

Early Elevated Troponin Levels After Ischemic Stroke Suggests a Cardioembolic Source

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Background and Purpose—Elevated cardiac troponin is a marker of cardiac disease and has been recently shown to be associated with embolic stroke risk. We hypothesize that early elevated troponin levels in the acute stroke setting are more prevalent in patients with embolic stroke subtypes (cardioembolic and embolic stroke of unknown source) as opposed to noncardioembolic subtypes (large-vessel disease, small-vessel disease, and other).

Methods—We abstracted data from our prospective ischemic stroke database and included all patients with ischemic stroke during an 18-month period. Per our laboratory, we defined positive troponin as ≥ 0.1 ng/mL and intermediate as ≥ 0.06 ng/mL and < 0.1 ng/mL. Unadjusted and adjusted regression models were built to determine the association between stroke subtype (embolic stroke of unknown source and cardioembolic subtypes) and positive and intermediate troponin levels, adjusting for key confounders, including demographics (age and sex), clinical characteristics (hypertension, hyperlipidemia, diabetes mellitus, renal function, coronary heart disease, congestive heart failure, current smoking, and National Institutes of Health Stroke Scale score), cardiac variables (left atrial diameter, wall-motion abnormalities, ejection fraction, and PR interval on ECG), and insular involvement of infarct.

Results—We identified 1234 patients, of whom 1129 had admission troponin levels available; 10.0% (113/1129) of these had a positive troponin. In fully adjusted models, there was an association between troponin positivity and embolic stroke of unknown source subtype (adjusted odds ratio, 4.46; 95% confidence interval, 1.03–7.97; $P=0.003$) and cardioembolic stroke subtype (odds ratio, 5.00; 95% confidence interval, 1.83–13.63; $P=0.002$).

Conclusions—We found that early positive troponin after ischemic stroke may be independently associated with a cardiac embolic source. Future studies are needed to confirm our findings using high-sensitivity troponin assays and to test optimal secondary prevention strategies in patients with embolic stroke of unknown source and positive troponin. (*Stroke*. 2018;49:121-126. DOI: 10.1161/STROKEAHA.117.019395.)

Key Words: heart diseases ■ heart failure ■ odds ratio ■ smoking ■ troponin

Stroke is a leading cause of mortality and morbidity worldwide,^{1,2} with an estimated prevalence of 2.7%³ and annual incidence of 795 000 per year in the United States.¹ Recently, atrial dysfunction or cardiopathy, defined by the presence of specific serum biomarkers, ECG findings, or echocardiographic findings, has been implicated as one of the mechanisms of ischemic stroke.⁴ Among the serum biomarkers is cardiac troponin T, which represents a marker of ischemic heart disease and is used to diagnose acute myocardial infarction.⁵ Recent studies have also suggested that high-sensitivity

cardiac troponin levels are associated with ischemic stroke, particularly those related to embolic causes.⁶

Other studies have shown that there is an association between elevated admission troponin levels and atrial fibrillation in patients with ischemic stroke.^{7,8} Furthermore, elevated troponin levels are thought to have an independent association with poor outcome after ischemic stroke.^{9,10} However, there is limited data on the association between elevated troponin and stroke subtypes,^{7,11} independent of clinical and echocardiographic markers of ischemic heart disease.

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Embolic stroke of unknown source (ESUS) denotes embolic stroke of undetermined source with a significant proportion considered to be related to a proximal cardio-aortic source, and less-common causes include substenotic atherosclerosis and ill-defined hypercoagulability.¹² We hypothesize that there is an independent association between early positive troponin levels after ischemic stroke and embolic stroke subtypes (cardioembolic and ESUS) and, therefore, designed this retrospective cohort study using data from a large single-center prospective stroke registry to test our hypothesis.

