Am J Transl Res 2021;13(12):13870-13877
www.ajtr.org /ISSN:1943-8141/AJTR0137328

Original Article

Long-term follow-up of diabetic patients with non-ST-segment elevation myocardial infarction

Zhifeng Li[1], Shaopeng Huang[2], Rui Yang[3], Jieyuan Li[1], Guoqiang Chen[1]

[1]Department of General Medicine, Foshan First People's Hospital, Foshan 528000, Guangdong Province, China; [2]Department of General Medicine, No. 7 People's Hospital of Nanhai District, Foshan 528248, Guangdong Province, China; [3]Department of General Medicine, Zhujiang Hospital of Southern Medical University, Guangzhou 510280, Guangdong Province, China

Received July 13, 2021; Accepted November 11, 2021; Epub December 15, 2021; Published December 30, 2021

Abstract: Objective: Non-ST-segment elevation myocardial infarction (NSTEMI) is prevalent in patients with diabetes mellitus (DM). The long-term follow-up outcomes of this group of patients remain misunderstood. This study was aimed at investigating long-term follow-up outcomes of diabetic patients discharged with NSTEMI. Methods: All diabetic patients discharged with MI were recruited and followed up in this study. Patients who had elevated serum troponin, but no ST segment elevation were considered as NSTEMI. A structured follow-up was conducted at 3 months, 6 months, 12 months, and 24 months. Independent risk factors for all-cause and cardiovascular mortality were analyzed. Results: A total of 743 diabetic patients with MI enrolled for analysis, with 132 patients being recognized as NSTEMI. The mean age was 70.4±8.3 years. The mean follow-up was 21.3±6.1 months. NSTEMI (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.08-2.23), age ≥75 years (HR 1.17, 95% CI 1.04-1.31), hypertension (HR 1.51, 95% CI 1.03-2.21), heart failure (HF) (HR 3.23, 95% CI 2.28-4.57), and previous MI (HR 2.01, 95% CI 1.44-2.79) were independent risk factors for all-cause mortality. Administration of beta-blocker (HR 0.62, 95% CI 0.45-0.85) was associated with a lower incidence of all-cause mortality. Predictors for cardiovascular mortality included elderly, hypertension, HF, previous MI, and MI with atypical chest pain. Conclusions: Multiple risk factors contribute to a higher incidence of composite outcomes in diabetic patients with MI. STEMI poses a greater threat to adverse events, which warrants more investigations.

Keywords: Diabetes mellitus, myocardial infarction, non-ST-segment elevation, mortality

Introduction

Among patients with diabetes mellitus (DM), coronary artery disease is commonly encountered. DM is one of the major risk factors of cardiovascular disease. The control of blood glucose level doesn't reduce the incidence of cardiovascular events [1]. Multiple center research reported that DM patients with cardiovascular disease had inadequate and less aggressive management [2]. Hyperglycemia in diabetic patients poses significant impairment for the artery system [3]. For example, Xia et al. found that patients with hypertension and diabetes had a greater degree of vascular damage. The more obvious the degree of arteriosclerosis, the greater the range of physiological indicators than the control with normal level [4].

Patients with coronary artery disease, with DM usually had more severe coronary lesions compared with non-diabetic counterparts [5]. Patients with microalbuminuria had more severe coronary vessel lesions and cardiac function damage [6]. Scientists have found that diabetes mellitus is an important cardiovascular risk factor of premature myocardial infarction in women [7]. Once MI occurred, diabetic patients are more prone to be presented without ST segment elevation (NSTEMI), that induces a delayed diagnosis and treatment [8]. The missing optimal therapeutic time-window of reperfusion of culprit coronary artery has been associated with negative composite events, including extensive myocardial infarction, prolonged admission duration, and a higher mortality rate [9-11]. Those who survived NSTEMI

and were discharged from the hospital tended to have recurrent coronary artery events [12].

