Original article

Frequency and clinical correlates of bipolar features in acute coronary syndrome patients

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A B S T R A C T

Background: Depression and acute coronary syndrome (ACS) are both extremely prevalent diseases. Studies aimed at evaluating whether depression is an independent risk factor for cardiac events provided no definitive results. In most of these studies, depression has been broadly defined with no differentiation between unipolar (MDD) versus bipolar forms (BD). The aim of this study was to evaluate the frequency of DSM-IV BD (bipolar I and bipolar II subtypes, cyclothymia), as well as temperamental or isolated bipolar features in a sample of 171 patients hospitalized for ACS. We also explored whether these psychopathological conditions were associated with some clinical characteristics of ACS.

Methods: Patients with ACS admitted to three neighboring Cardiac Intensive Care Units (CICUs) in a 12-month continuous period of time were eligible for inclusion if they met the criteria for either acute myocardial infarct with or without ST-segment elevation or unstable angina, verified by standard ACS criteria. All patients underwent standardized cardiological and psychopathological evaluations.

Results: Of the 171 ACS patients enrolled, 37 patients (21.7%) were found to have a DSM-IV mood disorder. Of these, 20 (11.7%) had bipolar type I or type II or cyclothymia, while 17 (10%) were the cases of MDD. Rapid mood switches ranged from 11% of ACS patients with no mood disorders, to 47% of those with MDD to 55% of those with BD. Linear regression analysis showed that a diagnosis of BD (p = .023), but not that of MDD (p = .721), was associated with a significant younger age at the index episode of ACS. A history of previous coronary events was more frequent in ACS patients with BD than in those with MDD.

Conclusions: Our data indicate that bipolar features and diagnosis are frequent in ACS patients. Bipolar disorder has a negative impact on cardiac symptomatology. Further research in this area is warranted.

1. Introduction

It is well known that depression is highly prevalent among patients with acute coronary syndrome (ACS). The syndrome of major depression is present in approximately 15–23% of patients with cardiac disease, including those suffering from ACS [21,29]. Such rates are substantially higher than that seen in the general population (4 to 5%) or primary care patients (8 to 10%) making depression a condition affecting millions of patients with ACS annually [26,40]. Depression is a risk factor for the development of ACS, and worsens outcome when present in patients with established ACS, suggesting that depression is associated with both physiological and psychosocial changes that are deleterious to the cardiovascular system [12,19,34,37]. Depressive disorders increase the risk of rehospitalization after myocardial infarction and their treatment were found to have a positive impact on cardiac outcome [5,7,21,33].

Compared to the large body of literature on major depression and ACS, the association between bipolar disorder and ACS received less attention by researchers. Data from the National Comorbidity Survey Replication (NCS-R) showed that cardiovascular diseases are associated with bipolar disorder in women (OR = 2.8) after controlling for obesity, high blood pressure, smoking, diabetes and anxiety disorders [15]. Other studies...
reported that subjects with bipolar disorder show a two-fold cardiovascular mortality when compared with general population estimates [2,16,31]. Rush et al. [35] examined the association between mood symptoms and 10-year CVD risk estimated by Framingham risk score in a cohort of patients with bipolar disorder. They found that depressive symptoms were strongly associated with increased odds of long-term CVD risk. Depressive symptoms were also significantly associated with elevated blood pressure, glucose and BMI in bipolar patients.

The reasons for such associations have yet to be determined. Several studies in patients with BD observed an activation of pro-inflammatory cytokines during manic, depressed or euthymic episodes of bipolar illness; some markers seem to be more specifically related to bipolar disorder than to major depression [3]. Metabolic syndrome, a composite measure of many cardiovascular risk factors, is more common in patients with bipolar disorder than in the general population and may at least in part account for the increased cardiovascular risk in this population [39]. Intriguingly, manic/hypomanic symptom burden has been shown to predict cardiovascular mortality [16] and endothelial dysfunction [17], raising questions about other explanations for elevated cardiovascular risk among bipolar patients. For example, in the Zurich Cohort Study, Angst et al. [2] found that group with bipolar I or II disorder had the highest risk for cardiovascular deaths and the group with major depression the highest for deaths by suicide.

