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Association of Troponin I Level with Severity and In-hospital Outcome in Patients with Acute Ischemic Stroke

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Abstract:

Background: *Troponin I is recognized as sensitive and specific marker of myocardial injury. But elevation of troponin I can occur after acute ischemic stroke in absence of primary cardiac causes.* ***Objective:*** *The study was planned to evaluate the association of troponin I level with severity of neurological disability in acute Ischemic Stroke patient and their in-hospital outcome.* ***Methods:*** *This cross-sectional study was conducted in the department of Neurology and department of Medicine, Mymensingh Medical College & Hospital from July, 2018 to June, 2019. Total 115 purposively selected patients with acute ischemic stroke were evaluated. Diagnosis was confirmed by CT scan of brain. Serum troponin I was measured for each patients within 24 hours of admission. National Institute of Health Stroke Scale (NIHSS) was used to assess severity of stroke within 48hours of admission. Modified Rankin Scale (mRS) was used to evaluate outcome during discharge.* ***Results:*** *Mean age of acute ischemic stroke patients was 59.5±13.8 years with male predominance (62.6%). Mean age of elevated troponin I group was significantly higher than that of non-elevated group (70.9 vs. 57.2 years). Almost half of the respondents (44.3%) scored 1-4 (minor stroke), 38.3% had scored 5-15 (moderate stroke), 14.8% had scored 16-20 (Moderate to severe stroke) and 2.6% had scored greater than 20 (severe stroke). Moderate to severe stroke was significantly higher in elevated TnI group compare to non-elevated TnI group. Elevated troponin I (TnI) was found in 19(16.5%) cases and 96(83.5%) patients had TnI level<0.3 ng/ml (Non-elevated). The mean serum cardiac troponin I values in all patients was 0.294±0.547ng/mL. Comparing to patients with non-elevated TnI group, patients with elevated TnI had higher mean NIHSS scores on admission (16.4 vs. 5.35). The mean mRs score was also higher for the elevated TnI group compare to non-elevated TnI group during discharge (5.21 vs. 2.57). The mean length of hospital stay (days) was higher in elevated TnI group compare to non-elevated TnI group (7.42 vs. 4.03). Multivariate analysis revealed that age e" 60 years (Odd ratio [OR] 1.12, CI [1.01–2.94]), NIHSS score e"12 on admission (OR 4.29, CI [1.04–11.29]), and elevated TnI (OR 2.58, CI [2.07–6.02]) were associated with in-hospital outcome.* ***Conclusion:*** *Elevated serum TnI levels were associated with increased severity of acute ischemic stroke and in-hospital outcome.*

Key words: *Troponin I, Acute ischemic stroke, severity, outcome*

Introduction:

Stroke is the third most common cause of death in the developed world after heart disease and cancer after the age of 40[1]. About one-fifth of patient with stroke will die within a month of event and half of those who survive will be left with physical disability[2]. According to the latest WHO data published in 2017 Stroke deaths in Bangladesh reached 128,190 or 16.27% of total deaths[3]. Acute stroke is conferred as significant increase in adverse outcomes during short and long term follow up. A subset of patient with stroke might be

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at higher risk at long term adverse cardio-vascular outcomes. Troponin-I is a highly sensitive and specific marker for myocardial necrosis that is used in the diagnosis and prognosis of patients with acute coronary syndrome. However, troponin elevation has been documented in multiple clinical settings in the absence of ACS[1,2]. Increase in troponin has been documented in all types of stroke including ischemic stroke and subarachnoid hemorrhage[4]. In a meta-analysis of 15 studies involving 2901 patients, elevated troponin were documented in 18.1% patients with stroke that included patient with ECG changes suggestive of myocardial ischaemia[2]. Troponin I elevation has also been documented in acute stroke without any evidence of acute coronary syndrome[5]. Elevated troponin I level in patient with acute ischemic stroke predicts poor outcome and mortality. Some studies have shown an increase in all cause mortality with Troponin I elevation in acute stroke during in-hospital and short term follow-up[6-8]. An increase in all cause mortality has been documented in patient with or without ischemic ECG changes[6-8]. In several studies the elevation of troponin was associated with stroke severity on hospital admission, short and long term clinical outcome an increased risk of mortality indicating prognostic significance of increased troponin in acute ischemic stroke[7-9].