Methods

Patient Population

We used data from a large, prospective registry of all consecutive patients with acute ischemic stroke admitted to our facility between January 1, 2016, and June 30, 2017, collected in a Research Electronic Data Capture database (REDCap; Vanderbilt University, Nashville, TN) as part of an institutional quality improvement project. The data are not publicly available because this was not part of our institutional protocol. Patients underwent a standard diagnostic evaluation for ischemic stroke, which included laboratory testing, neuroimaging, vascular imaging, 12-lead ECG, cardiac telemetry for at least 24 hours, and transthoracic echocardiography; stroke subtype was prospectively adjudicated by the inpatient vascular neurology attending based on the ESUS consensus criteria.¹³

Primary Predictor

Our primary predictor of interest was admission troponin level. Blood samples were obtained as part of the routine clinical care on arrival to the hospital as a standard component of diagnostic evaluation. Cardiac troponin I levels were measured within 24 hours from hospital arrival by a 3-site sandwich immunoassay (ADVIA Centaur TnI-Ultra Assay; Siemens Medical Solutions, Inc, Malvern, PA). The lower limit of detection of this assay is 0.006 ng/mL, whereas the upper limit is 50 ng/mL; its analytic sensitivity is 0.006 ng/mL. According to our laboratory assays, a negative troponin I was considered any value <0.06 ng/mL, whereas intermediate was considered any value between 0.06 and 0.1 ng/mL. Positive cardiac troponin I was defined as any value ≥0.1 ng/mL.

Covariates

Covariates were abstracted from the database including the following:

- Clinical and demographic variables: age, sex, history of hypertension, history of diabetes mellitus, history of hyperlipidemia, history of coronary heart disease, history of atrial fibrillation, history of transient ischemic attack or stroke, history of congestive heart failure, current smoking, and National Institutes of Health Stroke Scale (NIHSS) score.
- Laboratory variables: estimated glomerular filtration rate, defined as either <60 or ≥60.
- ECG variables: PR interval (in milliseconds).
- Echocardiographic variables, as obtained from transthoracic echocardiography: anteroposterior diameter of the left atrium (in millimeter), ejection fraction, and presence of wall-motion abnormalities.
- Neuroimaging variables: brain magnetic resonance imaging and computed tomographic scans were reviewed by an investigator (S.Y.) blinded to troponin levels to assess for the presence of insular involvement.
- Acute stroke treatment: intravenous thrombolytic therapy and mechanical thrombectomy.
- Functional outcome: modified Rankin Scale obtained at 90 days via a structured telephone call, with good outcome defined as modified Rankin Scale 0 to 1 at 90 days.

Outcome

Our primary outcome of interest was ischemic stroke subtype as determined by each patient's attending vascular neurologist at the time of discharge using the ESUS criteria and divided into 3 groups: cardioembolic, ESUS, and noncardioembolic (NCE). Stroke subtype data entered in Research Electronic Data Capture (REDCap) is routinely verified by a second vascular neurologist (S.Y.), and in cases of disagreement on stroke subtype, the 2 vascular neurologists convened to arrive at a consensus. In cases where it is possible that the patient may have competing mechanisms, vascular neurologists were encouraged to state the most likely subtype based on their best clinical judgment.

Statistical Analysis

Patients were divided into 2 groups: those with positive serum troponin and those with negative/intermediate serum troponin. We compared clinical characteristics, laboratory values, ECG and echocardiographic data, acute stroke treatments, and functional outcomes between the 2 groups. We used *t* tests for continuous variables and Fisher test for categorical variables. We then performed multivariable regression analyses to determine the association between troponin positivity and stroke subtype, adjusting for covariates according to 4 models: model 1, which adjusted for age, sex, and estimated glomerular filtration rate; model 2, which included the covariates from model 1 plus NIHSS score and comorbidity covariates, including a history of hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, prior transient ischemic attack or stroke, congestive heart failure, and current smoking; model 3, which included the covariates from model 2 plus PR interval on ECG and echocardiographic data, including ejection fraction, presence of wall-motion abnormalities, and left atrial diameter; and model 4, which included the covariates from model 3 plus insular involvement on neuroimaging. In addition, we performed a sensitivity analysis using the same models but dividing patients into 3 groups (negative troponin, intermediate troponin, and positive troponin). Analysis was performed using SPSS, version 18.0 (Chicago, IL), and *P*<0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Sample

We identified 1234 patients with ischemic stroke during the study period, of whom 1129 patients (91.5%) had admission troponin levels available, and stroke subtype could not be determined in 9 patients. The proportion of patients within each stroke subtype category was similar among patients with and without troponin level available: cardioembolic (33.1% [371/1120] versus 30.8% [32/104]; *P*=0.66), ESUS (39.2% [439/1120] versus 43.3% [45/104]; *P*=0.46), and NCE (27.7% [310/1120] versus 26.0% [27/104]; *P*=0.82).

