The association between depressive symptom scores, plasma C-reactive protein levels and postoperative length of stay in patients undergoing coronary artery bypass grafting

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Research Article

Keywords: coronary artery bypass graft, depression, C-reactive protein

Posted Date: February 22nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1243193/v1

Abstract

Background

This study aimed to identify the association of preoperative depressive symptoms and C-reactive protein (CRP) levels with postoperative recovery time of patients undergoing coronary artery bypass grafting (CABG).

Methods

The study included 212 elective CABG patients subdivided into two groups based on the presence or absence of preoperative depressive symptoms measured by the Beck Depression Inventory (BDI-II) and the PRIME-MD/PHQ-9 test score. The CRP was measured before surgery, and sequentially (1-6 days postoperatively) during the patient's in-hospital stay. Three summary scores of postoperative CRP response were generated: I) “early” (1-3) II) “persistent” (3-6) and III) “overall” (1-6 postoperative day).

Results

CABG patients with longer postoperative hospital length of stay (LOS > 7 days) have significantly higher total BDI-II (P = 0.014), and CRP measured on days 3 (P = 0.009), 4 (P = 0.001), 5 (P = 0.001), and 6 (P = 0.001) postoperatively, as well as higher “persistent” (P < 0.001) and “overall” (P = 0.004) CRP response. Association of “persistent” and “overall” CRP response to longer postoperative hospital LOS was also confirmed by binary logistic regression analysis. Patients with longer hospital LOS also had lower (P = 0.001) preoperative hemoglobin, a higher EuroSCORE II (P < 0.001), longer ventilation time (P = 0.016), and prolonged intensive care unit length of stay (P = 0.022) when compared to the group with shorter postoperative LOS (< 7 days). Significantly lower preoperative hemoglobin levels (P = 0.044), higher EuroSCORE II (P < 0.001), and longer ventilation time (P = 0.029) was also recorded among patients with elevated depressive symptoms (BDI-II >13).

Conclusions

Depressive symptoms are associated with higher operative risk expressed by calculating EuroSCORE II value, longer postoperative hospital LOS, higher preoperative and on the first postoperative day CRP values. There is also a positive correlation with the former and smoking, a slightly lower ejection fraction and significant anemia. A higher CRP on and after the third postoperative day is a positive predictor of an increase in length of postoperative hospital stay. Clinically compromised elderly CABG patients with pronounced comorbidities and female CABG patients were more prone to preoperative depression.

1. Background

Coronary artery disease (CAD) is a major form of heart disease and one of the leading causes of morbidity and mortality throughout the world (1). The traditional risk factors associated with initiation and progression of atherosclerotic lesions in the coronary artery walls include increasing age (> 45 years

in men and > 55 years in women), gender, unhealthy lifestyle behaviors (physical inactivity, smoking, and unbalanced diet) obesity, high blood cholesterol levels, diabetes, hypertension, family history and race (2). In addition, the patient's psychological state in terms of depression, anxiety, anger, and stress have also been implicated as potential risk factors in the development of an increased incidence of morbidity and mortality of CAD (3). Depression is highly prevalent (31% and 45%) in CAD patients, including those with stable CAD, unstable angina, or myocardial infarction (4). The prevalence of significant depressive symptoms is diagnosed in more than 20% of CAD patients while many more of them have subsyndromal depressive symptoms that are below the diagnostic threshold (4, 5). Therefore, depressive symptoms are frequently under-diagnosed and consequently left untreated in CAD patients although they may exist for a long time before the onset of CAD (5, 6). The bidirectional mechanisms responsible for the co-morbidity of depression and CAD are complex and multifactorial (7). Various pathophysiological triggers including neuroendocrine dysregulation, activation of the inflammatory response, increased platelet activation and aggregation, oxidative stress and endothelial dysfunction may all be involved in the relationship between depressive symptoms and CAD (3, 8–10). Individuals with depressive disorders tend to have elevated levels of inflammatory markers and pro-inflammatory cytokines that also undermine their response to conventional antidepressant therapy (10, 11). Among them, C-reactive protein (CRP), a marker of the acute phase response, has been used most extensively in clinical practice. Increased concentrations of peripheral blood CRP have been found in a subset of patients with acute depression when compared to control groups (12, 13). The relationship between the preoperative depression and anxiety with increased hospital length of stay (LOS) following the CABG procedures was also reported (14–16). However, more than half of the patients undergoing CABG are not routinely assessed and/or treated for depressive syndromes (14, 15). There is also a lack of studies determining the combined effect of depression and inflammation in CABG patients (17, 18). Therefore, the present study is aimed at assessing the relationship between preoperative depressive symptoms and C-reactive protein (CRP) plasma levels with the postoperative recovery of patients undergoing elective CABG surgery.

2. Methods

This study was designed as a prospective observational (non-interventional) study. All participants signed informed consent forms and the study protocol was approved by the Ethics Committee of the University Hospital Centre Zagreb, Croatia (Approval number of the Ethics Committee UHC Zagreb, Class: 8.1-11/84-3).

2.1. Patients

In the present prospective observational study, eligible patients undergoing elective CABG surgery (n = 257) were consecutively recruited at the Department of Cardiac Surgery, University Hospital Centre Zagreb, Croatia between December 2014 and March 2016. All participants signed informed consent, and the study protocol was approved by the Ethics Committee of the University Hospital Centre Zagreb, Croatia (Approval number: Class: 8.1-11/84-3). Eligibility criteria included patients undergoing elective CABG surgery, who were 18 years of age or older, and were able to complete the questionnaires in the

Croatian language. CABG procedures encompass both on-pump and off-pump surgical procedures. A flow chart displaying the recruitment and retention of participants through the present study is shown in Figure 1. Patients who were unwilling to participate (n = 22), and patients that have died after the surgery (n = 4) were excluded from the study. Patients missing some of the laboratory data were noted (n = 19) and were also excluded from the study (see Figure 1). Consequently, 212 CABG surgery patients (mean age: 61.61 ± 7.94 years, 171 (80.7%) males) with complete data for all variables at baseline and follow-up, were included in the present study.

2.2. Measures

2.2.1. Predictor variables: depression

The severity of the patient's depressive symptoms at baseline (preoperative assessment) was determined by two standardized questionnaires: (1) Primary Care Evaluation of Mental Disorders (PRIME-MD)/The Patient Health Questionnaire (PHQ)-9 test, and (2) the Beck Depression Inventory (BDI-II) test (19, 20). Both questionnaires were completed by each patient included in the study under the supervision and assistance of the physician when deemed necessary.

The PRIME-MD/PHQ-9 test is a 9-question depression scale that is often used by family physicians to quickly assess patients with depressive symptoms (19). The total rating of the PRIME-MD/PHQ-9 test was calculated as follows: a score ranging from 0 to 4 indicates CABG patients with minimal or no depressive symptoms; 5-9 in those with mild depressive symptoms, 10-14 indicates patients with moderate depressive symptoms, and 15-19 indicates patients with moderately to severe expressed depressive symptoms and finally PRIME-MD/PHQ-9 test score values from 20 to 27 indicate those exhibiting highest depressive symptoms (19). For statistical analysis of the obtained data, a binary variable was generated according to accepted cut-off values with a PRIME-MD/PHQ-9 binary test score of 0-4 indicating non-depressed patients and a score > 4 indicating CABG patients with mild to severe depressive symptoms.

Similarly, the BDI-II depression inventory test represents a 21-question multiple-choice self-report inventory, in which the patients were asked how they felt over the last two weeks (20). Each answer of the BDI-II test ranges from 1 to 3, and the total ratings were calculated as follows: score 0-13 scale indicates patients with minimal depressive symptoms; 14-19 those with mild depressive symptoms, and score of 20-28 patients with moderately expressed depressive symptoms while 29-63 total rating score designates CABG patients with highly depressive symptoms (20). In this case, a binary variable generated according to accepted cut-off values divides patients into a non-depressed group with a BDI-II score ranging from 0 to 13, and a mildly to severely depressed group which has a BDI-II score > 13

2.2.2. Mediators: C-reactive protein

The inflammatory activity of CABG patients included in the present study was monitored by the measurement of CRP values in the patient's peripheral circulation preoperatively and postoperatively.

Baseline CRP values were determined preoperatively upon admission to the Department of Cardiac Surgery. In the postoperative course, the CRP values were measured on the first, second, third, fourth, fifth, and sixth postoperative day. To obtain the samples, 5 ml of peripheral blood from each patient was drawn into plasma separator tubes by vacuum puncture from the forearm at baseline and postoperatively, as designated. Blood was subsequently centrifuged for 10 minutes at 3700 rpm (revolutions per minute) and the resulting plasma was placed into Eppendorf tubes and frozen at -80^{0}C until further analysis. CRP measurement was performed using commercial immunoturbidimetry assay (Tina-quant® C-Reactive Protein Gen.3, Roche Diagnostics) in the Roche Cobas c 501 modules (Roche Diagnostics) following the manufacturer's guidelines.

Overall, three summary scores of postoperative CRP values were generated. The first summary score used the mean CRP values measured on days 1, 2, and 3 postoperatively while the second CRP summary score used the mean CRP values measured on days 4, 5 and 6 postoperatively. Likewise, the third summary score used the mean CRP values on days 1, 2, 3, 4, 5, and 6 postoperatively. The postoperative CRP responses to CABG surgery were calculated as differentials scores by subtracting the baseline CRP value from the mean postoperative CRP scores and termed as an "early", "persistent" and "overall" postoperative response, as previously described (18).