The notion is supported by the fact that stroke and myocardial infarction share common risk factors and by the high prevalence of coronary artery disease in stroke patient[10]. Acute stroke related increased sympathetic activity with excessive catecholamine release results in coagulative myocytolysis may be the cause for this effect[11].

Neurogenic cardiac damage is another possible cause. Cardiac injury might result from autonomic imbalance after stroke affecting cortical areas controlling autonomic function e.g. insular cortex. A subsequent catecholamine surge may include global LV dysfunction[12, 13].

Another study was done in Taiwan which shows that Elevation of Troponin I during acute stroke is a strong independent predictor for both poor outcome and in-hospital mortality[14].

This study was done to evaluate the association of troponin I with severity of neurological disability in acute ischemic stroke patients and their in-hospital outcome.

Objective of the study: To find out the association between serum Troponin I level with severity and in-hospital outcome of acute ischemic stroke.

Methods:

This was a cross-sectional descriptive study carried out in the Department of Neurology and Medicine, Mymensingh Medical College & Hospital, Mymensingh from July 2018 to June 2019. Total 115 patients with acute ischemic stroke (within 72 hours of onset) and confirmed by CT scan who admitted in Department of Neurology were included in this study. Purposive type of non-probability sampling technique was used.

Total duration for the study was two years. Patients who admitted in Department of Neurology and Medicine ward, Mymensingh Medical College Hospital with acute ischemic stroke within 48 hours of onset of stroke (from history) were included in the study. Patient with old ischemic stroke, hemorrhagic stroke (diagnosed on history and computed tomography or MRI of brain), stroke with renal impairment, heart failure, COPD, Sepsis (diagnosed on history, examination and investigations), patient age 18 below were excluded from the study. Before starting the data collection, all patients were described about the study objectives and details procedure of the study. They were clearly informed that this participation is voluntary. Informed written consent was ensured before participation of all patients. On admission, Patients medical history and data from physical examination were recorded on a standard questionnaire by the investigator. Clinical history and physical examination were evaluated with special attention to severity of the disease and comorbidities: age, sex, smoking habits, hyperlipidemia, hypertension, diabetes mellitus, coronary artery disease, family history of cerebrovascular events, and current medication. Data were checked by the supervisor of the study and in case of discrepancies; both investigators and guide in consensus reevaluated the patient. Blood samples for determination of serum TnI values were taken within 24 hours of admission. Serum TnI concentration was determined. The severity of neurological disability was evaluated in

patients with clinically confirmed ischemic stroke using National Institute of Health (NIH) stroke scale within 48 hours of admission. Modified Rankin Scale (mRS) was used to evaluate functional outcome during discharge. All collected data were recorded in a separate case record form.

Results:

Table-I

Socio-demographic characteristics of the study subjects

Variables	Frequency	Percent
Age Group		
≤30 years	5	4.3
31 to 40 years	7	6.1
41 to 50 years	21	18.3
51 to 60 years	29	25.2
61 to 70 years	36	31.3
71 to 80 years	10	8.7
>80 years	7	6.1
Gender		
Male	72	62.6
Female	43	37.4

Results are expressed as frequency and percent.

Majority respondents were belonging to age group 61-70 years (31.3%) and followed by in decreasing order 51-60 years (25.2%), 41-50 years (18.3%). The mean age was 59.5±13.8 years.Among 115 respondents 63% were male and 37% were female. The male: female ratio was 1.7:1.

Table-II

Distribution of the study subjects by serum troponin I level

Troponin I Level	Frequency	Percentage
Non-elevated Troponin I (0-0.30)	96	83.5
Elevated Troponin I (>0.3)	19	16.5
Total	115	100.0

Results are expressed as frequency and percent.

Elevated Troponin I (TnI) was found in 19(16.5%) cases and 96(83.5%) patients had TnI level 0 to 0.30 ng/ml. The mean serum troponin I values in all patients was 0.294±0.547 ng/mL.

