ORIGINAL RESEARCH

Association Between Depression and Outcomes in Chinese Patients With Myocardial Infarction and Nonobstructive Coronary Arteries

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***Background*—**Myocardial infarction with nonobstructive coronary arteries (MINOCA) occurs in ≈10% of all patients with myocardial infarction. Studies on effects of depression on MINOCA outcomes are lacking. Therefore, the aim of this study was to examine the association of depression with clinical outcomes in Chinese patients with MINOCA.

***Methods and Results*—**We conducted a prospective cohort study of 633 participants with MINOCA and followed up for 3 years. End points were defined as all-cause mortality and cardiovascular events. Diagnosis of depression was ascertained using the psychiatric interview based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. During the follow-up period, all-cause death occurred in 93 individuals and cardiovascular events developed in 170 individuals. Kaplan-Meier curves showed a significant association of depression with all-cause mortality (log-rank $P<0.001$) and cardiovascular events (log-rank $P<0.001$). Multiple Cox regression identified the new diagnosis of depression as an independent prognostic factor for all-cause mortality as well as cardiovascular events (adjusted hazard ratio, 7.250; 95% CI, 4.735–11.100; $P<0.001$; and hazard ratio, 3.411; 95% CI, 2.490–4.674; $P<0.001$, respectively).

***Conclusions*—**The new diagnosis of depression at the time of myocardial infarction is associated with increased risk of adverse clinical outcomes in patients with MINOCA. **(*J Am Heart Assoc*. 2019;8:e011180. DOI: 10.1161/JAHA.118.011180.)**

Key Words: cardiac disease • depression • outcome

Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a syndrome with many potential causes, characterized by clinical signs of myocardial infarction with normal or near-normal coronary arteries on angiography.[1,2] MINOCA occurs in ≈10% of all those with acute myocardial infarction, and there is an overrepresentation of women compared with those with obstructive coronary arteris.[3–5] Deaths are more likely to occur in women without obstructive coronary arteries.[6] MINOCA is an exclusion diagnosis and may be the result of several potential causes, including plaque disruption, coronary artery spasm, thromboembolism, dissection, microvascular dysfunction, ischemic myocardial injury attributable to supply/demand mismatch, and myocarditis or Takotsubo cardiomyopathy.[1,7]

Depression is common among patients with coronary heart disease, with prevalence ranging from 20% to 30%.[8,9] Accumulating evidence has shown that depression is associated with increased risk of adverse clinical outcomes in patients with myocardial infarction, independent of traditional cardiovascular risk factors.[10–13] Studies of effects of antidepressant medication on prognosis of patients with myocardial infarction have reached different conclusions.[8,14] Despite the high prevalence and poor clinical outcomes, mood and depression are often neglected and left untreated in this population.[15,16]

Emerging studies on mental health in patients with MINOCA showed that depression is frequent, with prevalence similar to patients with coronary heart disease.[17] To date, however, the association between depression and clinical outcomes has not been examined in patients with MINOCA. In addition, there are ethnic differences in depression among patients with coronary artery disease.[18] No proper data on the prevalence of depression in Chinese patients with MINOCA exist. Therefore, we aimed to measure the prevalence of depression in Chinese patients with MINOCA and to determine the association between depression and clinical outcomes in patients with MINOCA.

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Clinical Perspective

What Is New?

- Depression is frequent in patients with myocardial infarction with nonobstructive coronary arteries.
- Depression is associated with increased risk of adverse outcomes in patients with myocardial infarction.

What Are the Clinical Implications?

- These data support the notion that depression predicts adverse outcomes in patients with myocardial infarction.
- Future studies should evaluate whether depression treatment may improve clinical outcomes in patients with myocardial infarction with nonobstructive coronary arteries.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Setting and Participants

Patients with MINOCA were recruited consecutively from the Cardiology Department of the First Affiliated Hospital of Jiaxing University between October 2012 and November 2014. Inclusion criteria included the following: (1) Chinese ethnicity; (2) fulfilling the diagnostic criteria for acute myocardial infarction (*International Classification of Diseases, 10th Revision [ICD-10]* codes I21-I22); (3) coronary angiography performed during the hospitalization showing a stenosis of ≤50%; and (4) willingness to give written informed consent. Exclusion criteria were as follows: (1) patients with dementia or cognitive dysfunction; (2) patients with a history of depression or other psychiatric disorders (clinical diagnosis or previous treatment)[19]; (3) patients with previous myocardial infarction, severe chronic obstructive pulmonary, renal disease, atrial fibrillation, cancer, pulmonary embolism, and myocarditis; and (4) patients who died within 30 days after discharge. Informed consent was obtained from each patient before enrollment, and the study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of First Affiliated Hospital of Jiaxing University.

