Impact of Serum Troponin I Levels on Short-term Outcomes Following an Acute Ischemic Stroke

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ABSTRACT

BACKGROUND

There is a complex relationship between coronary artery disease and stroke. Troponin I has been investigated for its potential as a prognostic biomarker in determining outcome and mortality after an acute cerebrovascular insult such as an ischemia. Several studies have been done mostly in Western countries leaving very little data for patients of Asian/Southeast Asian descent. Its implications in the prognosis and management of acute ischemic stroke may guide clinicians in rendering the most suitable care for their patients.

OBJECTIVE

This study aims to identify the impact of serum troponin I levels on short-term functional outcome after an acute ischemic cerebrovascular event. It also intends to evaluate the role of cardiac troponin I in identifying the prognosis and in-hospital mortality among patients with acute ischemic stroke.

METHODS

A prospective cohort study was done from August 2019 to February 2020 including 65 adult acute ischemic stroke patients (35 males and 30 females) coming to consult within 48 hours from ictus. Baseline electrocardiogram was done. Patients without evidence of an acute ACS and other cardiac diseases were included. Blood samples for determination of serum troponin I were collected. Patients were monitored for development of complications and incidence of in-hospital mortality. Sixty days from onset, short-term functional outcome was assessed by determining change in NIHSS score. Modified Rankin Scale (mRS) was used to assess degree of disability on follow-up.

RESULTS

Out of 65 patients initially enrolled, 23 (35.38%) had abnormally elevated troponin I. Patients with history of previous stroke and higher NIHSS scores on admission tend to have elevated troponin I. Patients with elevated troponin I had worse short-term functional outcome and were dependent in performing daily activities. This study did not demonstrate a predictive value of elevated troponin I for in-hospital mortality.

CONCLUSION

In patients with acute ischemic stroke, elevation of serum TnI has been observed even in the absence of a definite clinical acute coronary syndrome. Presence of previous stroke and more severe neurologic deficits has been shown to be related to elevations in TnI. This elevation in TnI, in turn, is associated with poor short-term outcome limiting patients' functionality and independence. Managing these patients necessitate aggressive but judicious use of different diagnostic and treatment modalities to prevent adverse coronary events. These events are likely to be prevented when early recognition and proper management has been provided.

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INTRODUCTION

Stroke is defined as 'a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in the case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin.[1] It is the most common cause of mortality especially in middle income countries, together with ischemic heart disease (IHD) which may develop to silent myocardial infarction in 25-40% of cases.[2] In the Philippines, stroke ranks the second most common cause of mortality.[3]

Biochemical markers such as cardiac troponins are valuable risk and prognostic biomarkers. In IHD, troponin I (TnI) has a principal role in the management hence, this biomarker is routinely assessed in these patients. However, in conditions other than an acute coronary syndrome (ACS), TnI has also been found to be elevated. Such conditions include acute heart failure, pulmonary embolism, stroke, sepsis, use of cocaine, and chronic kidney disease.[4] Since 2000, TnI has been investigated in the setting of acute stroke but still with conflicting results.[5] Elevation in TnI has been found in almost all types of cerebrovascular events — ischemic[6] [7], intracerebral hemorrhage[8], and subarachnoid hemorrhage.[9,10] Several studies have already investigated TnI elevation in the setting of acute ischemic stroke. Most of these studies have been done in Egypt.[11,12] Germany[13], United States of America (USA)[14], and Korea[15]. Interestingly, TnI has been tested more widely in acute ischemic stroke patients in these regions. However, these studies had conflicting results. The value of TnI as a prognostic biomarker especially in patients of Asian/Southeast Asian descent remains uncertain.

