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Research article

Depression and the risk of adverse outcomes at 5 years in patients with coronary heart disease

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ABSTRACT

Background: Cardiovascular diseases are a public health concern worldwide, with high rates of morbidity and mortality. Depression is a frequent comorbidity in coronary heart disease (CHD). It can be caused by the experience of suffering from heart disease, but it can also influence the prognosis of the CHD. The prevalence of depression in patients with cardiovascular disease is twice as high as that in the general population.

Aim: Assess the influence of depression in the prognosis at 5 years in patients with CHD.

Methods: 145 patients diagnosed with CHD were recruited between September 2013 and June 2015. Depression was assessed based on the PHQ-9 results at the time of hospitalization and 3 months after discharged. Sociodemographic and clinical variables were collected. A 5-year follow-up was carried out to verify death, reinfarction or any adverse outcome.

Results: 20% of the study population had depression at hospital admission compared with 11% at 3 months. Depression at 3 months after discharged was a differentiating factor to present complications (42.6 months, CI 95% 27.3–57.9) compared with patients without depression (55 months, CI 95%, 50.9–59.1) (Log-Rank $p = 0.034$). In the unadjusted model, the risk of heart complications increased with patients that have comorbidities, such as diabetes (HR 2.78, 95% CI 1.21–6.3) or hypothyroidism (HR 2.5 95% CI 1.09–5.7). Also, patients with post-hospitalization depression at 3 months were 3 times (95% CI 1.023–8.8) more likely to have complications during the follow-up period than nondepressed patients. After risk factor adjustment, the HR for depression was 2.01 (95% CI 0.57–6.9).

Findings: Patients with depression at 3 months following the coronary event, presented complications sooner than those without depression.

1. Introduction

Non-communicable chronic diseases, primarily cardiovascular diseases (CVDs), are a growing public health concern worldwide. CVDs were the main cause of death in 2012 and were responsible for 17.5 million deaths (46%). Of these deaths, it is estimated that 7.4 million were caused by ischemic heart disease [1]. In the United States, 31.9% deaths were caused by CVDs in 2010 and the prevalence of CVDs is expected to increase by 10% between 2010 and 2030 [2]. In Colombia, between 2008 and 2012, the diseases of the circulatory system were the primary cause of death, with a mortality rate of 129.8 deaths per 100.000 inhabitants [3].

Although the majority of CVDs studies have focused mainly on the role of biological factors (e.g., dyslipidemia, hypertension, diabetes mellitus, a sedentary lifestyle, overweight, smoking), in recent years, studies that have focused on the role of psychological factors in the etiology and prognosis of these diseases, have gained strength [4, 5]. Anxiety, depression, and stress are among the most significant psychological risk factors for coronary heart disease, even after controlling biological risk factors [5, 6].

Major depression is considered a risk factor for coronary episodes in the healthy population. The prevalence of depression in patients with CVD is twice than in the general population; 1 in 5 patients with heart disease has depression, which makes them more susceptible to physical

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limitations, low life quality, recurrence, mortality, and higher health care costs. Furthermore, the mutually reinforcing bidirectional association between depression and CVD is clear [7, 8, 9]. Patients with coronary heart disease and depression have higher rehospitalization rates, a higher incidence of chest pain, and a greater risk of major cardiovascular events [10].

This study focused on evaluate the presence of depression in patients with coronary events during the acute event (time 0) and at 3 months post-hospitalization, and the prognosis at 5 years in terms of cardiovascular complications, reinfarction, and death.

2. Materials and methods

Between September 2013 and June 2015, 156 patients with chest pain were recruited during a hospital stay at the coronary care unit of a private facility; 145 patients with coronary disease were eligible and provided written consent. This study was conducted following the Helsinki Declaration parameters for research on humans. All procedures were approved by the ethics committee of the medical institution where the study was conducted (Report No. 018).