The mean age of all patients in our cohort was 71.6±0.4 years, and 54.3% were men. Troponin levels were positive in 11.9% (134/1129) and intermediate in 25.1% (283/1129) of patients who had admission troponin levels available. An ECG was performed on all patients, whereas a transthoracic echocardiogram was performed in 95.8% (1082/1129) of patients.

The distribution of stroke subtypes in our cohort was as follows: 33.2% cardioembolic, 40.3% ESUS, and 26.5% NCE (54.0% [182/337] with large-vessel disease, 38.9% [131/337] with small-vessel disease, and 7.1% [24/337] with another defined mechanism).

Univariable Models for Predictors of Positive Troponin

On univariable analyses, patients with positive troponin were significantly more likely to be older and have hypertension,

coronary heart disease, congestive heart failure, smoking, atrial fibrillation, higher admission NIHSS, estimated glomerular filtration rate <60, larger left atrial diameter, lower ejection fraction, and the presence of wall-motion abnormalities compared with the troponin-negative/intermediate group (Table 1). When compared with patients with intermediate/negative troponin levels, patients with elevated troponin also had higher rates of cardioembolic (79.0% versus 50.4%; $P<0.001$) and ESUS (75.7% versus 56.1%; $P=0.002$) stroke subtypes compared with NCE stroke. Troponin-positive patients were more likely to undergo mechanical thrombectomy (31.3% versus 17.7%; $P<0.001$) and less likely to have good functional outcome at 90 days (10.8% versus 30.7%; $P<0.001$).

Multivariable Models on the Association Between ESUS Subtype and Positive Troponin

In unadjusted models, there was an association between ESUS subtype and positive troponin (odds ratio [OR], 2.44; 95% confidence interval [CI], 1.38–4.30; $P=0.002$) with high specificity (0.95) but low sensitivity (0.12). This association

persisted after adjusting for potential confounders, such as echocardiographic variables (model 3: adjusted OR, 4.04; 95% CI, 1.52–10.75; $P=0.005$) and insular involvement (model 4: adjusted OR, 4.46; 95% CI, 1.65–12.06; $P=0.003$; Table 2).

Multivariable Models on the Association Between Cardioembolic Subtype and Positive Troponin

In unadjusted models, there was an association between cardioembolic subtype and positive troponin (OR, 3.70; 95% CI, 2.12–6.47; $P<0.001$) with high specificity (0.95) but low sensitivity (0.17). This association persisted after adjusting for potential confounders, such as echocardiographic variables (model 3: adjusted OR, 4.24; 95% CI, 1.58–11.37; $P=0.004$) and insular involvement (model 4: adjusted OR, 5.00; 95% CI, 1.83–13.63; $P=0.002$; Table 2).

Additional Analyses

We performed additional analyses comparing troponin levels between patients with ESUS, cardioembolic, and NCE. In these analyses, when compared with troponin levels in

