Association of Serum Troponin Obtained During Stroke Codes with Cardioembolic Strokes

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Background: Troponin is a marker of cardiac ischemia and is elevated in about 30% of stroke patients. We investigated if the elevation of troponin during an acute stroke code is associated with a cardioembolic source. *Methods:* We performed a retrospective chart review of patients evaluated for acute strokes from July 2014 to March 2018. Patients included in the study were all given intravenous alteplase, had blood drawn for troponins during the acute stroke code and had confirmation of a new stroke on neuroimaging during hospitalization. Patients who were on dialysis or had a glomerular filtration rate of less than or equal to 40 ml/minutes on initial laboratory evaluation were excluded. Stroke etiology was classified into noncardioembolic (NCE) and cardioembolic (CE), according to Trial of Org 10172 in Acute Stroke Treatment criteria. The NCE group was compared with the CE group with respect to troponin levels. Troponin was considered as a dichotomous categorical variable, with a cut-off point at greater than or equal to.05 ng/ml. *Results:* 144 patients met the inclusion criteria. In our cohort, 40.74% of patients in the CE group had troponin levels of greater than or equal to .05 ng/mL compared to 12.22% in NCE group. A troponin level of greater than or equal to.05 ng/ml obtained during a stroke code showed a significant difference between cardioembolic and noncardioembolic strokes (OR, 4.94; 95% CI, 2.15-11.35; $P < .001$), with high specificity (87.78%) but low sensitivity (40.74%) to exclude noncardioembolic stroke. *Conclusions:* A troponin level of greater than or equal to .05 ng/ml obtained during a stroke code showed a significant difference between CE and NCE strokes. This finding may have implications for clinical workup, and patients with admission troponin levels of greater than or equal to .05 ng/mL may need further clinical investigations to look for a cardioembolic source. A troponin level of greater than or equal to .05 ng/ml may prompt a more thorough search for a cardioembolic source in cases in which such a source is not identified on initial evaluation.

Key Words: Cardioembolic stroke—diagnosis of stroke etiology—stroke emergency cerebrovascular care—stroke etiology

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Introduction

In the United States, stroke affects nearly 795,000 people and kills around 140,000 people every year.[1,2] Around 87% of all strokes are ischemic in nature.[1] Cardioembolic strokes make up approximately 20% to 30% of all ischemic strokes.[3] Cardioembolic strokes are associated with higher morbidity compared to noncardioembolic strokes given their ability to occlude larger vessels causing ischemic damage to a larger area of the brain.[3,4]

Poststroke mortality secondary to cardiac events is common after an acute ischemic stroke.[5] Taking into account the association of cardiovascular disease with stroke, the American Heart Association/American Stroke Association recommends evaluating serum troponin in patients with an acute ischemic stroke.[6,7] Troponin is a marker of cardiac

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ischemia and is utilized to diagnose acute myocardial infarction.[8,9] It is elevated in around 30% of all stroke patients.[10-12] Recent studies have suggested that elevated troponin during the first few hours of stroke is associated with embolic etiology.[13,14] We try to investigate if the elevation of troponin, obtained during an acute stroke code, can be predictive of a cardioembolic source.

Material and Methods

We performed a retrospective chart review of electronic medical records of patients evaluated for stroke codes at a comprehensive stroke center between 7/1/2014 to 3/31/2018. The computed tomography head , magnetic resonance imaging of brain, echocardiographic (transthoracic or transesophageal), vascular imaging (either carotid Doppler, computed tomography angiogram, magnetic resonance angiogram or a conventional angiogram), electrocardiogram (EKG) telemetry monitoring data recorded on chart was reviewed to classify stroke into different subtypes. Stroke etiology was classified as large vessel disease (LVD), cardioembolic (CE), small vessel (SVD), other determined etiology (ODE) or undetermined etiology (UE), according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. The LVD, SVD, ODE, and UE groups were combined to form a noncardioembolic (NCE) group and compared with the CE group.

