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ORIGINAL RESEARCH

Predictors of Short- and Long-Term Mortality in Hospitalized Veterans With Elevated Troponin

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BACKGROUND: Cardiac troponin elevation is associated with mortality. We compared the mortality risk related to elevated troponin from acute coronary syndrome (ACS) and non-ACS causes in a hospitalized elderly veteran population.

METHODS AND RESULTS: As part of a quality initiative at our Veterans Affairs hospital, all patients with elevated troponin were evaluated by a cardiologist to determine if ACS was present and to recommend management. We selected a sample (n = 761) of consecutive patients studied between February 2006 and February 2007 and examined all-cause mortality over extended follow-up. Nearly all were men (99.1%), and about half had coronary disease (n = 385, 50.5%) and diabetes (n = 339, 44.4%). ACS patients had lower mortality that non-ACS patients. Mortality began to diverge at 30 days; at 1 year it was 42.0% versus 29.0% (odds ratio [OR]: 0.56, 95% confidence interval [CI]: 0.41-0.78) and at 6 years 77.7% versus 58.7% (OR: 0.41, 95% CI: 0.30-0.56). Cox regression models for mortality at multiple time points yielded several independent factors associated with mortality; however, the distribution of the factors was not sufficient to explain the observed difference in mortality.

CONCLUSIONS: In this elderly, male veteran population, mortality related to an elevated troponin was higher at 1 and 6 years for non-ACS patients compared with ACS patients. Factors independently associated with a higher mortality risk were predominantly markers of general systemic illness, but did not elucidate the reasons why troponin elevation secondary to non-ACS causes carries this higher risk. A better understanding of these cardiac troponin elevations and implications for future mortality requires additional investigation. *Journal of Hospital Medicine* 2016;11:773–777. © 2016 Society of Hospital Medicine

Acute coronary syndromes (ACS) are potentially lethal and present with a wide variety of symptoms. As such, physicians frequently order cardiac biomarkers, such as cardiac troponin, for patients with acute complaints. Elevated troponin is associated with higher risk of mortality regardless of the causes, which can be myriad, both chronic and acute.[1] Among patients with an elevated troponin, distinguishing ACS from non-ACS can be challenging.

Making the distinction between ACS and non-ACS troponin elevation is crucial because the underlying pathophysiology and subsequent management strategies are markedly different.[2] According to evidence-based practice guidelines, ACS is managed with antiplatelet drugs, statins, and percutaneous coronary intervention, improving clinical outcomes.[3] In contrast, care for patients with non-ACS troponin elevations is usually supportive, with a focus on the underlying conditions. The lack of specific treatment options for such patients is concerning given that several series have suggested that non-ACS troponin patients may have a higher mortality risk than ACS patients.[4–6] Non-ACS troponin elevation can be the result of a multitude of conditions.[7,8] What remains unclear at this point is whether the excess mortality observed with non-ACS troponin elevation is due to myocardial damage or to the underlying conditions that predispose to troponin release.

Using data from a quality improvement (QI) project collected at our Veterans Affairs (VA) medical center, we investigated the mortality risk associated with ACS and non-ACS troponin elevation including an analysis of factors associated with mortality. We hypothesized that non-ACS troponin elevation will have a higher mortality risk than troponin elevation due to ACS, and that important contributors to this relationship could be identified to provide direction for future investigation directed at modifying this mortality risk.

METHODS

We analyzed data that were prospectively collected for a quality initiative between 2006 and 2007. The project was a collaborative endeavor between cardiology, hospital medicine, and emergency medicine with the process goal of better identifying patients with ACS to hopefully improve outcomes. The QI team was consulted in real time to assist with treatment recommendations; no retrospective decisions were

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made regarding whether or not ACS was present. As the goal of the project was to improve cardiovascular outcomes, consultative advice was freely provided, and no physicians or teams were subject to any adverse repercussions for their diagnoses or management decisions.