2.2.3. Outcomes: length of stay

The duration of postoperative length of stay (LOS) as a measure of clinical recovery was collected from the patient's clinical records. CABG patients with the poorest recovery and the greatest in-hospital complications are expected to have the longest LOS after a CABG procedure. Due to this, the duration of the patient's intensive care unit (ICU) length of stay was recorded as well. The policy of the Department of Cardiac Surgery, University Hospital Centre Zagreb, was to discharge patients with an uncomplicated course within 7 days of the CABG procedure.

2.2.4. Covariates: clinical and demographic parameters

The patient's clinical and demographic data was taken during the interview following admission and from the patient's clinical records. The clinical risk for individual patients was assessed with values calculated using The European System for Cardiac Operative Risk Evaluation (EuroSCORE II). EuroSCORE II represents a composite measure of procedural mortality risk based on 18 factors encompassing patient-related factors (age, gender, race, etc.), cardiac-related factors (i.e., NYHA, CCS, recent MI (myocardial infarction), etc.) and operation-related factors (i.e., urgency, surgery on thoracic aorta, etc.) (21). Items were scored following the 'logistic EuroSCORE' method to generate an estimate of the percentage of mortality risk, predicting the patient's chances of dying during or shortly after undergoing a cardiac surgery procedure. Other patient characteristics that were recorded included: age, gender, preoperative body mass index (BMI), smoking status (current smoker/non-smoker), and prescribed medications (including the use of antidepressants, statins, acetylsalicylic acid, angiotensin-converting enzyme (ACE) inhibitors, and beta-blockers). Patient-related or a family history of cardiovascular disease, diabetes, and hypertension were also recorded. In addition, characteristics associated with the existence

of the preoperative MI and risks relative to the operative procedure such as a systolic function of the myocardium, number of grafts made intraoperatively and use of cardiopulmonary bypass were recorded as well.

2.3. Statistical analysis

The normality of data distribution was analyzed implementing the Shapiro-Wilk test. The data is presented as frequencies (n and percentages) and as a mean ± SD (standard deviation) for those which are normally distributed or median, and interquartile range (IQR) for non-normally distributed variables. The groups were compared using the t-test or Mann-Whitney/Kruskal-Wallis test for continuous variables, respectively. The Pearson $\chi 2$ or Fisher exact test were used for group comparisons of categorical variables. The association between the binary cut-off values of baseline depression scores (BDI-II: ≤ 13 vs. > 13; PHQ-9: ≤ 4 vs. > 4) and postoperative LOS values were analyzed using non-adjusted and adjusted binary logarithmic regression analysis and presented with an OR (odds ratio) of 95% CI (confidence interval). The covariates that may potentially influence the clinical outcome such as age at time of surgery, gender, BMI, current smoking status, preoperative hemoglobin levels, diabetes, cardiopulmonary bypass, number of grafts, EuroSCORE-II, prescribed medications (β-blockers and statin use), extubation time and postoperative atrial fibrillation were included in the adjusted binary logistic regression analysis based on statistical significance of Spearman's correlation analysis. However, to avoid double adjustment, variables such as age and gender (included in EuroSCORE-II) were not included in the so-called fully adjusted model. The same approach for non-adjusted and adjusted binary logistic regression was also used to analyze the association between baseline and postoperative CRP values (“early”, “persistent” and “overall” postoperative response) and postoperative hospital LOS (< 7 days vs. > 7 days). In addition, baseline CRP values, as a separate variable, were also included in the adjusted binary logistic regression models to assess the relative contribution of both preoperative and postoperative CRP values on postoperative hospital LOS. Linear regression model was also used to assess the association between depression scores (BDI-II: ≤ 13 vs. > 13; PHQ-9: ≤ 4 vs. > 4) and baseline and postoperative CRP values (“early”, “persistent” and “overall” postoperative response) with smoking status, BMI, number of grafts, cardiopulmonary bypass, diabetes, preoperative hemoglobin levels, EuroSCORE-II values, prescribed medications (β-blockers and statin use), extubation time, and postoperative atrial fibrillation used as covariates.

3. Results

3.1. Patient demographic and clinical data

The patient demographic, pre and postoperative clinical characteristics are listed in Table 1. The mean age of the patient cohort at the time of surgery was 61.61 ± 7.94 years with an age range between 39 and 80 years. The majority of patients were male (80.7%), overweight (BMI > 25 = 80.7%), and hypertensive (87.3%) with diabetes mellitus present in more than a quarter (36.3%) of participants. In addition, the majority of patients have prescribed beta-blockers, acetylsalicylic acid, ACE inhibitors and/or statin

medications while only two participants (0.9%) were on antidepressants (Table 2). Also, most of the patients (52.4%) included in the present study received 3 coronary artery bypass grafts. The mean postoperative length of stay was 9.25 ± 0.3 days, with a range of 6–36 days while the mean ICU LOS was 2.64 ± 0.09 days with a range of 1-10 days. Most of the patients were within a normal score range for baseline (preoperative) depressive symptoms in both the BDI-II (≤ 13; 87.7%) and PHQ-9 tests (≤ 4; 55.2%). However, for 26 (12.3%) patients the BDI-II baseline score was > 13 whereas 95 patients (44.8%) had PHQ-9 baseline test score > 4.

Table 1
Demographic, and clinical characteristics of CABG patients (N = 212)

characteristics	***Value***
Age (years); Mean ± SD	61.61 ± 7.94
Gender (male); n (%)	171 (80.7)
Smoking (yes); n (%)	32 (15.1)
BMI (kg/m^2); Median [IQR]	28.34 (25.75-30.71)
Body Surface Area (BSA), m^2; Mean ± SD	2.02±.2.00
Medications; n (%)	
Beta-blockers	179 (84.4)
Acetylsalicylic acid	187 (88.2)
AC inhibitors	132 (62.3)
Statin medications	191 (90.1)
Antidepressants	2 (0.9)
Co-morbidities; n (%)	
Hypertension	185 (87.3)
Diabetes	77 (36.3)
DMI	33 (15.6)
Hyperlipidemia	159 (75.0)
The familiar history of cardiac diseases	132 (62.3)
Preoperative myocardial infarction (MI)	110 (51.9)
Clinical factors	
Preoperative leukocyte number; Median [IQR]	7.30 (6.22- 8.70)
Preoperative Platelate number; Median [IQR]	214.0 (177.3- 254.5)
Ejection Fraction (%); Median [IQR]	55.0 (45.0- 60.0)
preoperative GUK; Median [IQR]	6.20 (5.28- 7.32)
Preoperative Hemoglobin (Hb); Median [IQR]	141.0 (131.0- 152.0)

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.

characteristics	*Value*
EuroSCORE-II; Median [IQR]	1.05 (0.68- 1.95)
ICU days; Median [IQR]	2.0 (2.0-3.0)
Extubating time (ET); Median [IQR]	7.00 (5.0- 10.0)
Days at department; Median [IQR]	8.0 (7.0-10.0)
On pump; n(%)	193 (91.0)
Extracorporeal Circulation length; Median [IQR]	79.5 (63.0- 98.3)
Clamp length; Median [IQR]	57.0 (43.0- 69.00)
Number of grafts; Median [IQR]	3.0 (2.0-3.0)
Number of grafts; n (%)	
I	15 (7.1)
II	80 (37.7)
III	111 (52.4)
IV	6 (2.8)
Postoperative FA/atrial fibrillation; n (%)	44 (20.8)
Length of postoperative hospital stay; n (%)	
≤ 7 days	88 (41.5)
>7 days	124 (58.5)
CRP values; *Median [IQR]*	
Preoperative CRP (mg/dL)	2.25 (1.0-4.7)
CRP I	66.75 (48.45- 91.20)
CRP II	136.15 (108.50- 182.53)
CRP III	130.60 (97.00- 174.75)
CRP IV	90.85 (73.63-126.65)
CRP V	69.35 (52.38-90.33)
CRP VI	52.10 (37.80- 69.95)

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.

characteristics	*Value*
Early CRP Change score	107.17 (86.80-146.91)
Persistent CRP Change score	68.45 (51.85- 90.92)
Overall CRP Change score	89.66 (73.49- 116.43)
Depression symptoms	
Total BDI-II score; Median [IQR]	8.00 (5.0-11.0)
Binary BDI-II values; n (%)	
None (≤13)	186 (87.7)
Mild to Severe (>13)	26 (12.3)
Total PRIME-MD score; Median [IQR]	4.0 (2.0-6.0)
Binary PRIME-MD values; n (%)	
None (≤4)	117 (55.2)
Mild to severe (>4)	95 (44.8)

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.

