Original Article

Association between N-terminal proB-type Natriuretic Peptide and Depressive Symptoms in Patients with Acute Myocardial Infarction

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Abstract

Background: While depression and certain cardiac biomarkers are associated with acute myocardial infarction (AMI), the relationship between them remains largely unexplored. We examined the association between depressive symptoms and biomarkers in patients with AMI.
Methods: We performed a cross-sectional study using data from 103 patients with AMI between March 2013 and September 2014. The levels of depression, N-terminal proB-type natriuretic peptide (NT-proBNP), and troponin I (TnI) were measured at baseline. The patients were divided into two groups: those with depressive symptoms and those without depressive symptoms according to Zung Self-rating Depression Scale (SDS) score. Baseline comparisons between two groups were made using Student's *t*-test for continuous variables, Chi-square or Fisher's exact test for categorical variables, and Wilcoxon test for variables in skewed distribution. Binomial logistic regression and multivariate linear regression were performed to assess the association between depressive symptoms and biomarkers while adjusting for demographic and clinical variables.
Results: Patients with depressive symptoms had significantly higher NT-proBNP levels as compared to patients without depressive symptoms (1135.0 [131.5, 2474.0] vs. 384.0 [133.0, 990.0], $Z = -2.470$, $P = 0.013$). Depressive symptoms were associated with higher NT-proBNP levels (odds ratio [*OR*] = 2.348, 95% *CI*: 1.344 to 4.103, $P = 0.003$) and higher body mass index (*OR* = 1.169, 95% confidence interval [*CI*]: 1.016 to 1.345, $P = 0.029$). The total SDS score was associated with the NT-proBNP level ($\beta = 0.327$, 95% *CI*: 1.674 to 6.119, $P = 0.001$) after multivariable adjustment. In particular, NT-proBNP was associated with three of the depressive dimensions, including core depression ($\beta = 0.299$, 95% *CI*: 0.551 to 2.428, $P = 0.002$), cognitive depression ($\beta = 0.320$, 95% *CI*: 0.476 to 1.811, $P = 0.001$), and somatic depression ($\beta = 0.333$, 95% *CI*: 0.240 to 0.847, $P = 0.001$). Neither the overall depressive symptomatology nor the individual depressive dimensions were associated with TnI levels.
Conclusions: Depressive symptoms, especially core depression, cognitive depression, and somatic depression, were related to high NT-proBNP levels in patients with AMI.

Key words: Biomarker; Depressive Symptoms; Myocardial Infarction; N-terminal proB-type Natriuretic Peptide; Troponin I

Introduction

Depression is a risk factor for morbidity and mortality in patients with coronary heart disease, especially after acute myocardial infarction (AMI).[1,2] A number of studies have demonstrated that a considerable percentage of patients with AMI experiences depressive symptoms,[3,4] which has an adverse impact on the cardiovascular prognosis.[5] However, little is known about how depressive symptoms contribute to cardiovascular disease.

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N-terminal proB-type natriuretic peptide (NT-proBNP) is a type of neurohormone synthesized and released mainly from

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the ventricular myocardium. This biological marker has been identified as a vital predictor of mortality and subsequent myocardial infarction (MI) in patients with AMI.[6-9] Prior evidence indicated that patients with major depressive disorder (MDD) had increased NT-proBNP levels,[10] and results from several surveys suggested that NT-proBNP levels were correlated with depressive symptoms in patients with cardiovascular diseases.[11,12] However, the above findings are not conclusive, with some studies failing to find a statistically significant association between NT-proBNP levels and depression.[13,14] Given the high prevalence of depressive symptoms in patients with AMI, assessing the relationship between depressive symptoms and clinical biomarker levels is particularly relevant.

In this study, we examined the association between depressive symptoms and NT-proBNP levels in patients who had recently experienced an AMI. In addition to the neurohormonal biomarkers (NT-proBNP), the study also included troponin I (TnI), a marker for myocardial injury based on prior studies.[13,14] We hypothesized that an association would exist between depressive symptoms and certain cardiac biomarkers in patients with AMI. Demonstrating this correlation could provide important insights into the potential pathways mediating depression associated with AMI.

