Quartiles of Peak Troponin Are Associated with Long-term Risk of Death in Type 1 and STEMI, but Not in Type 2 or NSTEMI Patients

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ABSTRACT

Background: The prognostic value of peak cardiac troponin (cTn) in different types of acute myocardial infarction (AMI) under the universal clinical classification is unknown.

Hypothesis: We tested the hypothesis that the prognostic value of cTn varies with its peak level and type of AMI.

Methods: We studied 345 consecutive patients with AMI with mean follow-up of 30.6 months according to quartiles of peak cTn level (QPTL) and the type of AMI. The study outcomes were the major adverse cardiovascular events (MACE; composite of all causes of mortality and recurrent AMI) and the individual components of MACE.

Results: The study included patients with AMI Type 1 (n = 276), type 2 (n = 54), ST-segment elevation myocardial infarction (STEMI; n = 159), and non-ST-segment elevation myocardial infarction (NSTEMI; n = 186). Overall, peak cTn level was an independent predictor of MACE (hazard ratio [HR]: 1.001, 95% confidence interval [CI]: 1.000–1.003, $P = 0.01$) and death (HR: 1.002, 95% CI: 1.001–1.004, $P = 0.003$), but not of recurrent AMI. The highest risk of MACE and death was in the highest QPTL (61.6%, $P = .016$ and 66.3%, $P = 0.021$, respectively) while the highest risk of recurrent AMI was in the lowest QPTL (83.7%, $P = 0.04$). Quartiles of peak cTn level were significantly associated with increased risk of MACE and death in patients with Type 1 (all $P = 0.01$) and STEMI ($P = 0.01$ and $P = 0.02$, respectively), but no association existed in type 2 or NSTEMI patients.

Conclusions: Overall, peak cTn predicts the risk of MACE and death but not the risk of AMI. While in Type 1 and STEMI patients, QPTL are associated with risk of MACE and death, no association exists in type 2 or NSTEMI patients.

Introduction

The universal clinical classification (UCC) of acute myocardial infarction (AMI) recommends cardiac troponin as the preferred biomarker of cardiomyocyte necrosis.[1,2] Cardiac troponin (cTn) has higher sensitivity and specificity for necrosis, its peak level better correlates with infarct size, and is a better predictor of short-term[3–6] and long-term[5–12] risk of death than creatine kinase-MB (CK-MB).[13–18] However, the long-term outcomes of patients with AMI based on peak cTn level in different categories of the UCC as compared to the ST-segment classification are unknown. We aimed to identify subgroups of AMI patients at higher risk who may benefit from more intense interventions.

Methods

Study Population

This is a prospective cohort study of 345 consecutive patients from a single tertiary hospital with a discharge diagnosis of AMI from December 31, 2004 until December 31, 2006 who met the study criteria. Patients were followed prospectively for a minimum of 24 months until December 31, 2007. We performed a retrospective reclassification of AMI based on the 2007 UCC.

Inclusion and Exclusion Criteria

We included male and female patients, age > 30 years old, who met the UCC criteria for AMI (Appendix 1),[1] had angiographic documentation of ≥ 50% obstructive coronary artery disease (CAD), and completed at least 24 months

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of follow-up. We excluded patients: (1) with no evidence of rise and/or fall of cTn with at least 1 value above the 99th percentile of the upper reference limit (> 0.001μg/L), (2) with elevations of cTn in the absence of overt ischemic heart disease (Appendix 2),[1] (3) with metastatic cancer, (4) on comfort care only, or (5) refusing standard care for AMI.

Specific Aims and Study Hypothesis

We aimed to examine the long-term prognostic value of peak cTn in patients with AMI in a multivariate analysis. In addition, we studied the relationship between quartiles of peak cTn level (QPTL) and long-term outcomes in different types of AMI according to the UCC and ST-segment classifications. We tested the hypothesis that the prognostic value of cTn varies with its peak level and by type of AMI.

Study Outcomes

The study outcomes were major adverse cardiovascular events (MACE; composite of all causes of death and recurrent nonfatal AMI) and the individual components of MACE.

Study Follow-up and Outcomes Adjudication

Trained hospital personnel collected the data prospectively using the American College of Cardiology National Cardiovascular Data Registry's (NCDR); http://www.accncdr.com/WebNCDR/Common instrument for patients with AMI. The date of death was confirmed by cross-checking the National Death Index (NDI; www. cdc.gov/nchs) and Social Security Death Index (SSDI; ssdi.rootsweb.com) databases, and by reviewing death notes in the medical record. These databases were cross-checked on December 31, 2008 to ensure we captured all patients who died. Only 1 patient in our study did not have a social security number and was lost to follow-up. The date of the recurrent AMI was confirmed by cross-checking the institutional AMI admission roster list of patients and the billing records. Two physician investigators independently reviewed the medical records to complete the case report form, classify the type of AMI, and adjudicate outcomes. When disagreement existed, a third physician investigator resolved the conflict.