As a part of a diagnostic evaluation, patients who present as acute stroke codes have their blood drawn for troponin level as a part of stroke code protocol on arrival to our hospital. Inclusion criteria were: (1) Patients who were given intravenous alteplase (IV-rtPA), (2) Patients who had their blood drawn for a troponin level during the acute stroke code, (3) Patients with evidence of a new stroke on follow-up neuroimaging during their hospitalization. Exclusion criteria were: (1) Patients who were on dialysis or had a glomerular filtration rate less than or equal to 40 ml/minutes on initial laboratory evaluation, (2) Patients who did not have a troponin level drawn during a stroke code, (3) Patients without a proof of a new stroke on follow-up neuroimaging during their hospitalization.

We divided patients into 2 separate groups: those with serum troponins greater than or equal to .05 ng/mL and those with serum troponin levels below that. We analyzed various factors recorded upon a patient's presentation such as presenting systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), blood glucose, NIHSS score, verify Aspirin, verify Plavix, age, sex, platelet count, international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), hemoglobin A1c (Hb A1C), low-density lipoprotein (LDL), onset to treatment time, onset to troponin draw time, weight, sex, atrial fibrillation (AF), dilated cardiomyopathy (defined as ejection fraction of <40%), duration of hospital stay, presence of a dense MCA (middle cerebral artery) sign, presence of lambl excrescence, presence of valvular abnormalities, discharge disposition, presence of early infarct signs on computed tomography (CT) Head and development of symptomatic intracerebral hemorrhage (sICH) and compared them between the groups with troponin levels of greater than or equal to .05 ng/mL, and those below that. We then also compared these variables according to stroke etiology, between stroke cardioembolic (CE) or noncardioembolic (NCE) etiology groups. The primary outcome was to determine the association of serum troponins with the CE stroke group. We used European-Australasian Cooperative Acute Stroke Study-II's definition of sICH, i.e., an ICH that causes an increase in the National Institutes of Health Stroke Scale (NIHSS) score by greater than or equal to 4 points within 7 days post-IV-rtPA.

For statistical analysis, stroke subtypes were treated as categorical variables. The troponin level was considered as a dichotomous categorical variable with a cut-off point at greater than or equal to .05 ng/mL. Presenting SBP, DBP, MAP, blood glucose, NIHSS score, verify Aspirin, verify Plavix, age, platelet count, INR, PT, PTT, Hb A1C, LDL, onset to treatment time, onset to troponin draw time, and weight were considered as continuous variables with presence of sICH, sex, AF, dilated cardiomyopathy, discharge disposition (home versus facility), presence of a dense MCA sign, presence of lambl excrescence, presence of valvular abnormalities and early infarct signs on computed tomography head were considered as categorical variables. Student's t-test was used to compare continuous variables while chi-square was used to compare categorical variables.

After univariable analyses, a multivariate analysis using binary logistic regression was performed to determine variables with a significant association with a troponin level of greater than or equal to .05 ng/mL. For multivariable analysis, only variables with a $P < .1$ with respect to a troponin level of greater than or equal to .05 ng/m in the univariable analysis were included in the multivariable model. A multivariate analysis using binary logistic regression was also performed to determine variables with a significant association with CE etiology. Again, for multivariable analysis, only variables with a $P < .1$ with respect to CE etiology in the univariable analysis were included in the multivariable model. Statistical analysis was conducted using Microsoft Excel (2016) and IBM SPSS (version 23). The *P*-value of less than .05 was considered statistically significant.

Results

We screened 224 patients who presented as an acute stroke code and were given IV-rt-PA at University Hospital, Newark, New Jersey, from July 2014 to March 2018. 144 met our inclusion criteria. Our cohort comprised of 54.86 % males and had a mean age of 63.99 ± 14.26 years. The mean onset to treatment time was 136 ± 50 minutes.

The mean time troponin value was reported from the lab from the last time the time of symptom onset was 135.82 ± 49.77 minutes. In our cohort of 144 patients, the majority were classified into UE (42.36%), followed by CE (37.5%), LVD (11.8%), SVD (6.94%) and ODE (1.38%) groups. The NCE group was a combination of LVD, SVD, ODE, and UE groups which comprised 90 (62.5%) patients.