Baseline Characteristics

Baseline data were obtained from the patient record system and confirmed with each patient at enrollment. These data involved demographics, traditional cardiac risk factors, electrocardiographic changes on admission, and discharge medications with antiplatelets, β blockers, renin-angiotensin-aldosterone system inhibitors, and statins. Traditional risk factors were defined as presence of current smoking, hypertension, diabetes mellitus, and hyperlipidemia.

Assessment of Depression

Each patient was screened for depressive symptoms using the 17-item Hamilton Depression Scale[20] during or shortly after the admission for acute myocardial infarction. Patients with a 17-item Hamilton Depression Scale score of ≥7 were given the Chinese version of the Structured Clinical Interview of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, for diagnosis of depression. The structured psychiatric interview, which takes 30 to 45 minutes to complete, was performed by psychiatrists who were blind to the medical documents of patients.

Primary and Secondary End Points

Patients were followed up for 3 year from depression ascertainment. The primary end point in the current study was defined as all-cause mortality. The secondary end points were cardiovascular events, consisting of cardiac death, recurrent myocardial infarction, heart failure, and ischemic stroke. End point ascertainment was performed on the same patient by 2 researchers who were blinded to admission depression status. Events were first determined by searching the patient record system. All patients were then contacted to examine whether any events had occurred outside the hospital; the data were collected from the discharge summary from the medical institution where the event occurred.

Statistical Analysis

The categorical variables are presented as percentage frequency and compared by χ^2 test or Fisher's exact test. The continuous variables are presented as mean±SD or median (25th–75th percentile) and compared by Student *t* test or Mann-Whitney *U* test. Kaplan-Meier analyses were used to examine unadjusted outcomes (all-cause mortality and cardiovascular events) between the depressed and nondepressed patients by the log-rank statistic. Cox regression analyses were used to determine the associations between depression and outcomes by comparing the 2 patient groups after adjusting for the following: age, sex, traditional cardiac risk factors, electrocardiographic changes, and medications. Results were estimated as hazard ratios (HRs) with 95% CIs. A 2-sided $P<0.05$ was considered statistically significant for all tests. All analyses were performed with SPSS 22.0 (SPSS Inc, Chicago, IL).

Results

Baseline Characteristics Stratified by Depression Status

Of 677 patients with MINOCA at baseline, 44 were excluded from this analysis: 3 with dementia, 2 with a history of depression, 5 with previous myocardial infarction, 6 with severe chronic obstructive pulmonary disease, 6 with renal disease, 5 with atrial fibrillation, 9 who refused to participate in the current study, and 8 who died within 30 days after discharge. Hence, the study cohort in the current study contained 633 patients with MINOCA. There were no significant differences in demographic and clinical characteristics between our cohort and those excluded. Of the 633 patients who formed the study sample, 166 (26.2%, 92 women) were diagnosed with depression and 422 were not. Only 32 depressed patients (19.2%) agreed to take an antidepressant medication with selective serotonin reuptake inhibitors; and the other 134 depressed patients (80.8%) chose to go to the psychiatric hospital to confirm the diagnosis of depression, which made it difficult for us to obtain the information about their medication. Patients with depression had higher all-cause mortality (P=0.001) and cardiovascular events (P<0.001) compared with those without depression (Table 1). There were no significant differences between the 2 patient groups in sex, age, traditional cardiac risk factors, ST-segment elevation on admission, and medications at discharge (Table 1).

Table 1. Baseline Characteristics of the Study Cohort Stratified by Depression

Characteristics	Not Depressed (n=467)	Depressed (n=167)	*P* Value
Demographics			
Age, mean±SD, y	64.4±13.0	64.0±11.1	0.699
Female sex, n (%)	287 (61.5)	92 (55.4)	0.173
Risk factors, n (%)			
Current smoking	90 (19.3)	28 (16.9)	0.494
Hypertension	234 (50.1)	84 (50.6)	0.913
Diabetes mellitus	85 (18.2)	33 (19.9)	0.633
Hyperlipidemia	141 (30.2)	54 (32.5)	0.575
Electrocardiographic changes on admission, n (%)			
ST-segment elevation	74 (15.8)	26 (15.7)	0.956
Medications at discharge, n (%)			
Antiplatelets	423 (90.6)	153 (92.2)	0.539
β Blockers	387 (82.9)	141 (82.9)	0.538
RAAS inhibitors	322 (69.0)	107 (64.5)	0.287
Statins	389 (83.3)	133 (80.1)	0.355
Outcomes, n (%)			
All-cause mortality	56 (12.0)	37 (22.3)	0.001
Cardiovascular events	108 (23.1)	62 (37.3)	<0.001

RAAS indicates renin-angiotensin-aldosterone system.

