

Prevalence and Significance of Elevated Troponin I and Statin use Among Unselected Critically Ill Patients

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Abstract

Objectives: to determine the prevalence and significance of elevated troponin, myocardial infarction (MI), and statin use on mortality among unselected critically ill patients

Design: non-blinded prospective observational cohort study

Disclosures: None

Setting: mixed medical-surgical university tertiary critical care unit

Patients: all consecutive unselected patients admitted to the intensive care unit during a representative four month period

Interventions: none

Measurements and main results: among 335 consecutive patients with an average age of 54.3 years and APACHE II score of 21.2, troponin I was elevated (> 0.15 mcg/L) in 94 patients (28%). EKG changes were present in 119 (35%). MI occurred after admission in 39 patients (12%), of whom 15 died (38%). Overall mortality was 94 (28%). In the multivariable analysis of mortality, the following were significant (Odds Ratio, p value): age (1.03, 0.01), APACHE II score (1.10, 0.0001), troponin elevation > 0.15 mcg/L (3.21, 0.003), MI (2.75, 0.04), and statin use (0.35, 0.02). Non-significant factors included body-mass index, diagnostic group, preexisting heart disease or diabetes, and use of beta blockers, angiotensin-converting enzyme inhibitors (ACEI), or aspirin. ACEI was associated with increased mortality in the univariable analysis.

Conclusions: Isolated elevated troponin I is closely associated with mortality among unselected critically ill patients. Statin use was associated with reduced mortality in the same patients. Further examination of this association, to determine mechanism, and to evaluate prevention, is appropriate.

Introduction

The significance of elevated troponin in the critically ill, in the absence of EKG changes or clinical findings suggestive of MI, remains uncertain and has been debated for some time. [1-8] Numerous associations have been observed and an effect on mortality has been suspected, but causal mechanism, associations, appropriate investigations, and possible therapies remain speculative. [9-14].

Troponin is a biomarker (along with creatinine phosphokinase (CK) and the CK-MB band) that, when elevated in association with electrocardiogram (EKG) changes, a classical history of chest pain, or other evidence (at echocardiogram, MIBI, or autopsy) supports the diagnosis of MI as defined by consensus of the American College of Cardiology and also of the European Society of Cardiology. [15] However, critically ill patients are often ventilated and sedated or otherwise unable to provide a classic history, the utility of the EKG among the critically ill is unclear, and routine invasive testing of patients with abnormal troponin values would be prohibitively expensive. Moreover, the abnormalities of troponin seen among critically ill patients are frequently an order of magnitude or more below those seen with classic MI. These features justifiably lead clinicians to question the importance of troponin values that are detectable but not otherwise usually associated with manifestations of classic myocardial injury.

Troponin is found in the body in three forms, which are troponin I, troponin T, and troponin C. Of these, troponins I and T are specific to myocardial cells and sensitive to myocardial injury. Although classic MI is ischemic, myocardial injury can also be inflammatory, infectious, or traumatic.

This study was done to evaluate the major hypotheses:

Abnormalities of serum troponin are not associated with mortality.

Related to this, several secondary hypotheses were considered for evaluation:

1. clinically detectable abnormalities of serum troponin are uncommon among the critically ill
2. MI occurring after admission to the ICU is not associated with mortality
3. medications (including statins, angiotensin-converting enzyme inhibitors (ACEI), beta blockers, and aspirin) used before or during critical care admission are not associated with mortality

Methods

Approval for this study was obtained from the Health Research Ethics Board of the University of Alberta.

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The General Systems Intensive Care Unit (GSICU) of the University of Alberta hospital is a 30-bed medical-surgical tertiary care unit. All consecutive patients admitted during a representative four month period were studied. Patients with an admitting diagnosis of MI or congestive heart failure were excluded. No changes to admission policy nor standards of practice were performed during this period. All blood sampling and EKG testing was done as per the usual ordering practice of the attending staff and housestaff. Serum troponin was assessed at the discretion of the attending staff based on usual criteria for clinical suspicion. The standard troponin assay at the University of Alberta hospital is the troponin I assay (*Roche).

