Symptoms Predictive of Acute Myocardial Infarction in the Troponin Era: Analysis From the TRAPID-AMI Study

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Abstract: The TRAPID-AMI (High Sensitivity Cardiac Troponin T assay for rapid Rule-out of Acute Myocardial Infarction) study evaluated a rapid "rule-out" acute myocardial infarction (AMI). We evaluated what symptoms were associated with AMI as part of a substudy of TRAPID-AMI. There were 1282 patients evaluated from 12 centers in Europe, the United States of America, and Australia from 2011 to 2013. Multiple symptom variables were prospectively obtained and evaluated for association with the final diagnosis of AMI. Multivariate logistic regression analysis was done, and odds ratios (OR) were calculated. There were 213/1282 (17%) AMIs. Four independent predictors for the diagnosis of AMI were identified: radiation to right arm or shoulder [OR = 3.0; confidence interval (CI): 1.8–5.0], chest pressure (OR = 2.5; CI: 1.3–4.6), worsened by physical activity (OR = 1.7; CI: 1.2–2.5), and radiation to left arm or shoulder (OR = 1.7; CI: 1.1–2.4). In the entire group, 131 (10%) had radiation to right arm or shoulder, 897 (70%) had chest pressure, 385 (30%) worsened with physical activity, and 448 (35%) had radiation to left arm or shoulder. Duration of symptoms was not predictive of AMI. There were no symptoms predictive of non-AMI. Relationship between AMI size and symptoms was also studied. For 213 AMI patients, cardiac troponins I values were divided into 4 quartiles. Symptoms including pulling chest pain, supramammillary right location, and right arm/shoulder radiation were significantly more likely to occur in patients with larger AMIs. In a large multicenter trial, only 4 symptoms were associated with the diagnosis of AMI, and no symptoms that were associated with a non-AMI diagnosis.

Key Words: myocardial infarction, symptoms, troponin

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It is estimated that in the United States each year more than 780,000 persons will experience an acute myocardial infarction (AMI).[1] In addition, 8 to 10 million individuals are evaluated for chest pain (CP) each year in emergency departments in the United States, making CP the second most common complaint.[2,3] However, only 15%–20% of these individuals are ultimately diagnosed with acute coronary syndrome (ACS).[4,5] CP accounts for ≈10% of all patient visits in the emergency department in the United States.[6] The estimated cost in evaluating these patients is $10–12 billion annually.[7] The electrocardiogram (ECG) and serial cardiac troponin (cTn) values are essential components in the evaluation of patients with possible ACS.[8–11] However, more than half of patients will have a nondiagnostic ECG.[12] The clinical presentation of AMI is most often CP, but some patients with AMI present with atypical symptoms rather than CP. It has been reported that that 33% of patients with AMI present without CP.[13]

A history consistent with AMI is an important element in the 2012 Universal Definition of AMI.[14] The first description of ischemic CP was described by Heberden in 1978: a painful sensation in the breast accompanied by a strangling sensation, anxiety, and occasional radiation of pain to the left arm, associated with exertion and relieved by rest.[15] The identification of typical symptoms in AMI has predominantly been based on studies utilizing creatine kinase-MB to identify myocardial necrosis.[16–20] Obtaining a good medical history, including CP characteristics, is a key component for the physician in the medical decision-making process. CP can be indicative of not only AMI but also various other disease processes, including pulmonary embolism and aortic dissection, which all have enormous impact on diagnostic and therapeutic strategies. History is integral in not only guiding management but also determining disposition between home, observation, or inpatient hospital admission. To streamline CP evaluation, multiple risk stratification scores for evaluating patients with possible ACS have been developed, including the HEART score[21] and the Emergency Department Assessment of Chest Pain score,[22] both of which include aspects of the presenting history.

Within a multicenter international trial, we sought to identify which symptoms, including quality of CP and associated symptoms, at presentation were associated with the diagnosis of AMI using a cTn definition of AMI. In addition, we analyzed symptoms in relation to the size of the AMI.