All these data derive from studies conducted in samples of patients with bipolar disorder. However, we are unaware of any studies evaluating the frequency and clinical correlates of bipolar disorder in a clinical sample of patients with coronary heart disease. The aim of our study was to explore frequency of bipolar disorders (type I and type II and cyclothymia) and bipolar features (affective temperaments, euphoric and mixed states indicators) in a sample of 171 patients with ACS afferent to three neighboring acute cardiac units in a defined period of time. In particular, we were interested in evaluating whether bipolarity was associated to different clinical characteristics of ACS. The study was conducted within the framework of a prospective follow-up study of ACS patients.

2. Methods

2.1. Study population

Patients with ACS admitted to three Cardiac Intensive Care Units (CICUs) were eligible for inclusion if they met the criteria for either acute myocardial infarct with ST-segment elevation (STEMI) or without ST-segment elevation (NSTEMI) or unstable angina (UA), verified by standard ACS criteria. The three units were located in a northwest area of Italy, with an average distance of 40 miles from each other and serving similar geographic catchment areas in terms of socio-demographic characteristics. Exclusion criteria were neoplastic disease, severe pulmonary, hepatic or renal insufficiency, infections requiring antibiotics, autoimmune disease, immunosuppressive therapy, severe anaemia and severe degenerative disease of the central nervous system.

Two comparisons groups, one with mood disorders without cardiovascular risk factors and one with healthy individual with no mental or physical illness, were recruited to investigate biological and genetic correlates (data not presented here). The study was conducted in accordance with the Declaration of Helsinki, was approved by the local ethics committees and written informed consent was obtained from all patients.

2.2. Cardiological evaluation

Data on patients’ demographics, medical history, clinical characteristics, electrocardiographic findings, ACS definition and treatment interventions, as well as in-hospital outcomes were reported in a detailed standardized case record form, adapted from the Blitz Study [8], by a trained cardiologist in each CICU. The details on symptoms onset, first medical help seeking and arrival at hospital CICU were collected as soon as patients could be interviewed. Particular care was taken in assessing the timing of hospital CICU arrival, ECG execution, and reperfusion treatment. Additional items included length of stay in the CICU and overall hospital stay, timing of invasive procedures and transfer to a tertiary care hospital to undergo coronary angiography and/or revascularization.

2.3. Risk factors evaluation

All subjects were assessed at the time of enrolment for the following measures: resting blood pressure, cardiovascular risk factors, including tobacco smoking, diabetes mellitus, hypercholesterolemia and hypertension. The body height and weight, blood pressure, and body mass index (BMI) of all subjects were measured. Hypertension was defined as either resting systolic or diastolic blood pressure greater or equal to 140/90 mmHg at two different times or on antihypertensive medications. Diabetes mellitus was defined as a serum fasting glucose greater or equal to 7.1 mmol/l or on hypoglycemic medications. Hypercholesterolemia was defined as a fasting total serum cholesterol level greater or equal to 4.9 mmol/l or on anti-cholesterol drugs. Smoking status was recorded as current smoker or past smoker.

Fasting blood samples were obtained from all subjects to determine serum creatinine, glucose, C-reactive protein level and lipid levels.

2.4. Psychiatric assessment

All patients were evaluated by the Structured Clinical Interview for Psychiatric Disorders (SCID-I) [18] to determine the presence of Axis I psychiatric disorders according to DSM-IV criteria. Data on use of psychotropic medications was collected in the SCID-I appropriate section.

2.4.1. 17-Item Hamilton depression rating scale (HDRS)

The presence and severity of current depression was assessed by the 17-Item HDRS [22]. The HDRS provides an indication of depression and, over time, a guide to recovery. It is widely used and accepted outcome measures for evaluating the severity of depression symptoms in ACS patients. The HDRS was administered by a trained professional using a semistructured interview. Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe. Nine are scored from 0–2. Scores below or of 5 define the absence of clinically relevant depression; scores between 6 and 13 indicate mild depression; from 14 to 18 moderate depression; from 19 to above severe depression [35].

