SREE CHITRA TIRUNAL INSTITUTE FORMEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM, KERALA

PREDICTORS OF LEPTOMENINGEAL COLLATERALS AND CORRELATION WITH OUTCOME IN ACUTE ISCHEMIC STROKE

Thesis submitted in partial fulfilment of the rules and regulations for

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By

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DECLARATION

I, Dr. Sharath Chandra Shetty, hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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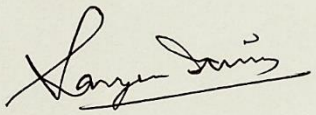

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Dr. Sharath Chandra Shetty

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SYNOPSIS

BACKGROUND AND PURPOSE:

Leptomeningeal arterial collaterals are pre-existing anastomoses that cross-connect distal arterioles of the cerebral arteries. They stabilize cerebral blood flow in case of occlusion or stenosis of primary vessel as seen in acute ischemic stroke. The collateral status determines the volume of ischemic core and the outcome after the recanalization. The magnitude of collateral flow varies from individual to individual. There has been no clear understanding as to what factors determines the collateral flow. The studies in this regard are also sparse.

The purpose of the study was to analyze the factors associated with the collateral status in a cohort of Acute Ischemic Stroke (AIS) patients with large vessel occlusion and to correlate the collateral status with baseline stroke severity and functional outcome at 3 months.

MATERIALS AND METHODS:

All consecutive patients with acute ischemic stroke in the anterior circulation with CT angiogram done within 24 hours of stroke onset were included. The patients with Intracranial ICA, M1 and M2

occlusion were included. The collateral status was assessed based on scoring system by Tan and rLMC (regional leptomeningeal Collateral scoring). The functional outcome was defined as modified Rankin scale at 90 days.

RESULTS:

The study population consisted of 239 patients with 63.5% of males. The mean age was 59.5± 13.5 years. The mean NIHSS was 14.94 ± 5.7. 48% patients underwent mechanical thrombectomy and 27% underwent intravenous thrombolysis. Hypertension was seen in 144 patients (60.2%), dyslipidemia in 124 patients (51.8%), diabetes in 97 patients (40.5%), 57 patients (23.8%) had coronary artery disease and 13 patients had renal dysfunction. Majority of the patients had proximal M1 occlusion (n=146, 61.08%) followed by distal M1 (n=48, 20%) and M2 occlusion (n=29, 12.1%). 189 patients (79%) had clot burden score≥6. An excellent outcome was seen in 133 patients (55.6%). Univariate analysis showed male sex (p-0.034), renal dysfunction (p-0.021) and lower clot burden score (p-0.03) predicted poor collateral status. Multivariate analysis showed significant association of renal dysfunction (p-0.039, CI-0.75-2.62) and lower clot burden score (p-0.007, CI- 0.20-0.77) with poor collateral status. With regard to stroke severity only the poor collateral status (p-0.002, CI-1.62-13.99) was

found to have significant association. Multivariate analysis showed poor collateral status (p-0.014, CI-1.18-4.35) and greater baseline stroke severity (0.0001, CI-2.57-15.99) were associated with the poor functional outcome at 90 days.

CONCLUSION:

Renal dysfunction and lower clot burden score were associated with poor collateral status in patients with acute ischemic stroke. Patients with poor collateral status had greater stroke severity. A greater baseline stroke severity and poor collateral status were associated with poor functional outcome.

INTRODUCTION

Stroke is currently the second leading cause of death worldwide. Ischemic heart disease and stroke together accounted for 15.2 million deaths (15–15.6 million) in 2015(1). Stroke is the commonest cause of chronic adult disability(2). Stroke affects 33 million individuals worldwide each year. Recently the significance of leptomeningeal collateral status in acute ischemic stroke is being recognised with regards to various aspects of acute ischemic stroke including the severity of stroke, volume of infarct(3), efficacy of revascularisation(4) and functional outcome(5).

What are these leptomeningeal collaterals ??

Leptomeningeal arterial collaterals are the cross connecting channels between the distal arterioles of the cerebral arteries. They stabilize cerebral blood flow in case of occlusion or stenosis of primary vessel as seen in acute ischemic stroke. The importance of leptomeningeal collateral status in acute ischemic stroke has been recently recognised. The collateral status determines the stroke severity, volume of infarct, the outcome of revascularisation procedures and the functional outcome.

The question that next arises is that, what determines the collateral status?

There has been limited evidence in the literature in the context of factors affecting the collateral status and it is a rapidly growing and evolving area of clinical and research interest. Further studies are needed in this regard to better delineate the factors affecting collateral status and determining the best management approaches.

The magnitude of collateral flow varies from individual to individual. There has been no clear understanding of as to what determines the collateral flow. The studies in this regard are also sparse. Apart from the genetic and environmental factors, recent studies have shown other factors associated with collateral status.

In this study, we have investigated the factors associated with degree of collateral status in a cohort of Acute Ischemic Stroke (AIS) patients. The demographic, clinical, biochemical, and radiological variables were assessed in relation to the collaterals status.

REVIEW OF LITERATURE

Historical overview

Leptomeningeal arterial collaterals cross-connect the terminal arterioles of the cerebral arteries. The term 'leptomeningeal' is derived from the Greek word leptos meaning thin, with regard to the appearance of the pia mater and arachnoid mater. The leptomenigeal collateral vessels were first described by Thomas Willis in his book "Cerebri Anatome" (1664)(6). Otto Heubner, a German physician first demonstrated their presence in his 1874 work "Die luetische Erkrankung Der Hirnaterien". He injected the major intracranial vessels, in an attempt to establish the interconnections of these vessels and the territories these arteries supply. He found that even after the circle of Willis' anastomoses were blocked off, the whole cerebral arterial tree was filled(7). Later in the 1950s and 60s H.M. Vander Eecken and R.D. Adams described comprehensively the anatomy of the leptomeningeal collateral circulation.(8) The concept of the ischemic penumbra, was defined by Astrup et al in 1981. The blood flow in leptomeningeal vessels is key for its recovery.(9)

The cerebral collateral circulation is the alternate network of vessels which maintain cerebral blood flow when principal conduits fail.

Arterial insufficiency such as hemodynamic compromise, thromboembolism or a combination of these lead to recruitment of collaterals. The collateral circulation is served by extracranial and intracranial vessels. Extracranial contribution is by the facial, middle meningeal and maxillary arteries to the ophthalmic artery and dural arteriolar anastomoses from the occipital artery and middle meningeal artery through the parietal foramen and mastoid foramen. The intracranial component is divided into primary and secondary collaterals. Primary collaterals include arterial segments of circle of willis. Secondary collaterals are constituted by the ophthalmic artery and the leptomeningeal vessels. Primary collaterals are the immediate alternate source of blood supply to ischemic tissue, whereas secondary collaterals take time for enhancing the cerebral blood flow.

