Original Article:

In-hospital medical, neurological complications and outcome in patients with acute stroke: a prospective study

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ABSTRACT

Background: Sparse published data are available regarding the occurrence of medical and neurological complications in patients with acute stroke and their relation to outcome.

Methods: In this prospective single centre study, done over one year period, 460 patients with acute stroke were studied. Stroke characteristics, severity, risk factors were documented. Predefined complications were monitored during in-hospital stay. The outcome was measured using modified Rankin scale (mRS) at the time of discharge.

Results: Overall, 121 (26.3%) patients developed complications. Majority of patients (44/121,36.4%) developed complications in the first one week hospital stay. The prevalence of neurological and medical complications was 15% and 11.3% respectively. Raised intracranial pressure (ICP) [n=37 (8%)], and pneumonia [n=20 (4.3%)] were more frequently observed complications. Acute stroke patients with complications had a statistically significant poor outcome (mRS 3 to 6) than patients without complications [n=103/121 (85.1%) vs. n=219/339 (64.6%); p <0.001)]. On multivariable analysis, dyslipidaemia [odds ratio (OR) 5.128; p=0.001], hypertension (OR 2.037; p=0.002), age less than 45 years (OR 1.799; p=0.004), stroke severity with moderately severe to severe stroke (OR 4.067; p<0.001) were statistically significant predictors for the occurrence of complications.

Conclusions: The mortality and morbidity were more within stroke patients with complications compared with those without complications. Efforts should be directed at preventing the occurrence of medical and surgical complications in patients with acute stroke by optimising the care of there patients.

Key words: *Stroke, Complications, Outcome*

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INTRODUCTION

The current World Health Organization (WHO) definition of stroke is "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin".[1] Stroke ranks 2 among top 10 leading causes of death in the world.[2] Each year, approximately 795,000 people are experiencing new or recurrent stroke in the USA. Of these, 610,000 are first stroke events and 185,000 are recurrent stroke events. Stroke caused 1 of 20 deaths in the United States in 2011.[3] The stroke prevalence among men of different age groups is 0.2 %, 1.9%, 6.1%, 15.8% respectively between 20-39 years, 40-59 years, 60-79 years, above 80 years age groups.[3] The stroke prevalence among women of different age groups is 0.7%, 2.2%, 5.2%, 14% respectively between 20-39 years, 40-59 years, 60-79 years and above 80 years age groups.[3]

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In India, the overall age adjusted prevalence rate for stroke is estimated to be 84-262/ 100,000 in rural and 334-424/100,000 in urban areas and the adjusted annual incidence of stroke is 124/100,000 in rural area and 145/ 100,000 in urban areas.[4] In India, 41% of deaths and 72% of disability adjusted life years are caused by stroke among non-communicable diseases.[5] Like many other serious medical illnesses the clinical course of the stroke can be complicated. The complications followed by stroke can cause neurological deterioration, and sometimes this may be confused to be worsening of stroke. The medical and neurological complications after acute stroke may adversely impact the outcome in patients with stroke. Prevention of these complications improves the outcome of acute stroke. As there is limited data existing regarding the frequency of such complications occurring in the first days after the stroke and the relationship of these complications to outcome, the present study was undertaken.

MATERIAL AND METHODS

All patients with acute stroke admitted to the neurology intensive care unit, and neurology wards at Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, a tertiary care teaching hospital in South India, between November 2012 and October 2013 were prospectively studied. Pregnant women, patients presenting with neurological deficits due to trauma, neoplasm, and infections were excluded from the study. The study was cleared by the Institutional Ethics Committee. Patients were enrolled into the study after obtaining a written informed consent from them or from the next responsible attendants in case the patient was unconscious.

