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Clinical significance of diabetes on symptom and patient delay among patients with acute myocardial infarction—an analysis from China Acute Myocardial Infarction (CAMI) registry

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Abstract

Background Diabetes is frequently associated with poor prognosis among acute myocardial infarction (AMI) patients. Patients with these comorbidities often have atypical symptoms and subsequent delay in treatment. Few studies have reported detailed AMI symptoms in patients with diabetes. This study compared AMI symptoms and presentation characteristics between diabetics and non-diabetics. **Methods** We included patients from the China AMI registry diagnosed with AMI between January 2013 and September 2014. Baseline characteristics, symptomology, and delay in treatment were compared between diabetics and non-diabetics. Multivariable logistic regression analysis was used to explore independent predictors of atypical symptoms. **Results** A total of 4450 (20.2%) patients had diabetes. They were older, more often women, higher in body mass index, and more likely to have non-ST segment elevation myocardial infarction. Fewer diabetic patients presented with persistent precordial chest pain (63.1% *vs*. 68%, $P < 0.0001$), diaphoresis (60.1% *vs*. 65.6%, $P < 0.0001$), fatigue (16.7% *vs*. 18.3%, $P = 0.0123$), and incontinence (0.4% *vs*. 0.7%, $P = 0.0093$). Time to hospital presentation was longer among patients with diabetes than those without. In multivariable analysis, diabetes was identified as an independent predictor of atypical symptoms (OR: 1.112, 95% CI: 1.034–1.196). **Conclusions** Our study is the first large-scale study providing evidence that diabetics are less likely to present with typical chest pain and more likely to experience treatment delay when suffering from an AMI. Our results may increase clinician awareness of recognizing AMI patients rapidly to reduce diagnosis and treatment delay, particularly in the context of diabetes.

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Keywords: Acute myocardial infarction; Diabetes; Symptoms; Patient delay

1 Introduction

Diabetes has become an increasing burden all over the world. In 2014, the global prevalence of diabetes among adults was 8.5% with 422 million suffering from the disease.[1] Diabetes is associated with poor prognosis among patients with acute myocardial infarction (AMI).[2] Patients with diabetes are more likely to present with atypical symptoms[3] and are slower to receive treatment[4] when they have an AMI.

It is important for patients with diabetes to recognize possible symptoms of AMI and minimize their delay in seeking care. There are few large-scale studies of symptomology in patients with AMI complicated by diabetes. In the studies that have been performed, patients were simply classified into "chest pain" and "no chest pain" groups without detailed description of symptoms. These studies enrolled patients from Europe, the United States,[5,6] Japan[7] and Korea,[8] but there is limited data regarding the impact of diabetes on symptoms of AMI among Chinese patients.

The aim of this study was to describe symptoms and admission characteristics of AMI patients complicated by diabetes.

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2 Methods

2.1 Study population

Details of the China Acute Myocardial Infarction (CAMI) Registry have been previously described.[9] Briefly, the CAMI registry included 108 participating hospitals in 27 provinces and 4 municipalities in Mainland China, assuring a comprehensive representation of hospitals in China. From January 2013 to September 2014, a total of 26,082 patients were included in the CAMI registry. Patients diagnosed with AMI as defined by the third universal definition of myocardial infarction[10] were eligible. According to this definition, AMI is diagnosed by clinical evidence of myocardial necrosis consistent with myocardial ischemia, detection of a rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile upper reference limit (URL), and at least one of the following symptoms of ischemia: new or presumed-new significant ST-segment or T-wave (ST-T) changes or left bundle branch block (LBBB), development of pathological Q waves on ECG, imaging evidence of new loss of viable myocardium or new regional wall abnormality, or identification of intracoronary thrombus by angiography or autopsy.

Subjects with missing or invalid data for admission diagnosis, age, body mass index (BMI), and symptomology were excluded from the analysis. In the end, a total of 21,994 patients were included. They were divided into a diabetes group and a non-diabetes group according to the presence of diabetes (Figure 1).

This study was registered on www.clinicaltrials.gov (NCT01874691). Written informed consent was obtained from eligible patients before registration.