The flow of blood through the anterior communicating artery and backward flow in proximal anterior cerebral artery provide the collateral support in the anterior part of the circle of Willis. The posterior communicating arteries forms the collateral support between the anterior and posterior aspects of the cerebral circulation in either directions. The maximum number and greatest size of the anastomotic vessels are between middle and anterior cerebral arteries, with minimal and smaller

connections between middle and posterior cerebral vessels and even much less prominent terminal anastomoses between posterior and anterior cerebral arteries. Moya Moya syndrome represents the classical example of excessive collateralization, recruiting a wide range of deep parenchymal and leptomeningeal and vessels. Collateral vessels are actually formed during the prenatal period, but secondary changes may occur due to the pathophysiological conditions. The collateral recruitment depends on the patency and calibre of primary pathways which are the most immediate to compensate for decreased blood flow and also on the sufficiency and efficiency of secondary collateral routes. The primary collaterals are the immediate source of cerebral blood flow to ischemic brain regions. Secondary collaterals such as leptomeningeal vascular channels require time to open up and perfuse the ischemic zone.

The factors leading to the development and formation of collaterals are not clear, but however decreased blood pressure in downstream vessels is considered an important variable(10). The opening of collaterals is determined by several compensatory metabolic, hemodynamic and neural mechanisms. Angiogenesis stimulates collateral growth and recruitment at the borders of an ischemic region(11). Animal studies

shown that hypertension decreases the rate of development of collaterals, and the resultant anastomoses are also significantly narrower, with poor collateral capacity(12).The collateral circulation determines the infarct volume, which in turn determines the clinical outcome in the setting of anterior circulation stroke due to major artery occlusion(13). Patients with smaller clot extent are much likely to have lower baseline NIHSS scores and smaller baseline infarcts, have smaller final infarct size and achieve a good clinical outcome. Recanalization rates are also higher following intravenous rtPA in patients with smaller clot extent. Collateral status predicts final infarct size but does not independently predict clinical outcome(14). A study by BK Menon et al in 2015 suggest that the baseline computed tomographic angiography collateral status is a robust determinant of final clinical outcome and could be used to select appropriate patients for endovascular therapy(15). Angiographic collateral status also determines the recanalization rate after endovascular revascularization therapy in acute ischemic stroke. The beneficial effects were not observed in patients with poor collaterals when therapeutic revascularization was achieved. Therefore, angiographic collateral grade may help guide decision-making in treatment of acute cerebral ischemia(4). The collateral circulation through retrograde filling allows access of neuroprotective

and thrombolytic agents (extrinsic, intrinsic, or both) to distal aspects of clot. The presence of good collaterals is also critcal for dissolution of fragmented proximal thrombi. A study done in 2014, showed that better collaterals are associated with lower blood sugars, lower blood pressure, smaller baseline infarcts, and greater likelihood of successful revascularization and good clinical outcomes(16).

The influence of comorbidities, risk factors and other clinical variables affecting the collateral status in humans is not clear. Animal studies showed that hypertension decreases the formation of collaterals, and the anastomoses are narrower, with diminished collateral capacity. Also the development of collaterals does not assure their persistence. Factors such as hemodynamic fluctuations influence the persistence and endurance of collaterals. The factors that likely determine the collateral status are duration of ischemia, age and associated comorbidities. Chronic hypoperfusion as in cases of intracranial stenotic disease or extracranial carotid stenosis induces collateral development. However, the relationship of collaterals in relation to cerebral blood flow and the symptomatology remains unclear. The clinical features of carotid occlusive disease depends on multiple variables including degree of luminal stenosis, time course and status of the collateral circulation

which ultimately affect the cerebral perfusion pressure. The collateral circulation also determines the cerebral perfusion pressure in acute ischemic stroke. It is important in maintaining perfusion to penumbral regions. On the other hand, these collateral vessels may also facilitate clearance of the fragmented thrombus from more proximal locations.

Revascularization with restoration of antegrade blood flow is crucial for favorable outcome in patients undergoing revascularization therapy. And collateral status is the strongest predictor for effective therapeutic revascularization. Thus collateral status also predicts the clinical outcome. Retrograde collateral filling may allow access of neuroprotective and thrombolytic agents (intrinsic, extrinsic, or both) to distal aspects of clot. These collaterals are also critical for dissolution of fragmented proximal thrombi. The collateral status influences the degree of ischemic injury over the hypoperfused region and is thus associated with infarct growth(17). It also predicts the risk of haemorrhagic transformation(18), with the poor collateral status being associated with haemorrhagic transformation.

Good collateral status is associated with a greater baseline penumbra, and also maintains penumbra by preventing infarct core expansion until reperfusion occurs(19). The large CTP (CT Perfusion) mismatch ratio is

a pre-requisite for a favourable clinical outcome in patients with a proximal intracranial vessel occlusion, and good collateral status further increase the probability of a favourable outcome. Even without major reperfusion or complete re-canalization, the good collateral status itself improves cerebral perfusion and thus limits infarct core expansion (19). A study by Bijoy K Menon et al, demonstrated that the endovascular treatment in the time window is likely to benefit patients with good and intermediate collateral status compared to patients with poor collaterals(15). Baseline CTA collateral status affects the clinical outcome in acute ischemic stroke(19). Poor baseline CTA collateral status is associated with severe ischemia, large baseline infarcts, and large thrombus burden(20).

The genetic and environmental factors largely determine the variability in leptomeningeal collateral status. Animal studies have shown that genetic factors, aging and endothelial dysfunction are associated with variation in collateral status. The evidence from studies on coronary vascular bed in humans have suggests that cardiovascular risk factors like dyslipidemia, hypertension, hyperglycemia, obesity, aging and smoking may contribute to variability in collateral status. However, with regard to leptomeningeal collateral status, many of these associations

remain unclear, and causative mechanisms are unknown(21). Studies in this regard are also sparse. Metabolic syndrome, hyperuricemia, and aging bear an independent association with leptomeningeal collateral status at baseline in patients with acute ischemic stroke(22).

Higher systolic blood pressure and hypertension at presentation were found to predict poor collateral status at baseline(23), and statin use the good collateral status, in acute ischemic stroke(24).

Patients with metabolic syndrome are hypothesized to have endothelial dysfunction, insulin resistance, decreased circulating adiponectin, and greater expression of plasminogen activator inhibitor-1(25) which negatively influence vascular remodelling and potentially cause microvascular rarefaction and cerebral arteriolar constriction (external and luminal)(26).

It was found that LDL particles directly affect the endothelial and smooth muscle cells(27) and inhibit their migration and proliferation, and HDL would reverse these effects(28). Studies in this context have shown that oxidized LDL inhibits VEGF-induced endothelial cell migration by inhibiting Akt/endothelial NOS pathway. This leads to decreased formation of collateral vessels(29).