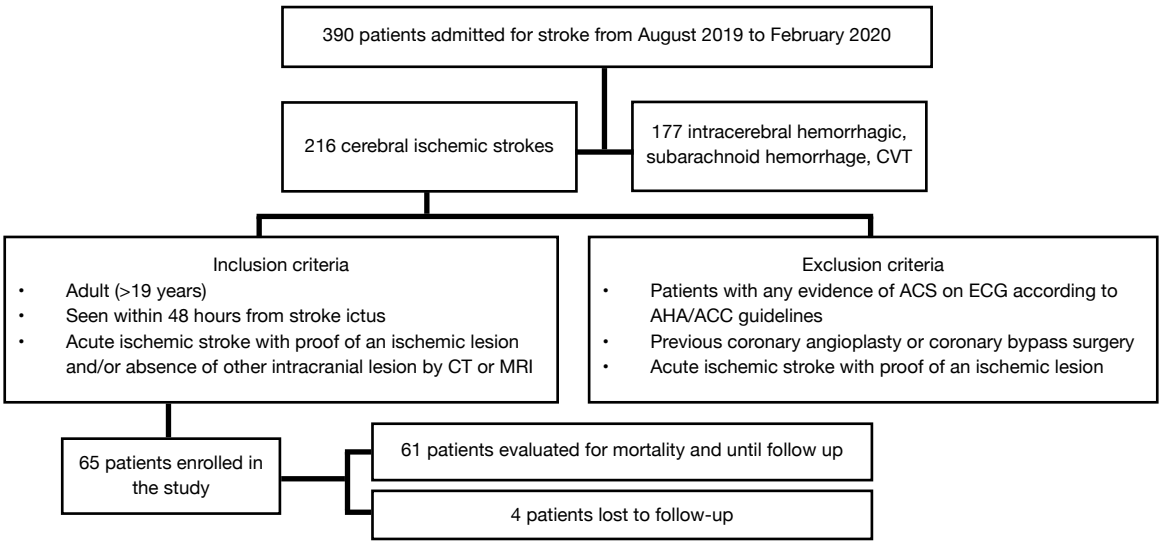
OBJECTIVES

This study primarily aimed to identify the impact of serum TnI levels on short-term functional outcome after an acute ischemic cerebrovascular event. It also intends to evaluate the role of cardiac TnI in identifying the prognosis and in-hospital mortality among patients with acute ischemic stroke.

PATIENTS AND METHODS

Upon approval by the Institutional Review Board, we conducted a single-center, prospective cohort study including patients with established acute ischemic strokes who were consecutively admitted at the Department of Neurology of Jose R. Reyes Memorial Medical Center (JRRMMC) in Sta. Cruz, Manila during the period from August 2019 to February 2020. *Figure 1* illustrates the selection process of patients enrolled in this study. Patients who were invited to

Figure 1. Selection process of patients enrolled



participate were those who satisfied the inclusion criteria — adult (>19 years old) patients with a diagnosis of acute ischemic stroke that was confirmed by clinical presentation and proof of an ischemic lesion and/or absence of a corresponding intracranial lesion other than infarction by brain computed tomography (CT) or magnetic resonance imaging (MRI). Only patients who came to consult within 48 hours from onset of stroke were included in the study. A written informed consent from the patient or the nearest of kin was obtained prior to inclusion. All patients underwent detailed history-taking. Basic demographic data including age, sex, presence of co-morbidities such as hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia, and history of previous stroke were obtained. Patients underwent general physical examination and thorough neurologic examination. Stroke severity on admission was assessed using the National Institute of Health Stroke Scale (NIHSS). Baseline chest radiography and electrocardiography (ECG) were obtained. Patients with evidence of acute coronary syndrome in accord with the AHA/ACC guidelines were excluded from the study.[16,17]An electrocardiogram (ECG) was considered consistent with acute coronary syndrome (ACS) if there is ST depression, persistent ST elevation, or anterior ST segment depression indicative of true posterior myocardial infarction (MI). ECGs with ischemic T wave inversion, new Q waves, new left bundle branch blocks, previous coronary angioplasty or coronary bypass surgery were also excluded from the study. Patients with other probable debilitating conditions with the possibility of serum TnI elevation and negative effect on prognosis, such as congestive heart failure, valvular heart disease and renal impairment were excluded.

