

Relation of Elevated Troponin-I with Clinical Severity and Outcome of Subarachnoid Hemorrhage

*ISLAM SMS¹, BHATTACHARJEE M², OYSHI AS³, MIA E⁴, HAQUE MA⁵, SADAT MN⁶

Abstract

Background: Patients with subarachnoid hemorrhage (SAH) often experience myocardial injury at the time of bleeding. Cardiac dysfunction after SAH is frequently associated with elevation of serum troponin I level. Elevation of troponin I may predicts cardiopulmonary and neurological complications and poor outcome. **Objective:** To describe the incidence of myocardial injury and the effects of the injury on clinical severity & 3-months functional recovery. **Methods:** This prospective observational study was conducted over 72 patients with SAH in patient department of Neurology, Neurosurgery & Medicine ward of Mymensingh Medical College Hospital during the period of December 2021 to January 2024. Predictor variables reflecting demographics (age, sex, occupation), radiological (Fisher scale) and neurological (Hunt-Hess grade) information were recorded. Serum troponin I level was measured at admission, within 5 days of symptoms onset. A troponin I level ≥ 0.3 ng/ml was defined as an indicator of cardiac injury following SAH. Patients were interviewed at 3 months to evaluate functional recovery with Glasgow Outcome Scale (GOS). Statistics included χ^2 analysis, t-test and binary logistic regression on SPSS 27.0. **Results:** Out of 72 patients 26.4% were in between 50-59 years age group & female: male ratio was 1.25. Among the risk factors, hypertension was most common (47.2%). The most frequently occurring Hunt-Hess grading was grade 3(41.7%) & Fisher scale was score 3(48.6%). Troponin I was elevated in 26.4% of patients & the troponin I value was strongly correlated with Hunt-Hess grade ($P < 0.05$). On 3 months follow up, 33.3% had poor outcome on Glasgow Outcome Scale (GOS) & the troponin I value was also strongly correlated with GOS score ($P < 0.05$). Even after controls for age, gender and Hunt-Hess grades, higher levels remained a significant predictor of poor functional recovery ($P < 0.05$) **Conclusion:** Elevated level of troponin I reflects higher incidence of myocardial injury after SAH. The present study demonstrates that raised troponin I is related to more severe neurological injury and is a predictor of poor functional recovery.

Keywords: Subarachnoid hemorrhage, Troponin I, Myocardial injury.

Introduction:

A stroke is a serious life-threatening medical condition. It occurs when the blood supply to a part of the brain is compromised. World Health Organization defined stroke as 'rapidly developed clinical signs of focal and or global disturbance of cerebral function, lasting more than 24 hours or

leading to death, with no apparent cause other than of vascular origin'¹. It is the leading cause of disability in worldwide and the second leading cause of death². Annually, about 15 million of people suffer from stroke throughout the world. Among them, 5 million die and another 5 million become disabled permanently². Stroke is a life-

1. Dr. S. M. Sazzad Islam, Neurology Resident, Department of Neurology, Mymensingh Medical College, Mymensingh, Bangladesh.
 2. Dr. Manabendra Bhattacharjee, Prof. & Head, Department of Neurology, Mymensingh Medical College, Mymensingh, Bangladesh.
 3. Dr. Afrida Sabrin Oyshi, Intern, Community Based Medical college, Mymensingh, Bangladesh.
 4. Dr. Ershad Mia, Medical Officer, Department of Neurology, Mymensingh Medical College, Mymensingh, Bangladesh.
 5. Dr. Md Akramul Haque, Neurology Resident, Department of Neurology, Mymensingh Medical College, Mymensingh, Bangladesh.
 6. Dr. Md. Nazmus Sadat, Neurology Resident, Department of Neurology, Mymensingh Medical College, Mymensingh, Bangladesh.
- Corresponding Author:** Dr. S. M. Sazzad Islam, Neurology Resident, Department of Neurology, Mymensingh Medical College, Mymensingh, Bangladesh.

threatening medical emergency and urgent treatment is needed. If a person receives early treatment for a stroke, the less damage is likely to happen. Strokes primarily classified as arterial and venous stroke. Arterial stroke is two types: ischemic and hemorrhagic. Hemorrhagic stroke may be - intracerebral, intraventricular or subarachnoid hemorrhage³. Among them, subarachnoid hemorrhages are most devastating and catastrophic event.