A detailed clinical history was recorded specifically focussing on the risk factors for stroke. All the participants were subjected to a thorough physical examination, consisting of general physical examination, detailed neurological examination and examination of other systems. All patients underwent to computerized tomography (CT) of the brain (plain) (Siemens Somatom Emotion Spiral CT Scanner, Muenchen, Germany) and/or magnetic resonance imaging (MRI) of the brain [T2 weighted (T2W) and diffusion weighted (DWI) images and magnetic resonance angiogram (MRA)] (Siemens Symphony Maestro Class MRI Scanner, Muenchen, Germany). Ischaemic stroke subtypes were classified as per Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system[6] based on clinical features and on data collected by tests such as brain imaging (CT/ MRI) cardiac imaging (echocardiography), duplex imaging of extra-cranial arteries, and laboratory assessments for a prothrombotic states.

In all the patients with stroke, the following laboratory testing were carried out: complete haemogram, coagulation profile [bleeding time, clotting time, prothrombin time with international normalized ratio (INR), and activated partial thromboplastin time], lipid profile (serum triglycerides, cholesterol, low density lipoprotein, very low density lipoprotein, high density lipoprotein), fasting and post-prandial plasma glucose, electro-cardiogram, two-dimensional echo cardio graphy, carotid and vertebral arterial doppler study. Dyslipidaemia was defined as elevated triglyceride (TG) (> 150 mg/dL), low density lipoprotein (LDL) cholesterol (> 130 mg/dL), and low high density lipoprotein (HDL) cholesterol levels (< 40 mg/dL) as per the third report of the National Cholesterol Education Program Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Tretment Panel III) (NCEP ATP III).[7]

In case of young patients with stroke (aged < 45 years), the following laboratory tests were also carried out: rheumatoid factor, anti-nuclear

antibody, anti-double stranded deoxy ribonucleic acid (anti-ds DNA) antibody, protein C and S, antithrombin III, serum homocysteine [cut-off > 15μmol/L was considered as hyperhomocysteinaemia],[8] anticardiolipin antibody, Venereal Disease Research Laboratory (VDRL) test, serological testing for human immunodeficiency virus (HIV) infection. Polycythemia was also considered in this study If haemoglobin level was >18.5 g/dL in men and >16.5 g/dL in women, polycythaemia was considered to be present.[9]

Patients with ischaemic stroke were treated with anti-platelet agents, statins, measures for lowering intracranial pressure as applicable and symptomatic treatment for headache and management of risk factors. Thrombolytic therapy was considered in eligible patients. Patients with haemorrhagic strokes were treated with measures for lowering of intracranial pressure, anti-hypertensive drugs, and symptomatic treatment. Patients with large infarcts, haemorrhages with mass effect and raised intracranial pressure were managed with decompressive craniectomy. The further course of illness, from hospital admission to the time of discharge or death, was assessed by the progression of presenting complaints, neurological deficits. All the patients recruited in the study were assessed every day during hospital stay for below mentioned predefined complications (Table 1).[1,10-12]

Statistical analysis

The data were recorded on a predesigned proforma and managed using Microsoft Excel 2013 (Microsoft Corp, Redmond, WA). All the entries were double-checked for any possible error. Descriptive statistics for the categorical variables were performed by computing the frequencies (percentages) in each category. For the continuous variables, approximate normality of the distribution was assessed. Variables following normal distribution were summarized by mean and standard deviation. Variables that are not normally distributed were summarized as median [interquartile range (IQR)]. Multivariable analysis was undertaken for predicting the occurrence of complications. Multivariable analysis was carried out in two stages. Univariate analysis was carried out to compare the demographic, clinical, and laboratory variables between patients with and without complications using unpaired t-test, Mann-Whitney U-test for continuous variables and Chi-square test for categorical variables. Continuous variables found to be significant ($p<0.3$) on univariate analysis were categorized into binary variables. Variable that were found significant ($p<0.3$) on univriate analysis were included in multivariable model as predictor variables (covariates). Multivariable analysis was carried out using step-wise binary logistic regression (forward-conditional method). The statistical software IBM SPSS Statistics Version 20 (IBM Corp Somers NY, USA); Systat 12, Version 12.00.08 (Systat Software, Inc, Chicago IL, USA); and MedCalc Version 11.3.0 for Windows 2000/XP/Vista/7 (MedCalc Software bvba, Belgium) were used for statistical calculations.

