SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM, KERALA

PREDICTORS OF HEMORRHAGIC TRANSFORMATION IN ACUTE ISCHEMIC STROKE AND ITS OUTCOME

Dissertation submitted in partial fulfillment of the rules and regulations for

Post-Doctoral Fellowship in Stroke

By

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DECLARATION

I, Dr Manju Surendran hereby declare that this project was undertaken by me under the supervision of Dr Sylaja P N, Professor and HOD, In-charge Comprehensive Care Centre for Stroke, Department of Neurology, Sree Chithra Tirunal Institute of Medical Science and Technology.

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DECLARATION

The candidate, Dr Manju Surendran has completed the minimum required project for completion of Post Doctoral Fellowship in Stroke

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Introduction:

Intravenous alteplase improves outcome in selected patients with acute ischemic stroke when given within 4.5 hours from onset.(1) Despite its efficacy, the use of alteplase is limited by the risk of hemorrhagic complications, particularly symptomatic intracranial hemorrhage (sICH). The risk of sICH varies based on the patient population and the definition of sICH used .A number of definitions of sICH have been used for use in clinical trials of thrombolytic therapy(1–6).The ECASS (European Cooperative Acute Stroke Study) II definition have the highest interrater agreement.(2) The incidence of sICH after alteplase varies from 2% to 7% in clinical trials and prospective stroke registries.(7)

A number of clinical, laboratory, and radiographic factors are associated with the risk of sICH post thrombolysis. In a systematic review and meta-analysis of 55 studies, older age, greater stroke severity, higher baseline glucose, hypertension, congestive heart failure, renal impairment, diabetes mellitus, ischemic heart disease, atrial fibrillation, baseline antiplatelet use, leukoaraiosis, and visible acute infarction on brain imaging were all associated with increased risk of sICH post thrombolysis but current smoking was associated with a reduced risk. (8)Statin use was also associated with sICH in this meta-analysis based on a small number of subjects but this observation was not confirmed in the subsequent studies.(9) Time from symptom onset to alteplase was not associated with sICH risk in this meta-analysis, but it was observed in other studies.(10). Unfavourable vessel anatomy and multiple passes can increase the risk of hemorrhagic transformation. Microhemorrhages on pretreatment magnetic resonance imaging have also been associated with an increased risk of sICH after alteplase.(11) Many factors associated with sICH are dependant on one another and this limits the assessment of the independent additive risk of each factor. Atrial fibrillation, warfarin use independent of the prothrombin time, age, and clinical stroke severity have been found to increase risk of sICH.(12)

Many scoring systems have been developed integrating multiple factors to better predict risk of sICH post thrombolysis in acute ischemic stroke patients. At least 7 such risk prediction scores have been proposed. They are Multi centre Stroke Survey(MSS)(6),Hemorrhage after Thrombolysis(HAT)(13),SEDAN[15] ,Safe implementation of thrombolysis in stroke (SITS-ICH)(14),GRASPS- GWTG(Get with the guidelines) (6),Totaled health risk in vascular events(THRIVE)(15)and stroke prognostication using age and NIH stroke scale(SPAN)(16). Validation studies in different populations of alteplase-treated patients have shown similar

predictive values for the various scores.(17,18) Risk scores helps in prognosticating patients as well as it can select patients that requires more intensive monitoring. The outcome of these patients depends on the type of hemorrhagic transformation. HI1 and HI2 subtype may not be even symptomatic while in PH2 subtype the mortality can be upto 50%.

It has been observed that there is a difference in the risk of hemorrhagic transformation post thrombolysis in Asian and non-asian population. Prior studies have identified higher risk of intracranial haemorrhage in Asian patients with acute ischaemic stroke treated with intra venous recombinant tissue plasminogen activator.(6) The mechanism is not fully understood however the racial differences in presence of intracranial atherosclerotic diseases and blood coagulation–fibrinolysis factors may play a role. Currently there is no data on the predictors of Haemorrhagic transformation post thrombolysis from the Indian population. The current study aims to assess the factors that predict symptomatic intracerebral hemorrhage in acute ischemic stroke patients post IV thrombolysis and also the predictors of outcome in such patients.

