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Short Term Hospital Outcome of Intracerebral Hemorrhage on The Basis of Admission Serum Calcium Level

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Abstract **Original Research Article**

Background: Spontaneous intracerebral haemorrhage (ICH) accounts for approximately 15% of all strokes and is a leading cause of disability, with a one-month mortality rate of 40%. Whereas factors predicting short-term mortality are well known, data regarding long-term outcome are scarce and imprecise. Only a few studies revealed association of serum calcium level with outcome of stroke particularly ischaemic stroke but data regarding intracerebral hemorrhage is very limited. Therefore, to reveal the short-term hospital outcome of intracerebral hemorrhage patient on the basis of admission serum calcium level is the objective of the study. ***Methods:*** This study was a hospital based observational study and conducted at the Department of Neurology, Neurosurgery and Medicine in Dhaka Medical College Hospital. People who were suffering from intracerebral haemorrhage and were admitted in the department of Neurology, Neurosurgery and Medicine were approached for inclusion in the study according to inclusion and exclusion criteria. Ethical issues were ensured properly. After written informed consent history and physical examination were done. Diagnosis was confirmed by researcher with the aid of CT scan. Total 365 consecutive samples were collected and incompletion of data was considered exclusion of the study. Following radiological confirmation blood were drawn to measure serum calcium level with maintaining all aseptic precautions. For analysis patients' corrected serum calcium level were divided into three tertiles: T1 = <2.20 mmol/l, T2 = 2.20 to 2.40 mmol/l and T3 = >2.40 mmol/l. The principal investigator interviewed each patient individually and in case of unconscious patient; history was collected from attendant of the patient. All these were registered, documented and analyzed in the statistical program Statistical Package for Social Science (SPSS) version 20.0. ***Results:*** Out of a total of 365 patients, Mean age of the population was 58.43(±12.33)SD (range 32-75) years and frequent age group was 61-70 (n=145, 39.7%) years. 58% (n=210) were male and 42% (n=155) were female. Frequency of monthly income range (taka), ≤5000, in between 5001-10000, 10001-20000 were 33.7%, 31.0%, 28.8%,6.6% respectively. 281 (77%) patients had high blood pressure & 68 patients (18.6%) had diabetes mellitus (DM) as a risk factor. Analysis of MRS showed frequency of excellent outcome & mortality at day 14 & day 30 were 37.0% (n=135), 50.7% (n=185) and 29.0% (n=106), 37.3% (n=136) respectively. Among the study participants mean adjusted serum calcium was 2.27 (±0.25 SD) mmol/l and 365 patients were distributed into three tertile in 119 (T1), 124 (T2) and 122 (T3) subsequently. Factor analysis in relation of serum calcium level showed Age (Older), Sex (male) and Triglyceride level were associated with lower calcium level and all were statistically significant (p value were <.004, <.001 &<.001). Univariate analysis comparing the highest and lowest tertiles indicated that an elevated calcium level was associated with 5.1- and 3.1-fold increases in the odds for day 14- and 30-days excellent outcome, respectively. After adjustment for age, sex, and other potential risk factors, patients in the highest quartile still had significantly increased odds of day 14 and 30 day excellent outcome; the corresponding odds ratios (ORs) were 4.6 (95% confidence interval [CI], (2.41 – 8.93) and 3.31 (95% CI, 1.88 – 5.83). Similarly, Mortality assessment by univariate analysis comparing the highest and lowest tertiles indicated that an elevated calcium level was associated with 2.1- and 3.1-fold decrease in the odds for day 14- and 30-days mortality, respectively. Following adjustment of (multivariate analysis) potential risk factors, patients in the lowest quartile still had significantly increased odds of day 14- and 30-day mortality; the corresponding odds ratios (ORs) were 2.07 (95% CI,1.13 – 3.80), and 3.09 (95% CI, 1.74 – 5.50). ***Conclusion:*** Worse outcome of ICH was significantly associated with decrease serum calcium level. And there was a linear association of poor outcome with degree of hypocalcaemia.

Keywords: Spontaneous intracerebral haemorrhage, ischaemic stroke, serum calcium.

INTRODUCTION

Stroke is the second leading cause of death worldwide and one of the leading causes of disability [1]. Due to advancement of science and technology there is increasing life expectancy is seen all over the world though the burden of stroke is likely to increase worldwide particularly in middle and low income countries [2, 3]. According to an estimates of world health organization (WHO) suggests majority of deaths (86%) related to stroke worldwide occurred in developing countries and South Asia is thought to be the highest contributor, probably accounting for more than 40% of global stroke deaths [4, 5]. In this region, stroke mortality rates might be as high as those for coronary artery disease, and both stroke and coronary heart disease occur about 10 years earlier, on average, than in the rest of the world [6].

