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High sensitivity-troponin elevation secondary to non-coronary diagnoses and death and recurrent myocardial infarction: An examination against criteria of causality

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Abstract

Background: Myonecrosis provoked by illness unrelated to unstable coronary plaque is common, but uncertainty about a cause-effect relationship with future events challenges the appropriateness of initiating therapies known to be effective in cardiac conditions. We examined the causal relationship between troponin elevation in non-coronary diagnoses and late cardiac events using the Bradford Hills criteria for causality.

Methods and results: Patients presenting acutely to South Australian public hospitals receiving at least one troponin between September 2011–September 2012 were included. Diagnoses were classified as coronary, non-coronary cardiac and non-cardiac using the *International Classification of Diseases*, version 10 Australian Modified, codes. The relationship between peak in-hospital troponin, using a high-sensitivity troponin T assay and adjudicated cardiac and non-cardiac mortality, and subsequent myocardial infarction (MI) was assessed using competing-risk flexible parametric survival models. Troponin results were available for 38,161 patients of whom, 12,645 (33.6%), 3237 (8.5%), and 22,079 (57.9%) patients were discharged with coronary, non-coronary cardiac and non-cardiac diagnoses, respectively. Troponin >14 ng/l was observed in 43.6%. The relationship between troponin and cardiac mortality was stronger among the non-coronary diagnosis group (troponin 1000 ng/l: coronary hazard ratio: 5.1 (95% confidence interval (CI) 4.0–6.6) vs non-coronary hazard ratio: 16.3 (95% CI 12.6–22.4)). The temporal hazard for cardiac death was marked within 30 days in both groups. Among non-coronary diagnoses, the hazard for recurrent MI was higher but did not vary with time.

Conclusions: Consistency with causal criteria between secondary myonecrosis and cardiac events suggest the potential benefit for extending cardiac specific interventions to this population if supported in trials appropriately designed to address competing risks. Troponin elevation precipitated by non-coronary events is common and demonstrates an associations with late mortality that are analogous to spontaneous MI resulting from unstable coronary plaque. These observations help inform the design of randomized clinical trials exploring the benefits and risk of therapies with established benefits in other cardiac conditions. Such studies will need to appropriately account for competing risks in this population of patients.

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Introduction

Myonecrosis deemed secondary to non-coronary conditions, as opposed to acute coronary syndrome (ACS) due to unstable coronary plaque, is extremely common and remains a substantial clinical dilemma.[1–3] Mechanisms underlying secondary myonecrosis are often multifactorial and include supply-demand ischemia (i.e. type 2 myocardial infarction (MI)), direct myocardial toxicity and, potentially unrecognized plaque rupture (i.e. type 1 MI).[1,2]

Clinically elucidating these mechanisms to inform rational treatment approaches remains challenging and applying the third universal definition of MI criteria does not necessarily enhance clinical management decision-making.[4,5]

The development of troponin assays with greater sensitivity has markedly increased the recognition of myonecrosis seemingly unrelated to coronary plaque rupture.[6,7] While an increase in the risk of late mortality has been observed, it remains unclear whether this risk is completely attributable to the precipitating condition (i.e. troponin serving as a marker of severity for the non-cardiac condition) versus a cardiac risk related to the extent of myocardial injury.[8–10] Determining whether myonecrosis is on the causal pathway for subsequent cardiac events in patients with underlying non-coronary illnesses may provide a rationale for assessing cardiac specific therapies established for the management of spontaneous MI and other cardiac conditions.

Criteria used to explore causality elucidated by Bradford Hills include: coherence of mechanistic understandings and epidemiological observations; biological plausibility for an exposure effect; the strength of association or biological gradient where an increased exposure is associated with an increased effect; specificity of the association between exposure and outcome; and consistency of association within differing clinical contexts; the temporal relationship between exposure and subsequent outcome; and analogy.[11,12] We examined the relationship between myonecrosis detected by a high-sensitivity troponin T (hs-TnT) assay deemed secondary to acute non-coronary illness and late cardiac outcomes through an adapted paradigm of causality, contrasting this with ACS presentations in a health service-wide study.

Methods

Study population

The study population comprised all patients presenting acutely to all publically funded hospitals in South Australia who received at least one troponin test between September 2011–September 2012. Patients were followed for a minimum of 12 months, and results of all pathology testing performed over this time, including all troponin, creatinine and hemoglobin, were linked with hospital *International Classification of Diseases*, version 10 Australian Modified, (ICD-10 AM) primary and secondary diagnosis codes. Contiguous admissions among transferred patients and subsequent readmissions to all public hospitals within the state were determined by linkage. The first admission within the 12-month sampling period, without a preceding admission in the prior six months, was considered the index admission, with all subsequent non-contiguous admissions to any hospital defined as a readmission. Deaths and their cause were identified through hospital records and state death registry. The Human Research Ethics Committee of the South Australian Department of Health provided approval to access to all datasets and this study complies with the Declaration of Helsinki.