The prognosis of diabetic patients discharged with NSTEMI has never been investigated. The present study aimed at providing a single-center, long-term follow-up results of diabetic patients discharged with NSTEMI. Independent risk factors for the negative prognosis of this population were also analyzed.

Materials and methods

Consequtive patients with MI discharged from the Department of General Medicine, Foshan First People's Hospital between January 2015 and December 2017 were recorded, among which 807 were diagnosed with DM. All medical history, medication, and demographic characteristics were collected using the Electronic Medical Record System in our hospital. The diagnosis of medical history was according to the International Classification of Diseases-9th Revision and International Classification of Diseases-10th Revision (ICD-9/10). The serum level of glycated hemoglobin (HbA1c) was recorded before discharge. Patients with HbA1c >6.9% were considered as suboptimal DM control. A structured follow-up posterior to discharge was performed at 3 months, 6 months, 12 months, and 24 months through in-hospital, outpatient, or telephone follow-up. A total of 743 (92.1%) patients finished the two years of follow-up. Events regarding all-cause mortality, cardiovascular mortality, cardiovascular readmission, and recurrent MI were recorded. MI patients without presentation of ST-segment elevation were grouped as NSTEMI. All the patients signed the informed consent at discharge.

Inclusion criteria: Patients were diagnosed with MI and DM; patients with complete data; patients agreed to be followed up after discharge. Exclusion criteria: patients over 18 years old; patients with heart surgery history; patients with other diseases such as cancer that may affect the results of this study.

Patients' in-hospital and post-discharge management did not interfere. All patients' information was anonymous. This study was approved by the Ethical Committee of our hospital (approval No. 20210017). All the research approaches were carried out according the Declaration of Helsinki.

Statistical analysis

Mean ± standard deviation (SD) and median (inter-quartile range [IQR]) were used for describing normally distributed and skewed data respectively. Numbers and percentages (%) were used to describe categorical variables. Differences between groups were compared by student's T test, Mann-Whitney U test, or chi-square test wherever appropriate. Cox-regression analysis was used to investigate risk factors associated with outcome events. All variables with P<0.1 in univariable analysis were included in multivariable analysis. Kaplan-Meier curves were used to demonstrate event rates of subgroups of patients. Differences between groups were tested by log-rank test. All tests were conducted using SPSS Statistic, version 25.0 (IBM, SPSS, Inc). The significance cut-off point was set at *P*-value <0.05 (two tailed).

Results

A total of 743 diabetic patients with MI were discharged from the hospital, among which 132 (17.8%) had no ST-segment elevation on electrocardiography. This group of patients was deemed as STEMI. Patients' characteristics were shown in **Table 1**. 60.3% were male gender. The mean age was 70.4±8.3, with 44.1% aged over 75 years and 76.2% over 65 years. Compared with patients presenting with MI with ST-segment elevation, those subjects with NSTEMI were older (P<0.001), had higher systolic and diastolic blood pressure (P<0.001), higher prevalence of hypertension, heart failure (HF) (P<0.001), previous MI (P=0.023), and were more prone to receive calcium channel blocker (P=0.002, **Table 1**).

All-cause and cardiovascular mortality rates during follow-up

At two-year of follow-up, 160 (21.5%) patients died with an annual incidence of 10.3%/y. 144 (19.4%) were cardiovascular death with an annual incidence of 9.2%/y. Other reasons for mortality included cerebrovascular disease, chronic kidney disease, and pulmonary disease (**Figure 1**). Patients with NSTEMI had significantly higher all-cause mortality compared with patients with STEMI (hazard ratio [HR] 2.18, 95% confidence interval [CI] 1.55-3.08; P< 0.001). Kaplan-Meier curves showed a significant difference between STEMI and NSTEMI

Table 1. Baseline characteristics of patients stratified by optimal or poor blood glucose control