The inclusion criteria were patients aged >18 years, with an ischemic heart disease diagnosis (<1 month of progression) confirmed by coronary angiography, with cognitive, neurological, motor, and psychiatric capacity for suitable processing of the mental health tests. Participants diagnosed with other cardiovascular diseases such as myocarditis, pericarditis, and pulmonary thromboembolism were subsequently excluded following coronary angiography.

2.1. Procedures

2.1.1. Sociodemographic variables

Details of age, sex, marital status, socioeconomic background, educational level, occupation, and date of admission were obtained.

2.1.2. Clinical variables

Physiological variables such as weight, size, body mass index (BMI), blood pressure (BP), heart rate (HR), oxygen saturation (SaO_2), total cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), glycemia, C-reactive protein (CRP) were collected, besides ejection fraction (EF) by echocardiography. Personal history of diabetes, obesity and overweight, hypertension, dyslipidemia, previous coronary heart disease, congestive heart failure, hypothyroidism, smoking, and a sedentary lifestyle were established as compounding factors. The cardiovascular risk factors and pathological antecedents existing in this population were collected from the medical records, which were filled out by cardiologists.

2.1.3. Psychological variables

PHQ-9 was used to measure depression, a questionnaire that evaluates the nine criteria of the DSM-IV on a scale of 0 (not at all) to 3 (almost every day). This test is not only useful for diagnosing depression, but also a reliable and valid tool for assessing the severity of condition. A total score of <8 indicates that the person does not have depression, a total score of 8 or 9 indicates possible depression, and a total score of ≥10 indicates probable depression. The test has a sensitivity and an accuracy rate of 88% [11, 12]. PHQ-9 is sensitive and specific for major depression as well as for clinically significant depression in patients with cardiac disease [13]. Depression is an established risk factor in coronary heart disease [14], with an impact on cardiac prognosis. This study analyzed the repercussions of clinically significant depression (PHQ-9 ≥ 10) on the prognosis of these patients, for which the PHQ-9 variable was dichotomized in depressed (≥10) and non-depressed patients (PHQ-9 < 10) [15, 16, 17].

2.1.4. Events of interest or time-to-event outcomes

Reinfarction, death, cardiovascular death, and cardiovascular complications (arrhythmias, cerebrovascular event, stable or unstable angina without infarction, congestive heart failure, or acute pulmonary edema).

2.2. Study protocol

This study carried out three different information gathering phases. During the first phase, psychological variables were obtained at the time of admission and 3 months after discharge, by two psychology students who were trained beforehand on standardization and application of the questionnaire. The second phase was conducted by trained physicians, gathering clinical and sociodemographic variables found within the patients' medical records. The final phase consisted in the verification of the adverse outcomes (reinfarction, complications, and death) at 63 months of follow-up, from the beginning of the study until December 1st, 2018, by checking medical records and through phone calls.

2.3. Statistical analysis

The data were analyzed using the statistics program SPSS (V25.0). The descriptive analysis of the qualitative variables was performed using frequencies and proportions. The quantitative variables were analyzed using median and interquartile range (IQR).

Log rank tests were performed to assess a statistically significant trend in terms of time, until adverse outcomes have presented for each of the socio demographic and medical variables.

Multivariate Cox proportional hazards regression analysis was performed to evaluate the relationship between depression and the time to clinical events. These multivariate and survival analyses were performed with each of the interest clinical events (death, reinfarction, complications) as the dependent variable.

These analyses of the prognosis of death, reinfarction, or complications were conducted at two time-points: at the time of hospitalization for the coronary event (admission) and at the first follow-up appointment at 3 months after discharge. The comparison of the prognoses of interest in the presence of depression at these two time-points was necessary as the patients might have experienced depression either due to the clinical condition or due to hospitalization.

The model was built either with variables that showed a statistically significant association or with those that are acknowledged in the literature.

Additionally, the difference between patients who abandoned the study and those who were followed, was evaluated using Pearson's chi-square, for each of the variables.

