Characteristics of Depressive Symptoms in Cardiovascular Disease

Christine Harrer¹, Nae-Yuh Wang², James Fauerbach², Una D McCann² and Marlene S Williams²*

¹Department of Cognitive Science, University of Vienna, Austria
²Department of Medicine, Johns Hopkins University, USA

Abstract

Depression often goes undiagnosed in patients with cardiovascular disease, which might be due to the particular symptoms in this group. We set out to characterize the features of depressive symptoms in two cohorts of patients with cardiovascular disease. We enrolled 287 patients admitted with cardiovascular disease; 152 had stable Coronary Artery Disease (CAD), and 135 had Acute Coronary Syndrome (ACS). Depression symptom severity was assessed using the Beck Depression Inventory-II (BDI-II). Results from the BDI-II were analyzed by factor analysis in order to distinguish somatic and cognitive-affective symptoms. Somatic symptoms were more prevalent than cognitive-affective symptoms in the entire group. Overall, ACS patients reported more severe somatic and cognitive-affective symptoms than patients in the stable CAD group. The most severe complaint in both groups was a change in sleeping patterns. The most frequently reported symptoms in both groups were loss of energy, fatigue, and altered sleep patterns, and occurred at similar rates in the two groups. Symptoms in males and females were reported at similar rates in both groups, with only a few exceptions. These findings highlight specific depressive symptoms that may assist in making the diagnosis of depression in cardiovascular disease patients.

Keywords: Acute coronary syndrome; Beck Depression Inventory-II; Cardiovascular disease; Coronary artery disease; Depressive symptoms; Somatic and cognitive-affective symptoms

Introduction

According to the World Health Organization (WHO), cardiovascular disease was the leading cause of death world-wide in 2012 [1], and ischemic heart disease and depression were determined to be the main contributors to the global burden of disease. Depression is an acknowledged risk-factor for cardiovascular mortality and morbidity [2], and surviving an acute coronary event may increase the risk of developing depression [3]. Even though there is a high prevalence of major depression and depressive symptomatology in patients with cardiovascular disease (approximately 20% and 31.1% respectively) [3], screening for depression in this population is not common practice and, as such, is often undiagnosed [4]. The characteristics of depressive symptoms in patients with cardiovascular disease may be one factor that confounds screening for depression.

Several studies have examined symptom-categories of depression in cardiovascular disease patients using the BDI-II in an effort to validate differing symptoms in this unique cohort [3,5-8]. A 2-factor analysis method categorizing symptoms into somatic and cognitive-affective factors has been well documented [9-11] and has been investigated among cardiovascular disease patients [12]. Studies have found that somatic symptoms are a top concern in patients with cardiovascular disease, and that somatic symptoms of depression are more likely to be associated with mortality and cardiovascular events in these patients than cognitive-affective symptoms of depression [13,14]. The REMOTE-HF clinical trial demonstrated that somatic depressive symptoms are independently associated with increased mortality in patients with heart failure [15]. Whether or not there are differences between stable CAD patients and those with acute coronary syndrome has not been previously reported. For this reason, we examined the prevalence of somatic and cognitive-affective symptoms in acute coronary syndrome patients and compared these symptoms to a cohort with stable CAD to fill this gap in the literature. We sought to determine whether there were unique features of depressive symptoms that distinguished the two populations. We hypothesized that there may be differences in the prevalence of somatic symptoms compared to cognitive-affective symptoms in the two cohorts, and that there may be different depressive symptoms that distinguish...
the two groups.

**Methods**

**Participants and study design**

We enrolled 300 patients with CAD (155 stable CAD and 145 ACS patients) between 2011 and 2015. Symptoms of depression were assessed by the Beck Depression Inventory-II scale (BDI-II). Patients admitted to the in-patient cardiology service at a single urban academic medical center between 2011 and 2015 with an ACS (unstable angina or acute myocardial infarction as defined by the WHO) [16] were approached for participation in this study, were screened, and if eligible, were enrolled within the first 72 h of hospitalization. In total, 145 ACS patients were enrolled in this study. Additionally, 155 stable CAD patients were recruited from outpatient cardiology clinics. The inclusion criteria for all participants were as follows: (1) Age >21 years, (2) stable CAD or ACS, (3) ability to provide written informed consent (4) ongoing aspirin use. The exclusion criteria included: (1) Age ≤ 21 years; (2) current use of antidepressants; (3) current or previous (14 days) use of glycoprotein IIb/IIIa; (4) active narcotic use by personal report or laboratory testing; (5) inability to give informed consent; (6) baseline platelet count <100 K/µl, or (7) chronic disease with a <1 year expected mortality.

