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Causes of Troponin Elevation and Associated Mortality in Young Patients

Candace Wu, MPH^a, Avinainder Singh, MBBS^a, Bradley Collins, BS^a, Amber Fatima, MBBS^a, Arman Qamar, MD^b, Ankur Gupta, MD, PhD^a, Jon Hainer, BS^a, Josh Klein, BS^a, Petr Jarolim, MD, PhD^c, Marcelo Di Carli, MD^a, Khurram Nasir, MD, MPH^d, Deepak L. Bhatt, MD, MPH^b, and Ron Blankstein, MD^a

^aCardiovascular Imaging Program, Departments of Medicine and Radiology, Harvard Medical School, Boston, Mass

^bCardiovascular Division, Department of Medicine, Harvard Medical School, Boston, Mass

^cDepartment of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass

^dMiami Cardiac and Vascular Institute, Baptist Health South Florida, Miami, Fla

Abstract

BACKGROUND—While increased serum troponin levels are often due to myocardial infarction, increased levels may also be found in a variety of other clinical scenarios. Although these causes of troponin elevation have been characterized in several studies in older adults, they have not been well characterized in younger individuals.

METHODS—We conducted a retrospective review of patients 50 years of age or younger who presented with elevated serum troponin levels to 2 large tertiary care centers between January 2000 and April 2016. Patients with prior known coronary artery disease were excluded. The cause of troponin elevation was adjudicated via review of electronic medical records. All-cause death was determined using the Social Security Administration's death master file.

RESULTS—Of the 6081 cases meeting inclusion criteria, 3574 (58.8%) patients had a myocardial infarction, while 2507 (41.2%) had another cause of troponin elevation. Over a median follow-up of 8.7 years, all-cause mortality was higher in patients with nonmyocardial infarction causes of troponin elevation compared with those with myocardial infarction (adjusted hazard ratio [HR] 1.30; 95% confidence interval [CI], 1.15–1.46; $P < .001$). Specifically, mortality was higher in those with central nervous system pathologies (adjusted HR 2.21; 95% CI, 1.85–2.63; $P < .001$), nonischemic cardiomyopathies (adjusted HR 1.66; 95% CI, 1.37–2.02; $P < .001$), and end-stage renal disease (adjusted HR 1.36; 95% CI, 1.07–1.73; $P = .013$). However, mortality was lower in

Requests for reprints should be addressed to Ron Blankstein, MD, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. rblankstein@bwh.harvard.edu.

SUPPLEMENTARY DATA

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patients with myocarditis compared with those with an acute myocardial infarction (adjusted HR 0.43; 95% CI: 0.31–0.59; $P < .001$).

CONCLUSION—There is a broad differential for troponin elevation in young patients, which differs based on demographic features. Most nonmyocardial infarction causes of troponin elevation are associated with higher all-cause mortality compared with acute myocardial infarction.

Keywords

Cardiac contusion; Cardiac troponin; Cardiomyopathy; End-stage renal disease; Myocardial infarction; Myocarditis; Myositis; Pulmonary embolism; Rhabdomyolysis; Seizure; Stroke; Subarachnoid hemorrhage

INTRODUCTION

Myocardial infarction is a relatively uncommon disease in young individuals, and the proportion of cases of myocardial infarction occurring in young patients has been found to vary between 2% and 10% in the past few decades.^{1–3} While myocardial infarction in the young is an important public health issue, there are many other causes of troponin elevation that may be more prevalent in younger individuals.^{4,5} As a result, young patients presenting with elevated troponins pose a diagnostic challenge given their low pretest probability for atherosclerotic disease.

Prior studies have shown that among children and adolescents younger than 20 years of age presenting with chest pain, the most common causes of troponin elevation include myocarditis and vasospasm secondary to drug use.^{6–8} Similarly, several studies have characterized the causes of troponin elevation in older adults with an average age of 60–70 years.^{9–11} Causes of troponin elevation other than acute coronary syndrome in these older cohorts include sepsis, tachycardia, heart failure, pulmonary embolism, stroke, cerebral hemorrhage, and respiratory failure.

