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Recognizing Increased Risk of Depressive Comorbidity after Myocardial Infarction: Looking for 4 Symptoms of Anxiety-Depression

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Key Words

Myocardial infarction · Mixed anxiety-depression · Depressive comorbidity

Abstract

Background: Screening for depression in myocardial infarction (MI) patients must be improved: (1) depression often goes unrecognized and (2) anxiety has been largely overlooked as an essential feature of depression in these patients. We therefore examined the co-occurrence of anxiety and depression after MI, and the validity of a brief mixed anxiety-depression index as a simple way to identify post-MI patients at increased risk of comorbid depression. **Methods:** One month after MI, 176 patients underwent a psychiatric interview and completed the Beck Depression Inventory (BDI) and the Symptoms of Anxiety-Depression index (SAD₄) containing four symptoms of anxiety (tension, restlessness) and depression (feeling blue, hopelessness). **Results:** Thirty-one MI patients (18%) had comorbid depression and 37 (21%) depressive or anxiety disorder. High factor loadings and item-total correlations (SAD₄, $\alpha = 0.86$) confirmed that symptoms of anxiety and depression co-occurred after MI. Mixed anxiety-depression (SAD₄ ≥ 3)

was present in 90% of depressed MI patients and in 100% of severely depressed patients. After adjustment for standard depression symptoms (BDI; OR = 4.4, 95% CI 1.6–12.1, $p = 0.004$), left ventricular ejection fraction, age and sex, mixed anxiety-depression symptomatology was associated with an increased risk of depressive comorbidity (OR = 11.2, 95% CI 3.0–42.5, $p < 0.0001$). Mixed anxiety-depression was also independently associated with depressive or anxiety disorder (OR = 9.2, 95% CI 3.0–27.6, $p < 0.0001$). **Conclusions:** Anxiety is underrecognized in post-MI patients; however, the present findings suggest that anxiety symptomatology should not be overlooked in these patients. Depressive comorbidity after MI is characterized by symptoms of mixed anxiety-depression, after controlling for standard depression symptoms. The SAD₄ represents an easy way to recognize the increased risk of post-MI depression.

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Introduction

Comorbidity increases the risk of adverse outcomes in heart disease such as mortality and high medical costs [1]. These outcomes may be improved by recognizing psychi-

atric comorbidities that complicate treatment strategies of heart disease [2]. Depression is a common comorbidity in myocardial infarction (MI) patients [3], but many questions about post-MI depression remain unresolved. Its prevalence is related to time and method of assessment [3] and there is a need to focus on subclinical or prodromal symptoms [4] such as demoralization [5, 6] and anxiety [7, 8].

Anxiety is a prominent feature of depression in the acute [9], prodromal [10] and residual [4] phase. It activates the hypothalamic-pituitary-adrenal axis [11], enhances fibrin turnover [12] and reduces heart rate variability [13], causing an increase in cardiac risk. Accordingly, anxiety predicts cardiac events in middle-aged men [14] and post-MI patients [7, 8], over and above the effect of depression. Treatment of anxiety protects against ventricular tachycardia [15] and recurrent depression [16], while untreated anxiety decreases the effect of antidepressants [17].

Anxiety and depression symptoms tend to co-occur in patients recovering from an MI [18]; however, this issue has been largely overlooked [8]. Moreover, depression often goes unrecognized in MI patients [19] and health care workers should enhance the level of clinical suspicion for depression in these patients [20]. However, our methods for screening post-MI depression must be improved by using a limited number of questions [21], and the best way to accomplish this remains to be defined [19]. Health care workers often have to rely on intuition to estimate the risk of comorbid depression. A better approach would be to construct a brief index that can be used to identify high-risk patients. Such an index is likely to include both depression and anxiety symptoms.

Accordingly, the present study examines (a) the extent to which post-MI depression is characterized by symptoms of mixed anxiety-depression, and (b) whether a brief index of mixed anxiety-depression may benefit the identification of MI patients at risk of comorbid depression.

Method

Patients

Subjects were 176 consecutive post-MI patients (134 men/42 women; mean age = 60.1 ± 10.7 years) from the Maastricht University Hospital who were screened for depression using the Beck Depression Inventory (BDI) [22], the Symptom Check List-90 [23] and the Hospital Anxiety and Depression Scale [24]. The State-Trait Anxiety Inventory (STAI) [25] was added as a measure of self-reported anxiety levels. MI diagnoses were made by a cardiologist according to electrocardiographic signs of MI, enzyme as-

partate aminotransferase levels of at least 80 U/l, and clinical criteria. Exclusion criteria were recurrent MI or inability to fill out scales. Patients who refused to participate in the study (29%) were older and were more likely to be women ($p = 0.03$) [18]. The local Ethics Committee approved this study and all patients gave their written informed consent.