In our cohort, 40.74% of patients in the CE group had troponin levels of greater than or equal to .05 ng/mL compared to 12.22% in the NCE group. We found that a troponin level of greater than or equal to 0.05 ng/mL obtained during a stroke code showed a significant difference between cardioembolic and noncardioembolic strokes (OR, 4.94; 95% CI, 2.15-11.35; $P < .001$), with high specificity (87.78%) but low sensitivity (40.74%) to exclude noncardioembolic stroke.

On univariate analysis, we found that several variables had a significant difference between groups with troponin levels greater than or equal to .05 ng/mL or less: presence of AF (95% CI, 1.10-5.54; *P*.026), dilated cardiomyopathy (95% CI, 2.05-13.67; $P < .001$), CE etiology (95% CI, 2.15-11.35; $P < .001$), and serum LDL (95% CI, −4.59-34.77; *P*.011). In multivariable analysis, there was a significant association between a troponin level of greater than or equal to .05 ng/mL with respect to CE etiology (OR, .25; 95% CI, .08-.8; *P*.018). Univariate and multivariate analyses of characteristics between groups with troponin levels greater than or equal to.05 ng/mL or less at our University Hospital, Newark's cohort (n = 144), is described in Table 1.

We also found that several variables had a significant difference between CE and NCE groups: age (95% CI, −10.34-−.74; *P*.024), presence of AF (95% CI, 7.56-47; $P < .001$), onset to treatment time (95% CI, 1.44-32.18; *P*.032), onset to troponin draw time (95% CI, 6.85-39.56; *P*.001), dilated cardiomyopathy (95% CI, 2.79-23.51; $P < .001$), serum LDL (95% CI, 6.59-32.37; *P*.003), presenting NIHSS Score (95% CI, −6.44−2.33; $P < .001$), platelet count (95% CI, 2.1-58.19; *P*.035), presence of lambl excrescence (95% CI, .017-1.08; *P*.029), and serum troponin greater than or equal to .05 ng/mL (95% CI, 2.15-11.35; $P < .001$). In multivariable regression analysis, there was a significant difference between CE and NCE stroke groups with respect to AF (OR, .04; 95% CI, .02-.14; $P < .001$), dilated cardiomyopathy (OR, .08; 95% CI, .02-.37; *P*.002), and a troponin level of greater than or equal to.05 ng/mL (95% CI, .01-.345; *P*.033). Univariate and multivariate analyses of characteristics of CE and NCE groups at our University Hospital, Newark's cohort (n = 144) is described in Table 2.

Discussion

Our study aimed to test if serum troponins obtained during the first blood draw obtained during a stroke code is associated with a CE etiology of stroke. Early recognition of CE strokes may enable the utilization of targeted diagnostic and treatment modalities towards them.[7] In our retrospective analysis, we found that a troponin level of greater than or equal to .05 ng/mL obtained during a stroke code showed a significant difference between cardioembolic and noncardioembolic strokes (OR, 4.94; 95% CI, 2.15-11.35; $P < .001$), with high specificity (87.78%) but low sensitivity (40.74%) to exclude noncardioembolic stroke. Our findings suggest that a level of troponin above greater than or equal to .05 ng/mL obtained during a stroke code may point towards CE as the likely potential etiology of stroke, and targeted investigations like echocardiogram should be expedited. Our finding has implications for clinical workup and patients with troponin levels of greater than or equal to .05 ng/mL may need through clinical investigations to look for a cardioembolic source. Anticoagulation is the treatment of choice for secondary prevention of stroke in most cases of cardioembolic etiologies of stroke and can reduce stroke risk by approximately 70% in patients with AF, which is the most common CE risk factor.[15] However, our study only implies an association of troponin levels with cardioembolic strokes, rather than causation.