Methodology:

The study was a Hospital based Retrospective Cohort study. All patients with acute ischemic stroke of age more than 18 years who were admitted in the Stroke unit of Sree Chitra Tirunal Institute for Medical Sciences and Technology, who underwent IV thrombolysis were included in the study. Those patients without follow up CT and who had a premorbid mRS >=3 were excluded. The clinical and demographic data were collected. The risk factors like diabetes, hypertension, coronary artery disease, chronic kidney disease and previous stroke were noted. The medication history including antiplatelets, statins and anticoagulants were collected. The blood sugar and the blood pressure at admission was documented. Stroke severity at the onset was assessed by NIHSS Score and was documented. Base line CT was reviewed to assess the early ischemic changes and ASPECTS was documented. Vascular imaging was reviewed to document the location of the clot. The collateral status was graded as good, intermediate and poor. The lab variables were obtained from the blood sample collected at the time of admission. The aetiology of stroke was classified as per TOAST classification . Follow up imaging done at 24 hours was reviewed. Hemorrhagic transformation was graded as HI1, HI2, PH1 and PH2 as per ECASS classification. Any worsening of the NIHSS was noted and the repeat imaging taken at that time was reviewed. The functional outcome was assessed by modified Rankin scale (mRS). The mRS at discharge and at 3 month follow up was documented. A mRS 0-2 was taken as good outcome and more than 2 was taken as poor outcome. The primary endpoint was mRS at 3months.

Statistical analysis:

Normally distributed variables will be compared using independent samples t test and non-normally distributed variables will be compared using Mann-Whitney U test. Categorical variables will be expressed as composition ratio or rate and comparisons would be performed using Pearson X2 or Fishers exact test. Logistic stepwise regression will be done to identify factors associated with functional outcome and haemorrhagic transformation. The factors which were found significant were also adjusted using a multivariate regression model. Statistical analysis will be done using STATA software and P value<0.05 will be considered statistically significant.

Results:

A total of 348 consecutive acute ischemic stroke patients who underwent IV thrombolysis were included in the study. The mean age of the study cohort was 62 years (SD-12.6) with a male predominance 72.1 % (249/348). More than sixty percent of the patients were hypertensive (212/348), 60.9% of them being diabetic (170/348) and dyslipidemia was noticed in 17.5 % of patients (61/348). Among the study subjects, 18.1 % (63/348) were smokers and 13.2 % (46/348) were alcoholics. Close to one-fourth of the study cohort had coronary artery disease (82/348), 8.5% (28/348) had valvular heart disease, 15% (52/348) had history of prior stroke. Twenty-nine percent of the patients (100/348) had prior antiplatelet of whom 9% (33) were on dual antiplatelet therapy and 4% (13/348) were on anticoagulants. The median door to needle time was 33 minutes(range:13 minutes -120 minutes). Of the study subjects, 65(18.6 %) had hemorrhagic transformation of the infarct, out of which 25(7.1 %) had parenchymal hematoma. HI 1 was seen in 23 patients (6.6%), HI 2 in 17 (4.9%), PH1 in 10 (2.9%) and PH2 in 15(4%). The most common aetiology was undetermined (41.1%) followed by cardioembolism (25.4%) and large vessel atherosclerosis (16.6%). Sixteen percent of the patients underwent mechanical thrombectomy. Good outcomes were observed in 44% of the patients at discharge and 67% (215/348) at 3 month follow up. Thirteen patients (4%) died within 3 months of occurrence of stroke.