Table 2
The association between patients demographic and clinical characteristics with the postoperative length of stay

Characteristics	*Length of postoperative hospital stay ≤ 7 days* *N=88*	*Length of postoperative hospital stay >7 days* *N=124*	*P-values*
Age (years); Mean ± SD	59.0 (53.0-65.0)	64.0 (58.0-69.0)	**<0.001***
Gender; n (%)			0.081
Male	76 (86.4)	95 (76.6)	
Female	12 (13.6)	29 (23.4)	
Smoking; n (%)			**0.003***
Yes	21 (24.4)	11 (8.9)	
No	65 (75.6)	113 (91.1)	
BMI (kg/m^2); Median [IQR]	28.10 (25.32-30.33)	28.41 (25.99-31.10)	0.460
Body Surface Area (BSA), m^2; Mean ± SD	2.03±0.189	2.01±0.209	0.492
Medications; n (%)			
Beta blockers	81 (92.0)	98 (80.3)	**0.029***
Acetylsalicylic acid	82 (93.2)	105 (84.7)	0.083
AC inhibitors	58 (65.9)	74 (59.7)	0.390
Statin medications	80 (90.9)	111 (91.0)	1.000
Antidepressants	1 (1.1)	1 (0.8)	1.000
Co-morbidities; n (%)			
Hypertension	76 (86.4)	109 (87.9)	0.835
Diabetes	23 (26.1)	54 (43.5)	**0.013***
DMI	11 (12.5)	22 (17.7)	0.341
Hyperlipidemia	70 (79.5)	89 (71.8)	0.260

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Statistical analysis was performed by Pearson χ2 or Fisher exact test for categorical variables and by Mann-Whitney U test or Kruskal-Wallis test for continuous variables, respectively. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.* Statistically significant P-values.

Characteristics	*Length of postoperative hospital stay ≤ 7 days* *N=88*	*Length of postoperative hospital stay >7 days* *N=124*	*P-values*
Familiar history of cardiac diseases	54 (62.1)	78 (63.4)	0.885
Preoperative myocardial infarction (MI)	42 (47.7)	68 (54.8)	0.331
Clinical factors			
Preoperative leukocyte number; Median [IQR]	7.10 (6.20-8.58)	7.40 (6.33-8.78)	0.490
Preoperative Platelate number; Median [IQR]	215.00 (189.25-257.00)	212.50 (175.25-249.00)	0.297
Ejection Fraction (%); Median [IQR]	55.00 (48.13-60.75)	55.0 (45.00-60.00)	0.325
preoperative GUK; Median [IQR]	5.9 (5.2-7.2)	6.3 (5.3-7.7)	0.195
Preoperative Hemoglobin (Hb) ; Median [IQR]	146.5 (138.0-154.0)	139.5 (127.4-151.0)	**0.001***
EuroSCORE-II; Median [IQR]	0.85 (0.66-1.27)	1.33 (0.89-2.66)	**<0.001***
ICU days; Median [IQR]	2.0 (2.0-3.0)	3.0 (2.0-3.0)	**0.022***
Extubating time (ET); Median [IQR]	7.0 (5.0-9.0)	8.0 (6.0-11.0)	**0.016***
Days at department; Median [IQR]	7.00 (6.25-7.00)	9.00 (8.00-12.00)	**<0.001***
On pump; n(%)	81 (92.0)	112 (90.3)	0.809
Extracorporeal Circulation length; Median [IQR]	78.0 (63.5-97.0)	80.0 (63.0-100.0)	0.763
Clamp length; Median [IQR]	57.0 (44.0-70.0)	57.0 (42.0-69.0)	0.856
Number of grafts; Median [IQR]	3.0 (20.-3.0)	3.0 (20.-3.0)	0.400
Number of grafts; n (%)			0.272
I	8 (9.1)	7 (5.6)	

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Statistical analysis was performed by Pearson $\chi 2$ or Fisher exact test for categorical variables and by Mann-Whitney U test or Kruskal-Wallis test for continuous variables, respectively. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.* Statistically significant P-values.

Characteristics	*Length of postoperative hospital stay ≤ 7 days* *N=88*	*Length of postoperative hospital stay >7 days* *N=124*	*P-values*
II	28 (31.8)	52 (41.9)	
III	48 (54.5)	63 (50.8)	
IV	4 (4.5)	2 (1.6)	
Postoperative FA/atrial fibrillation;, n (%)	8 (9.1)	36 (29.0)	**<0.001***
CRP values; Median [IQR]			
Preoperative CRP (mg/dL)	1.80 (1.00-3.38)	2.50 (1.21-4.85)	0.113
CRP I	63.10 (51.23-89.85)	70.25 (48.08-91.30)	0.536
CRP II	130.10 (103.63-173.38)	140.40 (108.53-185.18)	0.350
CRP III	115.15 (90.20-166.20)	139.85 (107.50-180.28)	**0.009***
CRP IV	85.05 (66.70-111.50)	101.15 (78.80-135.88)	**0.001***
CRP V	61.90 (48.00-75.00)	76.90 (58.70-103.40)	**0.001***
CRP VI	45.90 (34.55-58.30)	58.15 (40.80-77.03)	**0.001***
Early CRP Change score	102.57 (83.47-139.92)	109.32 (92.23-148.46)	0.112
Persistent CRP Change score	61.00 (47.98-78.90)	77.90 (58.22-100.83)	<0.001*
Overall CRP Change score	83.56 (68.33-105.93)	95.06 (77.54-124.56)	0.004*
Depression symptoms			
Continuous BDI-II score; Median [IQR]	7.00 (4.00-10.75)	9.00 (6.00-12.00)	**0.014***
Binary BDI-II score; n (%)			0.137
None (≤13)	81 (92.0)	105 (84.7)	
Mild to Severe (>13)	7 (8.0)	19 (15.3)	
Total PRIME-MD score; Median [IQR]	4.00 (2.00-6.75)	4.00 (2.00-6.00)	0.733

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Statistical analysis was performed by Pearson $\chi 2$ or Fisher exact test for categorical variables and by Mann-Whitney U test or Kruskal-Wallis test for continuous variables, respectively. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.* Statistically significant P-values.

Characteristics	*Length of postoperative hospital stay ≤ 7 days* *N=88*	*Length of postoperative hospital stay >7 days* *N=124*	*P-values*
Binary PRIME-MD score; n (%)			0.676
None (≤4)	47 (53.4)	70 (56.5)	
Mild to severe (>4)	41 (46.6)	54 (43.5)	

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Statistical analysis was performed by Pearson $\chi 2$ or Fisher exact test for categorical variables and by Mann-Whitney U test or Kruskal-Wallis test for continuous variables, respectively. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.* Statistically significant P-values.

3.2. The association between patient demographic and clinical characteristics with postoperative length of stay

A longer postoperative length of stay (LOS) (> 7 days) was significantly associated with the older patient group (P > 0.001), current smoking status (P = 0.003), use of β-blockers (P = 0.029), and diabetes (P = 0.013) (Table 2). The patient group with longer postoperative LOS also had significantly lower preoperative hemoglobin levels (P = 0.001), higher EuroSCORE-II values (P < 0.001), longer ventilation (P = 0.016), and longer overall hospital (P < 0.001) and ICU LOS (P = 0.022). The patient group with longer hospital LOS (> 7 days) also have a higher frequency of postoperative atrial fibrillation (29.9¸ P < 0.001) when compared with the group with shorter (≤ 7 days) hospital LOS. A longer LOS (> 7 days) was also significantly associated with higher postoperative CRP values measured on day 3 (P = 0.009), day 4 (P = 0.001), day 5 (P = 0.001) and day 6 (P = 0.001), as well as a change in the “persistent” (P < 0.001) and “overall” (P = 0.005) CRP value (Table 2). However, preoperative CRP values and “early” changes in CRP values were not associated with the duration of postoperative length of stay.

Regarding the association of the patient’s depressive symptoms to the postoperative length of stay, only continuous BDI-II scores at baseline were significantly associated (P = 0.014) with longer postoperative LOS (> 7 days). However, no statistically significant association was detected with binary BDI-II or continuous and binary PRIME-MD depression scores (Table 2).

3.3. The association of BDI-II and PHQ-9 depression scores with patient demographic and clinical data

As can be seen in Table 3, depressive symptoms determined by a BDI-II score of > 13 was associated with current smoking status (P = 0.026), lower preoperative hemoglobin (P = 0.044), and higher EuroSCORE-II values (P < 0.001); and with longer ventilation time (P = 0.029) and overall hospital LOS (P = 0.025).

However, no statistically significant association was found in respect to gender and BDI-II scores and the patient's postoperative LOS (≤ 7 days vs. > 7 days) or LOS in the ICU (Table 3). Patients with depressive symptoms determined by a BDI-II score of > 13 exhibited higher preoperative (baseline) CRP values (P = 0.007) and higher day 1 postoperative CRP values (P = 0.046). The depressed patient group also had lower ejection fraction values (measured in percent), but the results were not statistically significant (P = 0.066). No statistically significant association was found between either BDI-II scores and "early", "persistent" and "overall" postoperative changes in CRP values or between BDI-II scores and patient comorbidities or medications used (Table 3). Interestingly, while only two participants in our patient cohort were using antidepressants, all of them were in the non-depressed patient group.

In contrast, depressive symptoms determined by the PRIME-MD/PHQ-9 test (PRIME-MD > 4) were associated only with gender (P = 0.024) and lower preoperative hemoglobin levels (P = 0.036) (Table 3). EuroSCORE-II values were also higher in patients with a PRIME-MD score of > 4; however, this was not statistically significant (P = 0.075). Interestingly, in the PRIME-MD analysis of the patient's depression status, participants using antidepressants were equally distributed between the depressed and non-depressed patient groups. No statistically significant difference was found regarding preoperative CRP values or in the "early", "persistent" and "overall" postoperative CRP response between the PRIME-MD ≤ 4 and PRIME-MD > 4 patient groups (Table 3).