Definition and Classification of Acute Myocardial Infarction

Acute myocardial infarction was defined according to the UCC definition (Appendix 1)[1] and the subtypes of AMI according to the ST-segment classification[15,19] and the UCC (Appendix 3).[1] Only patients with Type 1 and type 2 AMI were included in this analysis. Types 3, 4a, 4b, and 5, while identified and tabulated, were not included due to the paucity of patients in these subgroups.

Definition of Quartiles of Peak cTn Levels

We defined the QPTL as 1st QPTL (cTn = 0.01–7.1 nanograms per milliliter [ng/mL]), 2nd QPTL (cTn = 7.2–22.35 ng/mL), 3rd QPTL (cTn = 22.36–85.72 ng/mL), and 4th QPTL (cTn = 85.73–500 ng/mL).

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation (SD) and compared using the t test, while categorical variables were summarized as frequencies and compared using the χ^2 test. Other statistical tests were used as appropriate. All tests were 2-sided with a P value < 0.05 considered significant. We performed a multivariate Cox proportional hazards analysis to identify independent predictors of outcomes. Peak cTn was entered both as a continuous variable and in quartiles (QPTL) in the multivariate analysis. Cumulative survival free of outcomes curves were constructed by the Kaplan-Meier method and the statistical differences between the curves were assessed by log-rank test. Statistical analysis was performed with SPSS/PC (version 14.0, SPSS Inc., Chicago, IL) software package by an independent statistician. The study was approved by the institutional review board. Informed consent was not necessary due to the observational nature of the study.

Results

Baseline Characteristics

The study population consisted of 345 patients with AMI, including ST-segment elevation myocardial infarction (STEMI; n = 159, 46.1%), non-ST-segment elevation myocardial infarction (NSTEMI; n = 186, 53.9%), Type 1 (n = 276, 80%), type 2 (n = 54, 15.7%), type 3 (n = 5, 1.4%), type 4a (n = 2, 0.6%), type 4b (n = 5, 1.4%), and type 5 (n = 3, 0.9%; Appendix 4). In the initial cohort of consecutive patients with a discharge diagnosis of AMI, 66 did not meet the inclusion and/or met the exclusion criteria and were not part of the analysis. Of these, 49 patients had no angiographic documentation of ≥ 50% obstructive CAD, 3 had no evidence of rise and/or fall of cTn, 7 had elevations of cTn in the absence of overt ischemic heart disease, 1 had metastatic cancer, 1 was on comfort care only, 4 refused the standard care for AMI, and 3 met multiple exclusion criteria.

The general demographic, clinical, laboratory, and angiographic characteristics of the study population are summarized in Table 1. Type 1 and type 2 patients were not significantly different. However, NSTEMI, as compared to STEMI, were slightly older and had more history of atherosclerosis, diabetes, hypertension, and 3-vessel CAD. The peak CK, CK-MB, and cTn levels were higher in patients with Type 1 compared to type 2 and in STEMI compared to NSTEMI patients (all $P < .01$). The 25th, 50th, and 75th percentile of peak cTn were 18.9, 41.4, and 158.5 ng/mL for STEMI and 4.8, 11.3, and 30.9 ng/mL for NSTEMI. Type 1 AMI patients were similarly distributed across QPTL, while a higher proportion of STEMI patients had cTn in the 4th QPTL (40%) as compared to the 1st QPTL (11.3%).

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Table 1. Demographic and Clinical Characteristics of Patients With Acute Myocardial Infarction