However, causes of troponin elevation have not been well characterized in young adults under the age of 50 years. A delineation of the different causes of troponin elevation in young adults is clinically important, with associated diagnostic, prognostic, and therapeutic implications. Thus, the aim of this study was to evaluate the various causes of troponin elevation in a large cohort of patients younger than 50 years of age, including potential differences based on demographic characteristics, and to investigate their association with all-cause mortality.

METHODS

Study Population

We included all patients 50 years of age or younger who presented to either of 2 large tertiary hospitals within Partners HealthCare between January 2000 and April 2016 and had elevated cardiac troponins (I or T) or International Classification of Diseases, Ninth Revision (ICD-9) or ICD-10 codes for acute myocardial infarction. Those with a history of

coronary artery disease (defined as prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), missing medical data, or cardiac surgery within the past 30 days were excluded. The Partners HealthCare Institutional Review Board approved this study for retrospective review of electronic medical records.

Data Source

Data were provided by the Research Patient Data Registry (RPDR) at Partners HealthCare, which captures clinical data from several hospital systems, including Brigham and Women's Hospital and Massachusetts General Hospital, and stores the data in one central data warehouse. It provides demographic information, clinical diagnoses and notes, health history, laboratory results, medications, procedure reports, and imaging studies. RPDR is linked to the Social Security Administration's death master file and provides vital status information.

Clinical Data

A detailed review of electronic medical records including admission, progress and discharge notes, cardiology consult notes, electrocardiograms, and imaging studies was conducted to obtain data in a systematic manner and adjudicate causes of troponin elevation. Demographic data and laboratory values were also obtained through the RPDR. Income was estimated based on household zip codes using the 2015 inflation-adjusted median household income data provided by the US Census Bureau.¹² Income tertiles were defined according to the 2015 US income percentiles. The presence of comorbidities such as diabetes, hypertension, and hyperlipidemia prior to admission or diagnosed upon admission was obtained using ICD-9 and ICD-10 codes. Long-term survival of patients after discharge was ascertained via the Social Security Administration's death master file.

Adjudication of Acute Myocardial Infarction

Medical records were reviewed by a team of trained study physicians. Each patient was classified as having a myocardial infarction or other cause of troponin elevation using the established European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, World Heart Federation third universal definition of myocardial infarction.¹³ The criteria for acute myocardial infarction included the detection of an increase or decrease of cardiac biomarkers with at least one abnormal value above the upper reference limit of the assay and at least one of the following: 1) symptoms of ischemia; 2) new ST-segment T-wave changes or new left bundle branch block; 3) development of pathological Q waves on electrocardiogram; 4) new loss of viable myocardium or regional wall motion abnormalities on imaging; or 5) identification of an intracoronary thrombus by imaging or autopsy. In the event of uncertainty about the diagnosis of myocardial infarction, the full adjudication committee reviewed the cases and a diagnosis was adjudicated by consensus.

Adjudication of Nonmyocardial Infarction Causes of Troponin Elevation

Nonmyocardial infarction causes of troponin elevation were adjudicated based on predetermined criteria and included the following: 1) Acute pulmonary embolism; 2)

Myocarditis—discharge diagnosis or findings suggestive of myocarditis on imaging or pathology; 3) Cardiomyopathy—infiltrative cardiomyopathies such as amyloidosis or sarcoidosis, ejection fraction < 30% prior to admission, or prior cardiac transplantation; 4) End-stage renal disease—stage 5 chronic kidney disease, chronic dialysis, or renal transplant recipient; 5) Central nervous system pathology—stroke, seizure, or subarachnoid hemorrhage; 6) Trauma—specifically chest wall trauma; 7) Rhabdomyolysis/myositis—diagnosed based on history and elevated creatine kinase with normal MB fraction; and 8) Other—elevated troponin with unknown etiology and not meeting any of the above criteria.