Standardized Psychiatric Interview

Patients were interviewed 1 month after hospitalization for MI by the second author (J.J.S.); DSM-IV criteria for major/minor depression were assessed by the Structured Clinical Interview (SCID-I) [26]. Patients were diagnosed with major depression if they fulfilled at least one core criterion (depressed mood or loss of interest) and at least 4 out of 5 additional criteria (sleep difficulties, loss of appetite/weight, fatigue, difficulty concentrating, psychomotor agitation/retardation, low self-esteem/guilt, thoughts of suicide) with a duration of at least 2 weeks [27]. Minor depression was included as a clinical diagnosis because subclinical levels of depression may also adversely affect cardiac prognosis [28, 29], and was considered present if patients fulfilled 1–3 additional DSM-IV criteria. The 17-item Hamilton Depression Scale (HAMD-17) was used to rate depression severity [30] and a cut-off score >17 was used to identify patients with more severe depression. In addition to depression, anxiety disorder was also diagnosed with the SCID-I.

Symptoms of Mixed Anxiety-Depression

One month after MI, all patients completed the BDI [22], Symptom Check List-90 [23], Hospital Anxiety and Depression Scale [24] and STAI [25]. Factor analysis of these scale scores yielded one dominant mixed anxiety-depression factor [9] as a core of distress (data not shown). Symptoms that correlated highly with this first unrotated factor were selected to comprise an index of mixed anxiety-depression symptomatology containing two anxiety items (tension, restlessness) and two depression items (feeling blue, hopelessness). This 4-item index correlated with the STAI anxiety scale (0.69) and with the BDI depression scale (0.71), and was labeled the Symptoms of Mixed Anxiety-Depression index (SAD₄; see Appendix). The BDI [22] was used as a comparison measure to validate the SAD₄ because it is commonly used in post-MI patients, and a BDI score ≥ 10 has been associated with a poor prognosis [3].

Endpoints and Statistical Analyses

The primary endpoint was the SCID-I diagnosis of major/minor depression according to DSM-IV criteria [26, 27]. The secondary endpoint was psychiatric disorder, defined as a composite of depressive and/or anxiety disorder. Left ventricular ejection fraction (LVEF) was used to control for disease severity as a determinant of distress. LVEF $\leq 50\%$ has been associated with increased risk of cardiac events [31] and was used to identify patients with significant cardiac disorder. Factor analysis and Cronbach's α were used to test the reliability of the mixed anxiety-depression scale. Differences in mean standard depression/anxiety scores between MI patients who had high versus low mixed anxiety-depression scale scores were examined. Crosstabulation was used to examine the relation between mixed anxiety-depression and diagnosis of clinical depression. Logistic regression analysis was used to test a model of clinical depression, with the BDI, the mixed anxiety-depression scale, LVEF $\leq 50\%$, sex and age as independent variables. All

Table 1. Mean depression and anxiety scores of post-MI patients who score high or low on the SAD₄ scale

	Low score on SAD ₄ (n = 107)	High score on SAD ₄ (n = 69)	F ¹	p
<i>Depression</i>				
BDI	4.7 (3.4)	11.3 (7.2)	65.2	0.0001
SCL-90	3.3 (3.0)	14.4 (8.9)	140.5	0.0001
HADS	1.7 (1.9)	5.1 (3.1)	84.3	0.0001
<i>Anxiety</i>				
STAI	31.2 (9.9)	44.8 (10.2)	77.8	0.0001
SCL-90	1.7 (2.0)	8.5 (6.3)	107.3	0.0001
HADS	3.5 (2.2)	8.9 (3.6)	150.9	0.0001
<i>Disease severity</i>				
LVEF	53.7 (9.9)	53.5 (10.5)	0.03	0.876

Standard deviations appear in parentheses. SCL-90 = Symptom Check List-90; HADS = Hospital Anxiety and Depression Scale.

¹ Degrees of freedom = 1, 174.

of these variables were entered at the same time. This analysis was also used to test a model of psychiatric disorder as a combined endpoint.

