Original Article

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Angiographic characteristics and in-hospital mortality among patients with ST-segment elevation myocardial infarction presenting without typical chest pain: an analysis of China Acute Myocardial Infarction registry

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Abstract

Background: Patients with ST-segment elevation myocardial infarction (STEMI) who present without typical chest pain are associated with a poor outcome. However, whether angiographic characteristics are related to a higher risk of mortality in this population is unclear. This study aimed to investigate whether the higher mortality risk in patients with STEMI without chest pain could be explained by their "high-risk" angiographic characteristics.

Methods: We used data of 12,145 patients with STEMI who was registered in China Acute Myocardial Infarction registry from January 2013 to September 2014. We compared the infarct-related artery (IRA), thrombolysis in myocardial infarction (TIMI) flow grade in the IRA, and other angiographic characteristics between patients without and those with chest pain. Multivariable logistic regression model was used to identify independent risk factor of in-hospital mortality.

Results: The 2922 (24.1%) patients with STEMI presented without typical chest pain. These patients had a higher TIMI flow grade (mean TIMI flow grade: 1.00 *vs.* 0.94, $P = 0.02$) and a lower rate of IRA disease of the left anterior descending artery (44.6% *vs.* 51.2%, $\chi^2 = 35.63$, $P < 0.01$) than did those with typical chest pain. Patients without chest pain were older, more likely to have diabetes, longer time to hospital and higher Killip classification, and less likely to receive optimal medication treatment and primary percutaneous coronary intervention and higher In-hospital mortality (3.3% *vs.* 2.2%, $\chi^2 = 10.57$, $P < 0.01$). After adjusting for multi-variables, presentation without chest pain was still an independent predictor of in-hospital death among patients with STEMI (adjusted odds ratio: 1.36, 95% confidence interval: 1.02–1.83).

Conclusions: Presentation without chest pain is common and associated with a higher in-hospital mortality risk in patients with acute myocardial infarction. Our results indicate that their poor prognosis is associated with baseline patient characteristics and delayed treatment, but not angiographic lesion characteristics.

Clinical trial registration: NCT01874691, https://clinicaltrials.gov.

Keywords: Myocardial infarction; Symptom assessment; Coronary angiography; Patient outcome assessment

Introduction

Although chest pain is the cornerstone of diagnosis for acute myocardial infarction (AMI), approximately one-third of these patients experience atypical symptoms other than chest discomfort.[1] Patients without chest pain were more common in female, older, and to present with non-ST-segment elevation myocardial infarction (STEMI).[2,3] Additionally, patients without chest pain were associated with less evidence-based treatment and worse in-hospital outcomes.[4,5]

Coronary angiography is currently the most common method for interventional cardiologists to assess coronary lesions and make revascularization decisions. Angiographic lesion characteristics are important prognostic factors, which may contribute to the difference in outcome between patients with and without chest pain. However, to date, there have been few large-scale studies

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on angiographic characteristics of patients with STEMI without typical chest pain.

The current study aimed to describe and compare angiographic characteristics and in-hospital outcomes of patients with STEMI with typical chest pain *vs.* those without typical chest pain, and to examine whether there is a difference in prognosis between the two groups, and if so, whether it can be explained by angiographic characteristics.

Methods

Ethical approval

The study was approved by the Institutional Review Board Central Committee at Fuwai Hospital, National Center for Cardiovascular Diseases, China (No. 2012-431). Written informed consent was obtained from eligible patients before registration.

Study population

A detailed description of the China Acute Myocardial Infarction (CAMI) registry has been reported previously.[6] Briefly, the CAMI registry was a prospective, multi-center registry that was conducted in China. The CAMI registry enrolled Chinese patients who were diagnosed with AMI. A total of 107 hospitals covering 27 provinces and four municipalities in China participated in the project, assuring a good representation of Chinese patients with AMI. This project was registered at www.clinicaltrials.gov and the registration number was NCT01874691.