Cardioembolic strokes make up approximately 20% to 30% of all ischemic strokes.[3] With better control of risk factors like hyperlipidemia and hypertension, the proportion of CE strokes has increased in developed countries, despite the reduction in the overall incidence of strokes.[16,17] CE strokes have multiple etiologies and can result from AF, low Ejection Fraction , cardiac thrombus, myocardial infarction, valvular heart abnormalities, myxoma, and restrictive cardiomyopathies.[3,18] Several classification systems can be used to divide ischemic strokes into subtypes.[18] We used the TOAST classification system for our research as it provides a simple nonoverlapping classification for various stroke subtypes.[18,19] Troponin elevation in acute stroke is often associated with underlying cardiac disease states like atrial fibrillation, myocardial ischemia, and congestive heart failure, but it is also found in renal dysfunction.[20-22] Recently studies have shown an independent association between early elevated troponin levels and cardioembolic and in embolic strokes of undetermined significance.[13,14] Elevated serum troponin levels have also been linked with visceral infarcts suggesting it to be a serum biomarker for an embolic phenomenon.[23]

The interest in the evaluation of cardiac enzymes in association with acute strokes is not new and has existed since the 1970s.[24] Studies have suggested that elevated troponin is associated with AF, abnormal echocardiographic findings like left atrial appendage thrombus, and the development of future stroke in patients with AF.[25-28] The exact cause of its elevation in stroke patients is uncertain, and adrenal sympathetic activation is thought to be causative.[29-34] Association of troponin elevation with right insular cortex strokes is well known in the literature.[35] The insular cortex is considered to play an essential role in the regulation of autonomic and cardiac function.[32-34,36] Elevated troponin value in the setting of an acute stroke is thought to be associated with higher mortality.[28,37-39]

Table 1. *Univariate and multivariate analyses of characteristics of groups with troponin levels ≥.05 ng/mL or less*

Variables	Group with troponin ≥.05 ng/mL (N = 33)	Group with troponin <.05 ng/mL (N = 111)	Univariate analysis *P*	Multivariate analysis *P*
Age (years)	64.1 ± 16.45	63.96 ± 13.7	95% CI, −5.76-5.49 *P* .962	
Sex [male, n (%)]	22 (66.67)	57 (51.35)	95% CI, .84-4.28; *P* .121	
NIHSS score	13.46 ± 5.39	11.17 ± 6.59	95% CI, −4.78-.19; *P* .07	OR, .99; 95% CI, .92-1.07; *P*.789
Atrial fibrillation [n (%)]	15 (45.45)	28 (25.22)	**95% CI, 1.10-5.54; *P* .026**	OR, 1.2; 95% CI, .39-3.78; *P* .755
Dilated cardiomyopathy [n (%)]	12 (37.5)	10 (9.26)	**95% CI, 2.05-13.67; *P* < .001**	OR, 0.37; 95% CI, .13-1.07; *P*.064
Cardioembolic etiology [n (%)]	**22 (66.67)**	**32 (28.83)**	**95% CI, 2.15-11.35; *P* < .001**	**OR, .25; 95% CI, .08-.8; *P* .018**
Blood glucose (mg/dL)	146.76 ± 65.83	141.08 ± 66.27	95% CI, −31.62-20.25; *P* .665	
SBP (mm Hg)	158.1 ± 33.25	159.19 ± 29.4	95% CI, −10.78-12.98; *P* .855	
DBP (mm Hg)	91.76 ± 19.43	89.79 ± 21.98	95% CI, −10.38-6.45; *P* .644	
MAP (mm Hg)	113.88 ± 22.14	111.85 ± 22.62	95% CI, −10.85-6.80; *P* .651	
Hb A1C (%)	6.08 ± 1.48	6.35 ± 1.78	95% CI, −.41-.95; *P*.44	
LDL (mg/dL)	86.54 ± 32.09	106.21 ± 39.53	**95% CI, −4.59-34.77; *P* .011**	OR, .99; 95% CI, .98-1.01; *P*.129
Hemoglobin (g/dL)	13.32 ± 1.81	13.14 ± 2	95% CI, −.94-.59; *P* .652	
Platelet (x1000 microl)	209.25 ± 80	233.56 ± 83.75	95% CI, −8.22-56.84; *P* .142	
INR	1.15 ± .15	1.13 ± .96	95% CI, −.35-.31; *P* .887	
PT (seconds)	14.61 ± 1.6	14.18 ± 6.77	95% CI, −2.78-1.92; *P* .719	
PTT (seconds)	28.45 ± 4.06	29.64 ± 16.83	95% CI, −4.67-7.04; *P* .689	
Verify Aspirin	527.86 ± 120.65	552.99 ± 94.58	95% CI, −17.78-68.05; *P* .249	
Verify Plavix	239.86 ± 44.65	242.97 ± 65.05	95% CI, −23.29-29.52; *P* .816	
Presence of early infarct signs [n (%)]	18 (54.54)	67 (60.36)	95% CI, .36-1.72; *P* .551	
Dense MCA sign [n (%)]	9 (30.0)	44 (40.37)	95% CI, .26-1.51; *P* .301	
Valvular abnormalities [n (%)]	0	2 (1.8)	95% CI, .47-2.37; *P* .437	
Lambl excrescence [n (%)]	2 (6.06)	10 (9.0)	95% CI, .13-3.13; *P* .591	
SICH [n (%)]	4 (12.12)	15 (13.5)	95% CI, .27-2.87; *P* .836	
Stay duration (days)	18.88 ± 40.68	9.32 ± 15.68	95% CI, −24.26-5.13; *P* .195	
Onset to troponin draw time (minutes)	105.58 ± 51.23	110.53 ± 55.61	95% CI, −16.48-26.37; *P* .649	
Onset to treatment time (minutes)	135.34 ± 44.17	135.97 ± 51.73	95% CI, −19.01-20.27; *P* .949	
Disposition (home versus facility)	3 (9.09)	10 (9.0)	95% CI, .26-3.91; *P* .988	