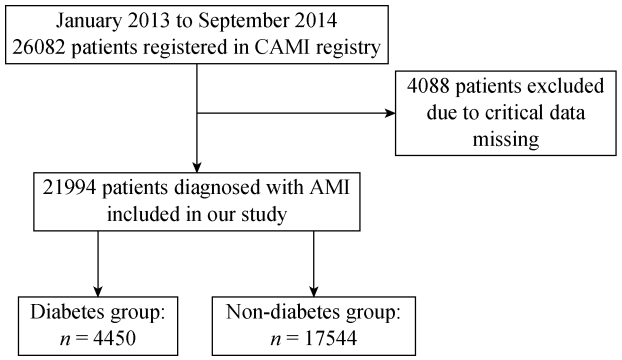

Figure 1. Study flow chart. From January 2013 to September 2014, a total number of 26,082 AMI patients were registered in CAMI registry. We excluded 4088 patients due to missing or invalid data on age, BMI, on admission diagnosis and symptomology and finally included 21,994 patients. Among these patients, 4450 patients had diabetes and 17544 patients were non-diabetes. CAMI: China acute myocardial infarction.

2.2 Data collection and definition

The CAMI registry adopted multiple measures to assure data quality. The investigators at each participating site received detailed training on the protocol and standardized data collection. The data entry system also had a real-time automatic logic and range algorithm to ensure the completeness, validity, and accuracy of the data quality. In addition, the data management team performed data checks regularly and sent queries for participating hospitals to review and revise the missing or invalid data. We extracted data on patient demographics, medical history, clinical presentation, time to hospital, and admission diagnosis. Symptom assessment included persistent chest pain (≥ 20 min), diaphoresis, nausea, vomiting, syncope, fatigue, and incontinence. Silent MI was defined as a heart attack with few symptoms. Atypical MI was defined as presentation without typical chest pain. The key point that differentiates atypical from typical AMI is typical precordial chest pain symptoms consistent with myocardial necrosis. The diabetes group included patients who used oral medication or insulin or those with known medical history of diabetes prior to hospital presentation, but did not include those with new-onset diabetes during hospitalization.

2.3 Statistical analysis

Continuous variables were presented as mean ± SD or median (25th and 75th percentiles) and compared using Student t tests or rank tests, as appropriate. Categorical variables were described using frequencies and compared using chi-square tests. A multivariable logistic regression model was introduced to explore independent predictors of atypical symptoms. The following factors were initially fitted in the model: age; sex; heart rate; blood pressure; BMI; prior history of primary percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, angina, stroke, diabetes, hypertension, hyperlipidemia, or heart failure (HF); type of MI; anterior wall MI; Killip classification; prodromal symptoms; smoking status; and family history of coronary artery disease (CAD). After stepwise selection, those variables with $P < 0.05$ were retained in the model. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, North Carolina).

3 Results

3.1 Baseline characteristics

Among the 21,994 patients eligible for our analysis, 4,450 (20.2%) patients had diabetes. Table 1 compares baseline characteristics between patients with and without

diabetes. Patient age ranged from 16 to 100 years, with a mean age of 62.9 ± 12.5 years. Compared with those without diabetes, patients with diabetes were older (mean age 64.4 *vs*. 62.6 years), more often women (33.2% *vs*. 23.8%), had higher BMI (24.6 *vs*. 24.0 kg/m^2), and were more likely to present with non-ST segment elevation myocardial infarction (NSTEMI) (31.6% *vs*. 24.4%). Patients in the diabetes group also had higher prevalence of prior MI, heart failure, and CABG. Regarding traditional CAD risk factors, patients with diabetes were more likely to have hypertension and hyperlipidemia, but less likely to be a smoker (all $P < 0.0001$).

Table 1. Baseline characteristics of patients with *vs*. without diabetes.

Variables	Diabetes group (*n* = 4450)	Non-diabetes group (*n* = 17544)	*P* value
Age, yrs	64.4 ± 11.1	62.6 ± 12.8	< 0.0001
Female	1479 (33.2%)	4178 (23.8%)	< 0.0001
BMI, kg/m^2	24.6 ± 3.3	24.0 ± 3.2	< 0.0001
STEMI	3045 (68.4%)	13270 (75.6%)	< 0.0001
NSTEMI	1405 (31.6%)	4274 (24.4%)	< 0.0001
Prior MI	506 (11.4%)	1136 (6.5%)	< 0.0001
Prior heart failure	196 (4.4%)	381 (2.2%)	< 0.0001
Prior PCI	237 (5.3%)	548 (3.1%)	< 0.0001
Prior CABG	39 (0.9%)	54 (0.3%)	< 0.0001
Hypertension	2956 (66.4%)	8364 (47.7%)	< 0.0001
Hyperlipidemia	497 (11.2%)	1086 (6.2%)	< 0.0001
Smoking	2015 (45.3%)	9992 (56.9%)	< 0.0001
Premature CAD	171 (3.8%)	586 (3.3%)	0.1051

Values are presented as mean ± SD and *n* (%) unless otherwise indicated. BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; MI: myocardial infarction; NSTEMI: non- ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

3.2 Clinical presentation

Symptoms for all patients are shown in Table 2. A total of 71 (1.6%) patients in the diabetes group and 237 (1.3%) patients in the non-diabetes group experienced no symptoms ($P = 0.2223$).