A cardiologist-led team was created to improve quality of care for myocardial infarction patients by evaluating all patients at our facility with an elevated troponin. On a daily basis, a specialist clinical coordinator (nurse practitioner or physician assistant) received a list of all patients with elevated troponin from the chemistry lab. The coordinator reviewed the patients' medical records with a cardiologist. A "positive" troponin was defined as a troponin T level of greater than 0.03 ng/mL (99th percentile at our facility). Each attending cardiologist prospectively determined if troponin elevation was related to clinical findings consistent with an ACS based on review of the patients' symptoms (duration, quality, severity, chronicity, and alleviating/aggravating factors), medical history, and noninvasive cardiac testing including electrocardiograms, cardiac biomarkers, and any other available imaging tests.

We have previously demonstrated that the cardiologists at our facility have a similar rate of diagnosing ACS.[9] All cardiologists at our facility maintain current American Board of Internal Medicine certification in cardiovascular disease and have academic appointments at the University of Florida College of Medicine. All patients were followed prospectively, and data on their medical history, acute evaluation, and outcomes were tracked in an electronic database. Given the higher risk of mortality with ST-elevation myocardial infarction, such patients were excluded from this investigation. By definition, patients with unstable angina do not have elevated biomarkers and thus would not have been included in the database to begin with. Prospectively recorded data elements included: age, gender, chief complaint, tobacco use, presence of hypertension, hyperlipidemia, prior coronary disease, chronic kidney disease, diabetes mellitus, cardiac troponin values, serum creatinine, electrocardiogram (ECG) variables, Thrombolysis in Myocardial Infarction (TIMI) score, and if the patient was placed under hospice care or an active do-not-resuscitate (DNR) order. Additional data elements gathered at a later date included maximum temperature, white blood cell count, N-terminal pro-brain natriuretic peptide (NT-proBNP), administration of advanced cardiac life support (ACLS), and admission to an intensive care unit (ICU). All consecutive patients with elevated troponin were included in the database; if patients were included more than once, we used their index evaluation only. All patients with troponin elevation after revascularization (percutaneous coronary intervention or coronary bypass surgery) were excluded. Our investigational design was reviewed by our institutional review board, who waived the requirement for formal written informed consent and approved use of data from this QI project for research purposes.

We focused this investigation on an analysis of all-cause mortality in February 2014. We analyzed mortality at 30 days, 1 year, and 6 years. As secondary outcomes we analyzed the likelihood of the patients' chief complaint for the diagnosis of ACS and evaluated predictors of mortality based on Cox proportional hazard modeling. Mortality within the VA system is reliably tracked and compares favorably to the Social Security National Death Index Master File for accuracy.[10,11]

Categorical variables were compared by χ^2 test. The Student t test was used to compare normally distributed continuous variables, and nonparametric tests were used for non-normal distributions as appropriate. Mortality data at 30 days, 1 year, and 6 years were compared by log-rank test and Kaplan-Meier graphs. A formal power analysis was not performed; the entire available population was included. A Cox proportional hazard model was created to estimate mortality risk at each time point. Variables included in our Cox regression model were age, gender, history of coronary artery disease (CAD), hypertension, diabetes mellitus or hyperlipidemia, ACS diagnosis, dynamic ECG changes, TIMI risk score, initial troponin level, creatinine level at time of initial troponin (per mg/dL), presence of fever, maximum white blood cell count, NT-proBNP level (per 1000 pg/mL), if ACLS was performed, if the patient was under hospice care, if there was a DNR order, and if they required ICU admission. This model was also constructed independently for the ACS and non-ACS cohorts for mortality at 1 year. A forward stepwise model was used. Statistical results were considered significant at $P < 0.05$. Statistical analyses were performed using SPSS version 21 (IBM, Armonk, NY).

RESULTS

Among the 761 patients, 502 (66.0%) were classified as non-ACS and 259 (34.0%) as ACS (Table 1). The mean age was higher in the non-ACS group (71 years vs 69 years in the ACS group, $P = 0.006$). Hypertension, diabetes mellitus, and prior CAD were frequent in both groups and not significantly different. Median initial troponin T was higher in the ACS group (0.12 ng/mL vs 0.06 ng/mL, $P < 0.001$) as were the frequency of a TIMI risk score >2 (92.5% vs 74.3%, $P < 0.001$) and new ECG changes (29.7% vs 8.2%, $P < 0.001$). Hospice, DNR orders, and administration of ACLS were not different between groups; however, admission to the ICU was more frequent in the ACS group (44.8% vs 31.9%, $P < 0.001$). Chest pain was the symptom with the highest positive predictive value for the diagnosis of ACS (63.3%), whereas the least predictive was altered mental status or confusion (18.0%) (Figure 1).