Results

Twenty patients met criteria for major and 11 for minor depression. This post-MI depression rate of 31/176 = 18% is in line with that of other studies [8]. The mean HAMD-17 score was 17.0 (SD = 6.2) for depressed and 7.3 (SD = 4.5) for nondepressed patients ($p < 0.0001$). Mean BDI (7.3) and STAI (36.5) scores were similar to those reported in other medical populations [18].

SAD₄ as an Index of Mixed Anxiety-Depression Symptoms

Factor loadings between 0.77 and 0.88 confirmed that symptoms of depression (feeling blue, hopelessness) and anxiety (tension, restlessness) co-occurred as one post-MI symptom dimension. Item-total correlations between 0.61/0.76 and Cronbach's $\alpha = 0.86$ indicated good internal consistency of the SAD₄ and warranted summing of item scores to comprise a rating of mixed anxiety-depression (range 0–16). Using the upper tertile as a cut-off (score = 3), 69 post-MI patients were classified as having high scores on the anxiety-depression scale (SAD₄ \geq 3) and 107 as having low scores (SAD₄ \leq 2). High SAD₄ scorers had 2- to 3-fold increased scores on standard depression and anxiety scales as compared to low SAD₄ scorers,

supporting the validity of the SAD₄ as an index of mixed anxiety-depression (table 1). Scores on the SAD₄ were not a function of the severity of cardiac disorder.

SAD₄ and Risk of Depressive Comorbidity

Elevated SAD₄ scores also indicated an increased risk of depressive comorbidity after MI. Nineteen out of 69 patients with high SAD₄ scores were diagnosed with major (28%) and 9 with minor (13%) depression; the corresponding figures for the 107 low SAD₄ scorers were 1 (1%) and 2 (2%), respectively ($p < 0.0001$). Mixed anxiety-depression (SAD₄ \geq 3) was present in 90% (28/31) of depressed patients (fig. 1a); standard depressive symptoms (BDI score \geq 10) only in 71% (22/31). All of the 20 severely depressed patients had high scores on the mixed anxiety-depression scale (fig. 1b). Logistic regression analysis indicated that mixed anxiety-depression symptoms were associated with increased risk of clinical depression (OR = 11.2, $p < 0.0001$) after controlling for BDI scores (OR = 4.4, $p = 0.004$), sex, age and LVEF (table 2, top). Hence, the SAD₄ index was successful in detecting the risk of depressive comorbidity above and beyond standard depressive symptoms.

SAD₄ and Risk of Depressive/Anxiety Disorder

The SAD₄ was also related to the composite endpoint of depressive and/or anxiety disorder. Eleven patients had an anxiety disorder; 5 of them also had clinical depression. Among patients with depression and/or anxiety, 62% (23/37) had standard depressive symptoms (fig. 2a)

Fig. 1. Percentage of patients with mixed anxiety-depression, stratified by diagnosis (a) and severity (b) of clinical depression. The SCID-I was used to diagnose clinical depression, and the HAMD-17 (score >17) to identify patients with more severe depression. The number of patients is presented on top of each bar.

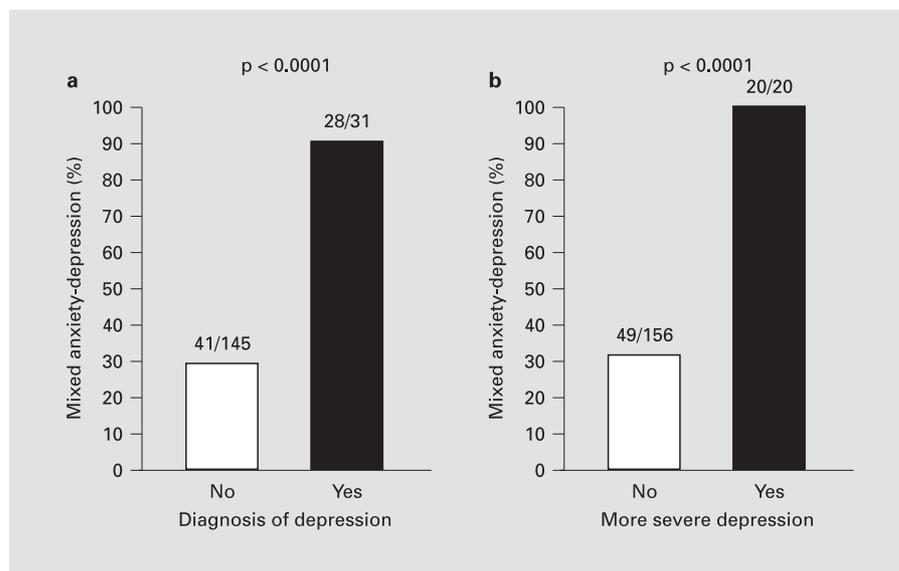


Table 2. SAD₄: independently associated with psychiatric comorbidity in post-MI patients