Subarachnoid hemorrhage is defined as rapidly developing signs of neurological dysfunction because of bleeding into the subarachnoid space⁴. It is an acute neurological emergency with high rate of mortality and morbidity even with recent advancement of therapy. The overall global incidence of SAH is approximately 7.9 per 100 000 person years⁵. In India, the incidence is 2.6 to 7.5 and Kashmir has highest incidence⁶ but in Bangladesh no actual incidence study was found. SAH may be traumatic or non-traumatic. The most common cause of SAH is traumatic brain injury, remainder cases are caused by spontaneous rupture of a blood vessel. The cause of spontaneous SAH can be classified into aneurysmal (85%), and non-aneurysmal hemorrhage⁷. Non-aneurysmal hemorrhages include peri mesencephalic, vascular malformation, intracranial arterial dissection, drugs like cocaine, cerebral amyloid angiopathy in adult, cerebral vasculitis etc. Subarachnoid hemorrhage accounts 5% of all strokes⁸. In our country, no data are available about actual prevalence of SAH. Worldwide prevalence is 8.4 where men is 3.3 and female 5.069. The reported prevalence of stroke in Bangladesh was 0.3%¹⁰ although another nationwide study discovered a stroke prevalence of 11.39 per 1000 people, with the Mymensingh division having the highest rate. Among them 4.6% was subarachnoid hemorrhage¹¹. Approximately 80% of non-traumatic SAHs are from ruptured aneurysm. Aneurysms are usually formed at the bifurcation of arteries. Hemodynamic stress is the initiating factor for intracranial aneurysm (IA) formation¹². The peak age of occurrence of SAH is between 50 to 60 years and it is 1.6 times more common

in female than male¹³. Risk factors of SAH can be modifiable and non-modifiable- Modifiable risk factors are hypertension, smoking, Alcohol abuse, sympathomimetic drug (cocaine) abuse, and non-modifiable risk factors are increased age, female gender, first degree family member with SAH, ADPKD, sickle cell disease, alpha 1 antitrypsin deficiency¹⁴. Complications of SAH are common, may be neurological or non-neurological, some complication appears early, some are late. Neurological complications include re-bleeding, seizure, hydrocephalus, ischemia etc. Most common and important non neurological complication of SAH is cardiac problems including myocardial injury, cardiac wall motion dysfunction, neurogenic pulmonary oedema and arrhythmias¹⁵. Both neurological and non-neurological complications affect the outcome of patients.

Elevation of cardiac enzymes occurs in 20% – 40% of cases of SAH¹⁶. Pathologically, there is sub endocardial contraction band necrosis formation which is a type of reversible myocardial injury that follows SAH. It is thought to result from the excessive release of catecholamines within the myocardium¹⁷. Recently numerous studies have shown that troponin I is a sensitive and specific marker for this form of cardiac dysfunction¹⁸. Levels of troponin I is correlated to cardiac stress as compared with doppler studies for the assessment of diastolic function¹⁹. Its level peak about two days following SAH, may remain elevated up to two weeks. Highly positive cardiac troponin I is associated with clinical neurological severity²⁰. In addition, troponin I elevation has been considered as a predictor of various cardiac complications, pulmonary problems, cerebral infarction and overall poor outcome²¹ Furthermore, troponin I assessment is easy and convenient to perform immediately after hospitalization. Normal range of troponin I may vary in different method of assessment but a value less than 0.3 ng/ml considered to normal value in florescence immunoassay method¹⁵. The aim of this study is to evaluate the relation of elevated troponin I with clinical severity, assess the functional recovery and disability in non-traumatic subarachnoid hemorrhage.