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METHODS

Study Design and Population

The study population consisted of a substudy analysis of the TRAPID-AMI (High Sensitivity Cardiac Troponin T assay for Rapid Rule-out of Acute Myocardial Infarction) study, which was a multicenter, international diagnostic study in the emergency department evaluating a rapid "rule-out" AMI protocol over 1 hour using changes in high sensitivity cTnT (Roche Diagnostics). More details of the study have previously been published.[23] There were 1282 patients evaluated in the emergency department for possible AMI from 12 centers in Europe, the United States of America, and Australia studied from 2011 to 2013. Patients were interviewed by research personnel to determine demographics and presenting symptoms at time of presentation to the emergency department. Multiple variables related to symptoms were prospectively obtained by research personnel. To perform the study, blood was drawn as quickly as possible, so a definite ECG interpretation was not required before inclusion. Accordingly, ST-segment elevation myocardial infarction (MI) patients were not excluded. Patients were excluded if they had renal failure requiring hemodialysis, and all participants provided written informed consent. Institutional review board approval was obtained before initiation of study.

Investigational cTn Analysis

Blood samples for determination of high sensitivity cTnT (Roche Diagnostics, Penzberg, Germany) and cardiac troponin I-Ultra (cTnI-Ultra; Siemens Healthcare, Malvern, PA) were collected at presentation and 1, 2, and 4–14 hours. After centrifugation, samples were frozen at −80°C until assayed using the Elecsys 2010 (Roche Diagnostics) instrument. The limit of detection, 10% coefficient of variation, and 99th percentile of a reference population have been reported at 5, 13, and 14 ng/L, respectively.[24] The cTnI-Ultra assay was performed using the Siemens ADVIA Centaur immunoassay system with a limit of detection, 10% coefficient of variation, and 99th percentile of 6, 30, and 40 ng/L, respectively.[25,26]

Outcomes

The diagnosis of AMI was centrally adjudicated by 2 independent cardiologists in accordance with the universal definition of AMI[14] and adjudicated by a third cardiologist in case of disagreement, using all available clinical information and serial measurements of cTnI-Ultra (Siemens Healthcare). AMI was diagnosed when there was evidence of myocardial necrosis on the basis of a significant rise or fall pattern of the cTn concentration in a setting consistent with myocardial ischemia (ischemic symptoms, ECG changes, or imaging evidence). The 99th percentile of this assay (40 ng/L) was used as a cutoff for myocardial necrosis. An absolute change of 20 ng/L or greater with the cTnI-Ultra assay during the study was used to define a significant rise and fall.[27]

Statistical Analysis

The statistical software used for analysis was version 9.4 of SAS (SAS Institute Inc, Cary, NC). The study variables have been summarized using means and SDs for numeric data along with frequencies and percentages for categorical data. The AMI group has been compared to the non-AMI group using 2-sample *t* tests for normally distributed numeric variables, Wilcoxon rank-sum tests for non-normally distributed numeric variables, the standard χ^2 test for nonsparse categorical variables, the Fisher exact test for sparse categorical variables, and the Cochran-Armitage trend test for ordinal variables. Variables with *P* values less than 0.25 from the AMI versus non-AMI presenting symptoms comparisons have participated in a multivariable logistic regression analysis as potential predictors of AMI. *P* values less than 0.05 have been considered statistically significant for both the group comparison results and the multivariable regression model. Furthermore, within the set of 213 AMI patients, the various patient demographics, comorbidities, and symptoms have been compared across the 4 quartiles of maximum TnI-Ultra using the Cochran-Armitage trend test. Again, for this exploratory study, *P* values less than 0.05 have been considered statistically significant.

RESULTS

Baseline demographic variables and electrocardiographic findings are shown for the study population (Table 1). Factors associated with the final diagnosis of AMI included older age, white, hypertension, smoking, prior AMI, history of percutaneous coronary intervention, cerebrovascular disease, and congestive heart failure. The electrocardiographic findings of left bundle branch block, paced ventricular rhythm, pathological Q waves, significant ST elevation, significant ST depression, and T wave inversion were also associated with a final diagnosis of AMI. Multiple variables related to CP symptoms by MI were prospectively obtained (Table 2).

TABLE 1. Demographics, Comorbidities, and ECG Characteristics by AMI Final Diagnosis Status