2.4.2. Beck depression inventory-II (BDI-II)

Baseline depressive symptoms were also evaluated by the BDI-II [4]. The BDI-II contains 21 questions, each answer being scored on a scale value of 0 to 3. The cutoffs used differ from the original: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms. The BDI-II showed concurrent validity with the Hamilton Depression Rating Scale. The BDI-II evaluates two components: the affective component (e.g., mood) and the physical or “somatic” component (e.g., loss of appetite). The purpose of the two subscales is to help determine the primary component of a patient’s depression.
2.4.3. Hamilton anxiety rating scale (HARS)

The HARS [23] was one of the first rating scales developed to measure the severity of anxiety symptoms, and is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where less than 17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe.

2.4.4. Assessment of bipolar spectrum features

2.4.4.1. Mood Spectrum Self-Report (MOODS-SR). The MOODS-SR [14] was also administered. This self-report instrument, derived from the corresponding structured interview [13], explores features associated with mood disorders. It focuses on the presence of manic and depressive symptoms, traits, and lifestyles that may characterize the “temperamental” affective dysregulations that make up both fully syndromal and subthreshold mood disturbances. The MOODS-SR consists of 161 items coded as present or absent for one or more periods of at least 3 to 5 days through the subject’s lifetime. The lifetime version includes either isolated or clustered symptoms and traits across individual’s lifetime. Five mania/hypomania factors (psychomotor activation, mixed instability, mixed irritability and euphoria) were derived in a factor analysis of 68 mania/hypomania spectrum items [9].

2.4.4.2. Rapid mood switching. Rapid mood switching (mood changing rapidly from happy to sad and back again) was operationalized according to MacKinnon et al. [30] by using the MOODS-SR question: “Have you ever switched back and forth quickly between feeling high and feeling normal or depressed?” Affirmative answers were followed by a request to specify the frequency of mood switches and other three probe questions related to mood instability: “You felt like crying and laughing at the same time?”, “You had trouble controlling your temper: for example, you felt that you really needed to even the score?”, “You found yourself shouting at people or starting arguments or fights even over minor matters?”.

2.4.4.3. The Temperament Evaluation of Memphis, Pisa, Paris and San Diego-autoquestionnaire version (TEMPS-A). The TEMPS-A is a self-report questionnaire designed to measure temperamental variations in psychiatric patients and healthy volunteers [1]. Its constituent subscales and items were formulated on the basis of the diagnostic criteria for affective temperaments (cyclothymic, dysthymic, irritable and hypertymnic). The TEMPS-A in its shortened version of 39 (out of the originally proposed 110) items has shown excellent internal consistency. For research and clinical purposes, the TEMPS-A instrument has been standardized in patients with mood disorders, relatives of bipolar probands and normal controls, and can be used to explore and test various hypotheses about the origin, genetics, and clinical aspects of mood disorders.

2.5. Statistical analyses

The data were analyzed using the Statistical Package for Social Sciences (SPSS) version 20 (SPSS, Chicago, IL, USA). Frequency distribution, cross tabulation and tests of statistical significance were carried out. Comparisons among groups on categorical variables were performed by the chi-square tests with adjusted standardized residuals. For continuous variables, ANOVAs with Tukey's post-hoc test were performed. Predictors of individual's age at ACS index episode (dependent variable) were investigated by a linear regression analysis using risk factors (smoke, hypertension, diabetes, family loading for ACS) and psychiatric diagnoses (bipolar disorder, major depression) as independent variables. Comparisons were considered statistically significant at the 5% (p ≤ .05).

3. Results

3.1. Baseline characteristics

The sample consisted of 171 adult patients admitted with ACS (n = 97 STEMI, age 58 ± 11 years; n = 57 NSTEMI, age 60 ± 7 years; n = 17 UA, age 62 ± 13 years) enrolled in a 1-month continuous period of time (Table 1). Sixty-five percent of the patients were hospitalized for their first ACS event. The majority of the patients were Caucasian males (135; 78.9%), with a mean age of 60.4 years ± 10.4; females were 36 (21.1%) with a mean age of 62.8 ± 11.9. A total of 13 (35%) females and 35 (25.9%) males had BDI-II scores of 14 or higher. Females were more likely to currently be taking psychotropic drugs (21.3%) than males (10.6%) (p < 0.001).

