

## “Effect of Risk Factors on Short Term Mortality in Patients of Stroke with Hyperglycaemia”

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### Abstract

### Original Research Article

**Background:** Stroke is the third most common cause of death in the developed world after ischaemic heart disease and all cancers and is the most common cause of physical disability. It is established by several studies that stroke patients having hyperglycaemia on admission have adverse short term outcomes in terms of mortality and also increased rate of haemorrhagic conversion after thrombolytic therapy in ischaemic stroke. If we can explore other factors having significant effects on short term mortality along with hyperglycaemia, poor outcomes of stroke patients would be predicted more accurately. Moreover this study will open a number of new windows of thinking. **Objectives:** To study the effect of hyperglycaemia on the 30 day prognosis of patients admitted with stroke and its relationship with other risk factors. **Materials and methods:** It was a hospital based prospective study carried out in patients admitted in the Neuro-Medicine and Medicine units of Rajshahi Medical College Hospital admitted with the diagnosis of Stroke as confirmed by imaging of the brain (CT scan or MRI) From January 2008 to January 2009. 100 consecutive patients of stroke having a raised blood sugar level (above 10.0 mmol/l) formed the study group while 100 similar patients of stroke with normal blood sugar level (less than 8.00 mmol/l) constituted the control group. **Results:** Total 200 patients were enrolled. Highest number of both male and female patients were between ages 51 and 65 (42.2% male & 53.3% female). Highest mortality was from age group 35-50 years (20.1%), which was statistically significant ( $p < .05$ ). Mortality was more in male both among normoglycaemic (4.8) and hyperglycaemic group; here mortality was significantly higher in male ( $p < .05$ ). Moreover patients with Glasgow coma scale below 8 on admission had the highest mortality. **Conclusion:** Male sex, middle age (35-50 years), and Glasgow coma scale below 8 were established as poor outcome predictors in stroke patients along with hyperglycaemia. Several studies support these findings except the factor named Middle age. More large scale studies should be conducted to look into the matter.

**Keywords:** Hyperglycemia, Stroke, Outcome, Mortality.

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## INTRODUCTION

Stroke is the third most common cause of death in the developed world after ischaemic heart disease and all cancers and is the most common cause of physical disability. Although confounded by other factors, such as severity of the infarct, hyperglycaemia in the face of stroke worsens clinical outcome. Capes *et al.* [1], show in their study, nondiabetic hyperglycaemic ischaemic stroke patients have a threefold higher 30 days mortality and diabetic patients have a twofold higher 30 days mortality. In several trials involving thrombolytic and anticoagulation therapy in patients with stroke, hyperglycemia appears to be an independent risk factor for worsened outcome. Moreover hyperglycaemia has been suggested as an

independent risk factor in haemorrhagic conversion of the stroke after administration of thrombolytic therapy. It is well known that DM is an important risk factor for stroke and may be one of the factors causing stroke at younger ages in groups such as Hispanic Americans that have relatively high incidence of DM. “The pathological changes associated with atherosclerosis in diabetic patients are similar to those seen in the non-diabetic population but they occur earlier in life and are most extensive and severe. Diabetes amplifies the effects of the other cardiovascular major risk factors: smoking, hypertension and dyslipidaemia” [2]. Furthermore, “mortality is significantly related to a high level of blood glucose on admission”. The proposed mechanism by which hyperglycaemia worsens outcome and increases rate of mortality from stroke are –(a)

