ORIGINAL ARTICLE

Higher anxiety score in patients with non-obstructive coronary artery disease

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Background: There is insufficient evidence on the relationship between psychological distress and patients with non-obstructive coronary artery disease (NOCAD) who experience angina symptoms despite having non-significant narrowing or normal coronary arteries. Therefore, our aim is to evaluate the psychological distress status in patients with NOCAD. **Materials and Methods:** In this prospective cross-sectional study, patients with symptomatic angina scheduled for coronary angiography were screened and invited to participate, alongside a control group of non-symptomatic individuals. Symptomatic patients were categorized as having obstructive (OCAD) or NOCAD based on angiogram results. All participants completed the Hospital Anxiety and Depression Scale (HADS) to assess their psychological state and provided blood samples for stress biomarker analysis. **Results:** A total of 124 subjects participated in this study. The prevalence of anxiety and depression (HADS score ≥8) in patients with OCAD and NOCAD were 26.2% and 25%, respectively. The HADS anxiety (HADS–A) score was higher in both OCAD ($P < 0.001$) and NOCAD ($P = 0.001$) patients compared to controls. In addition, the HADS depression score was higher in OCAD patients as compared to the control. Notably, the HADS–A score was associated with NOCAD (odds ratio [95% confidence interval], 1.213 [1.029, 1.499]; $P = 0.021$). Furthermore, cortisol levels were higher in OCAD as compared to controls ($P = 0.028$). **Conclusion:** Higher anxiety scores indicate significant emotional distress in patients with NOCAD. Furthermore, anxiety shows a notable association with NOCAD in patients presenting with angina.

Key words: Anxiety, coronary artery disease, cortisol, depression, non-obstructive coronary artery disease

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INTRODUCTION

In patients with symptomatic angina who undergo coronary angiography, no significant obstruction or normal coronary arteries were found in around 40% and up to 70% of these patients, often leading to a diagnosis of non-obstructive coronary artery disease (NOCAD).[1,2] Unfortunately, patients with NOCAD are frequently managed improperly and continue to be symptomatic.[1] Despite the absence of significant occlusion, patients with NOCAD experience angina chest pains like OCAD patients. In addition, they face a higher risk of stroke or heart failure, myocardial infarction, cardiovascular death, and all-cause mortality compared to the normal population.[3] Moreover, the quality of life of patients with NOCAD is adversely affected due to repeated hospitalizations and coronary angiograms, which also lead to increased healthcare expenditure.[4]

Psychological distress, particularly anxiety and depression, is often linked to CAD and its negative effects. A meta-analysis study revealed that anxiety is related to elevated mortality risk in patients with CAD. In addition, the presence of anxiety in patients with

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stable CAD is associated with the risk of poorer outcomes.[5] Psychological distress, namely anxiety and depression are common in patients with CAD[6] and is significantly correlated with the severity of the disease.[7] Another meta-analysis found that initially healthy individuals with anxiety may have a greater risk of developing CAD and increased cardiac mortality.[8] Similarly, a review indicates that in patients with established CAD, depression raises the risk of incident CAD and contributes to cardiovascular morbidity and mortality.[9] In stable CAD patients, both anxiety and depression significantly predict the 2-year major adverse cardiac events (MACEs), and it has also been shown that anxiety and depression increased the risk of these patients having MACEs, with the odds ratios of 2.09 and 2.85, respectively.[10]

In addition to anxiety and depression, general psychological stress has been found to significantly contribute to the progression and advancement of cardiovascular disease (CVD). The risk of CVD, such as stroke and coronary heart disease (CHD), increases from 1.1 to 1.6-fold in individuals experiencing work-related or personal stress.[11] One way to measure stress is by using stress biomarkers. When the stress occurs, these biomarkers, primarily cortisol, are released following the activation of the hypothalamus–pituitary–adrenal (HPA) axis. Cortisol levels can be analyzed from various samples, including saliva, blood, and hair.[11] In addition, dopamine release has been associated with psychological stress.[12] Dopamine, an important neurotransmitter for reward and pleasure systems in the brain, seems to have a complex relationship with stress. Previous studies have shown that acute stress often results in an increased release of dopamine, which may enhance motivation. In contrast, chronic stress tends to decrease dopamine release, potentially leading to depression.[13] In patients who have gone coronary angiography, an association has been observed between cortisol levels and traditional cardiovascular risk factors.[14] However, the association between cortisol levels and NOCAD has not been extensively studied, highlighting an urgent need for further investigation in this area.