3.2. Frequency of mood disorders

Out of the 171 ACS patients evaluated by the SCID-I, 37 (21.7%) were found to have a mood disorder. As shown in Table 2, overall,

Table 1
Socio-demographic characteristics of patients (n = 171) with acute coronary syndrome (ACS) according to subtype of ACS.

<table>
<thead>
<tr>
<th></th>
<th>STEMI n=97</th>
<th>NSTEMI n=57</th>
<th>UA n=17</th>
<th>F, χ²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (overall mean ±SD)</td>
<td>60.1 ± 10.7</td>
<td>63.2 ± 9.3</td>
<td>63.2 ± 9.4</td>
<td>F=3.315</td>
<td>0.039</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>22 (23.4%)</td>
<td>15 (26.8%)</td>
<td>5 (31.2%)</td>
<td>χ²=7.509</td>
<td>0.276</td>
</tr>
<tr>
<td>Medium</td>
<td>27 (28.2%)</td>
<td>17 (30.4%)</td>
<td>5 (31.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>34 (36.2%)</td>
<td>21 (37.5%)</td>
<td>2 (12.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laurea Degree</td>
<td>11 (11.7%)</td>
<td>3 (5.4%)</td>
<td>4 (25.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Employment status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>1 (1%)</td>
<td>3 (5.3%)</td>
<td>1 (5.9%)</td>
<td>χ²=5.439</td>
<td>0.245</td>
</tr>
<tr>
<td>Employed</td>
<td>51 (52.6%)</td>
<td>36 (63.2%)</td>
<td>9 (52.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>45 (46.4%)</td>
<td>18 (31.6%)</td>
<td>7 (41.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>74 (76.3%)</td>
<td>45 (78.9%)</td>
<td>13 (76.5%)</td>
<td>χ²=1.147</td>
<td>0.782</td>
</tr>
<tr>
<td>Single/Divorced</td>
<td>17 (17.5%)</td>
<td>8 (14.3%)</td>
<td>2 (11.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widower</td>
<td>6 (6.2%)</td>
<td>4 (7%)</td>
<td>2 (11.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender (male)</strong></td>
<td>80 (82.5%)</td>
<td>46 (80.7%)</td>
<td>9 (52.9%)</td>
<td>χ²=7.749</td>
<td>0.021</td>
</tr>
</tbody>
</table>

STEMI: ST-elevation myocardial infarction; NSTEMI: no ST-elevation myocardial infarction; UA: unstable angina.

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20 ACS patients (11.7%) had a DSM-IV bipolar I, II or cyclothymia diagnosis (ACS/BD), 17 (10%) were the cases of major depression (ACS/MDD), while the remaining 134 (78.3%) subjects did not have BD or MDD (ACS/noBD/MDD).

### 3.3. Depression, anxiety and mania/mixed factors scores

As shown in Table 3, the three groups differed on HDRS total scores (p < 0.001), but not on HARS total scores (p = 0.358). As to mania, post-hoc tests showed that scores on ‘Psychomotor Activation’ (increased energy levels and activity, crowded or racing thoughts, shifting interests, talkativeness) were significantly higher among ACS patients with BD (p < .001) and, to lesser extent, in patients with MDD (p < .05) compared to those without mood disorders. Table 3 also shows that features of mixed mood states (‘mixed instability’) scored significantly higher in ACS patients with bipolar disorders (p < .001) than in ACS patients without mood disorders. Rapid mood switches have been found to be more frequent among ACS/BP group than in the ACS/noBD/MDD group (p < .001).

### 3.4. Cardiological correlates of bipolar features

As shown in Table 4, the mean age at the time of index episode of ACS was significantly younger in the ACS group with a history of bipolar disorder (55.5 ± 8.1) compared to ACS patients with no mood disorders (61.7 ± 11) (p = 0.04). A history of previous coronary events (myocardial infarction, unstable angina) was more frequent in ACS patients with bipolar disorder (35%) than in ACS group with major depression (17.3%) or the ACS group with no mood disorders (16.4%). This difference only approached statistical significance (p = 0.056). The frequency of smoking, diabetes and hypertension did not differ among the three ACS groups.