Abbreviations: DBP, diastolic blood pressure; Hb A1C, hemoglobin A1c; INR, International Normalized Ratio; LDL, low-density lipoprotein; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time; PTT, partial thromboplastin Time; SBP, systolic blood pressure; SICH, symptomatic intracerebral hemorrhage.

Table 2. *Univariate and multivariate analyses of characteristics of cardioembolic and noncardioembolic groups*

Variables	Cardioembolic group (N = 54)	Noncardioembolic group (N = 90)	Univariate analysis *P*	Multivariate analysis *P*
Age (years)	67.45 ± 13.71	61.92 ± 14.34	**95% CI, −10.34−0.74; *P* 0.024**	OR, 1; 95% CI, .96-1.04; *P*.838
Sex [male, n (%)]	31 (57.41)	48 (53.33)	95% CI, .60-2.33; *P*.634	
NIHSS score	14.43 ± 6.03	10.05 ± 6.06	**95% CI, −6.44−2.33; *P* < .001**	OR, 1.07; 95% CI, .97-1.17; *P*.209
Atrial fibrillation [n (%)]	**35 (64.81)**	**8 (8.89)**	**95% CI, 7.56-47; *P* < .001**	**OR, .04; 95% CI, .02-.14; *P* < .001**
Dilated cardiomyopathy [n (%)]	**18 (33.33)**	**5 (5.81)**	**95% CI, 2.79-23.51; *P* < .001**	**OR, .08; 95% CI, .02-.37; *P* .002**
Troponin ≥ .05 ng/mL [n (%)]	**22 (40.74)**	**11 (12.22)**	**95% CI, 2.15-11.35; *P* < .001**	**OR, .26; 95% CI, .08-.93; *P* .037**
Blood glucose (mg/dL)	134.99 ± 52.97	146.82 ± 72.6	95% CI, −10.62-34.28; *P* .299	
SBP (mm Hg)	161.56 ± 32.27	157.37 ± 28.97	95% CI, −14.48-6.11; *P* .422	
DBP (mm Hg)	91.33 ± 20.09	89.61 ± 22.18	95% CI, −9.07-5.64; *P* .645	
MAP (mm Hg)	113.61 ± 22.57	111.54 ± 22.47	95% CI, −9.74-5.59; *P* .593	
Hb A1C (%)	6.27 ± 1.56	6.3 ± 1.82	95% CI, −0.57-0.62; *P* .927	
LDL (mg/dL)	89.71 ± 34.16	109.19 ± 39.73	**95% CI, 6.59-32.37; *P* .003**	OR, 1.01; 95% CI, .99-1.02; *P*.769
Hemoglobin (g/dL)	13.22±1.87	13.16 ± 2	95% CI, −0.73-0.61; *P* .852	
Platelet (x1000 microl)	209.19 ± 83.35	239.33 ± 81.58	**95% CI, 2.1-58.19; *P* .035**	OR, 1; 95% CI, .99-1.01; *P*.321
INR	1.13 ± .14	1.13 ± 1.06	95% CI, −.29-.29; *P* .994	
PT (seconds)	14.52 ± 1.48	14.13 ± 7.5	95% CI, −2.44-1.65; *P* 0.704	
PTT (seconds)	29.21 ± 3.74	29.46 ± 18.66	95% CI, −4.84-5.34; *P* 0.923	
Verify aspirin	529.58 ± 111.45	558.15 ± 93.29	95% CI, −8.27-65.41; P .127	
Verify plavix	239.79 ± 68.08	243.78 ± 56.77	95% CI, −18.59-26.59; *P* .727	
Presence of early infarct signs [n (%)]	34 (62.96)	51 (56.67)	95% CI, .65-2.60; *P* .457	
Dense MCA sign [n (%)]	21 (41.18)	32 (36.36)	95% CI, .60-2.48; *P* .573	
Valvular abnormalities [n (%)]	1 (1.85)	1 (1.11)	95% CI, .10-27.41; *P* .611	
Lambl excrescence [n (%)]	1 (1.85)	11 (12.22)	**95% CI, .017-1.08; *P* .029**	OR, 12.68; 95% CI, 1-161.11; *P*.05
SICH [n (%)]	8 (14.81)	11 (12.22)	95% CI, .47-3.33; *P* .656	
Stay duration (days)	13.75 ± 22.37	10.17 ± 24.95	95% CI, -11.75-4.6; *P* .389	
Onset to troponin draw time (minutes)	94.89 ± 38.56	118.09 ± 60.69	**95% CI, 6.85-39.56; *P* .001**	OR, 1; 95% CI, .98-1.02; *P*.461
Onset to treatment time (minutes)	125.32 ± 37.93	142.13 ± 55.18	**95% CI, 1.44-32.18; *P* .032**	OR, 1; 95% CI, .98-1.02; *P*.874
Disposition (home versus facility)	6 (11.11)	7 (7.78)	95% CI, .47-4.67; *P* .499	