In addition, Spearman's correlation analysis revealed a significant positive correlation between gender and continuous BDI-II (r_s = 0.174, P = 0.011) and PRIME-MD (r_s = 0.183, P = 0.008) as well as binary BDI-II (r_s = 0.145, P = 0.035) and PRIME-MD values (r_s = 0.0.159, P = 0. 020). A positive correlation was also detected with smoking (continuous BDI-II: r_s = 0.171, P = 0.013; binary BDI-II: r_s = 0.162, P = 0.018), diabetes (continuous BDI-II: r_s = 0.204, P = 0.003; binary BDI-II: r_s = 0.136, P = 0.048; continuous PRIME-MD: r_s = 0.139, P = 0.043) and EuroSCORE-II values (continuous BDI-II: r_s = 0.328, P > 0.001; binary BDI-II: r_s = 0.335, P > 0.001; continuous PRIME-MD: r_s = 0.146, P = 0.033) while preoperative hemoglobin levels showed a negative correlation with depression scores (continuous BDI-II: r_s = -0.143, P = 0.037; binary BDI-II: r_s = -0.139, P = 0.044; continuous PRIME-MD: r_s = -0.138, P = 0.044; binary PRIME-MD: r_s = -0.145, P = 0.035).

Table 3
The association between depression symptom scores (BDI-II and PRIME-MD) and patients demographic and clinical data

Characteristics	*BDI-II ≤13 N=186*	*BDI-II > 13 N=26*	*P-values*	*PRIME-MD ≤ 4 N=117*	*PRIME-MD > 4 N=95*	*P-values*
Age (years); Mean ± SD	61.57±7.857	61.88±8.696	0.850	62.40±7.43	60.63±8.47	0.107
Gender; n (%)			0.059			**0.024***
male	154 (82.8)	17 (65.4)		101 (86.3)	70 (73.7)	
female	32 (17.2)	9 (34.6)		16 (13.7)	25 (26.3)	
Smoking; n (%)			**0.026***			0.087
Yes	24 (13.0)	8 (30.8)		13 (11.3)	19 (20.0)	
No	160 (87.0)	18 (69.2)		102 (88.7)	76 (80.0)	
BMI (kg/m^2); Median [IQR]	28.2 (25.7-30.7)	28.4 (25.6-31.8)	0.672	28.1 (25.6-30.6)	28.4 (26.1-31.1)	0.564
Body Surface Area (BSA), m^2; Mean ± SD	2.02±0.20	1.96±0.21	0.126	2.03±0.19	1.99±0.22	0.236
Medications; n (%)						
Beta blockers	160 (86.5)	19 (76.0)	0.224	99 (85.3)	80 (85.1)	1.000
Acetylsalicylic acid	165 (88.7)	22 (84.6)	0.521	101 (86.3)	86 (90.5)	0.397
AC inhibitors	114 (61.3)	18 (69.2)	0.520	73 (62.4)	59 (62.1)	1.000
Statin medications	169 (91.4)	22 (88.0)	0.480	106 (91.4)	85 (90.5)	1.000
Antidepressants	2 (1.1)	0 (0.0)	1.000	1 (0.9)	1 (1.1)	1.000
Co-morbidities; n (%)						
Hypertension	163 (87.6)	22 (84.6)	0.752	104 (88.9)	81 (85.3)	0.535
Diabetes	63 (33.9)	14 (53.8)	**0.053**	36 (30.8)	41 (43.2)	0.085

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Statistical analysis was performed by Pearson χ2 or Fisher exact test for categorical variables and by Mann-Whitney U test or Kruskal-Wallis test for continuous variables, respectively. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.* Statistically significant P-values.

Characteristics	*BDI-II ≤13 N=186*	*BDI-II > 13 N=26*	*P-values*	*PRIME-MD ≤ 4 N=117*	*PRIME-MD > 4 N=95*	*P-values*
DMI	26 (14.0)	7 (26.9)	0.143	18 (15.4)	15 (15.8)	1.000
Hyperlipidemia	141 (75.8)	18 (69.2)	0.630	85 (72.6)	74 (77.9)	0.427
Familiar history of cardiac diseases	118 (64.1)	14 (53.8)	0.386	69 (59.5)	63 (67.0)	0.315
Preoperative myocardial infarction (MI)	93 (50.0)	17 (65.4)	0.150	60 (51.3)	50 (52.6)	0.890
Clinical factors						
Preoperative leukocyte number; Median [IQR]	7.2 (6.2-8.6)	7.7 (6.5-9.4)	0.310	7.4 (6.3-8.6)	7.2 (6.2-9.2)	0.993
Preoperative Platelate number; Median [IQR]	212.0 (178.0-250.8)	230.0 (167.8-277.5)	0.412	212.0 (179.0-249.0)	220.0 (174.0-266.0)	0.267
preoperative GUK; Median [IQR]	6.1 (5.2-7.3)	6.5 (5.3-8.8)	0.359	6.1 (5.3-7.6)	6.3 (5.2-7.3)	0.779
Preoperative Hemoglobin (Hb); Median [IQR]	142.0 (134.0-152.0)	136.5 (120.3-153.5)	**0.044***	145.0 (136.0-152.0)	140.0 (128.0-153.0)	**0.036***
Ejection Fraction (%);Median [IQR]	55.0 (45.0-60.0)	50.0 (44.5-56.3)	0.066	55.0 (45.0-60.0)	55.0 (47.5-60.0)	0.611
EuroSCORE-II; Median [IQR]	0.99 (0.68-1.71)	2.63 (1.9-5.22)	**<0.001***	1.0 (0.68-1.75)	1.12 (0.76-2.48)	0.075
ICU days; median [IQR]	3.0 (2.0-3.0)	2.0 (2.0-3.0)	0.175	2.0 (2.0-3.0)	3.0 (2.0-3.0)	0.731
Extubating time (ET); Median [IQR]	7.0 (5.0-10.0)	9.0 (6.75-12.25)	**0.029***	7.0 (5.0-10.0)	7.0 (5.0-10.0)	0.502
Days at department; Median [IQR]	8.0 (7.0-9.0)	10.00 (7.00-11.25)	**0.025***	8.0 (7.0-9.0)	8.0 (7.0-10.0)	0.907
On pump; n(%)	170 (91.4)	23 (88.5)	0.711	104 (88.9)	89 (93.7)	0.240

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Statistical analysis was performed by Pearson $\chi 2$ or Fisher exact test for categorical variables and by Mann-Whitney U test or Kruskal-Wallis test for continuous variables, respectively. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.* Statistically significant P-values.

Characteristics	*BDI-II ≤13 N=186*	*BDI-II > 13 N=26*	*P-values*	*PRIME-MD ≤ 4 N=117*	*PRIME-MD > 4 N=95*	*P-values*
Extracorporeal Circulation length; Median [IQR]	80.0 (63.0-99.0)	76.0 (60.0-92.0)	0.478	80.0 (62.0-101.0)	79.0 (63.5-93.0)	0.640
Clamp length; Median [IQR]	57.0 (43.0-71.0)	54.0 (45.0-62.0)	0.553	56.0 (42.5-74.0)	57.5 (43.3-65.0)	0.832
Number of grafts; Median [IQR]	3.0 (2.0-3.0)	3.0 (2.0-3.0)	0.749	3.0 (2.0-3.0)	3.0 (2.0-3.0)	0.471
Number of grafts; n (%)			1.000			0.709
I	13 (7.0)	2 (7.7)		10 (8.5)	5 (5.3)	
II	70 (37.6)	10 (38.5)		45 (38.5)	35 (36.8)	
III	97 (52.2)	14 (53.8)		58 (49.6)	53 (55.8)	
IV	6 (3.2)	0 (0.0)		4 (3.4)	2 (2.1)	
Postoperative FA (atrial fibrillation), n (%)	36 (19.4)	8 (30.8)	0.198	24 (20.5)	20 (21.1)	1.000
Length of postoperative hospital stay; n (%)			0.137			0.676
≤ 7 days	81 (43.5)	7 (26.9)		47 (40.2)	41(43.2)	
>7 days	105 (56.5)	19 (73.1)		70 (59.8)	54 (576.8)	
CRP values; Median [IQR]						
Preoperative CRP (mg/dL)	2.1 (1.0-4.0)	4.8 (1.6-8.3)	**0.007***	2.1 (1.0-3.8)	2.3 (1.2-5.4)	0.176
CRP I	63.8 (47.8-89.6)	78.6 (66.2-100.4)	**0.046***	68.1 (50.1-94.6)	63.6 (48.0-86.6)	0.285
CRP II	135.2 (104.7-180.9)	144.3 (122.9-195.3)	0.188	135.4 (104.2-182.7)	140.1 (108.6-180.4)	0.965

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Statistical analysis was performed by Pearson $\chi 2$ or Fisher exact test for categorical variables and by Mann-Whitney U test or Kruskal-Wallis test for continuous variables, respectively. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.* Statistically significant P-values.