The most common symptoms in both groups were persistent precordial chest pain, diaphoresis, chest distress, and radiation pain. Patients in the diabetes group were less likely to present with persistent precordial chest pain (63.1% *vs*. 68%, $P < 0.0001$), diaphoresis (60.1% *vs*. 65.6%, $P < 0.0001$), fatigue (16.7% *vs*. 18.3%, $P = 0.0123$), and incontinence (0.4% *vs*. 0.7%, $P = 0.0093$). Prevalence of other symptoms was similar between the two groups.

Table 2. Symptom presentation of patients with *vs*. without diabetes.

Symptom	Diabetes group (*n* = 4450)	Non-diabetes group (*n* = 17,544)	*P* value
No symptom	71 (1.6%)	237 (1.4%)	0.22223
Persistent precordial chest pain	2806 (63.1%)	11926 (68.0%)	< 0.0001
Diaphoresis	2675 (60.1%)	11502 (65.6%)	< 0.0001
Chest distress	1760 (39.6%)	6894 (39.3%)	0.7558
Radiation pain	1370 (30.8%)	5646 (32.2%)	0.0738
Nausea/Vomiting	1165 (26.2%)	4835 (27.6%)	0.0641
Shortness of breath	1028 (23.1%)	3827 (21.8%)	0.0655
Fatigue	741 (16.7%)	3202 (18.3%)	0.0123
Palpitation	560 (12.6%)	2384 (13.6%)	0.0769
Dysphoria	166 (3.7%)	760 (4.3%)	0.0702
Recurrent angina pectoris	144 (3.2%)	607 (3.5%)	0.4597
Persistent back pain	125 (2.8%)	469 (2.7%)	0.6196
Syncope	115 (2.6%)	486 (2.8%)	0.4940
Persistent upper abdomen pain	99 (2.2%)	418 (2.4%)	0.5320
Mandibular/Tooth pain	44 (1.0%)	215 (1.2%)	0.1818
Incontinence	31 (0.4%)	68 (0.7%)	0.0093

Values are presented as mean ± SD and *n* (%) unless otherwise indicated.

3.3 Time to hospital presentation

Table 3 shows time to hospital presentation for patients in both the diabetes and the non-diabetes groups. Patients with diabetes were more likely to have a delay in presenting to a hospital than patients without diabetes. Compared with the non-diabetes group, patients with diabetes were less likely to present to a hospital in the timeframes: (1) less than 3 h, (2) 3–6 h, or (3) 6–12 h after symptom presentation. However, they were more likely to present to the hospital more than 12 h after symptom onset than patients without diabetes ($P = 0.0003$).

Table 3. Time to hospital of patients with *vs*. without diabetes.

Time to hospital	Diabetes group (*n* = 4450)	Non-diabetes group (*n* = 17544)	*P* value
< 3 h	898 (20.2%)	3758 (21.4%)	
3–6 h	1013 (22.8%)	4210 (24.0%)	
6–12 h	650 (14.6%)	2767 (15.8%)	0.0003
12–24 h	512 (11.5%)	1951 (11.1%)	
1–7 days	1377 (30.9%)	4858 (27.7%)	

3.4 Independent predictors of atypical symptoms

Independent predictors of symptoms without chest pain are shown in Table 4. After adjusting for confounders including age, sex, diabetes, type of MI, anterior wall MI, Killip classification, heart rate, blood pressure, predromal

Table 4. Independent predictors of atypical symptoms.

Variables	Odds ratio (95% CI)	*P* value
Age (per one year increase)	1.016 (1.013–1.019)	< 0.0001
Diabetes mellitus	1.112 (1.034–1.196)	0.0042
STEMI *vs*. NSTEMI	0.507 (0.475–0.541)	< 0.0001
Killip classification IV *vs*. I	1.691 (1.462–1.954)	< 0.0001
Heart rate (per 1 beats/min increase)	1.006 (1.004, 1.007)	< 0.0001
Systolic blood pressure (per 1 mmHg increase)	0.998 (0.997–1.000)	0.0256
Presence of predromal symptoms	0.790 (0.741–0.843)	< 0.0001

Adjusted for age, sex, diabetes, type of MI, anterior wall MI, Killip classification, heart rate, blood pressure, prodromal symptoms, BMI, hypertension, smoking status, PCI, prior CABG, renal failure, prior angina, hyperlipidemia, family history of CAD, prior stroke, prior HF. BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; MI: myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention.

symptoms, BMI, hypertension, smoking status, PCI, prior CABG, renal failure, prior angina, hyperlipidemia, family history of CAD, prior stroke, and prior HF, diabetes remained an independent predictor of atypical symptoms (those without chest pain) (odds ratio [OR]: 1.112, 95% confidence interval (CI): 1.034–1.196).