The study was approved by the Johns Hopkins Institutional Review Board, and all patients provided informed consent. Upon consent, depression measures were assessed within 72 h of presentation for the ACS patients and at enrollment for the stable CAD patients.

**Depression and severity**

Depression severity and symptom identification was determined using the 21-item Beck Depression Inventory Second Edition (BDI-II) [9]. Of note, the BDI-II has previously been found to be suitable for assessment of patients with cardiovascular disease [17]. The BDI-II is a self-report questionnaire composed of 21 questions, and each question investigates a different symptom in the two-week period prior to completing the questionnaire. Each symptom is rated using a Likert-scale, with each question consisting of four statements that are scored from 0 to 3 (the patient selects the sentence that most accurately describes their circumstances). A higher score indicates greater perceived symptom severity, and a total BDI-II test score is determined via summation scores from each question. Total BDI-II test scores can range from 0 to 63, and indicate different depression groups such as: no symptoms of depression (0), minimal symptoms of depression (<10), mild-to-moderate symptoms of depression (10-18), moderate-to-severe symptoms of depression (19-29), and severe (≥ 30) symptoms of depression [9]. Therefore, a score lower than 10 indicates a low probability of clinically significant depression and a total score of 10 or higher indicates a higher probability of depression.

**Depressive symptoms**

Assessment of depression symptomatology followed the 2-factor analysis method categorizing symptoms assessed in the BDI-II into a somatic factor and a cognitive-affective factor [7,9]. The somatic factor is comprised of 7 symptoms (BDI-II items 15-21) including loss of energy, changes in sleep pattern, irritability, appetite change, concentration difficulty, fatigue, and loss of interest in sex. The cognitive-affective factor is comprised of 14 symptoms (BDI-II items 1-14) including sadness, pessimism, past failure, loss of pleasure, feelings of guilt, punishment feelings, self-dislike, self-criticism, suicidal thoughts or wishes, crying, agitation, loss of interest, indecisiveness, and feelings of worthlessness. The prevalence of the somatic factor was determined by adding the scores for questions 15-21 then dividing this score by the total score of all questions (1-21) for the entire group of patients. Similarly, the prevalence of the cognitive-affective score was determined by adding the scores for questions 1-14 then dividing this score by the total score of all questions (1-21) for the entire group of patients. The resulting percentage was defined as the prevalence of each factor among the total patient population.

**Symptom of highest severity**

Responses to each question on the BDI-II vary between 0-3, with 0 indicating no severity and 3 being the highest severity. When patients scored an individual BDI question with a score of 2 or greater, we interpreted this as a symptom that was more severe than those questions that were scored 0 or 1. We then listed the symptoms chosen to be the most severe in the ACS group and compared these to those listed in the CAD group.

**Prevalence of reported symptoms:** The scores for each question were added, and then divided by the total score of all questions, to calculate the prevalence of each symptom within the two groups. The resulting percentage was defined as the prevalence of each factor among the total patient population.

**Prevalence of each factor (cognitive-affective factor vs. somatic factor)**

The scores for each question were added for each factor (cognitive affective factor vs. somatic factor) then divided by the total score of all questions to calculate the prevalence of each factor among the total patient population.

**Statistical Analysis**

Distributions of demographic and clinical characteristics of the study sample are described as means and standard deviations for continuous variables, and as frequency (%) for categorical variables. In the case of non-normally distributed ordinal variables, results are described as median values including lower and upper quartiles. Sigma Plot Version 12 and Stata was used for all statistical investigations.
considering \( p \leq 0.05 \) as statistically significant. Descriptive statistics and modeling were used for preliminary data analysis and data visualization. Chi-Square and Mann-Whitney U tests were the primary comparison tests employed. In particular, the Chi-Square test was used to compare frequency distributions of non-parametric variables; Chi-Square tests were used to compare the frequency of specific symptoms reported in the two patient groups, as well as the frequency of specific symptoms in the genders. Significance testing of the individual somatic and cognitive-affective symptoms included post-hoc Bonferroni corrections, defining significance level as \( p<0.0167 \) (0.05/3 tests). The Mann-Whitney U-test was used for comparison of non-normally distributed variables in the two groups, such as total BDI-II scores, total cognitive-affective scores and total somatic scores. Covariates considered were age and gender. Variables described by mean (+/- SD) were tested by t- tests and/or ANOVAs, while variables described by median (IQR) were tested with Mann-Whitney U-tests.