Characteristics	Total (n=743)	STEMI (n=611)	NSTEMI (n=132)	*P* value
Demographics				
Age (mean ± SD)	70.4±8.3	70.0±8.5	72.4±6.9	0.001
≥.0 (n, %)	328 (44.1)	244 (39.9)	84 (63.6)	<0.001
≥0. (n, %)	566 (76.2)	457 (74.8)	109 (82.6)	0.057
Male (n, %)	448 (60.3)	361 (59.1)	87 (65.9)	0.146
BMI (kg/m^2)	27.2±1.4	27.2±1.3	27.2±1.7	0.637
HR (bpm)	70±9	70±92	71±6	0.289
SBP (mmHg)	140±11	139±11	144±11	<0.001
DBP (mmHg)	75±10	74±10	80±6	<0.001
Medical history (n, %)				
Hyperlipidemia	635 (85.5)	517 (84.6)	118 (89.4)	0.158
Hypertension	497 (66.9)	388 (63.5)	109 (82.6)	<0.001
Heart failure	222 (29.9)	160 (26.2)	62 (47.02)	<0.001
Myocardial infarction	154 (20.7)	117 (19.1)	37 (28.0)	0.023
Renal dysfunction	243 (32.7)	179 (29.3)	64 (48.5)	<0.001
Stroke	41 (5.5)	31 (5.1)	10 (7.6)	0.254
COPD	69 (9.3)	57 (9.3)	12 (9.1)	0.932
Medication or intervention (n, %)				
Antiplatelet	743 (100.0)	611 (100.0)	132 (100.0)	1.000
ACEI/ARBs	505 (68.0)	421 (68.9)	84 (63.6)	0.240
BB	472 (63.5)	390 (63.8)	82 (62.1)	0.712
CCB	369 (49.7)	287 (47.0)	82 (62.1)	0.002
Diuretics	370 (49.8)	314 (51.4)	56 (42.4)	0.062

Note: ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin Receptor Blockers; BB: beta blocker; BMI: body mass index; CCB: calcium channel blocker; COPD: chronic obstructive sleep apnea; DBP: diastolic blood pressure; HF: heart failure; HR: heart rate; PCI: percutaneous coronary artery intervention; NSTEMI: Non-ST-segment elevation myocardial infarction; SBP: systolic blood pressure; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction.

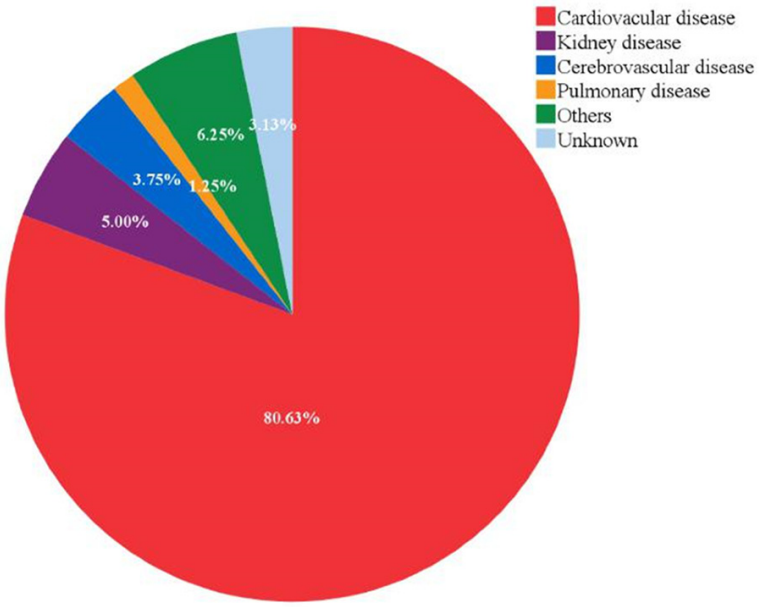

Figure 1. Reason for death in diabetic patients with myocardial infarction.

patients regarding all-cause mortality (Log-rank P<0.001, **Figure 2**).