Hyperuricemia is associated with cardiovascular risk and heightened arteriolar stiffness which are hypothesized to be due to endothelial dysfunction (30) and vascular smooth muscle cell proliferation. (31). Increasing age results in worsening of the collateral status.(32),11 The age-associated leptomeningeal collateral rarefaction(33) is the hypothesized mechanism for this. Experimental studies suggest that endothelial nitric oxide synthase derived nitric oxide is a critical maintenance factor for collateral vessels, and hence endothelial dysfunction results in rarefaction of collateral vessels. Animal studies suggest that chronic hypertension results in impairment of dilatation of collateral blood vessels(34). Elevated D-dimer levels are also hypothesized to be one of the factors affecting collateral status which potentiate proinflammatory cytokines and cause endothelial dysfunction(35). Nitin Malik et al in 2014, showed that increased age and statin use corresponds to poor collateral score(36). However, this result was contradictory to later studies which showed that pre stroke statin use is associated with associated with better cerebral collateral supply(24). With aging, a ‘‘pruning’’ process occurs in native collaterals that begins as narrowing of vessel diameter and extends retrograde to include distal arterioles(32). Brunner et al, in their study suggested that male gender is associated with poor collateral score (37). A study by

Limo et al, suggested that subjects with greater leptomeningeal collaterals had lower systolic blood pressure at admission and lower prevalence of hypertension. They also found that subjects with good leptomeningeal collateral status had lower prevalence of other cardiovascular risk factors as well, but statistical significance was not achieved with any of them. (23). Romano G et al, based on their study suggested that those with lower blood pressure had best collaterals, whereas persistent hypertension resulted in poor collaterals (38). In the context of blood glucose level it was found that higher blood glucose levels at admission was found to be associated with poor collateral status (39). The mechanism hypothesized for this is that acute hyperglycemia limits collateral status by promoting constriction of leptomeningeal arteries through endothelial dysfunction(40). One of the molecular mechanisms that leads to impaired endothelial function is the dysfunction of the eNOS/NO pathway due to a risk factor associated elevation in reactive oxygen species. Thus, the mitochondrial superoxide overproduction due to diabetes and hyperglycaemia diminishes phosphorylation of the Akt site on eNOS, causing posttranscriptional eNOS inhibition(41). Additionally, high glucose concentration affects endothelial cell architecture and proliferation, and induces delays in phases(42) of endothelial cell cycling. (43)

It was also found that CT angiography collateral status is one of the strong predictors of long-term functional outcome in stroke patients with intracranial large vessel occlusion. Further it was also found that the greater stroke severity (higher NIHSS at presentation) corresponds to poor collateral status(44). Also studies have shown that the greater the time to baseline imaging the poor is the collateral status(45). Further studies also showed that, shorter time to baseline imaging is associated with good collateral status (46).

Ovbiagele et al found that statin use corresponds to better collateral blood flow. (24). The mechanism hypothesized for beneficial effect of statins on collateral status is that

1) Statins increase nitric oxide synthesis with resultant vasodilatation and enhanced flow and

2) And also promote the proliferation, migration, and survival of circulating endothelial progenitor cells thereby augmenting ischemia-induced neovascularization (angiogenesis)(47).

In 2016, Seeters et al suggested that a proximal MCA occlusion, admission glucose level and an incompletely formed ipsilateral posterior circle of Willis predicted poor leptomeningeal collateral status(48).

A recent study in 2019 by Stefania et al, showed that lesser age, non-smoking status, dyslipidemia, no previous statin use and lower serum creatinine predicted favourable collateral status (49). They also suggested that better collaterals were associated with lower stroke severity, lower frequency of cortical signs (except for hemineglect), higher ASPECTS and lower clot burden. Smoking, aging and impaired renal function were hypothesized to reduce collateral extent by either diminishing dilatory capacity of the pial vessels or by causing endothelial dysfunction. Also recent evidence from MRCLEAN registry showed that male sex, older age, high glucose levels, and occlusion of the intracranial internal carotid artery with occlusion of the terminus are associated with poor collateral status in Acute ischemic stroke(50).

AIMS AND OBJECTIVES

1. The main aim of the study is to assess the factors associated with collateral status
2. To assess the association between collateral status and stroke severity and functional outcome

MATERIALS AND METHODS

The study was initiated after obtaining institutional review board approval. The study was retrospective as well as prospective study and we included patients between the time period of 2011 to 2020.

Inclusion Criteria

1) All the patients with acute ischemic stroke involving the anterior circulation with intracranial large vessel occlusion.
2) The CT angiography should be performed within 24hours of symptom onset.
3) The patients with intracranial ICA, M1 and M2 occlusion.

Exclusion criteria

1) Patients with previous stroke
2) Patients with extracranial carotid artery disease

Demographic data, medical history and vascular risk factors (arterial hypertension, diabetes mellitus, dyslipidemia, smoking, coronary artery disease and atrial fibrillation), were noted. We collected pre-stroke modified Rankin scale (mRs) and details of prior medications at the time of stroke. Stroke severity was scored by National Institutes of Health Stroke Scale (NIHSS). Stroke severity was labeled as mild with

NIHSS of 0-5 and moderate and severe as NIHSS of 6-14 and >15 respectively. The blood pressure, blood sugar at admission and biochemical parameters were noted. The etiology of the stroke was classified according to the TOAST classification.

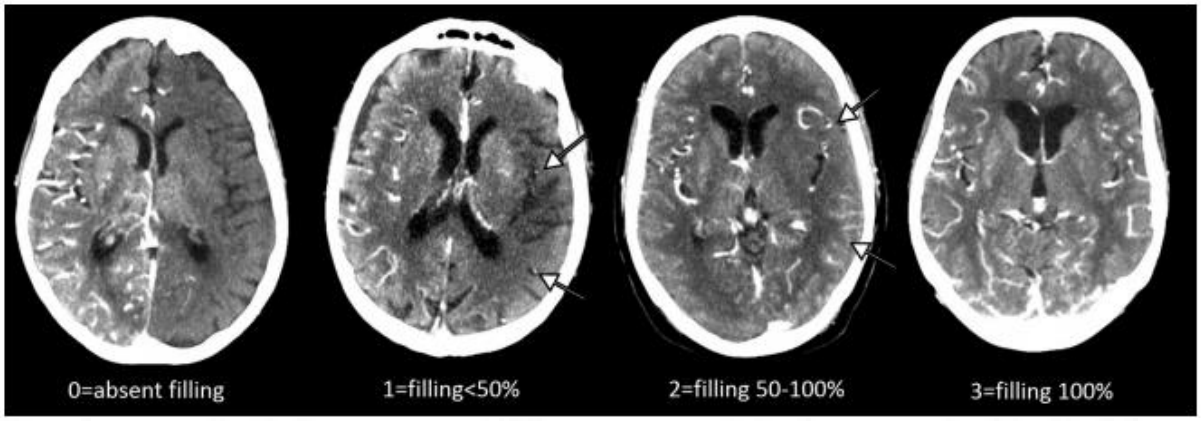
CT-angiography was performed using multidetector scanners. 256-section scanner (brilliance ict Philips, Philips healthcare, Netherlands) used an automated trigger technique for injection of contrast at 5 mL/s for a total of 50 mL with 30 ml normal saline as bolus chase. Scanning was performed from the aortic arch to the vertex. The 256 section scanner used a collimation of 128x 0.625mm, a pitch of 0.993, and a rotation time of 0.5 seconds to acquire the raw data, which was reconstructed at 0.9mm-thick with 50% overlap for axial images. Thinner sections (0.9 mm at 50% overlap) were used to reconstruct axial images of the circle of Willis. Images of the cervical carotid arteries were reconstructed in the sagittal plane at 0.48mm thickness.

The collateral status was assessed based on combined Tan and rLMC (regional leptomeningeal scoring) system. We correlated the collateral status with demographic, clinical and imaging variables. Imaging was read by a Neuroradiologist and the principal investigator. The collateral

status was divided into “good” and “poor” groups based on combined Tan and rLMC scoring.