Intracerebral hemorrhage occurs when a blood vessel within the brain parenchyma ruptures as a complication of a pre-existing lesion (vascular malformation or tumor) or in the absence of a single clear underlying lesion [7]. It is the second most common subtype of stroke after ischemic stroke and accounts for approximately 10 % to 20 % of all strokes [8].

Several studies were conducted to find out the risk factors and the predictors of short term and long-term survival of ICH patients. Among them two important predictor were identified and they are baseline hematoma volume and hematoma expansion. It has been suggested that a lower serum calcium level is associated with higher hematoma volume in patients with ICH, as well as hemorrhagic transformation after intravenous thrombolysis for acute ischemic stroke [9]. However, systematic studies on the topic are currently lacking, and the underlying mechanisms are poorly understood. One possibility is that serum calcium is involved in platelet function and in several steps of the coagulation cascade [10]. Therefore, the purpose of the study is to explore the short-term hospital outcome of intracerebral hemorrhage on the basis of admission serum calcium level.

Identifying the risk factors and predictors of short term and long-term outcome of the patient is an essential step and several risk factors were identified. Among them most recently serum calcium has been identified as a predictor and study showed there is association of serum calcium level and short term and long-term outcome of the ischemic stroke [11]. It was stated that prognosis of the ICH patient is dependent of initial hematoma especially when the size is larger [12]. A study conducted by Morotti *et al*., suggests that a lower calcium level (free or ionized) on admission is associated with a larger initial ICH size and a higher risk of hematoma expansion [9]. This prospective cohort study of 2103 patient has revealed that only 10.9% of enrolled patients had a reduced serum calcium level (defined as a total calcium level of 8.4 mg/dL or less), that was associated with higher baseline ICH volumes. Conversely, higher calcium levels were associated with a reduced risk of ICH expansion after adjustment for other risk factors [9]. Both associations were statistically significant.

OBJECTIVE

General Objective

- To determine the relation between serum calcium level and short-term outcome of intracerebral hemorrhage (ICH).

Specific Objective

1) To assess the clinical presentation of the patients admitted due to intracerebral hemorrhage.
2) To observe the corrected calcium level on admission
3) To find out the short time outcome of the patients according to modified rankin scale (MRS)

METHODOLOGY

Study design: It was an observational study.

Study place: Department of Neurology, Neurosurgery and Medicine, Dhaka Medical College Hospital.

Study Period: This study was conducted for a period of 2 years started from July 2015 to June 2017.

Study population: Patients suffering from non–traumatic intracerebral hemorrhage.

Inclusion Criteria

- Age ≥18 years
- All cases and both sexes of acute intracerebral hemorrhage confirmed by CT scan of head
- Patient who willing to give informed written consent
- Patient who are willing to give blood sample for serum calcium estimation

Exclusion Criteria

- Secondary cause acute intracerebral hemorrhage
- Diagnosed case of hypercalcemia due to any cause
- Multi-organ failure at the time of diagnosis

Sample size: The sample size of this study was determined by following equation.

Sampling technique

Non-probability purposive consecutive sampling method was used to select sample population.

Data collection technique

Patient with intracerebral haemorrhage following admission in the department of Neurology,

Neurosurgery and Medicine were sorted out according to inclusion and exclusion criteria and was confirmed by aconsultant neurologist. All of the study population were counseled regarding the study aim, objectives, and usefulness of the study. Written informed consent were collected from each patient and interview was taken by the researcher himself with a semi-structured questionnaire.

Data processing and analysis

Differences between the groups were analyzed using the $\chi 2$ test for categorical variables and the Student t-test or the Mann-Whitney U test for continuous variables. To test for significant associations between MRS distribution at day 14 and day 30 and serum levels of albumin-corrected calcium, logistic regression analyses were used. Excellent outcome were considered MRS 0-1. For logistic regression models and Cox proportional hazard models, adjusted variables with *p* values <0.05 were selected by univariate analysis.