NSTEMI was also significantly associated with cardiovascular mortality (HR 3.66, 95% CI 2.62-5.12, P<0.001). Kaplan-Meier curves demonstrated that patients with NSTEMI had a significantly lower survival rate compared with patients with STEMI (Log-rank P<0.001, **Figure 3**).

Predictors for mortality during follow-up

After adjusting co-founders, we found that aged ≥75 y (HR 1.17, 95% CI 1.04-1.31),

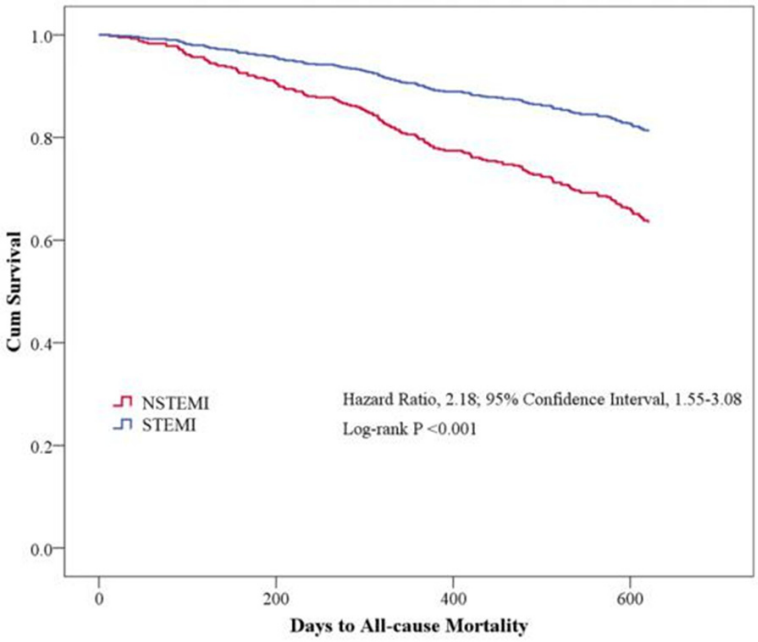

Figure 2. All-cause mortality rate regarding symptom presentation during myocardial infarction. Note: NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

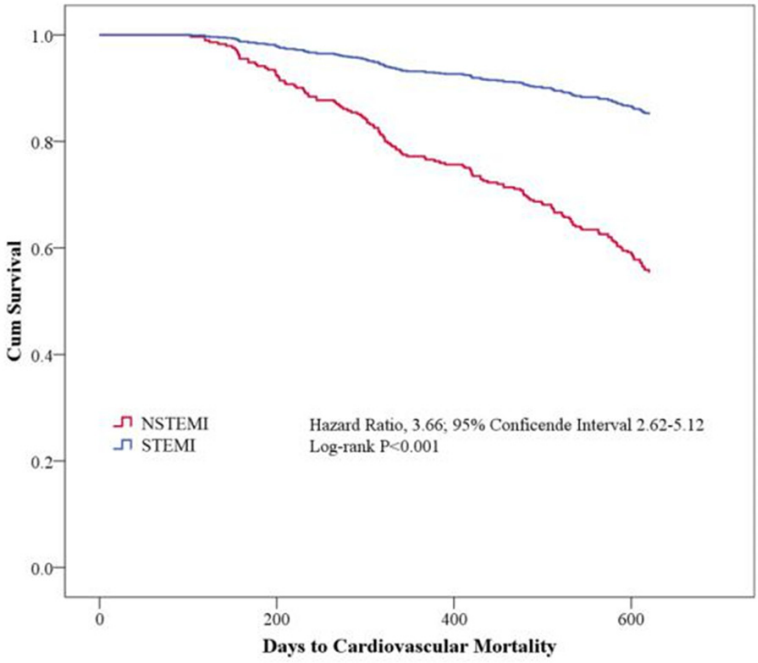

Figure 3. Cardiovascular mortality rate regarding ST-segment manifestation during myocardial infarction. Note: NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

hypertension (HR 1.51, 95% CI 1.03-2.21), HF (HR 3.23, 95% CI 2.28-4.57), previous MI (HR 2.01, 95% CI 1.44-2.79), and NSTEMI (HR 1.55, 95% CI 1.08-2.23) were independently related with all-cause mortality (**Table 2**). Administration of angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARBs) and beta-blockers were associated with 24% and 38% reduced risk of all-cause mortality (**Table 2**).