Tan system of collateral scoring:

The extent of filling of the collaterals in occluded MCA territory on the involved cerebral hemisphere is assessed and graded accordingly.



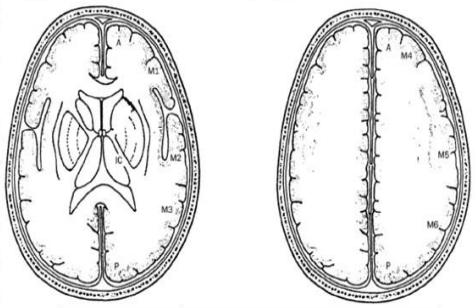
Score 0 indicates no filling of collaterals. Score of 1 indicates collateral supply filling <50% but >0% of the occluded MCA territory. A score of 2 is given for collateral supply filling >50% but <100% of the occluded MCA territory. A score of 3 is given for 100% collateral supply of the occluded MCA territory.

Scores 0 and 1 are considered as poor collateral status and grade 2 and 3 as good collateral status.

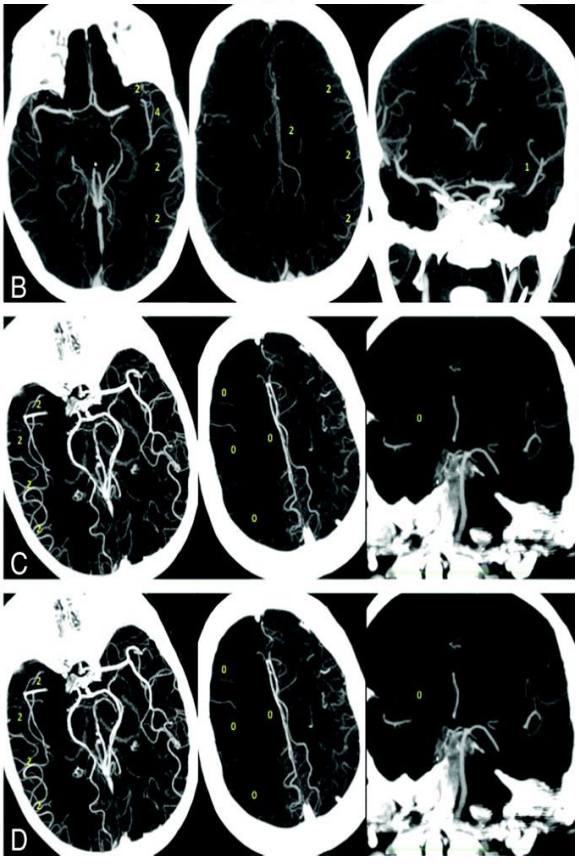
Regional Leptomeningeal collateral score (rLMC score):

In this scoring system, the collateral vessel filling of the affected hemispheric regions is compared with that corresponding regions of the

healthy hemisphere. Score 0 indicates collateral artery is not seen, score 1 indicates artery is less prominent, and score 2 indicates artery is equal or more prominent when compared to the corresponding region in the contralateral hemisphere. The regions where this collateral filling is assessed include all the 6 regions of the ASPECTS system(M1-M6), basal ganglia, sylvian sulcus and ACA territory region. All the regions will be scored from 0-2. Except for in case of Sylvian sulcus, where scoring was done as 0 for artery not seen, 2 for artery less prominent, and 4 for artery equal or more prominent, when compared to opposite hemisphere.



Regions	Score 0 occlusion (0 – artery not seen, 1- less prominent, 2- equal or more prominent when compared to a matching region in the opposite hemisphere)
M1	
Sylvian Sulcus	
M2	
M3	
M4	
M5	
M6	
ACA	
Basal Ganglia	
rLMC score	____/20



The extent of the thrombus in the intracranial vasculature was quantified using Clot burden score.

Clot burden score is used to determine the extent of the clot. It is a 10-point score in which one or two points are deducted depending on location of clot in the intracranial anterior circulation vasculature. The scoring is given as, infraclinoidal internal carotid artery (ICA; 1 point), supraclinoidal ICA (2 points), proximal M1 middle cerebral artery (MCA; 2 points), distal M1 MCA (2 points), M2 MCA branch (1 point for each branch), and anterior cerebral artery (ACA; 1 point).

Clinical outcome was measured at 3 months with the Modified Rankin Scale (mRs) either in person at the outpatient stroke clinic, or by standardized telephone interview. Those with mRS≤2 were defined as having good functional outcome and with mRS≥3 as poor functional outcome.

STATISTICAL METHODS

The data was entered in Microsoft Excel and analysed using Intercooled STATA 14.1 software package (Stata Corp, Texas, USA). Categorical variables were described in proportions and numerical variables were analysed using mean and Standard Deviation. The outcomes analysed in this study were collateral status, stroke severity and the functional outcome at 3 months. The collateral status was defined as good and poor based on combined Tan and rLMC scoring systems. The good collateral status in Tan system and the intermediate and good collateral status in rLMC system were together categorised as good collateral status. The stroke severity was defined as mild with NIHSS of 0-5, moderate with NIHSS of 6-14 and severe as NIHHS > 15. Overall, the stroke severity was categorised as two groups with mild stroke as one group and the moderate and severe stroke as another group. The functional outcome at 3 months was defined as poor with mRS of ≥3 and good with mRS ≤ 2 at 3 months. We then analysed the correlation between demographic, clinical, metabolic and radiological factors with the outcomes. The Pearson Chi-square test was used to test the association between the above mentioned factors and outcome variables. Binary logistic regression was used to estimate the odds ratios and 95% confidence

Intervals. The variables found to be significant in bivariate analysis were taken for multivariate analysis.

RESULTS

The study included patients admitted in comprehensive stroke care unit, SCTIMST within 24hours of onset of ischemic stroke during a nine year time period (2011-2020). The patients having intracranial large vessel occlusion (intracranial ICA, M1 and M2) presenting within 24 hours were included in the study. 239 patients fulfilled the inclusion criteria and were included in the study**.**

1. COHORT CHARACTERISTICS

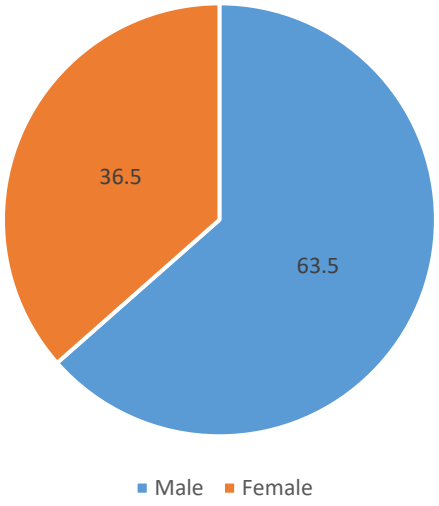
1.1 Mean age-

- Mean age of the patients admitted was 59.5± 13.5 years

1.2 Gender Distribution

There were 152(63.5%) males and 87(36.5%) females. (Figure 1)

Figure 1 : Gender distribution of patients



1.3 Risk factors

The various risk factors are summarized in Table 1. Hypertension was present in 144 patients, 97 patients were diabetic and dyslipidemia was present in 124 patients. 57 patients had coronary artery disease. 74 patients were smokers and 13 patients were found to have renal dysfunction.

