



Minor elevations in troponin T values enhance risk assessment in emergency department patients with suspected myocardial ischemia: analysis of novel troponin T cut-off values

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Abstract

Background: A consensus document developed by a joint committee of the European Society of Cardiology and the American College of Cardiology redefines myocardial infarction (MI) using an increase of troponin I or T as compared to a reference control population (i.e., troponin T (TnT) of 0.01 µg/l). A clinical problem arises when an arbitrary cut-off point is selected for determination of MI (i.e., TnT ≥ 0.1 µg/l), as minor elevations of troponin are associated with increased cardiovascular risk in selected patients with acute coronary syndromes. **Methods:** We prospectively studied 420 unselected patients being evaluated for suspected myocardial ischemia in the emergency department (ED). We compared a 99th percentile MI cut-off limit for TnT, determined by constructing a standard receiver operator curve from our ED population in whom an acute coronary syndrome was excluded, to a standard MI cut-off limit of 0.1 µg/l in assessing cardiovascular risk. We also assessed the prognostic value of detectable TnT concentrations below this 99th percentile MI cut-off, but above the upper reference limit of healthy controls. **Results:** The diagnosis of acute coronary syndromes (ACS) was more frequent in groups with higher TnT concentrations: 16.8% with a normal TnT (<0.03 µg/l), 29.5% with detectable TnT below the 99th percentile MI limit (0.03–0.066 µg/l), 64.3% with detectable TnT between the 99th percentile and standard MI cut-offs (0.067–0.099 µg/l), and 85.4% with TnT ≥ 0.1 µg/l ($p < 0.001$ for the trend). Thirty-day cardiovascular event rates increased for any detectable concentration of troponin: 1.3% with normal TnT, 4.8% with detectable TnT below the 99th percentile MI limit, 15.4% with TnT between the 99th percentile and standard MI cut-off limits, and 12.5% with TnT ≥ 0.1 µg/l ($p < 0.01$ for the trend). **Conclusion:** Using an MI cut-off concentration for TnT from a “non-ACS reference” population would fail to detect a positive TnT in 11.7% of subjects with an acute coronary syndrome.

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Keywords: Troponin T; Myocardial ischemia; Risk assessment

1. Introduction

Cardiac troponins are now the preferred biomarker for myocardial necrosis [1–3] given the near absolute sensitivity and specificity of troponins as compared to

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37 CK-MB. A consensus document [1] was developed
38 by the Joint Committee of the European Society of
39 Cardiology and the American College of Cardiology
40 (ESC/ACC) to revise the definition of myocardial
41 infarction (MI) using more accurate criteria than the
42 World Health Organization (WHO) criteria [2]. The
43 WHO classification relies on two of three criteria
44 consisting of ischemic symptoms, cardiac enzyme rise
45 and a typical ECG pattern with evolution of Q waves.
46 The revised definition of MI requires an elevation of
47 either cardiac troponins (I or T) or the MB fraction of
48 creatine kinase (CK-MB), and one of the two remain-
49 ing criteria. The ESC/ACC suggested that an abnor-
50 mal troponin measurement should be defined as that
51 exceeding the 99th percentile of a reference popula-
52 tion with a coefficient of variation (CV) of $\leq 10\%$.

53 Detection of MI is only a partial goal, however, as
54 recent emphasis has switched from the diagnosis of
55 MI to risk stratification to identify patients prone to
56 in-hospital and recurrent cardiac events [4]. The
57 superiority of cardiac troponins for the diagnosis of
58 MI was extended to risk stratification in the recent
59 guidelines for the management of unstable angina and
60 non-ST segment MI [5]. An elevated troponin identi-
61 fies a high-risk patient with an \sim nine-fold increased
62 risk for MI or death in the next 30 days [6] who may
63 benefit from aggressive medical therapies or an early
64 invasive strategy [7,8].