Between January 1, 2013 and September 30, 2014, a consecutive cohort comprising 26,591 patients were enrolled in the CAMI registry. Eligible patients were diagnosed with AMI in accordance with the third universal definition of myocardial infarction.[7] For our study, the inclusion criteria were patients who were diagnosed with STEMI and those who underwent primary or selected percutaneous coronary intervention (PCI). By extracting data from the CAMI registry, we identified a cohort of 12,345 patients who met the inclusion criteria. We excluded 200 patients with missing or invalid data on age, with a final cohort of 12,145 patients for analysis.

Data collection and definitions

In the CAMI registry, data were collected by local well-trained cardiologists and were submitted through a secure data capture system, which helped assure accuracy of the data. In our study, we extracted data on patients' demographics, clinical presentation, medical history, coronary angiographic characteristics, management, and in-hospital mortality via electronic case report forms. Data on AMI symptoms in CAMI registry were collected in accordance with the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Task Force on clinical data standards[8] and National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network (NCDR ACTION) registry (http://www.NCDR.com). Symptoms presentation was registered as chest pain, chest pressure or discomfort, sweating, abdomen pain, back pain, jaw pain, dyspnea, syncope, sweating, nausea or vomiting. In our study, typical chest pain was defined as precordial or retrosternal chest pain lasting for more than 20 min, or other chest pressure or discomfort. Atypical symptom was defined as sweating, abdomen pain, back pain, jaw pain, dyspnea, syncope, sweating, nausea, or vomiting.

Coronary angiograms were interpreted by local interventional cardiologists. The thrombolysis in myocardial infarction (TIMI) flow grade was defined as previously.[9] The primary endpoint was all-cause in-hospital death. Other standardized definitions of the history and physical examinations are well described in the ACC/AHA Task Force on clinical Data Standards and the NCDR ACTION-Get With the Guidelines element dictionary.[10,11]

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (25th and 75th percentiles), and categorical variables are presented as counts (frequencies). The Student's *t* test and Chi-square test were used to examine the difference between the two study groups for continuous and categorical variables, respectively. The non-parametric median test was used for comparison of medians. We used multivariate analysis to investigate independent risk factors of in-hospital mortality. Univariate analysis was first performed to explore the association between each variable and in-hospital mortality. Then variables with $P < 0.25$ were fitted in the multivariate model using stepwise selection method with entry and exit criteria $P < 0.05$. We did not calculate sample size since this was a registry-based retrospective study and we wanted to enroll as many patients as possible. All *P* values were two-tailed, and a *P* value of <0.05 was considered statistically significant. All analyses were performed with the SAS 9.4 system (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

The 2922 (24.1%) STEMI presented without typical chest pain on admission. Patients without chest pain were significantly older (60.99 ± 11.78 years *vs.* 59.73 ± 11.80 years, $t = -5.04$, $P < 0.01$) and more likely to have diabetes (20.0% *vs.* 17.8%, $\chi^2 = 7.32$, $P < 0.01$) compared to patients with typical chest pain. Patients without chest pain had a longer time to hospital admission and higher Killip classification compared to patients with typical chest pain [Table 1].

Angiographic characteristics

Patients without chest pain had a significantly higher proportion of infarct-related artery (IRA) disease of the right coronary artery (RCA) (42.9% *vs.* 36.9%, $\chi^2 = 31.00$, $P < 0.01$) and a lower rate of IRA disease in the left anterior descending coronary artery (44.6% *vs.*

Table 1: Baseline characteristics of patients with STEMI with or without chest pain.