Methods

Participants and study design

We performed a cross-sectional study in patients with AMI. The participants were enrolled between March 2013 and September 2014 in the Cardiac Intensive Care Unit of the Shanxi Provincial Cardiovascular Hospital in China. Patients were included if they were admitted within 24 h of the onset of symptoms. The inclusion criterion was the confirmed diagnosis of AMI according to the European Society of Cardiology Committee/American College of Cardiology Foundation Committee criteria,[15] including elevated cardiac marker levels, prolonged myocardial ischemic symptoms, or characteristic electrocardiographic ST changes. Patients had to be aged ≥18 years and able to complete interviews. Patients were excluded if they were transferred to the participating hospital from another facility after more than 24 h, unwilling to participate in the study, or unable to provide informed consent. Patients were also excluded if they had suffered a cardiac arrest or cardiogenic shock before admission. Patients with other macrovascular diseases, psychosis history, or other life-threatening comorbidities (such as cancer, renal failure), or involved in other studies were excluded from the study. A total of 121 patients were eligible for this study, but 6 (5.0%) were too clinically fragile to participate, and 12 (9.9%) patients were excluded due to missing data. Subsequently, 103 AMI patients were finally enrolled. Ethical approval for the study was obtained from the Shanxi Medical University Ethics Committee, and all participants provided written informed consent.

Data collection

The data from the patients were collected through standardized patient interviews conducted during the first 24 h after admission. The baseline values for the following clinical parameters were obtained: age, sex, marital status, body mass index (BMI), current smoking status, history of hypertension, history of diabetes mellitus, history of depression, and family history of coronary artery disease, blood pressure, left ventricular ejection fraction (LVEF), blood urea nitrogen (BUN), creatinine (Cr), white blood cell count (WBC), Killip class, electrocardiographic findings, number of coronary arteries with stenosis, and methods of treatment.

Psychological measurements

The Zung Self-rating Depression Scale (SDS)[16] was used to assess depressive symptoms in the patients with AMI during admission. The SDS is a 20-item self-report measure of depression. The respondents describe how often they experience each of the symptoms on a four-level scale, with values ranging from "a little of the time" to "most of the time". Consistent with previous studies,[14,17] the scale was divided into four factors: core depressive factor, cognitive factor, anxiety factor, and somatic factor. The total SDS score and the score for each individual factor were calculated separately. Depressive symptoms were defined as present when a patient had an SDS score of ≥50. The patients were divided into two groups: those with depressive symptoms (SDS score ≥50) and those without depressive symptoms (SDS score <50). In addition, the Zung Self-rating Anxiety Scale (SAS) was used to assess the anxiety levels at admission.[18] The type D personality scale (DS-14) was used to identify type D personality.[19] DS-14 comprises two seven-item subscales: negative affection (NA) and social inhabitation (SI). Type D personality is defined by a cutoff score of ≥10 on both subscales (NA ≥10 and SI ≥10). The SDS, SAS, and DS14 are widely used and are known to show good validity and reliability.[17-19]

Assessment of cardiac biomarkers

Baseline blood plasma samples were collected from patients with AMI at admission. After collection, the blood samples were refrigerated and immediately transferred to the laboratory where the NT-proBNP and TnI biomarker levels were analyzed within 24 h. The NT-proBNP level was measured using Vitek immunodiagnostic assay system (VIDAS, BioMerieux, France), while the TnI level was measured using immunochemiluminometric assay on a UniCel DXI 800 system (Beckman Coulter, USA).

Statistical analysis

Baseline comparisons between patients' groups with and without depressive symptoms were made using Student's *t*-test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Due to the skewed distribution of the biomarker data, the NT-proBNP and TnI levels were compared between groups using Wilcoxon test.