The baseline characteristics and functional outcome stratified by hemorrhagic transformation, sICH and mRS at discharge has been shown in the table 1,4 and 7. Hemorrhagic Transformation was significantly more common among patients with ischemic disease (p-0.03), , prior antiplatelet (p-0.005) especially dual antiplatelet and statin use (p-0.023). Patients with hemorrhagic transformation had more severe stroke ($p<0.05$) and hyperglycemia (p-0.01) on admission They also had higher mean creatinine (p-0.01) and poor aspects in admission CT (p-0.006). Poor outcome at discharge and 3 months were also more in the hemorrhagic transformation group ($p<0.05$). On Multivariate analysis as shown in Table 2 , there were higher odds of occurance of ischemic heart disease, prior antiplatelet and statin use, severe strokes, poorly controlled diabetes with admission blood sugar>180mg/dl, poor CT-ASPECTS, large vessel occlusion, mechanical thrombectomy and cardio-embolic etiology among patients with hemorrhagic transformation. On Multivariate regression modelling as

shown in Table 3, hyperglycemia at the time of admission with a random blood sugar more than 180 mg/dl and cardio-embolic etiology retained significance in predicting hemorrhagic transformation after thrombolysis in ischemic stroke patients.

Among the 6.92 % patients (24/348) developing symptomatic ICH (sICH). They had severe strokes (0.005), hyperglycemia (0.001), renal dysfunction (0.002) and poor ASPECTS on admission CT(p-0.05).sICH was also found associated with mechanical thrombectomy.(p-0.015).Poor outcome at 3months was also noticed in patients with sICH ($p<0.05$). On multivariate analysis(Table 5) it was found that strokes with NIHSS more than 15, blood sugar>180 mg/dl, renal dysfunction with creatinine>1.2, CT ASPECTS<=5, cardioembolic aetiology and mechanical thrombectomy were associated with sICH. On multivariate regression modelling(Table 6), blood sugar>180 mg/dl and cardioembolic aetiology were significant predictors of sICH post-thrombolysis.

Poor Outcome at 3 months was found in patients with atrial fibrillation, severe strokes with an NIHSS >15, diabetes with admission blood sugar > 180mg/dl, large vessel occlusion with poor collaterals and mechanical thrombectomy. On Multivariate analysis(Table 8), history of diabetes with admission blood sugar>180 mg/dl, severe strokes with an NIHSS >15, atrial fibrillation, large vessel occlusion with poor collaterals had higher odds for poor outcome. When the above variables were adjusted using a multivariate regression model (Table 9), severe strokes with NIHSS >15, admission blood sugar more than 180 mg/dl and large vessel occlusion were found to be predictors of poor outcome in these patients.

Table 1 : Univariate analysis of factors associated with hemorrhagic transformation

Variable	No Hemorrhagic Transformation n (%)	Hemorrhagic Transformation n(%)	p value
Age >60 yrs	62.02(12.75)	65(12.29)	0.25
Male	200(70.67%)	49(75.38%)	0.44
Risk Factors			
Hypertension	170(60.07%)	42(64.62%)	0.49
Diabetes	132(46.64%)	38(58.46%)	0.08
Dyslipidemia	46(6.25%)	15(23.08%)	0.192
Ischemic Heart Disease	60(21.2%)	22(33.85%)	0.03
Renal Failure	8(2.83%)	5(7.69%)	0.062
Smoking	52(18.37%)	11(16.92%)	0.784
Drug History			
Prior anticoagulant use	10(3.53%)	3(4.62%)	0.678
Prior antiplatelet use	72(25.44%)	28(43.08%)	0.005
Dual antiplatelet use	22(7.77%)	11(16.92%)	0.021
Statin use	81(28.62%)	28(43.08%)	0.023
Clinical Characteristics			
NIHSS>15	56(19.79%)	23(35.38%)	0.007
NIHSS mean	10.83+-5.39	14+-5.44	<0.05
Systolic BP>180 mm of Hg	51(18%)	12(18.46%)	0.93
Diastolic BP >90 mm of Hg	101(35.69%)	25(38.46%)	0.67
Door to needle time (mean in minutes)	35.33+-12.4	37.7+-9.8	0.15
Onset to treatment time> 3 hours	120(42.55%)	33(50.77%)	0.229
Cardioembolism	58(20.49%)	29(44.62%)	0.000
Investigations			
RBS mean(mg/dl)	161+-65.13	184.98+-66.73	0.01