Data were extracted from each patient's medical record as follows: age, sex, diagnostic group (medical or surgical), height, weight, troponin I (mcg/L), APACHE II score, presence of chronic disease state (diabetes, atherosclerotic heart disease e.g. angina, MI, congestive heart failure), medication use (statin, beta blocker, ACEI, aspirin), and survival status at discharge (alive or dead). Troponin I was recorded as a continuous variable initially. The troponin I was then dichotomized in the analyses into elevated (any value greater than or equal to 0.15 mcg/L, which was the 99th percentile of normal volunteers) or non-elevated. Body-mass index (BMI) was calculated from the standard formula (BMI = mass/ (height)²), using SI units. Electrocardiograms were categorized according to the presence or absence of Q waves and ST segment changes, their direction (elevated or depressed), and their location (anterior, inferior, or lateral). This classification scheme included an excessive number of categories, and for the outcome analysis, the EKG findings were dichotomized as normal or not-normal. Patients who developed EKG changes after ICU admission that were associated with any troponin elevation were defined as having MI.

Mortality was the primary outcome variable (dependent), and all other variables were considered as independent variables. The analysis consisted of initial descriptive statistics (means and frequency distributions of continuous and categorical variables respectively) and univariable analysis of each variable with respect to mortality. The multivariable analysis of mortality was performed in a reverse stepwise logistic fashion with sequential elimination of the least significant variables until all residual terms in the model were significant at $p < 0.05$. SAS ® (SAS institute, Cary NC) was employed in all analyses. Variables that were strongly felt to be significant on clinical grounds were retained in the model (e.g. MI).

Results

Three hundred thirty-five consecutive patients were admitted to the GSICU during the study period (Table 1). No patients were admitted with a primary diagnosis of MI, and all 335 were included in the study. Of these, 183 were male and 152 were female (55% vs 45%), and the mean age was 54.3 years (range 18 to 91). The mean APACHE II score was 21.2 (predicted mortality: 39%, observed mortality: 28%). Medical causes accounted for 239 admissions, and surgical causes for 96 (71% vs 29%). Troponin I was elevated (> 0.15 mcg/L) during the ICU stay at some time in 94 patients, and not in the other 241 patients. EKG changes were seen in 119 patients (36%). MI occurred after ICU admission in 39 patients (all with both EKG change and elevated biomarker), of whom 15 died. The mean BMI of the study patients was 28. The remaining characteristics of the study sample are described in Table 1.

In the univariable analyses (Table 2a, Table 2b, Table 3), age and APACHE II score were closely associated with mortality ($p < 0.0001$ for both). Admission diagnosis was associated with mortality, with medical admissions faring worse ($p < 0.02$). Patients with any elevation

in troponin I had elevated mortality ($p = 0.0006$). Patients that suffered an MI in ICU had elevated mortality (38%) although the p value was 0.14. Considering medications, ACEI were associated with a higher mortality ($p < 0.05$). The remaining medications and disease conditions were not associated with mortality in the univariable analysis.

In the multivariable logistic regression analysis (Table 4), age, APACHE II score, MI, and any elevation in troponin were associated with increased mortality ($p < 0.01$, $p < 0.0001$, $p < 0.003$ and $p < 0.04$ respectively). Statin use was associated with decreased mortality ($p < 0.02$). Interaction terms were tested among all of the terms remaining in the model, but none were found to be significant.