All tests were two-tailed, and p value of <0.05 was considered significant.

3. Results

The study was conducted on 145 patients, in Figure 1, a flowchart of patients' selection and follow-up is presented. Table 1 displays the baseline sociodemographic and clinical characteristics.

In terms of complications, 45 patients were found to present the following at the time of hospitalization: 17 with arrhythmias (37.8%); 9 with congestive heart failure (20%); 8 with infectious complications (17.8%), and 6 with bleeding complications (13.3%).

Laboratory and clinical imaging variables were procured from the patients' medical records on inclusion in the study and at 3 months post-hospitalization (Table 2).

EF, ejection fraction; CRP, C-reactive protein; HDL, high-density lipoproteins; LDL, low-density lipoproteins; HbA1c, glycosylated hemoglobin; TSH, thyroid-stimulating hormone; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BF, breathing frequency; SaO_2, arterial oxygen saturation; BMI, body mass index.

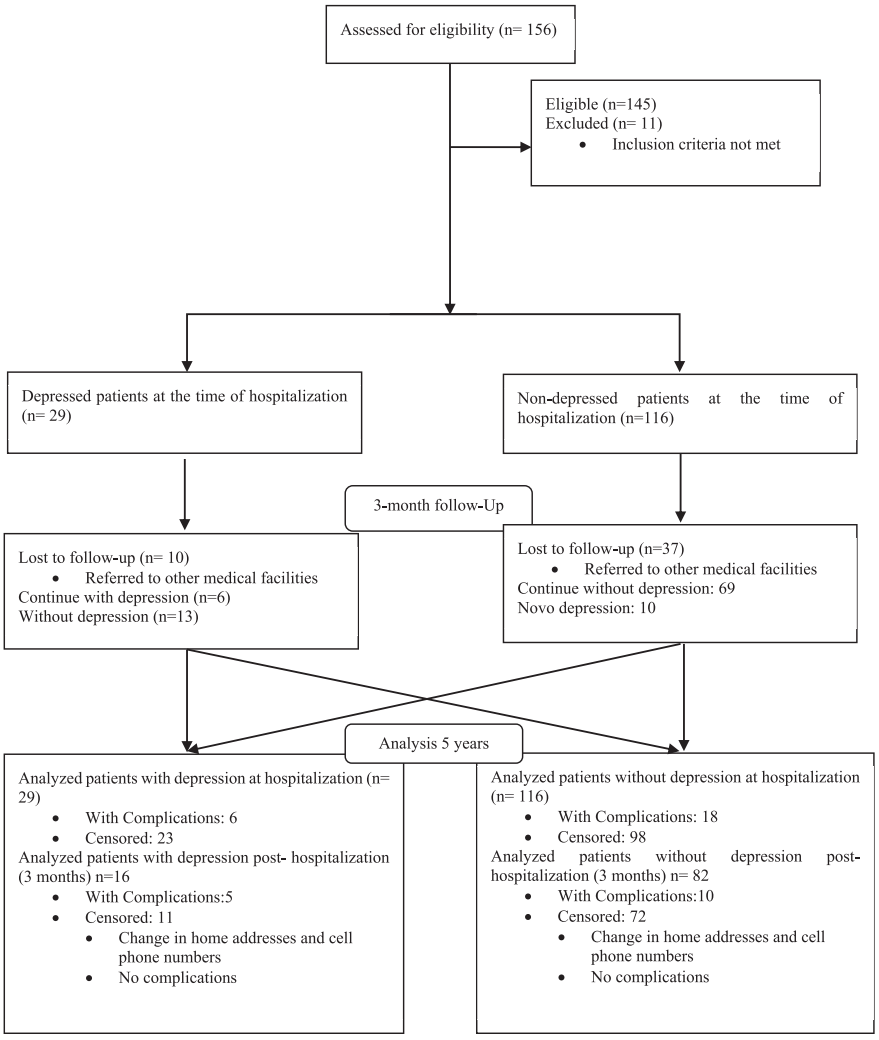

Figure 1. Flowchart of patient selection and follow-up.