### 3.5. Results of linear regression analysis

A linear regression model was performed to evaluate the association between a lifetime diagnosis of bipolar depression or major depressive disorder and the individual’s age at the time of current hospitalization for ACS (dependent variable).

A number of possible confounding factors were also used in the model as independent variables (smoking, diabetes, hypertension, family loading for ACS). The results showed that smoking (p = .030), diabetes (p = .024), hypertension (p = .0001) and a diagnosis of bipolar disorder (p = .023) independently predicted an earlier age at the index ACS episode. Conversely, a history of MDD and a family loading for ACS did not predict an earlier age of the event (Table 5).

### 4. Discussion

Our study was purposely designed to evaluate frequency of bipolar disorders in a large sample of patients admitted to three Acute Cardiology Units for an acute coronary event. We found an overall frequency of DSM-IV mood disorders of about 22% of our ACS patients. Such a prevalence is consistent with that found in

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**Table 2**

Frequency of DSM-IV mood disorders and temperamental characteristics in patients with acute coronary syndrome (n = 171).

<table>
<thead>
<tr>
<th>Disorder</th>
<th>STEMI n = 97</th>
<th>NSTEMI n = 57</th>
<th>UA n = 17</th>
<th>Chi square</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression</td>
<td>8 (8.2%)</td>
<td>5 (8.8%)</td>
<td>4 (23.5%)</td>
<td>3.904</td>
<td>0.142</td>
</tr>
<tr>
<td>Bipolar I Disorder</td>
<td>3 (3.2%)</td>
<td>3 (5.3%)</td>
<td>0</td>
<td>Not performed</td>
<td></td>
</tr>
<tr>
<td>Bipolar II Disorder</td>
<td>5 (5.2%)</td>
<td>3 (5.3%)</td>
<td>0</td>
<td>Not performed</td>
<td></td>
</tr>
<tr>
<td>Cyclothymia</td>
<td>4 (4.1%)</td>
<td>2 (3.5%)</td>
<td>0</td>
<td>Not performed</td>
<td></td>
</tr>
</tbody>
</table>

**Temperamental characteristics**

- Depressive: 1.1 ± 1.4
- Cyclothymic: 1.7 ± 2.5
- Irritable: 1.4 ± 1.9
- Hyperthymic: 3.6 ± 2.2

ANOVA, F value

- Depressive: 1.1 ± 1.4
- Cyclothymic: 1.7 ± 2.5
- Irritable: 1.4 ± 1.9
- Hyperthymic: 3.6 ± 2.2

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**Table 3**

Depression, anxiety and mania-hypomania factors scores in patients with ACS at index episode.

<table>
<thead>
<tr>
<th>Factor</th>
<th>ACS WITH BD n = 20</th>
<th>ACS WITH MDD n = 17</th>
<th>ACS no BD/MDD n = 134</th>
<th>ANOVA, F value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton Depression Rating Scale</td>
<td>5.3 ± 3.9</td>
<td>9.3 ± 5.8</td>
<td>4.7 ± 4.2</td>
<td>7.780</td>
<td>0.001</td>
</tr>
<tr>
<td>Hamilton Anxiety Rating Scale</td>
<td>7.4 ± 3.9</td>
<td>5.3 ± 4.8</td>
<td>4.7 ± 4.2</td>
<td>1.780</td>
<td>0.358</td>
</tr>
<tr>
<td>Mania-Hypomania factor scores</td>
<td>5.3 ± 3.7</td>
<td>4.8 ± 3.3</td>
<td>2.6 ± 2.1</td>
<td>8.081</td>
<td>0.001</td>
</tr>
<tr>
<td>Psychomotor Activation (PA)</td>
<td>3.1 ± 1.4</td>
<td>1.4 ± 2.1</td>
<td>0.9 ± 1.4</td>
<td>6.841</td>
<td>0.002</td>
</tr>
<tr>
<td>Mixed Instability (MIN)</td>
<td>2.6 ± 2.8</td>
<td>2.8 ± 2.2</td>
<td>1.3 ± 1.5</td>
<td>4.052</td>
<td>0.021</td>
</tr>
<tr>
<td>Mixed Irritability (MIR)</td>
<td>3.4 ± 1.4</td>
<td>2.4 ± 0.9</td>
<td>2.7 ± 1.5</td>
<td>1.509</td>
<td>0.227</td>
</tr>
<tr>
<td>Rapid Mood Switching</td>
<td>11 (53%)</td>
<td>8 (47%)</td>
<td>14 (11%)</td>
<td>17.807</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ACS/BD: DSM-IV bipolar I, II or cyclothymia; ACS/MDD: DSM-IV major depression; ACS/noBD/MDD: no BD or MDD; SR: standardized residuals.

