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Abstract

Purpose of Review Cardiac troponin levels in the blood are an important biomarker of acute coronary events, but may also be elevated in the context of acute ischemic stroke without an obvious concurrent myocardial insult. The objective of this study and systematic review is to determine how high the circulating troponin I level can rise due to ischemic stroke.

Recent Findings Anonymized medical records from Vanderbilt University Medical Center were reviewed identifying 151,972 unique acute ischemic stroke events, of which 1,226 met criteria for inclusion in this study. Included patients had at least one measurement of troponin I level documented during the hospital visit when an acute ischemic stroke was diagnosed and were free of known cardiac/coronary disease, renal impairment, sepsis or other confounders. In this group, 20.6% had a circulating troponin I level elevated over the reference range, but 99% were below 2.13 ng/mL. This is significantly lower than the distribution observed in a cohort of 89,423 unique cases of acute coronary syndrome ($p<2.2^{-16}$). A systematic review of published literature further supported the conclusion that troponin I level may increase due to an acute ischemic stroke, but rarely rises above 2 ng/mL.

Summary Because of the shared risk factors between stroke and coronary artery disease, clinicians caring for patients with acute ischemic stroke should always have a high index of suspicion for co-morbid cardiac and cardiovascular disease. In general, troponin I levels greater than 2 ng/mL should not be attributed to an acute ischemic stroke, but should prompt a thorough evaluation for coronary artery disease.

Introduction

Cardiac troponin is a tripartite complex whose components are sensitive markers of myocardial injury. In the familiar clinical paradigm of coronary artery disease (CAD), plasma elevation of cardiac-specific troponin I and T subunits permits the rapid identification and stratification of patients with myocardial infarction (MI)[1,2].

Cardiac troponin elevation has also been reported in up to 34% of patients with acute stroke, and increased stroke severity may be associated with greater magnitude of troponin elevation[3-9]. Elevated cardiac biomarkers in these patients may be ascribed to either ischemic or nonischemic disease. Ischemic causes include coronary artery occlusion and oxygen supply-demand imbalance leading to acute MI, while nonischemic causes encompass acute neurologic insults such as the stroke itself, acute non-neurologic insults such as pulmonary embolism, and chronic diseases such as renal failure[1,10]. While poorly understood, nonischemic neurogenic myocardial damage in stroke patients has been proposed to occur via cortically induced autonomic imbalance with increased sympathetic activity leading to contraction band necrosis.[10-12] Indeed, elevated circulating epinephrine has been associated with increased troponin I in ischemic stroke[13]. Given the demographic overlap between cardiovascular and cerebrovascular diseases, determining the cause(s) of troponin elevation in patients with acute ischemic stroke is clinically challenging - even more so is determining the appropriate timing and extent of cardiac workup in the setting of acute stroke.

Here, we aim to facilitate clinical decision-making in suspected comorbid cardiac and neurologic disease by quantitatively differentiating troponin elevation attributable to actionable ischemic cardiac disease from that due to ischemic stroke. Our patient population includes individuals diagnosed with acute ischemic stroke at Vanderbilt University Medical Center, a prominent tertiary referral center in Middle Tennessee. This setup enables us to examine the largest to-date cohort of patients at the epicenter of our nation's stroke belt[14].

Methods

Medical Record Review

We obtained data for this study from Vanderbilt's Synthetic Derivative, a HIPAA-compliant deidentified mirror of our hospital's electronic medical record that contains records for over 2.8 million patients over 20 years, and which was created for research purposes. This study was approved by the Vanderbilt University Medical Center Institutional Review Board (#171169).

