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Increased High-Sensitivity Troponin-T Levels Are Associated with Mortality After Ischemic Stroke

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Abstract Biomarkers for diagnosis, treatment, and outcome prediction after stroke are lacking. Therefore, we aimed to evaluate the association between increased serum troponin, stroke severity, and mortality. Unselected patients with acute ischemic stroke assessed for troponin levels were included over the span of 1 year. Risk-factor profile, stroke etiology, stroke severity, and mortality during acute admission were recorded. The study included 212 patients, and 35 had increased troponin levels. Elevated troponin levels were associated with older age (82.1±10.7 vs. 72.2±12.6, $p<0.001$), poor kidney function (calculated GFR 58.7±29.8 vs. 82.7±28.4, $p<0.001$), and known ischemic heart disease (51.4 % vs. 33.9 %, $p=0.049$). Patients with increased troponin had increased stroke severity on admission (National Institutes of Health Stroke Scale (NIHSS) 16.0±9.4 vs. 10.4±8.0, $p<0.001$). This association remained significant after multivariate analysis but was nonlinear. Mortality rates were significantly higher in patients with increased troponin (37.1 vs. 5.6 %, $p<0.001$). On multivariate analysis, elevated troponin (odds ratio [OR] 22.57, 95 % CI 4.4–116.6), absence of ischemic heart disease (OR 10.3, 95 % CI 1.8–57.6), and admission NIHSS score (OR 1.59 for every 5 points, 95 % CI 1.1–2.4) were associated with mortality. This study indicates that elevated troponin is an independent marker for severe deficits on presentation and for mortality in stroke patients.

Keywords Stroke · Cerebrovascular disease · Biomarker · Troponin

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Introduction

Determining the prognosis after stroke is important for patients, families, medical staff, social services, and insurance providers. A plethora of biomarkers for prediction of outcome after stroke have been assessed thus far with mixed results (Whiteley et al. 2009). Increased levels of cardiac markers such as myoglobin, creatinine kinase isoenzyme MB (CK-MB), and troponin were consistently found to be associated with poor outcomes in stroke patients. The troponin proteins are a family of proteins found mainly in striated and cardiac muscle that play an important role in muscle contraction. Current assays can detect very small quantities of troponin and are therefore referred to as high-sensitivity troponin-T (hs-Tnt) and high-sensitivity troponin-I (hs-TnI). Previous studies that explored the significance of elevated troponin levels among stroke patients were inconsistent in their inclusion criteria, outcome definitions, percentage of patients with elevated troponins included, and the type of troponin isoenzyme measured (Faiz et al. 2014a, b; Kerr et al. 2009; Song et al. 2008). Furthermore, most of these studies did not focus on the neurological disability but rather studied mortality ratios. Therefore, the current study aimed to explore whether there was an association between a positive hs-TnT test and neurological disability or mortality in stroke patients and whether this association was dose dependent.

Methods

Consecutive acute ischemic stroke patients admitted over the span of 1 year were screened. We included patients in which a test for hs-TnT was taken in the first 48 h after admission. There were no prespecified criteria for obtaining the test, and testing was left to the admitting physician's discretion.

We compared patients with a positive troponin test (>0.03 μg/L) and controls with a negative troponin test.

Demographics and risk factor profile were assessed, and stroke etiology was determined with the TOAST classification (Adams et al. 1993). The primary outcomes were National Institutes of Health Stroke Scale (NIHSS) score on admission and mortality.

Statistical analysis was performed with SPSS (IBM). Associations between quantitative and qualitative variables were assessed with the *t* test if there were two categories of the qualitative variable. Comparisons of quantitative variables of three or more categories were performed using the ANOVA test with Dunnett T3 test for multiple comparisons. Association between two categorical variables was tested using the χ^2 or Fisher's exact test. Association between two quantitative variables was calculated with the Pearson correlation coefficient.

A multivariate model was devised based on the univariate comparisons. The model included all variables that were found to be significantly associated with an outcome ($p<0.05$). We used a multivariate linear model (ANCOVA) when the outcome was quantitative and logistic regression when the outcome was dichotomous. All statistical tests were two-way analyses with a $p<0.05$ considered statistically significant.