Platelet Count (mean-lacs/dl)	2.21+-1.6	2.02+-0.5	0.32
Creatinine(mg/dl)	1.01+-0.35	1.2+-1.31	0.01
Cholesterol(mg/dl)	186.08+-53.06	183.78+-62.55	0.761
LDL(mg/dl)	122.13+-45.85	115.17+-48.1	0.30
ASPECTS <=5	21(7.42%)	12(18.46%)	0.006
Large Vessel Occlusion	75(26.5%)	27(41.54%)	0.016
Mechanical Thrombectomy	36(12.72%)	19(29.23%)	0.001
Poor outcome at 3 months	74(28.24%)	31(53.45%)	<0.05

Table 2: Multivariate analysis of factors associated with hemorrhagic transformation

Variable	Odds Ratio	95% Confidence Interval	p value
Risk Factors			
Ischemic Heart Disease	1.90	1.05-3.42	0.03
Drug History			
Prior antiplatelet use	2.21	1.26-3.87	0.005
Statin use	1.88	1.08-3.28	0.25
Clinical Characteristics			
NIHSS>15	2.21	1.23-3.99	0.008
Cardioembolism	3.15	1.77-5.51	0.000
Mechanical Thrombectomy	2.83	1.49-5.36	0.001
Investigations			
RBS >180 mg/dl	1.81	1.03-3.18	0.037
ASPECTS <5	2.82	1.31-6.09	0.008
Large Vessel Occlusion	1.97	1.12-3.44	0.017

Table 3: Multivariate regression model of predictors of Hemorrhagic transformation

Variable	Odds Ratio	p value	95% Confidence Interval
Drug History			
Prior antiplatelet use	2.08	0.171	0.72-5.75
Statin use	1.11	0.84	0.39-3.13
Clinical Characteristics			
NIHSS>15	1.53	0.216	0.77-3.00
Cardioembolism	2.75	0.001	1.51-5.03
Mechanical Thrombectomy	2.18	0.059	0.97-4.91
Investigations			
RBS >180 mg/dl	1.94	0.03	1.05-3.57
ASPECTS <5	1.77	0.203	0.73-4.30
Large Vessel Occlusion	1.31	0.416	0.63-2.69

Table 4 :Univariate analysis of factors associated with Symptomatic Intracerebral Hemorrhage

Variables	No SICH n(%)	SICH n(%)	p value
Age(yrs)	62.17(12.78)	65(11.11)	0.29
Male	231(71.52%)	17(70.83%)	0.94
Risk Factors			
Hypertension	196(60.68%)	16(66.67%)	0.562
Diabetes	155(47.99%)	15(62.5%)	0.17
Dyslipidemia	55(17.03%)	6(25%)	0.322
Ischemic Heart Disease	74(22.91%)	7(29.17%)	0.485
Renal Failure	12(3.72%)	1(4.17%)	0.91
Smoking	61(18.89%)	2(8.33%)	0.19
Drug History			
Prior anticoagulant use	11(3.4%)	2(8.33%)	0.22
Prior antiplatelet use	90(27.86%)	9(37.5%)	0.313
Statin use	100(30.96%)	8(33.33%)	0.809
Clinical Characteristics			
NIHSS>15	68(21.05%)	11(45.83%)	0.005
NIHSS mean	11.14±5.48	15.16±5.07	0.006
RBS (mean in mg/dl)	163.29±64.4	208± 73.55	0.001
Systolic BP>180 mm of Hg	58(17.96%)	5(20.83%)	0.72
Diastolic BP >90 mm of Hg	117(36.22%)	9(37.5%)	0.90
Door to needle time (mean in minutes)	35.63±12.29	37.95±8.3	0.36
Onset to treatment time >3 hours	141(43.79%)	11(45.83%)	0.84
Cardioembolism	77(22.60)	14(58.33%)	0.000
Investigations			
Platelet Count (mean in lacs/dl)	2.2±1.52	1.94±0.41	0.41
Creatinine (mean in mg/dl)	1.02±0.40	1.53±1.98	0.002

Cholesterol(mean in mg/dl)	186.66±54.83	177.54±50.59	0.43
LDL(mean in mg/dl)	121.69±47.06	109.5±33.9	0.23
ASPECTS <=5	28(8.67%)	5(20.83%)	0.05
Large vessel occlusion	91(28.17%)	11(45.83%)	0.067
Mechanical Thrombectomy	47(14.55%)	8(33.33%)	0.015
Outcome			
Poor outcome at 3 months	91(30.23%)	14(73.68%)	<0.05