Association of Depression With MINOCA Outcomes

During the follow-up of 3 years, all-cause death occurred in 93 individuals and cardiovascular events developed in 170 individuals: 44 cardiac deaths, 51 recurrent myocardial infarctions, 46 heart failures, and 29 ischemic strokes. Kaplan-Meier curves showed a significant association of depression status with all-cause mortality (log-rank P<0.001; Figure[A]) and cardiovascular events (log-rank P<0.001; Figure[B]). In univariate Cox regression analyses, depression was significantly associated with increased risks of all-cause mortality as well as cardiovascular events (HR, 8.573; 95% CI, 5.663–12.980; P<0.001; and HR, 3.970; 95% CI, 2.919–5.401; P<0.001, respectively). After adjusting for demographic and clinical variables in multiple Cox regression models, depression remained an independent prognostic factor for all-cause mortality as well as cardiovascular events (HR, 7.250; 95% CI, 4.735–11.100; P<0.001; and HR, 3.411; 95% CI, 2.490–4.674; P<0.001, respectively) (Tables 2 and 3). Moreover, ST-segment elevation and medications, including renin-angiotensin-aldosterone system inhibitors and statins, were significantly associated with clinical outcomes (Tables 2 and 3), agreeing with the findings of previous studies.

Discussion

To the best of our knowledge, this is the first study to measure the prevalence of depression in Chinese patients with MINOCA and determine the possible association of depression with clinical outcomes in patients with MINOCA. We observed that depression is common among Chinese patients with MINOCA, with prevalence similar to other populations.[17] More important, our results demonstrated that depression increases the risks of all-cause mortality and cardiovascular events in patients with MINOCA.

The exact mechanisms for the association of depression with adverse clinical outcomes are unclear. Depression has been associated with increased catecholamine levels and might characterize individuals susceptible to Takotsubo cardiomyopathy.[21–23] Moreover, a recent study has shown an important role of depression in coronary artery spasm.[24] As mentioned earlier, Takotsubo cardiomyopathy and coronary artery spasm are common and potential pathogenetic

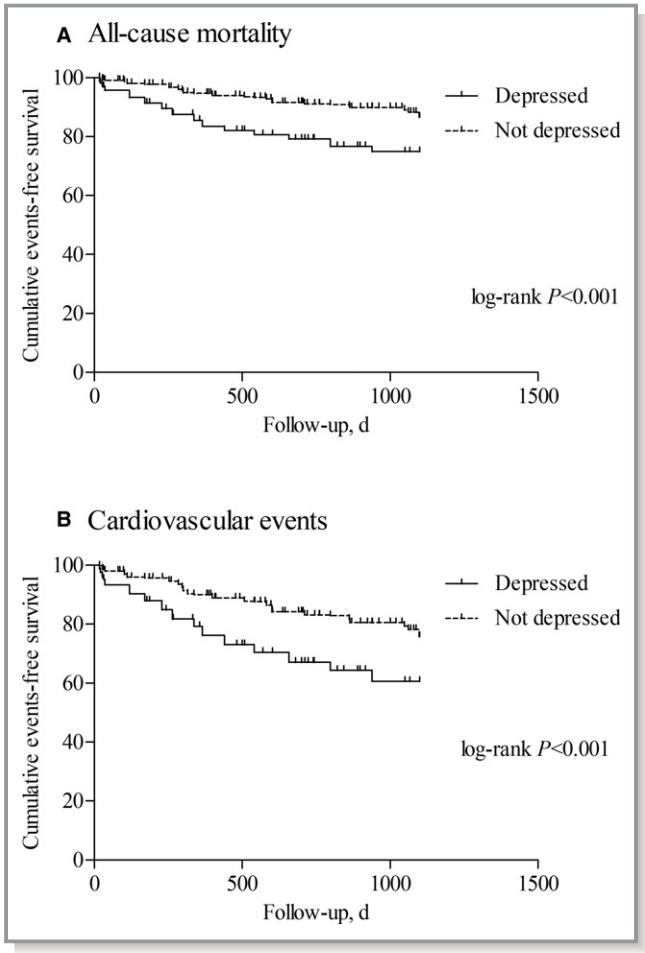

Figure. Cumulative event-free survival (Kaplan-Meier curves) for outcomes (all-cause mortality [**A**] and cardiovascular events [**B**]) in patients with and without depression.