Clinically significant depression was reported in 20% patients at time 0, and 11% patients at 3 months post-hospitalization. No statistically significant association was found in the analysis of the association of depression with the demographic variables and the pathological history.

3.1. Time-to-event analysis

Three different events were assessed for the predictive analysis of this study: death, reinfarction, and complications. The considered complications were congestive heart failure or acute pulmonary edema, cardiovascular event, arrhythmias, and stable or unstable pectoral angina without infarction. Ninety six of the 145 patients completed the 5 years follow-up (drop-out rate of 33.7%). No statistically significant difference was found between the patients who left the study and those who were followed.

Log rank tests were performed to assess a statistically significant trend in terms of time until adverse outcomes, for each of the sociodemographic and medical variables, finding significance with depression at 3 months, hypothyroidism ($p = 0.023$), and diabetes ($p = 0.011$). Patients with depression at 3 months after the coronary event were found to have complications earlier with the mean time of 42.6 months, compared to 55 months for patients without depression (Log-Rank $p = 0.034$) (Figure 2). No statistically significant difference was found for medical history of heart failure among patients with or without complications at 5 year ($p = 0.12$). Depression was not a differentiating factor for complications at the time of hospitalization.

In the unadjusted models, the risk of heart complications increased with patients that have comorbidities, such as diabetes (HR 2.78, 95% CI 1.21–6.3) or hypothyroidism (HR 2.5 95% CI 1.09–5.7). Also, patients with post-hospitalization depression at 3 months were 3 times (95% CI 1.023–8.8) more likely to have complications during the follow-up period than nondepressed patients (Table 3). After adjustment for several CVD risk factors and ejection fraction by echocardiography at the hospitalization, the HR for depression was 2.5 (95% CI 0.83–7.8) (Table 3).

This study found no difference in the median time to death or reinfarction between patients with and without depression at the time of hospitalization for a coronary heart event and at 3 months post-hospitalization.

4. Discussion

The purpose of this study was to assess the influence of depression on the prognosis of patients with coronary heart disease, in terms of cardiovascular complications, reinfarction, and death.

Depression was reported in 20% patients at time 0 and 11% patients at 3 months post-hospitalization. These figures are lower than those reported in other studies. It has been reported in literature that 20% of ambulatory patients with coronary heart disease can present depression [18], whereas 50% may present depression during hospitalization for acute coronary syndrome [19]. It has also been described how these patients may also develop post-infarction depression symptoms weeks

Table 1. Baseline sociodemographic and clinical characteristics.

	n (%)
Age (*Me, IQR)*	65 (13.5)
Males	96 (66.2)
Married or living with partner	89 (61.4)
Socioeconomic background	
Low	127 (87.6)
Medium	5 (3.4)
Educational level	
Primary	90 (62.1)
Incomplete secondary	19 (13.1)
High School diploma	13 (9)
Diagnosis	
AMI	77 (53.1)
Unstable angina	26 (17.9)
Stable angina	13 (9)
Atherosclerotic heart disease	20 (13.8)
Interventions	
Angioplasty with stent	65 (44.8)
Heart bypass	40 (27.6)
Pharmaceutical management	27 (18.6)
Medical history	
Hypertension	112 (77.2)
Hyperlipidemia	97 (66.9)
Overweight/obesity	76 (52.4)
Diabetes mellitus	55 (37.9)
Current smoking	23 (15.9)
Hypothyroidism	31 (21.4)
History of AMI	36 (24.8)
History of CHF	8 (5.5)

n, number of patients; Me, Median; IQR, interquartile range; AMI, acute myocardial infarction. CHF, congestive heart failure.