	Type 1 (n = 276)	Type 2 (n = 54)	*P* Value	STEMI (n = 159)	NSTEMI (n = 186)	*P* Value
Age (mean ± SD)	63.0 ± 11	61.1 ± 14	.35	61.1 ± 12	63.8 ± 11	.04
Males (%)	191 (69.2)	36 (66.7)	.75	110 (69.2)	125 (67.2)	.64
White (%)	193 (69.9)	35 (64.8)	.52	114 (71.7)	125 (67.2)	.35
BMI > 30 (%)	121 (43.8)	19 (35.2)	.29	60 (37.7)	84 (45.2)	.19
Current smokers (%)	118 (42.7)	22 (40.7)	.92	71 (44.7)	75 (40.3)	.36
Diabetes (%)	98 (35.5)	19 (35.2)	1	47 (29.6)	74 (39.8)	.07
Hypertension (%)	199 (72.1)	39 (72.2)	1	103 (64.8)	145 (78)	.01
Hyperlipidemia (%)	153 (55.4)	32 (59.3)	.55	80 (50.3)	112 (60.2)	.10
CAD (%)	138 (50)	26 (48.1)	.67	66 (41.5)	104 (55.9)	.01
CEAD (%)	40 (14.5)	9 (16.7)	.67	14 (8.8)	37 (19.9)	.006
PAD (%)	30 (10.9)	7 (13)	.63	8 (5)	31 (16.7)	.001
CKD (%)	45 (16.3)	13 (24.1)	.17	22 (13.8)	39 (21)	.12
Peak CK (mean ± SD)	1258 ± 179	647.4 ± 797	<.01	1884 ± 2243	629.7 ± 767	<.01
Peak CK-MB (mean ± SD)	88.0 ± 115	54.4 ± 62	<.01	132.2 ± 152	52.1 ± 68	<.01
Peak cTn level (mean ± SD)	74.2 ± 122	38.2 ± 72	<.01	117 ± 150	31.4 ± 56	<.01
Q1 (%)	67 (24.3)	18 (33.3)	.1	18 (11.3)	68 (36.5)	<.01
Q2 (%)	70 (25.4)	13 (24.1)	1	31 (19.5)	55 (29.6)	.03
Q3 (%)	67 (24.3)	16 (29.6)	.3	47 (29.5)	40 (21.5)	.1
Q4 (%)	72 (26.1)	7 (13)	.03	63 (39.6)	23 (12.4)	<.01
EF (mean ± SD)	45.1 ± 12	43.6 ± 13	.45	44 ± 11	46 ± 13	.25
Total cholesterol (mean ± SD)	169.1 ± 47	180.5 ± 56	.23	169 ± 41	171 ± 55	.69
LDL (mean ± SD)	103.7 ± 42	109.6 ± 43	.46	107 ± 42	102 ± 42	.33
HDL (mean ± SD)	37.2 ± 11	35.2 ± 8	.19	37.2 ± 11	36.8 ± 11	.76
Triglycerides (mean ± SD)	150 ± 123	170 ± 134	.40	145.4 ± 137	156.1 ± 112	.47
3-vessel CAD	85 (30.8)	14 (25.9)	.73	37 (23.3)	67 (36)	.01
PCI within 24 hrs of admission (%)	146 (52.9)	17 (31.5)	.35	110 (69.2)	44 (23.7)	<.01
Discharge medications (%)						
Aspirin	244 (88.4)	48 (88.9)	.68	143 (89.9)	159 (85.5)	.08
Clopidogrel	203 (73.5)	40 (74.1)	.44	126 (79.2)	125 (67.2)	.38
β-Blocker	234 (84.8)	52 (96.3)	.37	138 (86.8)	158 (84.9)	.07

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Table 1. (*Continued*)

	Type 1 (n = 276)	Type 2 (n = 54)	*P* Value	STEMI (n = 159)	NSTEMI (n = 186)	*P* Value
ACEI/ARB	210 (76.1)	42 (77.8)	.48	100 (62.9)	104 (55.9)	.34
Statin	161 (58.3)	35 (64.8)	.63	124 (78)	136 (73.1)	.81

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (kg/m²); CAD, coronary artery disease; CEAD, cerebral arterial disease; CK, creatine phosphokinase; CKD, chronic kidney disease; CK-MB, creatine phosphokinase-MB (ng/mL); cTn, cardiac troponin (ng/mL); EF, ejection fraction (%); HDL, high-density lipoprotein cholesterol (mg/dL); LDL, low-density lipoprotein cholesterol (mg/dL); NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; Q1, 1st quartile (0.1–7.1 ng/mL); Q2, 2nd quartile (7.2–22.35 ng/mL); Q3, 3rd quartile (22.36–85.72 ng/mL); Q4, 4th quartile (85.73–500 ng/mL); QPTL, quartile of peak cTn level; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.