- As defined by Cassano et al., 2012 [6]; PA: increased energy levels and activity, crowded or racing thoughts, shifting interests, talkativeness; MIN: sexual promiscuity, alcohol-related mood changes and irritability, frequently changing jobs, residences, friends, and hobbies; MIR: irritability associated with the use of medications and medical illnesses; EU: mood elevation, high sense of humor, feeling persistently good or high; Post-hoc Tukey’s tests:
  - Major depression: group 1 vs group 3, p < .001, group 2 vs group 3, p < .05.

- Chi square 2012 [6]: group 1 vs group 3, p < .001.

- As defined by MacKinnon et al., 2003 [22], Mood changing rapidly from happy to sad and back again.
most previous studies reporting data on frequency of depressive syndromes in cardiovascular patients [26].

Interestingly, among ACS individuals with mood disorders, about 50% was found to have either a bipolar I or II subtype or cyclothymia according to the DSM-IV criteria. Data from the NCS-R indicate that comorbidity between bipolar disorder and cardiovascular disorders was among the most burdensome societal-level conditions [24]. In our study, patients with bipolar disorder were younger at the time of index ACS event and had a higher frequency of previous coronary events than patients with MDD or those with no mood disorders.

The association of bipolarity with age at index ACS episode was significant after controlling for important ACS risk factors such as smoking, diabetes and hypertension. It is interesting to note that smoking, although to a lesser extent than the bipolar diagnosis, predicted an earlier ACS event. Heavy cigarette smoking is common in bipolar patients; it starts in adolescence and rapidly reaches prevalence rates of about 60% in various studies [44]. Further studies to explore in detail the association among bipolarity, smoking and ACS are warranted.

Our data corroborate the hypothesis of an excess of cardiovascular risk in individuals with bipolar disorder compared to those with unipolar depression as reported in recent studies showing that cardiovascular diseases are the primary causes of premature mortality in persons with BD [2,20,28,41,42]. Whether the relationship between bipolar symptoms and cardiovascular risk reported in the literature is mediated by physiological mechanisms intrinsic to the disease process or reflects propensity to engage in long-term maladaptive health-related behaviors is an issue deserving further investigations [38,42]. It is noteworthy that, in our study, psychopathological state assessments indicate the presence of a substantial burden of bipolar mixed features (i.e., psychomotor activation, mood instability, irritability, rapid mood switches), rather than pure euphoric or depressive states [9,25]. Data from literature suggest that mixed episodes that risk-taking behaviors and alcohol abuse may be more prevalent in mixed than non-mixed manic episodes and are associated with poor outcome. Furthermore, mixed states have been found to be more likely than other episodes to be associated with medical disorders, including cardiovascular disorders [10,40]. These data warrant exploring more in depth whether mixed states are associated with factors of lifestyle (such as nutrition and alcohol consumption) that, in turn, increased cardiovascular risk in contrast to the more cautious lifestyle of patients with patients with non-bipolar depressive syndromes [32].

Patients with bipolar disorder are known to suffer a considerable number of associated pathologies that may manifest at earlier ages and with increased frequency than in the general population [27,38]. Weiner et al. [43] reviewed old and recent studies on cardiovascular mortality in bipolar disorder patients. In studies that specifically assessed cardiovascular mortality, bipolar disorder has been associated with a near doubling of risk and has a 10-year earlier mortality rate when compared to general population estimates. This may be explained by the elevated burden of cardiovascular risk factors found in this population. Individuals with bipolar disorder have higher rates of metabolic syndromes and risk factors for cardiovascular disease (e.g., obesity, hyperglycemia, hypertension, and type 2 diabetes) than the general population [11]. Accordingly, it is important to have precise and comprehensive diagnostic criteria to reliably identify features of bipolarity in patients with ischemic cardiac diseases. Identifying those depressed patients at the highest risk would greatly assist in risk stratification and in the design of appropriate treatments to improve survival in these patients. Furthermore, recognizing bipolar features in ACS patients with prevailing depressive symptoms has important implications for psychotropic treatment choice [6,33,36].