Binomial logistic regression was performed to assess the association between depressive symptoms (response variable) and multiple independent variables. Taking the sample size into account, we selected seven variables which had the smallest *P* values in the single-factor analysis as independent variables. The variables, including current smoking status, BMI, pulse pressure, NT-proBNP, TnI, number of coronary arteries with stenosis, and percutaneous coronary intervention (PCI) treatment, were entered into the analysis using backward selection. The NT-proBNP and TnI levels were treated as categorical variables, and the cutoff points were the clustering centroids (NT-proBNP: 600.0, 2000.0; TnI: 8.0, 23.0) using a two-step cluster analysis. The pulse pressure variable was classified according to the 25th and 75th percentiles (40.0, 62.0).

To gain further insights into which depressive dimensions are associated with these biomarkers, we evaluated the association between the SDS depressive dimensions, SDS total score, SAS total score, and biomarker levels (NT-proBNP, TnI) after controlling for the effects of current smoking status, BMI, pulse pressure, number of coronary arteries with stenosis, and PCI treatment, using multivariate linear regression analyses.

Data collection and analysis were performed using SPSS for Windows (version 17.0; SPSS, Chicago, IL, USA). All the tests were two-tailed and the significance threshold was $P = 0.05$.

Results

Sample characteristics

Of the 103 patients with AMI, 36 patients (35.0%) were found to have depressive symptoms. Table 1 summarizes the baseline characteristics of the patients with and without depressive symptoms. The BMI was significantly higher in the group with depressive symptoms than that in patients without depression ($t = -2.240$, $P = 0.027$). None of the patients in the two groups reported a clinical diagnosis of depressive disorder before admission. There were no significant differences in age, sex, marriage status, current smoking status, medical histories, and family history of coronary artery disease, blood pressure, LVEF, BUN, Cr, WBC, AMI severities, or types of treatment between patients with or without depressive symptoms. No significant difference was determined in the type D personality between AMI patients with depressive symptoms (27.8%) and patients without depressive symptoms (20.9%).

Distribution of biomarker levels

Table 2 presents the median and the 25th and 75th percentiles of the NT-proBNP and TnI levels in patients with AMI with and without depressive symptoms. In particular, patients with depressive symptoms had significantly higher NT-proBNP levels as compared to patients without depressive symptoms ($Z = -2.470$, $P = 0.013$). The TnI levels were not significantly different between the patients with and without depressive symptoms.

Associations between depressive symptoms and biomarker levels

The optimal model of logistic regression showed that depressive symptoms were associated with higher NT-proBNP levels (odds ratio [*OR*] = 2.348, $P = 0.003$) and higher BMI ($OR = 1.169$, $P = 0.029$) after controlling for the effects of all the other clinical variables. The NT-proBNP levels and BMI tended to be associated with an increased risk for depressive symptoms in patients with AMI. The results are presented in Table 3.

Using multivariate linear regression, we first evaluated the relationship between the total SDS score and the predictor variables. The results showed a significant association between the total SDS score and the NT-proBNP level ($\beta = 0.327$, $P = 0.001$) after multivariable adjustment, which was consistent with the results mentioned above [Table 4].

Next, we separately examined the relationships between each depressive dimension and the biomarker levels. Core depression ($\beta = 0.299$, $P = 0.002$), cognitive depression ($\beta = 0.320$, $P = 0.001$), and somatic depression ($\beta = 0.333$, $P = 0.001$) were associated with high NT-proBNP levels. Since the NT-proBNP levels were not seen to be significantly associated with the SDS anxiety factor, the anxiety factor was not included in the model. To verify this, we finally used the total SAS score as the response variable; the results showed that the NT-proBNP level was not associated with anxiety either. There was no evidence of an association between depression and TnI levels either for overall SDS score or for any of the depressive dimensions [Table 4].

Discussion

In this study, we evaluated whether AMI biomarkers, including NT-proBNP and TnI, can potentially mediate the depressive symptoms associated with cardiovascular disease. The results suggested that patients with depressive symptoms had higher NT-proBNP levels compared to patients without depressive symptoms. In particular, the NT-proBNP level was associated with three depressive dimensions, including core, cognitive, and somatic depressive factors. Thus, NT-proBNP might be used as a biomarker for overall depressive symptomatology, core depression, cognitive depression, and somatic depression dimensions.