Characteristics	*BDI-II ≤13 N=186*	*BDI-II > 13 N=26*	*P-values*	*PRIME-MD ≤ 4 N=117*	*PRIME-MD > 4 N=95*	*P-values*
CRP III	130.20 (96.65-168.13)	141.6 (102.4-187.8)	0.518	134.5 (97.2-180.2)	120.1 (95.2-165.8)	0.330
CRP IV	90.8 (72.3-126.8)	96.9 (78.4-127.0)	0.538	94.8 (76.1-132.1)	87.40 (69.0-115.4)	0.079
CRP V	69.4 (51.2-90.6)	70.3 (56.3-86.3)	0.841	73.6 (54.3-92.8)	65.7 (50.2-87.2)	0.159
CRP VI	52.1 (37.6-69.9)	52.6 (41.8-71.6)	0.704	54.1 (39.1-70.1)	51.6 (35.6-68.3)	0.529
Early CRP Change score	103.7 (86.1-145.1)	119.9 (96.0-150.8)	0.212	107.7 (86.5-148.1)	106.5 (87.8-138.5)	0.504
Persistent CRP Change score	68.1 (51.8-91.1)	74.2 (52.1-88.4)	0.834	70.3 (53.8-93.4)	66.1 (49.8-84.8)	0.134
Overall CRP Change score	89.5 (72.7-116.2)	95.9 (78.6-119.4)	0.419	93.5 (72.6-118.4)	85.3 (73.8-113.8)	0.209

Data are presented as counts (n) and percentages (%) for categorical variables and as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Statistical analysis was performed by Pearson $\chi 2$ or Fisher exact test for categorical variables and by Mann-Whitney U test or Kruskal-Wallis test for continuous variables, respectively. BMI, body mass index; CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; ICU, intensive care unit; PRIME-MD, Primary Care Evaluation of Mental Disorders.* Statistically significant P-values.

3.4. The predictive role of baseline depressive symptoms and changes in CRP values on the patient's postoperative hospital length of stay

The results from three different logistic regression models [non-adjusted, age and sex-adjusted and fully adjusted model (current smoking status, EuroSCORE-II, pre-operative (baseline) hemoglobin levels, diabetes, the use of β-blockers, extubation/ventilation time, and postoperative atrial fibrillation)] predicting the postoperative LOS are presented in Table 4. Non-adjusted binary logistic regression analysis showed that when compared to the non-depression group (BDI-II ≤ 13), classified by the Beck Depression Inventory, patients in the mild to severe depression group (BDI-II > 13), had more than two times greater odds (OD = 0.2094, P = 0.113) of a postoperative hospital stay longer than one week. Their odds ratio remained similar (OD = 2.033 fold, P = 0.152) to the age and gender-adjusted models; however, in both models the obtained values were not statistically significant, and the only variable significantly

associated with the prolonged length of stay was the age of the patient undergoing the CABG procedure (OD = 1.082, P < 0.001). The fully adjusted model encompassing the following covariables significantly correlated with postoperative LOS were: age (Spearman's r = 0.281, P < 0.001), current smoking status (r = - 0.213, P = 0.002), EuroSCORE-II value (r = 0.318, P < 0,001), preoperative (baseline) hemoglobin levels (r = -0.230, P = 0.001), diabetes (r = 0.178, P = 0.009), the use of β-blockers (r = -0.163, P = 0.018), ventilation time (r = 0.165, P = 0.016) and postoperative atrial fibrillation (r = 0.242, P< 0.001); (data not shown), with the exception of age that was already incorporated into EuroSCORE-II, the mild to severe depression group (BDI-II > 13) exhibited only 1.127 higher odds of postoperative hospital stay of longer than one week which remained statistically nonsignificant (Table 4).

However, as largely expected, the fully adjusted model revealed EuroSCORE-II values (OR = 1.557, CI = 1.065 - 2.276, P = 0.022) and postoperative atrial fibrillation (OR = 2.546, CI = 1.015 - 6.384; P = 0.046) as positive predictors and current smoking status (OR = 0.222, CI = 0.083 - 0.597, P = 0.003), preoperative (baseline) hemoglobin levels (OR = 0.974, CI = 0.950 - 0.998, P = 0.034), and β-blocker medications (OR = 0.219, CI = 0.074 - 0.642, P = 0.006) as negative predictors of postoperative LOS. Additional adjustment for BMI, cardiopulmonary bypass, number of grafts and use of statin medications additionally decreased the odds of prolonged LOS (OR = 1.026, CI = 0.294 - 3.586, P = 0.967) in the mild to severe depression group (BDI-II > 13); but a EuroSCORE-II value (OR = 1.653, CI = 1.103 - 2.477, P = 0.015), current smoking status (OR = 0.232, CI = 0.085 - 0.629, P = 0.004), preoperative hemoglobin levels (OR = 0.972, CI = 0.948 - 0.997, P = 0.026) and the use of β-blocker medications (OR = 0.217, CI = 0.073 - 0.647, P = 0.006) have remained as positive and negative predictors, respectively.

Surprisingly, non-adjusted binary logistic regression analysis showed that when compared to the non-depression group (PRIME-MD $\leq$ 4), classified by the Primary Care Evaluation of Mental Disorders PHQ-9 test, patients in the mild to severe depression group (PRIME-MD > 4) had a lower odds ratio (OR = 0.884) of postoperative hospital stay longer than one week (Table 3). However, as in the case of the BDI-II score, the obtained values were not statistically significant. Their odds slightly increased in the age and gender-adjusted model of binary logistic regression (OR = 0.934) revealing that the age of the patient undergoing CABG procedure as the most significant predictor of prolonged postoperative hospital LOS (OR = 1.081, CI = 1.040 - 1.123, P < 0.001). In the fully adjusted model [current smoking status, EuroSCORE-II, preoperative (baseline) hemoglobin levels, diabetes, the use of β-blockers, extubation/ventilation time, and postoperative atrial fibrillation] patients in the mild to severe depression group (PRIME-MD > 4) showed even lower odds (OR = 0.654) of postoperative LOS longer than one week when compared to the non-depressed patient group (PRIME-MD $\leq$ 4). This model also revealed that the EuroSCORE-II value (OR = 1.578, CI = 1.087 - 2.290, P = 0.016) and postoperative atrial fibrillation (OR = 2.547, CI = 1.007 - 6.442; P = 0.048) as positive and current smoking status (OR = 0.242, CI = 0.091 - 0.643, P = 0.004), preoperative (baseline) hemoglobin levels (OR = 0.972, CI = 0.948 - 0.997, P = 0.029), and β-blocker medications (OR = 0.214, CI = 0.073 - 0.633, P = 0.005) as negative predictors of prolonged postoperative LOS.

Such was the case for the BDI-II depression score, additional adjustment of binary logistic regression analysis for BMI, cardiopulmonary bypass, number of grafts and use of statin medications have

additionally decreased the odds in the mild to severe depression group (PRIME-MD > 4) for prolonged length of hospital stay (OR = 0.589, CI = 0.299 - 1.162, P = 0.127) and the EuroSCORE-II value (OR = 1.694, CI = 1.141 - 2.515, P = 0.009), current smoking status (OR = 0.254, CI = 0.095 - 0.681, P = 0.006), preoperative hemoglobin levels (OR = 0.970, CI = 0.945 - 0.995, P = 0.019) and the use of and β-blocker medications (OR = 0.210, CI = 0.070 - 0.632, P = 0.006) as positive and negative predictors, respectively.

The last three binary logistic regression analyses described in Table 4 present non-adjusted and adjusted results of binary logistic regression in the changes in “early” (1-3 postoperative day), “persistent” (4-6 postoperative day) and “overall” (1-6 postoperative days) CRP predicting the length of postoperative hospital stay.

The results showed that for every increase in early postoperative CRP units there was only a 0.5% increase in the odds of extended hospital stay in fully adjusted models, but this was not statistically significant (P = 0.233) (Table 4). Current smoking status (OR = 0.243, CI = 0.091 - 0.642, P = 0.004), EuroSCORE-II values (OR = 1.601, CI = 1.097 - 2.335, P = 0.015), lower preoperative hemoglobin levels (OR = 0.971, CI = 0.946 - 0.997, P = 0.030) and the use of β-blocker medications (OR = 0.224, CI = 0.076 - 0.663, P = 0.007) were also identified as significant predictors of prolonged postoperative hospital length of stay in this model. Additional adjustment for BMI, cardiopulmonary bypass, number of grafts and use of statin medications did not significantly alter the results obtained in the fully adjusted model.

In contrast to the results obtained for early CRP level changes, every unit increase in persistent postoperative CRP resulted in a 1.6% increase in the odds of extended hospital stay in the fully adjusted model (P = 0.006) (Table 4). Current smoking status (OR = 0.283, CI = 0.104 - 0.768, P = 0.013), EuroSCORE-II values (OR = 1.613, CI = 1.100 - 2.365, P = 0.014), lower preoperative hemoglobin levels (OR = 0.971, CI = 0.946 - 0.997, P = 0.028) and use of β-blocker medications (OR = 0.219, CI = 0.071 - 0.671, P = 0.008) were identified as well significant predictors of prolonged postoperative LOS in this model. Furthermore, in this model, additional adjustment for BMI, cardiopulmonary bypass, number of grafts and use of statin medications did not significantly alter the results obtained in the fully adjusted model. Interestingly, in the age (OR = 1.083, CI = 1.040 - 1.127, P <0.001) and gender adjusted model, female patients had more than three times (OR = 3.198; CI =1.384 - 7.390, P = 0.007) greater odds for prolonged length of stay. Female patients also had greater odds of prolonged postoperative hospital stay (OR = 2.906; CI = 1.269-6.655, P = 0.012) in the age and gender (OR = 1.087, CI = 1.044 - 1.131, P < 0.001) adjusted model for binary logistic regression of overall postoperative CRP changes.