Variable	Odds ratio	95% CI	p
<i>Clinical depression</i> ¹			
Significant			
Mixed anxiety-depression (SAD ₄ ≥ 3)	11.2	3.0–42.5	0.0001
Standard depression scale (BDI ≥ 10)	4.4	1.6–12.1	0.004
Not significant			
Female sex	1.5	0.54–4.4	0.42
Age ²	0.96	0.92–1.0	0.08
LVEF ≤ 50%	1.5	0.58–4.1	0.39
<i>Depression/anxiety</i> ³			
Significant			
Mixed anxiety-depression (SAD ₄ ≥ 3)	9.2	3.0–27.6	0.0001
Standard depression scale (BDI ≥ 10)	2.8	1.1–7.1	0.035
Female sex	3.2	1.2–8.5	0.022
Age ²	0.96	0.92–0.99	0.046
Not significant			
LVEF ≤ 50%	1.5	0.58–3.7	0.42

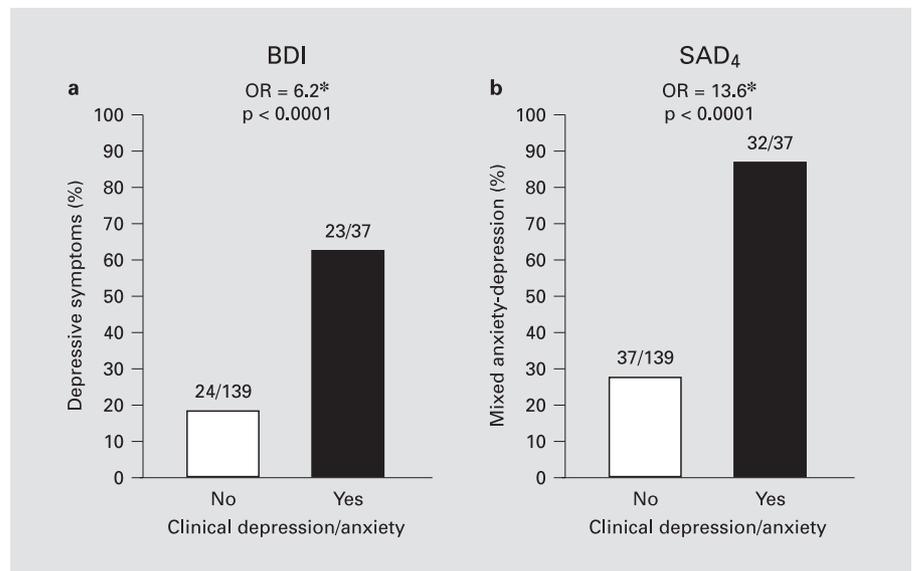
¹ Major and minor depression coded as 1.
² Estimated per one year increase in age.
³ Depression and anxiety disorder coded as 1.

while 87% (32/37) had mixed anxiety-depression symptoms (fig. 2b; SAD₄ ≥ 3). Standard depression symptoms (BDI; OR = 2.8, p = 0.035), female sex and younger age were associated with psychiatric disorder. After controlling for these variables, elevated SAD₄ scores (OR = 9.2, p < 0.0001) once again were associated with an increased risk of psychiatric comorbidity (table 2, bottom).

Discussion

The present findings showed that anxiety is a prominent feature of depression not only in psychiatric [4, 9] but also in post-MI patients, and that the 4-item SAD₄ is a reliable and brief index of mixed anxiety-depression symptoms after MI. This brief index was closely related

Fig. 2. Percentage of patients with standard depression symptoms (a) and mixed anxiety-depression symptoms (b), stratified by diagnosis of clinical depression or anxiety. The number of patients is presented on top of each bar. BDI ≥ 10 ; SAD₄ ≥ 3 . Asterisk = Adjusted for sex and age.



to frequently used anxiety/depression scales and indicated a substantially increased risk of clinical depression, after controlling for standard depression symptoms, cardiac disorder, age and sex. These findings were replicated when using a composite endpoint of depressive/anxiety disorder. Hence, this study underscores the role of anxiety in characterizing post-MI depression, and in recognizing the potential risk of depressive comorbidity that may affect clinical outcomes.