While there is substantial data on the role of psychological factors in patients with OCAD, information regarding the involvement of psychological factors such as anxiety and depression in patients with NOCAD is still limited. It remains unclear whether NOCAD patients experience higher levels of psychological stress compared to individuals without angina. The stress levels in NOCAD patients have not been extensively studied. In this study, we hypothesized that patients with NOCAD might have higher psychological stress levels as compared to the healthy population. Therefore, our research aimed to evaluate the score of psychological components using validated questionnaires and to measure stress biomarkers (cortisol and dopamine) in patients with OCAD, NOCAD, and non-symptomatic controls. We also explored the association of psychological symptoms and blood biomarkers with NOCAD. The outcomes of this study could offer valuable insights into whether NOCAD patients experience significant psychological distress, which would be beneficial for intervention strategies.

MATERIALS AND METHODS

Study design and patients

This prospective cross-sectional study was conducted at the Hospital Pakar Universiti Sains Malaysia in Kelantan, Malaysia, from July 2022 to June 2024. Participants were recruited using a convenient sampling method. We invited symptomatic patients who met the inclusion and exclusion criteria to participate in the study. These patients, suspected of having coronary artery disease (CAD) and scheduled for a coronary angiography examination in our Invasive Cardiology Laboratory, were screened prior to the procedure. They came to the hospital primarily due to typical or atypical chest pain and sought medical advice and treatment. The sample size was determined using the PS Power and Sample Size Calculations software (version 3.0). The significance level (α) and statistical power were set at 0.05 and 0.8, respectively. An expected mean difference (δ) of 4.4 in the Hospital Anxiety and Depression Scale–Anxiety (HADS–A) score between NOCAD patients and healthy controls, with a standard deviation (SD) (σ) of 7.4, was used for the calculation.[15] The required sample size was 45 participants per group.

Patients with a history of congestive heart failure, cardiomyopathy, valvular heart disease, myocardial infarction, chronic kidney disease, previous revascularization procedures, or prior coronary angiography were excluded from the study. In addition, a control group consisting of participants without symptoms of angina and with no history of ischemic heart disease or serious conditions such as terminal illnesses, cancer, or liver disease, was recruited from among the staff, students, or next of kin of the patients. This group was interviewed to assess their eligibility for participation in the study.

This study received approval from the human research ethics committee at our institution with reference number: USM/JEPeM/18010077 and was conducted in accordance with the principles outlined in the Declaration of Helsinki. Participants were informed about the study's purpose, procedures, possible risks, and benefits by a study representative. They were given time to ask questions, and consent was only taken once they showed understanding. Participation was voluntary, with the option to withdraw at

any time without consequence. Consent was documented through signed forms. This process ensured that participants provided informed and voluntary consent, with a clear understanding of the study procedures and requirements.

Demographic and medical history

Demographics and medical history of study participants were obtained from their medical records, interview session and physical examinations. For all subjects, the weight and height were measured using a digital weighing scale and a stadiometer, respectively. Systolic and diastolic blood pressure (DBP) were assessed using an automatic digital blood pressure monitor, following previously described methods.[16] In addition, cardiac risk factors, including gender, diabetes mellitus, hypertension, hyperlipidemia, family history of heart disease, and smoking history, were documented. These cardiac risk factors were defined as previously described.[17]

Coronary angiography

A coronary angiography procedure was conducted on symptomatic patients by an experienced cardiologist in our invasive cardiology laboratory. During the procedure, seven views of the left coronary artery and three views of the right coronary artery (RCA) were obtained for assessment. The percentage of vessel occlusion was determined using quantitative computed tomography coronary angiography, which employed an automated edge-detection system (Azurion, Philips, Netherlands). Any lesions present in the RCA, left anterior descending artery (LAD), left circumflex artery (LCx), and their respective branches were documented. Based on the existence of stenosis in the main arteries (RCA, LAD, and LCx), patients were categorized into obstructive or NOCAD groups. Patients were classified as OCAD if they had a luminal diameter reduction of 50% or more due to stenosis in any of the main arteries. In contrast, those without stenosis or with a luminal diameter reduction of <50% were classified as NOCAD.[18]

Psychological assessment

Psychological symptoms were assessed during the recruitment session using self-reported questionnaires to screen for chronic and current levels of anxiety and depression among the study participants.