Table-III

Association between age and troponin I level

Age Group	All subjects (n=115) Count (%)	Troponin level		p-value
		Elevated (n=19) Count (%)	Not Elevated (n=96) Count (%)	
≤30 years	5(4.3)	0(0.0)	5(5.2)	0.03*
31 to 40 years	7(6.1)	0(0.0)	7(7.3)	
41 to 50 years	21(18.3)	1(5.3)	20(20.8)	
51 to 60 years	29(25.2)	3(15.8)	26(27.1)	
61 to 70 years	36(31.3)	7(36.8)	29(30.2)	
71 to 80 years	10(8.7)	6(31.6)	4(4.2)	
>80 years	7(6.1)	2(10.5)	5(5.2)	
Total	115(100.0)	19(100.0)	96(100.0)	
Mean±SD	59.5±13.8	70.9.±9.1	57.2±13.5	<0.001*

Results are expressed as frequency, percent and mean±SD.

p-values were determined by *Chi-square test and **Unpaired t- test, *significant.

The Chi-square test indicates that there is statistical significant association between age and troponin I level ($p<0.05$). The mean age of elevated troponin I group was 70.9±9.1 years whereas the mean age for non-elevated group was 57.2±13.5 years. Unpaired t-test indicate that mean age was significantly higher in elevated troponin I level compare to non-elevated group ($p<0.001$).

Table-IV

Distribution of the study subjects by comorbidities related to troponin I level

Comorbidities	All subjects (n=115) Count (%)	Troponin level		p-value
		Elevated (n=19) Count (%)	Not Elevated (n=96) Count (%)	
Hypertension	50(43.5)	13(68.4)	37(38.5)	0.016*
Diabetes mellitus	40(34.8)	11(57.9)	29(30.2)	0.021*
Smoking	42(36.5)	11(57.9)	31(36.5)	0.034*
Alcohol	6(5.2)	1(5.3)	5(5.2)	0.992^{ns}
Dyslipidemia	22(19.1)	8(42.1)	14(14.6)	0.005*
OCP	8(7.0)	0(0.0)	8(8.3)	0.192^{ns}
Family history of stroke	12(10.4)	4(21.1)	8(8.3)	0.098^{ns}
Family history of IHD	39(33.9)	3(15.8)	36(37.5)	0.068^{ns}

Results are expressed as frequency and percent.
p-values were determined by Chi-square test, *significant, ns= not significant.
Chi-square test indicates that hypertension, diabetes mellitus, dyslipidemia and smoking were significantly associated with elevated TnI level ($p<0.05$).

Table-V

Distribution of the study subjects by stroke severity related to troponin I level

Stroke Severity	All subjects (n=115) Count (%)	Troponin level		p-value
		Elevated (n=19) Count (%)	Not Elevated (n=96) Count (%)	
Normal	0(0.0)	0(0.0)	0(0.0)	<0.001*
Minor Stroke	51(44.3)	0(0.0)	51(53.1)	
Moderate Stroke	44(38.3)	6(31.6)	38(39.6)	
Moderate to Severe Stroke	17(14.8)	10(52.6)	7(7.3)	
Severe Stroke (>20)	3(2.6)	3(15.8)	0(0.0)	
Total	115(100.0)	19(100.0)	96(100.0)	

Results are expressed as frequency and percent.
p-value was determined by Chi-square test, *significant.
NIHSS-National Institute of Health Stroke Scale: Normal (0), Minor Stroke (1-4), Moderate Stroke (5-15), Moderate to Severe Stroke (16-20), Severe Stroke (>20).

The chi-square test indicates that there is an association between stroke severity and serum troponin I level as p-value is less than .001. Moderate to severe stroke was significantly higher in elevated TnI group compare to non-elevated TnI group.

Table-VI

Comparison of NIHSS score between elevated TnI and non-elevated TnI group

Troponin Level	NIHSS Score (Mean±SD)	p-value
Elevated	16.4±3.16	<0. 001*
Not Elevated	5.35±3.38	
Total	7.17±5.29	

Results are expressed as mean±SD.
p-value was determined by unpaired t- test, *significant.
NIHSS-National Institute of Health Stroke Scale.