Materials and methods

Study design and setting:

This was a prospective observational study done in Department of Neurology, Mymensingh Medical College Hospital, Mymensingh from December, 2021 to January, 2024.

Study population

Patient with CT defined subarachnoid hemorrhage fulfilling inclusion criteria and exclusion criteria was included in the study group. A total of 72 adult patients included in this study. Purposive type of non-probability sampling method was followed in this study.

Data collection and analysis

Data was collected by principal investigator. Detailed history was taken and thorough physical examination was done. Patients demographic profile including age, sex, residence, occupation and income status were recorded. Hunt-Hess score was used to assess severity of neurological disability and serum troponin I level was measured within 5 days of onset of symptoms. CT scan of brain and other routine investigations were done. Fisher scale was used to assess the amount blood in subarachnoid space. A troponin I level ≥ 0.3 ng/ml was defined as an indicator of cardiac injury following SAH. Patients were interviewed at 3 months to evaluate functional recovery with Glasgow Outcome Scale (GOS). Statistics included χ^2 analysis, t-test and binary logistic regression on SPSS 27.0. H-H grade 4-5 considered as severe grade and grade 1-3 considered as less severe grade. Fisher grade 3-4 was belonged to more severe grade. GOS score ≤ 3 at follow up was considered as poor outcome.

Ethical aspect:

This study was done with prior approval from "Institutional Review Board (IRB)" of Mymensingh Medical College, Mymensingh. All hospital records included in this study were taken after permission from proper authority. The aims and objectives of the study were explained to the patient and their attendants in easily understandable local language. Then informed written consent was taken from each patient or attendant. It was assured that all

information were kept confidential and the procedure will helpful for doctor and patients in making rational approach of case management. It was also assured that the investigations which were done for the study purpose will not impose any financial burden to the patient

Results:

This prospective observational study was done in Mymensingh Medical college Hospital (MMCH). In this study 72 Subarachnoid hemorrhage patients were included. Baseline clinical status, Hunt-Hess scale and Fisher scale on imaging was documented. Troponin I level was measured within 5 days of event. The patients were followed up at three months with GOS score. Among them, 19 patients had elevated troponin I level. On three months follow up, 24 patients had poor outcome on GOS Scale (GOS Scale ≤ 3).

Table I showed the distribution of the study subjects by demographic profile. The majority of population was in age group 50-59 years. The mean age of the study population was 53.61 ± 16.19 years. It also shows majority of respondents were female 40 (55.6 %) and 32 (44.4%) of respondents were male. Female to male ratio was 1.25:1.0.

Table-I
Distribution of the study subjects by demographic profile (n=72)

Demographic profile	Frequency	Percentage
Age		
18-29	6	8.3
30-39	5	6.9
40-49	12	16.7
50-59	19	26.4
60-69	16	22.2
>70	14	19.4
Mean $\pm$ SD	53.61 $\pm$ 16.19	
Gender		
Male	32	44.4
Female	40	55.6

Distribution of respondents by risk factors was done in table II. Among common risk factors, about half of the respondents were hypertensive 34 (47.2%). And 19 (26.4%) were smoker, 2 (2.8%) were alcoholic and 2 (2.8%) had history of substance abuse.

Table II
Distribution of respondents by risk factors.

Risk factors	Number	Percentage
Hypertension	34	47.2
Smoking	19	26.4
Alcohol	2	2.8
Substance abuse	2	2.8

Table shows that 19 responders (26.4%) had significant elevation of serum troponin I level.

Table-III
Distribution of respondents by Troponin I level

Troponin I level (ng/ml)	Number (n=72)	Percentage
Normal (<0.3 ng/ml)	53	73.6
Elevated (>0.3 ng/ml)	19	26.4

Table IV shows most of the respondents had H-H Grade -3 (41.7%). Rest of the respondents had H-H Grade-2 (37.5%), H-H Grade -4 (15.3%), H-H Grade-5 (5.6%). No one was found in H-H Grade-1.

Table-IV
Distribution of respondents by Hunt Hess grade.