The current findings provided important insights into the association between depression and AMI. First, we examined depressive symptomatology as a whole, multidimensional entity so that we can have a more comprehensive understanding of whether previous research findings were confounded due to considering depression as homogeneous. Second, this study revealed the positive association between depressive symptoms and NT-proBNP levels in patients with acute stages of AMI.

The association between depression and NT-proBNP levels has been studied in different clinical studies.[10,20,21] In elderly patients with type 2 diabetes, a relatively weak

Table 1: Baseline characteristics of AMI patients with and without depressive symptoms

Variables	AMI patients with depressive symptoms (SDS ≥50) (*n* = 36)	AMI patients without depressive symptoms (SDS <50) (*n* = 67)	Statistical values	*P*
Age (years)	62.86 ± 14.98	61.16 ± 12.58	−0.610*	0.543
Male	27 (75.0)	54 (80.6)	0.437†	0.509
Married	34 (94.4)	65 (97.0)	0.415†	0.520
BMI (kg/m^2)	24.77 ± 3.45	23.29 ± 3.04	−2.240*	0.027
Current smoking	19 (52.8)	42 (62.7)	0.952†	0.329
Hypertension	19 (52.8)	29 (43.3)	0.848†	0.410
Diabetes mellitus	9 (25.0)	18 (26.9)	0.042†	0.837
Family history of CAD	6 (16.7)	12 (17.9)	0.025†	0.874
Systolic blood pressure (mmHg)	130.89 ± 25.36	127.55 ± 21.05	−0.077*	0.939
Diastolic blood pressure (mmHg)	78.28 ± 14.28	78.09 ± 10.40	−0.713*	0.477
Pulse pressure (mmHg)	52.61 ± 15.34	49.41 ± 14.98	−1.099*	0.316
LVEF (%)	48.97 ± 11.09	47.57 ± 10.62	−0.630*	0.530
BUN (mmol/L)	5.35 ± 1.85	5.17 ± 2.10	−0.430*	0.668
Creatinine (μmol/L)	49.93 ± 16.00	52.84 ± 19.91	0.805*	0.423
WBC count (×10^3/μl)	9.13 ± 4.62	9.00 ± 4.39	−0.141*	0.888
ST-elevation AMI	27 (75.0)	55 (82.1)	0.725†	0.394
Killip class			0.452†	0.798
I	18 (50.0)	32 (47.8)		
II	13 (36.1)	28 (41.8)		
III	5 (13.9)	7 (10.4)		
IV	0	0		
Diseased vessels (>75% stenosis)			5.438†	0.142
0	8 (22.2)	5 (7.5)		
1	16 (44.4)	29 (43.3)		
2	8 (22.2)	21 (31.3)		
3	4 (11.1)	12 (17.9)		
Reperfusion therapy				
Thrombolytic therapy	8 (22.2)	10 (14.9)	0.865†	0.352
PCI	18 (50.0)	42 (62.7)	1.550†	0.213
Medication				
Acetylsalicylic acid	33 (91.7)	63 (94.0)	0.206†	0.693
Clopidogrel	32 (88.9)	61 (91.0)	0.124†	0.737
Statins	33 (91.7)	62 (92.5)	0.025†	0.875
β-blocker	29 (80.6)	52 (77.6)	0.121†	0.728
ACEI/ARB	28 (77.8)	55 (82.1)	0.278†	0.598
Type D personality	10 (27.8)	14 (20.9)	0.621†	0.431
Depressive symptoms				
SDS total score	54.78 ± 4.57	39.69 ± 6.47	−13.738*	<0.001
Core depressive factor	18.11 ± 2.67	12.69 ± 3.03	−9.017*	<0.001
Cognitive factor	11.36 ± 1.85	7.46 ± 2.19	−9.070*	<0.001
Anxiety factor	4.61 ± 1.30	4.01 ± 1.26	−2.267*	0.026
Somatic factor	5.61 ± 1.23	4.39 ± 1.09	−5.207*	<0.001
SAS total score	39.16 ± 7.82	34.46 ± 5.71	−3.004*	0.004