The mean NIHSS score of the respondent was 7.17±5.29. Comparing to patients with non-elevated TnI, patients with elevated TnI were higher mean NIHSS scores on admission (16.4 vs. 5.35). Unpaired t-test indicated that there were significant difference between the mean NIHSS scores for elevated TnI and non-elevated TnI groups (p<0.001).

Table-VII

Comparison of length of hospital stay between elevated TnI and non-elevated TnI level

Troponin Level	Hospital Stay (days) (Mean±SD)	p-value
Elevated	7.42±1.39	<0. 001*
Not Elevated	4.03±1.30	
Total	4.59±1.82	

Results are expressed as mean±SD.
p-value was determined by unpaired t- test, *significant.
The mean length of hospital stay for all respondents was 4.59±1.82 days. The mean length of hospital stay for elevated TnI group was higher compared to non-elevated TnI group (7.42 vs. 4.03) and the mean difference for these groups was statistically significant (p<0.001).

Table-VIII

Distribution of the study subjects by Modified Rankin Scale Score at admission related to troponin I level

Modified Rankin Scale Score	Troponin Level		Total	p-value
	Elevated	Not Elevated		
0	0(0.0)	0(0.0)	0(0.0)	<0.05*
1	0(0.0)	12(12.5)	12(10.4)	
2	0(0.0)	14(14.6)	14(12.2)	
3	4(21.1)	21(21.9)	25(21.7)	
4	8(42.1)	45(46.9)	53(46.1)	
5	7(36.8)	4(4.2)	11(9.6)	
6 (Death)	0(0.0)	0(0.0)	0(0.0)	
Total	19(100.0)	96(100.0)	115(100.0)	
mRS score (Mean±SD)	3.79±0.58	3.15±1.13	3.32±1.14	<0.001**

Results are expressed as frequency, percent and mean±SD.
p-values were determined by *Chi-square test and **Unpaired t- test, *significant.
The mean mRs score of respondents at admission was 3.32±1.14.

Table-IX

Distribution of the study subjects by Modified Rankin Scale Scoreat discharge related to troponin I level

Modified Rankin Scale Score	All subjects (n=115) Count (%)	Troponin level		p-value
		Elevated (n=19) Count (%)	Not Elevated (n=96) Count (%)	
0	0(0.0)	0(0.0)	0(0.0)	<0.05*
1	39(33.9)	0(0.0)	39(40.6)	
2	10(8.7)	0(0.0)	10(10.4)	
3	6(5.2)	0(0.0)	6(6.3)	
4	39(33.9)	2(10.5)	37(38.5)	
5	13 (11.3)	11(57.9)	2(2.08)	
6 (Death)	8(7.0)	6(31.6)	2(2.08)	
Total	115(100.0)	19(100.0)	96(100.0)	
mRS score (Mean±SD)	3.01±1.70	5.21±0.63	2.57±1.49	<0.001*

Results are expressed as frequency, percent and mean±SD.

p-values were determined by *Chi-square test and **Unpaired t- test, *significant.

The mean mRs score of respondents during discharge was 3.01±1.70. The mean mRs score for elevated TnI patients was 5.21 which significantly higher than the non-elevated TnI group patients 2.57 (p<0.001).

Table-X

Regression model of factors influencing poor outcomes in patients with acute ischemic stroke

Variables	Poor outcome (mRS>2)*		
	Adjusted OR	95% CI	p-value
Age e" 60 years	1.134	1.12-1.74	0.038
Hypertension	0.711	0.233-2.167	0.549
DM	1.943	0.483-7.820	0.350
Dyslipidemia	0.242	0.033-1.788	0.164
Smoking	0.893	0.268-2.975	0.854
NIHSS at Admission (e"12)	4.102	4.047-12.10	0.001
Elevated TnI Level	2.369	2.219-7.522	0.001

CI-Confidence intervals, OR-Odd ratio, *Multiple logistic regressions.

Multivariate analysis revealed that age ≥60 years (OR 1.134 CI [1.1–1.74]), NIHSS score ≥12 on admission (OR 4.102, CI [4.047–12.10]), and elevated TnI (OR 2.369, CI [2.219–7.522]) were associated with in-hospital outcome.

