cases

The analyses of location of the infarcts showed that in majority of the cases (n-155, 34.1 %) infarcts were cortical whereas subcortical infarcts were seen in 132 (29%) patients. Mixed cortical and subcortical infarcts were seen in 91 (20%) patients. Brainstem and cerebellar infarcts were seen in 55 (12.1%) and 22 (4.8%) patients.
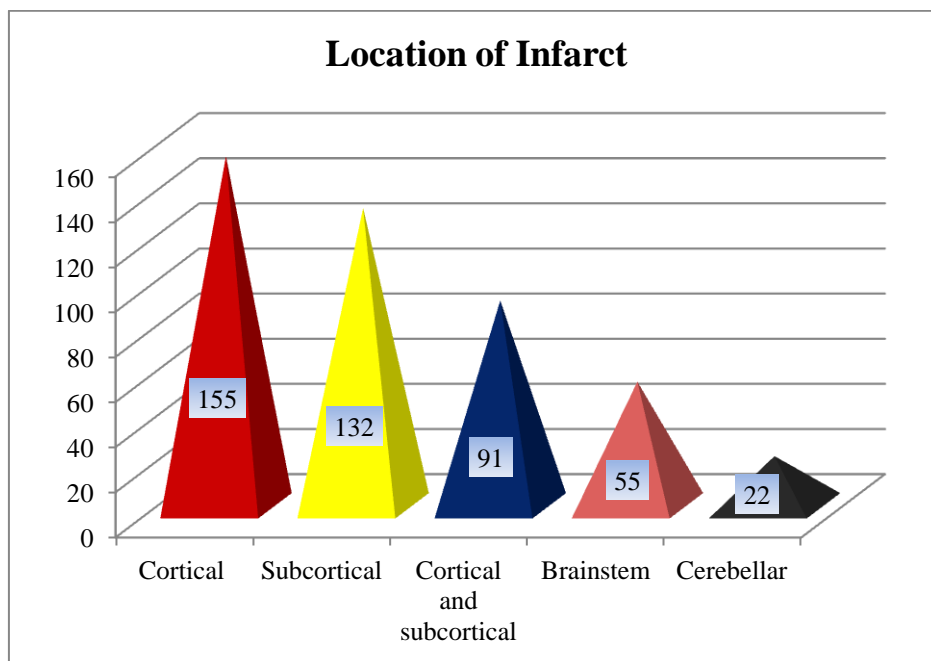
Location of Infarct

Cortical: 155, Subcortical: 132, Cortical and subcortical: 91, Brainstem: 55, Cerebellar: 22

Figure 4: Distribution of the infarcts on the basis of location

Out of 402 patients who were discharged from the hospital 192 (47.76%) patients required hospitalization for less than 1 week. 104 (25.87%) patients remained admitted for a duration of 1-2 weeksand 61 (15.17%) patients needed hospitalization for 2-3 weeks. 45 (11.19%) patients remained admitted for more than 3 weeks duration. Mean duration of hospital stay was found to be 9.81 +/- 7.17 days.

Table 2: Hospital Stay in the studied cases

Hospital Stay	No of Patients	Percentage
Less than 1 week	192	47.76%
1-2 weeks	104	25.87%
2-3 weeks	61	15.17%
More than 3 weeks	45	11.19%
Total	402	100%
Mean Hospital Stay : 9.81 +/- 7.17 days		

The analysis of outcome of the studied cases showed that out of 455 cases 53 (11.65%) patients expired during their treatment. The mean Glasgow coma scale (GCS) at the time of admission of the patients who expired was 3.98 +/- 1.62 whereas the mean Glasgow coma scale of the patients who were eventually successfully discharged was 9.24 +/- 3.72. The difference was found to be statistically significant (P < 0.05). Out of 402 patients who survived 293 (64.40%) patients were discharged with a good GCS (13-15) whereas 79 (17.36%) patients were discharged with moderate GCS (9-12). Remaining 30 (6.59%) patients were discharged against medical advice with poor GCS (<8).
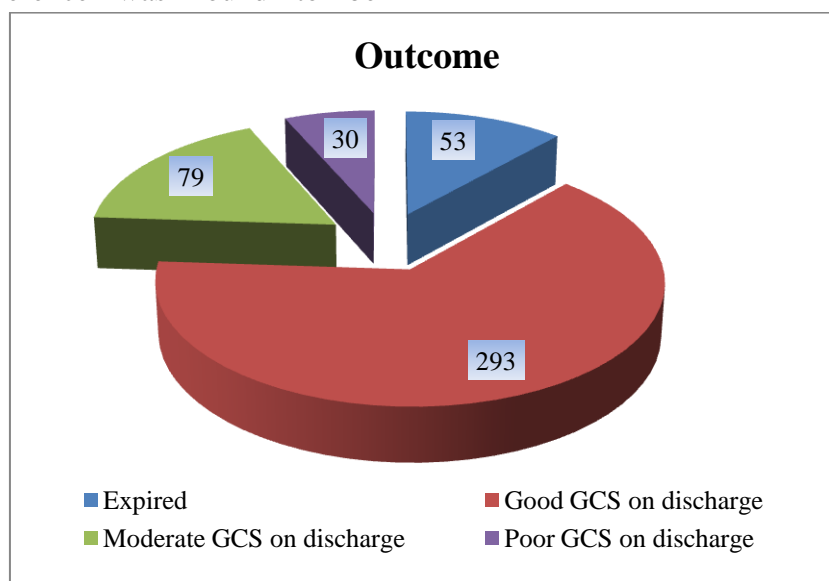