RESULTS

Four hundred and seventy seven patients with clinical diagnosis of acute stroke were enrolled in the study. Seventeen patients were excluded as imaging confirmation was not done in 7 patients and 10 patients were discharged at the request or against medical advice. The remaining 460 patients were included in the study (Figure 1). Their mean age was 57.6 ± 13.5 years. There were 279 (61%) males. The following risk factors were noted on admission of these acute stroke patients: hypertension (n=312, 67.8%); diabetes mellitus (n=133, 28.9%); old age (> 65 years) (n=132, 28.7%); tobacco smoking (n=74,16.1%), alcohol consumption (n=71,15.4%); previous stroke (n=61,13.3%); dyslipidaemia (n=56,12.2%),

Table 1: Complications in patients with acute stroke

Neurological complications	
	Recurrent stroke
	Clinical features lasting more than 24 hours consistent with the WHO definition of stroke[1]
	Seizure
	Clinical diagnosis of focal and/or generalized seizure in a previously non epileptic patient
	Raised intracranial pressure
	Clinical features consistent with diagnosis of raised intracranial pressure and neuroimaging evidence of mass effect and midline shift resulting from infarct or bleed
	Haemorrhagic conversion of infarct
	Neuroimaging evidence of bleeding into infarct with deterioration of clinical condition
Medical complications	
	Pneumonia
	Fever and crepitations on chest auscultation and / or radiographic evidence of pneumonia and / or purulent sputum.
	Urinary tract infection
	Clinical symptoms of urinary tract infection and positive urine culture
	Other infections
	Any febrile illness lasting longer than 24 hours.
	Acute myocardial infarction
	Presence of elevated cardiac troponin plus any one of the following features; symptoms of ischemia, new ST-T changes or new left bundle branch block, development of pathologic q waves, imaging evidence of loss of viable myocardium or new regional wall motion abnormality
	Congestive heart failure
	Congestive heart failure was diagnosed as per Framingham criteria,[10] if 2 major or 1 major with 2 minor criteria present. Major criteria: paroxysmal nocturnal dyspnea, neck vein distension, crepitations, radiographic cardiomegaly, acute pulmonary edema, S3 gallop, increased central venous pressure (>16 cm H_2O), hepato-jugular reflex, weight loss >4.5 kg in 5 days in response to treatment. Minor criteria: bilateral ankle oedema, nocturnal cough, dyspnoea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by 1/3 from maximum record, tachycardia (heart rate >120 beats/minute)
Falls	
	Any documented falls regardless of cause. Fall with serious injury was defined as one that resulted in fracture, radiological investigation, neurological investigation or suturing of wound
Pressure sore	
	Any skin break or necrosis resulting from either pressure or trivial trauma (skin trauma directly resulting from falls was not included)
Deep vein thrombosis	
	Clinical diagnosis of deep vein thrombosis with evidence of deep vein thrombosis on doppler study of venous system of limbs
Pulmonary embolism	
	The diagnosis of pulmonary embolism is considered in the presence of the following features; clinical symptoms and signs of deep vein thrombosis, heart rate > 100 beats/minute, bed rest for more than 3 days or surgery in last four weeks, previous history of deep vein thrombosis or pulmonary embolism, hemoptysis, cancer treatment currently or in the last 6 months or receiving palliative care[11]
Other complications	
	Any documented complication resulting in specific medical or surgical intervention (e.g., gastrointestinal tract hemorrhage, hematuria, constipation, arthritis, altered glucose homeostasis).
	All the patients were assessed for functional status at the end of their hospital stay using modified Rankin Scale (mRS)[12] which were classified as complete recovery (score 0 to 1), partial recovery and independent (score 2), partial recovery and dependent (score 3 to 5), and death (score 6). The mRS 3 to 6 was considered as poor outcome. The outcome was studied in terms of in-hospital course, frequency of medical and neurological complications during in-hospital stay and outcome in patients presenting with acute stroke. These details were recorded in the study proforma