after discharge. Depression symptoms have also been frequently noted in patients during the period following AMI, reaching a prevalence of 45% [20]. The difference observed between the values of depression reported in this study compared with the literature may be derived from the tests applied. Thombs et al. [21] identified 24 original research studies published between 1986 and 2004 in which 14326 patients were evaluated through standardized interviews or validated questionnaires to assess depression. These researchers found that the prevalence of depression in individuals with acute coronary syndrome varies depending on the method of evaluation used. They also observed that it depended on the type of diagnosis identified and reported (major depression, minor depression, and dysthymia), the duration of the symptoms, necessary to establish the diagnosis, and the time of evaluation in relation to the AMI, excluding the possibility of depression being due to the features of the population, sample size, regional differences, or the quality of the evidence.

Considering the type of test used, it was observed that the values obtained in this study are similar to others that have used the PHQ-9 questionnaire at the time of AMI [22, 23]. A systematic review in 2014 [6] found differences depending on the type of questionnaire or the use of structured interviews, recommending the use of questionnaires and well-validated cut-off scores, as well as structured interviews to evaluate depression in future studies on the prognosis of depression after acute coronary syndrome. However, it has been demonstrated that the PHQ-9 has a significant concordance with psychiatric interviews; furthermore, it allows for greater coverage than a structured diagnostic interview [24].

Regarding time-to-event analysis, in the unadjusted model, this study found that having comorbidities, such as diabetes, hypothyroidism or post-hospitalization depression leads to a significant difference in the average time to present long-term cardiovascular complications. It is known that hypothyroidism has effects on cardiac function and is associated with an increased cardiovascular disease risk [25, 26], and that diabetes mellitus is a major risk factor of coronary artery diseases [27]. Clinical outcomes in coronary disease in patients with diabetes or hypothyroidism are poor despite improvements in medications and interventions.

The findings in depression are similar to those reported by Strik et al. [28], who states that major and minor depression predict an increased use of health care services, either for rehospitalization (OR 1.98; CI 95%, 1.0–3.93; $p = 0.04$) or for outpatient services (OR 3.75; CI 95%, 1.86–7.58; $p < 0.001$) without being able to predict death or reinfarction.

This study did not find that depression in patients during hospitalization and at 3 months is a differential predictor of cardiovascular mortality compared with patients without depression. However, major

Table 2. Clinical variables in an acute coronary event and at 3 months post-hospitalization.

	Time 0		Follow-up 1	
	n	Me (IQR)	n	Me (IQR)
EF echocardiography	141	50 (21)	39	55 (15)
Troponin I	108	1.30 (9.6)	0	-
CRP	13	8.23 (77.83)	0	-
Ultrasensitive CRP	15	17.8 (42.96)	0	-
Cholesterol	116	185 (75.5)	18	174.5 (81.5)
Triglycerides	115	160 (137.8)	18	145 (101.8)
HDL	111	38.5 (14.2)	18	42 (14.3)
LDL	105	112 (73.5)	16	90 (35.7)
TSH	108	2.39 (2.56)	0	-
Glycemia	42	125.5 (43.8)	13	103 (28.5)
HbA1c	63	6.1 (2)	5	6.2 (1.7)
SBP	145	132 (36.5)	95	120 (10)
DBP	145	75 (18.5)	95	70 (20)
HR	145	70 (17.5)	94	70 (8.5)
BF	145	18 (3)	86	18 (2)
SaO_2	143	94 (3)	1	-
BMI	144	25.7 (5.2)	71	25.7 (4.7)

n, number of people; Me, Median; IQR, interquartile range.