Table 1. Risk Factor profile

Risk Factors	**N(%)**
Hypertension	144(60.2%)
Diabetes mellitus	97 (40.5%)
Dyslipidemia	124 (51.8%)
Smoking	74 (30.9%)
Coronary artery disease	57 (23.8%)
Valvular heart disease	36 (15%)
Renal dysfunction	13 (5.4%)

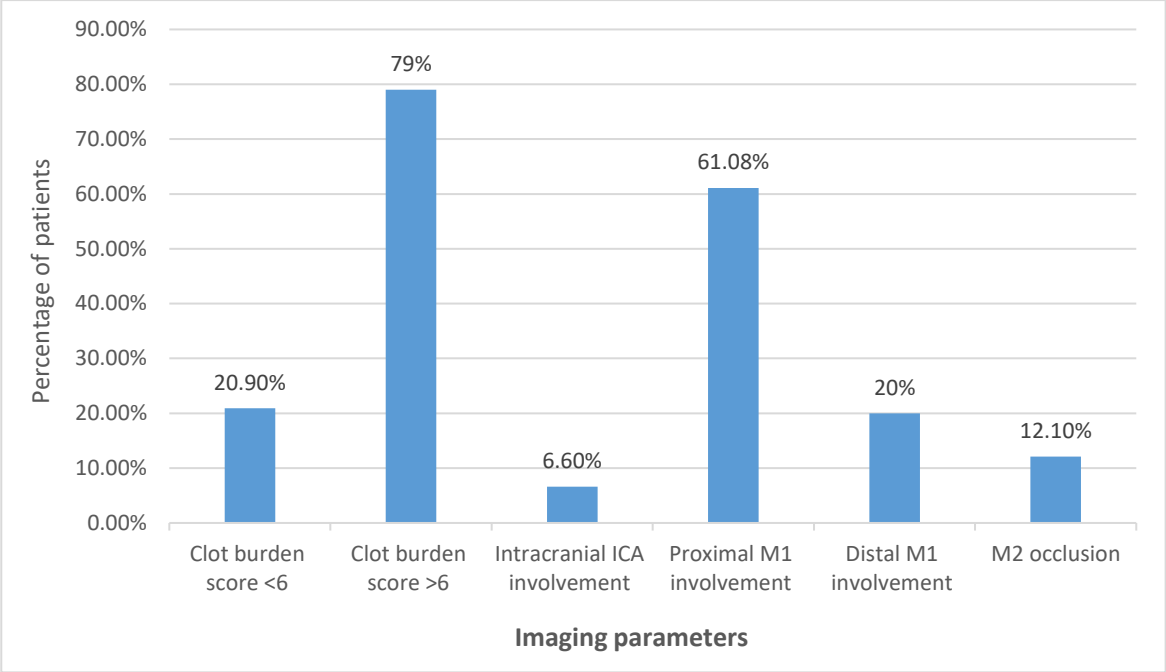
128 patients had high blood pressure at admission. 127 patients were above the age of 60 years. Haemorrhagic transformation was seen in 56

patients. 14 patients had mild stroke, 95 had moderate and 130 had severe stroke.

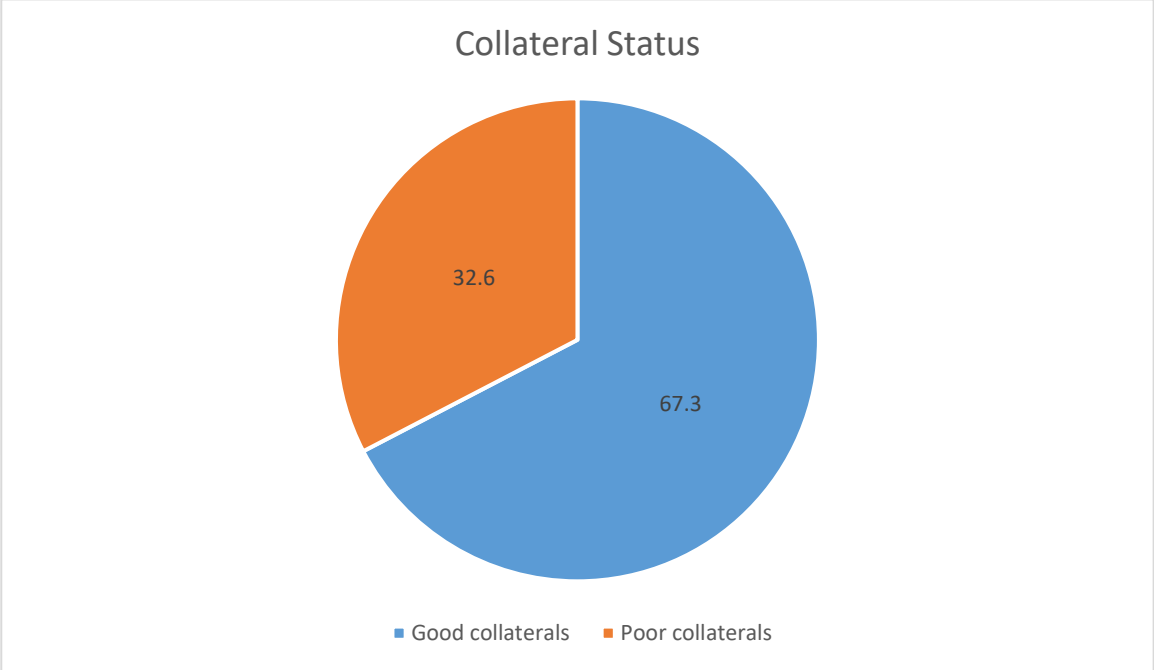
49 patients were on antiplatelet therapy, 31 patients on anticoagulation and 47 on statins prior to stroke onset.

Table 2. Imaging profile

Imaging parameter	**N(%)**
Clot burden score <6	50 (20.9%)
>=6	189 (79%)
Intracranial ICA involvement	16 (6.6%)
Proximal M1 involvement	146 (61.08%)
Distal MCA-M1	48 (20%)
MCA - M2 occlusion	29 (12.1%)



67.3% (n=161) patients had good collaterals and 32.6%(n=78) had poor collaterals.



115 patients underwent mechanical thrombectomy and 25 patients underwent bridging thrombolysis.