Troponin Assays

Laboratory records were reviewed for elevated cardiac troponins I or T. During the course of the study period, different assays were used to measure troponin levels. Therefore, each peak troponin value was standardized by dividing it by the upper limit of normal for the particular assay that was used. Categories of standardized peak troponin levels were based on those previously described.¹³

Statistical Analysis

Baseline characteristics of patients diagnosed with myocardial infarction vs other causes of troponin elevation were compared using chi-squared tests for all categorical variables and the Mann-Whitney *U* test for age, as it had a skewed distribution. Continuous data were reported using median $\pm$ interquartile range for nonnormal distributions. Other associations were assessed with univariable and multivariable regression analyses. Candidate variables for multivariable models were selected based on known clinical significance. Kaplan-Meier curves were constructed and compared with the log-rank test. Cox proportional hazards modeling was utilized to identify predictors of all-cause mortality. All statistical analyses were performed using Stata 14.2 (StataCorp, College Station, Texas).

RESULTS

Baseline Characteristics and Causes of Troponin Elevation

During the 16-year period of available data, there were 6081 patients who presented with elevated troponins and met inclusion criteria. Of the 6081 patients, 3574 (58.8%) had a myocardial infarction (Figure 1). Other causes of troponin elevation included 501 (8.2%) with myocarditis, 493 (8.1%) with a central nervous system pathology, 442 (7.3%) with cardiomyopathy, 337 (5.5%) with end-stage renal disease, 334 (5.5%) with chest wall trauma, 237 (3.9%) with pulmonary embolism, and 163 (2.7%) with rhabdomyolysis/myositis.

Baseline characteristics of the study population are summarized in Table 1. Patients with myocardial infarction were, on average, older (44 years vs 39 years), more likely to be men (69.9% vs 65.9%), and more likely to be white (74.8% vs 70.9%) than those with other causes of troponin elevation. Additionally, patients with nonmyocardial infarction causes had a lower prevalence of cardiovascular risk factors, higher creatinine levels, and lower standardized peak troponin values.

Standardized peak troponin levels for each cause of troponin elevation are shown in Supplementary Figure 1 (available online in the Appendix). While the majority of patients presenting with myocardial infarction and myocarditis had standardized peak troponin values >10 times the upper limit of normal, the majority of those presenting with the other causes of troponin elevation unrelated to myocardial infarction had lower standardized troponin levels.

Causes of Troponin Elevation by Age

Table 2 shows the distribution of nonmyocardial infarction causes of troponin elevation stratified by age. Patients 40 to 50 years of age were more likely to present with cardiomyopathy (19.6% vs 15.7%, $P = .001$) compared with younger patients. In contrast, patients younger than 40 years of age were more likely than older patients to present with myocarditis, chest wall trauma, or rhabdomyolysis/myositis (P for all $< .001$). The age distribution for the individual causes of troponin elevation is shown in Figure 2. The median age at which patients presented with troponin elevation was highest among those with myocardial infarction and lowest among those presenting after chest wall trauma.

Causes of Troponin Elevation by Sex and Race

With regard to differences in nonmyocardial infarction causes of troponin elevation between sexes, women were more likely to present with pulmonary embolism (15.1% vs 6.5%, $P < .001$) or central nervous system pathology (26.5% vs 16.1%, $P < .001$) compared with men, while men were more likely to present with chest wall trauma (16.1% vs 8.0%, $P < .001$) (Figure 3). When nonmyocardial infarction causes were stratified by race, African American patients were more likely to present with cardiomyopathy and end-stage renal disease, while Hispanic patients were more likely to present with myocarditis (Figure 4). Compared with white patients, African Americans were more likely to have a pulmonary embolism (12.1% vs 10.0%, $P < .05$), cardiomyopathy (22.1% vs 17.3%, $P < .001$), or end-stage renal disease (20.3% vs 11.7%, $P < .001$).