TABLE 1. Subject Characteristics and Outcomes

	Non-ACS, N = 502	ACS, N = 259	*P* Value
Baseline characteristics, n (%)			
Age, y	71 ± 11	69 ± 11	0.006
Female	6 (1.2%)	1 (0.4%)	0.27
Coronary artery disease	244 (48.6%)	141 (54.4%)	0.13
Hypertension	381 (75.9%)	203 (78.4%)	0.44
Diabetes mellitus	220 (43.8%)	119 (45.9%)	0.58
Hyperlipidemia	268 (53.4%)	170 (65.6%)	0.001
Current smoker	24 (4.8%)	49 (18.9%)	<0.001
Clinical presentation			
Initial troponin T, ng/mL, median [IQR]	0.06 [0.04–0.11]	0.12 [0.05–0.32]	<0.001
White cell count, $\times 10^9$/L, median [IQR]	10 [8.0–14.0]	11 [8.0–15.0]	0.005
NT-proBNP, pg/mL, median [IQR]	3,531 [1,201–10,519]	1,932 [319–9,100]	0.001
Creatinine, mg/dL, median [IQR]	1.6 [1.1–2.4]	1.1 [0.9–1.5]	<0.001
New ECG changes, no. (%)	41 (8.2%)	77 (29.7%)	<0.001
TIMI score over 2, no. (%)	365 (74.3%)	235 (92.5%)	<0.001
Fever (over 100.4° F), no. (%)	75 (15.0%)	38 (14.7%)	0.91
Hospice, no. (%)	8 (1.6%)	5 (1.9%)	0.73
Do not resuscitate, no. (%)	62 (12.4%)	30 (11.6%)	0.76
Intensive care admission, no. (%)	160 (31.9%)	116 (44.8%)	<0.001
ACLS administered, no. (%)	38 (7.6%)	17 (6.6%)	0.6
Outcomes, no. (%)			
Death, 30 days	67 (13.3%)	30 (11.6%)	0.49
Death, 1 year	211 (42.0%)	75 (29.0%)	<0.001
Death, 6 years	390 (77.7%)	152 (58.7%)	<0.001

NOTE: Continuous variables are presented as mean ± standard deviation or median [IQR]. Categorical variables are presented as no. (%). **Abbreviations:** ACLS, advanced cardiac life support; ACS, acute coronary syndrome; ECG, electrocardiogram; IQR, interquartile range; MI, myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction.

Mortality at 30 days was not different between the 2 groups, but mortality was higher for the non-ACS cohort at 1 year and at 6 years (Table 1). Kaplan-Meier curves demonstrate that mortality for the 2 cohorts begins to diverge between 30 and 60 days until approximately 2 years when the curves again are parallel (Figure 2).

In Cox proportional hazards models, 5 factors were associated with higher mortality at 30 days, 1 year, and at 6 years: age, hospice, DNR order, need for ACLS, and admission to the ICU (Table 2). Additionally, at 1 and 6 years, NT-proBNP and non-ACS were associated with higher mortality. At 6 years, creatinine was an additional significant factor. We separated the ACS and non-ACS cohorts and performed the same

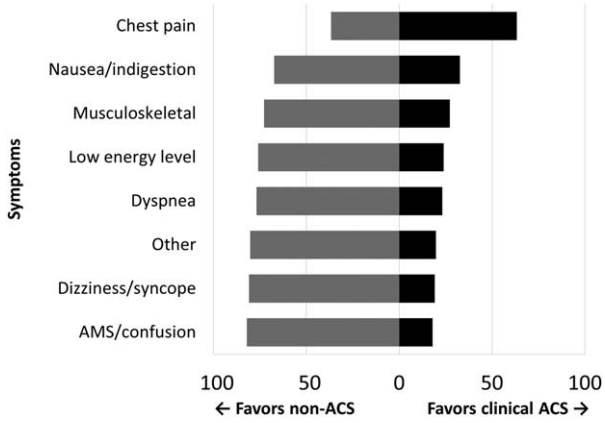

FIG. 1. Distribution of symptoms and correlation with diagnosis of acute coronary syndrome. Each bar represents a different primary symptom reported by a patient at the time of presentation. The width of each bar indicates the percentage of each symptom group that was diagnosed with an ACS (black segment) and the percentage without ACS (grey segment). Chest pain was the most strongly associated with ACS whereas confusion was the least. Abbreviations: ACS, acute coronary syndrome; AMS, altered mental status.