Variable	Non-AMI (N = 1069)	AMI (N = 213)	Comparison *P*
Age, y (mean ± SD)	60.5 ± 14.7	67.3 ± 14.4	<0.001 (T)
Sex			
Female	414 (38.7%)	63 (29.6%)	0.012 (C)
Male	655 (61.3%)	150 (70.4%)	
Race			
White	887 (83.0%)	198 (93.0%)	<0.001 (C)
Black	127 (11.9%)	9 (4.2%)	
Other	55 (5.1%)	6 (2.8%)	
History and comorbidities			
Hypertension	649 (61.3%)	156 (73.9%)	<0.001 (C)
Diabetes	217 (20.5%)	53 (25.4%)	0.118 (C)
Ever smoked	617 (58.7%)	139 (66.2%)	0.042 (C)
History of MI	248 (23.3%)	71 (34.0%)	0.001 (C)
History of coronary intervention	310 (29.3%)	78 (37.5%)	0.019 (C)
History of cerebrovascular disease	97 (9.1%)	33 (15.6%)	0.004 (C)
History of congestive heart failure	77 (7.3%)	30 (14.3%)	<0.001 (C)
ECG rhythm			
Left ventricular hypertrophy	51 (5.0%)	14 (7.0%)	0.261 (C)
Left bundle branch block	24 (2.3%)	12 (5.9%)	0.005 (C)
Right bundle branch block	42 (4.1%)	13 (6.4%)	0.141 (C)
Paced ventricular complex	15 (1.4%)	8 (3.9%)	0.017 (C)
Pathological Q waves	88 (8.6%)	31 (15.7%)	0.002 (C)
Significant ST elevation	40 (4.0%)	20 (10.2%)	<0.001 (C)
Significant ST depression	101 (10.0%)	63 (32.8%)	<0.001 (C)
T-inversion	130 (12.9%)	54 (28.0%)	<0.001 (C)

C indicates χ^2 test; T, 2-sample *t* test.

TABLE 2. Chest Pain Symptoms by AMI Final Diagnosis Status

Variable	Non-AMI (N = 1069)	AMI (N = 213)	*P*
Time to peak in minutes	370.6±1227.5	368.9±1312.4	0.434 (W)
Time to peak intervals, min			
<5	384 (39.9%)	64 (33.2%)	0.158 (C-A)
5–30	190 (19.8%)	45 (23.3%)	
>30	388 (40.3%)	84 (43.5%)	
Pressure	721 (72.0%)	176 (87.6%)	<0.001 (C)
Burning	252 (25.5%)	23 (11.7%)	<0.001 (C)
Stabbing	91 (9.3%)	22 (11.2%)	0.395 (C)
Pulling	57 (5.8%)	7 (3.6%)	0.206 (C)
Supramammilary right	75 (7.0%)	24 (11.3%)	0.034 (C)
Supramammilary left	341 (31.9%)	56 (26.3%)	0.106 (C)
Intramammilary	700 (65.5%)	166 (77.9%)	<0.001 (C)
Inframammilary right	55 (5.1%)	10 (4.7%)	0.785 (C)
Inframammilary left	225 (21.0%)	29 (13.6%)	0.013 (C)
Only extrathoracic	39 (3.6%)	8 (3.8%)	0.939 (C)
Physical activity dependent	303 (30.4%)	82 (41.2%)	0.003 (C)
Pressure on point dependent	163 (16.6%)	22 (11.4%)	0.067 (C)
Movement dependent	149 (15.0%)	16 (8.2%)	0.011 (C)
Breathing/coughing dependent	238 (23.9%)	30 (15.3%)	0.008 (C)
Emotional/psychological dependent	144 (15.4%)	18 (9.4%)	0.030 (C)
Cervical radiation	191 (17.9%)	47 (22.1%)	0.150 (C)
Right shoulder or arm radiation	80 (7.5%)	51 (23.9%)	<0.001 (C)
Left shoulder or arm radiation	349 (32.6%)	99 (46.5%)	<0.001 (C
Dorsal radiation	153 (14.3%)	36 (16.9%)	0.330 (C)
Ventral radiation	67 (6.3%)	11 (5.2%)	0.539 (C)
Right leg radiation	1 (0.1%)	0 (0.0%)	1.000 (F)
Left leg radiation	7 (0.7%)	0 (0.0%)	0.608 (F)
Dyspnea	530 (49.6%)	114 (53.5%)	0.299 (C)
Intensity of pain intervals			
Mild (0–2)	63 (5.9%)	10 (4.7%)	0.141 (C-A)
Moderate (3–8)	857 (80.3%)	165 (77.8%)	
Severe (9–10)	147 (13.8%)	37 (17.5%)	
Abrupt start of pain	584 (55.7%)	113 (53.6%)	0.563 (C)
Similar pain episode intervals			
Never	279 (26.2%)	56 (26.3%)	0.343 (C-A)
Today	107 (10.0%)	24 (11.3%)	
1–30 d	383 (36.0%)	88 (41.3%)	
>30 d	296 (27.8%)	45 (21.1%)	

C-A indicates Cochran-Armitage trend test; F, Fisher exact test; W, Wilcoxon rank-sum test.