Causes of Troponin Elevation and All-Cause Mortality

During a median follow-up of 8.7 years, there were 1601 (26.3%) deaths. All-cause mortality was higher in those with a cause of troponin elevation other than myocardial infarction compared with those with myocardial infarction (log-rank $P < .0001$) (Figure 5). Kaplan-Meier curves for each of the causes of troponin elevation are shown in Supplementary Figure 2 (available online in the Appendix). In a Cox proportional hazards analysis adjusting for age, sex, race/ethnicity, income level, creatinine, standardized peak troponin, diabetes, hypertension, hyperlipidemia, and year of admission, all-cause mortality was higher in patients with nonmyocardial infarction causes compared with those presenting with myocardial infarction (adjusted HR 1.30; 95% CI, 1.15–1.46; $P < .001$). Notably, mortality was higher in those with central nervous system pathologies (adjusted HR 2.21; 95% CI, 1.85–2.63; $P < .001$), cardiomyopathies (adjusted HR 1.66; 95% CI, 1.37–2.02; $P < .001$), and end-stage renal disease (adjusted HR 1.36; 95% CI, 1.07–1.73; $P = .013$) (Figure 6). On the other hand, all-cause mortality was lowest in patients with myocarditis when compared with myocardial infarction (adjusted HR 0.43; 95% CI, 0.31–0.59; $P < .001$).

DISCUSSION

To our knowledge, our study is the largest to comprehensively characterize the causes of troponin elevation and associated mortality among young adults. While our results highlight the fact that there is a broad differential for troponin elevation, we demonstrated that young patients with troponin elevation from causes other than myocardial infarction, which represented 41% of our study cohort, have a significantly higher all-cause mortality when compared with those who present with myocardial infarction, even after adjusting for demographics, baseline cardiovascular risk factors, and degree of troponin elevation. While patients who experienced a myocardial infarction were older, had higher levels of troponin, and were more likely to have risk factors for coronary artery disease, those who had other causes were younger and were more likely to be non white. Within this group of patients who did not experience a myocardial infarction, patients who were younger were more likely to have experienced myocarditis, chest wall trauma, or rhabdomyolysis/myositis as the cause of their troponin elevation.

Given our study design, which only included younger patients who may be less likely to have atherosclerotic disease, it might be expected that a higher proportion of patients would have causes of troponin elevation unrelated to myocardial infarction. However, we found that more patients had a myocardial infarction. Moreover, consistent with previous studies in young patients,^{2,3,14} the majority of patients presenting with acute myocardial infarction were men.

Among patients presenting with nonmyocardial infarction causes, women were more likely to present with pulmonary embolism or central nervous system pathology compared with men, while men were more likely to present following chest wall trauma. These findings might be expected given the likelihood of risk factors such as pregnancy or oral contraceptive use in this age cohort, although we did not ascertain pregnancy, oral contraceptive use, or smoking status in this study. Furthermore, men may be more likely to present with trauma, as they may be more likely to engage in risk-taking physical activities. There was also more heterogeneity in what causes troponin elevation in African Americans as they were more likely to present with pulmonary embolism, cardiomyopathy, or end-stage renal disease compared with white patients.

There are several mechanisms that lead to troponin elevation in patients without myocardial infarction. Heart failure can cause troponin elevation secondary to myocardial stretch, which leads to apoptosis and subsequent myocyte injury and death.^{15,16} In addition, pulmonary diseases such as pulmonary embolism and pulmonary hypertension cause increased right heart strain, which contributes to myocardial injury.^{4,17} Patients with renal insufficiency also have higher baseline troponin levels, making the diagnosis of myocardial infarction more difficult in this population.^{18–20} Although the underlying mechanism is not fully understood, elevated levels are likely secondary to reduced renal clearance in addition to comorbid disease conditions associated with troponin release such as severe heart failure and kidney-related anemia.⁵ Following a subarachnoid hemorrhage, severe cardiac injury can occur in association with left ventricular systolic dysfunction and pulmonary edema.²¹ Although the exact mechanism is debated, animal models suggest that myocardial necrosis may be due to

excessive sympathetic stimulation of cardiac nerves secondary to increased release of norepinephrine.²² Additional causes of troponin elevation include cardiac contusions and myocarditis as a result of direct myocyte damage.^{4,17} It is important to recognize that not every patient who presents with one of these pathologies will have elevated troponin levels, which raises the question of whether certain patients have a particular predisposition that warrants early recognition, prevention, diagnosis, and management or whether these patients have more severe underlying acute illness.⁵