65 As small degrees of myocardial necrosis can be
66 reliably detected with a highly sensitive and specific
67 marker such as troponin T (TnT) or I (TnI), the
68 National Academy of Clinical Biochemistry (NACB)
69 had previously recommended two decision limits: a
70 lower cut-off value at the detection limit to establish
71 the presence of true myocardial injury and a higher
72 value to qualify as MI [9]. Similarly, recent acute
73 coronary syndrome guidelines suggest different cut-
74 off values for TnT representing a slightly elevated
75 value ($>0.01 \mu\text{g/l}$ but $<0.1 \mu\text{g/l}$) or a markedly
76 increased value ($\geq 0.1 \mu\text{g/l}$) to identify intermediate
77 and high risk patients, respectively [5]. Depending on
78 the cut-off value chosen, the timing of the blood
79 draws, and the duration of follow up, a positive
80 troponin has a wide range of sensitivity (38–63%)
81 and specificity (77–95%) for future adverse cardiac
82 event rates [10].

83 Ideally, the TnT cut-off should be calculated using
84 logistic analysis to determine the value associated

with the highest odds ratios for predicting MI and 85
near term events for a particular assay. However, this 86
is impractical for most hospital laboratories and due to 87
psychological and socioeconomic concerns it may be 88
inappropriate to label all ischemic episodes associated 89
with slightly elevated troponin values as an acute MI. 90
Although the detection limit for TnT is $0.01 \mu\text{g/l}$, a 91
single MI cut-off limit of $\geq 0.1 \mu\text{g/l}$ is typically 92
recommended. Recent multicenter trials have exam- 93
ined multiple TnT cut-off values in assessing risk in 94
large cohorts of patients with acute coronary syn- 95
dromes and found that adverse outcomes increased 96
with increasing TnT concentrations, even at values 97
below the accepted $0.1 \mu\text{g/l}$ MI cut-off limit [11,12]. 98
However, as the positive predictive value of minor 99
troponin elevations was examined only in a high-risk 100
cohort with unstable angina or non-ST elevation MI, 101
caution should be exercised in generalizing these 102
results to a heterogenous population. As chest pain 103
is frequently absent at the time of presentation in acute 104
MI patients [13], cardiac biomarkers are routinely 105
obtained in a more diverse patient population. 106

107 We prospectively evaluated serial TnT values, as
108 well as clinical and electrocardiographic (ECG) vari-
109 ables, in 420 patients with suspected myocardial
110 ischemia in whom serial CK-MB and TnT determi-
111 nations were drawn in the ED, irrespective of the
112 presence of chest pain. We constructed a standardized
113 receiver operator curve (ROC) curve to establish a
114 TnT MI cut-off at the 99th percentile of TnT from our
115 ED population patients with suspected myocardial
116 ischemia in whom an acute coronary event was
117 excluded. Given the excellent specificity of TnT, we
118 hypothesized that increases in TnT values above this
119 99th percentile cut-off of a candidate reference pop-
120 ulation, but below the standard MI cut-off value,
121 would be predictive of near term cardiac risk in a
122 heterogeneous population with suspected myocardial
123 ischemia.

2. Methods 124

2.1. Study population 125

126 We prospectively evaluated serial TnT determina- 127
tions in 420 serial patients presenting to the ED with 128
chest pain or other symptoms suggestive of myocar- 129

130 dial ischemia for >30 min in duration in the absence
131 of ST elevation in whom serial TnT and CK-MB
132 determinations were obtained. Patients ≥ 21 years
133 were eligible if they were without the following
134 exclusion criteria: ST elevation at presentation, recent
135 trauma, renal disease (creatinine ≥ 2 mg/dl), pregnan-
136 cy, resuscitation, defibrillation or cardioversion in the
137 ED. The median time from onset of symptoms to
138 presentation in the ED was 5.4 h (range 0.5–56 h).

140 2.2. Laboratory protocol

141 TnT and CK-MB activity were assayed on speci-
142 mens collected at 0, 3 and 12 h after presentation.
143 Over 90% of patients had both the 0- and 3-h assay
144 collected and approximately 50% had a 12-h sample
145 collected (as low risk patients were frequently sent
146 home after two negative TnT samples). The TnT assay
147 (Elecsys Troponin T STAT) was a third generation
148 chemiluminescent immunoassay performed on the
149 Elecsys 2010 analyzer (Roche Diagnostics, Indian-
150 apolis, IN). The manufacturer's suggested cut-off limit
151 is ≥ 0.1 $\mu\text{g/l}$ for an abnormal result. The CK-MB was
152 measured on the Vitros analyzer (Ortho Ektachem
153 950, Ortho Clinical Diagnostics, Raritan, NJ). A
154 CK-MB value of ≥ 17 U/l, in the setting of an
155 elevated total CK, was used as the cut-off value for
156 an abnormal result based on prior prospective valida-
157 tion at our institution using the aforementioned CK-
158 MB activity assay [14].