The majority of reasons for mortality could attribute to cardiovascular disease. We analyzed independent predictors for cardiovascular mortality. Hypertension (HR 2.33, 95% CI 1.46-3.71), HF (HR 3.07, 95% CI 2.13-4.43), previous MI (HR 2.22, 95% CI 1.58-3.14), and NSTEMI (HR 2.44, 95% CI 1.69-3.51) were intimately associated with cardiovascular mortality. Similarly, ACEI/ARBs and BB reduced the mortality risk by 70% and 37% respectively (**Table 3**).

Discussion

Previous studies have reported that diabetes and MI are risk factors for coronary heart disease [13]. Diabetics with MI usually have a poor prognosis in coronary treatment [14]. Patients with NSTEMI are not rare, especially in those with DM [15]. Unlike STEMI, the degree of stenosis and physiology of ischemia are different in patients with NSTEMI [16]. A lack of alerting electrocardiography manifestation may lead to delayed treatment, covering misdiagnosis and a longer time from MI occurrence to reperfusion of culprit artery [17]. The prevalence, predictors, and outcomes of patients with NSTEMI have clear characteristics. This was

Table 2. Predictors for all-cause mortality during the follow-up

Risk factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥75 y	1.57	1.15-2.15	0.004	1.17	1.04-1.31	0.037
Male gender	1.21	0.88-1.67	0.246			
Hypertension	1.69	1.18-2.44	0.005	1.51	1.03-2.21	0.036
Hyperlipidemia	0.70	0.47-1.03	0.067	0.74	0.50-1.10	0.134
HF	3.36	2.46-4.58	<0.001	3.23	2.28-4.57	<0.001
Renal dysfunction	1.16	0.84-1.60	0.379			
Previous MI	2.33	1.68-3.22	<0.001	2.01	1.44-2.79	<0.001
COPD	1.34	0.83-2.16	0.236			
ACEI/ARBs	0.68	0.50-0.94	0.017	0.76	0.55-1.06	0.102
BB	0.61	0.45-0.84	0.002	0.62	0.45-0.85	0.003
CCB	1.09	0.80-1.49	0.570			
NSTEMI	2.18	1.55-3.08	<0.001	1.55	1.08-2.23	0.019

Note: ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin Receptor Blockers; BB: beta blocker; CCB: calcium channel blocker; COPD: chronic obstructive sleep apnea; HF: heart failure; HR: heart rate; NSTEMI: Non-ST-segment elevation myocardial infarction; MI: myocardial infarction; CI: confidence interval.

Table 3. Predictors for cardiovascular mortality during the follow-up

Risk factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age ≥75 y	2.03	1.45-2.83	<0.001	1.05	0.72-1.52	0.800
Male gender	1.09	0.78-1.52	0.632			
Hypertension	2.94	1.87-4.64	<0.001	2.33	1.46-3.71	<0.001
Hyperlipidemia	0.83	0.55-1.28	0.393			
HF	3.60	2.60-5.01	<0.001	3.07	2.13-4.43	<0.001
Renal dysfunction	1.46	1.05-2.04	0.026	0.95	0.66-1.37	0.790
Previous MI	2.72	1.94-3.80	<0.001	2.22	1.58-3.14	<0.001
COPD	1.15	0.68-1.97	0.603			
ACEI/ARBs	0.58	0.42-0.81	0.001	0.70	0.50-0.98	0.039
BB	0.58	0.42-0.81	<0.001	0.63	0.44-0.88	0.007
CCB	1.30	0.94-1.81	0.113			
NSTEMI	3.66	2.62-5.12	<0.001	2.44	1.69-3.51	<0.001

Note: ACEI: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin Receptor Blockers; BB: beta blocker; CCB: calcium channel blocker; COPD: chronic obstructive sleep apnea; HF: heart failure; HR: heart rate; NSTEMI: Non-ST-segment elevation myocardial infarction; MI: myocardial infarction; CI: confidence interval.

the first study investigating the role of NSTEMI in patients discharged with MI and diabetes.