**Results**

**Sample characteristics**

Of the 300 patients initially recruited, 13 patients were excluded (1 incomplete BDI-II, 6 no blood draw, 2 screen failure, 2 inability to give informed consent, 2 withdrew consent) leaving 287 patients who completed BDI-II assessments. As seen in Table 1, the mean age of the participants was approximately 62 years, and were more likely to be Caucasian (79%). Females comprised approximately 28% of the sample. Most patients had hypertension (80%) and hyperlipidemia (83%); roughly one-third of patients had diabetes mellitus (34%), approximately one-fourth reported a history of depression (26%) and were current smokers (26%). The mean body mass index was approximately 31 kg/m². No enrolled participants were being treated with antidepressant medications.

**Depressive symptom characteristics**

Somatic symptoms in the entire cohort accounted for 51.4% of total BDI-II scores, compared to 48.6% for cognitive-affective symptoms. Somatic symptoms in the ACS cohort accounted for 50.4% of total BDI-II scores, compared to 49.6% for cognitive-affective symptoms, as seen in Table 2. In the stable CAD cohort, somatic symptoms accounted for 52.7% compared to 47.3%. The median somatic score among stable CAD patients was 3.0 compared to 5.0 in the ACS patients (\( p=0.002 \)), indicating that ACS patients, as
Table 1: Baseline Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Total (N=287)</th>
<th>Stable CAD (n=152)</th>
<th>ACS (n=135)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), (± SD)</td>
<td>62.2 ± 11.1</td>
<td>65.3 ± 9.8</td>
<td>58.8 ± 11.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age Distribution (y, ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>63.0 ± 10.2</td>
<td>64.8 ± 9.4</td>
<td>61.0 ± 10.8</td>
<td>0.127</td>
</tr>
<tr>
<td>Male</td>
<td>61.9 ± 11.4</td>
<td>65.5 ± 10.0</td>
<td>58.0 ± 11.6</td>
<td></td>
</tr>
<tr>
<td>Gender n (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>80 (27.9)</td>
<td>43 (28.3)</td>
<td>37 (27.4)</td>
<td>0.97</td>
</tr>
<tr>
<td>Race/Ethnicity n (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>227 (79.1)</td>
<td>127 (83.6)</td>
<td>100 (74.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>African American</td>
<td>48 (16.7)</td>
<td>21 (13.8)</td>
<td>27 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3 (1.0)</td>
<td>1 (0.7)</td>
<td>2 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Education n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Lower Level</td>
<td>61 (21.5)</td>
<td>29 (19.1)</td>
<td>32 (24.1)</td>
<td></td>
</tr>
<tr>
<td>High School Grad</td>
<td>82 (29.6)</td>
<td>41 (27.0)</td>
<td>41 (30.8)</td>
<td></td>
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<tr>
<td>College-Some</td>
<td>66 (23.2)</td>
<td>37 (24.3)</td>
<td>32 (24.1)</td>
<td></td>
</tr>
<tr>
<td>College Grad</td>
<td>50 (17.6)</td>
<td>27 (17.8)</td>
<td>23 (17.3)</td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>26 (9.1)</td>
<td>18 (11.8)</td>
<td>8 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Marital Status n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Single</td>
<td>64 (22.5)</td>
<td>24 (16.0)</td>
<td>40 (29.3)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>154 (54.2)</td>
<td>84 (56.0)</td>
<td>70 (52.2)</td>
<td></td>
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<tr>
<td>Divorced</td>
<td>32 (11.3)</td>
<td>18 (12.0)</td>
<td>14 (10.4)</td>
<td></td>
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<tr>
<td>Widowed</td>
<td>34 (12.0)</td>
<td>24 (16.0)</td>
<td>10 (7.5)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m², SD)</td>
<td>31.2 ± 6.9</td>
<td>31.5 ± 6.9</td>
<td>30.8 ± 7.0</td>
<td></td>
</tr>
<tr>
<td>Comorbidities n (%):</td>
<td></td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Hypertension</td>
<td>230 (80.4)</td>
<td>131 (86.8)</td>
<td>99 (73.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>238 (82.9)</td>
<td>141 (92.7)</td>
<td>97 (71.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>97 (34.0)</td>
<td>51 (34.0)</td>
<td>46 (34.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>History of CAD</td>
<td>215 (74.9)</td>
<td>152 (100)</td>
<td>63 (46.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of Depression</td>
<td>73 (25.7)</td>
<td>32 (21.2)</td>
<td>41 (30.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>75 (26.2)</td>
<td>25 (16.6)</td>
<td>50 (37.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SD: Standard Deviation; CAD: Coronary Artery Disease; ACS: Acute Coronary Syndrome; BDI-II: Beck Depression Inventory-II; BMI: Body Mass Index; MDD: Major Depressive Disorder
compared to patients with stable cardiovascular disease, judged that their somatic symptoms to be more severe. The median cognitive-affective score in stable CAD patients was 2.0, as compared to 4.0 in ACS patients (p=0.002). This, too, indicated that ACS patients judged their cognitive-affective symptoms to be more severe than did patients with stable CAD. Table 2 Symptoms reported as most severe among the entire group of patients were defined as having a BDI-II score of 2 or 3 (from a scale of 0-3, BDI-II score of ≥2). Out of a total of 6027 symptoms (21 items each from 287 patients), 398 symptoms were reported as severe. Among them 60% (238/398) of these symptoms were somatic symptoms. Overall, the frequency of severe somatic symptoms was higher than cognitive-affective symptoms (60% compared to 40%), as seen in Figure 1. A change in sleep patterns was reported as the most common severe symptom, and was reported by approximately 18.5% of the entire cohort (N=287).