Along with other routine ancillary procedures, blood samples were collected and sent to the institutional laboratory for semiquantitative measurement by immunochromatography for determination of serum TnI level within 48 hours after onset of neurologic deficits. Elevated TnI is defined as a serum level > 0.05 ng/mL. While admitted, patients were monitored for development of complications and incidence of in-hospital mortality. Short-term functional outcome was measured after sixty (60) days from onset of stroke based on timelines from other studies when damaged tissue is expected to have already been phagocytized and cavitation with surrounding gliosis have appeared.[12,18] Patients were followed up at the outpatient department. Short-term functional outcome was measured using the Modified Rankin Scale (mRS) which quantifies the degree of disability or dependence among patients who had cerebrovascular events. The mRs consists of 6 grades ranging from 0 to 5, with 0 being the best score and 5 corresponding to worse outcome and severe disability. Death was rated 6 in the mRs.[7] Patient outcomes were dichotomized to either independent (mRs<3) or dependent (mRs≥3). The National Institutes of Health Stroke Scale (NIHSS) was also used to identify neurological improvement. An improvement of 8 or more in the NIHSS score was considered a major neurological improvement.[19]

Sample Size

The target minimum sample size of 57 was achieved, with 61 remaining in the study until follow up. This computation used the proportion of patients with increased troponin levels among stroke patients based on previous studies.[11–14] Computation provides for 95% level of confidence. The formula is:

Sample size (n) =

$$[DEFF*Np(1-p)]/ [(d^2/Z^21-\alpha/2)* (N-1)+p*(1-p)]$$

Where:
p = probability of disease or exposure in the population
d = absolute precision on either side of the proportion
DEFF = design effect (equivalent to 1)
N = Total population size
Z = 1.96 for a confidence level of 95%

STATISTICAL ANALYSIS

The obtained data were tabulated and analyzed using Stata version 13. Continuous variables were expressed as mean with their corresponding standard deviation, while categorical variables were expressed as frequencies with their corresponding proportions. The means were compared by independent student's T test, while categorical variables were compared by Chi square test or Fisher's exact test when assumptions of Chi square test were not met. Odds ratios with their corresponding 95% confidence intervals were also calculated in a simple logistic regression model to assess independent factors that were significantly associated with poor outcome. A difference was considered to be statistically significant if the P value computed was less than 0.05. Using troponin levels as independent factor to predicting poor functional outcome, with 95% confidence interval, this study has a power of 99.52%.

RESULTS

Table 1 summarizes the demographic data and clinical characteristics. Patients were grouped according to their serum TnI levels on admission, either normal or elevated. Of the 65 patients who were initially enrolled, 23(35.38%) had elevated TnI measured within 48 hours of stroke onset. Between the two groups, there were no significant differences in age and sex. Hypertension (63.07%) was the most prevalent co-morbidity followed by diabetes mellitus (35.38%), presence of a previous stroke (21.54%), dyslipidemia (15.38%) and atrial fibrillation (3.08%) respectively. The two groups were also comparable in terms of these illnesses and other risk factors. Presence of a previous cerebrovascular disease was greater in patients with elevated TnI compared to their normal counterparts (43.38% vs 9.52%; p=0.001). Also, patients with elevated TnI I had more severe stroke as represented by higher mean of NIHSS scores upon admission (16.35 vs 8.98, p<0.0001).

TABLE 1. Baseline demographic data and clinical characteristics of patients with corresponding troponin I level. **Chi square test, ** Fisher's exact test, ***Independent t test*

	All pxs n=65	Troponin normal n=42	Troponin elevated n=23	P value
Age *Mean (SD)*	59.4 (11.86)	57.62 (11.41)	62.65 (12.22)	0.10***
Sex Male *n (%)* Female *n (%)*	35(53.85%) 30 (46.15%)	22(52.38%) 20(47.62)	13(56.52%) 10 (43.48%)	0.75*
HTN *n (%)*	41 (63.08%)	24 (57.14%)	17 (73.91%)	0.18*
DM *n (%)*	23 (35.38%)	13 (30.95%)	10 (43.48%)	0.31*
AF *n (%)*	2 (3.08%)	2 (4.76%)	0	0.54**
Dyslipidemia *n (%)*	10 (15.38%)	4 (9.52%)	6 (26.09%)	0.15**
Previous stroke *n (%)*	14 (21.54%)	4 (9.52%)	10 (43.48%)	0.001*
Smoking *n (%)*	35 (53.85%)	19 (45.24%)	16 (69.57%)	0.06*
Alcoholic drinker *n (%)*	37 (56.92%)	23 (54.76%)	14 (60.87%)	0.63*
NIHSS score upon admission *Mean (SD)*	11.58 (6.61)	8.98 (5.65)	16.35 (5.58)	<0.0001***