Table 1. Univariable Models for Predictors of Positive Troponin

	Troponin Level			P Value
	Negative (<0.06)	Intermediate (0.06–0.1)	Positive (≥ 0.1)	
	(n=710)	(n=283)	(n=134)	
	70.7 $\pm$ 15.2	71.5 $\pm$ 14.3	77.4 $\pm$ 12.6	<0.001
Sex (% men)	386 (54.4%)	155 (54.8%)	71 (53%)	0.942
Hypertension, n	513 (72.3%)	224 (79.2%)	115 (85.8%)	0.001
Diabetes mellitus, n	198 (27.9%)	69 (24.4%)	40 (29.9%)	0.411
Hyperlipidemia, n	335 (47.2%)	149 (52.7%)	63 (47.0%)	0.278
Coronary heart disease, n	129 (18.2%)	70 (24.7%)	42 (31.3%)	0.001
Prior stroke, n	164 (23.1%)	62 (21.9%)	29 (21.6%)	0.883
Congestive heart failure, n	52 (7.3%)	42 (14.9%)	28 (20.9%)	<0.001
Smoking, n	145 (20.4%)	51 (18%)	16 (11.9%)	0.065
NIHSS (median, IQR)	6 (2–14.5)	6 (2–12)	14 (5–21)	<0.001
eGFR <60, n	202 (28.6%)	80 (37.2%)	63 (50.4%)	<0.001
Left atrial diameter (mean SD)	37.1 $\pm$ 7.5 (n=487)	37.3 $\pm$ 7.9 (n=226)	40.9 $\pm$ 8.8 (n=104)	<0.001
Left atrial volume (mean SD)	60.1 $\pm$ 28.2 (n=468)	95.6 $\pm$ 40.6 (n=22)	68 $\pm$ 27.7 (n=76)	<0.001
Ejection fraction (median IQR)	65 (60–70)	60 (55–65)	60 (45–68)	<0.001
Wall-motion abnormalities, n	60 (10.2%)	11 (35.5%)	24 (26.1%)	<0.001
PR interval (mean SD)	174.1 $\pm$ 35.6 (n=556)	179.7 $\pm$ 32.4 (n=225)	177 $\pm$ 31.9 (n=88)	0.118
Intravenous thrombolytic therapy, n	261 (36.8%)	80 (28.3%)	45 (33.6%)	0.039
Mechanical thrombectomy, n	153 (21.6%)	23 (8.1%)	42 (31.3%)	<0.001
Insular location of infarct, n	234 (33%)	85 (30%)	52 (38.8%)	0.205
90-day mRS, 0–1; n	164 (31.1%)	15 (24.6%)	9 (10.8%)	0.001
Stroke subtype				
CE vs NCE	199 (46.2%)	108 (60.7%)	64 (79%)	<0.001
ESUS vs NCE	279 (54.6%)	105 (60%)	53 (75.7%)	0.003

CE indicates cardioembolic; eGFR, estimated glomerular filtration ratio; ESUS, embolic stroke of unknown source; IQR, interquartile range; mRS, modified Rankin Scale, NCE, noncardioembolic; and NIHSS, National Institutes of Health Stroke Scale.

Table 2. Multivariable Models Showing Association Between Troponin-Positive (Compared With Negative/Intermediate) and Stroke Subtype

	CE Stroke*		ESUS*	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Unadjusted	3.70 (2.12–6.47)	<0.001	2.44 (1.38–4.30)	0.002
Model 1	3.22 (1.78–5.85)	<0.001	2.79 (1.54–5.07)	0.001
Model 2	2.62 (1.36–5.08)	0.004	2.68 (1.40–5.13)	0.003
Model 3	4.24 (1.58–11.37)	0.004	4.04 (1.52–10.75)	0.005
Model 4	5.00 (1.83–13.63)	0.002	4.46 (1.65–12.06)	0.003

Model 1: adjusted for age, sex, and eGFR <60. Model 2: adjusted for model 1+hypertension, hyperlipidemia, diabetes mellitus, smoking, prior stroke, coronary artery disease, congestive heart failure, and admission NIHSS. Model 3: adjusted for model 2+PR interval, left atrial diameter, wall-motion abnormalities, and ejection fraction. Model 4: adjusted for model 3+insular location of infarct. CE indicates cardioembolic stroke; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESUS, embolic stroke of unknown source; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*Compared with noncardioembolic subtypes.

patients with NCE subtype, the median troponin level was higher in patients with ESUS subtype (median, 0.010; interquartile range, 0.003–0.075 versus median, 0.003; interquartile range, 0.003–0.075; $P=0.005$) and cardioembolic subtype (median, 0.039; interquartile range, 0.070–0.075 versus median, 0.003; interquartile range, 0.003–0.075; $P<0.001$).