Patient records were identified for inclusion or exclusion based on the presence or absence of specific PheWAS codes, which are high-level code aggregations of International Classification of Disease, ninth revision (ICD-9) codes[15]. We selected patient records with evidence of ischemic stroke demonstrated by presence of PheWAS code 433 (code definition) for inclusion in our review. Records with evidence of other conditions which may have confounded our results were excluded based on the presence of specific PheWAS codes (Table 1). We considered exclusion criteria in one of three different categories: conditions which could never be present in the patient record, conditions which could not be present within the past six weeks in the patient record, and conditions which could not be present within the past two weeks in the patient record, all with respect to the medical visit when the patient record was coded with PheWAS code 433. These decisions were made by consultation with experts in cardiology.

After the set of records had been defined, we selected the maximum troponin measurement associated with the hospital visit in which the code 433 (Cerebrovascular disease) was assigned. This way, each event only contributed one measurement to the analysis, eliminating bias from multiple collinear measurements within a single record. We report the percentage of troponin measurements that were elevated (>0.05 ng/mL), as well as the minimum, maximum, 1^{st}, 5^{th}, 25^{th}, 50^{th}, 75^{th}, 95^{th} and 99^{th} percentile of the distribution of those measurements. For comparison, we extracted troponin maximum troponin measurements from records with evidence of acute coronary syndrome events, and report the same distribution measures. Finally, we tested whether the maximum troponin measurements from ischemic stroke patients and from acute coronary syndrome patients followed the same distribution using a Mann-Whitney *U* test[16].

Systematic review

We systematically queried Medline, OVID and Embase databases to identify studies which reported the distribution of troponin I levels after acute ischemic strokes. Query keywords included: *(Elevated Cardiac Troponin or Elevated Troponin or Troponin Elevation or Elevation of Troponin) or (Increased Cardiac Troponin or Increased Troponin) or (Troponin Change) AND Stroke.* The reference lists from identified studies and key review articles were also reviewed to collect any articles missed in the search strategy. The results were manually de-duplicated. The relevance of identified records was assessed by reviewing the abstract and, when appropriate, the full manuscript. Only studies reporting estimates of the upper limit of troponin I levels after acute ischemic strokes were included (a minimum of one of the following: 95^{th} percentile, 99^{th} percentile, range or subject level data from which we could extract this information). Because of significant variability in the collection of data between the identified studies and relatively small number of studies, meta-analysis was not felt to be appropriate, but the results of each study are presented.

Results

Before exclusion of comorbidities, we identified 151,972 unique stroke events in the Synthetic Derivative. Our approach identified 1,226 unique events within records where patients were admitted to the hospital, were coded with PheWAS code 433, had at least one troponin measurement drawn, and did not have evidence of confounding causes of troponin elevation recorded. We also identified 89,423 unique events within records where patients were admitted to the hospital and coded for an acute coronary syndrome event. Demographics are shown in Table 2.

Of the records in our study, 20.6% (252/1226) of the stroke events and 43.7% (39095/89423) of the ACS events had maximum troponin levels that were elevated above the reference range. Troponin I values for stroke patients range from 0.000 to 94.170 ng/mL, and the 99th percentile was 2.132 ng/mL. For cardiac patients, the range was 0.000 to 1897.92 ng/mL, and the 99th percentile was 49.634 ng/mL (Table 3). For comparison with other studies, the mean troponin

Table 1. PheWAS codes used for inclusion and exclusion of medical records

	PheWAS code	PheWAS name
Required for inclusion in stroke population	433	Cerebrovascular accident
Excluded if EVER recorded	270.33	Amyloidosis
	394	Chronic rheumatic disease of the heart valves
	414	Other forms of chronic heart disease
	415	Pulmonary heart disease
	416	Cardiomegaly
	425	Cardiomyopathy
	428	Congestive heart failure, nonhypertensive
	429	Ill-defined descriptions and complications of heart disease
	429.1	Heart transplant/surgery
	585	Renal failure
	587	Kidney replaced by transplant
	589	Abnormal kidney function
	697	Sarcoidosis
	747	Cardiac and circulatory congenital anomalies
	854	Mechanical complications of cardiac/vascular device, implant, and graft
	972	Poisoning by agents affect the cardiovascular system
Excluded if recorded in prior 6 weeks	411	Ischemic heart disease
	420	Carditis
	427	Cardiac dysrhythmias
	452	Venous embolism and thrombosis
	452.1	Iatrogenic pulmonary embolism and infarction
	770	Myalgia and myositis NOS
	772.4	Rhabdomyolysis
Excluded of recorded in prior 2 weeks	038	Septicemia
	197	Chemotherapy
	580	Nephritis; nephrosis; renal sclerosis
	590	Pyelonephritis
	994	Sepsis and SIRS