Variables	With chest pain ($n = 9223$)	Without chest pain ($n = 2922$)	Statistics	P
Age (years)	59.73 ± 11.80	60.99 ± 11.78	−5.04*	<0.01
Female	1806/9223 (19.6)	561/2922 (19.2)	0.21†	0.65
BMI (kg/m^2)	24.66 ± 8.82	24.60 ± 12.98	0.22*	0.83
Prior MI	461/9165 (5.0)	139/2890 (4.8)	0.23†	0.63
Prior HF	60/8810 (0.7)	24/2770 (0.9)	0.97†	0.33
Prior PCI	291/9148 (3.2)	104/2869 (3.6)	1.32†	0.25
Prior CABG	14/9160 (0.2)	7/2881 (0.2)	0.95†	0.33
Hypertension	4418/9183 (48.1)	1368/2895 (47.3)	0.65†	0.42
Hyperlipidemia	718/9171 (7.8)	231/2894 (8.0)	0.07†	0.79
DM	1630/9169 (17.8)	579/2891 (20.0)	7.32†	<0.01
Family history of pre-mature CAD	388/9164 (4.2)	105/2889 (3.6)	2.06†	0.15
Smoking status			19.39†	<0.01
Non-smoker	3496/9151 (38.2)	1221/2887 (42.3)		
Previous smoker	835/9151 (9.1)	280/2887 (9.7)		
Current smoker	4820/9151 (52.7)	1386/2887 (48.0)		
Time to hospital			171.69†	<0.01
1–7 days	1390/9178 (15.1)	732/2883 (25.4)		
12.0–23.9 h	807/9178 (8.8)	283/2883 (9.8)		
6.0–11.9 h	1656/9178 (18.0)	503/2883 (17.4)		
3.0–5.9 h	2804/9178 (30.6)	746/2883 (25.9)		
<3.0 h	2521/9178 (27.5)	619/2883 (21.5)		
SBP (mmHg)	127.79 ± 24.39	125.56 ± 25.06	4.24*	<0.01
DBP (mmHg)	79.16 ± 15.60	77.47 ± 21.98	3.82*	<0.01
HR (beats/min)	76.33 ± 16.85	75.79 ± 17.28	1.50*	0.13
Killip classification			11.96†	<0.01
I	7401/9157 (80.8)	2264/2882 (78.6)		
II	1312/9157 (14.3)	434/2882 (15.1)		
III	201/9157 (2.2)	79/2882 (2.7)		
IV	243/9157 (2.7)	105/2882 (3.6)		

Values are presented as mean ± standard deviation and *n*/*N* (%). *t values, †χ^2 values. STEMI: ST-segment elevation myocardial infarction; BMI: Body mass index; MI: Myocardial infarction; HF: Heart failure; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; DM: Diabetes mellitus; CAD: Coronary artery disease; SBP: Systolic blood pressure DBP: Diastolic blood pressure; HR: Heart rate.

51.2%, $\chi^2 = 35.63$, $P < 0.01$) compared to patients with chest pain. Patients without chest pain had a significantly lower rate of thrombus (53.0% *vs.* 56.7%, $\chi^2 = 13.33$, $P = 0.01$) and higher mean TIMI flow grade (1.00 *vs.* 0.94, $t = -2.36$, $P = 0.02$) compared to patients with typical chest pain. No significant difference in the number of diseased vessels was found between the two groups [Table 2].

Management and outcomes

During hospitalization, patients without chest pain were significantly less likely to receive aspirin (97.4% *vs.* 98.0%, $\chi^2 = 8.86$, $P = 0.01$), thienopyridine (97.9% *vs.* 98.5%, $\chi^2 = 15.62$, $P < 0.01$), statins (97.5% *vs.* 98%, $\chi^2 = 9.66$, $P < 0.01$), heparin (90.0% *vs.* 93.3%, $\chi^2 = 29.52$, $P < 0.01$), β-blockers (70.6% *vs.* 73.2%, $\chi^2 = 9.59$, $P < 0.01$), and primary PCI (64.9% *vs.* 73.9%, $\chi^2 = 85.66$, $P < 0.01$) than patients with chest pain. Patients without chest pain were significantly more likely to receive an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (60.9% *vs.* 58.8%, $\chi^2 = 8.42$, $P = 0.01$) and elective PCI (45.7% *vs.* 37.3%, $\chi^2 = 63.51$, $P < 0.01$) than patients with chest pain [Table 3].