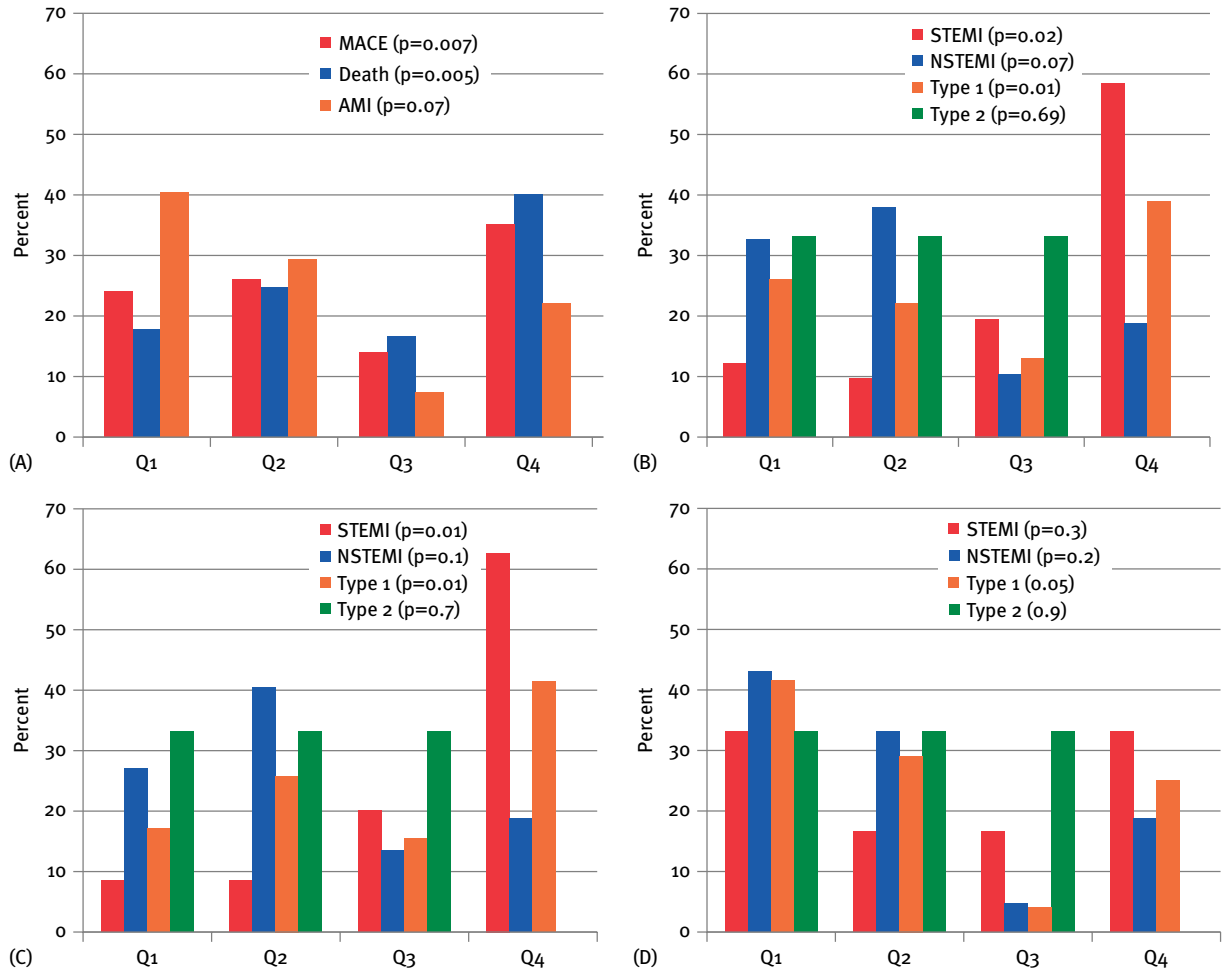

Figure 1. Outcomes per quartile of peak troponin level (A) overall, (B) MACE, (C) all causes of death, and (D) recurrent nonfatal AMI. Abbreviations: AMI, acute myocardial infarction; MACE, major adverse cardiovascular events; NSTEMI, non-ST-segment elevation myocardial infarction; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile; STEMI, ST-segment elevation myocardial infarction.

The opposite was true for NSTEMI (1st QPTL [36.5%] vs 4th QPTL [12.4%]) and for type 2 AMI (1st QPTL [33.3%] vs 4th QPTL [13%], Table 1).

Multivariate Analysis and Clinical Outcomes

The multivariate analysis revealed that continuous peak cTn level, but not QPTL was an independent predictor of

MACE and death. Peak cTn level (hazard ratio [HR]: 1.001, 95% confidence interval [CI]: 1.000–1.003, $P = .01$) and the UCC of AMI (HR: 0.441, 95% CI: 0.215–0.900, $P = 0.02$) were independent predictors of MACE at 30.6 months of follow-up. Similarly, peak cTn level (HR: 1.002, 95% CI: 1.001–1.004, $P = .003$) and the UCC of AMI (HR: 0.404, 95% CI: 0.182–0.896, $P = .02$) were independent predictors of death. CK-MB and ST-segment classification were not predictors of MACE or death. In contrast, peak CK-MB level (HR: 0.992, 95% CI: 0.984–0.999, $P = .02$) and ST-segment classification of AMI (HR: 3.115, 95% CI: 1.340–7.242, $P = .008$) were independent predictors of recurrent AMI while peak cTn level and the UCC were not.