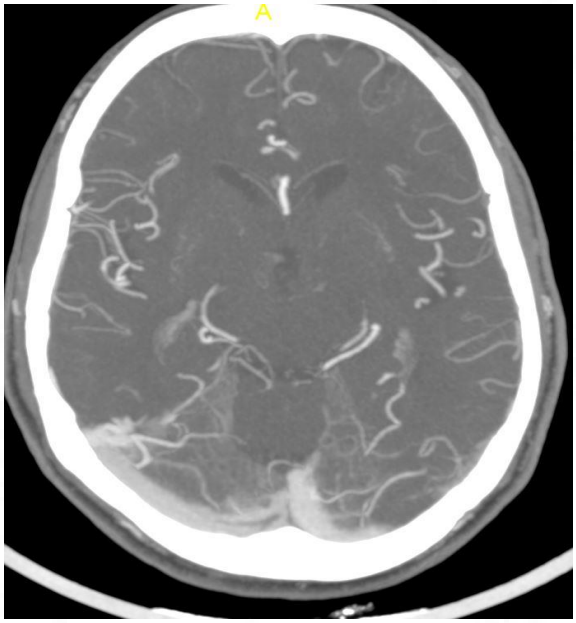
Table 3. Factors associated with collateral status

Variable	**Good collaterals n(%)**	**Poor collaterals n(%)**	**p-value**
Age 18-59yrs	71	37	
>60yrs	90	41	0.67
Sex Male	95	57	
Female	66	21	**0.034**
Hypertension	98	46	0.779
Diabetes mellitus	66	31	0.854
Smoking	44	30	0.08
Coronary artery disease	36	21	0.438
Valvular heart disease	29	7	0.067
Antiplatelet use	37	12	0.173
Anticoagulant use	21	10	0.948
Prior statin use	33	14	0.626

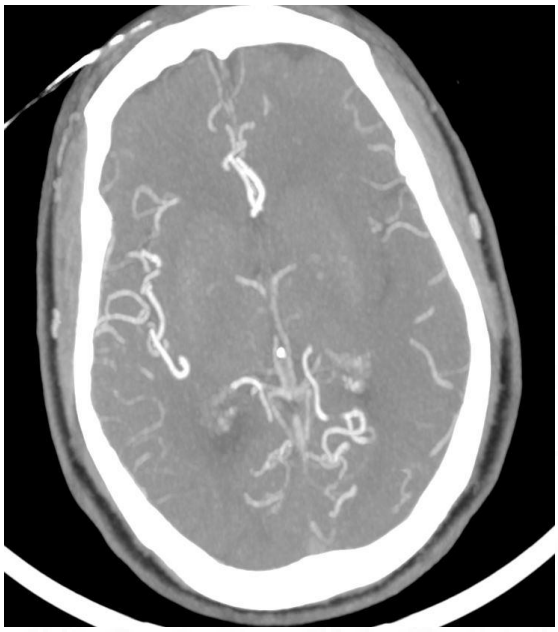
Variable	**Good collaterals n(%)**	**Poor collaterals n(%)**	**p-value**
Dyslipidemia	81	43	0.485
Renal dysfunction	5	8	**0.021**
Clot burden score≥6	136	53	**0.03**
Intracranial ICA involvement	8	8	0.125
Proximal MCA	95	49	0.572
Distal MCA	36	12	0.207
M2 occlusion	22	7	0.298

Of the 152 males, 95 had good collaterals and of the 87 females, 66 had good collaterals, suggesting a good collateral status in females (p-0.034). Renal dysfunction is associated with poor collateral status (p-0.021) and greater clot burden score (≥6) is associated with good collateral (p-0.03).

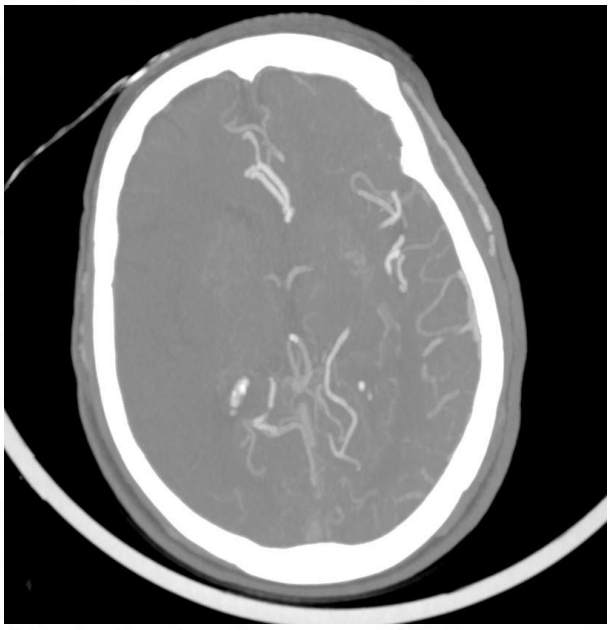
Overall, on bivariate analysis, male sex, lower clot burden score and renal dysfunction were found be associated with poor collaterals. No other factors were found to be associated with the collateral status.



60year old male with right hemiparesis, with left MCA-proximal M1 occlusion with CT Angiography showing good collateral status



55year old woman with right hemiparesis and aphasia, with left proximal M1 occlusion and CT angiography showing intermediate collateral status



63year old man with left hemiparesis, with right MCA proximal M1 occlusion and CT angiography showing poor collateral status

Table 4. Factors affecting stroke severity

Factor	Mild stroke (NIHSS 1-5)	Moderate and Severe (NIHSS >5)	p-value	Odds ratio	Confidence interval
Age 18-59	18	90			
>60	19	112	0.645	1.17	0.58-2.3
Sex Female	11	76			
Male	26	126	0.359	0.70	0.32-1.5
Hypertension	23	121	0.796	0.90	0.44-1.87
Dyslipidemia	15	109	0.133	0.58	0.28-1.18
Diabetes mellitus	18	79	0.277	1.4	0.72-2.98
Antiplatelet use	6	43	0.482	0.71	0.28-1.82

Factor	Mild stroke (NIHSS 1-5)	Moderate and Severe (NIHSS >5)	p-value	Odds ratio	Confidence interval
Good collaterals	33	128			
Poor collaterals	4	74	**0.002**	4.7	1.62-13.99
High BP at admission	19	92	0.515	1.26	0.62-2.54

Of all the various risk factors, clinical factors and imaging variables, only the collateral status was found to be associated with stroke severity, with poor collateral status being associated with greater stroke severity. Of the 78 patients with poor collateral status, 74 had moderate to severe stroke.

Table 5. Factors affecting functional outcome at 3 months

Factor		mRS ≤ 2	mRS ≥ 3	p-Value	Odds ratio	Confidence interval
Age	18-59	55	52			
	≥60	46	81	**0.02**	**1.86**	**1.10-3.14**
Sex	Female	43	42			
	Male	58	91	0.08	1.60	0.93-2.75
Hypertension		54	87	0.064	1.64	0.96-2.79
Diabetes mellitus		39	56	0.59	0.86	0.51-1.46
Dyslipidemia		55	65	0.397	1.25	0.74-2.10
Coronary Artery Disease		18	37	0.074	1.77	0.94-3.35
Valvular heart disease		18	16	0.213	1.58	0.76-3.29
Renal dysfunction		2	11	**0.036**	**4.5**	**1.00-20.77**
Collateral status						
	Good	81	76			
	Poor	20	57	**0.0001**	**3.03**	**1.67-5.52**

Factor	mRS ≤ 2	mRS ≥ 3	p-Value	Odds ratio	Confidence interval
Antiplatelet therapy	19	29	0.574	0.83	0.43-1.58
Prior statin use	21	25	0.725	1.12	0.58-2.14
Anticoagulation	13	16	0.864	1.07	0.48-2.34
High BP at admission	47	79	**0.051**	**1.68**	**0.99-2.83**
Stroke severity					
Mild	30	7			
Moderate and severe	71	126	**0.0001**	**7.6**	**3.17-18.20**

On bivariate analysis, age(>60years), collateral status, high blood pressure at admission, renal dysfunction and greater stroke severity were found to be significantly associated with functional outcome at 3 months. Of the 127 patients with age more than 60years, 81 patients had poor functional outcome at 3 months (p-0.02). Of 13 patients with renal dysfunction, 11 had poor functional outcome (p-0.036). After the bivariate analysis, further multivariate logistic regression analysis was

done to rule out confounding variable and to assess independent association of the variables.