poorer reperfusion due to vascular injury (b) Increased acidosis perhaps from lactic acid leading to further tissue injury. Both mechanisms have been suggested by experimental data. Parson's *et al.* [3], used MRI and MR spectroscopy in patients with hyperglycaemic stroke and reported that the detrimental effects of hyperglycemia may be due to metabolic acidosis in the infarcted brain parenchyma. However earlier animal studies Kawai *et al.* [4], suggest that hyperglycaemia has a detrimental effect on central vascular tree. Now, the specific mechanisms by which hyperglycaemia lead to poorer clinical outcome in patients receiving anticoagulants or thrombolytics is not known. Several mechanisms has been proposed including the following: (a) In some vascular beds hyperglycaemia causes glycosylation and thereby interferes with protein and enzyme functions, including those functions that regulate production of substances that cause vasodilatation and cellular adhesion with the vasculature. (b) Hyperglycaemia results in formation of advanced glycosylation end products that are toxic to endothelial cells and production of free radicals from various sources may result in further vascular injury. The risk of conversion of ischaemic to hemorrhagic stroke after thrombolytic therapy in hyperglycaemic patients may be present even at moderate elevation of serum glucose levels. Notably moderate hyperglycaemia is not an exclusion criterion for administration of rtPA. In patients with acute stroke, acceptable blood glucose level is 50 to 400 mg/dl. From 1988 to 1998 the total number of stroke deaths in the United States rose 5.3%. These recent increases are related most probably to increased diabetes and aging in United States. In a study carried out by Hu *et al* [5] among 25155 Finnish men and 26423 women aged 25 to 74 years showed that Diabetes present either at baseline or follow-up markedly increases the risk of stroke death. Hamidon and Raymond [6], in their study showed that admission hyperglycaemia is the single most important predictor of death in a patient with stroke. The above mentioned factors led us to think that if hyperglycemia alone or also other cardiovascular risk factors have detrimental effect on stroke. In Bangladesh, there is no large-scale study on this topic. So observing short term (30 days) mortality in patients of stroke with DM prospectively will be an important addition to our knowledge and help to formulate strategies to further improve management of such patients.

## OBJECTIVES

### General

1. To study the effect of hyperglycaemia on the 30 day prognosis of patients admitted with stroke and its relationship with other risk factors.

### Specific

1. To compare the effect of hyperglycaemia and normoglycaemia on the 30 day prognosis of patients with ischaemic and haemorrhagic stroke.

2. To compare the effect of ischaemic heart disease on the prognosis of hyperglycaemic and normoglycaemic patients having ischaemic and haemorrhagic stroke.
3. To study the effect of hypertension on the prognosis of hyperglycaemic and normoglycemic patients having ischaemic and hemorrhagic stroke.
4. To study the effect of smoking on the prognosis of hyperglycaemic and normoglycemic patients having ischemic and hemorrhagic stroke.
5. To study how the level of consciousness at presentation as represented by the Glasgow coma scale affects the prognosis of hyperglycaemic and normoglycemic patients having ischaemic and haemorrhagic stroke.
6. To study how previous intake of antiplatelet therapy affects prognosis of hyperglycaemic and normoglycaemic patients on the 30 day prognosis of patients with ischaemic and hemorrhagic stroke.
7. To see the effect of age and sex of the patients on the prognosis of these patients.
8. To determine and identify poor prognostic factors in different types of stroke patients.

## MATERIALS AND METHODS

It was a hospital based prospective study carried out in patients admitted in the Neuro-Medicine and Medicine units of Rajshahi Medical College Hospital admitted with the diagnosis of Stroke as confirmed by imaging of the brain (CT scan or MRI) From January 2008 to January 2009. 100 consecutive patients of stroke having a raised blood sugar level (above 10.0 mmol/l) formed the study group while 100 similar patients of stroke with normal blood sugar level (less than 8.00 mmol/l) constituted the control group.

### Inclusion criteria

1. Patients admitted with the clinical diagnosis of stroke and confirmed by CT scan or MRI of the Brain.
2. Patients having blood sugar level below 8.00 mmol/L or above 10 mmol. /L.
3. Patient's attendants accepted the inclusion of the patient in the study and provide their informed consent.

### Exclusion criteria

1. Patients having blood sugar level between 8.00 mmol/L and 10.00 mmol/L.
2. Patient dies immediately after admission before any investigation can be done.
3. Patients attendants refuse to give informed consent for inclusion of the patient in the study.

## METHODOLOGY

On admission the level of consciousness of the patient as represented by the Glasgow coma scale was recorded, his blood sugar level was estimated and the patient was classified as haemorrhagic or ischaemic

stroke according to the imaging finding. An ECG was done and according to the finding the patient was labelled as a patient of ischaemic heart disease or not. A patient was labelled as hypertensive if there was definite history of taking anti-hypertensive drugs or blood pressure was found to be persistently raised after stroke and/or anti-hypertensive therapy had to be started. Smoking history was also obtained. Demographic data of all patients was also recorded in the individual file of each patient. Each patient was followed up during the hospital stay to determine the prognosis. If any patient dies, then the cause of death, as determined by the treating doctors was recorded. If the patients were discharged, he was contacted over mobile telephone after 30 days and his prognosis was recorded.

## DATA COLLECTION

All data was collected by the Principal Investigator himself in an individual questionnaire for each patient.