When comparing symptoms reported as most severe (BDI-II score of ≥ 2) between ACS and CAD patients, changes in sleep patterns was reported as the symptom of highest severity among both patient populations (Figure 2a). However, ACS patients reported this change with a higher frequency (20%), when compared to CAD patients (17.1%).

We also compared the prevalence of symptoms reported among ACS and CAD patients. Loss of energy was the most commonly reported symptom in both patient populations, followed by fatigue and changes in sleeping patterns (Figure 2b). Among patients with stable CAD, women reported more crying (39.5% vs. 16.5%; p=0.002) and changes in sleeping patterns (62.8% vs. 45.0%; p=0.047) than men (Figure 3). Among ACS patients, men reported more pessimism than women (39.8% vs. 21.6%; p=0.049).

Discussion

Somatic symptoms were found to be more common than cognitive-affective symptoms with similar rates in patients with ACS and stable CAD. Taking into consideration that the somatic factor subclass is comprised of only 7 BDI-II items compared to 14 items encompassed in the cognitive-affective factor, this prevalence of somatic symptoms is quite substantial, and indicates that on average, patients rated somatic symptoms higher compared to cognitive-affective symptoms. Prior studies have shown that a 2-factor analysis provides an ability to distinguish somatic symptoms from cognitive-affective symptoms in patients with cardiovascular disease when compared to cohorts without coronary disease [7,8]. What has not been shown previously is the direct comparison of patients with ACS, as compared to those with stable CAD patients. In particular, the most severe symptoms reported by both groups were problems with sleep, loss of interest in sex, fatigue, and loss of energy. These symptoms were consistent between both cohorts. Other investigators have proposed that patients with cardiovascular disease may consider cognitive/affective symptoms to be less socially acceptable and more stigmatizing that somatic symptom and, as a result, report these symptoms less often [18]. Similarly, reporting bias has been proposed as an explanation for the increased prevalence of somatic symptoms in patients with cardiovascular disease, as it is considered easier for medical patients to report sleep or appetite disturbances than thoughts of hopelessness or suicide [19]. This issue may be unique to patients being assessed in a cardiac setting, given that we and others have enrolled these patients to assess depression post MI (i.e., they were not enrolled in a study of major depressive disorder, which may affect their willingness to report certain symptoms) [20]. Thombs et al., have reported that somatic symptoms accounted for 52.7% of total BDI-II scores in two separate groups of post-acute myocardial infarction patients [7]. Delisle et al. reported that somatic symptoms account for 66.3% and 62.1% of total BDI scores in two separate cohorts of hospitalized post-myocardial infarction patients [8]. However, these results are based on scores on the first edition of the Beck Depression Inventory (BDI) which may be inflated in hospitalized post-myocardial infarction patients [21]. As somatic symptoms of depression have been shown to predict all-cause mortality among ACS patients [14] and have consistently been found to be associated with adverse cardiovascular events in patients with heart disease [13], our results confirm and extend the importance of somatic symptoms among cardiovascular disease patients both stable and acute.

Somatic symptoms such as the loss of energy or fatigue and changes in sleep patterns commonly occur following acute myocardial infarction, which may contribute to missing the diagnosis of depression in this cohort [7,22]. The prevalence of somatic symptoms among cardiovascular disease patients has well been recorded in past and recent studies [23-25]. In fact, fatigue has long been confirmed as one of the risk factors for cardiovascular disease [23]. In our study, a loss of energy was the most frequently reported symptom, and a change in sleeping patterns was reported as the symptom of highest severity among the entire cardiovascular patient population.