160 2.3. Clinical data

161 The clinical data collected for this study included
162 history, physical examination, presence or absence of
163 and characteristics of chest pain (atypical or typical
164 based on the Goldman [15] criteria), ECG findings
165 and final diagnosis. The ECG at presentation was
166 interpreted in a blinded fashion as normal, non-diag-
167 nostic (paced rhythm or left bundle branch block), ST
168 segment depression (>1.0 mm in ≥ 2 or more con-
169 tiguous leads not known to be old or associated with
170 left ventricular hypertrophy) or as non-specific ST-T
171 wave changes. Patients were followed until discharge
172 for the development of acute coronary syndromes or
173 MI and for 30 days for non-fatal MI or death. Follow
174 up data was collected in 399/420 (95%) patients by
175 phone contact and hospital record review.

2.4. Final diagnosis

The diagnosis of acute non-ST elevation MI was
determined independently by a blinded observer (SZ)
based on serially measured CK-MB or TnT determi-
nations, clinical history and ECG findings as defined
by the manufacturer's MI cut-off concentration
(≥ 0.1 $\mu\text{g/l}$) [1]. Unstable angina was defined as
type IIIB according to the Braunwald classification
[16]. All other diagnoses were classified as either
cardiovascular (stable angina, congestive heart fail-
ure, syncope, stroke or dysrhythmia) or non-cardiac
(musculoskeletal, pulmonary or gastrointestinal) in
nature.

2.5. Statistical analysis

A receiver operator characteristic (ROC) curve for
the decision limit for MI was constructed from our ED
cohort with suspected myocardial ischemia in whom
serial biomarker determinations were performed. The
99th percentile for TnT in patients in whom an acute
coronary syndrome was excluded was determined to
be 0.067 $\mu\text{g/l}$ with a CV of 8%. This TnT value was
used as our MI cut-off limit. A TnT value of <0.03
 $\mu\text{g/l}$ was considered normal based on a 99th percentile
value of 0.01 $\mu\text{g/l}$ in reference controls and a 10% CV
limit of <0.03 $\mu\text{g/l}$ as suggested by the manufacturer
and recent studies [11]. We compared cardiac out-
comes in four groups based on the peak troponin T
values: group 1: TnT <0.03 $\mu\text{g/l}$ (normal TnT), group
2: TnT 0.03–0.066 $\mu\text{g/l}$ (TnT detectable below the
99th percentile MI cut-off), group3: TnT 0.67–0.099
 $\mu\text{g/l}$ (TnT detectable above the 99th percentile MI cut-
off, but below the standard MI cut-off limit) and group
4: TnT ≥ 0.1 $\mu\text{g/l}$ (TnT above the standard cut-off
limit). We examined if there was any difference
between groups with and without low concentrations
of detectable troponin in the serum (groups 1 and 2,
respectively) or between groups 3 and 4 with elevated
TnT values at differing cut-off values.

Descriptive statistics, analysis of variance, *t*-test
and cross-tabulation analysis with chi square test were
performed using SPSS software (Chicago, IL). We
used Magidson's GOLDminer (SPSS) method [17] to
predict an ordered response of a dependent variable.
The model fit is measured by the chi-square for the
regression.