This study has some limitations. The number of depressed patients ($n = 31$) is relatively small, but the 18% post-MI depression rate corresponds well with that reported by others. MI diagnoses were based on electrocardiographic signs and enzyme aspartate aminotransferase levels but did not include other enzymes or proteins. Initial findings on the SAD₄ are promising, but more studies are needed to confirm its value to screen for depression, anxiety or other post-MI symptoms of distress such as demoralization [5]. Strengths of this study include the use of a structured interview to diagnose clinical depression, validation of the SAD₄ index against the BDI as a frequently used measure of post-MI depression, and the use of standard anxiety scales to document the co-occurrence of depression and anxiety.

This study is innovative because it stresses the role of anxiety as a core feature of depression in patients recovering from an acute MI, and offers a simple way to identify high-risk patients. The recovery period following MI is a vulnerable time [1], with higher mortality/morbidity risks in patients with comorbid depression. Depression

represents a mixture of sadness, loneliness and guilt [32], but these typical symptoms are not frequently reported by MI patients [33]. Rather, they complain primarily of atypical symptoms – like worries – that may be responsible for the strong association between depression and anxiety symptoms that we observed in our study [34].

Anxiety results from perceptions of threat and inability to control upcoming situations [32]. This anxious apprehension and arousal results in physiological changes that may affect the cardiovascular system, such as enhanced activation of the hypothalamic-pituitary-adrenal axis [11], increased fibrin turnover [12] and reduced heart rate variability [13]. Cardiovascular disease is more prevalent in anxious individuals [14, 32] and anxiety was found to be predictive of recurrent cardiac events in post-MI patients, over and above the effect of depression [7, 8].

This study offers a practical clinical tool to health care professionals to easily detect the risk of depressive disorder in patient recovering from MI. These professionals should enhance their level of clinical suspicion for post-MI depression [20]; they often have to rely on their intuition, and depression often goes unrecognized in MI patients [19]. One third of patients may also experience anxiety at the time of the cardiac event; in contrast, only 1 out of 3 anxious patients are asked about such symptoms [8] and anxiety is largely ignored in depressed patients [35]. Hence, screening for post-MI depression must be improved by using a limited number of items [21] that include symptoms of anxiety [7, 8]. The SAD₄

provides clinicians with such an easy way to recognize the risk of depression in a more standardized way: it proved to be a reliable index of depression, poses minimal burden to patients and can easily be used in research and practice.

Recently, a two-step approach has been recommended for clinical practice [36]. First, clinicians should use brief scales, such as the SAD₄, in order to screen for potential emotional problems. Second, if these problems are indicated, patients should be passed to qualified professionals for further evaluation and, when indicated, specific treatment. Cognitive behavior treatment may improve long-term outcome of depression by acting on anxiety as an important prodromal symptom of relapse [16], and anxiolytics may protect against the triggering of arrhythmias [15].

The diagnosis of post-MI depression is related to time/method of assessment [3] and self-report scales tend to overestimate the prevalence of depression. For example, only 47% of MI patients with a BDI score ≥ 10 crossed

the threshold for a depression diagnosis in our study. Yet, the relation between distress and prognosis is not confined to clinical depression alone but also includes elevated symptom scores [7]. The present study adds new information showing that these symptoms of distress are characterized by mixed anxiety-depression in post-MI patients.

In sum, clinicians frequently underrecognize the risk of depression [19] and anxiety [7, 8] in post-MI patients. Inclusion of the SAD₄ as a screening tool in clinical research and practice may help to address these issues, and future research needs to investigate the role of anxiety as a prominent feature and possible psychobiological mediator of depression in post-MI patients.

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Appendix: SAD₄

SAD₄

Name: Date:

Below are a number of problems that ill people often have. Please read each item carefully and then circle the appropriate number next to that problem. Indicate how much each problem has bothered you lately.

0 = Not at all	1 = A little bit	2 = Moderately	3 = Quite a bit	4 = Very much		
(1) I feel blue	→	0	1	2	3	4
(2) I feel hopeless about the future	→	0	1	2	3	4
(3) I feel tense or keyed up	→	0	1	2	3	4
(4) I feel restless as if I have to be on the move	→	0	1	2	3	4

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