Discharge diagnosis classification

Trained independent coding professionals, applying standardized audited protocols, used medical record clinical documentation and imaging and pathology data to classify primary and secondary diagnoses for each clinical presentations. These data are routinely used to examine incidence of disease presentations and procedures for public reporting nationally. Hospital presentations were subsequently categorized as either coronary, and potential coronary (i.e. chest pain for cardiac exclusion) or non-coronary conditions based on their primary and secondary discharge ICD 10-AM coding (I20–I25 and R074). All diagnostic codes for patients transferred between hospitals were interrogated to ensure potential coronary and non-coronary cardiac diagnosis patients were identified. All remaining patients were classified as non-coronary admissions and were further sub-classified by organ system using the primary ICD-10 AM code. Patient discharged with a primary or secondary non-coronary cardiac diagnosis (i.e. heart failure, rheumatic and valvular disease (I00–I09, I33–I39, I42–I43, I50), hypertensive disease (I00–I15), pericarditis and myocarditis (I30–I32, I40–I41), or cardiac arrhythmias (I44–I49), but without a coronary diagnosis were sub-classified as a non-coronary cardiac diagnosis.

Non-cardiac organ system diagnoses comprised the ICD 10-AM individual chapters A–G, I–K, L–N and the

Table 1. Clinical characteristics according to diagnosis at index hospitalization.

	Coronary	Non-coronary		Total	*p*-value
	(*n*=12,845)	Cardiac (*n*=3237)	Non cardiac (*n*=22,079)	(*n*=38,161)	
Age in years, median (IQR)	60.0 (47.6–73.7)	72.7 (57.9–83.2)	71.2 (54.1–82.6)	67.1 (51.4–80.7)	<0.001
Female *n*, (%)	5712 (44.5)	1551 (47.9)	11233 (50.9)	18496 (50.9)	<0.001
Troponin >14 ng/l, *n*, (%)	4819 (37.5)	1966 (60.7)	9825 (44.5)	16610 (43.5)	<0.001
Single troponin result if TnT>14 ng/l, *n*, (%)	824 (17.1)	609 (31.0)	4566 (46.5)	5999 (36.1)	<0.001
Maximum in-hospital troponin, ng/l, median, (IQR)	7 (5–48)	21 (7–51)	12 (5–30)	11 (5–34)	<0.001
Universal definition rise and/or fall,[a] *n*, (%)	2943 (61.1)	699 (35.6)	2687 (27.4)	6329 (38.1)	<0.001
Diabetes, *n*, (%)	1283 (10.0)	450 (13.9)	2914 (13.2)	4647 (12.2)	<0.001
Hypertension, *n*, (%)	2326 (18.1)	944 (29.2)	4805 (21.8)	8075 (21.2)	<0.001
GFR ml/min/1.73m^2, median, (IQR)	78 (60–113)	70 (49–99)	76 (53–109)	76 (55–109)	0.0001
Baseline hemoglobin g/dl, median, (IQR)	13.8 (12.7–14.9)	13.5 (12.0–14.7)	13.3 (11.8–14.5)	13.5 (12.1–14.7)	<0.001
Prior MI, *n*, (%)	850 (6.6)	157 (4.9)	1000 (4.5)	2007 (5.3)	<0.001
Prior CCF, *n*, (%)	486 (3.8)	916 (28.3)	795 (3.6)	2197 (5.8)	<0.001
Prior CABG, *n*, (%)	148 (1.2)	45 (1.4)	204 (0.9)	397 (1.0)	0.016
Prior PCI, *n*, (%)	557 (4.3)	78 (2.4)	454 (2.1)	1089 (2.9)	<0.001
Known COPD, *n*, (%)	18 (0.1)	8 (0.3)	60 (0.3)	86 (0.2)	0.042
Prior CVA, *n*, (%)	7 (0.05)	0 (0)	20 (0.1)	27 (0.1)	0.138
Vascular disease, *n*, (%)	145 (1.1)	52 (1.6)	426 (1.9)	623 (1.6)	<0.001
Atrial fibrillation, *n*, (%)	825 (6.4)	1303 (40.3)	2108 (9.6)	4236 (11.1)	<0.001
Known renal disease, *n*, (%)	782 (6.1)	377 (11.7)	2310 (10.5)	3469 (9.1)	<0.001
Dialysis dependent, *n*, (%)	47 (0.4)	32 (1.0)	215 (1.0)	294 (0.8)	<0.001
Chronic liver disease, *n*, (%)	129 (1.0)	43 (1.3)	517 (2.3)	689 (1.8)	<0.001
Prior cancer, *n*, (%)	1087 (8.5)	370 (11.4)	3507 (15.9)	4964 (13.0)	<0.001
Dementia, *n*, (%)	86 (0.7)	39 (1.2)	581 (2.6)	706 (1.9)	<0.001
12-Month mortality, *n*, (%)	732 (5.7)	431 (13.3)	3312 (15.0)	4475 (11.7)	<0.001
12-Month cardiac mortality, *n*, (%)	404 (3.2)	209 (6.5)	716 (3.2)	1329 (3.5)	<0.001
12-Month non-cardiac mortality, *n*, (%)	328 (2.6)	222 (6.9)	2596 (11.8)	3146 (8.2)	<0.001
12-Month recurrent MI, *n*, (%)	478 (3.7)	132 (4.1)	515 (13.7)	1125 (3.0)	<0.001

CABG: coronary artery bypass graft; CCF: congestive cardiac failure; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; GFR: glomerular filtration rate; IQR: interquartile range;, MI: myocardial infarction; PCI: percutaneous coronary intervention.
[a]Percentage of patients with a positive troponin (>14 ng/l).

remainder grouped as a heterogeneous group of diagnoses (Supplementary Material, Table 1). Significant past medical conditions (e.g. diabetes, hypertension, liver disease) for each patient were determined by examining their hospitalizations for the preceding 10 years.