measurements were 0.22 ng/mL and 2.26 ng/mL for stroke patients and coronary disease patients, respectively. The Mann-Whitney test that the troponin measurements come from the same distribution was rejected ($p < 2.2^{-16}$).

Systemic literature review identified 96 relevant database entries and manual review of the references from the retrieved articles and from appropriate review literature identified 15 additional studies[17]. Of these, three studies reported the upper limits of the distribution of circulating troponin I levels in patients with acute ischemic stroke (Figure 1 and Table 4)[7,18,19]. Two additional studies reported the upper limits of troponin T levels[20,21]. Hasirci et al. reported cardiac troponin I level was elevated to 0.08 +- 0.22 ng/mL (n=155) with a maximum value of 1.93 ng/mL after anterior circulation stroke and to 0.08 +- 0.22 ng/mL (n=67) with a maximum value of 1.41 ng/mL) after posterior circulation stroke – suggesting that anterior versus posterior localization of the cerebral injury was not a major determinant in troponin level[7]. This study also reported that the degree of elevation of troponin correlated with the NIH stroke scale score. Su et al found troponin I levels were increased in 16.8% of patients with acute ischemic stroke (n=871). Because they reported subject level data, we were able to calculate that 95% of their subjects had a peak troponin value of less than 0.22 ng/mL and 99% were below 1.36 ng/mL[18]. They concluded that troponin elevation in acute ischemic stroke was more prevalent among older patients and correlated with both poor outcome and mortality. Subject level of their data combined with ours leads to an estimated 99th percentile troponin value of 2.1 in the pooled 2097 subjects, but it should be

Table 2. Demographics and selected clinical features of stroke and cardiac patients

	Stroke	Cardiac
Sex	47.9% Male, 5.7% Missing	54.9% Male, 2.4% Missing
Race	80.2% White, 6.6% Missing	73.6% White, 3.4% Missing
Age	IQR 55-75, 11.5% Missing	IQR 52-73; 3.8% Missing
Max Systolic	IQR 151-188, 1.5% Missing	IQR 139-174, 2.3% Missing
Max Pulse	IQR 74-96, 51.1% Missing	IQR 74-94, 52.7% Missing

Table 3. Distribution of troponin I levels in records with ischemic stroke and cardiac disease

Ischemic stroke (n=1,226)

	Min	1st	5th	25th	50th	75th	95th	99th	Max
Troponin I (ng/mL)	0	0	0.01	0.01	0.02	0.04	0.37	2.1	94.2

Cardiac ischemia (n=89,423)

	Min	1st	5th	25th	50th	75th	95th	99th	Max
Troponin I (ng/mL)	0	0.01	0.01	0.02	0.04	0.15	5.86	49.6	1897.9

noted this study did not exclude patients with known renal or cardiac disease. Cui et al evaluated 178 patients from China with acute ischemic stroke and found that troponin I level was elevated in 18.5% and peaked on the second day after stroke. They reported troponin I level after acute ischemic stroke were rarely more than six-times the upper limit of the reference range (a level of 0.20 ng/mL).