Every increased unit in overall postoperative CRP, in the fully adjusted model, resulted in a 1.1% increase in the odds ratio for prolonged postoperative length of stay (Table 4). Current smoking status (OR = 0.265, CI = 0.099 - 0.710, P = 0.008), EuroSCORE-II value (OR = 1.617, CI = 1.105 - 2.368, P = 0.013), lower preoperative hemoglobin levels (OR = 0.970, CI = 0.945 - 0.996, P = 0.022) and the use of β-blocker medications (OR = 0.224, CI = 0.075 - 0.675, P = 0.008) were identified as significant predictors of prolonged postoperative hospital length of stay in this model as well. Also, additional adjustment for BMI,

cardiopulmonary bypass, number of grafts and use of statin medications did not substantially alter the results obtained in the fully adjusted model.

Table 4
Depression symptoms and high-sensitivity C-reactive protein (CRP) as predictors of postoperative length of hospital stay.

Variable		*OR*	*95% CI*	*P-value*
BDI-II score: Non-adjusted	*None BDI ≤13*	1 (reference)	-	-
	Mild to severe BDI> 13	2.094	0.840-5.222	0.113
BDI-II score: Age and sex-adjusted	*None, BDI ≤13*	1 (reference)	-	-
	Mild to severe, BDI> 13	2.033	0.769-5.375	0.152
BDI-II score: fully adjusted	*None, BDI ≤13*	1 (reference)	-	-
	Mild to severe, BDI> 13	1.127	0.330-3.856	0.849
PRIME-MD score; non-adjusted	None, PRIME-MD ≤ 4	1 (reference)	-	-
	Mild to severe PRIME-MD > 4	0 .884	0 .511-1.531	0 .661
PRIME-MD; age and gender-adjusted	None, PRIME-MD ≤ 4	1 (reference)	-	-
	Mild to severe PRIME-MD > 4	0.934	0.518-1.683	0.820
PRIME-MD score; fully adjusted	None, PRIME-MD ≤ 4	1 (reference)	-	-
	Mild to severe PRIME-MD > 4	0.654	0.338-1.265	0.208
Early CRP Change score	*non-adjusted*	1.006	0.999-1.013	0.086
	Age and gender adjusted	1.009	1.002-1.016	0.018*
	Fully adjusted	1.005	0.997-1.013	0.241

Data are presented as odds ratio (OD) and 95% confidence intervals (CI). Statistical analysis was performed by non-adjusted, age and gender adjusted and fully adjusted [current smoking status, EuroSCORE-II, preoperative (baseline) hemoglobin levels, diabetes, the use of β-blockers, extubation/ventilation time, and postoperative atrial fibrillation] binary logistic regression analysis. CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; PRIME-MD, Primary Care Evaluation of Mental Disorders.* Statistically significant P-values.

Variable		*OR*	*95% CI*	*P-value*
Persistent CRP Change score	*non-adjusted*	1.019	1.009-1.029	<0.001*
	Age and gender adjusted	1.023	1.012-1.034	<0.001*
	Fully adjusted	1.016	1.005-1.028	0.005*
Overall CRP Change score	*non-adjusted*	1.014	1.005-1.023	0.003*
	Age and gender adjusted	1.018	1.008-1.028	<0.001*
	Fully adjusted	1.011	1.001-1.022	0.038*

Data are presented as odds ratio (OD) and 95% confidence intervals (CI). Statistical analysis was performed by non-adjusted, age and gender adjusted and fully adjusted [current smoking status, EuroSCORE-II, preoperative (baseline) hemoglobin levels, diabetes, the use of β-blockers, extubation/ventilation time, and postoperative atrial fibrillation] binary logistic regression analysis. CRP, high-sensitivity C-reactive protein; BDI-II, the Beck Depression Inventory; PRIME-MD, Primary Care Evaluation of Mental Disorders.* Statistically significant P-values.

3.5. Relationship of BDI-II and PHQ-9 depression scores with baseline and postoperative CRP levels

Linear regression analysis performed to examine the relationship between the BDI-II scores and preoperative and postoperative (“early”, “persistent” and “overall” postoperative response) CRP values [with smoking status, BMI, number of grafts, cardiopulmonary bypass, diabetes, preoperative hemoglobin levels, EuroSCORE-II values, prescribed medications (β-blockers and statin use), extubation time, and postoperative atrial fibrillation used as covariates] resulted with no significant resultant association. The only significant predictors detected in those models were as follows: current smoking status (t = 2.595, P = 0.010), EuroSCORE-II values (t = 2.603, P = 0.010), BMI (t = 2.112, P = 0.036) and preoperative hemoglobin levels (t = -2.714, P = 0.007) for baseline CRP; current smoking status (t = -2.490, P = 0.014), preoperative hemoglobin levels (t = 3.103 P = 0.002), postoperative atrial fibrillation (t = 2.578, P = 0.011) and preoperative CRP values (t = 2.114, P = 0.036) for early CRP change; current smoking (t = -2.402, P = 0.017), and postoperative atrial fibrillation (t = 2.131, P = 0.034) for persistent CRP change, and current smoking (t = -2.782, P = 0.006), and postoperative atrial fibrillation (t = 2.649, P = 0.009) for overall CRP change.

Linear regression analysis was performed to examine the relationship between the PRIME-MD score and preoperative and postoperative CRP values (“early”, “persistent” and “overall” postoperative response) also resulted with no statistically significant associations. Significant predictors detected in those models

were as follows: current smoking status (t = 2.631, P = 0.009), the EuroSCORE-II value (t = 2.844, P = 0.005), BMI (t = 2.118, P=0.035) and preoperative hemoglobin levels (t = -2.607, P = 0.010) for baseline CRP; current smoking status (t = -2.153, P = 0.033), preoperative hemoglobin levels (t = 2.869, P = 0.005), postoperative atrial fibrillation (t = 2.559, P = 0.011) and preoperative CRP (t = 2.2205, P = 0.029) for early CRP changes; current smoking (t = -2.427, P = 0.016), and postoperative atrial fibrillation (t = 2.100, P = 0.037) for persistent CRP change, current smoking (t = -2.615 P = 0.010), and postoperative atrial fibrillation (t = 2.632, P = 0.009) for overall CRP changes.

4. Discussion

This is only the second study that has prospectively examined the association between the preoperative depression and baseline and postoperative CRP levels and their impact on postoperative recovery in a cohort of CABG patients. Also, this is the first study in which preoperative depressive symptoms were measured by two evaluated depression score systems: the Beck Depression Inventory (BDI-II) and Primary Care Evaluation of Mental Disorders (PRIME-MD)/The Patient Health Questionnaire (PHQ)-9 test score.

In the present study, only 12.6% and 44.8% of CABG patients had mild-to-severe baseline (preoperative) depressive symptoms measured by BDI depression inventory and PRIME-MD test score, respectively. These results are within the range (0.6-60%) of previously reported studies (5, 14–18). The huge variability in reported estimates may be attributed to one or more of the following causes: clinical and demographic differences between samples, diverse inclusion and exclusion criteria, differences in questionnaires or clinical interviews used for measurement, different timing of measurement and different cut-off values used for determining high or low levels of depression.

In our study, only the median value of continuous preoperative BDI scores was significantly associated with longer postoperative hospital LOS (> 7 days) while no statistically significant association was found between the binary BDI (non-depressed: BDI-II ≤ 13 vs depressed: BDI-II > 13) or the continuous (median values) and binary PRIME-MD/PHQ-9 test score values (non-depressed: PRIME-MD ≤ 4 vs depressed: PRIME-MD > 4) with the patient's postoperative hospital or ICU length of stay. However, we did notice that patients with higher BDI scores (BDI-II >13) had increased, although statistically nonsignificant, odds of prolonged hospital stay. Also, the patient group with higher BDI showed significantly higher median values for the length of hospital stay compared to the non-depressed patient group.

Poole et al. reported that CABG patients with elevated preoperative BDI scores had significantly higher odds of a prolonged hospital stay of greater than one week compared with patients with low depressive symptoms (18). However, in their study, the cut-off value for the BDI score was set at ≤ 10 for the non-depressed and >10 for the depressed CABG patient group. Importantly when the same cut-off values were applied to our cohort of CABG patients no statistically significant association of binary BDI values and hospital LOS was detected.

The negative influence of higher levels of depressive symptoms on CABG patient outcomes and longer LOS was previously confirmed by several studies (14–16). AbuRuz et al. reported that every one-unit

increase in preoperative depressive symptoms increased the length of hospital stay by 0.37 days (14). Furthermore, in their patient cohort, females had higher levels of depressive symptoms compared to male patients and being female increased the length of stay by 0.18 days (14). Similar results were also reported in their previous study (15). The higher rate of preoperative depression among female CABG patients had also been reported by Yang et al. and Poole et al (17, 18).