H-H Grade	Number (n=72)	Percentage
Grade 1	00	00
Grade 2	27	37.5
Grade 3	30	41.7
Grade 4	11	15.3
Grade 5	04	5.6

Table V shows most of the respondents had Fisher score-3 (48.6%). Rest of the respondents had Fisher score-2 (26.4%), Fisher score-4 (25.0%), No one was found in Fisher score-1.

Table-V
Distribution of respondents by Fisher score.

H-H Grade	Number (n=72)	Percentage
Score 1	00	00
Score 2	19	26.4
Score 3	35	48.6
Score 4	18	25.0

Distribution of respondents at three-months outcome was done by GOS scale. GOS score ≤ 3 was included in poor outcome group. Table shows the most of the respondents were in favorable outcome group (66.7%) then in poor outcome group (33.3%).

Table-VI
Distribution of respondents by 3 months outcome on Glasgow outcome scale (n = 72)

Outcome (GOS Scale)	Frequency (n=72)	Percentage
Poor outcome group (<3)	24	33.3
Favorable outcome group (>3)	48	66.7

Table VII shows that elevated troponin I value was significantly related with more severe clinical grade assessed by Hunt & Hess scale. Statistically significant*.

Table-VII
Association of Troponin I level with H-H Scale for clinical severity.

Troponin I	Clinical severity (H-H Grade)		P-value
	Less severe (G1-3)	More severe (G 4-5)	
Normal	52 (98.1%)	1 (1.9%)	<0.001*
High	5 (26.3%)	14 (73.7%)	

Table VIII shows that elevated Troponin I value was significantly related to poor outcome at three months follow up assessed by GOS score. *Statistically significant.

Table-VIII
Association of Troponin I level with GOS score at Three months follow up

Troponin I	Outcome (GOS Scale)		P-value
	Good (G 4-5)	Poor (G 1-3)	
Normal	45 (84.9%)	8 (15.09%)	<0.001*
High	3 (15.7%)	16 (84.2%)	

Table-IX

Logistic regression analysis of elevated Troponin I level with neurological outcome at Three months follow up by GOS Scale.

Parameter	OR	95% CI	P value
Troponin I level (>0.03ng/ml)	3.285	1.237-7.054	<0.05*
Age	1.029	0.958-1.106	0.433
Gender	3.347	0.290-8.581	0.333
Hypertension	1.240	0.233-6.592	0.801
GCS (<10)	1.933	1.153-3.240	<0.05*
H-H Scale (4-5)	2.514	1.121-5.640	<0.05*
Fisher Grade (3-4)	0.372	0.107-1.291	0.119

OR (odds ratio) for Troponin I increases were obtained from GOS Scale with logistic regression analysis. Adjustment by age, gender, hypertension, GCS, H-H Scale, and Fisher Scale. Table IX shows odds ratio of Troponin I was 3.285, (95% CI 1.237-7.054). *Statistically significant.

Discussion:

In this study, mean age of respondents was 53.61 ± 16.19 years and majority of respondents were above 50 years of age (78%). Previously, one study showed mean age to be 56±14 years which matches with our findings²². This is similar with a Bangladeshi study with frequent age group of 50 to 60 years¹⁴.

Distribution of respondents in relation with gender, residence, education, occupation, social status was done. Among 72 respondents 55.6% were female, majority of respondents were from rural area (55.5%). This finding corresponded with a recent Bangladeshi study where they found 50% were female and 50% were male²³. In this study, there is slight female predominance with the Female to male ratio was 1.25:1 which corresponds to another Bangladeshi study where female to male ratio was 1.6:1. During menopause the protective effect of estrogen and progesterone have been withdrawn which contribute to increased incidence²⁴. Among them, most of the respondents were housewife 38(52.8%), followed by farmer 13(18.1%). Moreover, most of respondents were from lower middle class socioeconomic group 27(37.4 %). Siddiqui et al.²⁵ found 63% of the patients from low-income group, which was followed by middle

income group (33%). This study revealed several risk factors such as hypertension (47.2%), smoking (26.4%), substance use (2.8%) and alcohol abuse (2.8%).