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223 **3. Results**

224 The mean age of the patients studied was $64.6 \pm$
 225 15.6 years. Fifty-one percent of patients were males.
 226 Chest pain was the presenting complaint in 319 (76%)
 227 and was typical for myocardial ischemia in 58%.
 228 Thus, only 44% of the cohort presented with typical
 229 chest discomfort, while 24% presented without chest
 230 discomfort. Dyspnea was the most common present-
 231 ing symptom after chest pain followed in order by
 232 pain in the epigastrium, back or arms and palpitations
 233 or syncope. Diagnostic ST segment depression was
 234 present in only 12% of the entire cohort and 29% and
 235 25%, respectively, of unstable angina and MI patients.
 236 The ECG was normal in 26%, non-diagnostic in 8%
 237 (LBBB or paced) and showed non-specific ST-T
 238 changes in 54%. Only 31 patients (7.3%) had both
 239 typical chest pain and diagnostic ST segment depres-
 240 sion. For the entire cohort, the final diagnosis was an
 241 acute coronary syndrome (unstable angina or MI) in
 242 111/420 (26.4%). The final diagnosis was MI in 35
 243 (8.3%) and unstable angina in 76 (18.1%). Seventy-
 244 four percent of patients without an acute coronary
 245 syndrome had a cardiovascular diagnosis or non-
 246 cardiac diagnosis established.

247 The peak TnT concentrations were normal (<0.03
 248 $\mu\text{g/l}$) in 321 patients (76.2%), detectable below the
 249 99th percentile MI cut-off ($0.03\text{--}0.066 \mu\text{g/l}$) in 44
 250 (10.5%), detectable above the 99th percentile MI cut-

t1.1 Table 1
 t1.2 Troponin T levels and associated acute coronary events and 30-day cardiac event rates

t1.3	Troponin T level number (%)	Acute coronary syndrome* % (#)	30-day cardiac events** % (#)
t1.4	Normal ($<0.03 \mu\text{g/l}$), 321 (76.2%)	16.8% (54)	1.3% (4)
t1.5	Detectable below 99th percentile MI cut-off ($0.03\text{--}0.066 \mu\text{g/l}$), 44 (10.5%)	29.5% (13)	4.8% (2)
t1.6	Detectable between 99th percentile and standard MI cut-off ($0.067\text{--}0.099 \mu\text{g/l}$), 14 (3.3%)	64.3% (9)	15.4% (2)
t1.7	Above standard cut-off ($\geq 0.1 \mu\text{g/l}$), 41 (9.8%)	85.4% (35)	12.5% (5)

t1.8 * $p < 0.001$ for trend.

t1.9 ** $p < 0.01$ for trend.

Table 2

Sensitivity, specificity, positive predictive value and negative predictive value of TnT at different cut-off values

TnT cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0.03 $\mu\text{g/l}$	98.3	88.4	57.6	99.7
0.067 $\mu\text{g/l}$	75.9	96.7	80	96.2
0.1 $\mu\text{g/l}$	60.3	98.3	85.4	93.9

PPV = positive predictive value, NPV = negative predictive value.

off, but below the standard MI cut-off ($0.067\text{--}0.099$
 $\mu\text{g/l}$) in 14 (3.3%) and $\geq 0.1 \mu\text{g/l}$ (above the standard
 cut-off) in 41 (9.8%). The diagnosis of an acute
 coronary syndrome was associated with increasing
 TnT values (16.8% in patients with normal TnT,
 29.5% in patients with TnT values below the 99th
 percentile MI cut-off value, 64.3% in patients with
 TnT values between the 99th percentile and standard
 MI cut-offs, and 85.4% in patients with a TnT ≥ 0.1
 $\mu\text{g/l}$) ($p < 0.001$ for the trend) (Table 1). Of the
 remaining 14.6% of patients with a TnT $\geq 0.1 \mu\text{g/l}$
 without a diagnosis of MI, two thirds (4/6) had
 cardiovascular diagnoses known to be associated with
 elevated TnT concentrations (congestive heart failure,
 pulmonary embolism and tachyarrhythmia) in associ-
 ation with documented coronary artery disease. MI
 was diagnosed in only 1 (0.3%) patient with a TnT
 concentration below the 99th percentile ($<0.067 \mu\text{g/l}$).
 By using a MI cut-off concentration determined
 from a “non-ACS” patient population, TnT would fail
 to detect as positive 11.7% of ACS subjects. The
 sensitivity, specificity, and positive and negative pre-
 dictive values for MI for TnT at 0.03 and $0.067 \mu\text{g/l}$
 are shown in Table 2 as compared to the manufactur-
 er’s cut-off of $0.1 \mu\text{g/l}$.