Survival Analysis per QPTL

The overall risk of MACE (relative risk [RR]: 1.45, 95% CI: 1.43–1.48, $P = .006$) and death (RR: 2.22, 95% CI: 2.20–2.25, $P = 0.006$) were higher for patients in the 4th QPTL compared to the 1st QPTL (Figure 1). Patients in the 4th QPTL had a lower mean survival free of MACE and death of 24.8 and 26.4 months, respectively, compared to 27.8 and 30.9 months in the 1st QPTL (Figure 2 and Table 2). In contrast, the overall risk of recurrent AMI was higher for patients in the 1st QPTL compared to the 4th QPTL (RR: 1.83, 95% CI: 1.76–1.90, $P = 0.04$). For patients in the 1st QPTL the mean survival free of recurrent AMI was 32 months, compared to 33.7 months for patients in the 4th QPTL.

Clinical Outcomes and QPTL

Overall, the risk of MACE was significantly associated with QPTL ($P = 0.007$; Table 2). In fact, of the 99 patients who experienced MACE, 24 (24.2%) were in the 1st QPTL, while 35 (35.3%) were in the 4th QPTL (Figure 1). Similarly, risk of death was also significantly associated with QPTL ($P = 0.005$). Of the 72 patients who died, 13 (18.1%) were in the 1st QPTL while 29 (40.3%) were in the 4th QPTL. On the other hand, the risk of recurrent AMI was not associated with QPTL ($P = 0.07$).

Types of AMI, QPTL, and Clinical Outcomes

We observed a significant association between QPTL and the risk of MACE and death in patients with Type 1 (all $P = .01$) and STEMI ($P = 0.02$ and $P = 0.01$, respectively), but no association existed for type 2 and NSTEMI patients (Figure 3). Indeed, Type 1 patients in the 4th QPTL had 1.5 times (95% CI: 1.47–1.52, $P = .01$) higher risk of MACE and 2.4 times (95% CI: 2.38–2.42, $P = .01$) higher risk of death as compared to those in the 1st QPTL. Similarly, STEMI patients in the 4th QPTL had 4.8 times (95% CI: 4.75–4.84, $P = .02$) higher risk of MACE and 7.3 times (95% CI: 7.28–7.33, $P = 0.01$) higher risk of death than those in the 1st QPTL. No patients with type 2 AMI and cTn in the 4th QPTL experienced an event. There was a trend towards

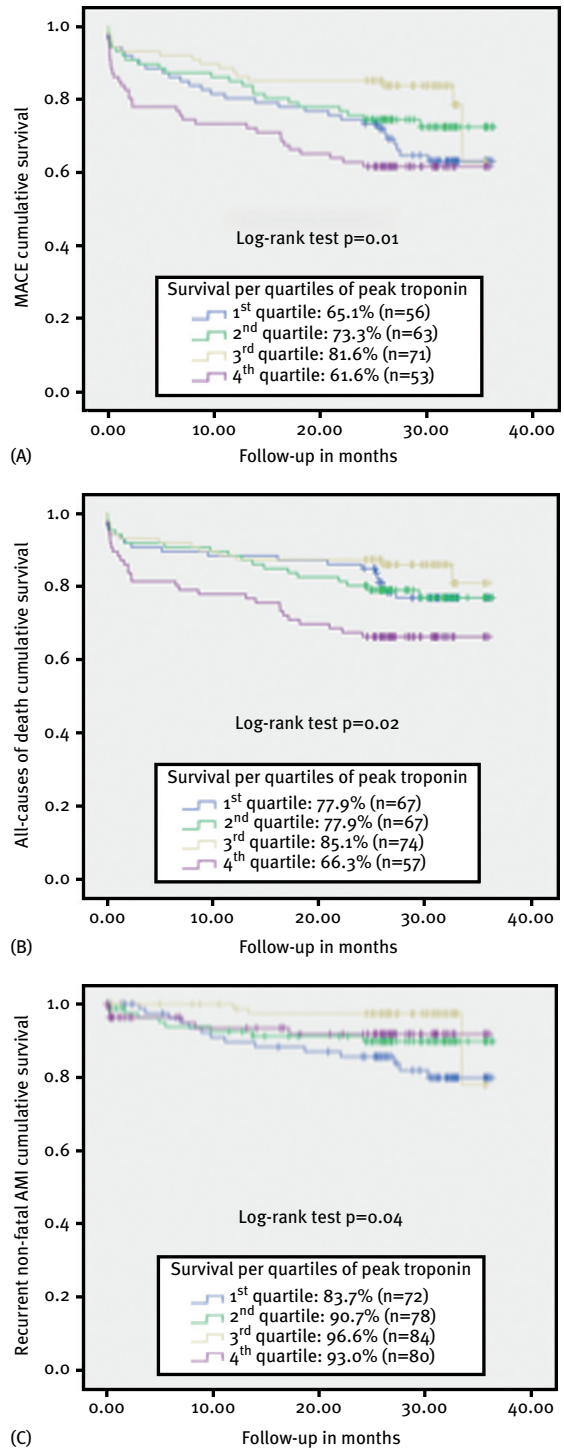

Figure 2. Kaplan-Meier cumulative survival free of events per quartile of peak troponin level (A) MACE, (B) all causes of death, and (C) recurrent nonfatal myocardial infarction. Abbreviations: MACE, major adverse cardiovascular events.