Patients without chest pain had significantly higher in-hospital (3.3% *vs.* 2.2%, $\chi^2 = 10.57$, $P < 0.01$) and 30-day mortality rates (4.1% *vs.* 2.8%, $\chi^2 = 12.06$, $P < 0.01$) than did those with chest pain. Patients without chest pain also had a significantly higher rate of cardiac shock (4.3% *vs.* 3.3%, $\chi^2 = 6.19$, $P = 0.01$) and cardiac arrest (2.0% *vs.* 1.2%, $\chi^2 = 8.05$, $P < 0.01$) during hospitalization than did those with chest pain [Table 3]. After adjusting for age, sex, diabetes, hypertension, hyperlipidemia, previous angina, previous myocardial infarction, previous PCI, previous heart failure, previous coronary artery bypass graft, premature coronary artery disease, systolic blood pressure, heart rate, Killip classification, body mass index, anterior wall infarction, time to hospital admission, cardiac arrest, heart failure, cardiac shock, white blood cell count, and smoking status, atypical symptoms were still an independent predictor of in-hospital mortality in patients with STEMI (odds ratio: 1.36, 95% confidence interval: 1.02–1.83) [Table 4].

Discussion

In analysis of a large-scale, prospective registry, we found that a large proportion of patients with STAMI presented without typical chest pain and had a higher

Table 2: Angiographic characteristics of patients with STEMI with and without chest pain.

Variables	With chest pain ($n = 9223$)	Without chest pain ($n = 2922$)	Statistics	P
TIMI flow grade			17.81*	<0.01
0	5077/8918 (56.9)	1442/2719 (53.0)		
1	1206/8918 (13.5)	416/2719 (15.3)		
2	772/8918 (8.7)	285/2719 (10.5)		
3	1863/8918 (20.9)	576/2719 (21.2)		
Mean TIMI flow grade	0.94 (0.91, 0.96)	1.00 (0.95, 1.04)	–2.36†	0.02
Thrombus			13.33*	<0.01
No thrombus	3867/8925 (43.3)	1279/2719 (47.0)		
Primary thrombus	4934/8925 (55.3)	1413/2719 (52.0)		
In-stent thrombus	124/8925 (1.4)	27/2719 (1.0)		
No. of diseased vessel				
Single	2902/8925 (32.5)	837/2706 (30.9)	2.40*	0.12
Double	2775/8925 (31.1)	852/2706 (31.5)	0.15*	0.70
Triple	3244/8925 (36.3)	1030/2706 (38.1)	2.62*	0.11
Lesion location				
LM	166/8925 (1.9)	63/2706 (2.3)	2.27*	0.13
LAD	4475/8747 (51.2)	1197/2685 (44.6)	35.63	<0.01
LCX	927/8747 (10.6)	286/2685 (10.7)	<0.01*	0.94
RCA	3225/8747 (36.9)	1151/2685 (42.9)	31.00*	<0.01
Graft	3/9223 (0.0)	5/2922 (0.2)	NA	0.02‡

Values are presented as *n/N* (%) or mean (95% confidence interval). *χ^2 value, †*t* value, ‡Fisher test was used to compare the rate of Graft lesion between groups. STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis in myocardial infarction; LM: Left main; LAD: Left anterior descending coronary artery; LCX: Left circumflex artery; RCA: Right coronary artery; NA: Not available.

Table 3: Management and outcome of patients with STEMI with and without chest pain.