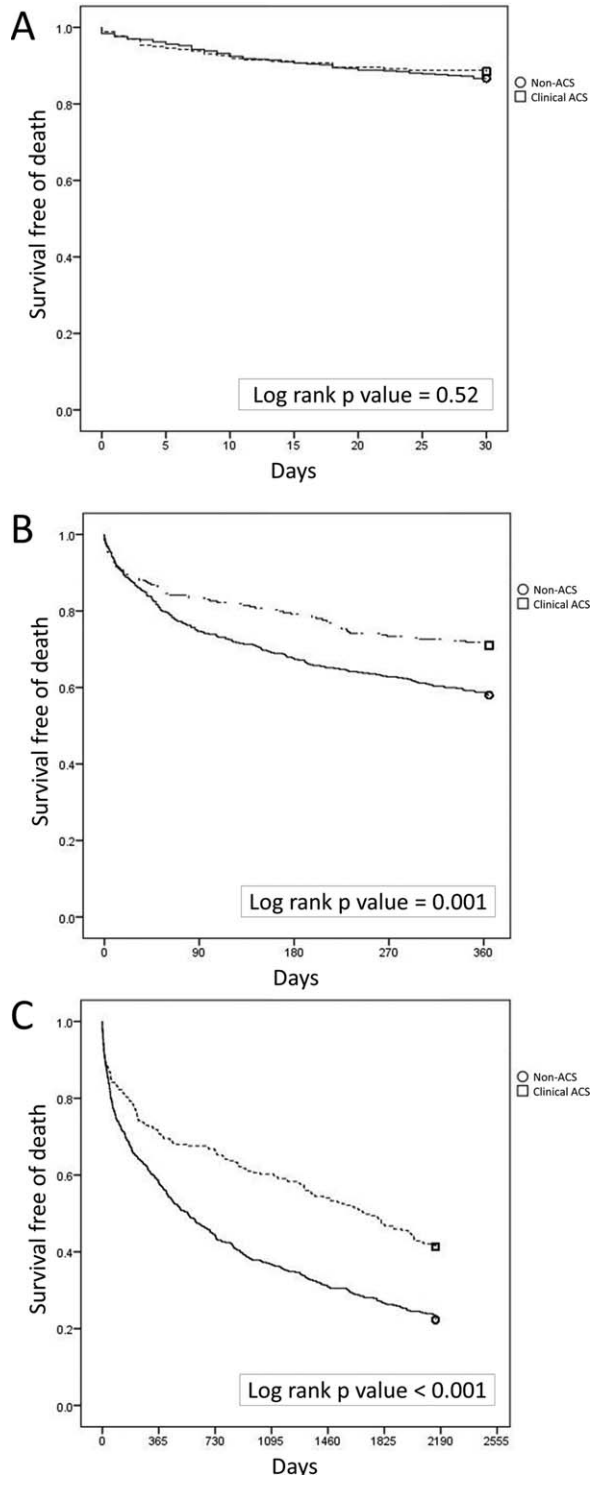

FIG. 2. Kaplan-Meier curves for mortality. In each panel, the dashed line represents the risk of mortality for non-ACS patients, whereas the solid line represents the risk for ACS patients. (A) Survival free of death up to 30 days. (B) Survival free of death up to 1 year. (C) Survival free of death through extended follow-up. Abbreviations: ACS, acute coronary syndrome.