Table 2. Functional outcome on follow-up (60 days after stroke onset) and mortality among stroke patients with troponin I levels. P<0.05 *Chi square test,

Functional outcome	All pxs n=61	Troponin normal n=38	Troponin elevated n=23	P value
Major neurological improvement on NIHSS. *n (%)*	4 (6.56%)	3 (7.89%)	1 (4.35%)	>0.9999**
No change in NIHSS *n (%)*	3 (4.92%)	2 (5.6%)	1 (4.35%)	
Dependent (MRS>=3) *n (%)*	24/59*** (40.68%)	8 (21.05%)	16/21*** (76.19%)	<0.0001*
Mortality *n (%)*	2 (3.28%)	0	2 (8.7%)	0.14**

Table 2 demonstrates the comparison of neurologic improvement, short-term functional outcome, and mortality between the groups of patients with elevated and normal TnI levels after 60 days. Only 4 patients achieved major neurologic improvement equivalent to 6.56% of the study population. Those with elevated TnI levels turned out to have greater degree of disability or dependence in performing daily activities (76.19% vs. 21.05%, p<0.0001) as reflected by the mean mRS scores. While admitted, 2 patients expired. One of them is an 89-year old female with severe stroke (NIHSS 25) who eventually developed pneumonia and respiratory failure. The other mortality is a 67-year old female (NIHSS 20) who succumbed to septic shock. No statistical significance was observed between the two populations regarding in-hospital mortality.

Logistic regression analysis was done to identify factors predicting poor functional outcome and/or death. *Table 3* demonstrates that presence of a previous stroke, NIHSS score ≥12 and elevated troponin I level within 48 hours from stroke onset were significant predictors of poor short-term functional outcome and/or death.

Table 3. Logistic regression analysis of factors predicting poor functional outcome (mRS>3) and death. *p<0.05

	OR (95% CI)	P value
Age	1.04	0.11
Sex Male (female reference)		
	0.75	0.58
HTN	2.04	0.20
DM	2.48	0.10
Dyslipidemia	1.85	0.40
Previous stroke	4.84	0.02*
Smoking	1.29	0.63
Alcoholic drinker	0.67	0.44
NIHSS score upon admission >=12	150	<0.0001*
Troponin elevated	13.5	<0.0001*

DISCUSSION

The production of cardiac enzymes in acute stroke was first identified in 1979. The acute and progressive rise in these enzymes suggested myocardial involvement in the setting of an acute cerebrovascular insult.[20] It was only in the year 2000 when troponin was associated with mortality in acute stroke.[21] The paramount role of TnI as a valuable biomarker in acute myocardial infarction (AMI) has already been established. [12,22] TnI has also been observed to be elevated in acute stroke even without clinical and/or electrophysiological evidences of AMI. With conflicting results, its value in the prognosis and management of these patients has remained controversial.[5] This study was conducted to evaluate primarily the impact of elevated TnI in the functional outcome and in-hospital mortality after an acute ischemic stroke.

In this study, 35.38% of patients had abnormally elevated serum TnI. Results from other studies revealed varying percentages of TnI elevation in acute stroke ranging from 7.8% to 34%.[11–14,23] In our study, age and sex between the normal TnI and elevated TnI groups were comparable. However, several studies have found that older individuals tend to have elevated TnI levels while sex did not influence its result. Hypertension and diabetes mellitus were the most prevalent risk factors but were not associated with TnI elevation.[6,7,11,12,24] In contrast, a study done in 2011 involving 121 subjects revealed that hypertensive patients tend to have elevated troponin I.[11] In another prospective cohort, diabetes mellitus was a significant risk factor.[12] Also differing from our findings, the results of another prospective study in Egypt observed higher percentage of patients with dyslipidemia in patients with normal TnI levels. Their rationale for this observation is that patients with dyslipidemia are more likely to have received statins that are established to have protective effects on arteriosclerotic plaques. Considering that this study was done in a tertiary government hospital delivering services to patients who belong to the low to middle socioeconomic class, compliance to medications is uncertain.