Discussion

Troponin elevation in ischemic stroke is a common phenomenon which leaves the clinician to wonder if the elevation is neurogenic or if an underlying cardiac pathology should be investigated. Here we show that cardiac troponin levels are increased in 20.6% of patients with acute ischemic stroke who do not have known coronary artery or renal disease. While it has been previously widely reported that troponin level may be increased due to an ischemic stroke, it was not clear from the existing literature if there was a threshold level beyond which a primary cerebral etiology is unlikely. We demonstrated that the distribution of cardiac troponin levels due to ischemic stroke differs from that in acute coronary syndromes in that the interquartile range of the measurements associated with ischemic strokes was essentially equal to the bottom 50% of the troponin measurements associated with acute coronary syndrome. Our data coupled with the systematic literature review suggests that elevation of cardiac troponin level to greater than 2 ng/mL is rarely due to an ischemic stroke. Moreover, coronary angiography in this population revealed a significant minority of patients had culprit coronary lesions[5]. In the TRELAS study, Mochmann *et al.* evaluated a group of patients with acute ischemic stroke, elevated troponin and no medical history of cardiac or renal disease and evaluated them with coronary angiography. They found a culprit coronary lesion in 7 of 29 cases (24%) and these patients had troponin levels nearly twice as high as those without a culprit lesion[5]. Additionally, Ahn et al followed 1692 Korean patients for an average of 33 months after acute ischemic stroke and reported a 46% mortality rate among those with elevated troponin level compared to 17% among those with a normal troponin level[22].

Table 4: Severity of troponinemia attributable to ischemic stroke: systematic review

Study	**N**	**Region of data collection**	Excluded subjects with active cardiac disease	Excluded subjects with chronic cardiac disease or renal disease	**Percent with elevated troponin***	**99th percentile or peak troponin level**
Current	1,226	Southeastern USA	Yes	Yes	20.6%	2.1 ng/mL
Fure 2006	279	Norway	No (65% had EKG changes)	No	9.6%	3.9 ng/mL (peak)
Hasirci 2013	222	Turkey	Yes	Yes	18.8%	1.9 ng/mL (peak)
Abdi 2015	114	Iran	No (22% had EKG changes)	No	17.6%	0.4 ng/mL (peak)
Su 2016	871	Taiwan	No	No	16.8%	1.4 ng/mL
Cui 2017	178	China	No (43% had EKG changes)	Yes	18.5%	0.2 ng/mL**

All studies reported troponin I levels except Fure et al and Abdi et al which reported troponin T levels.

* threshold for elevated troponin defined by the authors of the individual trials, ranged from 0.01 to 0.05 ng/mL.

** value estimated from author's description that troponin did not rise above 6-fold of the upper limit of their reference range (0.035 ng/mL).