We also performed analyses dividing troponin levels into 3 groups: negative, intermediate, and positive. In multivariable models, there was an association between positive troponin and cardioembolic subtype (adjusted OR, 3.54; 95% CI, 0.97–12.97; $P=0.05$) and ESUS (adjusted OR, 2.86; 95% CI, 1.03–7.97; $P=0.044$; Table 3). Furthermore, intermediate troponin was associated with cardioembolic subtype in minimally adjusted models (adjusted OR, 1.92; 95% CI, 1.21–3.05; $P=0.006$), but this association was no longer present after adding cardiac biomarkers to the model (model 3). Moreover, there was no association between intermediate troponin levels and ESUS stroke subtype.

Furthermore, additional analyses were performed to determine whether the association between ESUS and positive troponin was affected by age (<60 versus ≥60 years) or sex. These showed that the association did not vary by age or sex.

Discussion

In this study, we showed an independent association between early elevated troponin levels and cardioembolic and ESUS ischemic stroke subtypes, as compared with NCE subtypes. This association persisted even after adjusting for clinical and echocardiographic markers of cardiac dysfunction. Our findings, therefore, suggest that early troponin elevation in the setting of ischemic stroke may represent a marker of a cardioembolic source. Although a positive troponin level is highly specific for a cardioembolic source, an intermediate or negative troponin level does not rule out a cardioembolic source.

There may be several reasons for early troponin elevation in such a scenario. It is possible that troponin leakage may be evidence of mechanical injury incurred on the myocardium in the course of clot migration from its cardiac origin to the brain. It could also be a reflection of myocardial fibrosis in patients without known cardiac disease.¹⁴ Although it has been previously held that elevated troponin levels in the setting of acute stroke may be related to myocardial stress-induced injury mediated by neurogenic catecholamine release,¹⁵ our findings argue against this phenomenon being the sole responsible cause. If this was the case, then we would have also expected an association between the NIHSS score

Table 3. Multivariable Models Showing Association Between Troponin and Stroke Subtype

	Intermediate Troponin, 0.06–0.1 (n=283)*						Elevated Troponin, ≥0.1 (n=134)*					
	CE (n=108)†			ESUS (n=105)†			CE (n=64)†			ESUS (n=53)†		
	OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value
Unadjusted	1.80	1.26–2.57	0.001	1.247	0.88–1.77	0.215	4.39	2.49–7.74	<0.001	2.59	1.46–4.60	0.001
Model 1	1.88	1.25–2.84	0.003	1.277	0.86–1.90	0.227	3.76	2.01–7.01	<0.001	2.72	1.49–4.96	0.001
Model 2	1.92	1.21–3.05	0.006	1.118	0.73–1.72	0.613	3.02	1.50–6.05	0.002	2.58	1.33–5.01	0.005
Model 3	0.30	0.04–2.27	0.243	0.272	0.06–1.26	0.096	2.73	0.78–9.51	0.116	2.72	0.99–7.49	0.053
Model 4	0.31	0.03–2.83	0.301	0.274	0.06–1.28	0.100	3.54	0.97–12.97	0.057	2.86	1.03–7.97	0.044

Model 1: adjusted for age, sex, and eGFR <60. Model 2: adjusted for model 1+hypertension, hyperlipidemia, diabetes mellitus, smoking, prior stroke, coronary artery disease, congestive heart failure, and admission NIHSS. Model 3: adjusted for model 2+PR interval, left atrial diameter, wall-motion abnormalities, and ejection fraction. Model 4: adjusted for model 3+insular location of infarct. CE indicates cardioembolic stroke; CI, confidence interval; eGFR, estimated glomerular filtration rate; ESUS, embolic stroke of unknown source; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

*Compared with troponin-negative group (n=710).

†Compared with noncardioembolic subtypes.

(assuming a correlation between stroke severity and degree of catecholamine release) and troponin elevation, which we did not find. In our study, the association between troponin positivity and cardioembolic stroke subtypes also persisted even after adjusting for insular location of infarct, which has been shown to be associated with catecholamine release¹⁰ and elevated troponin levels in prior studies.^{10,16} Furthermore, because insular infarcts have been shown to be associated with atrial fibrillation detection on ECG monitoring,⁷ it is possible that insular strokes are associated with elevated troponin levels at least partially because of their association with cardioembolism. Most importantly, although this study proves an association between elevated troponin levels and ESUS and cardioembolic stroke subtypes, it does not demonstrate causality because cardiac troponin levels may have been elevated before the stroke.