The 30-day post hospital clinical event rate (death
 or non-fatal MI) was 3.3% (13/399) for the entire
 cohort. Clinical events rates were increased with every
 concentration of detectable TnT (1.3% with normal
 TnT, 4.8% with detectable TnT concentrations below
 the 99th percentile MI cut-off, 15.4% for detectable
 TnT above the 99th percentile but below the standard
 MI cut-off, and 12.5% for TnT $\geq 0.1 \mu\text{g/l}$; $p < 0.01$
 for all groups). Clinical events at follow-up were signif-
 icantly increased in patients with any TnT concentra-
 tion above the 99th percentile MI cut-off as compared
 to patients with lower values (13.2% vs. 1.7%;
 $p < 0.01$). Clinical events were similarly increased in

289 patients with increases in TnT below the 99th percent-
290 tile MI cut-off as compared to those with normal TnT
291 concentrations (4.8% vs. 1.3%; $p=0.01$). Outcomes
292 were similar in patients with TnT concentrations
293 between the 99th percentile MI cut-off and 0.1 $\mu\text{g}/$
294 l as compared to those above 0.1 $\mu\text{g}/\text{l}$ (15.4% vs.
295 12.5%; $p=0.71$). Utilizing the GOLDminer method,
296 TnT determinations accounted for 45% of the vari-
297 ability in predicted MI rates and 53% of the variability
298 in clinical event rates. Chest pain and ECG changes
299 did not add significantly to either predictive model
300 when TnT values were known.

301 4. Discussion

302 Minor elevations in TnT values are associated with
303 increased near term cardiovascular event rates in an
304 unselected group of patients with suspected myocar-
305 dial ischemia. TnT determinations above the 99th
306 percentile MI cut-off, based on ED patients without
307 acute coronary syndromes, have a similar prognostic
308 value to TnT concentrations above the traditional cut-
309 off limit. The presence of any detectable troponin T
310 added to risk, but the positive predictive value was
311 low. Our findings are consistent with prior studies of
312 the prognostic value of minor elevations in TnT
313 values in acute coronary syndromes [11,12]. Our
314 study is unique in that it enrolled a broad spectrum
315 of ED patients with suspected myocardial ischemia
316 and examined TnT values based on a reference ED
317 cohort (and not a healthy reference population). TnT
318 increases above the 99th percentile reference group
319 value had a similar prognostic value as TnT above the
320 standard cut-off limit. Both high and low risk patients
321 were enrolled in our study and a significant number of
322 patients presented without chest discomfort. As chest
323 pain is absent in up to one third of MI patients in the
324 National Registry of Myocardial Infarction database
325 [13], cardiac biomarkers are routinely employed in a
326 diverse ED population with a variety of cardiopulmo-
327 nary complaints. Minor increases in TnT, in the
328 absence of other conditions associated with increased
329 troponins, have prognostic significance and may iden-
330 tify patients who benefit from an early invasive
331 strategy [12].

332 The presence of ST segment depression and chest
333 pain at presentation added little to our predictive

model. However, in this diverse population diagnostic 334
ST depression was present in only 12% and was 335
frequently found in conjunction with an abnormal 336
TnT determination. Of note, strict ECG criteria were 337
employed and non-specific ST depression was com- 338
mon in acute coronary patients given a high preva- 339
lence of resting baseline ST changes, ventricular 340
hypertrophy and conduction delays. Typical chest 341
pain in conjunction with diagnostic ST changes was 342
also infrequent (7.3%). Thus, minor increases of TnT, 343
even in the absence of diagnostic ECG changes or 344
characteristic chest pain, are of prognostic importance. 345
In contrast, ST depression is more common in select- 346
ed patients with acute coronary syndromes and is 347
associated with increased cardiac event rates in this 348
population, both in the presence and absence of 349
increased troponin concentrations [18]. 350