Troponin sampling and classification

The indication and timing for troponin testing was clinically determined. All troponin samples were analyzed using a hs-TnT assay (Elecys Roche Diagnostics: no detectable troponin: 3 ng/l, threshold of detection: 5 ng/l; 99th percentile upper reference limit in a normal population (no acute disease): 14 ng/l). All troponin levels ≥5 ng/l were available for this analysis. Any troponin result >14 ng/l within the index hospitalization was defined as being elevated. The maximal in-hospital troponin level was transformed using a restricted cubic spline with knots at 14 ng/l (1× Upper Reference Limit (URL)), 75 ng/l (5×URL), 150 ng/l (10×URL), 300 ng/l (20×URL), and 750 ng/l (50×URL) to explore the continuous relationship between the maximum observed troponin level and outcome. Peak in-hospital troponin levels were also divided into ordinal categories (<14 ng/l, 14–74 ng/l, 75–149 ng/l, 150–749 ng/l, 750–1499 ng/l and ≥1500 ng/l) to enable temporal assessments. Troponin profiles for any given individual were considered to have "a rise and/or fall" (i.e. consistent with the universal definition of MI) if sequential values over the index hospitalization demonstrated a relative increase or decrease of >5 ng/l if the initial level ≤14 ng/l, and >8 ng/l relative change if the initial level was >14 ng/l.[3,13,14] All

assays were performed within a centralized laboratory with standardized testing and reporting protocols.

Outcomes

This analysis examined "all-cause", cardiac and non-cardiac mortality. Based on classifications available from death certificates, deaths were classified as cardiac if the primary, or associated cause of death was recorded as an acute cardiac condition (i.e. acute MI, acute pulmonary edema, cardiac arrhythmia and sudden cardiac death) or a chronic cardiac condition with no other antecedent non-cardiac cause of death (e.g. ischemic heart disease or heart failure). Deaths coded as primarily due to cancer, sepsis, failure of a non-cardiac organ, dementia or sepsis without a cardiac antecedent were coded as non-cardiac. Two clinicians determined cause of death separately with disagreements adjudicated by a third (<2% of deaths), without knowledge of troponin. Recurrent MI was defined as a readmission with an ICD-10 AM code for MI (I21–I25), validated by a documented concomitant rise and/or fall in troponin during that admission.

Statistical analysis

Analyses examined the relationship between troponin elevation and subsequent outcomes using the criteria of Bradford Hills for causality where applicable.[11] Consistency was examined by assessing the relative hazard ratio associated with a troponin elevation (>14 ng/l) and cardiac/non-cardiac mortality stratified primary organ system groups.

For subsequent analyses, patients were grouped as coronary, non-coronary cardiac and non-cardiac (i.e. the latter two termed non-coronary) to simplify the number of comparisons. Specificity of troponin elevation for all-cause, cardiac and non-cardiac and recurrent MI by 12-months was assessed as the proportion of these events observed among patients with and without initial troponin elevation within the aforementioned three diagnostic groups using a simple 2×2 contingency table with chi-square analysis. Strength of association (also biological gradient) between troponin and outcome was evaluated by examining the magnitude of troponin elevation as a continuous variable with spline-transformation and recurrent MI, and cardiac and non-cardiac mortality over the follow-up duration. The temporal relationships between troponin elevation, and outcomes were examined by assessing the troponin as categorized peak troponin level allowing these to interact with time as a time-varying co-variate.

Beyond the analysis of specificity, all other analyses employed cause-specific flexible parametric models with cardiac and non-cardiac mortality examined as competing risks.[15–17] Similarly, models for recurrent MI accounted for total mortality as a competing risk. For each model the distribution of knots was selected by optimizing the Akaike and Bayes information criteria in methods described by Hinchliffe and Lambert.[16] To attenuate the confounding by observed differences in the baseline characteristics between groups, gender, age in years, baseline glomerular filtration rate, baseline hemoglobin level, history of coronary artery disease, prior heart failure, prior valvular heart disease, known liver disease, chronic obstructive airways disease, requiring permanent dialysis, a history of malignancy, and dementia were included as covariates in the models. These flexible parametric models were used to predict instantaneous hazards for cardiac and non-cardiac mortality and recurrent MI, and the hazard ratios examining the strength of association between peak troponin levels used the estimated hazard at a troponin level of 5 ng/l as the base hazard. All analyses were undertaken using STATA 13.1 (College Station, Texas, USA) and a p-value of 0.05 was considered statistically significant.

Results

Patient characteristics

During the 12-month sampling period 39,806 individual index presentations without prior admission in the preceding six months with at least one troponin assessment were identified. After exclusion of 1645 (4.1%) patients with missing diagnostic coding, age, creatinine or hemoglobin values or cause of death information, 38,161 patients were available for analysis. A coronary or non-coronary cardiac diagnosis was included in the primary or secondary diagnostic codes in 12,845 (33.7%) and 3237 (8.5%), respectively, while the remaining patients 22,079 (57.9%) had non-cardiac organ system diagnoses. Table 1 describes the clinical characteristics of each of these diagnostic groups.