In our patient cohort, female patients were more prone to preoperative depression and longer hospital stay compared to male CABG patients.

The presence of preoperative depression increased the odds of other negative outcomes for CABG patients including a higher incidence of postoperative inflammation, decreased wound healing, and depressed patient resistance, all of which have a negative impact on patient postoperative LOS (6, 18, 22). All of them have a strong correlation with CRP levels and other inflammatory markers (18, 23). As already stated, inflammation, the key regulator of CRP synthesis, has a prominent role in the etiology of atherosclerotic cardiovascular diseases including CAD (8, 9).

In the study by Poole et al., the association of a higher BDI score with increased odds of prolonged hospital stay (>7 days) was partially mediated by slightly elevated early (baseline to 1–3 day follow-up) and even higher persistent (baseline to 4–8 day follow-up) postoperative CRP elevations (18). In their CABG cohort, an increase in early CRP change by one unit resulted in an increased chance of hospital stay greater than one week by 1% whereas the same increase in persistent CRP change resulted in 1.3% higher odds of longer hospital stay.

Similarly, in our cohort of CABG patients, both persistent and overall CRP elevation showed significantly higher odds of prolonged hospital stay (>7 days); with a one unit increase in CRP resulting in a 1.1% and 1.6% increase in the chance of longer hospital stay, respectively. Also, the CRP values measured on 3-6 days postoperatively were significantly higher among CABG patients with elevated preoperative BDI scores. The CABG patient group with an elevated baseline BDI score also had significantly higher preoperative CRP values, thus, further confirming the relationship between depressive symptoms, inflammation, and CAD.

However, linear regression models performed to examine the cross-sectional relationship between depressive scores and preoperative CRP levels resulted in no significant association. Nor were baseline BDI-II and PRIME-MD scores associated with a change in early, persistent, and overall CRP responses. The lack of association between BDI score and preoperative CRP levels was also reported by Poole et al (18). Nevertheless, in our patient cohort preoperative CRP values were identified as a significant predictor of early CRP response to CABG surgery.

The association between preoperative depression and baseline CRP levels in CABG patients was previously reported by Yang et al. (17). In their study, elevated preoperative serum levels of CRP were identified as an independent predictor for depression (assessed with the PRIME-MD/PHQ-9 test score) present not only preoperatively but also up to six months after the CABG procedure. Similarly, the results

of the present study also detected a significant association between the female gender and the presence of preoperative depressive symptoms.

In the present study smoking, EuroSCORE-II values and extubation time were also found to be significantly associated with higher BDI depression scores among CABG patients while higher preoperative hemoglobin levels were associated with higher values of both BDI and PRIME-MD depression scores. Furthermore, these variables were all significantly associated with a postoperative hospital stay of longer than one week.

The association between depression and smoking in CABG patients has been reported in several studies (5, 24, 25). In addition, Abbasi et al. reported that cigarette smoking was significantly more frequent in depressed young male patients with documented CAD (25).

Anemia associated with fatigue and adverse cardiac outcomes is relatively common in acute cardiac patients (26). Anemia is also associated with depression both in general and clinical populations (27). Anemia of inflammation (AI), also known as anemia of chronic disease (ACD), which is caused by immune activation is the most frequent anemic entity observed in hospitalized or chronically ill patients and is commonly encountered among patients with advanced atherosclerotic lesions, including CAD (28). Lanser et al. reported that patients with ACD presented with more progressed CAD and tended to have higher CRP values (28). In addition, Steptoe et al. reported that anemia contributes to depression following acute coronary syndrome and is associated with future cardiac morbidity (29).

Up until now, most of the EuroSCORE-II variables have been related to anxiety and depression and thus EuroSCORE II operational risk values might also be accountable for risks originating from preoperative anxiety and depressive symptoms (30). Therefore, there is a link between preoperatively expressed depression and EuroSCORE values that needs to be further explored. Furthermore, Cromhout et al. also believe that the development of a prognostic screening tool involving emotional, behavioral, social and functional factors is necessary to complement the risk assessment by EuroSCORE (31).

In our study, diabetes, regardless of insulin therapy, were more frequent among patients with elevated BDI and PRIME-MD depression test scores.

Diabetes is a well-known cardiovascular risk factor and the prevalence of depression is more than three times higher in people with diabetes compared to the general population without the disease (32).

When comparing the BDI test and PRIME-MD test score, the latter has proved to be less appropriate for the assessment of depression in our CABG patient cohort. Nevertheless, although it seems that the BDI-II scale represents a sound path for detecting depression in CABG patients, the need for careful adjustment of cut-off points and evidence-based interpretation of score values should be addressed before its usage in clinical decision making (42).

There are several strengths to our study; our study examined patients undergoing CABG at a single hospital and therefore removed the influence of inter-hospital variations in discharge policy. The design

of the study allowed for a temporal relationship between depression, CRP levels and length of stay to be analyzed. Also, the repeated assessment of CRP levels allowed us to test the contribution of both preoperative and postoperative inflammation to the postoperative recovery of CABG patients. There were also some limitations to the study; Firstly, the study encompasses a too-small group of patients to observe the impact on operative risk and patient mortality, secondly, other non-medical factors, such as, social housing constraints also likely to play a role in determining hospital length of stay. Such confounders were not able to be taken into account in our analyses.

Conclusion

We found that higher preoperative depressive symptoms measured by the Beck Depression Inventory (BDI-II) test were associated with higher a EuroSCORE-II value, longer postoperative hospital length of stay, higher preoperative (baseline) CRP values, and higher day 1 postoperative CRP values. They were also associated with elderly patients with more pronounced comorbidities and with the female gender, current smoking status, slightly lower ejection fraction and statistically significant anemia. Further work is needed to understand the processes through which depression and CRP levels interact to affect cardiac recovery. Replication of these findings in larger samples is required.

Abbreviations

ACD - anemia of chronic disease; ACE - angiotensin-converting enzyme; AI - Anemia of inflammation; BDI- Beck Depression Inventory; BMI - body mass index; CABG - coronary artery bypass grafting; CAD- coronary artery disease; CI -confidence interval; FA – atrial fibrillation; CRP- high sensitive C reactive protein; ICU – intensive care unit; IQR – interquartile range; LOS – length of stay; rpm - revolutions per minute; MI – myocardial infarction; OD – odds ratio; SD – standard deviation.

Declarations

Ethics approval and consent to participate

This study was designed as a prospective observational (non-interventional) study. All participants signed informed consent forms and the study protocol was approved by the Ethics Committee of the University Hospital Centre Zagreb, Croatia (Approval number of the Ethics Committee UHC Zagreb, Class: 8.1-11/84-3).

Consent for publication

Not applicable

Availability of data and materials

Most of the data generated and/or analyzed during the current study is included in the paper. The demographic and clinical characteristics of CABG patients and statistical datasets used and/or analyzed during the current study is available from the corresponding author upon reasonable request.

Competing interests

The authors report no conflicts of interest in this work.

Funding

This work received no external funding.

Authors' contributions

SI, VC, AMP, TS and BB made substantial contributions to the conception, design and acquisition of data. SI, FP, and TS contributed to the analysis and interpretation of data. SI, FP, VK, and MP were involved in the drafting of the manuscript and revising it critically for important intellectual content. VC and BB supervised the study. All authors have read and approved the final version of the manuscript.

Acknowledgments

Not applicable

Authors' information (optional)

Not applicable

References

1. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. J Cell Physiol. 2019;234(10):16812-16823.
2. Hajar R. Risk Factors for Coronary Artery Disease: Historical Perspectives. Heart Views. 2017;18(3):109-114.
3. Khawaja IS, Westermeyer JJ, Gajwani P, Feinstein RE. Depression and coronary artery disease: the association, mechanisms, and therapeutic implications. Psychiatry (Edgmont). 2009;6(1):38-51.
4. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. Biol Psychiatry. 2003;54(3):227-240.