Discussion:

This was a cross sectional descriptive study carried out on patient who admitted in Neurology and Medicine ward with acute ischemic stroke. Serum Troponin I level was measured within 24 hours of admission. National Institute of Health Stroke Scale (NIHSS) was used to assess severity of stroke within 48hours of admission. Modified Rankin Scale (mRS) was used to evaluate outcome during discharge.

In this study majority respondents were belonging to age group 61-70 years (31.3%) and followed by in decreasing order 51-60 years (25.2%), 41-50 years (18.3%). The mean age was 59.5±13.8 years. Elevated troponin I was observed in older

age. Mean age of elevated troponin I group was significantly higher than that of non-elevated group (70.9 vs. 57.2 years). On gender distribution, 72 (62.6%) patients were male and 43 (37.4%) patients were female. The male: female ratio was 1.7:1. A study done by Pynam et al.,[11] reported that the mean age was 58.8 ± 13.3 years; there were 230 (63.9%) males. Majority (27.8%) of the patients were in the sixth decade of life; 99 out of 360 (27.5%) were aged under 50 years. This result implies that stroke mostly occurs in elderly people. According to Hachinski, textbooks, the incidence rates to be about 25% to 30% higher among men[15].

In this study, hypertension (43.5%) was the most common risk factor, followed by tobacco smoking (36.5%), diabetes mellitus (34.8%), positive family history of IHD (33.9%), dyslipidaemia (22.0%) and family history of stroke (10.4%). Hypertension, diabetes mellitus, dyslipidaemia and smoking were significantly associated with elevated TnI level ($p<0.05$). Similar study by Pynam et al.,[11] reported various risk factors were hypertension in 242 (67.2%), old age (>70 years) in 67 (18.6%), diabetes mellitus in 138 (38.3%), tobacco smoking in 176 (48.9%), alcohol use in 136 (37.8%), coronary artery disease in 57 (15.8%), previous stroke in 80 (22.2%), rheumatic heart disease in 37 (10.3%), hyperhomocystinemia in 70 (19.4%), vasculitis in 14 (3.9%), peripheral artery disease in 34 (9.4%), thyroid disease in 11 (3.1%) and chronic liver disease in 2 patients hypertension (66.7%), followed by tobacco smoking (55.2%), diabetes mellitus (40.2%), alcoholism (40.2%) and dyslipidaemia (27.6%). Other similar observations were reported by Batal et al.,[16] and Raza et al.,[17].

Several studies have shown that cTnI is not only elevated in patients with myocardial injury but also is increased in patients with other diseases[8,18]. In the current study, our results demonstrated that cTnI could elevate in 19 (16.5%) patients with acute ischemic stroke. The mean serum cardiac troponin I values in all patients was 0.294±0.547 ng/mL. In this study, elevation of Troponin I is defined as level of troponin I more than 0.3 ng/mL where the non-elevated range is 0- 0.3 ng/mL. A study done by Hravnak et al.,[19], serum TnI level>0.3 ng/mL defined as elevated TnI group. In accordance the present study Pynam et al.,[11] considered serum TnI level > 0.01 µg/mL as cutoff, patients were classified into TnI positive and TnI negative groups. Eighty seven (24.2%) patients tested serum TnI positive and 273 (75.8%) tested serum TnI negative. Hasirc et al.[20] reported elevation of cTnI above 0.04 5Øßg/L was identified in 45 patients (18.8%).

Barber et al.,[21] observed abnormal troponin concentrations in 20% of patients with acute stroke. In most cases, the increase of TnI was accompanied by changes corresponding to myocardial ischaemia and an increase in epinephrine. The authors suggest a causal relationship between sympathetic activation and the increase in catecholamine and troponin levels, which is unfavorable for cardiomyocytes[22]. A study done by Batal et al.,[16] from Pittsburgh, positive TnI was reported in 18% of patients. In a study by Su et al.,[14] from Taiwan, positive TnI was noted in 16.8% of patients. However, in these studies, serum troponin levels of >0.1 µg/L were considered positive. In the present study, we also observed similar distribution of elevated (16.5%) and non-elevated serum TnI patients considering TnI level >0.30 ng/mL as elevated group. However, differences in the troponin assessment methods could also have contributed to the observational differences.