Association between troponin elevation and outcomes

During the index hospitalization, an elevated troponin (>14 ng/l) was identified on at least one occasion in 16,616 patients (43.6%). Prior coronary artery disease (CAD) was more common among patients with a coronary diagnosis (2167/12845 (16.9%)) than with non-coronary cardiac (479/3237 (14.8%)) or non-cardiac (2611/22,079 (11.8%)) diagnoses (p<0.0001). A "rise and/or fall" in troponin was evident in 2943/4819 (61.1%), 699/1966 (35.6%) and 2689/9825 (27.4%) (p<0.0001) of patients within the coronary, non-coronary cardiac and non-cardiac groups, respectively. By 12 months, the mortality rates among the three groups were 732/12,845 (5.7%), 431/3237 (13.3%) and 3312/22,079 (15.0%), respectively. Among patients with an elevated troponin, a rise and/or fall pattern was associated with a slightly greater risk of cardiac death (rise/fall: 623/6329 (9.8%) versus no rise/fall: 630/10281 (6.2%), p<0.001) and recurrent MI (rise/fall: 472/6329 (7.5%)

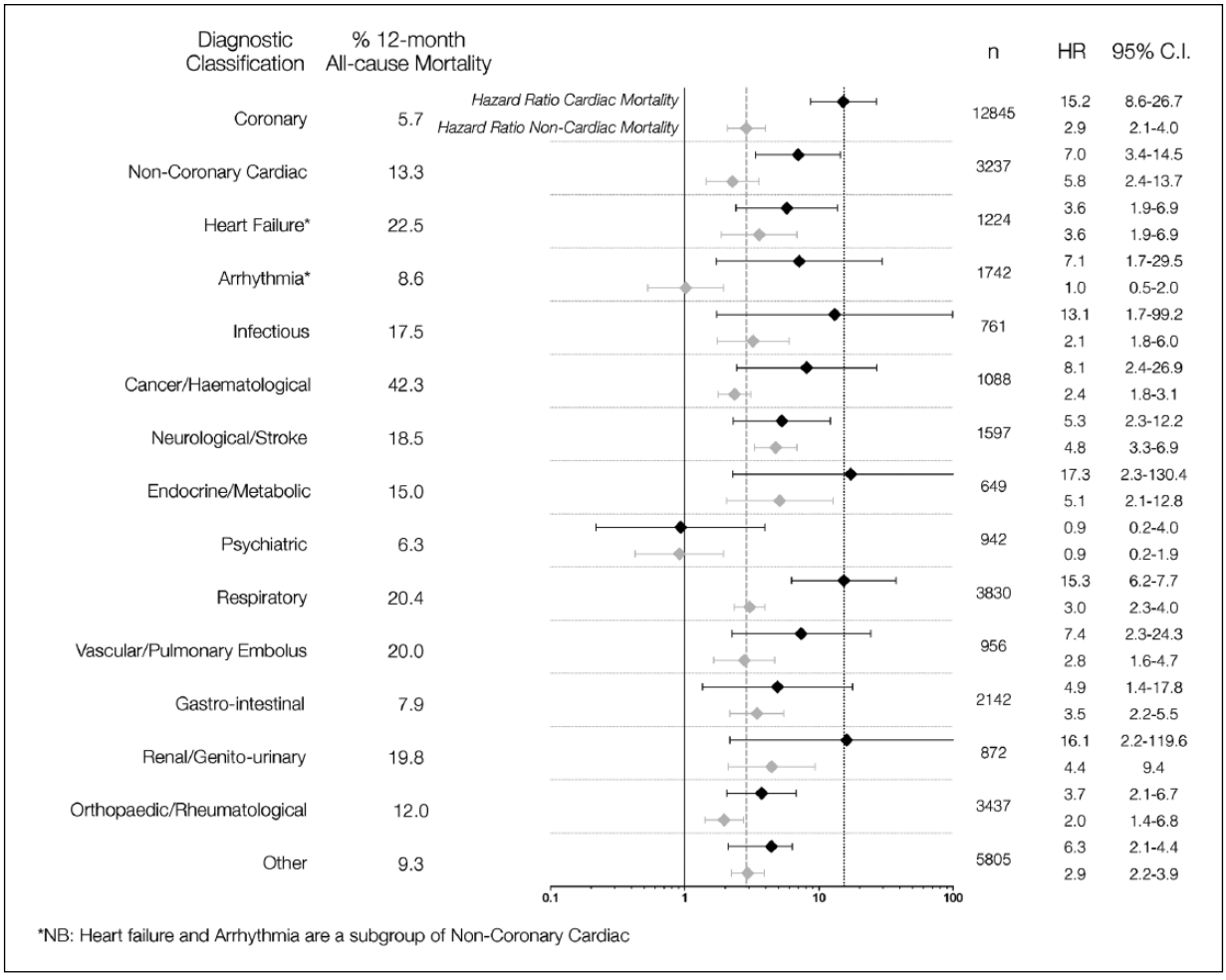

Figure 1. Cause-specific hazard ratios for mortality with elevated troponin (>14 ng/l) by primary diagnosis grouped by organ system. CI: confidence interval; HR: hazard ratio.

versus no rise/fall: 516/10281 (5.0%), $p<0.001$), and lower risk for non-cardiac death (rise/fall: 849/6329 (13.4%) versus no rise/fall: 1714/10281 (16.7%), $p<0.001$), although the overall rates of non-cardiac death remained higher.

Consistency of relationship between elevated troponin and mortality

Figure 1 depicts the cause-specific hazard ratios for cardiac and non-cardiac mortality associated with an elevated troponin across the 15 ICD-10 organ-specific groups. Hazard ratios associated with troponin elevation were generally higher for cardiac death compared with non-cardiac death, though the degree of risk varied across diagnostic groups. The relative hazard for non-cardiac death associated with any troponin elevation was more consistent across the diagnostic groups than for cardiac death with the exception of psychiatric disorders where troponin elevation was not associated an excess hazard ratio for cardiac or non cardiac death.