Among the cardiac laboratory parameters, the strongest predictor of poor outcome identified by the literature is the elevation of serum troponin I level¹⁷. The frequency of troponin I elevation (≥0.3 ng/ml) was 26.4% among the patients in this study, a result that is higher than the following studies by Gupte et al 26- 23%. In other studies, the reported frequency of Troponin I elevation was higher than our study; Jeon et al. -29.8%, Sarker et al.-43.3%, Ramappa-et al.-37%, Ahmadian et al.- 71.6%^{17,23,27,28}.

The main objective of this study was to find out the relation between troponin I with clinical severity and neurological outcome following subarachnoid hemorrhage. To date several similar studies were conducted worldwide with different results. Most of the studies found elevated troponin I is related with worse neurological grade and poor outcome, where only few studies found no significant relation. This finding matches with the study conducted by Miketic et al., Jeon et al., Mavridis et al., Oras et al., Jeon et al., Sarker et al., Ramappa et al., Duello et al., Stoica et al., Zhang et al.^{15,17,22,23,27, 29,30,31}. But this finding goes against findings by Anetsberger et al.³² where troponin I level was not independent predictor of worse outcome on three month follow up.

In this study, patients with elevated troponin I had more severe SAH symptoms as indicated by the Hunt-Hess grade. Patient with elevated troponin

I (≥ 0.3 ng/ml) have 73.7% with severe H-H grade (G 4-5) which was statically significant ($p < 0.05$). This finding corroborates those of both Ramappa et al. and Stoica et al.^{27,30} where severe H-H grade was 80.4% and 90% respectively. Poor Hunt/Hess grades have been also correlated with poor outcomes in SAH patient¹⁵. After logistic regression analysis, the H-H grade was significantly associated with poor outcome; odd ratio: 2.514, 95% confidence interval (CI) 1.121-5.640, which was statistically significant (P value < 0.05). The finding of Anetsberger et al.³² odd ratio: 2.703, 95% confidence interval (CI) 1.589-4.598 support this finding. However, no significant difference was found in fisher scale in between normal and elevated troponin I group; odd ratio 0.372, confidence interval (CI) 0.107-1.291, P value 0.119 ($p > 0.05$). Similar observation was found at Gupte et al.²⁶ where odd ratio was 1.25, CI 0.19–8.38 and P value 0.82.

In this study, 24(33.3%) patients had poor outcome at three months follow up with Glasgow Outcome scale (GOS score ≤ 3). Patients with elevated troponin I (≥ 0.3 ng/ml) had poor outcome (84.2%) compared with those with normal troponin I level (15.09%) which was statistically significant (P value < 0.05). Troponin I level was strongly correlated with GOS score on chi-square test. This finding consistent with Jeon et al.¹⁷ where 73.43% vs 33.56% had poor outcome on GOS scale whose elevated or normal troponin I respectively. After logistic regression analysis, the troponin I level was significantly associated with poor outcome odd ratio: 3.285, 95% confidence interval 1.237-7.054, which was statistically significant (P value < 0.05). This finding consistent with Miketic et al.¹⁵ where odd ratio: 2.7, 95% confidence interval 1.2-5.8. In this study, Troponin I of 0.3 ng/ml or greater is an independent predictor of poorer functional outcomes even after adjustments for other confounding factors such as age, sex and SAH severity. The findings of this study are also consistent with other studies - Oras et al., Duello et al.,^{22,29}.

Apart from troponin I, it is also observed in this study that statistically significant difference exists between good and poor outcome group with initial GCS score.

So, if we include troponin I in other prognostic parameter as a cheap, available method, it may predict poor functional outcome at follow up.

Conclusion:

This study shows that myocardial injury frequently occurs in SAH patients and raised S. Troponin I level is related to more severe neurological injury. There is also a significant relation between serum troponin I level and neurological outcome following SAH. So, troponin I level at admission is a good predictor of clinical severity and neurological outcome at three months.

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