There were 213/1282 (17%) AMIs, consisting of 21 ST-segment elevation MIs and 192 non–ST-segment elevation MIs. A total of 17 presenting symptoms variables were independently analyzed in relationship to a diagnosis of AMI on presentation (Table 3). For the multivariable logistic regression analysis that used CP symptoms to predict MI on presentation, 932 of the 1282 TRAPID patients had a full set of information and could be utilized for analysis.

TABLE 3. Multivariable Logistic Regression Results Using Chest Pain Symptoms to Predict AMI on Presentation

Variable	*P*	Odds Ratio	Odds Ratio 95% Confidence Limits	
Time to peak intervals	0.623	1.055	0.851	1.309
Pressure	0.004*	2.475	1.330	4.606
Physical activity dependent	0.006*	1.712	1.167	2.512
Right shoulder or arm radiation	<0.001*	3.016	1.803	5.045
Left shoulder or arm radiation	0.012*	1.654	1.118	2.447
Intramammilary	0.545	0.859	0.526	1.404
Inframammilary left	0.142	0.664	0.384	1.147
Burning	0.340	0.738	0.395	1.378
Pulling	0.913	0.949	0.373	2.417
Pressure on point dependent	0.189	0.637	0.325	1.249
Movement dependent	0.128	0.581	0.289	1.168
Breathing/coughing dependent	0.200	0.710	0.420	1.199
Emotional/psychological dependent	0.126	0.608	0.322	1.150
Cervical radiation	0.087	1.459	0.946	2.250
Supramammilary right	0.793	1.096	0.554	2.168
Supramammilary left	0.105	0.672	0.416	1.086
Intensity of pain intervals	0.175	1.367	0.870	2.146

Variables with comparison *P* values less than 0.25 from Table 2 were allowed to participate in this regression analysis.

On multivariable logistic regression analysis, 4 independent predictors for the diagnosis of AMI at presentation were identified: radiation to right arm or shoulder [odds ratio (OR) = 3.0; confidence interval [CI]: 1.8–5.0], chest pressure (OR = 2.5; CI: 1.3–4.6), worsened by physical activity (OR = 1.7; CI: 1.2–2.5), and radiation to left arm or shoulder (OR = 1.7; CI: 1.1–2.4; Table 3). Patients with 1 or more of these symptoms were more likely to have AMI (Fig. 1; $P < 0.05$). In the entire group, 131 (10%) had radiation to right arm or shoulder, 897 (70%) had chest pressure, 385 (30%) worsened with physical activity, and 448 (35%) had radiation to left arm or shoulder. Duration of symptoms was not predictive of AMI. No negative predictors of AMI were identified, including breathing or coughing dependent CP, palpation-induced CP, and movement dependent CP.

Relationship between myocardial infarct size and AMI symptoms was also studied. For 213 AMI patients, troponins were divided into 4 quartiles, defined as a maximum cTnI reading less than 130 ng/L (quartile 1), 130–740 ng/L (quartile 2), 740–5300 (quartile 3), and 5300 or greater (quartile 4). Pulling CP, supramammillary right location, and right arm/shoulder radiation were significantly more likely to occur within the higher quartile patients (Table 4). On the other hand, ventral radiation was significantly more likely to occur within the lower quartile patients.

DISCUSSION

In this international multicenter study where multiple symptoms were prospectively recorded in CP patients evaluated in the emergency department for possible AMI, we report several major findings. We found that there were only 4 symptoms that were independently predictive of AMI: radiation to right arm or shoulder (OR = 3.0; CI: 1.8–5.0), chest pressure (OR = 2.5; CI: 1.3–4.6), CP worsened by physical activity (OR = 1.7; CI: 1.2–2.5), and radiation to left arm or shoulder (OR = 1.7; CI: 1.1–2.4). No individual symptom was very predictive of AMI; however, if patients had more than