WHO = World Health Organization

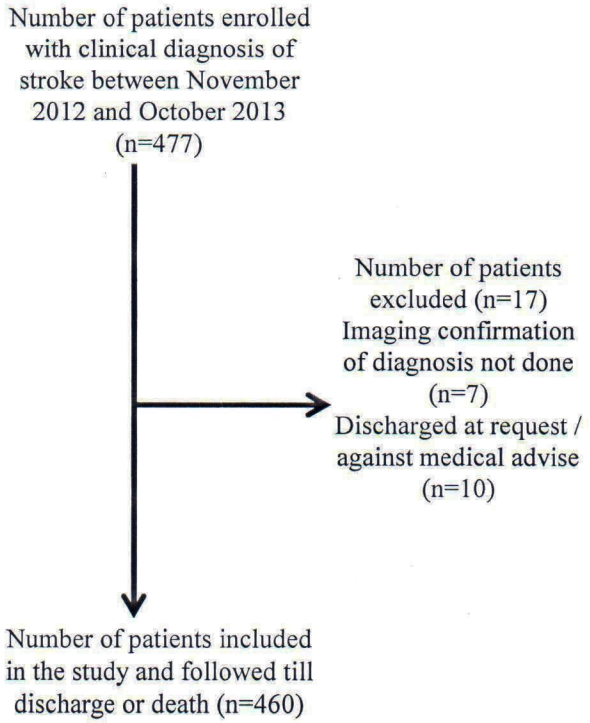

Figure 1: Study design

coronary artery disease (n=30,6.5%), rheumatic heart disease (n=26, 5.7%); arrhythmias (n=15, 3.3%), hyperhomocystinaemia (n=3) antiphospholipid syndrome (n=2), and polycythaemia in one patient.

In the present study, 76% patients presented with ischaemic stroke and 24% presented with haemorrhagic stroke. The distribution of infarcts in ischaemic stroke patients was as follows: anterior circulation 245 (53%), posterior circulation 88 (19%), in border zones 4 (1%), multiple territories 14(3%). The cause of ischaemic stroke as per TOAST classification[6] was as follows: large artery atherosclerosis (thrombosis/embolus) in 204 (58.3%), cardio-embolic stroke in 42 (12%), small vessel occlusion in 88 (25.1%), stroke of other determined aetiology in 9 (2.6%), stroke of undetermined aetiology in 7 (2%) patients. The sites of bleeding in haemorrhagic stroke supratentorial region 90 (19.6%), infratentorial region 12 (2.6%), intraventricular region 6 (1.3%), at multiple sites 1 (0.2%). Stroke severity assessed as per the National Institute of Health Stroke Scale (NIHSS)[13] was as follows: minor stroke in 95 (20.7%), moderate stroke in 322 (70%), moderate to severe stroke in 41 (8.9%), severe stroke in 1 (0.2%) patient. One patient had NIHSS 0, but included in the study as there was imaging evidence of infarction.

In the present study, 121 patients (26.3%) experienced complications during hospital stay (Table 2). The mean hospital stay of patients with acute stroke was 10.5 days ± 4.5 days. The majority of patients developed complications in the first one week hospital stay [44/121 (36.4%)]. The clinical characteristics in stroke patients with and without complications are shown in Table 3. On univariate analysis, compared with those without complications, patients with complications had a significantly higher prevalence of hypertension (p=0.022); dyslipidaemia (p=0.002); haemorrhagic stroke (p=0.024) and severe stroke (p<0.001) (Table 3).