Data are presented as *n* (%) or mean ± SD. *Student's *t*-test; †Chi-square test. AMI: Acute myocardial infarction; SDS: Zung Self-rating Depression Scale; BMI: Body mass index; CAD: Coronary artery disease; LVEF: Left ventricular ejection fraction; WBC: White blood cell; PCI: Percutaneous coronary intervention; ACEI: Angiotensin converting enzyme inhibitor; BUN: Blood urea nitrogen; SD: Standard deviation; ARB: Angiotensin receptor blocker; SAS: Zung Self-rating Anxiety Scale; 1 mmHg = 0.133 kPa.

association between NT-proBNP levels and depressive symptoms assessed on the Hospital Anxiety and Depression Scale (HADS) has been observed.[12] In patients with heart failure, individuals underwent depression assessment using the 17-item version Hamilton Depression Scale, and the results revealed that patients with severe depression showed a higher degree of BNP stimulation,[20] which was consistent with the results. Of interest, the plasma concentrations of NT-proBNP were positively correlated with the severity of depression in unmedicated patients with MDD.[10] On the other hand, some studies have found no association between NT-proBNP levels and MDD.[13,22] Another study used the 9-item Patient Health Questionnaire and reported that neither somatic nor cognitive depressive symptoms were

Table 2: NT-proBNP and TnI levels in AMI patients with and without depressive symptoms

Variables	AMI patients with depressive symptoms (n = 36)	AMI patients without depressive symptoms (n = 67)	Z	P
NT-proBNP (pg/ml)	1135.0 (131.5, 2474.0)	384.0 (133.0, 990.0)	−2.470	0.013
TnI (ng/ml)	1.0 (0.1, 16.9)	2.43 (0.5, 11.7)	−0.972	0.331

Data are presented as median (Q_1, Q_3). AMI: Acute myocardial infarction; NT-proBNP: N-terminal proB-type natriuretic peptide; TnI: Troponin I.

Table 3: Logistic regression analysis between AMI patients with and without depressive symptoms

Variables	Coefficients	SE	Wald	P	OR	95% CI for OR	
						Lower	Upper
NT-proBNP (pg/ml)	0.853	0.285	8.983	0.003	2.348	1.344	4.103
BMI (kg/m^2)	0.156	0.071	4.789	0.029	1.169	1.016	1.345

AMI: Acute myocardial infarction; NT-proBNP: N-terminal proB-type natriuretic peptide; BMI: Body mass index; *OR*: Odds ratio; *CI*: Confidence interval; SE: Standard error.

Table 4: Multivariate linear regression for SDS score, depressive dimensions, and SAS score in AMI patients

Dependent variables	Independent variables	Unstandardized coefficients		Standardized coefficients	t	P	95% CI for β	
		B	SE	β			Lower bound	Upper bound
SDS total score	NT-proBNP	3.896	1.120	0.327	3.478	0.001	1.674	6.119
Core depressive factor	NT-proBNP	1.490	0.473	0.299	3.149	0.002	0.551	2.428
Cognitive factor	NT-proBNP	1.144	0.336	0.320	3.400	0.001	0.476	1.811
Anxiety factor	Pulse pressure	−0.212	0.178	−0.118	−1.191	0.237	−0.565	0.141
Somatic factor	NT-proBNP	0.543	0.153	0.333	3.550	0.001	0.240	0.847
SAS total score	NT-proBNP	1.464	0.892	0.169	1.640	0.104	−0.309	3.236

SDS: Zung Self-rating Depression Scale; SAS: Zung Self-rating Anxiety Scale; AMI: Acute myocardial infarction; NT-proBNP: N-terminal proB-type natriuretic peptide; SE: Standard error; *CI*: Confidence interval.

significantly associated with NT-proBNP levels one month after AMI.[14] The difference might be partly due to the use of different tools and patient populations. It was reported that whether or not depressive symptoms are associated with cardiac disease seemed to depend on the measurement tools used.[23,24] Moreover, it should also be noticed that the depressive symptoms assessed by self-report scales were different from the clinical diagnosis of depressive disorder. Those patients who have typical depressive symptoms but do not fully fit the diagnostic criteria also deserve attentions.