Anxiety and depression were assessed using the HADS. HADS is a brief questionnaire that was developed to assess chronic anxiety and depression, which commonly coexist in a general medical population of patients.[19,20] HADS assesses non-physical symptoms, thus capable of diagnosing depression in individuals with major physical health issues. The questionnaire comprises seven questions each for anxiety and depression, with these questions interspersed within the questionnaire. Participants are required to immediately choose the answer that best describes how they have felt in the past week. The scores for anxiety and depression were counted separately. For both anxiety and depression scales, scores of 8–10 indicate mild levels, 11–14 indicate moderate levels, and 15–21 indicate severe levels. Scores below 7 suggest non-cases for both anxiety and depression, while scores of 8 and above indicate the case of anxiety or depression. The cutoff score of 8 or more has shown good specificity and sensitivity in classifying cases of anxiety and depression.[21] In this study, the Malay version of HADS was utilized. The validation of the local version has shown good sensitivity and specificity in identifying anxiety and depression within our population.[22]

Blood biomarkers

Blood samples from symptomatic patients were obtained by a nurse prior to the coronary angiography procedure, following standard pre-procedural preparation. For control participants, a study nurse collected fasting blood samples in the morning after an overnight fast. Eligible control participants were contacted in advance and invited to attend the laboratory for blood sample collection. Peripheral blood samples were collected from the upper arm and allowed to clot at room temperature before undergoing centrifugation. The serum was then collected and stored at −80°C until analysis. Serum cortisol and dopamine levels were measured using 96-well enzyme-linked immunosorbent assay kits. The protocols were followed according to the manufacturers' recommendations (Elabscience, China). Absorbance was measured at a wavelength of 450 nm using the Multiplate Varioskan Flash (Thermo Scientific, USA). A standard curve was established for each assay, and the levels of cortisol and dopamine were determined using the SkanIt RE for Varioskan Flash software (Thermo Scientific, USA).

Statistical analysis

All data were analyzed using the IBM® SPSS® Statistics software version 28 (IBM Corporation, Armonk, New York, USA). Normally and non-normally distributed numerical data were expressed as mean ± SD or median (interquartile range), respectively, while categorical data were presented as frequency and percentage. The distribution of the continuous variables was assessed for normality. One-way ANOVA was applied to compare normally distributed continuous variables, while the Kruskal–Wallis H test was used for non-normally distributed variables across the OCAD, NOCAD, and non-symptomatic control groups. Meanwhile, the Chi-square test was used to compare categorical variables. Logistic regression analysis was done to determine whether the occurrence of NOCAD is associated with psychological factor score, and the model fitness was assessed using the receiver operating curve. A two-tailed $P < 0.05$ was measured as significant.

RESULTS

Demographic and medical history

A total of 124 subjects participated in this study. Forty-three patients were categorized in the OCAD group, 41 patients in the NOCAD group, and 40 subjects in the non-symptomatic control group. Males constituted 54.8% of the total subjects, and the mean age was 51.80 ± 8.46 years old. Age, DBP, total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-C), and the incidence of diabetes, hypertension, and family history of heart disease were statistically different across all groups. These significantly different parameters were then assigned as potential cofounding factors in the comparative analysis of psychological assessment [Table 1].

Psychological assessment and blood biomarkers

In terms of psychological assessment, HADS–A and depression total score were significantly different across all groups. *Post hoc* analysis revealed HADS–A total score was significantly higher in OCAD and NOCAD groups than in the control group, while HADS depression total score was higher in the OCAD group as compared to the control group. The differences in HADS–A score between all groups remain significant after the adjustment of potential cofounding factors from the baseline characteristic analysis. For blood biomarkers, cortisol levels were higher in patients with OCAD as compared to the control group. No significant difference was seen in dopamine levels across all groups [Table 2].