4 Discussion

In this analysis of a nationwide prospective multicenter registry, we found that AMI patients with diabetes were less likely to present with persistent precordial chest pain, diaphoresis, fatigue, and incontinence when compared with those without diabetes. Patients in the diabetes group also had longer times to hospital presentation compared with those in the non-diabetes group. Multivariable analysis showed diabetes to be an independent predictor of atypical symptoms.

In this study, 4,450 out of 21,994 patients had diabetes. The prevalence of diabetes among AMI patients was 20.5%, which was lower than previously reported: 30% in the OASIS study,[11] 27% for NSTEMI patients and 21% for STEMI patients in the GRACE study,[5] and 29% in the NRMI study.[12] This finding may be explained the low awareness rate of diabetes in China, which was reported to be 30.1% in previous studies.[13]

The AMI patients in our study with diabetes were older, more often women, had higher BMI, and had more comorbidities. We also found that AMI patients with diabetes were more likely to present without typical symptoms, including persistent chest pain, diaphoresis, and radiation pain. History of diabetes was found to be an independent predictor of atypical presentation. These findings were in accordance with previously published studies.[5-7,14-17] However, our study further described and compared the specific components of typical symptoms (i.e., chest pain, chest distress, diaphoresis, and radiation pain) in patients with and without diabetes, demonstrating that diabetics were less likely to present with chest pain, diaphoresis, and radiation pain.

Mechanisms underlying atypical symptoms among diabetes have previously been proposed. The type and severity of AMI symptoms were dependent on activation of afferent neurons. Nerve impulses were then transmitted to autonomic nervous system and induce symptoms. Patients with diabetes had high prevalence of neuropathy, which led to atypical symptoms.[18] Multi-vessel disease and complex lesions were more common among diabetes, leading to more frequent angina pectoris and preconditioning.[19] In addition, patients with diabetes often have symptoms associated with hypoglycemia or comorbidities. Therefore, when patients with diabetes suffer a heart attack, it is hard for them to rapidly recognize whether these symptoms are cardiac in origin.

Other studies have shown contradictory results that frequency or intensity of chest pain or other symptoms did not differ between two groups.[20,21] However, these studies were conducted over a decade ago with a much smaller sample size (fewer than 2000), thereby limiting their power. It is reasonable to believe that patients with diabetes have different symptoms from non-diabetics.

Another major finding of our study is that among AMI patients, those with diabetes had a longer time to hospital presentation than those without diabetes. Similar results were also shown in other studies. Sheiferet analyzed 102,399 patients with AMI and discovered that diabetes was an independent predictor of delayed treatment (OR: 1.11, 95% CI: 1.07–1.14).[4] Another large-scale study with sample size of 482,377 also showed that delayed time to treatment ranged from 45–63 minutes.[22] Diabetes has also been identified as a predictor of longer door-to-balloon time.[23] Therefore, clinicians should put more efforts into educating the public about MI symptoms, particularly in diabetic patients. This may help patients recognize early symptoms of AMI more rapidly, reduce delay in seeking treatment, and improve patients' prognosis.

4.1 Limitations

Differences in the prevalences of AMI and diabetes may be potential bias for the association and should be investigated in future studies. AMI symptoms may be different between type 1 and type 2 diabetic patients. However, the

CAMI registry did not collect data regarding type of diabetes. All patients were divided by history of diabetes before presentation to a hospital. Some patients with newly diagnosed diabetes after AMI onset were classified into the non-diabetes group. Our study was an observational study that did not include follow-up data. Future studies should be conducted to explore the prognostic value of diabetes on short or long-term mortality among AMI patients.

4.2 Conclusions:

Our study is the first large-scale study to provide evidence that AMI patients with diabetes were more likely to have atypical symptoms and take a longer time to present to a hospital. The results of our study are of mechanistic insight and may make clinicians more aware of recognizing AMI patients rapidly and reducing delay in diagnosis and treatment, particularly in the context of diabetes. Our data provide solid scientific support to initiate large-scale follow-up studies on the prognostic contribution of diabetes to cardiovascular disease risk in AMI patients.

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