Abbreviations: DBP, diastolic blood pressure; Hb A1C, hemoglobin A1c; INR, International Normalized Ratio; LDL, low-density lipoprotein; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PT, prothrombin time; PTT, partial thromboplastin Time; SBP, systolic blood pressure; SICH, symptomatic intracerebral hemorrhage.

However, some studies have doubted this.[29] Few studies suggest troponin's value in the determination of outcome after IV-rtPA may be more in white than black patients.[40]

Our study had several limitations; firstly, it was a retrospective analysis of a relatively small number of patients. Our study was performed at a single center and may lack generalizability. There is a potential of misclassification of stroke subtypes; however, the TOAST criteria definitions specified were strictly adhered to. Another limitation of our study was that not all the patients in our cohort underwent a TEE (Transesophageal Echocardiogram), which could have potentially revealed an alternative cause of stroke.[41] However, everyone in our comprehensive stroke center undergoes an electrocardiogram, TTE (Transthoracic Echocardiogram) with at least 24 hours of telemetry to rule out a cardioembolic stroke. Further prospective studies involving a larger number of patients may be useful to confirm the utility of troponin obtained during acute stroke codes in establishing the likely etiology of stroke.

Conclusion

A troponin level of greater than or equal to .05 ng/mL obtained during a stroke code showed a significant difference between cardioembolic and noncardioembolic strokes. This finding may have implications for patient treatment, as anticoagulation is the treatment of choice for secondary prevention of stroke in most cases of cardioembolic stroke. A troponin level of greater than or equal to.05 ng/mL may prompt a more thorough search for a cardioembolic source in cases in which such a source is not identified on initial evaluation. Though the troponin level has low sensitivity, it has a reasonably high specificity with respect to cardioembolic strokes. Further prospective studies need to be performed to confirm the findings of our research.

Conflict of Interest

The authors declare no conflicts of interest.

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