Variables	With chest pain	Without chest pain	χ^2	P
Medications during hospitalization				
Aspirin	8983/9168 (98.0)	2806/2881 (97.4)	8.86	0.01
Thienopyridine	8963/9100 (98.5)	2793/2854 (97.9)	15.62	<0.01
Statins	8476/8647 (98.0)	2596/2663 (97.5)	9.66	<0.01
Heparin	8320/8922 (93.3)	2486/2761 (90.0)	29.52	<0.01
β-blocker	6638/9063 (73.2)	2003/2837 (70.6)	9.59	<0.01
ACEI/ARB	5329/9056 (58.8)	1724/2830 (60.9)	8.42	0.01
Primary PCI	6791/ 9190 (73.9)	1888/2909 (64.9)	85.66	<0.01
Selective PCI	3377/9048 (37.3)	1305/2854 (45.7)	63.51	<0.01
In-hospital death	199/9131 (2.2)	95/2890 (3.3)	10.57	<0.01
Death within 30 days	252/9162 (2.8)	118/2902 (4.1)	12.06	<0.01
Heart failure	987/9114 (10.8)	322/2874 (11.2)	0.31	0.58
Cardiac shock	299/9109 (3.3)	123/2870 (4.3)	6.19	0.01
Fatal cardiac arrhythmia	610/9110 (6.7)	186/2875 (6.5)	0.18	0.67
Recurrent myocardial ischemia	171/9105 (1.9)	49/2868 (1.7)	0.35	0.55
Recurrent myocardial infarction	38/9105 (0.4)	14/2872 (0.5)	0.24	0.62
Cardiac arrest	113/9101 (1.2)	57/2866 (2.0)	8.05	<0.01
Stroke	44/9104 (0.5)	20/2870 (0.7)	1.76	0.18

Values are presented as *n/N* (%). STEMI: ST-segment elevation myocardial infarction; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptors blocker; PCI: Percutaneous coronary intervention.

in-hospital mortality rate compared to patients with typical chest pain. However, patients without chest pain had less severe lesions as assessed by angiography compared to patients with typical chest pain. Patients without chest pain had a higher proportion of IRA disease of the RCA, a lower rate of thrombus, and a higher TIMI flow grade compared to patients with chest pain. These characteristics indicated lower risk lesions. Therefore, the worse outcome of patients without chest pain was not due to severity of lesions as assessed by angiography. Patients without chest pain were older, more likely to have diabetes and a higher Killip classification, and were less likely to receive primary PCI compared to patients with typical chest pain. These findings indicated that a poor prognosis of patients without chest pain was associated with baseline characteristics and poor management, but not with angiographic characteristics. Multivariable regression results indicated that atypical symptoms were independent predictors of an increased risk of in-hospital death.

Table 4: Independent predictors of in-hospital mortality ($n = 12,145$).

Variables	OR (95% CI)
Male *vs*. female	0.65 (0.47–0.89)
Presentation without *vs*. with chest pain	1.36 (1.02–1.83)
Age	
65–74 years *vs*. <65 years	1.77 (1.14–2.73)
≥75 years *vs*. <65 years	4.02 (2.58–6.27)
Non-smoker *vs*. current smoker	1.63 (1.18–2.27)
SBP (per 1 mmHg increase)	0.98 (0.97–0.99)
HR (per 1 beat/min increase)	1.02 (1.01–1.03)
Killip classification IV *vs*. I	4.34 (2.80–6.71)
Primary PCI (yes *vs*. no)	0.27 (0.17–0.43)
Culprit vessel	
LAD (no *vs*. yes)	0.74 (0.56–0.99)
LM (no *vs*. yes)	0.13 (0.06–0.27)
Treatment *vs*. stent implantation	
PTCA	2.69 (1.66–4.36)
Thrombus aspiration only	3.04 (1.73–5.33)
No intervention	1.84 (1.25–2.70)

OR: Odd ratio; CI: Confidential interval; SBP: Systolic blood pressure; HR: Heart rate; PCI: Percutaneous coronary intervention; LAD: Left anterior descending coronary artery; LM: Left main; PTCA: Percutaneous transluminal coronary angioplasty.