The prevalence of anxiety and depression (HADS score ≥8) in the symptomatic patients (NOCAD and OCAD) were 26.2% and 25%, respectively. Comparison between the levels of HADS–A demonstrated a trend in the number of subjects with moderate-to-high scores in OCAD and NOCAD groups which indicated higher anxiety levels in these groups than the control groups. However, no significant changes were noted in the level of HADS depression score among all groups [Table 3]. Furthermore, HADS–A total score was significantly associated with the occurrence of NOCAD [Table 4], with the area under the receiver-operator curves was 0.600 [Figure 1].

DISCUSSION

The current study demonstrated that patients with OCAD and NOCAD exhibited higher anxiety scores compared to non-symptomatic control subjects. Interestingly, anxiety was significantly associated with NOCAD. In summary, our study highlights the relationship between psychological distress, particularly anxiety, and NOCAD. Furthermore, cortisol levels, which serve as stress biomarkers, were also higher in patients with OCAD than in the control group, underscoring the importance of addressing mental health in cardiovascular care.

Table 1: Baseline characteristics of study participants (*n*=124)

Parameters	Control (*n*=40)	NOCAD (*n*=41)	OCAD (*n*=43)	*P*
Age (years)	49.85±7.68	51.07±9.22	54.30±7.96	0.044[a]
Gender, male/female, (*n*/*n*)	21/19	17/24	30/13	0.031[b]
BMI (kg/m^2)	28.76±4.37	28.94±4.71	28.59±4.33	0.942
SBP (mmHg)	125.89±16.32	124.94±17.96	125.85±18.03	0.954
DBP (mmHg)	81.71±8.54	75.76±10.16	76.55±8.11	0.007[a]
FBG (mmol/L)	4.75 (4.43–5.80)	5.36 (4.66–6.45)	6.28 (4.87–8.36)	0.028[c]
TC (mmol/L)	5.72 (4.76–6.46)	3.76 (3.45–4.96)	4.24 (3.26–5.17)	<0.001[c]
TG (mmol/L)	1.72 (1.30–2.42)	1.04 (0.69–1.37)	1.05 (0.85–1.56)	<0.001[c]
HDL-C (mmol/L)	1.28 (1.13–1.48)	1.23 (1.03–1.32)	1.21 (0.96–1.41)	0.346[c]
LDL-C (mmol/L)	3.31 (2.83–4.32)	2.12 (1.73–3.07)	2.32 (1.56–3.41)	<0.001[c]
Diabetes	7 (17.5)	9 (22.0)	23 (53.5)	0.001[b]
Hypertension	11 (28.2)	25 (61.0)	29 (67.4)	0.001[b]
Hyperlipidemia	30 (75.0)	33 (79.1)	39 (90.7)	0.163[b]
Family history of heart diseases	4 (10.3)	18 (43.9)	16 (37.2)	0.002[b]
Smoking status	5 (12.8)	6 (14.6)	12 (27.9)	0.152[b]
Antidiabetics	5 (12.5)	8 (19.5)	15 (34.9)	0.009[b]
ACEI/ARB	6 (15.0)	27 (65.9)	24 (55.8)	<0.001[b]
Beta blockers	2 (5.0)	20 (48.8)	20 (46.5)	<0.001[b]
Calcium channel blockers	4 (10.0)	18 (43.9)	12 (27.9)	0.001[b]
Lipid-lowering drugs	8 (20.0)	19 (46.3)	24 (55.8)	<0.001[b]

[a]One-way ANOVA, [b]Chi-square test, [c]Kruskal–Wallis *H*-test. Levene's test of homogeneity of variance, *P*>0.05 for all continuous parameters except for TG (*P*<0.05). Except for TG, the equality of variances assumption is met. Thus, the variance of the dependent variable is similar between groups. Data presented as mean±SD or median (IQR) for continuous variables and frequency (%) for categorical variables. ACEI=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin II receptor blockers; BMI=Body mass index; DBP=Diastolic blood pressure; FBG=Fasting blood glucose; HbA1c=Glycosylated hemoglobin; HDL-C=High density lipoprotein-cholesterol; HR=Heart rate; LDL-C=Low density lipoprotein-cholesterol; OCAD=Obstructive coronary artery disease; NOCAD=Non-OCAD; SBP=Systolic blood pressure; TC=Total cholesterol; TG=Triglyceride; SD=Standard deviation; IQR=Interquartile range