## STATISTICAL ANALYSIS

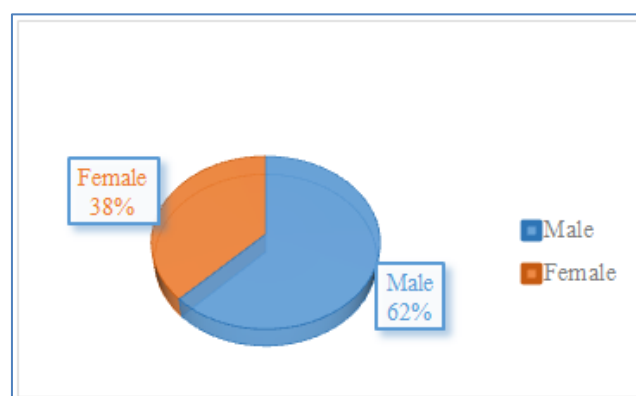
Data was processed in computer using SPSS for windows. Descriptive analytical techniques involving, frequency distribution, computation of percentage, mean, SD, etc was applied. Association between variable were conducted applying chi-square test. All parametric variables were expressed as mean  $\pm$  SD unless otherwise stated. The comparison between the groups was made by unpaired "t" test. P value  $< 0.05$  was considered as minimum level of significance.

## RESULTS AND OBSERVATIONS

This was a prospective study in which the effects of different risk factors on the short term mortality of patients with stroke with hyperglycaemia were studied. 100 patients with hyperglycaemia were studied and compared with 100 normoglycemic patients. Table 3.1 shows the distribution of the patients according to age and sex. Highest number of both male and female patients was between ages 51 and 65 (42.2% male & 53.3% female).

**Table-1: Frequency distribution of patients by age and sex (N=200)**

Age group(years)	Sex				Total	
	Male		Female		N	%
	N	%	N	%		
35-50	35	17.5	27	13.5	62	31
51-65	54	27	40	15	84	42
66-80	31	15.5	17	8.5	48	24
81>	5	2.5	1	0.5	6	3
Total	125	62.5	75	37.5	200	100



**Fig-1: Distribution of male and female patients.**

**Table-2: Frequency distribution of patients by age and short term mortality (N=200)**

Age group(years)	Normoglycaemia				Hyperglycaemia				Total	P-Value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%		
35-50	26	41.94	0	0	23	37.1	13	20.1	62	<b>P&lt;.001</b> <b>(x<sup>2</sup> =6.55)</b>
51-65	42	50	5	5.95	28	33.33	9	10.71	84	
66-80	19	39.6	3	6.25	21	43.8	5	10.42	48	
81>	5	83.33	0	0	0	0	1	16.66	6	
Total	92	46	8	4	72	36	28	14	200	

Amongst the hyperglycaemic patients the highest mortality was from age group 35-50 years(20.1%) ,which was statistically significant( $\chi^2 = 6.554, p < .001$ ). Also shows that amongst

normoglycaemic patients below 50 years no patient died; also notable no normoglycaemic patient above 81 years died [Table-2].

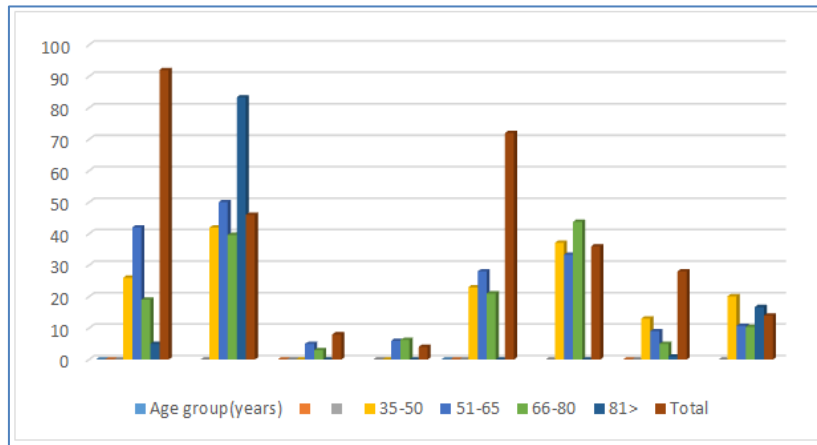


Fig-2: Distribution of patients by age and short term mortality.