Table 2. Rate of MACE, All Causes of Death, and Recurrent Nonfatal Acute Myocardial Infarction at 24 Months of Follow-up per Quartile of Peak Troponin Level

Clinical Outcome	Type of AMI	Q1 (n = 86)	Q2 (n = 86)	Q3 (n = 87)	Q4 (n = 86)	Total	*P* Value
MACE, n = 91 (26.4%)	Overall	24 (24.2)	26 (26.3)	14 (14.1)	35 (35.4)	99	.007
	Type 1	20 (26)	17 (22.1)	10 (13)	30 (39)	77	.01
	Type 2	3 (33.3)	3 (33.3)	3 (33.3)	0	9	.69
	STEMI	5 (12.2)	4 (9.8)	8 (19.5)	24 (58.5)	41	.02
	NSTEMI	19 (32.8)	22 (37.9)	6 (10.3)	11 (19)	58	.07
	Survival (mean [95% CI])[a]	27.8 (25.1–30.5)	29.2 (26.6–31.9)	30.6 (28.2–33)	24.8 (21.6–28)	28.3 (26.9–29.7)	.01
All causes of death, n = 72 (20.9%)	Overall	13 (18.1)	18 (25)	12 (16.7)	29 (40.3)	72	.005
	Type 1	10 (17.2)	15 (25.9)	9 (15.5)	24 (41.4)	58	.01
	Type 2	2 (33.3)	2 (33.3)	2 (33.3)	0	6	.76
	STEMI	3 (8.6)	3 (8.6)	7 (20)	22 (62.9)	35	.01
	NSTEMI	10 (27)	15 (40.5)	5 (13.5)	7 (18.9)	37	.11
	Survival (mean [95% CI])[a]	30.9 (28.5–33.3)	30.7 (28.2–33.1)	31.7 (29.5–34)	26.4 (23.4–29.4)	30.1 (28.8–31.4)	.02
Recurrent nonfatal AMI, n = 27 (7.8%)	Overall	11 (40.7)	8 (29.6)	2 (7.4)	6 (22.2)	27	.07
	Type 1	10 (41.7)	7 (29.2)	1 (4.2)	6 (25)	24	.05
	Type 2	1 (33.3)	1 (33.3)	1 (33.3)	0	3	.91
	STEMI	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	6	.37
	NSTEMI	9 (42.9)	7 (33.3)	1 (4.8)	4 (19)	21	.23
	Survival (mean [95% CI])[a]	32.1 (30–34.2)	33.5 (31.6–35.4)	34.7 (31.7–35.5)	33.6 (31.7–35.5)	33.7 (32.8–34.6)	.04

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; MACE, major adverse cardiovascular events; NSTEMI, non-ST-segment elevation myocardial infarction; Q1, 1st quartile (0.1–7.1 ng/mL); Q2, 2nd quartile (7.2–22.35 ng/mL); Q3, 3rd quartile (22.36–85.72 ng/mL); Q4, 4th quartile (85.73–500 ng/mL); STEMI, ST-segment elevation myocardial infarction.
Death equals all causes of death.
[a] Event-free mean survival time in months (95% CI).

a significant inverse association between QPTL and recurrent AMI in patients with Type 1 ($P = 0.05$). In fact, Type 1 patients in the 1st QPTL had 1.67 times (95% CI: 1.63–1.71, $P = 0.02$) higher risk of recurrent AMI than those in the 4th QPTL. No other type of AMI had a statistically significant association between QPTL and risk of recurrent AMI.

Discussion

Patients with Type 1 and STEMI have larger infarcts defined by higher peak cTn and CK-MB than type 2 and NSTEMI, which may be partially explained by the washout after reperfusion and the transmural extent of the infarction.[19] Despite this, as we previously reported, STEMI and NSTEMI patients have similar long-term risk of MACE, while Type 1 patients have significantly higher risk of MACE than type 2 patients.[20] Other studies have also found similar long-term mortality for NSTEMI and STEMI patients.[21–24]

Previous studies also suggest that AMI patients with positive cTn and negative CK-MB have a better prognosis.[11,25–27] We found that peak cTn level is an independent predictor of long-term risk of MACE and death, but not a predictor of recurrent AMI. In contrast, peak CK-MB is an independent predictor of recurrent AMI. The survival analysis demonstrated that, overall, patients in the 4th QPTL have higher risk of MACE and death with an early separation of the curves in the first month of follow-up. The opposite was