Specificity for death and MI

Among those patients who died by 12 months, an elevated troponin level was evident in 3816/4475 (85.3%) of patients. This proportion was higher among coronary or non-coronary cardiac diagnoses, compared with non-cardiac presentations. An elevated troponin level was observed during the index hospitalization in 988/1224 (80.7%) of patients experiencing a subsequent MI, with similar specificity across the three groups. (Table 2) Within each diagnostic group, the specificity of troponin elevation for late events was moderate, ranging from 41% for non-cardiac death in the non-coronary cardiac population, to 66% for all-cause mortality within the coronary population (Table 2).

Biological gradient and outcome

Patients with secondary myonecrosis more frequently exhibited peak troponin levels <100 ng/l (Figure 2). Focusing on

Table 2. Proportion of patients experiencing mortality or recurrent myocardial infarction (MI) within 12 months stratified by troponin level above upper reference limit (>14 ng/l) within the index hospitalization. Specificity: proportion of events among patients without troponin elevation.

Proportion of events in troponin positive patients				Specificity
Admission classification	Troponin≤14 ng/l (*n*/*N*, (%))	Troponin>14 ng/l (*n*/*N*, (%))	% Event in troponin (+) patients	% Event free in troponin ≤14 ng/l (*n*/*N*, (%))
Coronary diagnoses				
All death	63/8026 (0.8)	669/4819 (13.9)	91	7964/12115 (66)
Cardiac death	13/8026 (0.2)	391/8026 (8.1)	97	8031/12441 (64)
Non-cardiac death	50/8026 (0.6)	278/8026 (5.8)	85	7976/12517 (64)
12-month recurrent MI	83/8026 (0.6)	367/8026 (5.8)	82	7943/12395 (64)
Non-coronary cardiac diagnoses				
All death	33/1271 (2.6)	398/1966 (20.2)	93	1238/2806 (44)
Cardiac death	8/1271 (0.8)	201/1966 (10.2)	96	1263/3028 (42)
Non-cardiac death	25/1271 (2.0)	197/1966 (10.2)	89	1246/3015 (41)
12-month recurrent MI	24/1271 (1.9)	132/1966 (6.7)	85	1247/3081 (41)
Non-cardiac diagnoses				
All death	563/12254 (4.6)	2749/9825 (28.0)	83	11691/18676 (62)
Cardiac death	55/12254 (0.5)	661/9825 (6.7)	93	12199/21363 (57)
Non-cardiac death	508/12254 (4.1)	2088/9825 (6.7)	80	11746/18483 (60)
12-month recurrent MI	129/12254 (1.1)	489/9825 (5.0)	79	12125/21461 (57)

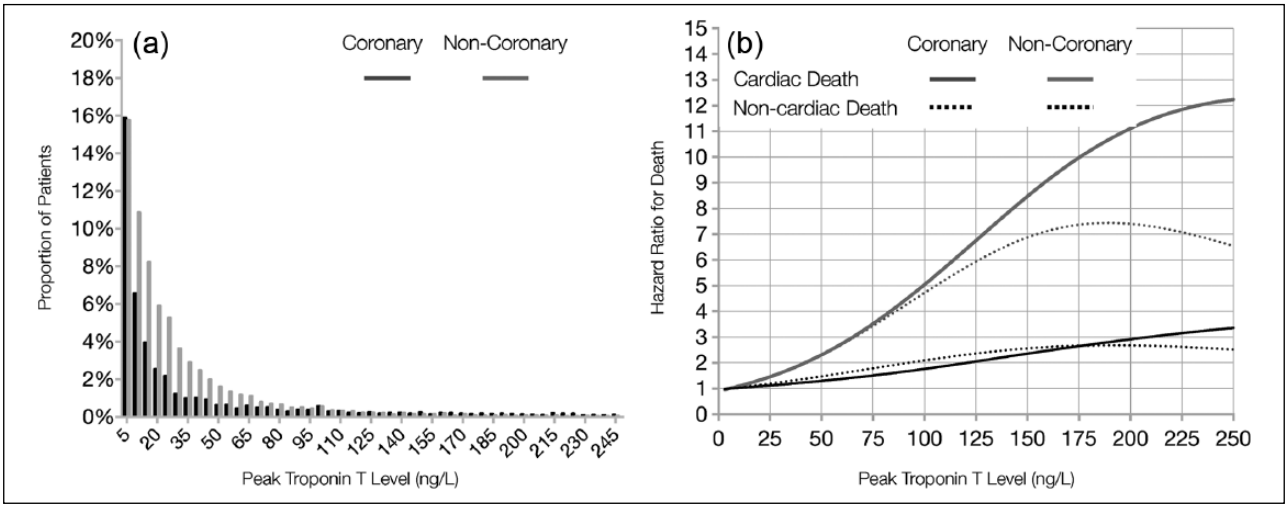

Figure 2. The frequency distribution (a) and relative hazard (b) between cubic spline transformed peak in-hospital troponin levels less than 250 ng/l and cardiac mortality (solid line with confidence intervals (CIs)) and non-cardiac (dotted line with CIs) among patients with coronary (black) and non-coronary diagnoses (grey).

peak elevations of troponin <250 ng/l demonstrates a steeper rise in the estimated risk of both cardiac and non-cardiac death, than observed among patients with a coronary diagnosis (Figure 2). However, with elevations beyond 100 ng/l, the risk of cardiac death exceeded that of non-cardiac death for non-coronary presentations. The risk of non-cardiac deaths appears to plateau at troponin levels of 150–200 ng/l then declines. This relationship is more marked with non-coronary diagnoses. Overall among patients with a non-coronary or non-cardiac diagnostic classification, the relative hazard was substantially higher than those with a coronary diagnosis for the same level of troponin elevation (Troponin level 1000 ng/l: coronary hazard ratio: 5.1 (95% CI 4.0–6.6) vs non-coronary hazard ratio: 16.8 (95% CI 12.6–22.4)) (Figure 3).