Figure 5: Outcome of patients with ischemic stroke

Discussion

Out of Out of 455 patients with stroke due to intracranial atherosclerosis included in this study there were 328 (72.09%) males and 127 (27.91%) females with a M:F ratio of 1:0.38. The male preponderance for the occurrence of stroke has been well established in various studies. Tarun Mishra et al conducted a cross sectional observation study of 64 patients with ischemic stroke. Out of the 64 studied cases there were 48 males (75%) and 16 females (25%) with a M:F ratio of 3:1[6]. The similar male preponderance in the incidence of stroke was reported by Chraa M et al[7] (M:F = 1.46:1) and Akbar DH et al (M:F= 1.4:1)[8]. The susceptibility of males for development of atherosclerosis and ischemic stroke has been subject of immense interest amongst the researchers. DI Carlo et al reported

that young female rodents exhibit a decreased inflammatory response to ischemic injury compared with males and on the basis of these findings concluded that estrogens works as a significant regulator of inflammatory pathways in females protecting them from atherosclerosis and its consequences[9].

IN our study the mean age of male and female patients was found to be 60.06 +/- 8.65 and 63.95 +/- 9.30 years respectively. It was found that the females were affected at a relatively older age as compared to males and the difference in the age between male and female patients was found to be statistically significant (P<0.05). Decreased incidence and slow progression of atherosclerosis and its complications is responsible for incidence of complications of atherosclerosis at a later age in females as compared to males. Caso V et al conducted a study to analyze gender differences in patients with acute ischemic stroke[10]. Out of 1136 studied cases the authors found that women were statistically older compared with men affected at 76.02 (+/- 12.93) and women affected at 72.68 (+/- 13.27) of median age, respectively. Similar findings of men getting affected at relatively earlier in life was reported by authors such as Yao X Y et al[11] and Foerch C et al[12].

Various risk factors in our study were found to be hypertension (54.29%) followed by diabetes mellitus (51.43%). The other risk factors seen were hyperlipidemia (37.14%), alcoholism (29.01%) and smoking (21.32%). Diabetes and hypertension as the significant risk factors for incidence of stroke has been reported by numerous studies. Huliyappa D et al conducted a hospital based, cross sectional study consisting of 236 stroke cases[13]. The authors reported that Overweight & obesity (63.4%) were the most common risk factor followed by hypertension (50%), cigarette & tobacco use (40.3%), alcohol consumption (36.5%) and diabetes (19.2%). Presence of hypertension as the one of the most significant risk factor for the occurrence of stroke has also been reported by the authors such as Hörnsten C et al[14] and Yu JG et al[15].

In our study on the basis of imaging it was found that the most common artery involved was middle cerebral artery (65.71%). Basilar artery was affected in 35 (7.69%) patients whereas posterior cerebral artery was involved in 33 (7.25 %) patients. Mixed arterial lesions were noted in 58 (12.75%) patients. In majority of the cases the infarcts were cortical (34.1%) whereas subcortical infarcts were seen in 132 (29%) patients. Majority of the studies have reported that middle cerebral artery is the most common intracranial artery to be affected by atherosclerosis. Assarzadegan F et al in a study of 1011 patients found that the stenosis in main cerebral arteries was seen in 709 (70.1%) patients, consisting of 488 MCA strokes, 208 PCA strokes, and 53 ACA strokes[16]. The authors like Lee K et al[17] and González Delgado Met al[18] also reported that in ischemic stroke middle cerebral artery is most commonly involved.

The outcome of patients with ischemic stroke usually depends upon etiology, presence of co-morbidities and extent of infarct. In our study 53 (11.65%) patients expired during the treatment. Whereas 293 (64.40%) patients were discharged with a good GCS (13-15) whereas 79 (17.36%) patients were discharged with moderate GCS (9-12). Remaining 30 (6.59%) patients were discharged against medical advice with poor GCS (<8). Mortality rate in our study was found to be less than mortality reported by authors such as the studies conducted by authors such as Shah B et al[19] and EkehB et al[20].

Conclusion

Intracranial atherosclerotic stenosis (ICAS) is a common cause of ischemic stroke in Indian population. Hypertension and diabetes remain the most important modifiable risk factors for the risk of stroke. Early diagnosis and proper management of these risk factors can reduce the incidence of stroke and its recurrence considerably.

Conflict of interest: None.

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