A prediction model was built based on variables that were associated with mortality in the multivariate analysis. In order to assess the goodness of fit of the model for prediction purposes, two measures were evaluated. The first was the Nagelkerke R square and the second was a classification table in which the sensitivity and specificity of the model were assessed. The calculation was based on comparing the observed outcome (mortality/survival) versus the predicted outcome. Based on the independent variables, the probability of mortality was calculated for each patient. For prediction purposes, if the probability was ≥50 %, the outcome was considered to be mortality, and if the probability was <50 %, the outcome was considered to be survival. Next, a comparison between the prediction model and the actual outcomes was performed to assess the sensitivity, specificity, and positive and negative predictive value of the model, given the prevalence of mortality as seen in the study population.

Results

Over the span of 1 year, 251 out of 620 consecutive patients with ischemic stroke admitted to our department were tested for blood troponin levels, and 212 were included in the final data analysis. Reasons for excluding patients from the final data analysis included uncertain diagnosis (e.g., transient ischemic attack, seizure, etc.), missing admission NIHSS scores, a troponin test performed more than 48 h after presentation, and insufficient data regarding risk factors.

The mean age of the entire cohort was 73.9±12.9, and 56 % were male. The mean NIHSS score for the whole study population was 11.3±8.5.

Hs-TnT was usually taken at admission to the emergency department independent of whether or not the patients were treated. Rather, the decision to obtain a troponin test was left to the physician's discretion. Thus, troponin levels were totally independent of acute treatments such as tPA or endovascular recanalization.

Of the 212 patients included in the study, 35 (16.5 %) had a troponin level >0.03 μg/L and comprised the study group, while the remaining 177 patients served as controls.

Patients with increased serum troponin levels were older (mean age 82.1±10.7 vs. 72.2±12.6, $p<0.001$) and more often had impaired renal function (calculated GFR of 58.7±29.8 vs. 82.7±28.4, $p<0.001$) and known ischemic heart disease (51.4 vs. 33.9 %, $p=0.049$). Hypertension and atrial fibrillation were also more prevalent in the patients group, but these differences did not reach statistical significance (88.6 vs. 74 %, $p=0.064$, and 42.9 vs. 28.2 %, $p=0.089$, respectively).

There were no significant differences between the groups in other parameters, including stroke etiology, gender, diabetes, hyperlipidemia, past stroke or TIA, and smoking (Table 1).

Admission NIHSS scores were significantly higher in patients with increased troponin levels (16.0±9.4 vs. 10.4 ±8.0, $p<0.001$). Other variables that were significantly associated with a higher NIHSS score were age, TOAST classification, presence of AF, and absence of hyperlipidemia. In order to evaluate if stroke severity in patients with a positive troponin test was explained by other variables, we performed an analysis of covariance. Elevated level of troponin, absence of hyperlipidemia, TOAST classification, and age remained significantly associated with a higher NIHSS score. The coefficient of determination (adjusted R square) according to this model was 0.34, meaning that 34 % of variance in NIHSS was explained by the aforementioned variables.

Next, we evaluated whether the correlation between the absolute values of troponin and admission NIHSS scores was linear. For this analysis, we included only patients with elevated troponin values. The Pearson correlation coefficient was 0.083 indicating very weak correlation (Fig. 1).

Out of 212 patients included, 23 died during the acute admission (10.8 %). The mortality among patients with elevated troponin levels was significantly higher compared with the control group (37 vs.5.5 %, $p<0.001$). Only 11.6 % of the survivors had elevated troponin compared with 56.5 % of patients that died (Fig. 2). The mean troponin value in patients who died was significantly higher compared to survivors (0.21±0.5 vs. 0.02±0.1, $p<0.001$; Fig. 3).