The estimated hazard ratio for recurrent MI also rises in association with increasing peak troponin levels, though a modest decline in risk is observed at very high troponin peaks among patients with a coronary discharge diagnosis. Similarly, the risk for recurrent MI rises more steeply with increasing peak troponin levels among patients with

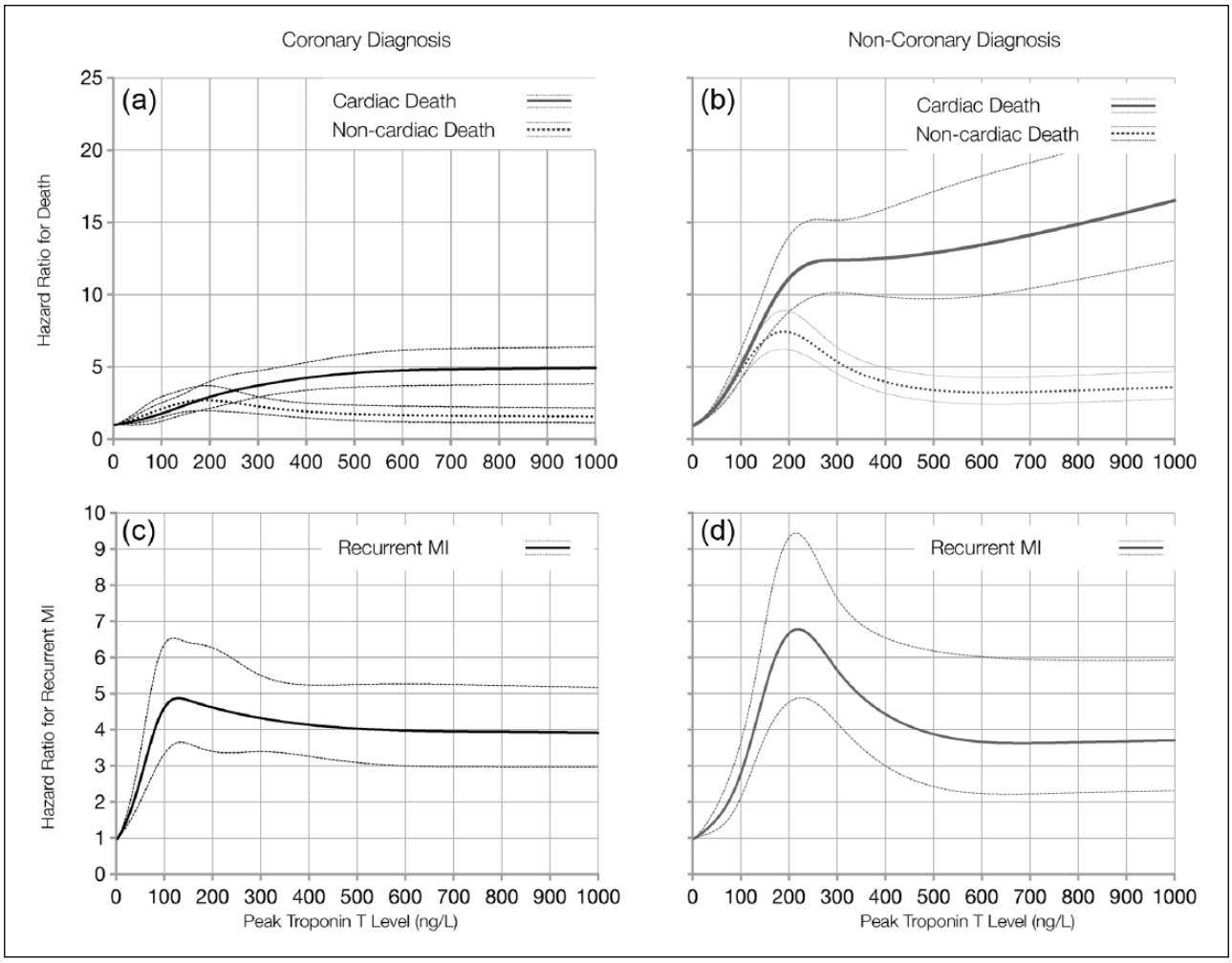

Figure 3. Relationship between cubic spline transformed peak in-hospital troponin levels and cardiac mortality (solid line with confidence intervals) and non-cardiac (dotted line with confidence intervals) (a)-(b), and recurrent myocardial infarction (NI) (c)-(d) among patients with coronary (a)-(c) and non-coronary diagnoses (b)-(d).

non-coronary discharge diagnosis, reaching a higher hazard ratio, with a more prominent decline in the risk with further increases in troponin peak levels (Figure 3).