When troponin was considered in quartiles, a strong gradient effect ($p = 0.0007$, X squared) was observed. In the lowest 'quartile', only one patient was found, so data from only three of the four quartiles

	Mean (range) or Absolute Value (%)
Age (years)	54.3 (18-91)
APACHE II	21.2 (12-51)
Troponin I peak (mcg/L)	1.5 (0-100)
Body Mass Index	28.0 (15.9-66.7)
Sex : Male	183 (55%)
Female	152 (45%)
Diagnosis : Medical	239 (71%)
Surgical	96 (29%)
Troponin Peak: < 0.15 mcg/L	122 (56%)
> 0.15 mcg/L	94 (44%)
Diabetes : No	273 (81%)
Yes	62 (19%)
Heart Disease : No	291 (87%)
Yes	44 (13%)
Statin Use : No	282 (84%)
Yes	53 (16%)
ACEI Use: No	270 (81%)
Yes	65 (19%)
ASA Use: No	283 (84%)
Yes	52 (16%)
Beta Blocker Use: No	276 (82%)
Yes	59 (18%)
EKG Abnormalities : No	82 (41%)
Yes	119 (59%)
MI : No	296 (88%)
Yes	39 (12%)

Table 1: Patient Descriptors (Categorical and Continuous).

	Survived (Mean (SD))	Died (Mean(SD))	p value
Age	49.7 (11.2)	57.3 (12.1)	0.0001
APACHE II	19.4 (13.2)	25.7 (15.0)	0.0001
Troponin Peak	0.8 (0.1)	2.6 (1.3)	0.09
Body Mass Index	28.1 (2.5)	27.6 (2.9)	0.65

Table 2a: Mortality, Bivariate Comparison, Continuous variables.

	Survived (%)	Died (%)	p value
Diagnosis : Medical	163 (68%)	76 (32%)	0.02
Surgical	72 (82%)	16 (18%)	
Troponin Peak < 0.15 mcg/L	90 (74%)	32 (26%)	0.0006
> 0.15 mcg/L	48 (51%)	46 (49%)	
Diabetes : No	195 (71%)	78 (29%)	0.86
Yes	45 (73%)	17 (27%)	
Heart Disease : No	211 (73%)	80 (27%)	0.37
Yes	29 (66%)	15 (34%)	
Statin Use : No	199 (72%)	79 (28%)	0.55
Yes	40 (71%)	16 (29%)	
ACEI Use: No	198 (74%)	70 (26%)	0.05
Yes	40 (62%)	25 (38%)	
ASA Use: No	201 (72%)	79 (28%)	0.71
Yes	36 (67%)	16 (33%)	
Beta Blocker Use: No	196 (72%)	78 (28%)	0.96
Yes	42 (71%)	17 (29%)	
EKG Abnormalities: No	61 (74%)	21 (26%)	0.74
Yes	86 (72%)	33 (28%)	
MI : No	215 (73%)	80 (27%)	0.14
Yes	24 (62%)	15 (38%)	
Sex : Male	131 (72%)	52 (28%)	0.98
Female	109 (72%)	43 (28%)	

Table 2b: Mortality, Bivariate Comparison, Categorical variables.

	Odds ratio (95% CL)	p Value
Age	1.03 (1.02, 1.05)	0.0001
Sex	0.99 (0.62, 1.60)	0.98
Diagnosis (Med/Surg)	2.10 (1.14, 3.85)	0.02
APACHE II	1.09 (1.06, 1.12)	0.0001
Troponin Elevation (Any)	2.70 (1.52, 4.77)	0.0007
Troponin Level	1.04 (0.98, 1.11)	0.20
MI	1.68 (0.84, 3.68)	0.14
Diabetes	1.06 (0.57, 1.96)	0.86
Heart Disease	0.73 (0.37, 1.44)	0.37
Statin Use	1.0 (0.53, 1.90)	0.55
ASA Use	1.13 (0.59, 2.15)	0.71
ACEI Use	1.77 (1.0, 3.12)	0.05
Beta Blocker Use	1.02 (0.55, 1.89)	0.95
EKG Abnormalities	1.12 (0.59, 2.11)	0.74
Body Mass Index	1.01 (0.97, 1.06)	0.64

Table 3: Mortality, Univariable Analysis.