Table 1 Comparison of baseline characteristics, etiology, and outcomes in patients with positive and negative troponin tests

Characteristic	Positive troponin test (n=35)	Negative troponin test (n=177)	p value
Male (%)	18 (51.4)	101 (57.1)	0.38
Age (±SD)	82.1±10.7	72.2±12.6	p<0.001
Diabetes (%)	14 (40)	68 (38.4)	0.86
Hyperlipidemia (%)	18 (51.4)	105 (59.3)	0.39
Ischemic heart disease (%)	18 (51.4)	60 (33.9)	0.049
Previous stroke/TIA (%)	13 (37.1)	58 (32.8)	0.62
Smoking (%)	9 (25.7)	47 (26.6)	0.92
Hypertension (%)	31 (88.6)	131 (74)	0.064
Atrial fibrillation (%)	15 (42.9)	50 (28.2)	0.087
TOAST classification (%)			0.13
Large artery	2 (5.7)	24 (13.6)	
Cardioembolism	6 (17.1)	44 (24.9)	
Small vessel	7 (20)	47 (26.6)	
Other determined	1 (2.9)	8 (4.5)	
Undetermined	19 (54.3)	54 (30.5)	
Cr (±SD)	118.0±52.2	83.5±27.6	p<0.01
CrCl (±SD)	58.7±29.8	82.73±28.4	p<0.001
NIHSS score (±SD)	16.0±9.42	10.43±8.01	<0.001
Mortality (%)	13 (37.1)	10 (5.6)	<0.001

Cr serum creatinine, *CrCl* creatinine clearance

Other variables that were significantly associated with mortality included admission NIHSS scores, absence of ischemic heart disease, and TOAST classification (Table 2).

Next, we performed a logistic regression analysis, and included variables were associated with mortality on single variable analysis, with a p value of less than 0.05 (Table 3). Variables that remained associated with mortality after the multivariate analysis were a positive troponin test (OR 22.6, 95 % CI 4.4–116.6), absence of ischemic heart disease (OR 10.3, 95 % CI 1.8–57.6), and admission NIHSS score (OR 1.59 for every 5 points, 95 % CI 1.1–2.4). When analyzed as a continuous variable admission, NIHSS remained significant (OR 1.1, 95 % CI 1.0–1.2).

A prediction model based on the variables above and the strength of their association to mortality successfully predicted survival in 98.4 % of patients who survived and death in 39.1 % of patients who died during hospitalization. Hence, this model had a high specificity of 98.4 % but a low sensitivity of only 39.1 %, with a positive predictive value of 75 %

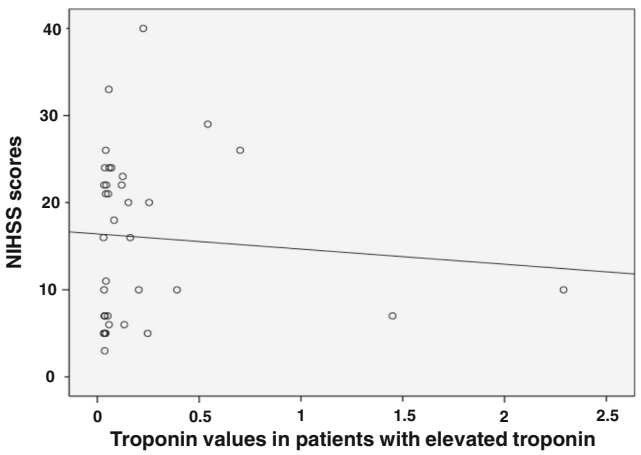

Fig. 1 Correlation between troponin values and NIHSS scores among patients with elevated troponin