Table-3: Frequency distribution of patients by sex and short term mortality (N=200)

Sex	Normoglycaemia		Hyperglycaemia		Total	P-Value				
	Alive		Died							
	N	%	N	%						
Male	59	47.2	6	4.8	43	34.4	17	13.6	125	p<.05 ( $\chi^2 = .65$ )
Female	33	44	2	2.66	29	38.7	11	14.7	75	
Total	92	46	8	4	72	36	28	14	200	

[Table-3] shows the distribution of mortality according to sex and glycaemic status. Short term mortality is more in male both among normoglycaemic

(4.8) and hyperglycaemic group. Here mortality is significantly higher in male( $\chi^2 = .55, p < .05$ ).

Table-4: Frequency distribution of patients by level of consciousness (G.C.S) and short term mortality (N=200)

Glasgow coma scale	Normoglycemia		Hyperglycemia		Total	P-Value				
	Alive		Died							
	N	%	N	%						
>12	30	50	0	0	27	45	3	5	60	p<.05 ( $\chi^2 = 12.59$ )
8-12	22	47.82	2	4.34	19	41.30	3	6.52	46	
<8	40	42.55	6	6.38	26	27.66	22	23.40	94	
Total	92	46	8	4	72	36	28	14	200	

[Table-4] shows the outcome of the patients according to the level of consciousness as assessed by the Glasgow coma scale. Amongst hyperglycaemic

patients, those having GCS < 8, mortality was the highest (23.40%) and those patients having GCS>12 had the lowest mortality (5%),[  $\chi^2 = 12.59, p < .05$ ].

Table-5: Frequency distribution of patients by Systolic B.P.and short term mortality (N=200)

Systolic B.P.(mm Hg)	Normoglycaemia		Hyperglycaemia		Total	P-Value				
	Alive		Died							
	N	%	N	%						
<140	47	2.14	4	3.96	39	38.61	11	10.89	101	p>.05
140-160	22	51.16	1	2.33	14	32.6	6	13.95	43	
161-180	18	54.55	1	3.03	10	3.03	4	12.12	33	
181-200	3	33.33	2	22.22	2	22.22	2	22.22	9	
>200	2	14.29	0	0	7	50	5	35.71	14	
total	92	46	8	4	72	36	28	14	200	

[Table-5] shows effect of systolic blood pressure on mortality in both normo and hyperglycaemic group. Although at all levels of SBP mortality was more in the hyperglycaemic patients than

the normoglycaemic patients except in 180-200mm Hg group (where the mortality is equal),but this difference was not statistically significant. [ $\chi^2 = 2.511, p > .05$ ].

**Table-6: Frequency distribution of patients by Diastolic B.P. and short term mortality (N=200)**

Diastolic B.P.(mm Hg)	Normoglycaemia				Hyperglycaemia				Total	P-Value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
<80	41	43.61	2	2.1	44	46.9	7	7.45	94	p>.05
81-90	22	61.11	2	5.6	10	27.8	2	5.56	36	
91-100	21	44.7	2	4.3	12	25.53	12	25.53	47	
101-110	4	57.14	0	0	1	14.3	2	28.57	7	
>110	4	25	2	12.5	5	31.25	5	31.25	16	
total	92	46	8	4	72	36	28	14	200	

[Table-6] shows effect of diastolic blood pressure on mortality in both normo and

hyperglycaemic group. Again we found no statistically significant difference here.

**Table-7: Frequency distribution of patients by ischaemic heart disease (as per ECG) and short term mortality (N=200)**

I.H.D	Normoglycaemia				Hyperglycaemia				Total	P-Value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
Yes	26	50.98	3	5.88	14	27.45	8	15.69	51	p>.05
No	66	44.3	5	3.35	58	38.93	20	13.42	149	
Total	92	46	8	4	72	36	28	14	200	

I.H.D: Ischaemic heart disease

normoglycaemia.amongst all groups, those patients having hyperglycaemia and ischaemic heart disease had the highest mortality (15.69%) but it was not statistically significant.