The results of the current study should be considered in the context of some limitations. The participating centers were not randomly selected. Substance abuse was considered an exclusion criterion. Frequency of bipolar disorder is relatively high compared to that of major depression, probably due to the fact that male gender is over represented in our sample. These factors may have led to a bias in terms of generalizability of our results. Several of our data were retrospectively collected and therefore submitted to recall bias. This might be also true for retrospective evaluation of age at onset of cardiovascular problems as well as of psychopathological symptoms that occurred across individual’s lifespan.

Apart from these limitations, this is the first study, to the best of our knowledge, exploring frequency and clinical correlates of bipolar features in a large sample of hospitalized patients with ACS. Despite data supporting an association between bipolar disorder and cardiovascular morbidity, many questions remain. Whether bipolar disorder leads to an increased risk of cardiovascular disease or whether cardiovascular disease elevates the likelihood that a person will suffer from bipolar disorder remain unanswered. Whether there is a temporal association between affective disorder and cardiovascular comorbidity is also unknown.

### Table 4
Cardiological correlates in ACS patients with bipolar disorder, major depression or no mood disorders.

<table>
<thead>
<tr>
<th></th>
<th>ACS with BD</th>
<th>ACS WITH MDD</th>
<th>ACS no BD/MDD</th>
<th>ANOVA, t value*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at index ACS episode (mean ± SD)</td>
<td>55.5 ± 8.1</td>
<td>60.6 ± 8.9</td>
<td>61.7 ± 11.0</td>
<td>3.055</td>
<td>0.05</td>
</tr>
<tr>
<td>History of previous coronary events</td>
<td></td>
<td></td>
<td></td>
<td>Chi square</td>
<td></td>
</tr>
<tr>
<td>Family loading for ACS</td>
<td>7 (35%)</td>
<td>3 (17.3%)</td>
<td>22 (16.4%)</td>
<td>8.889</td>
<td>0.046</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (35%)</td>
<td>6 (35.3%)</td>
<td>38 (28.3%)</td>
<td>1.354</td>
<td>0.507</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (25%)</td>
<td>11 (64.7%)</td>
<td>81 (60.4%)</td>
<td>2.636</td>
<td>0.268</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (60%)</td>
<td>9 (52.9%)</td>
<td>77 (57.5%)</td>
<td>0.540</td>
<td>0.973</td>
</tr>
</tbody>
</table>

* Post-hoc Tukey’s test: group 1 vs group 3, p = 0.04.

### Table 5
Linear regression for factors predictive of age at the time of the index ACS event.

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized coefficients</th>
<th>Standardized coefficients</th>
<th>t Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>60.242</td>
<td>1.807</td>
<td>33.329</td>
</tr>
<tr>
<td>Family loading for ACS</td>
<td>-2.998</td>
<td>1.681</td>
<td>-0.132</td>
</tr>
<tr>
<td>Smoking</td>
<td>-3.627</td>
<td>1.655</td>
<td>-0.165</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.6</td>
<td>2.02</td>
<td>0.171</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.934</td>
<td>1.617</td>
<td>0.277</td>
</tr>
<tr>
<td>Major depression</td>
<td>1.004</td>
<td>2.802</td>
<td>0.027</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>-5.519</td>
<td>2.398</td>
<td>-0.172</td>
</tr>
</tbody>
</table>

* Dependent variable: age at index ACS episode.
as is the nature of that association. Our study supports the emerging awareness of greater cardiovascular morbidity among bipolar patients and reveals a previously unreported association between bipolarity and individual's age at the time of ischemic episode in patients hospitalized for ACS [11]. These data should encourage further studies to assess pathophysiological links between affective bipolar syndromes and ischemic heart diseases.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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**References**