Table 2: Psychological score and blood biomarkers comparison (*n*=124)

Parameters	Control (*n*=40)	NOCAD (*n*=41)	OCAD (*n*=43)	Test statistics (df)	*P*	Bonferroni correction test (*P*)		
						OCAD versus control	NOCAD versus control	OCAD versus NOCAD
HADS anxiety total score	2.50 (0.00–6.00)	6.00 (3.00–8.00)	6.00 (3.75–8.25)	18.892 (2–124)	<0.001*	<0.001**	0.001**	1.000
HADS depression total score	3.00 (1.00–6.00)	5.00 (3.00–7.00)	6.00 (2.75–9.00)	8.110 (2–124)	0.017*	0.018**	0.127	1.000
Cortisol (ng/mL)	144.85 (107.25–184.80)	171.70 (129.25–246.80)	174.30 (139.90–227.90)	8.563 (2–124)	0.014*	0.016**	0.081	1.000
Dopamine (pg/mL)	1154.50 (854.45–1562.75)	1148.50 (735.18–1949.75)	1121.50 (682.33–1733.75)	1.454 (2–123)	0.483	0.776	1.000	1.000

*Significant differences using Kruskal–Wallis H-test, **Adjusted significant values using Bonferroni correction for multiple tests. Levene's test of homogeneity of variance, *P*>0.05 for all parameters except for dopamine (*P*<0.05). Except for dopamine, the equality of variances assumption is met. Thus, the variance of the dependent variable is similar between groups. Data presented as median (IQR). HADS=Hospital Anxiety and Depression Scale; OCAD=Obstructive coronary artery disease; NOCAD=Non-OCAD, IQR=Interquartile range

Table 3: Level of Hospital Anxiety and Depression Scale anxiety and depression (*n*=124)

Parameters	Control (*n*=40)	NOCAD (*n*=41)	OCAD (*n*=43)	*P*
Anxiety				
Low score/non-cases (0–7)	38 (95.0)	30 (73.2)	32 (74.4)	0.052
Moderate score/moderate cases (8–14)	2 (5.0)	11 (26.8)	10 (23.3)	
High score/severe cases (15–21)	0	0	1 (2.3)	
Depression				
Low score/non-cases (0–7)	31 (77.5)	34 (82.9)	29 (67.4)	0.387
Moderate score/moderate cases (8–14)	9 (22.5)	7 (17.1)	13 (30.2)	
High score/severe cases (15–21)	0	0	1 (2.3)	

Chi-square test. Data presented as frequency (%). OCAD=Obstructive coronary artery disease; NOCAD=Non-OCAD

Table 4: Logistic regression analysis of psychological score and blood biomarkers in predicting non-obstructive coronary artery disease (*n*=124)

Parameters	OR	95% CI	*P*
HADS anxiety total score	1.213	1.029–1.429	0.021*
HADS depression total score	0.940	0.802–1.101	0.443
Cortisol (ng/mL)	1.001	0.997–1.005	0.653
Dopamine (pg/mL)	1.001	1.000–1.002	0.052

*Significant association using logistic regression analysis. *P*=0.306, classification table=68.9%. Hosmer and Lemeshow test for multiple logistic. CI=Confidence interval; OR=Odds ratio; HADS=Hospital Anxiety and Depression Scale

Control subjects showed higher levels of DBP, TC, TG, and LDL-C compared to patients with OCAD and NOCAD. However, the DB*P* values in all groups remained within the normal range. This discrepancy may be attributed to undiagnosed cases among the control subjects, as they did not receive any interventions. In contrast, patients with OCAD and NOCAD were diagnosed and prescribed medications such as beta blockers, calcium channel blockers, and statins to manage their hypertension and hyperlipidemia. As a result, they exhibited lower levels of DBP, TC, TG, and LDL-C compared to the control group. In addition, it was expected that patients with OCAD and NOCAD would have a higher incidence of diabetes, hypertension, and a family history of heart disease, as these factors are well-known risk factors for cardiac disease.[17]