Other factors associated with elevated TnI were presence of a previous stroke and higher NIHSS scores on admission. Patients with severe stroke are undoubtedly more likely to have less mobility, limitations in activities of daily living and are likely to develop complications. Other investigators have also found such observation. A similar prospective study in Germany found that admission NIHSS score, along with sex and lesion size, had a significant influence on outcome and morbidity.[13] Further analysis revealed that these factors were also predictors of poor short-term functional outcome — which is the objective of this investigation. Other studies have also observed similar results. A retrospective study of 871 patients with acute ischemic stroke revealed higher mRS scores on discharge in patients with elevated TnI.[22]

The mortality rate in this study was comparably smaller compared to previous studies.[6,12,14,15] Although the 2 mortalities in the present study both had elevated troponin levels during admission, there was no significant difference. Other studies, however, have established the association of increased in hospital and long-term all-cause mortality in patients with elevated troponin I.[5,12,25] It can be remembered that this study excluded patients with other serious illnesses which may have led to such an observation.

Cardiac TnI I is deemed to be the most sensitive and specific biomarker of myocardial necrosis.[6] It appears in the bloodstream 5 to 6 hours after an acute MI, reaching its peak after 18-24.The release of free radicals brought about by myocardial necrosis prompts troponin leakage. In acute ischemic stroke, the elevation of TnI may be distinguished into two mechanisms, (1) myocardial injury due to coronary ischemia and (2) noncoronary myocardial injury.[7] Rupture of unstable coronary plaque or mismatch in the oxygen supply and demand cause the first type of myocardial injury while

the noncoronary causes may be secondary to neurogenic heart syndrome (NHS), severe infection or sepsis, multiple organ failure, and pulmonary embolism.[22] Of particular interest in this investigation is the 'neurally-mediated' activity due to an imbalance in the autonomic nervous system and intensified sympathetic tone.[20,26,27] This cortically induced imbalance in the has been proposed to cause catecholamine discharge.[26,28] Elevated levels of serum epinephrine were associated with elevations in TnI.[28] Such elevation augments the release of intracellular calcium in myocytes. A proposed mechanism is through the ryanodine receptor activation via the Ca^{2+}-induced Ca^{2+} release. This results in myocardial damage where myocytes die in a hypercontracted state with prominent contraction bands happening within minutes. This is associated with early calcification and mononuclear infiltration.[29] TnI levels may be a marker for the systemic severity of the acute cerebrovascular insult especially in cases of ischemia bringing a negative effect on the evolution of the disease.[6] Another possible implication is that elevations in TnI may be heralding signals of unstable plaques in the coronary circulation, signifying higher chances of adverse cardiac complications**.** Considering all these possibilities, serum TnI determination on admission appears to be worthwhile performing in this patient population.

Management of acute ischemic stroke patients who present with elevated TnI but without clinical or electrophysiological symptoms is a challenging task, balancing the advantages and risks that come with each diagnostic or treatment modality. To date, no randomized controlled trial was carried out yet identifying the best management approach for these patients who present with sole increase in TnI levels. Varying judgments of both the neurologist and the cardiologist eventually determine the management approach. It has been proposed that measurement of TnI may be a key element in detecting ACS associated with an acute neurogenic event such as stroke. Silent myocardial ischemia still occurs in 1 of 4 patients with suspected coronary artery disease. In diabetics, it may even be as high as 60%.[30] Prompt vigilance and aggressive management in these patients to prevent adverse events are definitely the goals of treatment.

CONCLUSION

In patients with acute ischemic stroke, elevation of serum TnI has been observed even in the absence of clinical and electrophysiological signs. Presence of previous stroke and more severe neurologic deficits have been shown to be related to elevations in TnI. This elevation in TnI, in turn, is associated with poor short-term outcome limiting patients' functionality and independence. Managing these patients necessitate aggressive but judicious use of different diagnostic and treatment modalities to prevent adverse coronary events. These events are likely to be prevented when early recognition and proper management has been provided.

DISCLOSURE

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