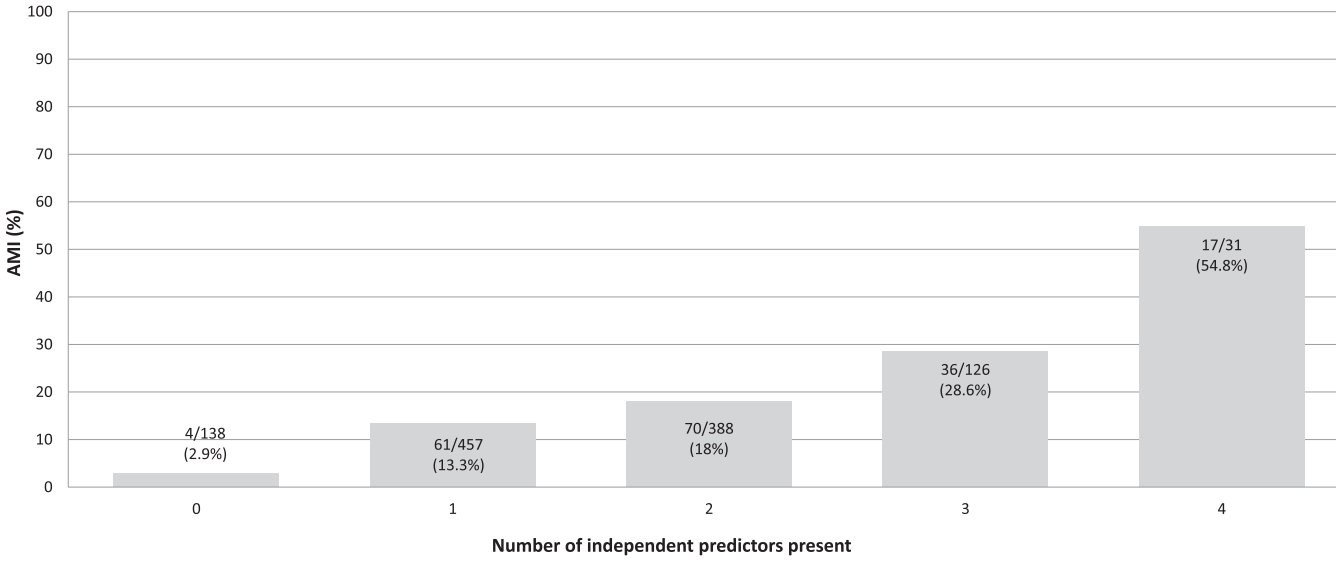

FIGURE 1. Acute myocardial infarction and the number of independent predictors.

1 of the 4 symptoms, the diagnosis of AMI was much more likely. For patients who had all 4 symptoms, 55% had a diagnosis of AMI, but there were only 31/1282 (2.4%) such patients in the overall study. Furthermore, in prior publications, CP that is described as pleuritic, sharp, positional, or worse on palpation was associated with a non-AMI diagnosis.[7,28] However, in our study, we did not find any symptoms that were independently associated with a non-AMI diagnosis.

Historically, it has been taught that normal duration of angina pectoris is 2–10 minutes, unstable angina 10–30 minutes, with AMI or nonischemic etiology resulting in more than 30 minutes of discomfort.[7] Intensity of pain, abrupt start of pain, and prior similar pain episode intervals were also not predictive of AMI. There was no correlation observed between duration of symptoms and diagnosis of AMI. The reasons for these findings are uncertain but might relate to smaller AMIs being identified by cTn as many prior studies used a creatine kinase-MB definition of AMI.

Some findings of this study are consistent with prior investigations. Chest pressure, CP worsened by physical exertion, radiation