Among patients who do not have a myocardial infarction, elevated troponin levels, regardless of etiology, have been shown to be associated with worse outcomes, both in the hospital and long term.^{23–33} Similar to a previous study in an older population, which found that mortality was higher in patients without acute coronary syndrome compared with those with acute coronary syndrome,⁹ increased troponins due to causes unrelated to myocardial infarction in our younger study population were associated with worse long-term outcomes compared with acute myocardial infarction. The high mortality rate associated with nonmyocardial infarction causes in even a young cohort highlights the importance of identifying appropriate management strategies aimed at treating the underlying causes as well as addressing any modifiable risk factors that could be contributing to the increased mortality observed in these patients. Nevertheless, increased troponins may be indicative of more severe underlying disease (ie, a more severe pulmonary embolism or larger central nervous system event), and as such, it remains unknown whether the increased risk conferred by having elevated cardiac biomarkers can be modified. Ultimately, short-term and long-term management of young patients with causes of troponin elevation other than myocardial infarction are not well defined, and additional research is necessary to determine the optimal management strategies for these patients.

Clinicians need to be aware of the differential for elevated cardiac biomarkers, as there are important diagnostic implications. Young patients presenting with elevated troponins pose a diagnostic challenge given their generally low pretest probability for atherosclerotic disease. From a diagnostic perspective, it is important to be able to determine whether biomarker elevation is cardiac or noncardiac in etiology in order to avoid unnecessary cardiac testing, which may impose additional health risks to patients and increase health care costs. The results of our study suggest that patient demographics may be informative when refining the diagnosis and determining the underlying etiology of troponin elevation.

As the high-sensitivity troponin assay, which was recently approved for use in the United States, becomes more widely available, more individuals will have detectable levels of cardiac troponin, and thus our findings would be even more relevant for understanding the various causes of troponin elevation in young individuals. Nevertheless, further data will be required about the diagnostic and prognostic implications of high-sensitivity troponins and whether they will confer a similar increase in mortality as has been observed with current assays.^{32–34} The ability to accurately discriminate those with acute myocardial infarction from other causes of troponin elevation that might portend a worse prognosis will be even more essential when high-sensitivity troponin assays are used more extensively.³⁵

LIMITATIONS

Our study evaluated a large cohort of patients over a 16-year time period. While patient records and details surrounding their hospitalizations were thoroughly and carefully reviewed, ICD codes were used for information about traditional baseline cardiovascular risk factors, and use of such codes has been shown to lack precision when compared with data that are collected prospectively. Although multivariable models were used, there may still be unmeasured and residual confounding. We did not differentiate between Type 1 and Type 2 myocardial infarction or account for treatment; both are factors that could influence prognosis.³⁶ Additionally, our analyses only evaluated all-cause mortality as the outcome, and we did not have information on cardiovascular death; however, the use of cardiovascular death is subject to misclassification bias.³⁷

CONCLUSION

We found that 41% of young patients with increased troponins at 2 large tertiary medical centers had a cause of troponin elevation other than myocardial infarction, which was associated with higher long-term all-cause mortality compared with acute myocardial infarction. There is a broad differential for troponin elevation in this population, which differs based on demographic features, and understanding these differences may have important diagnostic and prognostic implications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CLINICAL SIGNIFICANCE

- Understanding the broad differential for troponin elevation is essential as there are important diagnostic and prognostic implications.
- As high-sensitivity troponin assays become more widely available, more individuals will have detectable troponin levels, and the ability to accurately discriminate those with myocardial infarction from other causes will be even more important.