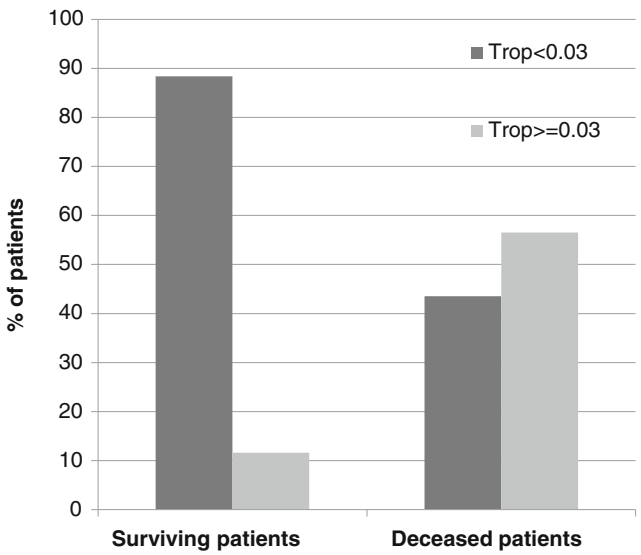

Fig. 2 Percentage of patients with elevated troponin according to survival status

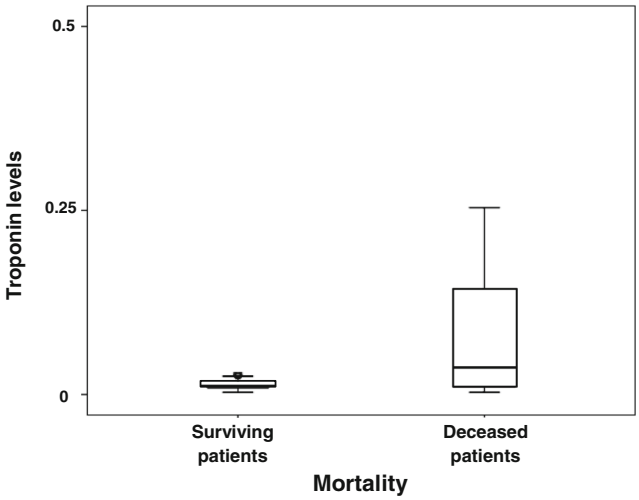

Fig. 3 Troponin levels according to survival status

and a negative predictive value of 93 %, given a 10.85 % prevalence of mortality, as seen in the current study.

Discussion

This study demonstrates the prognostic significance of elevated troponin in a group of unselected patients with ischemic stroke. Patients with increased hs-TnT had increased chances for severe strokes and mortality. However, the absolute troponin levels did not correlate linearly with stroke severity. A model based on stroke severity and presence of increased troponin at presentation had high specificity but low sensitivity for prediction of poor outcome or mortality at discharge.

In agreement with previous data, the current study also demonstrated associations between troponin and other important risk factors for stroke and mortality, such as older age, coronary artery disease, congestive heart failure, renal failure, and diabetes (Faiz et al. 2014a). However, the association between troponin and worse outcomes remained significant following a multivariate regression analysis that controlled for other risk factors. In fact, increased troponin appears to be the most significant prognostic factor for predicting mortality. Importantly, the significance of troponin as a prognostic factor was shown even after integrating the NIHSS score in the multivariate analysis.

These findings are in agreement with previous studies evaluating the prognostic significance of troponin in other conditions such as AF, heart failure, sepsis, pulmonary embolism, and even in patients without comorbidities (Agewall et al. 2011; Beaulieu-Boire et al. 2013; Oluleye et al. 2013).

Table 3 Multivariate logistic regression analysis for mortality

Variable	Adjusted OR	95 % CI	*p* value
No ischemic heart disease	10.31	1.84–57.61	0.008
NIHSS score[a]	1.59	1.1–2.4	0.023
Elevated troponin	22.57	4.4–116.6	<0.001