TABLE 4. Symptoms Related to Myocardial Infarct Size

	Quartiles of the Maximum TnI Ultra (N=213), ng/L				
	1 (<0.130)	**2 (0.130–0.738)**	**3 (0.739–5.303)**	**4 (≥5.304)**	**C-A *P***
Pressure chest pain	44 (83.0%)	46 (86.8%)	42 (79.2%)	44 (81.5%)	0.601
Stabbing chest pain	6 (11.3%)	5 (9.4%)	4 (7.5%)	7 (13.0%)	0.865
Burning chest pain	7 (13.2%)	4 (7.5%)	8 (15.1%)	4 (7.4%)	0.600
Pulling chest pain	0 (0.0%)	1 (1.9%)	2 (3.8%)	4 (7.4%)	0.037
Supramammillary right	3 (5.7%)	4 (7.5%)	5 (9.4%)	12 (22.2%)	0.009
Supramammillary left	14 (26.4%)	14 (26.4%)	11 (20.8%)	17 (31.5%)	0.717
Intramammillary	40 (75.5%)	39 (73.6%)	44 (83.0%)	43 (79.6%)	0.390
Inframammillary right	1 (1.9%)	4 (7.5%)	2 (3.8%)	3 (5.6%)	0.669
Inframammillary left	6 (11.3%)	9 (17.0%)	8 (15.1%)	6 (11.1%)	0.900
Only extrathoracic	2 (3.8%)	4 (7.5%)	1 (1.9%)	1 (1.9%)	0.346
Physical activity trigger	23 (43.4%)	24 (45.3%)	20 (37.7%)	15 (27.8%)	0.067
Pressure on point trigger	5 (9.4%)	9 (17.0%)	5 (9.4%)	3 (5.6%)	0.300
Movement trigger	4 (7.5%)	2 (3.8%)	5 (9.4%)	5 (9.3%)	0.566
Breathing/coughing trigger	10 (18.9%)	10 (18.9%)	5 (9.4%)	5 (9.3%)	0.073
Emotional/psychological trigger	4 (7.5%)	2 (3.8%)	5 (9.4%)	7 (13.0%)	0.229
Cervical radiation	13 (24.5%)	11 (20.8%)	10 (18.9%)	13 (24.1%)	0.02
Right shoulder or arm radiation	7 (13.2%)	12 (22.6%)	14 (26.4%)	18 (33.3%)	0.014
Left shoulder or arm radiation	23 (43.4%)	22 (41.5%)	27 (50.9%)	27 (50.0%)	0.339
Dorsal radiation	13 (24.5%)	7 (13.2%)	5 (9.4%)	11 (20.4%)	0.488
Ventral radiation	7 (13.2%)	2 (3.8%)	0 (0.0%)	2 (3.7%)	0.018
Dyspnea	27 (50.9%)	29 (54.7%)	31 (58.5%)	27 (50.0%)	0.981

C-A indicates Cochrane Armitage trend test.

to left arm or shoulder, and radiation to right arm or shoulder have been shown to be predictive of AMI.[29] However, our study is at variance with some prior trials. Of note, there were no symptoms that were predictive of non-AMI, which is different than some other trials[10,29] that have shown that some atypical symptoms are associated with a non-AMI diagnosis. In addition, prior prospective trials commonly used a creatine kinase-MB definition of AMI[16–20]; however, these were mostly single center and did not do multivariate analysis to determine independent prediction of AMI.

There are few studies that have used a cTn definition of AMI, were multicenter, collected history of symptoms prospectively, and used multivariate analysis in evaluating patients with possible AMI in the emergency department. However, these trials have some notable differences when compared to ours. Rubini Gimenez et al[29] studied sex-specific differences in 736 patients evaluated for possible ACS. Differences in methodology were including patients with unstable angina (not just AMI) and using the discharging physician diagnosis to determine ACS, not independent review. They demonstrated that independent predictors of ACS were right or left shoulder pain and right or left arm pain in females while shortness of breath was predictive of not ACS in males. However, this was a very high-risk population with 301 (41%) patients ultimately being diagnosed with ACS. Patients had to have ECG changes or an elevated cTn at presentation, which differentiates it from our study. Goodacre et al[30] studied 1576 patients and found that only radiation to the right arm was independently associated with an AMI diagnosis. However, this study enrollment required patients to have a normal or nondiagnostic ECG, which differentiates it from ours. Gimenez et al[31] studied sex-specific CP characteristics in 2475 patients evaluated for possible AMI. Independent predictors of AMI were radiation to both shoulders in men and women, chest pressure in men, radiation to the left side of the chest in men, and radiation to the right side of the chest in men. Certain symptoms were associated with a non-AMI diagnosis: pain worse with breathing or palpation in men and women, pain in the lower part of the chest in men and women, and stabbing CP in men.

Our study is the first to report on how the size of the MI may relate to specific symptoms. For 213 AMI patients, troponins were divided into 4 quartiles, representing variance in infarct size. We found that patients with larger AMIs were more likely to have pulling CP, pain in the right upper chest (right supramammillary area), and right arm/shoulder radiation. Conversely, patients with smaller AMIs were more likely to have radiation of the pain to the back (ventral radiation). However, these symptoms occurred very uncommonly during AMI (0%–6.6%).

There are several limitations to our study. Only patients with CP were included in this study, and therefore, we cannot comment on symptoms when patients did not have CP. This is clinically important as there have been reports of 33% of patients with AMI who do not have any CP.[13] Diaphoresis, syncope, and change in sensorium were also not recorded in this study and is also a limitation. In addition, patients with very atypical, likely noncardiac symptoms might not have been enrolled in the study if the clinical suspicion of MI was low. Therefore, this could introduce a bias against symptoms that might be predictive of non-AMI.

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DISCLOSURES

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