Temporal relationship between troponin and outcome

Figure 3 explores the temporal relationship between the degree of troponin elevation and the occurrence of death and recurrent MI. Among patients with both coronary and non-coronary diagnoses, the instantaneous hazard for mortality is highest in the days following admission and declines rapidly in the subsequent weeks. This pattern is similar for cardiac and non-cardiac death, and the degree of hazard is proportional to the magnitude of initial myocardial injury. Overall, the estimated hazard observed among patients with a non-coronary diagnosis is higher (At day 1, TnT>50×URL: 11.7 deaths/1000 patient-days) than those with a non-coronary diagnosis (At day 1, TnT>50×URL: 2.8 deaths/1000 patient-days), with the estimated cumulative incidence for total mortality at 30 days with these levels of troponin elevation of 20.5% and 2.9%, respectively.

The temporal relationship for recurrent MI was highest in the first 30 days following the index hospitalization, declining to a constant hazard throughout the remaining 12-month period among coronary diagnosis patients (Figure 4). In contrast, the hazard for recurrent MI among patients with a non-coronary hospitalization was constant over and proportional to the degree of troponin elevation over the follow-up period except for a small early excess hazard among those troponin elevations between 10–50 times the upper reference limit.

Discussion

Myonecrosis precipitated by non-coronary conditions is more commonly observed with the availability of high-sensitivity troponin assays. In a diversified population receiving troponin testing as part of physician determined care,

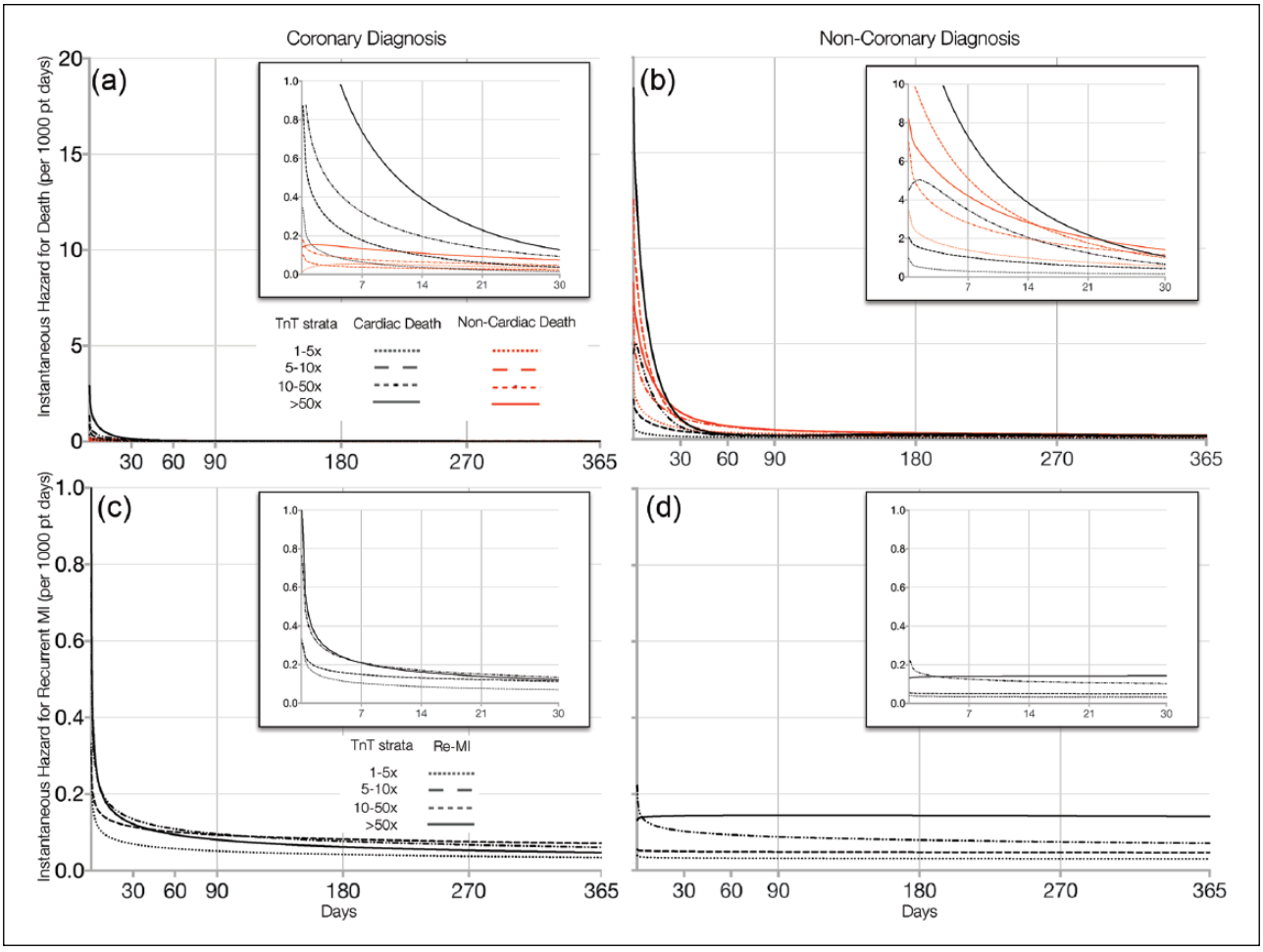

Figure 4. Temporal relationship between peak troponin (TnT) level and instantaneous hazard (events per 1000 patient days) for cardiac (black) and non-cardiac (red) mortality (a)-(b) and recurrent myocardial infarction (MI) (c)-(d) by increasing levels of peak in-hospital troponin among patients with coronary (a)-(c) and non-coronary diagnosis (b)-(d). Hazard within the first 30 days enlarged in the inset (Note: different scale in mortality insets).