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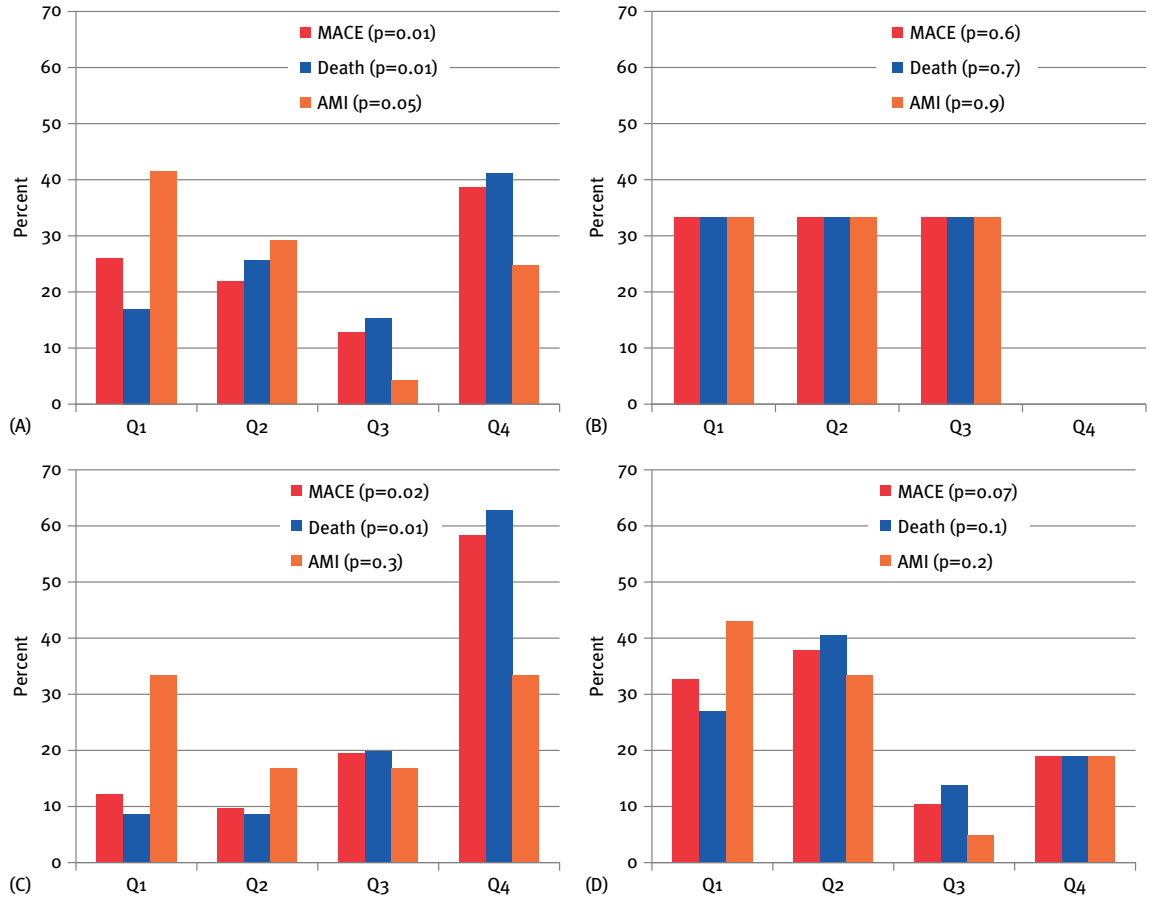

Figure 3. Type of acute myocardial infarction and outcomes per quartile of peak troponin level (A) Type 1, (B) type 2, (C) STEMI, and (D) NSTEMI. Abbreviations: AMI, acute myocardial infarction; MACE, major adverse cardiovascular events; NSTEMI, non-ST-segment elevation myocardial infarction; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile; STEMI, ST-segment elevation myocardial infarction.

true for patients in the 1st QPTL, who have a higher risk of recurrent AMI with late separation of the curves after 10 months of follow-up. Mueller et al found in 1024 patients with NSTEMI that cTn was an independent predictor of and had a linear relationship with 2-year mortality, with rates of 2.8%, 8.0%, 10.5%, and 14.8% from the lowest to highest cTn groups, respectively ($P < .001$). Contrary to our findings, they also reported that the rate of recurrent AMI was lower in the lowest cTn and higher in the highest cTn groups.[7]

Patients with Type 1 and STEMI have a significant association between QPTL and both MACE and death, but no association exists in type 2 and NSTEMI patients. Only Type 1 patients show a trend towards significant association between QPTL and the risk of recurrent AMI. Understanding the long-term risk of patients in the 1st QPTL (cTn < 7.1 ng/dL), the so-called low peak cTn level, is of high clinical importance and has not been well studied in different types of AMI. Type 1 and NSTEMI patients in the 1st QPTL have higher rates of death and recurrent AMI than type 2 and NSTEMI patients (Table 2). Calling the lowest QPTL a mild or small AMI may thus be misleading without considering the distinct long-term risk for different types of AMI.

