Association of Mild Transient Elevation of Troponin I Levels With Increased Mortality and Major Cardiovascular Events in the General Patient Population

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● ***Context.*—The prognostic value of mild elevation of cardiac-specific troponin I (cTnI) levels is poorly defined, which can make interpretation of such an elevation difficult.**

***Objective.*—To study the prognostic value of transient mild elevation of cTnI levels in the hospitalized patient population.**

***Design.*—We performed a case-control study that compared the outcome of patients hospitalized for any cause with at least 2 subsequent transient cTnI measurements of 0.1 ng/mL or higher and less than 1.5 ng/mL with matched controls with cTnI levels less than 0.1 ng/mL. A cohort of 118 patients (mean ± SD age, 67.4 ± 14.0 years; 35.6% men) was followed up for an average ± SD of 11.9 ± 7.9 months. Seventy-one cases were matched with 37 controls in terms of demographics, coronary artery disease risk factors, and reason for admission. End points were all-cause mortality and major cardiovascular end points, including cardiovascular mortality, myocardial infarction, and revascularization.**

***Results.*—The total event rate was significantly increased in the case group compared with the control group at 12, 6, and 3 months (62.0% vs 24.3%, 59.2% vs 16.2%, and 47.9% vs 5.4%, respectively; $P < .001$). At 12, 6, and 3 months, the cases had a significant increase in all-cause mortality (43.7% vs 16.2%, 40.8% vs 8.1%, and 33.8% vs 0.0%, respectively; $P = .005$) and major cardiovascular end points (26.8% vs 8.1%, 26.8% vs 8.1%, and 21.1% vs 5.4%, respectively; $P = .02$) compared with controls.**

***Conclusion.*—Transient mild elevation of cTnI levels in hospitalized patients is associated with an increase in all-cause mortality and major cardiovascular complications. Such elevations of cTnI levels can be considered a marker for both all-cause and cardiovascular morbidity and mortality.**

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Cardiac-specific troponin I (cTnI) has been under intensive investigation because of its specificity to cardiac muscle and sensitivity in the determination of minimal myocardial injury. The sensitivity and specificity of cTnI are generally high for myocardial infarction but vary with the assay used, the upper reference limit, time since injury, and the comparative method used to define infarction, making comparison among studies difficult. Elevated cTnI levels are highly indicative of myocardial injury in patients with high pretest probability.[1] As with other tests, the specificity of cTnI is decreased as the upper reference limits of the test and the pretest probability of the population tested are lowered. Therefore, it is common to find mild elevations of cTnI levels in inpatients with low pretest probabilities of myocardial injury, which has raised the question of what such an increase really represents.[2]

Previous studies of patients with acute coronary syndrome have shown abnormal cTnI levels to predict increased short- and long-term mortality and increased incidence of urgent revascularization and myocardial infarction.[3–6] Persistently elevated cTnI levels after discharge from the hospital after admission for severe heart failure is an independent predictor for increased 3-month mortality, and cTnI concentration has been found to correlate with in-hospital death after adult cardiac surgery.[7,8] Reelevation after percutaneous coronary intervention in patients with acute coronary syndrome is associated with increased 6-month mortality; however, minor cTnI level elevations after uncomplicated elective percutaneous coronary intervention are not predictive of late outcome.[9,10] Conflicting evidence exists regarding the prognostic role of cTnI in chronic renal failure.[11–13] Elevated cTnI levels predict myocardial dysfunction in patients with subarachnoid hemorrhage but do not predict myocardial contusion or late outcome after blunt chest trauma.[14,15]

There are limited data on the prognostic value of transient mild elevation of cTnI levels (<1.5 ng/mL) in the general patient population. Because of the high sensitivity for myocyte necrosis and the cardiac specificity of cTnI, the interpretation of mild elevation of cTnI levels in patients with minimal or no risk factors for coronary artery disease is often difficult. The purpose of this study was to study the prognostic value of transient mild elevation of cTnI levels in the hospitalized patient population.