myonecrosis detected using a hs-TnT assay was found to be more common and associated with greater estimated risk among patients admitted for non-coronary compared with coronary diagnoses. By examining the implications of troponin elevation for late events using an adaption of the Bradford Hills causality criteria, our findings would appear to satisfy many of these characteristics including: a risk pattern that is strikingly analogous to Type 1 MI; moderate specificity of troponin elevation for 12-month mortality and recurrent MI; a generally consistent hazard across a range of clinical diagnoses; a clear biological gradient between peak troponin levels and cardiac mortality (but not with non-cardiac mortality) but a plateauing relationship with recurrent MI; and a temporal profile of an early excess in the hazard of death, but not recurrent MI. The criteria of plausibility and coherence are met through the extensive evidence linking myonecrosis and left ventricular impairment in spontaneous and peri-procedural with subsequent events MI.[18–20] The remaining criterion of "experimentation" will require the conduct of randomized trials of current and emerging therapies aimed at limiting the extent or impact of myonecrosis among this substantial patient population who have been actively excluded from clinical trials for whom the cardiovascular evidence base remains limited.

The third universal definition of MI has sought to facilitate diagnosis and management by defining type 2 MI as supply-demand ischemia with corroborative evidence beyond biomarker changes such as ischemic changes on electrocardiogram (ECG) or myocardial imaging, or coronary lesions on coronary angiography.[3] Such corroborative evidence is often inconclusive, non-specific, and at times difficult to pursue clinically with invasive or computer tomography (CT) angiography when faced with patients experiencing significant co-morbidities. Even within the selective context of ACS trials, patients without documented obstructive coronary stenosis on coronary angiography are enrolled and poorer clinical outcomes have been observed.[21] Such studies have had limited powered to assess the impact

of specific therapies or interventions. This analysis demonstrates that, regardless of the universal definition, myonecrosis detected in the context of non-coronary conditions confers a greater biological gradient for mortality and particularly cardiac mortality, than seen with coronary conditions, combined with a similar temporal risk profile. Furthermore, higher peak troponin levels confer a greater hazard ratio for cardiac death as opposed to non-cardiac death, with these curves appearing to diverge at peak troponin levels of approximately 100–150 ng/l, suggesting a greater opportunity for providing benefits with cardiac specific therapies based on the peak troponin level.

The risk for recurrent MI in non-coronary conditions rises to a peak troponin around ~250 ng/l but then declines with increasing levels. This pattern has previously been documented within type I MI populations.[22] This decline in subsequent MI risk associated with supra-elevated troponin levels may reflect a lower likelihood for recurrent MI in the presence of large areas of initially infarcted myocardium, combined with the competing risk of mortality associated with extensive myocardial injury. However, in contrast to the temporal profile of recurrent MI seen with type 1 MI, the instantaneous hazard for recurrent MI in non-coronary diagnoses is constant over the duration of follow-up. This contrast is consistent with the differences in our current understanding of the underlying pathology (i.e. coronary plaque instability in type 1 MI versus supply-demand imbalance in type 2 MI). Therefore, significant clinical equipoise regarding the likely benefits of a strategy based on treating fixed coronary lesions to prevent future cardiac events remains.

These findings appear to suggest that secondary myonecrosis lies along the "causal pathway" to late events, though commentary on more proximate or distal factors along this pathway cannot be made. The extent that risk is "modifiable" and whether currently available cardiac therapies, specifically those targeting left ventricular dysfunction, late arrhythmias, and plaque stability, such as coronary angiography and possible revascularization, and anti-thrombotic pharmacotherapies, confer benefit are issues that carry significant implications for optimal clinical management in a very large proportion of patients. To date, trials of these therapeutic approaches have largely excluded such patients due to competing risks of non-cardiac events. Yet, cardiac events among these patients are substantial. Defining the magnitude of benefit and risk with cardiac-specific therapies, as well as the appropriate patient population can only be determined in large-scale randomized controlled trials designed to account for competing risks.

Limitations

Several limitations should be considered. It is recognized that the indication and timing of troponin sampling was at clinical discretion, and it remains possible that the measured peak troponin levels did not capture actual peak levels. Such random miss-classification may have confounded the assessment of the pattern of troponin elevation and estimates of the hazard. However, failure to detect subsequent troponin elevation among those with initial normal troponins would introduce a bias leading to conservative estimates of risk. Similarly, miscoding of discharge diagnostic classification, specifically the failure to clinically appreciate coronary plaque instability (type 1 MI) as an underlying cause for the troponin elevation may also have occurred, attesting to the challenges of diagnosing and coding MI in the context of other concurrent illness. As a consequence, both true type 1 MI due to new plaque rupture or type 2 MI due to supply demand ischemia may have occurred but remained un-diagnosed by the clinical teams despite the documented rise in troponin. Recognizing this challenge further underscore the difficulties on implementing current definitions of MI in the context of non-cardiac conditions, particularly in the absence of coronary imaging, and the potential opportunities for reducing mortality by extending cardiac therapies to this large population of patients.

Conclusion

A health-service wide analysis examining troponin elevation among patients with clinical conditions not considered due to ACS portends a causal relationship to cardiac mortality. These observations suggest the potential benefit for extending ACS therapies to this population if supported in clinical trials appropriately designed to address the issues of competing risk.

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Conflict of interest

All authors have no conflicts of interest to declare pertaining to the current submitted work.

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