RESULTS

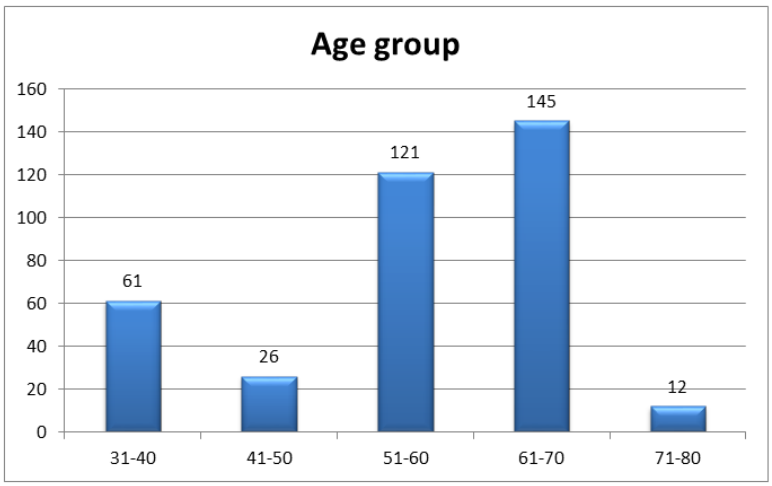

Figure 1: Age group of the patients (n=365)

Total 365 patients were studied. Minimum age was 32 and maximum age was 75 years. Mean age was 58.43(±12.33). Most of the patients (145, 39.7%) were aged in between 61 to 70 years followed by 121 patients (33.2%) in between 51 to 60 years of age. Among rest 61 patients (16.7%) was from 31 to 40 years group, 26 patients (7.1%) were from group 41 – 50 years and 12 patients (3.3%) were from group 71 to 80 years. figure 1shows a column chart of the distribution.

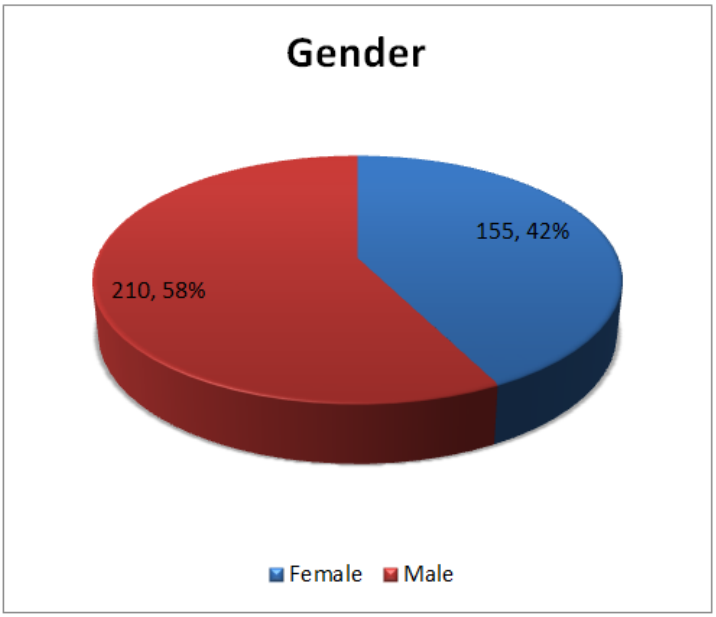

Figure 2: Distribution of patients according to gender (n= 365)

Among all the patients studied majority were male (210, 58%). 155 patients (42%) were females. A pie chart of sex distribution is shown in Figure 2.

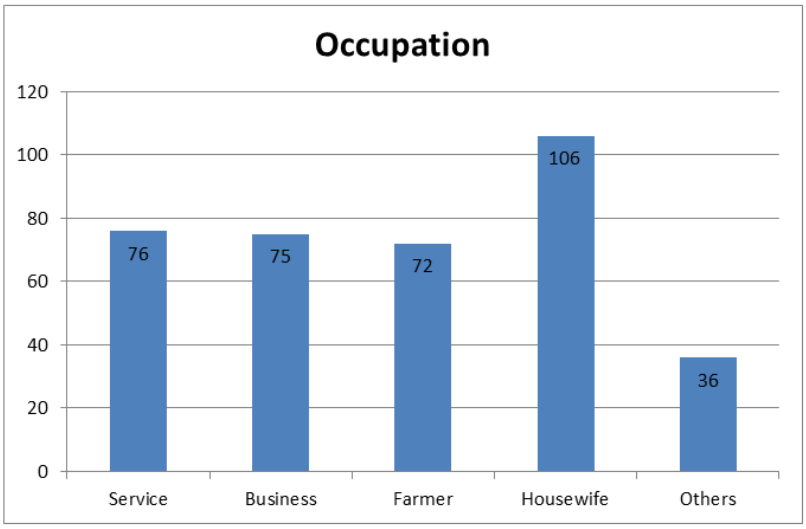

Figure 3: Distribution of patients according to occupation (n = 365)

Out of 365 patients majority were housewives (106, 29%). Among rest 76 patients (20.8%) were doing service, 75 patients (20.5%) were doing business and 72 patients (19.7%) were farmers. 36 patients (9.9%) were doing various other jobs. Figure 3 shows a column chart of the distribution.