TABLE 2. Cox Regression Model Variables Associated With Mortality at 30 Days, One Year, and During Extended Follow-up

	P Value	Hazard Ratio	95% CI
30 days			
Intensive care unit admission	<0.0001	2.18	1.28–3.72
Hospice	<0.0001	4.67	1.91–11.40
Do not resuscitate	<0.0001	3.19	1.94–5.24
ACLS performed	<0.0001	10.17	6.03–17.17
Age, per year	<0.0001	1.04	1.02–1.06
1 year			
Intensive care unit admission	<0.0001	1.66	1.26–2.20
Hospice	<0.0001	4.98	2.69–9.21
Do not resuscitate	<0.0001	2.52	1.83–3.47
Non-ACS	<0.0001	1.57	1.19–2.08
ACLS performed	<0.0001	6.03	4.17–8.72
Age, per year	<0.0001	1.03	1.02–1.04
NT-proBNP, per 1,000 pg/mL	<0.0001	1.02	1.01–1.03
Extended follow-up			
Intensive care unit admission	<0.0001	1.35	1.11–1.65
Hospice	<0.0001	3.81	2.13–6.81
Do not resuscitate	<0.0001	2.11	1.62–2.74
Non-ACS	<0.0001	1.53	1.25–1.88
ACLS performed	<0.0001	4.19	3.01–5.84
Age, per year	<0.0001	1.03	1.03–1.04
Creatinine, per mg/dL	0.02	1.06	1.01–1.12
NT-proBNP, per 1,000 pg/mL	<0.0001	1.02	1.02–1.03

NOTE: **Abbreviations:** ACLS, advanced cardiovascular life support; ACS, acute coronary syndrome; CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide.

model for 1-year mortality (Table 3). The models yielded similar factors associated with higher mortality: hospice, DNR order, need for ACLS, age, and NT-proBNP, with ICU admission being significant only in the non-ACS cohort.

DISCUSSION

Our findings confirm the important, but perhaps not well-recognized, fact that an elevated troponin without ACS is associated with higher mortality than with ACS. This has been previously observed in veteran and non-veteran populations.[4,6,8,12] The novel finding from our investigation is that mortality risk with troponin elevation is most strongly associated with unmodifiable clinical factors that are plausible explanations of risk. Furthermore, the distribution of these factors between our 2 cohorts does not sufficiently explain the difference in risk between ACS and non-ACS patients.

At each time point we evaluated, ICU admission and need for ACLS were associated with mortality. These are indicators of a severely ill population and are not surprising to find associated with mortality. Many hospitals have instituted some form of "pre-code" approach or rapid response team to identify patients before they need ACLS. These efforts, although well meaning, have not yielded convincing results of effectiveness.[13] Hospice and DNR patients were also, not surprisingly, associated with higher mortality. Although these factors were statistically significant, the low prevalence suggests that they are not clinically impactful on the primary questions of the investigation. These factors can be altered but are not intended as modifiable as they reflect the wishes of patients and their decision makers. The distribution of the factors in our model, however, did not adequately explain the higher risk of death with non-ACS troponin elevation. For example, ACLS administration, hospice care, and DNR orders were strong predictors but were similar between the groups. ICU admission was actually more common with ACS patients, despite strong association with mortality. Age and NT-proBNP were associated with mortality and higher in the non-ACS group; however the magnitude of hazard was less than for the other factors. These findings lead us back to the possible explanation that non-ACS troponin elevation stands as an independent risk factor, and that ACS patients have a distinct advantage in the myriad treatments available. If ACS patients were misdiagnosed as non-ACS and failed to receive appropriate treatments, that might have contributed to higher mortality; however, we consider that unlikely given that the goal of the QI project was to minimize missed ACS diagnoses.

The overall mortality risk in our study was high: 12.7% at 30 days and 37.6% at 1 year. This reflects the high-risk population with elevated troponin seen at our facility with ages nearly 70 years and high prevalence of multiple cardiovascular risk factors. Despite a high event rate, many clinically relevant risk factors were not retained in our Cox hazard model. Among sepsis patients, elevation in troponin is associated with mortality[14]; however, in our population neither fever or white blood cell count were significant mortality factors. The relationship between chronic kidney disease and troponin is complex. Renal dysfunction may result in troponin elevation and troponin elevation is a predictor of risk within kidney disease patients.[15] In our study, we did not evaluate chronic kidney disease as a predictor, instead opting to use the serum creatinine.