[a] For every 5 additional points on the NIHSS

Table 2 Comparison of survivors and non-survivors during hospitalization

Characteristic	Deceased (*n*=23)	Surviving (*n*=189)	*p* value
Male sex (%)	12 (52)	107 (56.6)	0.69
Age (±SD)	77.4±15.2	73.4±12.5	0.16
Diabetes (%)	8 (34.8)	74 (39.2)	0.68
Hyperlipidemia (%)	12 (52.2)	111 (58.7)	0.55
Ischemic heart disease (%)	4 (17.4)	74 (39.2)	0.04
Prior stroke/TIA (%)	8 (34.8)	63 (33.3)	0.89
Smoking (%)	8 (34.8)	48 (25.4)	0.34
Hypertension (%)	18 (78.3)	144 (76.2)	0.83
Atrial fibrillation (%)	6 (26.1)	59 (31.2)	0.61
TOAST classification (%)			<0.001
Large artery	5 (21.7)	21 (11.1)	
Cardioembolism	3 (13)	47 (24.9)	
Small vessel	0 (0)	54 (28.6)	
Other determined	3 (13)	6 (3.2)	
Undetermined	12 (52.2)	61 (32.3)	
Cr (±SD)	104.96±53.1	90.2±53.0	0.21
CrCl (±SD)	71.5±35.61	79.4 (29.51)	0.24
Positive troponin (%)	13 (37.1)	10 (5.6)	<0.001
NIHSS score (±SD)	21.2±8.2	10.2±7.7	<0.001

Cr serum creatinine, *CrCl* creatinine clearance

The mechanism causing the increase in troponin following stroke remains unclear but may involve an acute coronary syndrome preceding stroke (Agewall et al. 2011) or occurrence of atrial fibrillation either preceding (Hijazi et al. 2014) or following stroke (Beaulieu-Boire et al. 2013). Alternatively, exaggerated sympathetic responses to stroke, which occurs when the ischemic changes involve the autonomic centers, can cause a surge in catecholamine levels that may in turn impair cardiac function and trigger a rise in blood troponin levels (Masuda et al. 2002).

A rise in plasma hs-TnT levels is thought to represent myocardial damage since it was shown to be specific for the myocard. This specificity is present in early developmental stages in the embryo, where cardiac troponins are only expressed in beating heart tissue (Filipczyk et al. 2007) and are mediated by a number of mechanisms, including specific promoters for cardiac troponin (Harlan et al. 2008) and an amino acid sequence different from other troponin proteins (Akhter et al. 2012). However, later in life, the troponin complex is prevalent in other tissues as well, and there is evidence suggesting that under certain conditions, genes encoding the cardiac troponin complex (type c) can undergo activation and be expressed even in the brain (Lyckman et al. 2008). Furthermore, cardiac-specific troponin I has been shown to be expressed in non-small cell lung cancer cells (Chen et al. 2014). Therefore, it may be of importance to evaluate if troponin could have a different cellular origin, including brain tissue, in cases where troponin elevation is not due to cardiac pathology.

There are several potential limitations that may have affected outcomes. First, there may be a selection bias regarding the population in which troponin levels were assessed. Troponin was only examined in a subgroup of patients at the admitting physician discretion and was not systematically assessed in all patients presenting with ischemic stroke. We cannot rule out the possibility that the clinical presentation of tested patients was different from other patients which were not tested. For example, the mortality rates in the current study were higher than those observed in our entire stroke cohort or in other studies (Fonarow et al. 2012; Reeves et al. 2012) suggesting that patients included in this study represent a subset of patients with more severe stroke. Another limitation of the current study is lack of follow-up data on functional outcome at 3 months after stroke. Thus, modified Rankin scores of included patients and controls at day 90 after stroke may have contributed to the strength of prognostic validity of increased troponin, but this data is not available to us. However, our study also has the advantages of recruiting consecutive patients with no predefined selection criteria and thus may reflect real-life settings better than previous studies. Therefore, this study points to the possibility that hs-TnT is associated with mortality and thus a randomized study examining this possibility in a larger cohort of consecutive stroke patients.

Given the imperfect positive and negative predictive value of troponin measurements in stroke, the cost effectiveness of measuring troponin levels in all stroke patients needs to be further studied. The association between hs-TnT and poor outcome including death in a subset of patients with more severe stroke emphasizes the need for routine measurement of troponin levels in these patients. A possible implication of this study may be that the preferred target population for investigating the mechanisms that cause a rise in troponin is patients with severe stroke. Further investigation is needed to corroborate this hypothesis as well to establishing the mechanisms responsible for this surge in troponin.

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Conflict of Interest All authors have nothing to disclose

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