Table 5: Multivariate analysis of the factors predicting sICH

Variables	Odds Ratio	95% CI	P value
Clinical Characteristics			
NIHSS>15	3.17	1.36-7.39	0.007
Cardioembolism	4.79	2.04-11.24	0.000
Mechanical Thrombectomy	2.93	1.18-7.24	0.019
Investigations			
RBS >180 mg/dl	3.73	1.60-8.72	0.002
Creatinine >1.2	2.52	1.02-6.2	0.043
ASPECTS <=5	2.77	0.96-7.99	0.059
Large Vessel Occlusion	2.15	0.93-4.99	0.072

Table 6: Multivariate regression model of predictors of sICH

Variable	Odds Ratio	95% CI	P value
Clinical Characteristics			
NIHSS>15	2.09	0.80-5.46	0.130
Cardioembolism	4.63	1.72-11.001	0.002
Mechanical Thrombectomy	2.08	0.75-5.76	0.158
Investigations			
RBS >180 mg/dl	3.85	1.55-9.58	0.004
Creatinine>1.2	2.41	0.89-6.52	0.08
ASPECTS <5	1.81	0.50-6.45	0.35

Table 7: Univariate analysis of the predictors of outcome in Ischemic Stroke patients post IV thrombolysis at 3 months

Variable	Good Outcome n(%)	Poor Outcome n(%)	p value
Age>60 yrs	68.42%(130)	31.58%(60)	0.57
Male	69.74%(159)	30.26%(69)	0.126
Female	60.87%(56)	39.13(36)	
Risk Factors			
Hypertension	65.64%(128)	34.36%(67)	0.462
Diabetes	59.24%(93)	40.76%(64)	0.003
No Diabetes	74.8%(122)	21.15%(41)	
Dyslipidemia	72.41%(42)	27.59%(16)	0.34
CAD	75.34%(55)	24.66%(18)	0.09
Renal Failure	58.33%(7)	41.67%(5)	0.50
Atrial Fibrillation	52.17%(24)	45.83%(55)	<0.05
No Atrial Fibrillation	69.71%(191)	30.29%(83)	
Smoking	75.44%(43)	24.56%(14)	0.14
Drug History			
Prior anticoagulant use	61.54%(8)	38.46%(5)	0.65
Prior antiplatelet use	72.83%(67)	27.17%(25)	0.17
Dual antiplatelet	75.86%(22)	24.14%(7)	0.56
Statin use	69%(69)	31%(31)	0.64
Clinical Characteristics			
NIHSS<=15	74.4%(186)	24.6%(64)	<0.05
NIHSS>15	41.43%(29)	58.57%(41)	
Systolic BP>180 mm of Hg	57.63%(34)	42.37%(25)	0.083
Diastolic BP >90 mm of Hg	64.04%(43)	35.96%(41)	0.37
Onset to treatment time >3 hours	64.96%(89)	35.04%(48)	0.46
Investigations			
RBS>180mg/dl	53.76%(50)	46.24%(41)	0.001
RBS<=180 mg/dl	72.69%(165)	27.31%(62)	

Platelet <2 lac		63.77%(132)	36.23%(75)	0.07
Creatinine >1.2 mg/dl		67.24%(39)	32.76%(19)	0.99
Cholesterol <200 mg/dl		66.67%(128)	33.33%(64)	0.72
LDL <100 mg/dl		67.37%(64)	32.63%(31)	0.95
ASPECTS <=5		51.72(15)	48.28(14)	0.06
Poor Collaterals		33.33%(4)	66.67%(8)	0.01
Large Vessel Occlusion	No	74.3%(171)	25.65%(59)	<0.05
	Yes	48.89%(44)	51.11%(46)	
Mechanical Thrombectomy	No	69.49%(189)	30.51%(83)	0.03
	Yes	54.17%(26)	45.83%(105)	
Cardioembolism		61.84%(47)	38.16%(29)	0.256