	Odds ratio (95% CL)	p Value
APACHE II	1.10 (1.06, 1.15)	0.0001
Statin Use	0.35 (0.14, 0.87)	0.02
Troponin Elevation (Any)	3.21 (1.50, 6.85)	0.003
Age	1.03 (1.01, 1.05)	0.01
MI	2.75 (1.05, 7.19)	0.04

Table 4: Mortality, Multivariable Analysis.

Troponin I (mcg/L)	Survived	Died
< 0.15	141 (74%)	49 (26%)
0.15 – 0.37	34 (59%)	24 (41%)
> 0.37	39 (45%)	48 (55%)

Table 5: Mortality vs Troponin Level.

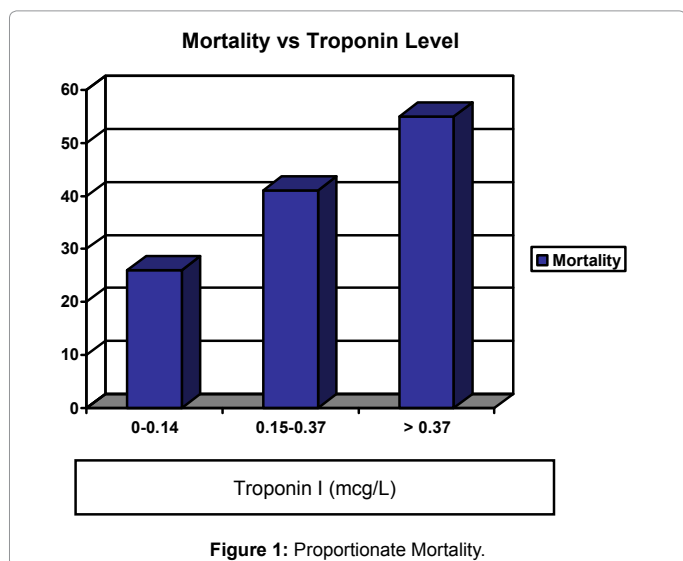


Figure 1: Proportionate Mortality.

are presented (Table 5, Figure 1). The independent values could not be grouped into four quartiles because the mode of elevated troponin I was approximately 0.15 mcg/L.

Discussion

In this study, 335 consecutive unselected patients admitted to a referral tertiary ICU were evaluated. This population had a similar gender composition and aggregate hospital mortality (28%) to most tertiary intensive care units, although the mortality was lower than predicted on the basis of APACHE II score. This medical-surgical unit did not admit patients with a primary diagnosis of myocardial ischemia or MI, as the latter patients were treated in a coronary care unit.

As expected, increasing age and higher APACHE II score were closely associated with increased mortality, in both the univariable and multivariable analyses.

A major observation in this study was that any increased troponin (troponin I > 0.15 mcg/L) was associated with increased mortality. This finding was significant when troponin elevation was dichotomized into elevated vs non-elevated. The association between any troponin elevation and mortality in the multivariable logistic analysis was very strong (Odds Ratio 3.21, $p < 0.003$). The association between MI and outcome was also strong in the multivariable analysis (OR 2.75, $p < 0.04$). However, increased troponin (isolated from EKG change) was much more prevalent than combined EKG change and increased troponin, and may be more useful clinically, given the known challenges in defining EKG changes with clarity and obtaining inter-observer agreement. [15,16]

Of note, our institution during the study performed the troponin I assay rather than the more precise troponin T assay. Employment of the troponin T assay should enhance the sensitivity and specificity of the diagnosis of MI.

The association between increased troponin and mortality is consistent with that observed in other populations. [1-8] Some of these have been more highly selected, suggesting associations among increasing troponin, mortality, and inflammatory states such as sepsis. [10,14] However, the association between troponin and mortality appears to be more widespread and has also been detected among patients with chronic obstructive pulmonary disease, congestive heart failure, subarachnoid intracranial hemorrhage, and myocardial contusion. [1-14] Furthermore, a recent meta-analysis of similar unselected critically ill patients as involved in this study demonstrated a strong association between increased troponin and mortality after controlling for age, disease status, and physiologic condition. [1] The odds ratio associated with troponin elevation in the latter meta-analysis was 2.5, in a similar range to the 3.21 observed in this study.