Table 1: Outcome and mortality of patients at day 14 and day 30

	Number of patients	Percentage
Excellent outcome at day 14	135	37.0 %
Excellent outcome at day 30	185	50.7 %
Mortality at day 14	106	29%
Mortality at day 30	136	37.3%

Excellent outcome is defined by having MRS score 0 and 1 at follow up. 37.0% patients had excellent outcome at day 14 and 50.7% patients had excellent outcome at day 30. 29% patients died at day 14 and 37.3% patients died at day 30.

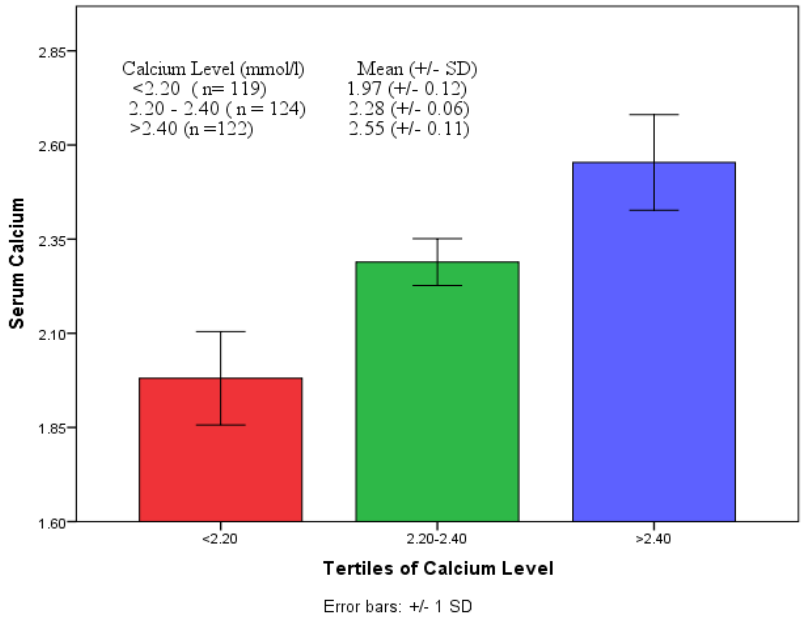

Figure 4: Distribution of adjusted serum calcium across different tertiles (n=365)

Normal Serum calcium level is defined as serum calcium between 2.20 to 2.70 mmol/l. In this study mean adjusted serum calcium was 2.27 (±0.25) mmol/l. For analysis patients were divided into three tertiles: T1 = <2.20 mmol/l, T2 = 2.20 to 2.40 mmol/l and T3 = >2.40 mmol/l. Among 365 patients 119, 124 and 122 patients fell into T1, T2 and T3 category respectively. Mean calcium level within each tertile is shown in Figure 4.

Table 2: Characteristics of study participants across serum calcium tertiles (n= 365)

Variables	*Serum Calcium Tertiles*			P value
	T1	**T2**	**T3**	
Calcium (mmol/L)	**<2.20**	**2.20 – 2.40**	**>2.40**	
N	119	124	122	
Age (±SD) in year	61.06 (±11.60)	55.79 (±12.39)	58.27 (±12.49)	**0.004***
Sex (Male)	84	64	62	**<0.001***
H/O smoking (Yes)	31	36	33	0.877**
DM (Present)	22	25	21	0.823**
HTN (Present)	95	91	95	0.420**
***ANOVA **Chi-Square Test**				

Patients who were older and who were male tended to have lower serum calcium level. Mean age of population (61.06 ±11.60 years) in serum calcium tertile T1 (<2.20 mmol/l) was significantly higher than other tertiles (55.79 ±12.39 and 58.27 ±12.49 for T2 and T3 respectively). p value was 0.004.