Table 8: Multivariate Analysis of predictors of outcome at 3 months

mRS at 3 months	Odds ratio	95% CI	p value
Risk Factors			
Diabetes	2.04	1.27-3.29	0.003
CAD	0.60	0.33-1.08	0.09
Atrial Fibrillation	2.10	1.19-3.97	0.021
Clinical Characteristics			
Onset to treatment time >3 hours	1.19	0.74-1.9	0.464
NIHSS >15	4.10	2.36-7.14	0.000
Cardioembolism	1.36	0.79-2.23	0.25
Investigations			
RBS>180mg/dl	2.28	1.38-3.77	0.001
ASPECTS <5	2.08	0.95-4.54	0.067
Large Vessel Occlusion	3.03	1.8-5.03	0.000
Poor Collaterals	4.35	1.27-14.7	0.01

Table 9: Multivariate regression model of predictors of outcome at 3 months

mRS at 3 months	Odds ratio	95% CI	P value
Clinical Characteristics			
NIHSS >15	3.58	1.96-6.35	0.000
Investigations			
RBS>180mg/dl	2.60	1.5-4.48	0.001
Large Vessel Occlusion	2.49	1.41-4.38	0.002
Poor Collaterals	2.63	0.67-10.26	0.164

Discussion:

Tissue plasminogen activator (tPA) administration remains the standard of care for acute ischemic stroke in the window-period. Patients treated with t-PA were at least 30 percent more likely to have minimal or no disability at three months on the assessment scales. However, hemorrhagic transformation of the infarct is a major concern post-thrombolysis. Hemorrhagic transformation post-thrombolysis has been found to be associated with many clinical and biochemical factors like high blood pressure, hyperglycemia, severe strokes and larger areas of hypoattenuation in CT scans (19). In the NINDS-tPA trial, the incidence of symptomatic ICH was 6.4% in the first 36 hours post-thrombolysis. (20)

Hemorrhagic transformation especially sICH was predictive of poor outcome in our study cohort. Hence, it is important to identify patients at higher risk for sICH which may allow early implementation of more aggressive preventive strategies (tighter control of blood pressure and glucose levels as well as avoidance of aggressive antithrombotic therapy in the early post-stroke phases) and can potentially lead to better outcome. In the literature, sICH has been linked to the use of thrombolytic drugs, advanced age, increased time to treatment, higher baseline National Institutes of Health Stroke Scale (NIHSS)score, high systolic blood pressure, hyperglycemia, diabetes mellitus, and the extent of ischemic injury prior to administration of therapy. (19)

Although older age is generally considered a risk for hemorrhagic transformation post-thrombolysis, there are some studies which showed no difference in symptomatic hemorrhagic transformation with advanced age. (22)(21) Similarly, we also didn't find a significant association of hemorrhagic transformation in advanced age patients with acute ischemic stroke post-thrombolysis. Also, males tend to have more risk for hemorrhagic transformation.(23) Nevertheless, hemorrhagic transformation risk was similar between males and females in our study. This may be due to the ethnic disparities in our population as compared to the available literature. Among acute ischemic stroke patients, cigarette smoking was shown to be protective factor for intracranial hemorrhage post-thrombolysis. Even in myocardial Infarction studies smokers had lesser incidence of ICH compared to non-smokers. (22) Administration of nicotine in animal models resulted in lesser activity of tPA in the brain capillaries and an increased activity of plasminogen activator inhibitor. (23) Thus endogenous reduction of tPA may be a possible mechanism contributing to this protective effect among smokers. However, we

observed similar incidence of hemorrhagic transformation among patients who smoke and who don't.