The major novelty of our study was examining whether angiographic characteristics accounted for a poor prognosis in patients without chest pain. However, lesion characteristics may be associated with atypical symptoms. Sympathetic afferent nerves predominate on the anterior wall and parasympathetic afferent nerves predominate on the inferior and posterior wall. Therefore, left anterior descending coronary artery infarction predominately activates sympathetic pathways, leading to chest pain symptoms, while RCA infarction predominately activates parasympathetic pathways, leading to nausea and emesis. Another mechanism underlying cardiac pain was associated with chemical mediators including acids, adenosine, bradykinin, etc. When these chemical mediators are released into the coronary artery, they excite cardiac afferent fibers and this lead to the sensation of pain. Our finding of patients without chest pain with a higher TIMI flow grade indicated better coronary blood flow and a smaller size of the myocardial infarction. Therefore, the proportion of chest pain may be lower in these patients.

A worse prognosis in patients without chest pain may be associated with baseline patients' characteristics and management. We found that patients with STEMI without typical chest pain were older than those with typical chest pain. Previous studies also indicated that in patients with myocardial infarction[12-14] and acute coronary syndrome,[15] older patients were more likely to present without chest pain. In addition to atypical symptomatology, older patients were more likely to have comorbidities, multi-organ degeneration, and adverse drug events.[16] Therefore, optimal management of older patients with myocardial infarction is still challenging. Future studies are required to investigate strategies for reducing diagnosis and treatment delays.

Our study showed that the proportion of diabetes was higher in patients without typical chest pain than in those with typical chest pain. Data on clinical presentation of patients with diabetes and AMI are conflicting. Many previous studies showed similar results as in our study in that patients with atypical symptoms had a higher rate of diabetes than did those with typical chest pain.[13-15]

In contrast to our results, another study enrolled 4028 patients with first myocardial infarction from Sweden and found that the prevalence of typical symptom did not differ significantly between two groups.[17] The difference may be explained by study population. Atypical symptoms in patients with diabetes were previously reported to be associated with neuropathies.[19] Patients with diabetes were more likely to have vagal and sympathetic nerve neuropathies, which may affect activation of afferent nerves, and subsequently, perception of symptoms.[18] Prior studies suggested Swedish patients had better glucose control than those from other countries.[19] Therefore it is possible that the proportion of autonomic neuropathy and subsequent atypical symptom presentation was also lower in this population. Previous studies have also reported prolongation of the angina perception threshold in patients with diabetes, which may also explain the atypical symptomatology.[20] Of note, hyperglycemia was associated with higher in-hospital mortality risk in patients with AMI.[21]

Consistent with our results, previous studies have shown that patients without chest pain were less likely to receive optimal management, whereas early revascularization was associated with improved outcome in patients with STEMI.[22] Additionally, a time to hospital admission >12 h and a longer door-to-balloon time[23] were more common in patients without typical chest pain than in those with typical chest pain.

This article had certain limitations. First, we only included patients with STEMI. Future studies should expand the study population to enroll patients with non-STEMI. Second, another possible reason for increased mortality in patients without chest pain may be associated with delayed treatment. However, we did not collect data on door to balloon time. Third, the synergy between PCI with Taxus and cardiac surgery (SYNTAX) score was not collected in the registry. This score is an important prognostic factor. Finally, CAMI registry did not collect data on specific diabetes medication.

In conclusion, presentation without chest pain is common in patients with STAMI and is associated with an increased risk of in-hospital mortality. However, the increased mortality risk could not be explained by "high-risk" angiographic features, which indicates that a worse prognosis is associated with baseline patients' characteristics and management, but not with angiographic characteristics. Further study should be conducted to investigate predictors of atypical symptoms and the mechanisms underlying a high in-hospital mortality rate in patients without typical chest pain.

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Conflicts of interest

None.

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