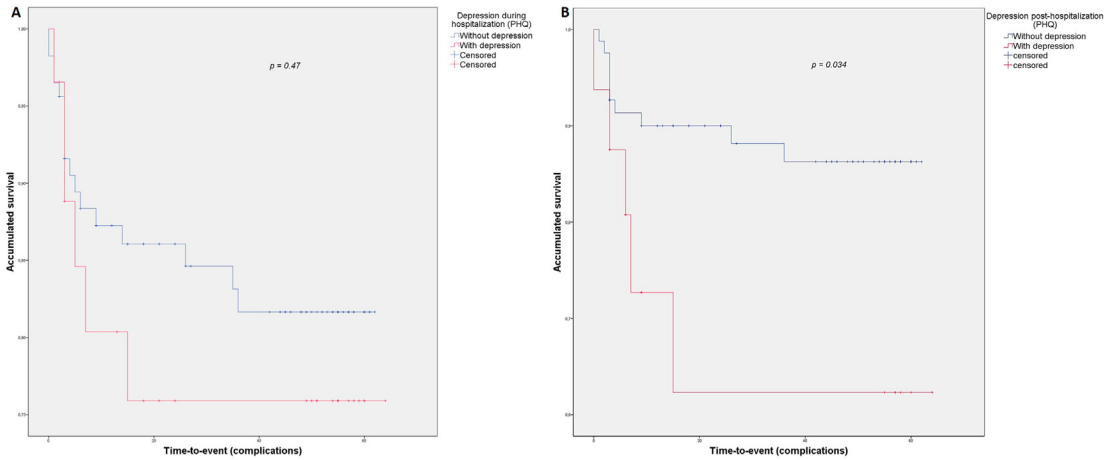

Figure 2. A. Complications at 5 years based on depression status in patients with coronary disease at the time of hospitalization. B. Complications at 5 years based on depression status in patients with coronary disease 3 months post-hospitalization.

Table 3. Complications at 5 years according to the covariables in Cox's regression.

		Crude HR (CI 95%)	Adjusted HR (CI 95%)
Hospitalization (admission)	Age	1.16 (0.34–3.9)	0.87 (0.25–3.02)
	Hypothyroidism	2.5 (1.09–5.7)*	1.86 (0.73–4.73)
	Depression	1.3 (0.53–3.36)	1.03 (0.38–2.74)
	Diabetes	2.78 (1.21–6.3)*	2.29 (0.93–5.62)
	History of CHF	2.4 (0.73–8.2)	1.25 (0.31–4.9)
	EF by echocardiography		
	≤39	1.28 (0.46–3.5)	0.94 (0.30–2.9)
	40-59	0.78 (0.29–2.1)	0.80 (0.29–2.1)
Post-hospitalization (3 months)	Age	1.16 (0.34–3.9)	0.34 (0.06–1.7)
	Hypothyroidism	2.5 (1.09–5.7)*	3.07 (0.88–10.7)
	Depression	3 (1.023–8.8)*	2.01 (0.57–6.9)
	Diabetes	2.78 (1.21–6.3)*	3.4 (0.9–12.1)
	History of CHF	2.4 (0.73–8.2)	1.89 (0.35–10.2)
	EF by echocardiography		
	≤39	1.28 (0.46–3.5)	0.51 (0.10–2.5)
	40-59	0.78 (0.29–2.1)	0.81 (0.23–2.8)

EF, ejection fraction; CHF, congestive heart failure. *p < 0.05.

depression, age, and left ventricular EF have been documented in the literature as independent factors for cardiac mortality at 10 years as reported by Connerney et al. [29], they observed that depression independently increases cardiac mortality by 1.8 times and that *de novo* depression post-cardiac intervention increases the risk of death from the same cause by 2-fold compared with patients who never had depression (HR, 2.1; 95% CI, 1.1–4.1; $p = 0.03$). In the study by Damen et al. [30] 1234 patients treated with percutaneous coronary intervention were followed up for 7 years. The researchers reported that depression remained independently associated with all mortality causes (HR, 1.63; 95% CI, 1.05–2.71; $p = 0.038$) after adjustment for sociodemographic and clinical features, anxiety, and type D personality.