High blood pressure (BP) and hyperglycemia are known factors that cause increased risk of hemorrhagic transformation. High BP augments the blood brain barrier damage and can cause hyperperfusion of the infarcted area post-vessel recanalization. But high blood pressure was not seen associated with hemorrhagic transformation in our study. This may be due to the strict control of BP in the post-thrombolysis phase in all our patients. However, poorly controlled diabetes mellitus and high serum glucose on admission was found to be associated with hemorrhagic transformation in our study patients. Chronic microvascular damage secondary to diabetes may predispose vessels to rupture in the setting of ischemia, whereas hyperglycemia may contribute to acute injury of the blood-brain barrier, leading to increased hemorrhage rates. (24)(25)

As endothelial and platelet dysfunction are associated with low GFR, Renal dysfunction could additionally be a factor involved in hemorrhagic transformation and sICH which was also seen in our study.(28) Renal failure can cause impairment in platelet function which may be the reason for the same. Our results also suggests that there is a higher risk of hemorrhagic transformation in patients with known ischaemic heart disease similar to previous studies.(29)

Cardioembolic stroke was identified a predictor for hemorrhagic transformation which was also observed in our study. (31) This is attributed to better recanalization as RBC rich clots are more likely to get lysed resulting in reperfusion which can result in hemorrhagic transformation.(32). Atrial fibrillation is a risk factor in for hemorrhagic transformation in acute ischemic stroke patients post-thrombolysis.(30) In patients in AF there may be a state of chronic hypoperfusion and the clot burden will be high. The collateral circulation will not be able to compensate for the decreased perfusion which will result in increased blood brain barrier permeability. Anticoagulant use may be another reason for this association. Also Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) analysis showed atrial fibrillation as an independent predictor of symptomatic intracerebral hemorrhage. The study had patients with international normalized ratio of ≤1.7 which suggests that atrial fibrillation may indeed have an effect on sICH, independent of anticoagulation.

Aspirin use alone has not been associated with hemorrhagic transformation but dual antiplatelets have been found to be association.(33) Also, Statin use has been found to increase hemorrhagic transformation in many studies. (34) Patients on antiplatetet and statin therapy

had more risk of hemorrhagic transformation in our study cohort. However, anticoagulant use which is associated with sICH as shown in previous studies (35) had no bearing on hemorrhagic transformation in our study patients.

High baseline NIHSS score and Poor ASPECTS indicate a large area of infarction resulting in more disruption of blood brain barrier and hemorrhagic transformation in our study patients similar to previous published studies. Greater symptom severity, as assessed by the National Institutes of Health Stroke Scale (NIHSS), was independently associated with sICH in many previous studies.(36) Symptom severity correlates with the infarct volume and the association is consistent with the fact that sICH is likely to occur in the context of extensive cerebral ischemia.

Longer door to needle time also prolongs the duration of ischemia and more damage to blood brain barrier as a result of release of free radicals and inflammatory markers and more hemorrhagic transformation.(37) However, there was no association found in our study which could be due to the standard stroke work flow followed for all acute ischemic strokes to minimize the door to needle time. Endovascular intervention has also been found to be associated with hemorrhagic transformation.(38) This can be related to the prior treatment with rtpa, unfavourable vessel anatomy and the multiple number of passes. The effect of hemorrhagic transformation on outcome depends on the type of hemorrhagic transformation.

Poor outcomes were more commonly associated with parenchymal hematoma than hemorrhagic infarction. In our cohort, hemorrhagic transformation and sICH was associated with poor outcome. Also hyperglycemia and severe strokes were seen associated with poor outcome. This observation was in line with the NINDS trial-post hoc analysis which showed that hyperglycemia was associated with poor outcome.(20)(39).Atrial fibrillation was found to be associated with poor outcome in many studies.(40) This may be due to larger clot burden and more severe strokes among patients with atrial fibrillation. Large vessel occlusion and poor collaterals leads to a larger infarct which ultimately leads to poor outcome.

Conclusions:

Clearer understanding of the predictors of ICH post IV thrombolysis is required to improve risk assessment, patient selection and early prognostication. High blood sugar on admission and cardioembolic etiology were found to be predictive of sICH. Hemorrhagic transformation and sICH are associated with poor outcome in these patients.

Limitations of the study:

Being a retrospective study conducted in a single center with a smaller cohort of patients, was a major limitation of the study. The factors identified in the study needs to be validated in a larger prospective cohort. Assessing the biomarkers predicting the risk of hemorrhagic transformation in acute ischemic stroke patients would have added more value to the study.