As suggested by the NACB and ESC/ACC com- 351
mittees [1,9], minor increases of TnT likely represent 352
true myocardial injury and have now been shown to 353
have prognostic significance in both low and high risk 354
groups with suspected myocardial ischemia in the 355
absence of ST segment elevation. Caution must be 356
used as precise troponin assays have been developed 357
that enable the detection of baseline concentrations of 358
TnT in healthy individuals. Residual troponin con- 359
centrations in healthy subjects likely represents apo- 360
ptotic turnover of myocardial tissue and not injury 361
[19] and may impair the specificity of TnT determi- 362
nations if lower cut-off values are used. Additionally, 363
there may be significant differences in the normal 364
reference ranges for troponins between males and 365
females and between Caucasians and African–Amer- 366
icans [20]. There can be up to a 13-fold variation 367
between the lowest and highest measured 99th per- 368
centile troponin values [20]. We agree, however, with 369
the NACB and AHA conclusions that elevations of 370
troponins between the upper limit of healthy controls 371
and MI limits reflect “myocardial injury” and should 372
prompt admission and aggressive treatment to reduce 373
cardiovascular risk in appropriate patients with sus- 374
pected myocardial ischemia. 375

The optimal troponin cut-off limit for therapeutic 376
decision making and prognostication remains elusive 377
at this time. The ESC/ACC joint committee recently 378
supported a single detection limit at the 99th percent- 379
tile of troponin concentrations among apparently 380
healthy controls at an appropriate concentration 381

(CV \leq 10%) of assay precision which is 0.01 $\mu\text{g/l}$ for TnT [1]. In patients with a clinical history consistent with myocardial ischemia, minor troponin increases add important prognostic information, but the positive predictive value is low. Utilizing a 99th percentile cut-off for a reference ED population with suspected myocardial ischemia improves the predictive value of minor TnT increases, but confirmation awaits further study. Caution is also advised as increases of cardiac troponins occur in other cardiopulmonary settings and will clearly complicate the interpretation of abnormal TnT values, especially in patients with a low clinical suspicion for myocardial ischemia [21]. If confirmed, the results from the current study will help in generalizing the predictive value of minor troponin increases in lower risk individuals. This approach may fail to identify some ACS patients with minor TnT elevations between the 99th percentile of an apparently healthy reference group and the 99th percentile of a “non-ACS” group. This approach is a trade-off between decreased diagnostic sensitivity and reduced specificity.

This study has several important limitations. Our 99th percentile MI detection limit for TnT differs markedly from that of a normal reference population (0.067 vs. 0.01 $\mu\text{g/l}$) and may not reflect the reference population at other institutions. A typical population of patients with suspected myocardial ischemia in whom a MI is “ruled out” contains many patients with conditions associated with TnT increases in the absence of acute coronary syndromes (congestive heart failure, pulmonary emboli, dysrhythmias, etc.). Additionally, many of these patients have established coronary artery disease and microvascular disease (left ventricular hypertrophy and diabetes) and may have silent ischemia, which can impact TnT concentrations [22–24]. In hemodialysis patients, an elevated TnT concentration is predictive of death and is a marker for extensive coronary artery disease in the absence of ischemic symptoms [22]. Similarly, microvascular disease from ventricular hypertrophy secondary to hypertension and diabetes has been proposed as a mechanism of elevated troponins in chronic renal failure patients [23,24]. Thus, it is not surprising that minor elevations of TnT are frequently found in patients with suspected myocardial ischemia, even in the absence of clinically apparent acute coronary syndromes.

Another major limitation of our study is the relatively small number of patients ($n=58$) with minor TnT increases below the standard 0.1 $\mu\text{g/l}$ cut-off limit. However, there appears to be a significant, albeit small, increment in risk even in patients with any detectable concentration of TnT below the 99th percentile MI cut-off as compared to patients with normal troponin concentrations (4.8% vs. 1.3%; $p=0.001$). Diagnostic ST segment depression added little to TnT determinations in the prediction of future cardiac events in our model, but there were relatively few patients with diagnostic ST depression in our study. As we employed strict ECG criteria in a diverse patient population, of which only one-quarter had acute coronary events, non-diagnostic ECG changes were fourfold as common as diagnostic ECG changes in our study population. The absence of diagnostic ECG changes is quite reflective of an unselected ED population of patients routinely ‘ruled out’ for MI and again calls attention to the utility of cardiac biomarkers in conjunction with clinical and electrocardiographic evaluation in clinical practice [25].

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