In the study, we used the SDS since the scale has been recommended as an effective tool for depressive symptoms.[25] Core depression primarily reflects the emotional symptoms of depression such as depressed mood. Cognitive depression appears to reflect poor concentration or difficulty to make decisions. Somatic depression includes decreased appetite and tachycardia symptoms. The findings illustrated that these three depressive dimensions rather than the anxiety factor of depression might affect patients with AMI because of their association with NT-proBNP levels. The anxiety factor of SDS refers to symptoms such as irritability and psychomotor agitation. The findings failed to show a relationship between anxiety and NT-proBNP levels, and the result was verified using the SAS measure.

BNP and its NT-proBNP are synthesized and released from the cardiac ventricles in response to increased ventricular wall stress.[6] They are known to be increased in patients with heart failure, as well as in patients with MI. The ventricular dysfunction and/or myocardial ischemia can cause an increase in cardiac BNP and NT-proBNP expression. Recently, it has been shown that these markers are closely linked to the prognosis as a powerful predictor of both short- and long-term mortality after MI.[6] In this study, AMI patients with depressive symptoms had significantly higher NT-proBNP levels as compared to patients without depressive symptoms, while there were no significant differences in cardiac impairment (LVEF and Killip class) between two groups. The common pathophysiology under AMI and depression might explain this finding. Both AMI and depression could lead to the elevation of neurohormone and increase the levels of circulating inflammatory cytokines. As a result, when AMI and depression act together, they could enhance the pathophysiological changes and finally exacerbate the clinical manifestations.[26] Aguiar *et al*.[20] showed that heart failure patients with severe depression presented higher BNP levels but less cardiac impairment than those without depression or with mild and moderate depression. As mentioned in the introduction, depression is a risk factor for morbidity and mortality in AMI patients; even existing depressive symptoms will have an adverse impact on the cardiovascular prognosis.[4,5] It is supposed that depression can contribute to AMI partly due to the synergistic action between AMI and depression on neurohormonal activation.

However, the mechanisms underlying this association remain unclear; one possibility is that patients with depression might have impaired endothelial function,[27] thereby leading to the increased NT-proBNP levels.[28] In the other hand, the MI can act as a stressor to cause the depressive symptoms through certain neurohormones. Besides, given the potential role of personality in developing depression among patients with MI,[29] we also assessed the type D personality of patients, and we did not find a significant difference in the type D personality between AMI patients with or without depressive symptoms.

Cardiac TnI is a biomarker that reflects the severity of cardiovascular diseases. In the research, after adjustment for clinical characteristics, the TnI levels were not associated with overall depressive symptomatology or each depressive dimensions. This was consistent with former research which showed neither depression nor depressive symptoms in patients with premature acute coronary syndrome were associated with the TnI levels.[30] The depression in acute coronary syndrome patients might not be explained by TnI levels.

The findings should be interpreted with caution. First, the SDS depressive symptoms were self-reported in this study, and we did not assess patients for MDD. Second, although we accounted for several potential confounding factors for the NT-proBNP and TnI levels, other indicators such as the exact time of onset of chest pain were also likely to influence the outcome. Third, it was a preliminary, single-center study and the patient sample was not large enough. A comprehensive multicenter study involving a larger population with AMI is needed. Finally, due to a cross-sectional design, this study tested only baseline levels of depressive symptoms and the biomarkers, and we were unable to assess the changes in these variables over time. Future research should consider repeated measurements to further clarify the relationship between depressive symptoms and NT-proBNP levels.

In conclusion, the NT-proBNP level was shown to be independently associated with depressive symptoms in patients with AMI after adjusting for the effects of potential confounding variables. The data indicated that NT-proBNP levels could possibly be one of the potential links between depressive symptoms and AMI. Suffering from depression might lead to an increased impairment in cardiac function in patients with AMI. It is unclear whether NT-proBNP directly mediates the relationship between depressive symptoms and AMI or only represents one of the many biomarkers associated with depression. Further studies are necessary to explore its relationship and the mechanisms underlying these associations.

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Conflicts of interest

There are no conflicts of interest.

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