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Table 1. Baseline Characteristics*

Characteristics	Cases (n = 71)	Controls (n = 37)	*P* Value
Women	48 (67.6)	24 (64.9)	.83
White	54 (76.1)	25 (67.6)	.37
Black	11 (15.5)	11 (29.7)	.13
Hispanic	6 (8.5)	1 (2.7)	.42
Age, mean ± SD, y	68.7 ± 14.1	67.0 ± 13.6	.55
Risk factors for coronary artery disease			
None	3 (4.2)	3 (8.1)	.41
1	17 (23.9)	3 (8.1)	.07
≥2	51 (71.8)	28 (83.8)	.24
Coronary artery disease	27 (38.0)	12 (32.4)	.67
Chronic renal insufficiency	22 (31.0)	8 (21.6)	.37
Chronic obstructive lung disease	8 (11.3)	5 (13.5)	.76
Creatinine, mean ± SD, mg/dL†	2.2 ± 2.0	1.3 ± 1.0	.02
Urea nitrogen, mean ± SD, mg/dL‡	38.1 ± 32.2	20.2 ± 12.2	.002

* Data are presented as number (percent) of patients unless otherwise indicated.
† To convert creatinine values to SI units (μmol/L), multiply by 88.4.
‡ To convert urea nitrogen values to SI units (mmol/L), multiply by 0.357.

Table 2. Reason for Hospitalization

Reason	Cases, No. (%)	Controls, No. (%)	*P* Value
Chest pain	13 (18.3)	7 (18.9)	>.99
Dyspnea	14 (19.7)	8 (21.6)	.81
Syncope	3 (4.2)	2 (5.4)	>.99
Infection	4 (5.7)	2 (5.4)	>.99
Noncardiovascular surgery	16 (22.6)	9 (24.4)	.82
Neurologic problem	2 (2.8)	3 (8.1)	.34
Gastrointestinal or genitourinary disorders	10 (14.1)	6 (16.2)	.78
Trauma	2 (2.8)	0 (0.0)	.55
Psychiatric problems	2 (2.8)	0 (0.0)	.54
Cerebrovascular accidents	3 (4.2)	0 (0.0)	.55
Arrhythmia	2 (2.8)	0 (0.0)	.55
Total	**71 (100.0)**	**37 (100.0)**	

METHODS

Study Protocol

This was a single tertiary care center case-control study in which the outcome of patients hospitalized at Loyola University Medical Center for any cause who had mild elevations of cTnI levels was compared with the outcome of matched controls. All patients who had cTnI levels measured during admission from July 2001 until January 2002 were screened for study participation. Cases were defined as hospitalized patients older than 18 years who had at least 2 subsequent transient cTnI measurements greater than or equal to 0.1 ng/mL and less than 1.5 ng/mL (Bayer Advia Centaur, Tarrytown, NY). Controls were defined as hospitalized patients with at least 1 cTnI measurement less than 0.1 ng/mL. Controls were matched with cases in terms of age, sex, ethnicity, risk factors for coronary artery disease, and reason for admission. Patients who had undergone revascularization procedure, cardiac surgery, or cardiopulmonary resuscitation just before abnormal cTnI measurements, patients with persistently elevated cTnI levels, and patients with at least 1 cTnI level of 1.5 ng/mL or higher were excluded.

Medical records of eligible patients were reviewed retrospectively and demographic information, admission and discharge diagnoses, duration of hospital stay, and coronary artery disease risk factors documented. Risk factors for coronary artery disease were history of hypertension, diabetes, hyperlipidemia, tobacco use, men older than 45 years, and women older than 55 years. Known coronary artery disease, chronic renal insufficiency, and diagnosis of obstructive pulmonary disease was also documented, in addition to serum creatinine, blood urea nitrogen, peak creatine kinase (CK), CK-MB fraction, and cTnI levels.

Patient Population

A cohort of 118 patients (mean ± SD age, 67.4 ± 14.0 years; 35.6% men) was identified and followed up for an average ± SD of 11.9 ± 7.9 months. Ten patients were excluded due to recent cardiovascular intervention or surgery, cardiopulmonary resuscitation, or chronically elevated cTnI levels. Seventy-one cases were matched with 37 controls in terms of age, sex, ethnicity, and coronary artery disease risk factors and reason for admission. There was no difference in terms of history of coronary artery disease, chronic renal insufficiency, and obstructive pulmonary disease between the 2 groups. The cases had significantly higher creatinine and blood urea nitrogen levels compared with controls (Table 1).

Most of the cases (22.6%) and controls (24.4%) were admitted for noncardiac surgery. Other admission reasons were as follows (in decreasing order of frequency): dyspnea, chest pain, gastrointestinal or genitourinary disorders, infectious disorders, neurologic problems, syncope, cerebrovascular accidents, trauma, psychiatric problems, and arrhythmia. There was no statistical significant difference between cases and controls in terms of reason for admission (Table 2).