Logistic regression analysis of the factors associated with collateral status showed that renal dysfunction and lower clot burden score were associated with poor collateral status.

Table 6. Logistic regression analysis of the factors associated with collateral status

Factors	**Odds ratio**	**P-value**	**Confidence interval**
Sex	1.4	0.288	0.75-2.62
Renal dysfunction	3.6	**0.039**	1.06-12.22
Clot Burden Score	0.39	**0.007**	0.20-0.77

Logistic regression analysis was not done in case of factors associated with stroke severity as collateral status is the only factor found to be associated with stroke severity in bivariate analysis.

Logistic regression analysis of the factors associated with functional outcome at 3 months showed that collateral status and stroke severity are associated with functional outcome. Poor collateral status and

greater stroke severity were associated poor functional outcome at 3 months.

Table 7. Logistic regression analysis of the factors associated with functional outcome

Factors	Odds ratio	P-value	95% Confidence interval
Sex(Male)	1.41	0.27	0.76 - 2.62
Age (60-88yrs)	1.80	0.57	0.981- 3.33
Hypertension	1.34	0.372	0.70 – 2.54
Coronary Artery Disease (CAD)	1.49	0.261	0.74 – 3.02
Renal dysfunction	2.60	0.24	0.52- 12.90
Collaterals status	2.27	**0.014**	1.18-4.35
Stroke severity	6.42	**0.0001**	2.57-15.99
High BP at admission	1.31	0.376	0.71-2.43

DISCUSSION

In this retrospective study of collaterals in patients with Acute Ischemic Stroke, we found that favourable collateral patterns could be predicted by greater clot burden score and lower serum creatinine levels. We also found that good collateral status was associated with lower baseline stroke severity and better functional outcome at 3 months. Studies till now have shown age as a predictor of collateral status, with the younger age being associated with good collateral status(22). It has been proposed that aging causes ‘collateral rarefaction’(32), a process which reduces the collateral density and diameter, probably secondary to prolonged endothelial dysfunction. However, we didn’t find any association of collateral status with the age.

In our study, no vascular risk factor was found to be associated with collateral status. But previous studies showed association between vascular risk factors and collateral status as mentioned below.

TUDY AND YEAR	RESULT
Ovbiagele B et al (2007)	Prior Statin use has been associated with good collaterals(24).
Menon BK et al (2013)	Metabolic syndrome, age and elevated uric acid levels predicted poor leptomeningeal collateral status in patients with acute ischemic stroke(22).
Malik N et al (2014)	Older age and prior statin use predicted poor collaterals(36).
MR CLEAN trial, Eveline J.A et al,(2020)	Older age, male sex, high blood glucose levels, and occlusion of the intracranial internal carotid artery with occlusion of the terminus are associated with poor collateral status in Acute ischemic stroke(50)
Stefania Nannoni (2019)	Younger age, non-smoking status, dyslipidemia and lower serum creatinine predicted better collaterals in patients with acute ischemic stroke and proximal MCA occlusion(49).

So the evidence till now is not clear pertaining to the predictors of collateral status. And a few studies are contradictory to each other especially with regard to the association of collateral status with dyslipidemia and prior statin use.

Ovbiagele et al in 2007, showed that statin use is associated with good collateral status(24), whereas Malik N et al, in 2014 showed that prior statin is associated with poor collateral status(36). Menon BK et al, in 2013, suggested that presence of dyslipidemia is associated with poor collateral status(22) whereas, Nannoni et al in 2019, showed that dyslipidemia predicted good collateral status(49).

The association of renal dysfunction with leptomeningeal collateral status has been demonstrated by only single study till now. This was the study done by Nannoni et al in 2019, where they demonstrated that renal dysfunction predicted poor collateral status(49). In our study we also found the same association of renal dysfunction with the collateral status. The exact mechanism of how renal dysfunction affects the collateral status is not known till now.

However, studies have shown the association of renal dysfunction with poor collateral status in coronary circulation. They hypothesized that

renal dysfunction causes endothelial dysfunction, which leads to decreased angiogenesis and subsequent poor collateral formation(51).

The effect of cardiovascular risk factors on collateral status have been studied mainly in relation to coronary collateral status. Only a limited data is available with regard to effect of cardiovascular risk factors on leptomeningeal collateral status. The evidence for mechanisms of effect of cardiovascular risk factors on collateral status has been mainly from animal studies. Evidence from animal studies on diabetes and collateral status suggest that diabetes leads to impaired collateral in response to arterial obstruction, and also diabetic animals exhibit altered biology of cellular function that could contribute to this defect.

Controversy also exists with regard to effect of statins on collateral status. Ovbiagele et al found that statin use corresponds to better collateral blood flow(24). Whereas study by Malik et al, suggests that prior statin use predicted poor collateral status, the hypothesis being reduced levels of VEGF due to statins and subsequent impairment of collateral formation(36).

A recent evidence from MR CLEAN registry showed that older age, male sex, high blood glucose levels, and intracranial internal carotid artery with occlusion of the terminus occlusions are associated with

poor computed tomography angiography collateral status in patients with acute ischemic stroke(50). Our study also didn't find any correlation between the cardiovascular risk factors and the degree of collateral status.

Our study didn't show any correlation between the statin use, cardiovascular risk factors and degree of collateral status. Overall the evidence in the context of association between risk factors and collateral status is not clear and a few studies are contradictory to each other. Hence further studies are required in this context to establish a proper correlation.

Another variable found to be associated with collateral status our study is the clot burden score. The higher clot burden score is associated with better collateral status and lower score corresponds to poor collateral status. The same association has been described by Nannoni et al in their study. Higher clot burden in the vessel may obstruct more orifices of arteries that could provide collateral flow. Inversely, we can hypothesize that poor collateral status may lead to clot extension, because patients with poor collaterals may have increased stasis around the clot and thus leads to clot extension(52).

In our study, we didn't find any correlation between the location of the thrombus and the collateral status. Previous studies however didn't focus on this correlation. A recent evidence from the MR CLEAN registry found that intracranial ICA with occlusion of the terminus occlusions were associated with poor collateral status.

No association of collateral status was found with coronary artery disease, valvular heart disease, prior antiplatelet use and anticoagulation use.

We also found that poor collateral status is associated with greater stroke severity and poor functional outcome at 3 months. This finding was consistent with the previous studies (53). A study by Bijoy K Menon et al, demonstrated that the endovascular treatment in the time window is likely to benefit patients with good and intermediate collateral status compared to patients with poor collaterals(15). Baseline CTA collateral status affects the clinical outcome in acute ischemic stroke(19), with poor collaterals associated with poor clinical outcome. Poor baseline CTA collateral status is associated with severe ischemia, large baseline infarcts and greater stroke severity, and large thrombus burden(20). Abundant collateral circulation predicted better clinical status and smaller volumes of infarct in acute ischemic stroke(54).

Strengths of the study:

1) Collateral status data was reviewed by a trained neuroradiologist who was blinded to the clinical diagnosis of the patient.
2) Two collateral scoring systems are used for grading of collateral status and the final classification of poor and good collateral status was done.
3) Association of variables like coronary artery disease, antiplatelet and anticoagulants with collateral status was addressed, which was not addressed in any previous studies.

