

Causes of Troponin Elevation and Associated Mortality in Young Patients

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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 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.

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INTRODUCTION

Myocardial infarction is a relatively uncommon disease in young individuals, and the proportion of cases of myocar-

dial 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

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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 $\leq 30\%$ 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

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.

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