Follow-up

Initial data were collected from medical records and the Electronic Medical Record at Loyola University Medical Center. The patients who had incomplete long-term information were contacted by telephone to determine their vital status and inquire whether they had experienced a subsequent myocardial infarction, undergone revascularization, or been admitted to a hospital for cardiac reasons. When telephone contact could not be made,

Table 3. Twelve-Month Outcomes*			
Outcome	**Cases (n = 71)**	**Controls (n = 37)**	***P* Value**
Length of stay, mean ± SD, d	12.3 ± 13.8	4.5 ± 4.0	<.001
All-cause mortality	31 (43.7)	6 (16.2)	.005
Major cardiovascular end points			
Revascularization	10 (14.1)	3 (8.1)	.54
Myocardial infarction	3 (4.2)	0 (0.0)	.55
Cardiovascular mortality	6 (8.5)	0 (0.0)	.09
Total	**19 (26.8)**	**3 (8.1)**	.02
Composite end points	44 (62.0)	9 (24.3)	<.001

* Data are presented as number (percent) of patients unless otherwise indicated.

the next of kin were subsequently contacted and asked for updated telephone numbers or vital status of the patients. The Social Security death index database was searched for the remaining patients whose information could be obtained in this manner. The study was reviewed and approved by Loyola University Medical Center's Institutional Review Board for Medical Research.

Laboratory Findings

Both cTnI and CK-MB fraction measurements were performed by a mass-based chemiluminescent immunoassay on the Bayer Advia Centaur analytical system. Total CK activity was measured on the Beckman Coulter LX-20 Chemical Analyzer (Beckman Instruments, Brea, Calif). Relative index value is calculated by dividing the CK-MB fraction by the total CK value and multiplying by 100. The reference range for cTnI is 0.1 ng/mL or less. The cTnI results of greater than 0.1 ng/mL are associated with increased risk of myocardial injury, whereas results greater than 1.5 ng/mL are consistent with acute myocardial infarction. The reference range for CK-MB fraction is 0 to 5 ng/mL. The CK-MB results for patients with total CK levels above the reference range (men, 52–200 IU/L; women, 35–165 IU/L) are expressed as relative index values using the calculation described herein. The reference range for the relative index value is 0 to 2.

Cardiac Imaging Studies

We documented whether the patients had undergone further cardiac evaluation during or after their hospital admission. The evaluation was reviewed, and the results of all cardiac imaging studies documented: 2-dimensional echocardiograms, dobutamine stress echocardiograms, stress or nonstress nuclear scans, and/or coronary angiograms. Abnormal cardiac imaging study was defined as wall motion abnormality on echocardiogram, evidence of new or old ischemia on stress echo or Myoview, and left ventricular dysfunction on echocardiogram, nuclear study, or ventriculogram. Any evidence of coronary artery disease on coronary angiogram was defined as abnormal.

Outcome Data

Primary end points were defined as all-cause mortality and major cardiovascular end points, including cardiovascular mortality, myocardial infarction, and revascularization. Secondary end points were readmission for cardiovascular reasons and length of stay. The patients were followed up for at least 12 months or until their first end point, and outcome analysis was performed at 3, 6, and 12 months.

Statistical Analysis

Statistical analyses were performed with InStat 2.01 statistical software for Macintosh (GraphPad, San Diego, Calif). Continuous variables were presented as mean ± 1 SD, and comparison between cases and controls were performed with the *t* test. Categorical variables were presented as numbers and percentages and compared using 2 × 2 contingency tables with the Fisher exact test. Kaplan-Meier curves were used for analysis of percent survival, total event rate, and rate of major cardiovascular end points. A 2-sided $P < .05$ was regarded as statistically significant. Data are presented as mean ± SD.

RESULTS

Cardiac Troponin I

The average cTnI level for cases was 0.48 ± 0.33 ng/mL (range, 0.13–1.47 ng/mL). The case average CK and CK-MB fraction values were 195.3 ± 222.9 IU/L (range, 21–1051 IU/L) and 4.4 ± 5.8 ng/mL (range, 0.1–45.4 ng/mL), respectively. Control cTnI, CK, and CK-MB fraction values were normal.