[Table-7] Demonstrates comparison between patients of IHD with both hyperglycaemia and

**Table-8: Frequency distribution of patients by smoking and short term mortality (N=200)**

Smoking	Normoglycaemia				Hyperglycaemia				Total	P-Value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
Yes	38	73.08	4	7.7	14	26.92	8	15.4	52	p>.05
No	54	34.5	4	2.7	58	39.2	20	13.51	148	
Total	92	46	8	4	72	36	28	14	200	

**Table-9: Frequency distribution of patients by lesion type and short term mortality (N=200)**

Lesion type	Normoglycaemia				Hyperglycaemia				Total	P-Value
	Alive		Died		Alive		Died			
	N	%	N	%	N	%	N	%	N	
Ischaemic	61	45.2	3	2.22	55	40.74	16	11.85	135	p>0.5
Haemorrhagic	29	46.03	5	7.9	17	27	12	19.04	63	
Subarachnoid haemorrhage	2	100	0	0	0	0	0	0	2	
Total	92	46	8	4	72	36	28	14	200	

[Table-8, 9] demonstrates effects of smoking and lesion type respectively on hyperglycemic stroke but we found no significant difference.

**Table-10: Frequency distribution of died patients by sex and glycaemic status (N=200)**

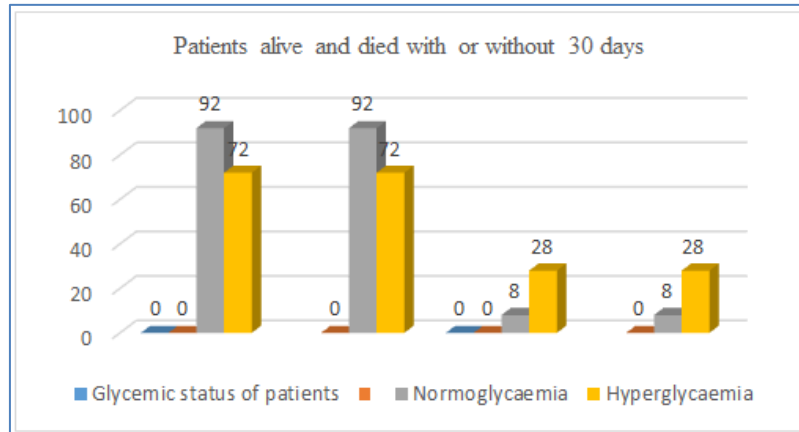
Sex of the patient	Died Patients with Normoglycaemia		Died patients with Hyperglycemia		Total	
	N	%	N	%	N	%
Male	6	16.7	17	47.2	23	63.9
Female	2	5.6	11	30.6	13	36.1
Total	8	22.2	28	77.8	36	100



[Table-10] shows comparison among died patients only. Out of total 36 death, male patients had the higher mortality (63.9%)( $p < .05$ ).

**Table-11: Frequency distribution of patients by glycaemic status and short term mortality (N=200)**

Glycemic status of patients	Patients alive at 30 days		Patients died within 30 days		Total
	N	%	N	%	
Normoglycaemia	92	92	8	8	100
Hyperglycaemia	72	72	28	28	100
Total	164	82	36	18	200



**Fig-3: Distribution of patients by glycaemic status and short term mortality.**

Former concepts were established by many small and large scale studies (some of those are mentioned earlier) also in our study we found higher short term mortality in hyperglycaemics [Table-11].

## DISCUSSION

A good number of studies have established that both hyperglycaemia on admission and preexisting diabetes increase the risk of short term mortality in stroke patients; also both the factors increase the haemorrhagic conversion of ischemic stroke after thrombolytic and anticoagulant therapy [1, 7-9]. Former concepts were established by many small and large scale studies (some of those are mentioned earlier) also in our study we found higher short term mortality in hyperglycaemics in this study. The same metaanalysis [1], revealed acute hyperglycemia predicts increased risk of in-hospital mortality after ischaemic stroke in nondiabetic patients and increased risk of poor functional recovery in nondiabetic stroke survivors. Williams *et al.* [9], observed in their study significantly increased mortality in stroke patients with hyperglycaemia on admission. Another important observation in this study was 40% of admitted stroke patients were hyperglycaemic. The later study also says that patients with hyperglycaemia were mostly women. But in our study in all age groups of stroke male patients were more in number and amongst died patients from both normo and hyperglycaemic groups male were significantly predominant( $p < .005$ ) in this study. This study more elaborately demonstrates more adverse outcomes in male patients of stroke. Here both in normoglycemic and hyperglycemic group mortality