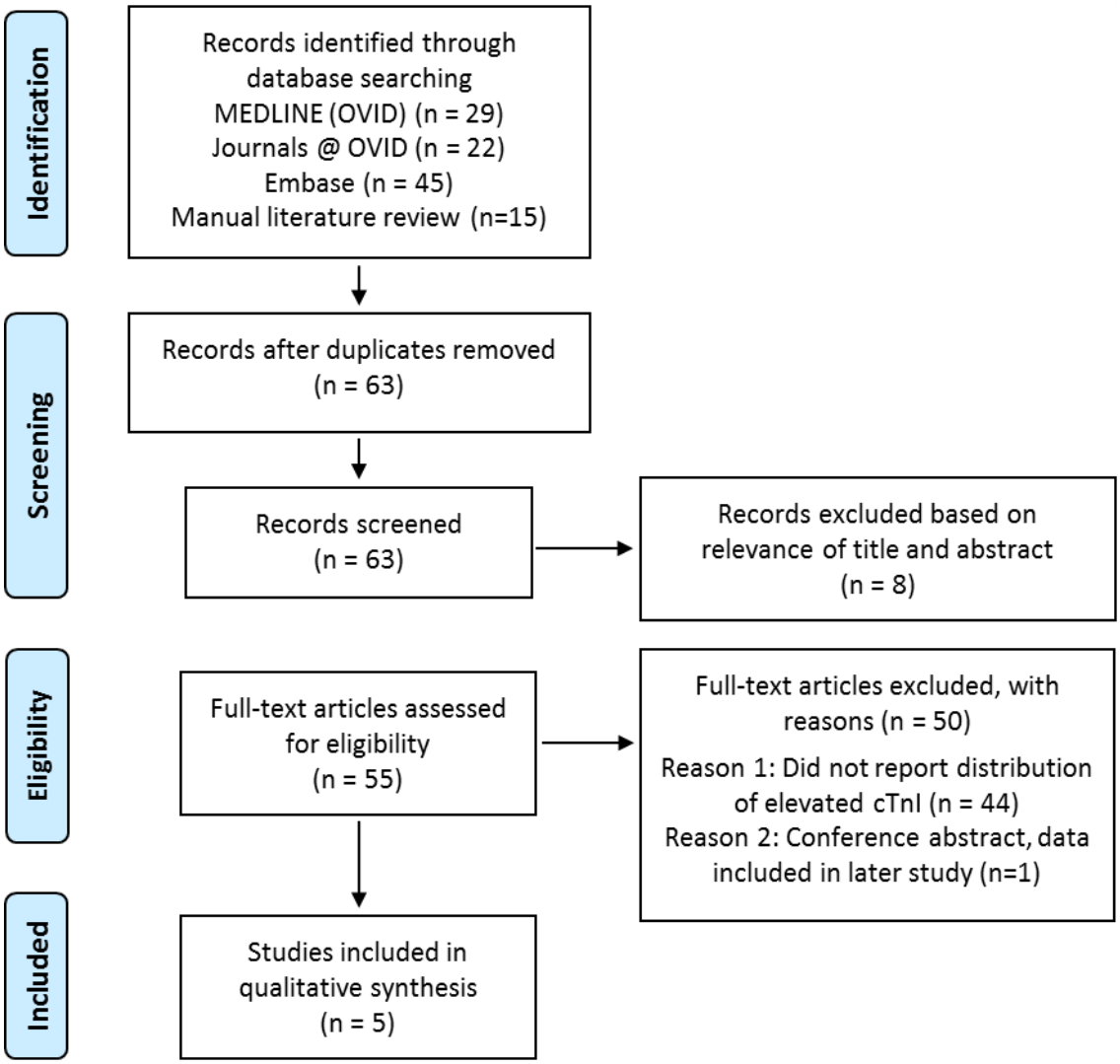

Figure 1. Flow diagram illustrating process of identification and selection of studies for inclusion in this qualitative synthesis.

Because the data for our study came from routine clinical practice it may be more representative of a general population of at-risk patients than studies which rely on strict inclusion and exclusion criteria in the context of a recruitment trial. However, the clinical nature of the data also presents a limitation, in that the meticulous data collection techniques employed in a cohort study are not enforced. Similarly, there are no embedded error checking mechanisms within the electronic medical record to ensure that the recorded values are correct or even biologically plausible. For this analysis, we selected the maximum troponin measurement for each hospital event. While it is necessary to make a selection of some kind so as not to bias the distribution in favor of records with multiple troponin measurements, it is possible that our choice to use the maximum may have affected our results. Even so, as our initial question focused on the level of troponin elevation that could be attributed to ischemic stroke alone, we believe the maximum troponin measurement for each event is a defensible choice.

Conclusions

This work demonstrates that, while troponin levels can become elevated due solely to ischemic stroke, the degree of troponin elevation is markedly lower than in patients with acute cardiac insults. With this knowledge, clinicians can make judicious decisions regarding when to pursue further cardiac workup in a patient with known ischemic stroke and an elevated troponin measurement.

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   *** This study evaluated a group of patients with acute ischemic stroke, elevated troponin and no medical history of cardiac or renal disease with coronary angiography. They found a culprit coronary lesion in 7 of 29 cases (24%) and these patients had troponin levels nearly twice as high as those without a culprit lesion.*
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