5. Correa-Rodríguez M, Abu Ejheisheh M, Suleiman-Martos N, Membrive-Jiménez MJ, Velando-Soriano A, Schmidt-RioValle J, et al. Prevalence of Depression in Coronary Artery Bypass Surgery: A Systematic Review and Meta-Analysis. *J Clin Med.* 2020;9(4):909.
6. Stenman M, Holzmann MJ, Sartipy U. Association between preoperative depression and long-term survival following coronary artery bypass surgery - A systematic review and meta-analysis. Int J Cardiol. 2016;222:462-466.
7. Khan SA, Shahzad U, Zarak MS, Channa J, Khan I, Ghani MOA. Association of Depression with Subclinical Coronary Atherosclerosis: a Systematic Review. J Cardiovasc Transl Res. 2021;14(4):685-705.
8. Chrysohoou C, Kollia N, Tousoulis D. The link between depression and atherosclerosis through the pathways of inflammation and endothelium dysfunction. Maturitas. 2018;109:1-5.
9. Baghai TC, Varallo-Bedarida G, Born C, Häfner S, Schüle C, Eser D, et al. Classical Risk Factors and Inflammatory Biomarkers: One of the Missing Biological Links between Cardiovascular Disease and Major Depressive Disorder. Int J Mol Sci. 2018;19(6):1740.
10. Morris G, Puri BK, Olive L, Carvalho A, Berk M, Walder K, et al. Endothelial dysfunction in neuroprogressive disorders-causes and suggested treatments. BMC Med. 2020;18(1):305.
11. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and clinical response to treatment in depression: A meta-analysis. Eur Neuropsychopharmacol. 2015;25(10):1532-1543.
12. Felger JC, Haroon E, Patel TA, Goldsmith DR, Wommack EC, Woolwine BJ, et al. What does plasma CRP tell us about peripheral and central inflammation in depression? Mol Psychiatry. 2020;25(6):1301-1311.
13. Wium-Andersen MK, Ørsted DD, Nielsen SF, Nordestgaard BG. Elevated C-reactive protein levels, psychological distress, and depression in 73, 131 individuals. JAMA Psychiatry. 2013;70(2):176-184
14. AbuRuz ME, Momani A, Shajrawi A. The Association Between Depressive Symptoms and Length of Hospital Stay Following Coronary Artery Bypass Graft is Moderated by Perceived Control. Risk Manag Healthc Policy. 2021;14:1499-1507.
15. AbuRuz ME. Preoperative depression predicted longer hospital length of stay among patients undergoing coronary artery bypass graft surgery. Risk Manag Healthc Policy. 2019;12:75-83.
16. Oxlad M, Stubberfield J, Stuklis R, Edwards J, Wade TD. Psychological risk factors for increased postoperative length of hospital stay following coronary artery bypass graft surgery. J Behav Med. 2006;29(2):179-190.
17. Yang L, Wang J, Zhang L, Hou J, Yuan X, Hu S, et al. Preoperative high-sensitivity C-reactive protein predicts depression in patients undergoing coronary artery bypass surgery: a single-center prospective observational study. J Thorac Cardiovasc Surg. 2012;144(2):500-505.
18. Poole L, Kidd T, Leigh E, Ronaldson A, Jahangiri M, Steptoe A. Depression, C-reactive protein and length of postoperative hospital stay in coronary artery bypass graft surgery patients. Brain Behav Immun. 2014;37(100):115-121.

19. Tamburrino MB, Lynch DJ, Nagel RW, Smith MK. Primary care evaluation of mental disorders (PRIME-MD) screening for minor depressive disorder in primary care. *Prim* Care Companion J Clin Psychiatry. 2009;11(6):339-343.
20. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess. 1996;67(3):588-597.
21. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, et al. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg. 1999; 15(6):816-22; discussion 822-3.
22. Stenman M, Holzmann MJ, Sartipy U. Relation of major depression to survival after coronary artery bypass grafting. *Am J Cardiol.* 2014;114(5):698-703.
23. Gegenava T, Gegenava M, Kavtaradze G. C-reactive protein level correlation with depression and anxiety among patients with coronary artery disease. Georgian Med News. 2011;(194):34-37.
24. Flaherty LB, Wood T, Cheng A, Khan AR. Pre-existing psychological depression confers increased risk of adverse cardiovascular outcomes following cardiac surgery: A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2017;154(5):1578-1586.e1.
25. Abbasi SH, Kassaian SE, Sadeghian S, Karimi A, Saadat S, Peyvandi F, et al. Factors Associated with Depressive Symptoms in Young Adults with Coronary Artery Disease: Tehran Heart Center's Premature Coronary Atherosclerosis Cohort (THC-PAC) Study. Iran J Psychiatry. 2016 Oct;11(4):214-223.
26. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, et al. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation. 2005;111(16):2042-9.
27. Hamer M, Molloy GJ. Cross-sectional and longitudinal associations between anemia and depressive symptoms in the English Longitudinal Study of Ageing. J Am Geriatr Soc. 2009;57(5):948-9.
28. Lanser L, Fuchs D, Scharnagl H, Grammer T, Kleber ME, März W, Weiss G, Kurz K. Anemia of Chronic Disease in Patients With Cardiovascular Disease. Front Cardiovasc Med. 2021;8:666638.
29. Steptoe A, Wikman A, Molloy GJ, Kaski JC. Anaemia and the development of depressive symptoms following acute coronary syndrome: longitudinal clinical observational study. BMJ Open. 2012;2(1):e000551.
30. Messerotti Benvenuti S, Palomba D, Zanatta P, Mazzarolo AP, Valfrè C. Biomedical and psychological risk in cardiac surgery: is EuroSCORE a more comprehensive risk measure than Stroke Index? Eur J Cardiothorac Surg. 2011;39(5):e102-6.
31. Cromhout PF, Kikkenborg Berg S., Moons P, Damgaard S. Nashef S, Thygesen LS. Updating EuroSCORE by including emotional, behavioural, social and functional factors to the risk assessment of patients undergoing cardiac surgery: a study protocol, BMJ Open. 2019; 9(7):e026745.
32. Bădescu SV, Tătaru C, Kobylinska L, Georgescu EL, Zahiu DM, Zăgrean AM, Zăgrean L. The association between Diabetes mellitus and Depression. J Med Life. 2016;9(2):120-5.

33. Wang YP, Gorenstein C. Assessment of depression in medical patients: a systematic review of the utility of the Beck Depression Inventory-II. Clinics (Sao Paulo). 2013;68(9):1274-87.

Figures

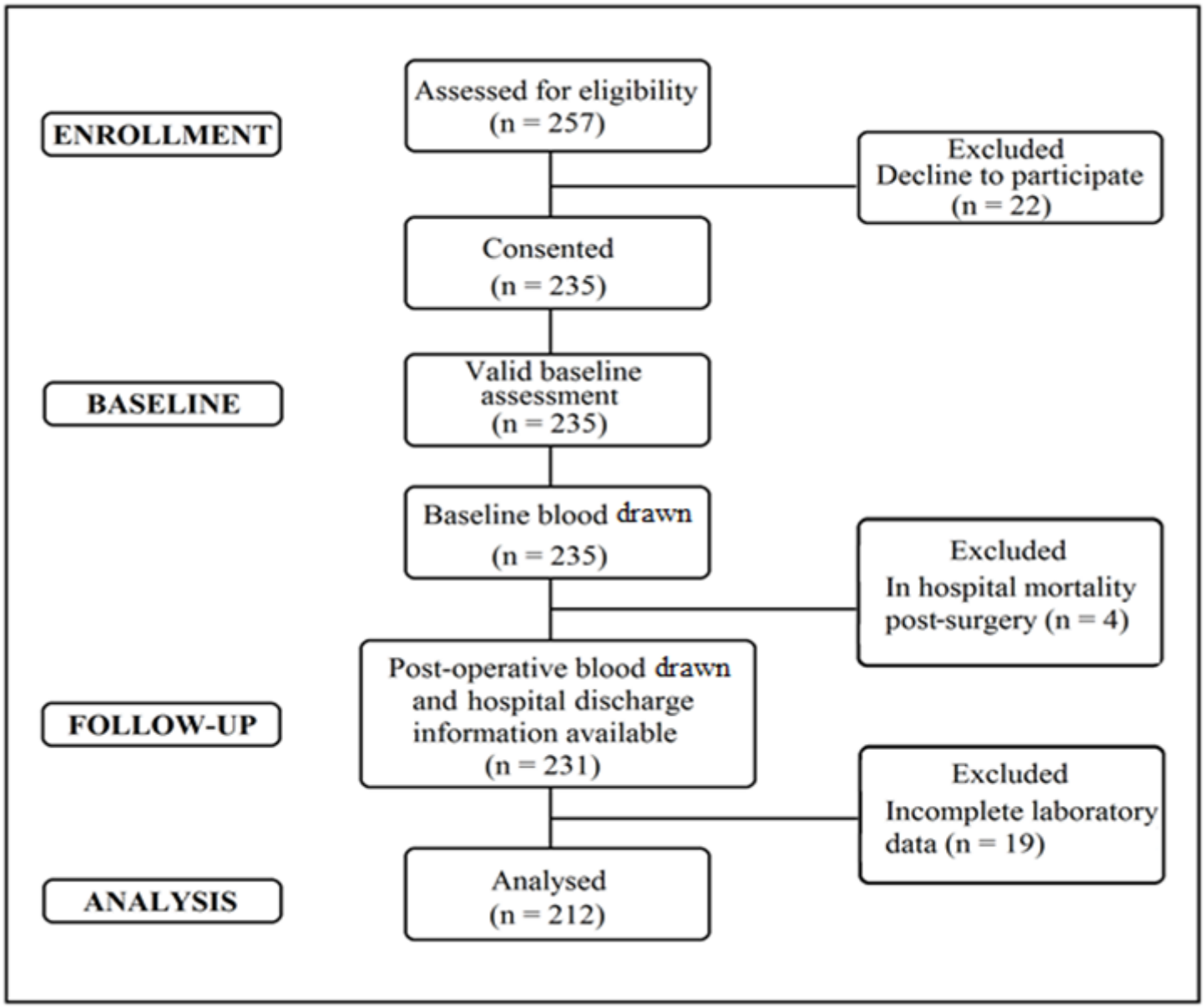

Figure 1

Flow diagram of coronary artery bypass grafting (CABG) patient's recruitment and retention.