This study represents two circumstances. The first circumstance is a relatively minor MI with limited impairment of the myocardium [18]. The second circumstance includes patients with an older age and a history of DM who tended to have no coronary artery occlusion lesion [19]. The latter group of patients represents a relatively more severe circumstance [20]. In this study, we found that compared with patients presenting with STEMI, those with NSTEMI were older, had higher systolic and diastolic blood pressure, higher prevalence of hypertension, heart failure, and previous MI. NSTEMI and unstable angina pectoris are frequent causes of hospital admission in the elderly [21]. Madala et al. found that the mean patient ages of the first NSTEMI were 74.6 +/- 14.3 years and 58.7 +/- 12.5 years for the patients with BMI less than 18.5 kg/m (2) and those with BMI >40.0 kg/m (2) cohorts, respectively (P<0.0001) [22]. Hypertension is a well-estab-

lished risk factor for cardiovascular disease. Low systolic blood pressure is an adverse prognosticator in acute coronary syndrome. Lee et al. reported that low SBP on presentation, but not prior hypertension, was independently associated with in-hospital mortality in non-ST-segment elevation acute coronary syndrome [23]. Another research also reported that patients with NSTEMI (n=152) were significantly older and had significantly more prior MI, heart failure, azotemia, bypass surgery, and peripheral vascular disease than patients with STEMI (n=729) [24]. All these findings were consistent with those in our study.

In past decades, reports have confirmed the effects of calcium channel blockers on acute myocardial ischemia [25, 26]. In this study, we also found that compared with patients presenting with STEMI, those with NSTEMI were more prone to receive calcium channel blockers. The reason may be that calcium channel blockers have myocardial protection effects during ischemia and reperfusion, and reduce cardiovascular damage [27, 28].

Some studies suggested that the value of platelet/lymphocyte ratio, albumin-globulin ratio, and cystatin C may be the marker of a predictor of all-cause mortality after NSTEMI [29-31]. In our study, patients with NSTEMI had significantly higher all-cause mortality compared with patients with STEM and hypertension, heart failure, previous MI, and NSTEMI were independent predictors for cardiovascular mortality. These indicators are all associated with the progress of cardiovascular diseases, but the mechanism needs further study.

We found that administration of ACEI/ARBs and BB were associated with 24% and 38% reduced risk of all-cause mortality and they reduced the mortality risk by 70% and 37% respectively. Previous studies also confirmed that ACEI/ARBs could benefit not only patients with MI, but also those after successful percutaneous coronary intervention in NSTEMI and DM patients [15, 32]. Early use of beta-blockers is a quality indicator for the treatment of patients with NSTEMI [33]. A study from Emery et al. suggested that patients with NSTEMI should receive early BB therapy as it has a beneficial impact on hospital and 6-month mortality in all patients, including those presenting with heart failure [34]. These previous reports were consistent with our study.

In conclusion, NSTEMI was associated with 118% increased risk of all-cause mortality, and 266% increased risk of cardiovascular mortality, compared with those presented with typical chest pain. These results suggest that among patients with a history of MI and DM, the absent of ST-segment elevation on electrocardiography during MI merits more attention. The sample size was small in this study. Follow-up time should be longer to collect more information in the future, researching the mechanism deeper.

Disclosure of conflict of interest

None.

Address correspondence to: Guoqiang Chen, Department of General Medicine, Foshan First People's Hospital, No. 81 Lingnan Avenue, Chancheng District, Foshan 528000, Guangdong Province, China. Tel: +86-18038860333; E-mail: ffph_cgq@126.com

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