The usual cause of significant troponin elevation is myocardial ischemia. Therapy in such cases is usually directed at reduction of myocardial oxygen consumption, maximizing myocardial blood flow, and optimizing platelet aggregation to minimize thrombosis progression. However, these treatments are directed at patients with classical MI, which occurs in association with classic symptoms and other laboratory test abnormalities. The pathologic basis of classic MI is myocardial cell death due to thrombo-embolism of coronary arteries. The mean troponin elevation observed in this study was small (1.5 mcg/mL) compared to those seen after classic MI, and as mentioned, clinicians may have had a tendency to disregard such values, or to perceive that these small elevations were not significant, or to postulate that they could not be due to myocardial cell death. However, since troponin I and troponin T are specific to myocardial cells, the only process through which these molecules could reach plasma would be through cell membrane injury, occurring at myocardial cell death. Accepting this, the remaining questions would be: are these small elevations significant, and if so, can something be done about them? Based on this study and the literature, these small elevations are clinically significantly associated with mortality. The issue of treatment remains unanswered.

Of the medications considered, only statin use was significantly associated in the multivariable analysis with mortality, and showed a decrease. Statins (hydroxymethyl coenzyme A reductase inhibitors) were introduced to practice because of their lipid-lowering capacity. [17,18] However, their effects on mevalonic acid metabolism have been found to be more pleiotropic than initially thought, and statins have been noted to have properties that can be characterized as anti-inflammatory, and possibly immune-modulatory. [19-31] Interestingly, atherosclerosis is

being increasingly recognized as having a substantial inflammatory component. [32-33] Consequently, the therapeutic effectiveness of statins in atherosclerosis may be due as much to anti-inflammatory effect as to serum lipid modulation. Extending this line of reasoning, statins may conceivably act in states of generalized inflammation e.g. septic shock, to modulate the endothelial inflammation that has been associated with plaque rupture, tissue factor exposure, and thrombosis. Nonetheless, adoption of statin administration to critically ill patients as a therapeutic strategy would be premature at this point, and further study is needed.

ACEI were associated with increased mortality in the univariable analysis, although this significance was lost in the multivariable analysis. Beta blockade and aspirin were not significant in either analysis, but this may reflect study size. The explanation for the increased mortality seen with ACEI is not obvious, and merits further study, as results in the literature with perioperative ACEI have been inconsistent. ACEI can reduce blood pressure substantially and for prolonged periods, and may impair organ perfusion in some circumstances. Perioperative betablockade had been recommended until the publication of the POISE trial, and is seldom advised currently. [34-35]

Limitations of this study include its size and observational nature. Regarding its observational nature, it was not sought to modify clinician behaviour at the outset in order to obtain a realistic assessment of current practice. Troponins and EKG were performed and interpreted at clinician discretion. Sequential troponins may have been higher if pursued, and management may have changed (with change in mortality) if patient risk had been appreciated. The diagnostic categories were broad, but enhanced specificity may be beneficial in order to identify patients at greatest risk of adverse event. Larger numbers of patients would also facilitate risk stratification, and would raise more hypotheses about specific medication effects. A larger number of patients would also likely confirm a gradient effect on mortality with increasing troponin.

In conclusion, this study strongly suggests that elevated troponin in the critically ill patient is associated with increased mortality. The presence of EKG changes in association with troponin elevation was statistically significant but less common than elevated troponin alone. Among the medications studied, statins were associated with reduced mortality. Further evaluation to determine prevalence of troponin elevation, groups of patients at elevated risk, and preventive and therapeutic strategies is appropriate.

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