Study Limitations

This study was conducted in a single institution with potential for selection, referral, and over-representation bias, and the results may not be generalizable to other regions. Second, we performed a retrospective redefinition of AMI based on the 2007 UCC,[1] which may be a source of misclassification bias despite our best efforts to minimize it. Third, we could have underestimated the rate of all causes of death and recurrent AMI. However, all patients in the study were followed prospectively and cross-checked using the NDI and SSDI databases to assess for death.

The sensitivity of the NDI is 97% to 98% and the specificity 100%.[28,29] Finally, the effects of other confounding variables and remaining bias cannot be completely excluded from the multivariate analysis.

Conclusions

Peak cTn level is an independent predictor of MACE and all causes of death but not of recurrent nonfatal AMI at 30.6 months mean follow-up. In contrast, peak CK-MB level is an independent predictor of recurrent nonfatal AMI. This is the first study reporting the clinical importance of QPTL on long-term clinical outcomes in different types of AMI under the UCC. The overall survival free of MACE, all causes of death, and recurrent nonfatal AMI is significantly different for patients in the different QPTL. While patients in the 4th QPTL overall have an early higher rate of MACE and all causes of death, patients in the 1st QPTL have a late higher rate of recurrent nonfatal AMI. Type 2 AMI has a similar rate of outcomes in the 1st, 2nd, and 3rd QPTL. Patients with Type 1 and STEMI have a significant association between QPTL and both MACE and death, but no association exists in type 2 and NSTEMI patients. Only Type 1 patients show a trend towards significant association between QPTL and the risk of recurrent AMI. In the near future, we aim to expand this research to patients with type 3, type 4a, type 4b, and type 5 AMI.

Acknowledgments

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Appendix 1

Definitions of acute myocardial infarction according to the 2007 expert consensus criteria for a universal definition (adapted):[1]

Acute myocardial infarction is present when there is evidence of myocardial necrosis (rise and/or a fall of troponin with at least 1 value above the 99th percentile of the upper reference limit, $> 0.001 \mu g/L$) in the clinical setting consistent with myocardial ischemia where any of the following criteria applies:

1. Symptoms of ischemia
2. ECG changes indicative of ischemia
3. Development of pathologic Q waves on the ECG
4. Image evidence of new loss of viable myocardium or new regional wall motion abnormality.

Appendix 2

Elevations of troponin in the absence of overt ischemic heart disease, as defined according to the 2007 expert consensus criteria for a universal definition of acute myocardial infarction (adapted):[1]

This includes cardiac contusion or other trauma including surgery, ablation, or pacing; congestive heart failure—acute and chronic; aortic dissection; aortic valve disease; hypertrophic cardiomyopathy; tachyarrhythmias or bradyarrhythmias, or heart block; apical ballooning syndrome or Takotsubo cardiomyopathy; rhabdomyolysis with cardiac injury; pulmonary embolism or severe pulmonary hypertension; renal failure; acute neurological disease, including stroke or subarachnoid hemorrhage; infiltrative diseases, for example, amyloidosis, hemochromatosis, sarcoidosis, and scleroderma; inflammatory diseases, for example, myocarditis or myocardial extension of endocarditis or pericarditis; drug toxicity or toxins; critically ill patients, especially those with respiratory failure or sepsis; burns, especially if affecting $> 30\%$ of body surface area; and extreme exertion.

Appendix 3

Universal clinical classification of acute myocardial infarction defines (adapted):[1]

- Type 1 as "spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection."
- Type 2 as "myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, for example, coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension."
- Type 3 as "sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST-elevation, or new left bundle branch block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood."
- Type 4a as "myocardial infarction associated with percutaneous coronary intervention with increase in troponin greater than $3 \times$ 99th percentile of the upper reference limit."
- Type 4b as "myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy."
- Type 5 as "myocardial infarction associated with coronary artery bypass graft with increase in troponin greater than $5 \times$ 99th percentile of the upper reference limit."

Appendix 4

Incidence and type of acute myocardial infarction according to universal and ST-segment classifications.

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Universal Classification of AMI (n = 345)							
	Type 1	Type 2	Type 3	Type 4a	Type 4b	Type 5	Total
Number	276	54	5	2	5	3	345
Percent	80	15.7	1.4	0.6	1.4	0.9	100

ST-Segment Classification of AMI			
	STEMI	NSTEMI	Total
Number	159	186	345
Percent	46.1	53.9	100

Abbreviations: AMI, acute myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

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