It has been shown that highly specific myocardial necrosis markers such as troponin can be increased in stroke victims, a phenomenon that has been explained by several pathophysiologic mechanisms: primary cardiac damage with secondary cardioembolic cerebral ischemia or primary cerebral ischemia with secondary cardiac damage caused by increased levels of catecholamines (caused by sympathetic system activation)[23]. Some studies showed that increased troponin I levels associated with a certain localisation of stroke: insular or right hemisphere[14-17].

NIHSS scores are mainly used to assess neurological disability in patients with stroke, and patients with higher scores, most often, experience a greater severity stroke. Some studies have shown that the NIHSS score is an independent risk factor

for troponin elevation in patients with stroke[14,24]. In the present study, majority (44.3%) patients scored minor stroke (1-4), 38.3% had scored moderate stroke (5-15), 14.8% had scored moderate to severe stroke (16-20) and 2.6% had scored severe stroke (>20).Moderate to severe stroke was significantly higher in elevated TnI group compare to non-elevated TnI group. Thalin et al.,[25] noted that stroke severity according to National Institutes of Health Stroke Scale was higher in the group with elevated cTnI.

Current study showed that the patients with elevated TnI had higher mean NIHSS scores on admission than the patients with non-elevated TnI group (16.4 vs. 5.35).Longer hospital staysignificantly associated with elevated serum TnI level (7.42 days vs. 4.03 days, $p < 0.01$). Similar observation was reported by Pynam et al.,[11] that positive serum TnI significantly related with long hospital stay ($p < 0.01$). Su, et al.,[14] conducted a retrospective study on 871 patients with acute ischemic stroke, and showed that elevated cTnI was an important predictive factor for in-hospital death and adverse outcomes in patients.

Our study revealed that the mean mRs score of respondents during discharge was 3.01±1.70. The mean mRs score for elevated TnI patients was 5.21 which significantly higher than the non-elevated TnI group patients 2.57 ($p<0.001$). Su et al.,[14] reported that higher median mRs score in elevated TnI group (4 vs 3).

In present study, multivariate logistic regression analysis revealed that age ≥60 years (OR 1.134 CI [1.1–1.74]), NIHSS score ≥12 on admission (OR 4.102, CI [4.047–12.10]), and elevated TnI (OR 2.369, CI [2.219–7.522]) were associated with in-hospital outcome. There is no doubt that advanced age, higher NIHSS score on admission, and elevated troponin I level associated with a poor outcome at discharge. In accordance with present study Su et al.,[14] reported that there were more poor outcomes (85%) and deaths (21%) in the high-positive group than in the low-positive group (74% and 6%, respectively). Faiz et al.,[26] also reported that age e" 76 years was independently associated with elevated troponin levels in patients with acute ischemic stroke. Another study done by Yildiz et al.,[27] reported that age ≥76 years, heart rate e" 82 bpm, evidence of clinical deterioration, NIHSS score ≥12 on admission, and abnormal TnI were associated with poor outcome. The results of our study indicate the possibility of assessing troponin I concentration as a biomarker in acute ischemic stroke patients to identify those at higher risk of poor outcome.

Conclusion:

About sixteen percent patients of acute ishchemic stroke had elevated Troponin I level. The mean NIHSS score for the patients with elevated TnI level was significantly higher than non-elevated TnI group which implies that elevated Troponin I level is associated with increased severity of neurological disability of the acute ischemic stroke patients. The mean mRs score was also higher for the elevated TnI group compare to non-elevated TnI group during discharge. Therefore elevation of TnI during acute ischemic stroke is a predictor of in-hospital functional outcome. Both neurologists and cardiologists need to pay more attention to possible concomitant cardiac disorders in patients with elevated troponin I levels during acute ischemic stroke. Based on the results, it might recommended-Longer monitoring, serial measurements, and a deeper cardiological workup in patients with elevated TnI levels at admission. cTnI elevation could occur in patients with acute ischemic stroke and is associated with poor short-term prognosis. Patients with elevated cTnI levels should be closely monitored and receive appropriate care to improve their prognosis

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