Table 3: Clinico-biochemical profile of study participants across serum calcium tertiles (n= 365)

Variables	*Serum Calcium Tertiles*			P value
	T1	**T2**	**T3**	
Calcium (mmol/L)	**<2.20**	**2.20 – 2.40**	**>2.40**	
N	119	124	122	
SBP	166.21 (±17.33)	165.40 (±17.69)	165.76 (±18.25)	0.938*
DBP	95.63 (±10.87)	92.86 (±8.53)	93.63 (±10.57)	0.089*
FBS	6.66 (±0.83)	6.47 (±0.92)	6.46 (±1.02)	0.165*
Total Cholesterol	181.38 (± 41.87)	194 (± 42.76)	187 (±43.17)	0.05*
LDL	116.00 (±36.11)	119 (±34.54)	117 (±35.41)	0.703*
TG	114.68 (±41.75)	149.65 (±36.73)	132 (±42.30)	**<0.001***
S. creatinine	1.21 (±0.73)	1.09 (± 0.25)	1.15 (±0.54)	0.196*
***ANOVA**				

Systolic blood pressure, diastolic blood pressure, Fasting blood sugar, total cholesterol (TC), low density lipoprotein (LDL) and serum creatinine showed homogenous distribution across serum adjusted calcium tertiles. Serum Triglyceride level was significantly higher in group T2 and T3.

Table 4: Odds ratios and 95% confidence intervals for 14 day and 30 day excellent outcome according to serum calcium quartiles among acute intra-cerebral hemorrhage stroke patients (n= 365)

Variables	*Serum Calcium Tertiles*			P value*
	T1	**T2**	**T3**	
Adjusted Calcium (mmol/L)	**<2.20**	**2.20 – 2.40**	**>2.40**	
No. of cases of excellent outcome	20	52	63	
At 14 days				
Crude	1	3.53 (1.94 – 6.44)	5.14 (2.83 – 9.34)	T2 <0.001 T3 <0.001
Adjusted*	1	2.44 (1.24 – 4.81)	4.67 (2.41 – 8.93)	T2 0.009 T3 <0.001
At 30 days				
No. of cases of excellent outcome	41	67	77	
Crude	1	2.20 (1.13 – 3.70)	3.14 (1.85 – 5.32)	T2 0.003 T3 <0.001
Adjusted*	1	2.23 (1.22 – 4.06)	3.31(1.88 – 5.83)	T2 0.001 T3 <0.001
*** Adjusted for age, history of DM, history of HTN, smoking, SBP, DBP, FBS, Serum lipid profile and Serum creatinine**				

Modified Rankin Score 0 or 1 was considered as excellent outcome at follow up. Patients who had adjusted serum calcium level at admission in between 2.20 to 2.40mmol/l have significantly higher odds of having excellent outcome at day 14 and day 30 after discharge than patients who had adjusted serum calcium level below 2.20 mmol/l. Patients in the T3 group (ie serum calcium >2.40 mmol) had still higher odds of having excellent outcome than T1 group and this finding was significant. When adjusted for age, h/o smoking, HTN, DM, SBP, DBP, FBS, Serum creatinine and serum lipid profile overall odds ratio decreased at 14 days but slightly increased at 30 days.

Table 5: Odds ratios and 95% confidence intervals for 14 day and 30 day mortality according to serum calcium quartiles among acute intra-cerebral hemorrhage stroke patients (n= 365)

Variables	***Serum Calcium Tertiles***			**P value***
	T1	**T2**	**T3**	
Adjusted Calcium (mmol/L)	**<2.20**	**2.20 – 2.40**	**>2.40**	
No. of cases died	46	32	28	
At 14 days				
Crude	2.16 (1.23 – 3.79)	1.18 (0.65 – 2.11)	1	T1 0.007 T2 0.577
Adjusted*	2.07 (1.13 – 3.80)	1.36 (0.73 – 2.55)	1	T1 0.018 T2 0.323
At 30 days				
No. of cases died	62	42	32	
Crude	3.15 (1.83 – 5.40)	1.45 (0.84 – 2.52)	1	T1 <0.001 T2 0.179
Adjusted*	3.09 (1.74 – 5.50)	1.64 (0.92 – 2.93)	1	T1 <0.001 T2 0.089
*** Adjusted for age, history of DM, history of HTN, smoking, SBP, DBP, FBS, Serum lipid profile and Serum creatinine**				

Patients who had adjusted serum calcium level at admission less than 2.20mmol/l have significantly higher odds of mortality at day 14 and day 30 after discharge than patients who had adjusted serum calcium level more than 2.40 mmol/l. Patients in the T2 group (ie serum calcium in between 2.20 and 2.40 mmol/l) had higher odds of mortality than T3 group, although this finding was not significant. When adjusted for age, h/o smoking, HTN, DM, SBP, DBP, FBS, Serum creatinine and serum lipid profile overall odds ratio decreased slightly for T1 and increased slightly for T2.