Although, in this study, depression was not found to be a predictive factor for reinfarction in patients with established coronary heart disease, Yu et al. [20] found that the presence of post-hospitalization depression (one month) together with a low EF (<60%) was correlated with a higher frequency of major cardiac events at 12 months (cardiovascular death, rehospitalization, reinfarction, or revascularization). Similarly, Boyle et al. [31] document that depression in patients with coronary heart disease is associated with mental stress-induced myocardial ischemia, increasing the risk of reinfarction in patients with emotional stress by 1.3 times (OR, 1.30; 95% CI, 1.06–1.60; $p = 0.013$).

As documented in this study and in those previously described, depression associated with a coronary event is a prognostic factor for complications owing to heart damage. Some authors propose pathways or processes to explain the psycho-cardiac relationship based on molecular biology. Such processes appear to be independent of traditional cardiovascular risk factors (diabetes, hypertension, smoking, obesity, and dyslipidemia), as suggested by Headrick et al. [32], who propose four intrinsic processes: increased sympathetic activity, a reduction in parasympathetic (vagal) activity, chronic activation of the hypothalamic-pituitary-adrenal (HHA) axis, and immunoinflammatory dysfunction.

Therefore, the cardiovascular complications evaluated in this study might be explained by different mechanisms that interact and prolong the proinflammatory and neuroendocrine process in an acute coronary event, in which depression plays a significant role as it interferes with the process of cardiac remodeling.

Among the difficulties faced during the study, patient follow-up should be highlighted, considering that a significant number did not attend the reviews or were referred to other medical facilities after discharge from hospital, leading to a reduction in the number of controls at the specialized center in which this study was conducted. This phenomenon may be explained by the dynamics of the health care system,

which does not guarantee continuity of treatment and follow-up at a single health center. Furthermore, the frequent change in home addresses and cell phone numbers of the participants further hindered telephone follow-up. Moreover, as the health care facility is a specialized unit, patients are remitted from different nationwide medical institutions, increasing the possibility of loss of individuals from the clinical cohort followed in this study.

Previous studies have highlighted the long-term negative implications of depression on the prognosis of coronary heart disease. However, after risk factor adjustment, the Cox's multivariate analyses findings were inconclusive owing to several limitations, such as the sample size, the low rate of presentation of events, patient drop-outs at follow-up, incomplete records for some of the variables considered for the analysis, and the varied nature of depression itself as an intrinsic and indirect predictive factor. A larger sample size, better follow-up, and ideally, multicenter studies are recommended for future studies.

The main strength of this study is the fact that it is the first study in Colombia to perform a longitudinal follow-up of a group of patients with coronary heart disease from a biopsychosocial perspective, in which psychological and biomarker assessments were achieved, allowing the assessment of the influence of depression on clinical results.

For future research, it is recommended that potential contribution of other concomitant psychiatric ailments are assessed (for example, anxiety disorder), which may independently or synergistically increase the risk of adverse events in patients with acute coronary syndrome [6]. *The Netherlands Study of Depression and Anxiety* (NESDA) [33] reported that people with anxiety disorders exhibit a three-fold increase in the prevalence of heart disease (OR, 2.70; CI 95%, 1.31–5.56).

Despite the negative results of this study in the Cox's multivariate analyses, some interesting and potentially important observations emerged. In Colombia, clinical practice guidelines for coronary heart disease do not recommend routine screening and treatment of depression in this population [34]. This study suggests the need to establish multidisciplinary interventions for patients with coronary heart disease, with the psychological and psychiatric assessment and management during the acute episode and throughout follow-up, with the aim of detecting persistent depression symptoms and providing appropriate treatment for this population, in order to improve the quality of life of patients and the course of the disease [35, 36, 37].

5. Conclusion

In summary, in a cohort of patients with coronary heart disease and depression, at 3 months after discharge and followed for 5 years, complications were presented earlier than in those non-depressed. An assessment of the mental health of this population is pertinent, which allows a transdisciplinary therapeutic approach in order to improve the quality of life of patients and the course of the disease.

Declarations

Author contribution statement

M. Henao and D. López: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

M. Lemos: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

P. Ríos: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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