Figure 1.
Causes of troponin elevation.

Figure 2.
Age at presentation with troponin elevation.

Figure 3.
 Nonmyocardial infarction causes of troponin elevation stratified by sex.

Figure 4.
Nonmyocardial infarction causes of troponin elevation stratified by race/ethnicity.

Figure 5. Kaplan-Meier curves of patients with myocardial infarction and nonmyocardial infarction causes of troponin elevation.

Figure 6.

Hazard ratios for all-cause mortality for each cause of troponin elevation compared with myocardial infarction. *Cox proportional hazards model adjusted for age, sex, race/ethnicity, income level, creatinine, standardized peak troponin, diabetes, hypertension, hyperlipidemia, and year of admission.

Table 1

Baseline Characteristics of the Study Population

Characteristic	Overall n = 6081	Myocardial Infarction n = 3574 (58.8%)	Nonmyocardial Infarction n = 2507 (41.2%)	P-Value
Age (years), median (IQR)	43 (35, 47)	44 (38, 47)	39 (29, 45)	<.001
Male, n (%)	4151 (68.3)	2499 (69.9)	1652 (65.9)	<.001
Race, n (%)				
white	4155 (73.2)	2499 (74.8)	1656 (70.9)	.001
African American	664 (11.7)	334 (10.0)	330 (14.1)	<.001
Hispanic	499 (8.8)	278 (8.3)	221 (9.5)	.14
Other	356 (6.3)	228 (6.8)	128 (5.5)	.04
Household income, n (%)				
1st tertile (<\$35,900)	374 (6.2)	211 (6.0)	163 (6.6)	.33
2nd tertile (\$35,900–\$84,000)	3934 (65.5)	2274 (64.4)	1660 (67.1)	.03
3rd tertile (\$84,000)	1700 (28.3)	1048 (29.7)	652 (26.3)	.005
Diabetes mellitus, n (%)	1148 (18.9)	735 (20.6)	413 (16.5)	<.001
Hypertension, n (%)	2772 (45.6)	1821 (51.0)	951 (37.9)	<.001
Hyperlipidemia, n (%)	1601 (26.3)	1233 (34.5)	368 (14.7)	<.001
Creatinine (mg/dL)				
<1.3	3630 (59.8)	2390 (66.9)	1240 (49.6)	<.001
1.3–2	1179 (19.4)	661 (18.5)	518 (20.7)	.033
>2.0	1262 (20.8)	519 (14.5)	743 (29.7)	<.001
Standardized peak troponin *, n (%)				
1–2.99	1539 (25.3)	739 (20.7)	800 (31.9)	<.001
3–4.99	744 (12.2)	359 (10.0)	385 (15.4)	
5–9.99	860 (14.1)	451 (12.6)	409 (16.3)	
10 +	2938 (48.3)	2025 (56.7)	913 (36.4)	

IQR = interquartile range.

* Peak troponin levels were standardized to the upper limit of normal for the assay used.

Table 2

Nonmyocardial Infarction Causes of Troponin Elevation Stratified by Age

Cause of Troponin Elevation, n (%)	Number of Cases n = 2507	<40 Years n = 1280 (51%)	40–50 Years n = 1227 (49%)	P-Value
Pulmonary embolism	237	85 (6.6)	152 (12.4)	.53
Myocarditis	501	332 (25.9)	169 (13.8)	<.001
Cardiomyopathy	442	201 (15.7)	241 (19.6)	.001
End-stage renal disease	337	115 (9.0)	222 (18.1)	.152
Central nervous system pathology	493	195 (15.2)	298 (24.3)	.404
Chest wall trauma	334	247 (19.3)	87 (7.1)	<.001
Rhabdomyolysis/myositis	163	105 (8.2)	58 (4.7)	<.001