Primary End Points

The 12-month outcome is given in Table 3. The total event rate was significantly increased in the case group compared with the control group at 12, 6, and 3 months (62.0% vs 24.3%, 59.2% vs 16.2%, and 47.9% vs 5.4%, respectively; $P < .001$). At 12, 6, and 3 months, the cases had a significant increase in all-cause mortality (43.7% vs 16.2%, 40.8% vs 8.1%, and 33.8% vs 0.0%, respectively; $P = .005$) and major cardiovascular end points (26.8% vs 8.1%, 26.8% vs 8.1%, and 21.1% vs 5.4%, respectively; $P = .02$) compared with controls.

At 12 and 6 months, a trend toward a statistically significant increased cardiovascular mortality in cases was observed (8.5% vs 0.0%, $P = .09$). However, despite the higher incidence of infarction ($P = .55$) and revascularization ($P = .54$) in the case group compared with controls, the difference was not statistically significant.

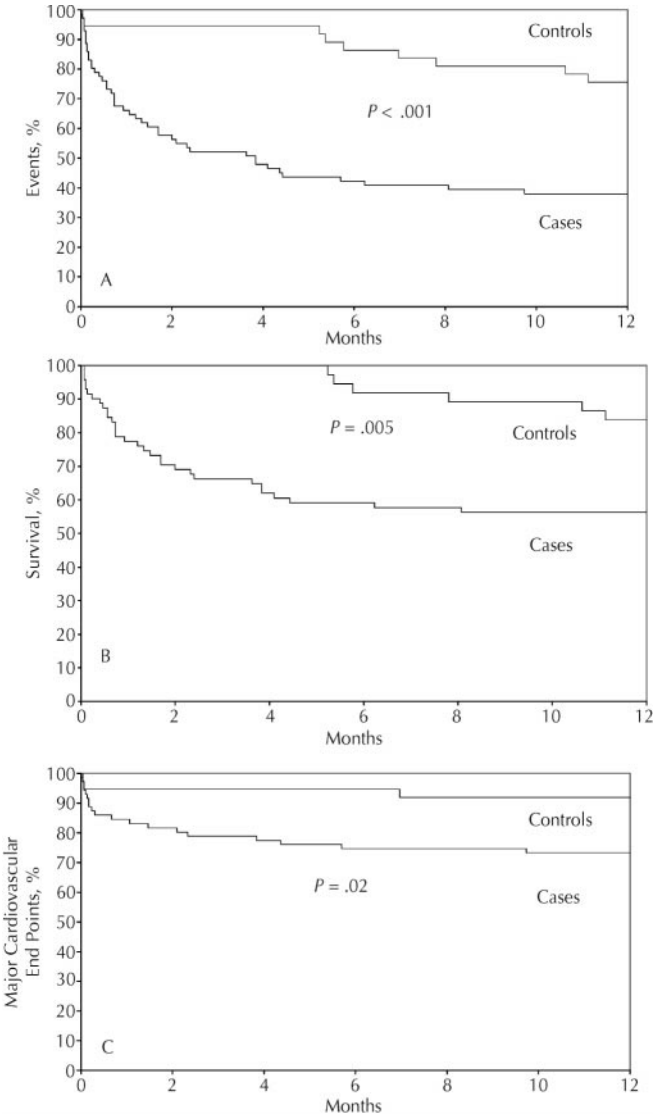
The figure presents Kaplan-Maier curves that show the total event rate, percentage of survival, and major cardiovascular end points during a 12-month period.

Secondary End Points

Average length of stay was significantly higher in cases than controls (12.3 ± 13.8 days vs 4.5 ± 4.0 days; $P < .001$). There was no statistically significant difference in number of readmissions for cardiovascular reasons between the 2 groups (8.5% vs 8.1%; $P = .75$).

Normal Versus Abnormal Imaging Study Results

Of the 71 cases, 16 patients had no further evaluation for their elevated cTnI levels, and 55 had at least 1 of the following cardiac imaging modalities: 2-dimensional echocardiogram, dobutamine stress echocardiogram, Myoview stress test, or coronary angiogram. Thirty-five of those 55 had abnormal imaging study results, and 20 had a normal result. When compared with controls at 12 months, the cases with abnormal cTnI levels and an abnormal imaging study result had a statistically significant higher rate of total events, all-cause deaths, and major cardiovascular



Kaplan-Meier curves showing total events (A), survival (B), and percentage of major cardiovascular end points (C) of cases versus controls during 12 months.

end points (25 [71.4%] vs 9 [24.3%]; $P < .001$; 14 [40.0%] vs 6 [16.2%]; $P = .03$; and 11 [31.4%] vs 3 [8.1%]; $P = .02$, respectively). However, there was no statistical difference between the group with abnormal cTnI levels and normal imaging study results and controls (Table 4).