Among 460 patients with stroke, 44 (9.6%) patients died. The majority of deaths were noticed in the first one week of admission of stroke patients [38/44, 86.4%]. A statistically significant higher mortality was observed in patients with complications compared to those without complications [41/121 (33.9%) Vs. 3/339 (0.9%); p<0.001]. A statistically significant prevalence of raised intracranial pressure

Table 2: Frequency of various complications in patients with acute stroke

Complication	No. (%)
Recurrent stroke	2 (0.4)
Seizures	13 (2.8)
Raised intracranial pressure	37 (8)
Hemorrhagic conversion of infarct	17 (3.7)
Pneumonia	20 (4.3)
Urinary tract infection	3 (0.7)
Other infections	5 (1.1)
Dyselectrolytemia	7 (1.5)
Myocardial infarction	1 (0.2)
Congestive heart failure	3 (0.7)
Pulmonary edema	1 (0.2)
Deep vein thrombosis	3 (0.7)
Pressure sore	5 (1.1)
Falls	6 (1.3)
Others	17 (3.7)

Table 3: Clinical characteristics in acute stroke patients with and without complications

Clinical character	Without complications (n=339) No.	With complications (n=121) No.	p-value
Gender			
Male	201	78	
Female	138	43	0.318
Stroke in young	52	24	0.253
Stroke type			
Ischaemic	267	83	
Haemorrhagic	72	38	0.024
Stroke severity			
Minor stroke	89	6	
Moderate stroke	231	91	
Moderate to severe stroke	18	23	
Severe stroke	0	1	<0.001
Risk factors			
Hypertension	240	72	0.022
Old age	95	37	0.594
Smoking	56	18	0.673
Alcohol	53	18	0.843
Dyslipidaemia	51	5	0.002
Previous stroke	40	21	0.122

(p<0.001), myocardial infarction (p=0.002), congestive heart failure (p=0.001), pulmonary oedema (p=0.002) was evident among patients who died is shown in (Table 4).

A majority (70%) of acute stroke patients in this study had poor outcome (modified Rankin scale 3 to 6). The acute stroke patients with complications had statistically significant poor outcome than patients without complications [103/121 (85.1%) Vs. 219/339 (64.6%); p<0.001]. A statistically significantly higher proportion of patients with poor outcome had developed complications, including raised intracranial pressure (p<0.001), pneumonia (p=0.026), myocardial infarction (p=0.024), congestive heart failure (p=0.005), pulmonary oedema (p=0.024) was evident among patients with high modified Rankin scale scores

Table 4: Comparison of prevalence of complications in acute stroke patients among survivors and non-survivors

Complications	Alive (n=416) (No.)	Dead (n=44) (No.)	p-value
Raised intracranial pressure	4	33	<0.001
	14	3	0.248
Haemorrhagic conversion of infarct	12	1	0.816
Seizures	2	0	0.645
Recurrent stroke	18	2	0.946
Pneumonia	3	0	0.572
Urinary tract infection	4	1	0.425
Other infections	6	1	0.669
Dyselectrolytemia	0	1	0.002
Myocardial infarction	2	1	0.001
Congestive heart failure	0	1	0.002
Pulmonary oedema	5	1	0.552
Falls	5	0	0.465
Bed sores	3	0	0.572
Deep vein thrombosis	15	2	0.753
Other complications			

suggestive of more disability and poor outcome. The independent predictors for development of complications are shown in Table 5. Presence of dyslipidaemia [odds ratio (OR) 5.128; p=0.001]; stroke severity (OR 4.067; p<0.001); presence of hypertension (OR 2.037; p=0.002); and age less than 45 years (OR=1.779; p=0.004) emerged as a significant independent predictors for development of complications.

DISCUSSION

Our study showed that the complication rate (26.3%) in this cohort of patients is comparable to the observations reported in a study from Germany (27.6%),[14] and two studies from Korea (27.6%)[15] 24.2%.[16] However, the complication rate observed in the present study (26.3%) was lower compared to the figures reported in the CAST-I study (42.9% - 63.8%)[17] and studies from Asia,[18] Scotland,[19] and Norway.[20] The probable reasons that might explain lower complications rate in the present study could be younger median age at presentation (57.6 ± 13.5 years), recording of complications only during hospital stay after onset of stroke to discharge or death, and not including psychiatric issues.