In addition, our study did not show an association between cardioembolic stroke subtypes and intermediate troponin levels. It is possible that the clinical troponin assays used in our study failed to identify patients with a cardioembolic source and minimally elevated troponin levels. Because high-sensitivity cardiac troponin T assays are more sensitive in detecting minimally elevated troponin levels,¹⁷ it is possible that using this assay may help determine an association between cardioembolic stroke subtypes and minimally elevated high-sensitivity cardiac troponin T levels and may improve the sensitivity in predicting a cardioembolic source.

Our findings carry important implications. Anticoagulation remains the treatment of choice for secondary stroke prevention in patients at risk of developing cardiac thromboemboli, particularly those with atrial fibrillation, mechanical heart valves, left ventricular thrombi, and low ejection fraction.^{18,19} Therefore, if early elevated troponin in the setting of ischemic stroke and ESUS can be predictive of a cardiac thromboembolic source, then it is also possible that patients with ESUS and early elevated troponin levels may also benefit from anticoagulation. In fact, although the WARSS trial (Warfarin-Aspirin Recurrent Stroke Study) showed no benefit of warfarin over aspirin in secondary stroke prevention,²⁰ warfarin was associated with a significantly reduced risk of stroke or death at 2 years in patients with elevations of another serum cardiac biomarker, NT-proBNP (N-terminal pro-B-type natriuretic peptide; hazard ratio, 0.3; 95% CI, 0.12–0.84; $P=0.021$).²¹ Therefore, our findings should prompt the consideration of further clinical studies investigating the role of anticoagulation versus antiplatelet agents in patients with ESUS and elevated troponin levels.

Strengths and Limitations

This study has several limitations. First, it is a single-center study, which may reduce the generalizability of our findings based on patient demographics. Second, although troponin levels were measured within 24 hours from hospital arrival, the time from stroke onset at which troponin levels were obtained varied among the patients in our cohort. Third, a small proportion of patients was missing potentially valuable echocardiographic data. Fourth, although stroke subtype adjudication was performed in a standardized way, it is possible that some stroke subtypes may have been

misclassified. Fifth, patients in the troponin-negative group only had a single troponin level on admission, and, therefore, it is possible that in some patients, the admission troponin was negative, but the subsequent troponin if checked would be positive, which might have resulted in patient reclassification. Sixth, we adjusted for a large number of conditions that would potentially lead to elevation of cardiac troponin levels, such as coronary heart disease, congestive heart failure, ejection fraction, and wall-motion abnormalities, and our findings persisted. We cannot exclude residual confounding, however. Finally, although we adjusted for admission NIHSS score, which has been shown to correlate with infarct volume, we lacked data on infarct volume, which better quantify stroke burden. However, despite these limitations, our study's strengths include its large sample size, its analysis, including models adjusting for a wide variety of cardiac biomarkers, and a standardized way of measuring troponin levels among patients.

Conclusions

Early elevated troponin levels after ischemic stroke may be independently associated with a cardiac embolic source. Prospective studies are needed to confirm our findings and to test optimal secondary prevention strategies in patients with ESUS and early elevated troponin.

Acknowledgments

Dr Yaghi contributed to the data collection, study concept and design, outcome adjudication, and preparation of the article. A.D. Chang did the data analysis. B.A. Ricci and M. Hemendinger contributed to the data collection. Dr Cutting contributed to outcome adjudication and data collection. Drs McTaggart and Jayaraman contributed to data collection and revision. K. Dakay and Drs Narwal, Mac Grory, Burton, Siket, Lerario, Madsen, Mehanna, and Reznik revised the article. Drs Merkler, Kamel, Elkind, and Furie contributed to article revision, study concept, and design. Dr Song contributed to the preparation and revision of the article.

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Disclosures

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