In-hospital Mortality

Twenty cases (28.2%) died during their hospital admission. Six of those were cardiovascular deaths, but noncardiovascular in-hospital deaths were most commonly due to sepsis (9.9%), then cerebrovascular accidents (2.8%), respiratory failure (2.8%), cancer (1.4%), burns (1.4%), and liver failure (1.4%). None of the controls died during their initial hospital admission.

Outcome of Cases With cTnI Levels of 0.4 ng/mL or Higher Versus Less Than 0.4 ng/mL

At the Loyola University Medical Center, the risk stratification cutoff for normal cTnI levels is below 0.1 ng/mL.[4] If the risk stratification threshold was raised to the 10% cardiovascular limit as has been considered[16] since the redefinition of myocardial infarction,[17] the cutoff would be 0.4 ng/mL. We analyzed our data further to examine how a different cutoff at 0.4 ng/mL might affect our results. Of the 71 patients in the case group who had cTnI levels of 0.1 ng/mL or higher, 34 had a cTnI level of less than 0.4 ng/mL and 37 had a cTnI level of greater than 0.4 ng/mL. Apart from peak cTnI, no statistical difference existed between these 2 groups.

When compared with controls, both case groups had statistically significant higher total event and all-cause death rates at 3 and 6 months. The composite end point event rate was statistically significantly increased in both groups compared with controls ($P = .02$ and $P < .001$), but only all-cause mortality remained significantly higher in the group with cTnI levels greater than 0.4 ng/mL ($P = .006$) (Table 5).

Compared with controls, major cardiovascular end points were significantly higher in the case group with higher cTnI levels at 3, 6, and 12 months ($P = .02$) but were not significantly different in the group with cTnI levels less than 0.4 ng/mL ($P = .18$) (Table 5).

COMMENT

Cardiac-specific troponin I has an unparalleled cardiac specificity mainly due to a unique 31–amino acid sequence, which made the development of highly specific antibodies for immunoassay possible.[18] The available assays for serum cTnI are based on antibodies with little or no cross-reactivity for skeletal muscle forms. The cutoff values for abnormal cTnI levels used in previous studies vary (range, 0.4–1.5 ng/mL), and there is no international standardization, which renders direct comparison among studies difficult. The World Health Organization criteria for myocardial infarction is as follows: (1) clinical history

Table 4. Two Case Groups With Either Normal or Abnormal Imaging Study Results Compared With Controls at 12 Months

Outcome	Normal, No. (%) (n = 20)	*P* Value*	Abnormal, No. (%) (n = 35)	*P* Value*
All-cause mortality	8 (40.0)	.06	14 (40.0)	.04
Major cardiovascular end points				
Revascularization	1 (5.0)	>.99	9 (25.7)	.06
Myocardial infarction	0 (0.0)	NA	2 (5.7)	.23
Cardiovascular mortality	2 (10.0)	.12	0 (0.0)	NA
Total	**3 (15.0)**	.65	**11 (31.4)**	.02
Composite end points	9 (45.0)	.14	25 (71.4)	<.001

* Compared with controls (see values in Table 3). NA indicates not available.

Table 5. Two Case Groups With Different Cardiac-Specific Troponin I (cTnI) Levels				
Outcome	cTnI < 0.4 ng/mL, No. (%) (n = 34)	*P* Value*	cTnI ≥ 0.4 ng/mL, No. (%) (n = 37)	*P* Value*
All-cause mortality	13 (38.2)	.06	18 (48.7)	.006
Major cardiovascular end points				
Revascularization	5 (14.7)	.50	5 (13.5)	.70
Myocardial infarction	0 (0.0)	NA	3 (8.1)	.24
Cardiovascular mortality	2 (5.6)	.20	4 (10.8)	.10
Total	**7 (20.3)**	.18	**12 (32.4)**	.02
Composite end points	18 (52.9)	.02	26 (70.3)	<.001

* Compared with controls (see values in Table 3). NA indicates not available.