The most frequently observed complications in the present study were raised intracranial pressure (8%), pneumonia (4.3%). The most frequently reported complications in the various studies were as follows; congestive heart failure (11%), urinary tract infection (11%), and pneumonia (10%) in the tirilazad mesylate,[21] urinary tract infection (15.5%), pneumonia (8.8%), and constipation (7%),[22] pneumonia (25.2%) in the CAST-I study.[17] Our study showed that the neurological complications were more frequently seen compared to medical complications (15% vs. 11.3%). Pulmonary embolism was not seen in this study. In the CAST-I study,[17] the reported neurological complications were 7.8%, and non-neurological complications were 38.1%. The differences in the prevalence of various complications reported in various studies could be due to the variations in the definitions used for defining the complications and variations in the standard of care in the study centres.

In the present study, there was no statistically significant difference in developing complications after acute stroke between male and female patients [(28% vs. 23.8%); p=0.318)]. The complications rate was significantly high among haemorrhagic stroke patients compared with ischaemic stroke patients [(34.5%) vs.(23.7%); p=0.024)]. The complications were significantly high in patients with moderate to severe stroke compared with moderate and minor stroke [(56.1%) vs. (28.3%) and (6.3%); p <0.001)]. There observations are comparable to other studies[19,20] where it was reported that stroke severity was the most important risk factor for the development of complications.

The mortality rate observed in this study was 9.6%. It was reported in a study[23] that mortality rate due to stroke varies from 15% -58%. Compared to stroke patients without complications, the mortality was higher in

Table 5: Independent predictors for development of complications

Variable	Coefficient	Significance	Odds ratio	95% Confidence intervals	
				Lower	Upper
Age < 45 years	0.587	0.004	1.799	1.212	2.667
Moderately severe to severe stroke	1.403	<0.001	4.067	2.070	7.993
Presence of hypertension	0.712	0.002	2.037	1.307	3.175
Presence of dyslipidaemia	1.633	0.001	5.128	1.942	13.514

patients with complications [(0.9%) vs. (33.9%); p<0.001)]. Patients with complications, such as, raised intracranial pressure (p<0.001), myocardial infarction (p=0.002), congestive heart failure (p=0.001), pulmonary edema (p=0.002) had a statistically significantly higher mortality compared to those without these complications. There were no deaths observed in stroke patients with deep vein thrombosis, bed sore, urinary tract infection.

The mean hospital stay of patients with acute stroke was 10.5 days ± 4.5 days. Majority of patients (36.4%) developed complications in the first one week of hospital stay. The majority of deaths (86.4%) were noticed in the first one week of admission of stroke patients. This is comparable to other studies.[23,24] Complications were more frequently reported in the first 4 days after admission in a study from Norway.[20]

In the present study acute stroke patients with complications had statistically significant poor outcome (mRS 3 to 6) than patients without complications [(85.1%) vs. (64.6%); p <0.001)]. Patients with complications such as, raised intracranial pressure (p<0.001), congestive heart failure (p=0.005), pulmonary oedema (p=0.024), pneumonia (p=0.026) were statistically significantly associated with poor outcome. Among clinical variables dyslipidaemia, hypertension, age < 45 years, stroke severity with moderately severe to severe stroke were independent predictors of occurrence of complications on multivariate analysis in this study. Hence physicians who are dealing with stroke patients should aware of these clinical variables and early identification of these may minimize complications. In young patients, probably delayed identification and presentation to stroke unit because of low threshold for identification of stroke in young age in developing countries, may explain the occurrence of complications.

The mortality and morbidity were more with stroke patients with complications than without complications. Medical complications are preventable with optimal care of the stroke patients. Complications can be limited to neurological complications which are caused by disease process *per se* if adequate care given to hospitalized stroke patients. Because complications were associated with stroke severity, treatment that reduces the size and severity of brain injury might prevent further complications.

This study is done in a tertiary hospital care setting. Therefore, the study is likely to have missed out the patients with massive stroke and complications who would have succumbed to their illness without ever reaching a hospital. The study assessed only the in-hospital complications. Due to logistic reasons the complications that would have occurred after discharge could not be studied

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