was significantly higher in male ( $p < .05$ ). Vaartjes *et al.* [10], conducted a cohort study in netherlands and showed significantly lower motality in female in cases of both ishchaemic and haemorrhagic stroke but in sabarachnoid hemorrhage no significant difference was noted. Ayala *et al.* [11], conducted a study during 1995 to 1998 and showed ‘age standardadized death rates from overall stroke are higher among men than women, but little is known about sex differences in stroke subtype by race/ethnicity. Age stood as an important short term mortality predictor in stroke in this study. Amongst hyperglycemic patients the highest mortality was from age group 35-50 years (20.1%), which is statistically significant ( $p < .05$ ). So this table opens a new window of thinking about the vulnerability of this middle aged group and less mortality of the frail order group, above 81 years of age; it should be kept in mind that, this may be due to the fact that number of patients above age 80 years was very low (6/200). Now it should be explored why and how this middle age (35-50) group is adversely affected by hyperglycemic stroke. This study expresses the importance of Glasgow coma scale on admission. Among hyperglycaemic patients having GCS below 8 had significantly ( $p < .05$ ) higher short term mortality than those with more than 12. Miah M.T. *et al.* [12], conducted an observational study in Dhaka medical college hospital and found 12.07% fatality among patients having GCS 3-8 and no mortality among 13 to 15.They recommended in their conclusion to consider GCS as an important mortality predictor in acute stroke. Handchuar *et al.* [13], conducted another study and expressed the same comment. Table-3.5 and3.6 try to correlate systolic and diastolic blood pressures respectively on admission with short term

mortality; but both table only show poor prognosis in case of hyperglycemics in all systolic and diastolic blood pressure groups; but elevated blood pressure neither systolic nor diastolic had any significant effect. Rabkin *et al.* [14], demonstrated systolic blood pressure and its 5-year change, each were significant predictors of short-term (30 days) mortality and concluded that high blood pressure and large positive 5-year change in systolic blood pressure before stroke occurrence are significant predictors of a poor prognosis. Due to poor quality of record keeping procedures in our country both on the inpatient and outpatient departments of various hospitals, it is difficult to carry out such a study where we can consider pre stroke blood pressure or 5 year change in blood pressure. A systematic review conducted by Williams *et al.* [10], also found high systolic blood pressure as important predictor of short term mortality. Considering the aforementioned studies we propose to conduct another study to evaluate effect of blood pressure on acute stroke mortality. This study tries to correlate short term mortality in stroke patients with ischaemic heart disease. Short term mortality was more in patients with ECG demonstrated heart disease although difference between IHD and non IHD mortality in hyperglycaemic stroke deaths was not statistically significant. Here we used only ECG as a diagnostic tool for defining IHD. In this study demonstrated no significant difference among smokers and non-smokers in terms of short term stroke mortality. Myint *et al.* [15], conducted a study which shows increased death rate in long term follow up after stroke who continued smoking. Another important finding regarding this issue was observed in another study conducted by vartiainen [16]. Here combined reduction in diastolic blood pressure, serum total cholesterol and smoking demonstrated reduction in post stroke death by two third and half in case of male and female respectively. Notably in our study continuation of smoking was not considered at all, again smoking was not quantified in terms of pack year. This study demonstrates effect of lesion subtype on short term mortality. No significant difference was noted between ischaemic and haemorrhagic stroke (although short term mortality among hemorrhagic stroke albeit more than ischemic stroke.) It is generally observed that mortality is more in patients of haemorrhagic stroke than in patients of ischemic stroke but in this study there was no significant difference of mortality in these two groups of patients. This may be due to the fact that it is a hospital based study in which only admitted patients are included. Patients of stroke are admitted in the hospital only when their general condition is very poor irrespective of the fact whether they suffered from ischemic or haemorrhagic stroke. So ischemic stroke patients whose general condition is not poor are not brought to the hospital. This also explains the fact why patients of ischaemic stroke are only double the number of haemorrhagic stroke patients while the actual ratio of ischaemic to haemorrhagic stroke patients is about 4:1. Since only very serious patients of ischemic stroke are

admitted to the hospital there is no significant difference in the mortality in patients of ischaemic and haemorrhagic stroke admitted in the hospital.

## CONCLUSION

The aim of the study was to explore the significant risk factors for short term mortality for stroke along with hyperglycemia. Now we can come to following conclusions: Male sex has significantly higher mortality in stroke patients ( $p < .05$ ). Middle age (35-50 years) becomes important short term stroke mortality predictor along with hyperglycemia. Glasgow coma scale below 8 at admission is a poor risk factor for short term outcome.

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