DISCUSSION

Serum calcium level during admission is one of the important prognostic factors of intracerebral haemorrhage. In JAMA Neurology, a study from Morotti and colleagues (Morotti A *el al.,* 2016) suggests that a lower calcium level (free or ionized) on admission is associated with a larger initial ICH size and a higher risk of hematoma expansion [9]. But, how does serum calcium level affect outcome in haemorrhagic stroke patients? This study tried to elucidate the answer to this question.

Total 365 patients of intracerebral haemorrhage were taken for this study. Minimum age was 32 and maximum age was 75 years. Mean age was 58.43(±12.33). Majority of the patients (39.7%) were aged in between 61 to 70 years followed by 33.2% in between 51 to 60 years of age. This implies total 72.9% of stroke patients were from 51 to 70 years of age. In a socio-demographic study of stroke patients conducted in a tertiary care hospital of Bangladesh.

In this study majority were housewives (29%). 20.8% were doing service, 20.5% were doing business and 19.7% were farmers and 9.9% were doing various other jobs. A slightly different figure was found by Siddiqui and colleagues. They found 20% businessman, 12% service holder and 19% housewives.

Excellent outcome was defined by having mRS score 0 and 1 at follow up. 37.0% patients had excellent outcome at day 14 and 50.7% patients had excellent outcome at day 30. 29% patients died at day 14 and 37.3% patients died at day 30. Shoujiang You and colleagues followed up ICH patients at discharge and at 90 days. In their study they found 45.2% patients having excellent outcome at day 90 [13]. Flaherty and colleagues found one month mortality of 48% and 44% in two cohorts of haemorrhagic stroke patients [14]. They reported 42% mortality at one month from other population-based studies. Findings of the present study correspond with above mentioned studies.

For analysis patients were divided into three tertiles: T1 = <2.20 mmol/l, T2 = 2.20 to 2.40 mmol/l and T3 = >2.40 mmol/l. Among 365 patients 119, 124 and 122 patients fell into T1, T2 and T3 category respectively. Shoujiang You and colleagues divided their population into 4 quartiles for analysis depending on level of calcium. Their categories were Q1 = <2.14 mmol/l, Q2 = 2.14 – 2.24 mmol/l, Q3 = 2.24-2.32 and Q4= ≥2.32 mmol/l. This division is arbitrary and for the comparison across graded levels of serum calcium.

When the highest and lowest tertiles were compared in univariate models, an elevated serum

calcium level was associated with a 5.14- fold increase in odds for excellent outcome at day 14 (OR, 5.14; 95% CI, 2.83-9.34, *P* = <0.001) and a 3.14-fold increase in odds for 30 days excellent outcome (OR, 3.14; 95% CI, 1.85-5.32; *P* = .003). After multivariate adjustment, the patients in the highest quartile still had significantly increased odds of 14 day and 30 day excellent outcome; 4.67(95% CI, 2.41-8.93) and 3.31 (95% CI, 1.88-5.83), respectively.

Again when the lowest and highest tertiles were compared in univariate models, an decreased serum calcium level was associated with a 2.16- fold increase in odds for mortality at day 14 (OR, 2.16; 95% CI, 1.23-3.79, *P* = 0.007) and a 3.15-fold increase in odds for 30 day mortality (OR, 3.15; 95% CI, 1.83-5.40; *P* = <0.001). After multivariate adjustment, the patients in the lowest quartile still had significantly increased odds of 14 day and 30 day mortality; 2.07(95% CI, 1.13-3.80) and 3.09 (95% CI, 1.74-5.50), respectively. This implies that adjusted serum calcium level less than 2.20 mmol/l in haemorrhagic stroke patients at admission is associated with increased short term mortality.

CONCLUSION

Association of serum calcium level with outcome of ICH patients was limited. In this study, serum calcium level has proven its association of poor outcome of ICH patients in short term follow up. Moreover, outcome becomes worse with the reduction of serum calcium level. Though, there seems to be a linear relation with this two factors but further cohort studies can conclude the fact.

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