mechanisms in MINOCA.[1,7] They may, therefore, be mediating mechanisms through which depression in this population can affect prognosis. In addition to physiological mechanisms, behavioral mechanisms may be involved in adverse clinical outcomes in patients with MINOCA. Depression may diminish an individual's adherence to medical treatment and rehabilitation programs.[25,26] Furthermore, depression is correlated with unhealthy behaviors, such as smoking, high-fat diet, lack of physical exercise, and disruptions of social relationships.[27–29] These unhealthy behaviors may be the result of psychological mechanisms related to depression. Therefore, the effect of depression on poor prognosis is likely the result of bio-psycho-social interaction.

The current study design has some strengths. First, in the present study, diagnosis of depression was ascertained using the psychiatric interview based on the *DSM-5*. Second, the well-known confounders that have significant effects on MINOCA outcomes, such as ST-segment elevation and medications, including renin-angiotensin-aldosterone system inhibitors and statins,[8,30] were all used for adjustment.

Table 2. Multiple Cox Regression of Variables Influencing All-Cause Mortality

Variables	HR (95% CI)	*P* Value
Age, y	1.015 (0.997–1.034)	0.099
Female sex	1.236 (0.813–1.878)	0.321
Current smoking	0.700 (0.411–1.190)	0.187
Hypertension	1.079 (0.713–1.633)	0.719
Diabetes mellitus	1.290 (0.721–2.311)	0.391
Hyperlipidemia	0.981 (0.622–1.546)	0.933
ST-segment elevation	5.643 (1.373–23.188)	0.016
Antiplatelets	0.903 (0.404–2.021)	0.805
β Blockers	0.809 (0.454–1.442)	0.472
RAAS inhibitors	0.472 (0.258–0.862)	0.015
Statins	0.398 (0.259–0.614)	<0.001
Depression	7.250 (4.735–11.100)	<0.001

HR indicates hazard ratio; RAAS, renin-angiotensin-aldosterone system.

Several limitations were observed in the current study. First, patients with previous myocardial infarction and atrial fibrillation were excluded, which may make us underestimate the incidence of MINOCA outcome events. Second, residual confounding may exist in the association with depression, such as marital status or socioeconomic status; however, we did not have the data on these variables. Third, patients in the study sample were enrolled from a single Cardiology Department at one hospital, thereby raising concerns on generalizations from its findings. Fourth, an unavoidable limitation is the exclusion of patients who refused to give written informed

Table 3. Multiple Cox Regression of Variables Influencing Cardiovascular Events

Variables	HR (95% CI)	*P* Value
Age, y	1.007 (0.995–1.020)	0.260
Female sex	1.157 (0.852–1.573)	0.350
Current smoking	0.887 (0.597–1.317)	0.551
Hypertension	0.920 (0.677–1.249)	0.592
Diabetes mellitus	0.776 (0.537–1.121)	0.177
Hyperlipidemia	1.014 (0.725–1.418)	0.935
ST-segment elevation	2.591 (1.348–4.979)	0.004
Antiplatelets	1.089 (0.642–1.847)	0.753
β Blockers	0.941 (0.617–1.435)	0.777
RAAS inhibitors	0.584 (0.393–0.869)	0.008
Statins	0.496 (0.360–0.681)	<0.001
Depression	3.411 (2.490–4.674)	<0.001

HR indicates hazard ratio; RAAS, renin-angiotensin-aldosterone system.

consent. We tried to minimize the potential bias by enrolling volunteers consecutively. Fifth, we did not assess other psychiatric comorbidities. Finally, we did not collect data on Takotsubo cardiomyopathy and structural heart disease, including significant valvular heart disease, cardiomyopathies, and left ventricular ejection fraction, because of most patients without intact information mentioned above, which might affect both the incidence of depression as well as mortality rates.

Conclusions

Depression is common among Chinese patients with MINOCA. More important, the new diagnosis of depression at the time of myocardial infarction is associated with increased risk of adverse clinical outcomes in patients with MINOCA. These results underscore the importance of monitoring depression in patients with MINOCA. Prospective interventional studies should be encouraged to determine whether depression treatment can actually improve clinical outcomes in this population.

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Disclosures

None.

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