TABLE 3. Cox Regression Model Variables Associated With Mortality at One Year for the ACS and Non-ACS Cohorts

	P Value	Hazard Ratio	95% CI
Non-ACS			
Intensive care unit admission	<0.0001	1.86	1.35–2.58
Hospice	<0.0001	7.55	3.57–15.93
Do not resuscitate	<0.0001	2.33	1.60–3.41
ACLS performed	<0.0001	4.42	2.83–6.92
Age, per year	<0.0001	1.03	1.01–1.04
NT-proBNP, per 1,000 pg/mL	0.002	1.02	1.01–1.03
Clinical ACS			
Hospice	0.036	3.17	1.08–9.32
Do not resuscitate	0.003	2.49	1.36–4.55
ACLS performed	<0.0001	12.04	6.33–22.91
Age, per year	<0.0001	1.05	1.02–1.07
NT-proBNP, per 1,000 pg/mL	0.001	1.04	1.01–1.06

NOTE: **Abbreviations:** ACLS, advanced cardiovascular life support; ACS, acute coronary syndrome; CI, confidence interval; NT-proBNP, N-terminal pro-brain natriuretic peptide.

This was not associated with mortality except at the 6-year time point.

The TIMI score was not associated with mortality in either the overall population or the ACS cohort. The proportion of patients in our cohort with TIMI score under 3 was 16.5% as compared with 21.6% in the original derivation study.[16] The limited data on the prognostic value of the TIMI score within a veteran population suggest a modest predictive capacity.[17] Our data raises the possibility that TIMI is not an optimal choice; however, our analysis only includes all-cause mortality, different from the original intended use of TIMI, predicting a variety of major cardiac events.

Our data confirm that ACS can be detected in a wide range of clinical presentations. Within our population of troponin positive patients, those with chest pain were most likely to be diagnosed with ACS, although one-third of chest pain patients were felt to have a non-ACS diagnosis. On the opposite end of the spectrum, an elevation in troponin with altered mental status or confusion was rarely diagnosed as ACS—only 18% of the time. Many symptoms were poor predictors of ACS; however, none were low enough to disregard. Our data would suggest that most patients with elevated troponin warrant evaluation by a cardiovascular expert.

Our study population came from a single VA hospital that is comprised of elderly and predominantly male patients limiting applicability to other populations. Despite this, other investigations in younger populations and with a higher proportion of women have found similar mortality trends.[4,8,12] We did not have sufficient data to determine the cause of death or to further classify as cardiac versus noncardiac; knowledge of the cause of the specific death may better inform future investigations into this important clinical question. Our investigation did not use a standardized definition to determine ACS, a notable limitation that could introduce bias or variation in care. Because all determinations about ACS were made prospectively as part of a QI project, we have little reason to suspect any systematic bias to the determination of ACS. With regard to variation in care, we have previously presented data demonstrating consistent rates of ACS diagnosis across the physicians at our facility.

Based on our investigation and others on this topic, non-ACS troponin elevation is a common, high-risk clinical scenario. In our cohort, non-ACS troponin elevation is about twice as frequent as ACS, and the problem is likely to grow dramatically within the next few years as ultrasensitive troponin assays are eventually approved for use in the United States. These assays are much more sensitive than the current assays, and may make it challenging to distinguish between someone with an acute supply/demand mismatch from someone with an elevated troponin due to chronic, but stable, illness such as CAD, heart failure, or diabetes. Non-ACS troponin elevation remains poorly understood, with no viable treatment options other than addressing the pathophysiology resulting in the troponin elevation. Due to the heterogeneity of the diagnoses and pathophysiological conditions that result in elevated troponin, a unifying treatment is not likely feasible.

In conclusion, in this elderly, male veteran population, the mortality impact associated with a cardiac troponin elevation was not limited to ACS, as mortality was high among those without ACS. Factors independently associated with this non-ACS mortality risk were plausible, but did not elucidate the reasons why non-ACS troponin elevation carries a higher risk. Attempting to better understand the biological basis for the troponin elevation in these non-ACS patients is a critical unmet need.

Disclosure: Nothing to report.

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