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Abbreviations

sICH-symptomatic intracranial hemorrhage

ECASS -European Cooperative Acute Stroke Study

HAT-Hemorrhage after Thrombolysis

SITS-ICH-Safe implementation of thrombolysis in stroke

GRASPS- GWTG-Get with the guidelines

THRIVE -Totaled health risk in vascular event

SPAN - stroke prognostication using age and NIH stroke scale

HI- Hemorrhagic infarction

PH-Parenchymal Hematoma

mRS-Modified Rankin Scale

NIHSS- National Institutes of Health Stroke Scale

TOAST- Trial of Org 10172 in acute stroke treatment

ASPECTS- The Alberta stroke program early CT score

tPA- tissue plasminogen activator

GFR-Glomorular Filtration Rate

RBC-Red Blood Cell

Proforma

Age-

Risk factors

Hypertension-

Diabetes-

Hyperlipidemia-

Atrial Fibrillation-

Previous Stroke-

Coronary artery disease-

Chronic Kidney Disease-

Chronic liver disease-

Addictions

Smoking-

Alcoholism-

Drug History

Single antiplatelet-

Dual antiplatelet-

Warfarin-

Statin-

NIHSS Score on admission-

Random Blood Sugar-

Systolic Blood Pressure-

Diastolic Blood Pressure-

Intra Venous Thrombolysis-

Door to needle time-

NIHSS at 24 hours

Hemoglobin-

Platelet-

Urea-

Creatinine

SGOT(serum glutamic-oxaloacetic transaminase)-

SGPT(serum glutamic-pyruvate transaminase)-

Total Protein-

Albumin-

PT(Prothrombin Time)

INR(International Normalised ratio)

APTT(Activated Partial Thromboplastin time)

Total cholesterol

LDL(Low Density glycoprotein)

HDL(High density glycoprotein)

TGL(triglyceride)

HBA1C (Glycated hemoglobin)

ECG-Atrial Fibrillation/No Atrial Fibrillation

Holter-

CT BRAIN

Description of infarct-

ASPECTS(Alberta stroke programme early CT score)-

CT angio-Large Vessel Occlusion/No Large Vessel Occlusion

length and location of the clot

Collateral status- good/intermediate/poor

Repeat CT-

Aetiology of stroke –

NIHSS at discharge-

mRS at discharge-

mRS at 3 months-

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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/2091/AUGUST/2023

13.10.2023

Dr. Manju Surendran
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Manju Surendran,

The Institutional Ethics Committee held on 24th August, 2023, reviewed and discussed your application to conduct the study titled "**PREDICTORS OF HEMORRHAGIC TRANSFORMATION IN PATIENTS WITH ACUTE ISCHEMIC STROKE AND ITS OUTCOME**" (IEC/2091).

Principal Investigator	Dr Manju Surendran, PDF Stroke, Department of Neurology, SCTIMST
Co-Principal Investigator(s)	Dr Sylaja, P.N, Professor and Head of Department, Neurology, SCTIMST Dr Sajith Sukumaran, Professor, Department of Neurology, SCTIMST Dr Sapna EratSreedharan, Professor, Department of Neurology, SCTIMST
Duration of the study	6 months

The following members of the Ethics Committee were present at the meeting held on 24th August, 2023

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
2.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
3.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
4.	Dr. P. Manickam	BSMS, MSc (Epid), PhD	Male	Health Science Expert/ Social Scientist	No
5.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
6.	Dr. Manikandan S	MBBS,MD,PDCC	Male	Clinician	Yes
7.	Dr. Syam K	MBBS, MD, DM	Male	Clinician	Yes
8.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 08.06.2023
2. Forwarding letter from the HOD dated 07.06.2023
3. Checklist Form
4. IEC Application Form
5. Project Proposal
6. Declaration form
7. CV of PI and Co-PIs
8. Proforma
9. SRC Recommendation letter

Revised submission

1. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 05.10.2023
2. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 08.06.2023
3. Forwarding letter from the HOD dated 07.06.2023
4. Checklist Form
5. IEC Application Form
6. Project Proposal
7. Declaration form
8. CV of PI and Co-PIs
9. Proforma

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

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INSTITUTIONAL ETHICS COMMITTEE (IEC) SCTIMST THIRUVANANTHAPURAM