Sleep disorder, poor quality of sleep and insomnia have been found to be correlated to cardiovascular disease [26,27] and depression [28]. Similar to our findings, Sepahvand et al. found that sleep disorders were the main complaint of heart disease patients [29]. Poor sleep and dysfunctional sleep have been associated with an increased risk for cardiac events [27], the development of heart disease [26,30] and a possible contributor to ACS pathogenesis [30,31]. Jackowska et al. have proposed that aberrant sleep patterns may increase the risk of cardiovascular outcomes via adverse impact on blood pressure and inflammation [32]. A correlation has long been established between dysfunctional sleep and mental illness. In particular, treatment-resistant or persistent depression is well-established to be associated with a worse cardiovascular outcome [33]. This relationship has been known to be bidirectional, with depression being a sign of unfulfilled need and poor emotional control [34]. The potential for a vicious cycle of depression and cardiac disease has well been established, with poor sleep quality accompanying depression and vice versa [35]. Therefore, the true relationship between sleep disorders and cardiac events remains to be determined.
with poor sleep [33,34]. Thus, based on the present and past research findings, sleep may be a potential important factor between depression and cardiovascular disease indicating a need for further investigation. For example, insomnia may represent depression symptom (e.g., if characterized by ruminination), or alternatively, could represent a symptom of worsening cardiovascular disease (e.g., if caused by shortness of breath). On the other hand, health risk behaviors (e.g., smoking, watching TV in bed) may be associated with poor sleep in either condition. Standard assessment such as those used here, may help refine aspects of the initial evaluation and, thereby, reveal the nature of somatic symptoms, associated pathology, and associated behavior. This, in turn, may prove useful for targeting patients with cardiovascular disease who may benefit from treatment for depression.

Finally, we were interested in gender differences in patients with stable cardiovascular disease and those with ACS. We found that the frequency of reported symptoms in both groups were similar between the genders, with only a few exceptions. Women with stable CAD reported more changes in sleeping patterns than men, and had a higher frequency of crying. Crying is known to be a more gender specific activity and researchers have found that inclusion of crying items in depression instruments may introduce a gender bias in the assessment of depression [35,36]. Men within the ACS group reported more pessimism than women in the same group. A prior study has also demonstrated that men have a significantly higher incidence of pessimism when measured by behavioral avoidance [36]. Dessotte et al. [37] performed a secondary analysis on two observational studies that enrolled patients hospitalized with heart disease using the BDI-I scale and found that women had increased somatic and cognitive-affective symptoms that are of particular concern clinically useful. Based on our results, there are specific somatic and cardiovascular disease patients with depression may prove to be of clinical relevance in the cardiovascular disease patient population.

For example, insomnia may represent depression symptom (e.g., if characterized by ruminination), or alternatively, could represent a symptom of worsening cardiovascular disease (e.g., if caused by shortness of breath). On the other hand, health risk behaviors (e.g., smoking, watching TV in bed) may be associated with poor sleep in either condition. Standard assessment such as those used here, may help refine aspects of the initial evaluation and, thereby, reveal the nature of somatic symptoms, associated pathology, and associated behavior. This, in turn, may prove useful for targeting patients with cardiovascular disease who may benefit from treatment for depression.

Focusing on the characteristics of depressive symptomatology may assist in the diagnosis of depression in these patients. Therefore, we believe that the current study adds to existing knowledge and may be of clinical relevance in the cardiovascular disease patient population. In addition, given that the loss of energy and a change in sleeping patterns was reported as the most concerning symptom in this cohort of patients, targeting specific somatic symptoms of depression, such as dysfunctional sleep, may have a beneficial effect on recovery of cardiovascular disease patients who have depression.

Future Research

Future studies could examine the validity of differences we found in somatic and cognitive symptoms between stable CAD and ACS patients. Future studies could also investigate potential mechanisms which may underlie symptoms rated most severe by these patients, such as the change in sleeping patterns and loss of energy. Mechanistic information linking cardiovascular disease and depression should be more intensely investigated. This is of high clinical importance as recent studies have found several potential links between depression and cardiovascular disease [40]. Future studies could also investigate the effect of treating symptoms of highest severity among a specific cardiovascular disease patient population, and the potential effects of such treatment on cardiovascular disease and depression progression.

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