of typical chest pain that lasted longer than 30 minutes; (2) evidence of ischemia electrocardiographic changes (ST-segment depression, ST-segment elevation, T-wave inversion); and (3) increase in CK-MB fraction mass concentration to more than 5.0 μg/L or with a change of 25% or more between 2 measurements. Studies based on these criteria have found cTnI initially to have low sensitivity (61.7%–63%) for acute infarction in the first 6 hours after onset of symptoms. After 6 hours, the sensitivity increases well above 80%. The specificity of cTnI in these same studies ranges from 92.2% to 100% even with early presentation from symptom onset.[17,19,20] As with other diagnostic tests, the false-positive result rate declines as the upper reference limit for the diagnosis is raised but so does the sensitivity for detection of minor degrees of myocardial injury.

Data from the Thrombolysis in Myocardial Infarction (TIMI) IIB trial showed that patients with acute coronary syndrome and cTnI levels greater than 0.1 ng/mL were 2.2 to 3 times more likely to experience infarction or die at 43 days compared with patients with normal or ''negative'' cTnI levels (<0.1 ng/mL).[4] The TIMI IIIB trial found mortality at 42 days in patients with cTnI levels less than 0.4, 0.4 to less than 1.0, and 1.0 to less than 2.0 ng/mL to be 1.0%, 1.7%, and 3.4%, respectively.[3] In the American College of Cardiology (ACC)/American Hospital Association guidelines for the treatment of patients with unstable angina and non–ST-segment elevation myocardial infarction, cTnI levels between more than 0.01 and less than 0.1 ng/mL place patients evaluated for acute coronary syndrome in the intermediate risk group.[16]

Based on evidence for the cTnI assay in the literature, our laboratory reports a cTnI level greater than 0.1 ng/mL to be abnormal and suggestive of myocardial damage and a cTnI level greater than 1.5 ng/mL indicative of a myocardial infarction. With the abnormal cutoff value so low, abnormal cTnI results tend to be common, which may lead to more frequent cardiac consultations and cardiac evaluation in patients with low risk of cardiac disease. It is unknown how much this practice improves patient care, but it invariably leads to increased cost, increase in patients' anxiety, increased susceptibility to adverse events, and prolonged hospital stay. (The case patients in our study had significantly longer hospital stays compared with the controls. This may be due to longer time needed to sort out abnormal cTnI levels or possibly they had more complications.)

The consensus document of The Joint European Society of Cardiology (ESC)/ACC on Myocardial Infarction Redefined suggested that an abnormal cTnI value should be defined as a measurement that exceeds the 99th percentile of a reference control group. Acceptable imprecision (coefficient of variation) at the 99th percentile for each assay should be defined as 10% or less.[21,22] By following the ESC/ACC recommendations for the assay used at our institution, we would have to redefine the cutoff at a single value of 0.35 or 0.4 ng/mL.

The long-term prognosis of patients with transient elevation of cTnI levels is largely unknown, and it is also unclear how a single cutoff for abnormal cTnI levels at 0.4 ng/mL would affect care for the general hospitalized patient. Our goal was to clarify the significance and prognostic value of mild elevation of cTnI levels in this patient population. We identified hospitalized patients with mild elevation of cTnI levels between 0.1 and 1.5 ng/mL and compared their 12-, 6-, and 3-month outcomes to the outcomes of matched controls with normal cTnI levels.

The cases with cTnI levels between 0.1 and 1.5 ng/mL had increased 12-, 6-, and 3-month all-cause mortality and major cardiovascular complications compared with controls. They also had longer hospital stays, higher blood urea nitrogen levels, and higher creatinine levels, but their readmission rate for cardiovascular reasons did not differ significantly. Patients with abnormal cTnI levels and normal cardiac imaging study results had similar outcomes as matched controls, opposed to patients with abnormal cTnI levels and an abnormal cardiac imaging study result, who did worse than controls. This would suggest that it is possible to further risk stratify patients with transient mild elevation of cTnI levels by cardiac imaging study, where a normal study result would indicate low 1-year risk of the events studied.