Limitations:

1) Retrospective design of the study
2) The sample size is relatively small
3) CT angiography was used for collateral assessment which may be less precise than digital subtraction angiography

CONCLUSIONS

Our study showed that renal dysfunction and lower clot burden score were associated with poor collateral status in acute ischemic stroke. And the greater stroke severity is associated with poor collaterals. Also greater stroke severity and poor collaterals were associated with poor functional outcome. Our data didn't show any association of collaterals with vascular risk factors except for renal dysfunction which could explain wide range variability of collateral grades in acute ischemic stroke..

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Proforma

1.1. Patient study number: ----------

1.2. Age ---------- years

1.3 Sex ---------- 1. Male 2. Female

1.4. Date of admission. ----------

1.5. Date of symptom onset----------

1.6 Phone No: ----------

2. Risk factors (1=yes, 2=No)

2.1. Hypertension---------- Duration in years ----------

2.2. Diabetes mellitus---------- Duration in years ---------

2.3. Current smoking---------- pack years ----------

2.4. Ex-smoker……Stopped ----------years back

2.5. Drug addiction ----------

2.6. Alcoholism----------

2.7. Coronary artery disease-------- Duration in years ----------

2.8. Valvular heart disease--------- Duration in years ----------

2.9. Congestive heart failure ---------- Duration in years ----------

2.10. Peripheral vascular disease-------

2.11. Hyperlipidaemia---------- Duration in years----------

2.12. Atrial fibrillation---------- Duration in years----------

2.13. Patients on treatment ----------

. If yes, Type of treatment ----------

2.14. Renal dysfunction

3. Previous statin use 1. Yes 2. No

3.1Current statin use 1. Yes 2. No

If Yes- Details of the statin use –type of statin and dose

4. Symptoms(1=yes, 2=No)

4.1. Visual disturbances ----------1. Amaurosis fugax 3. Hemianopia 4. Diplopia 5. Blurring of vision 6. None

4.2. Weakness ---------- 1. Face alone 2.arm 3.leg 4.arm and leg 5. Face arm and leg 6. None

4.3. Numbness/paresthesia ----------

4.4. Speech disturbances ----------1. Aphasia 2. Dysarthria3. Both 4. None

4.5. Vertigo----------

4.6. Ataxia----------

4.7. Confusion---------- 3.7.a. Loss of consciousness ----------

4.8. Headache ----------3.8.a. Neck pain ----------

4.9. Seizures ----------

5. Clinical Examination (1=yes, 2=No)

5.1. Pulse rate---------- (If Regular =1, Atrial fibrillation =2)

5.2. Blood pressure at ER Systolic---------- diastolic --------- (first documented BP)

5.3. Bruit ----------

5.4. Weakness ----------

5.5. Numbness----------

5.6. Cerebellar signs----------

5.7. Aphasia----------

5.8. Dysarthria ----------

5.9. Hemianopia----------

5.9a. Central retinal artery occlusion----------

5.9.1. Hemispatial neglect ----------

5.9.2. Final impression----------

1. Right hemispheric 2. Left hemispheric 3.Posterior circulation4.undetermined

5.9.3 NIHSS at admission ----------

5.9.4. GCS on admission ----------

5.9.5. MRS prior to stroke ----------

5.9.5a. mRS at stroke onset----------

5.9.5b. mRS at discharge----------

6. Investigations

6.1. Blood glucose in ER----------

6.2. Serum cholesterol----------

6.3. LDL--------

6.4. HDL----------

6.5. Serum triglycerides----------

6.6. ECG---------- 1. Normal 2.LVH 3.AF 4 Ischemic changes 4. Not done

Serum creatinine

GFR

6.7. Echo-trans thoracic ---------- 1. Normal 2.LV dysfunction 3. Mural thrombus 4. Valve disease 5.PFO 6. Infective endocarditis 7.Not done.

6.7a. If valve disease, specify ----------

6.8. Blood urea----------

6.9. Serum creatinine----------

6.9.1. eGFR----------

6.9.2 HBA1C----------

7.Diagnostic imaging

7.1. Onset to CT scan time

7.2 CT scan ---------- 1. Normal.2. New infarct 3. Old infarct 4. Small vessel

Ischaemic changes

CT ASPECTS at admission ---------- 5. Not done

If small vessel ischemic changes ----grade ----------

7.3. CT angio Extracranial ---------- 1. Normal 2. abnormal 3.not done

7.3.1. If abnormal, specify ----------

7.3.2. CT angio intracranial ----------1. Normal 2. abnormal 3.not done

7.3.3. If abnormal, specify----------1. Intracranial ICA 2.MCA-proximal/mid/distal

7.3.4 Clot burden score ----------

7.3.5. Collateral status----------

Collateral grading based on TAN system.

- **0**=No collateral supply to the occluded MCA territory.
- **1**=Collateral supply filling **≤50%** of the occluded MCA territory.
- **2**=Collateral supply filling **>50%** but **<100%**
- **3**= **100%** collateral supply
- scores of **0–1** are considered as **poor** and **2–3** as **good** collateral status

1.Poor 2. Good

Do you want to add one more grading system?

24hour follow-up CT ASPECTS

Haemorrhagic transformation of infarct at 24 hours ---------- yes . No

If yes ----------HI1 HI2 PH1 PH2

7.3.6 MRI scan ---------- 1. DWI negative 2. DWI positive single lesion 3. DWI Multiple lesions 4. Not done

7.3.7. Arterial territory of acute infarct---------- 1.ICA 2.ACA 3.MCA-complete 4. MCA-Inf div 5. MCA sup div 6. MCA subcortical

If small vessel ischemic changes grade ----------

7.3.8 Stroke subtype----------1. large artery atherosclerosis 2. Cardioembolic.3Other Specific causes.4. Undetermined 5. lacunar

8. **Thrombolysis**

8.1. If thrombolysed----------1. Yes 2. No

8.2. If yes ----------1. intravenous 2. Mechanical 3.Bridging

NIHSS at discharge ----------

Mrs at discharge ----------

8. 3 Month outcome

NIHSS at 3 months ----------

mRS at 3 months ----------

If died, date ----------

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1490 /NOVEMBER-2019 06.12.2019

Dr. Sharath Chandra Shetty
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Sharath Chandra Shetty,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "FACTORS PREDICTING LEPTOMENINGEAL COLLATERAL STATUS IN PATIENTS WITH ACUTE ISCHEMIC STROKE (IEC/1490)" on 5th November, 2019.

The following documents were reviewed:

Original submission

1. Covering Letter addressed to the Chairperson, IEC, SCTIMST date 25.09.2019 with checklist
2. TAC Approval Letter
3. IEC Application Form
4. Forwarding Letter from the HOD
5. Project Proposal
6. Proforma
7. CV of Principal Investigator and Co-Principal Investigators

Revised submission

1. Covering Letter addressed to the Chairperson, IEC, SCTIMST with checklist
2. TAC Approval Letter
3. IEC Application Form
4. Forwarding Letter from the HOD
5. Project Proposal
6. Proforma
7. CV of Principal Investigator and Co-Principal Investigators

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