Moreover, we were interested in whether the higher cutoff for an abnormal cTnI level would help further risk stratify this patient population. The 37 cases with cTnI levels between 0.4 and 1.5 ng/mL had a significantly higher rate of major cardiovascular end points than controls. However, despite having higher all-cause death and total events at 12, 6, and 3 months, the 34 patients in the case group with cTnI levels less than 0.4 ng/mL did not have higher major cardiovascular end points compared with controls. Five of these 34 patients had major cardiovascular end points in the first 3 months, including 1 cardiovascular death, and at 12 months 2 more had had revascularization. According to our results, this means that by changing the cutoff to a single 0.4-ng/mL level as recommended by ESC/ACC, almost 10% (7 of 71) of patients at high risk of having a major cardiovascular event in the next 12 months would have ''normal'' cTnI levels. How this would change the patient care or outcome is unknown.

Despite fewer patients in the control group, the 2 groups

were well matched in terms of sex, ethnicity, age, history of coronary artery disease, chronic renal insufficiency, chronic obstructive pulmonary disease, traditional risk factors for coronary artery disease, and reason for admission. The reason for the slightly higher number of women than men in both groups is unclear and most likely coincidental. Both patient groups consisted of a heterogeneous population with a wide spectrum of admission reasons, ranging from surgical to medical to psychiatric and neurologic problems.

History of renal insufficiency was equal in both groups of patients. However, average serum creatinine and blood urea nitrogen levels were significantly higher in the case group compared with the control group. This finding might suggest increased incidence of acute renal failure and that the case patient population was sicker, but it is also possible that the acute renal failure was secondary to myocardial damage and dysfunction. It is highly unlikely that the cTnI level elevation was due to renal insufficiency, since cTnI is generally not increased in patients with chronic renal failure.[23] However, troponin T, CK, and CK-MB fraction can be increased in renal insufficiency in the absence of myocardial disease.[24,25] Our results are in keeping with previous data that show a 2- to 5-fold increase in mortality of patients with end-stage renal failure and elevated cTnI and troponin T levels.[12]

Average CK levels were out of proportion to average cTnI and CK-MB fraction levels in the case patients. This disproportion can be explained by muscle trauma without myocardial injury in patients who had noncardiovascular surgery or trauma that led to CK levels that ranged from 21 to 1051 IU/L. This study was not designed to evaluate the prognostic value of CK or CK-MB fraction levels.

Limitations

Despite a limited number of patients, we were able to show a significant difference in outcome between cases and controls. It is possible that with a larger population studied the difference would have been even greater, especially in terms of cardiovascular complications.

We were able to obtain vital status on all our patients through medical records, telephone conversations, and the Social Security death index. The use of the death index has been validated in previous studies. Since our latest search in the Social Security database was performed well after the 12-month study period, it is unlikely that delay in documentation by the death index would have affected our results. We did not obtain the death certificates of the patients who died outside our institution to look for cause of death. Also, since much of our follow-up was made from hospital records from a single center, it is possible that some patients might have had an event elsewhere unknown to us. In trying to minimize this risk, we contacted patients and relatives by telephone. However, it is possible that some of the information obtained by that way might have been information misinterpreted by the patient or relative.

The selection of cases and controls could have caused bias. We excluded 10 patients, because they had recent cardiac intervention or cardiopulmonary resuscitation or they had chronically elevated cTnI levels. However, it is possible that the cases had higher acuity or had more complicated medical problems other than coronary artery disease risk factors, such as liver problems, malignancy, or cachexia. To control for this, the 2 groups were well matched in terms of age, sex, ethnicity, and reason for admission. The cases had slightly worse renal function than the controls, which may have been related to their overall worse clinical status but also could have been secondary to their cardiac problems that led to the elevated cTnI level.

Conclusion

Our data from this case-control single center study suggest that transient mild elevation of cTnI levels in hospitalized patients is associated with an increase in all-cause mortality and major cardiovascular complications. Opposed to cases with mild elevation of cTnI level and abnormal cardiac imaging study results who had an increased risk of major cardiovascular end points and death, patients with normal cardiac imaging study results had the same risk as matched controls, suggesting that cardiac imaging can aid in further risk stratification of those cases. Almost 10% of cases who had an increase in major cardiovascular end points had cTnI levels less than 0.4 ng/mL. Therefore, changing the cutoff for normal cTnI levels to a single value of 0.4 ng/mL would reduce the predictive value of cTnI for cardiovascular events in this patient population. In conclusion, mild elevation of cTnI levels between 0.1 and 1.5 ng/mL can be considered a marker for both all-cause and cardiovascular morbidity and mortality in a patient population admitted for any cause to a tertiary medical care center.

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