The current study found that patients with OCAD and NOCAD exhibited higher anxiety and depression scores compared to control subjects. The cutoff score of 8 was used to acknowledge the anxiety and depression cases. The use of a higher cutoff will reduce sensitivity but increase the specificity and positive predictive value. Meanwhile, using a lower cut-off point increased sensitivity, allowing more true positives to be identified. However, this approach also resulted in a decrease in specificity and positive predictive value. Thus, it is important to use an optimal cutoff point that enhances both sensitivity and specificity when interpreting the findings. Nevertheless, the cutoff point of 8/9 has been reported to be the best point for the detection of both anxiety and depression in our local population,[22] hence justifying the use of cutoff point of 8 in this study.

The prevalence of anxiety and depression (defined as HADS score ≥8) among our patients was 26.2% for OCAD and 25% for NOCAD. Similar to our findings, a previous study indicates that the prevalence of anxiety and depression among hospitalized patients with CAD ranges between 25% and 51%.[23] In a cohort study of patients with CHD, elevated levels of anxiety and depression were detected in approximately 20% of the study population and were significantly associated with increased mortality.[24] In addition, a study among Europeans CHD patients found the prevalence of anxiety and depression varied from 12%–63.7% to 8.2%–62.5%, respectively.[25] In relation to NOCAD, a study reported higher anxiety and depression scores as compared to the reference group of the general population.[26] Another study found that 27.9% of patients

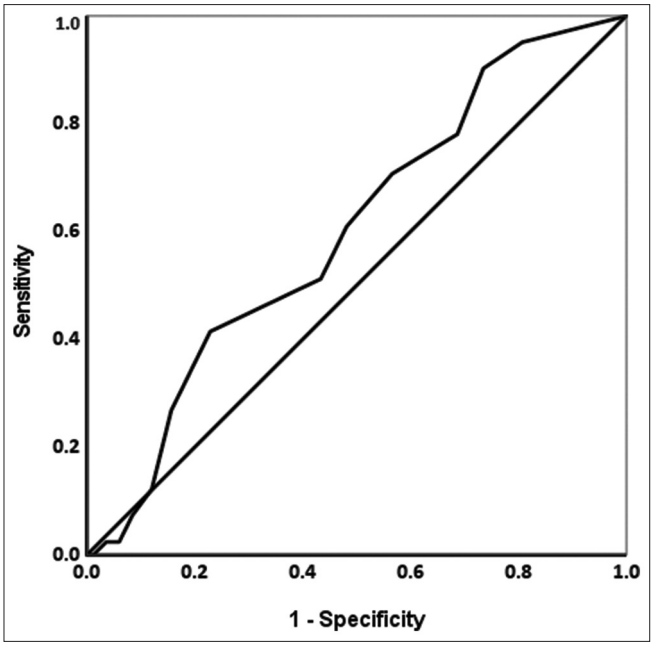

Figure 1: Receiver-operator curves showing accuracy for Hospital Anxiety and Depression Scale anxiety total score to predict non-obstructive coronary artery disease in all study population. Area under the curve = 0.600

with NOCAD were recognized to have an anxiety disorder.[27] Our findings, along with these studies, demonstrate that anxiety and depression are common in patients with both OCAD and NOCAD.

Furthermore, our findings showed no significant difference in anxiety and depression scores between patients with OCAD and NOCAD. A previous study has demonstrated similar results, where anxiety and depression scores in female patients with OCAD and NOCAD were not differed.[28] It can be postulated that patients with NOCAD experience anxiety and depression levels comparable to those of patients with OCAD.

Our findings indicate that patients with OCAD have higher serum cortisol levels compared to non-symptomatic controls, suggesting elevated stress levels in these patients. Cortisol is released during certain stress conditions to help maintain homeostasis following the activation of the HPA axis, which supports its common use as a stress biomarker.[11] Previous study has shown that serum cortisol levels increase in patients with acute coronary syndrome (ACS), associated with the progression of ischemia and myocardial injury. This, in turn, affects the clinical outcomes for ACS patients.[29] A review on mental stress and CAD highlights that stress has been extensively studied in relation to CVD. Numerous studies have demonstrated associations between stress measures and CVD risk factors, markers in CAD, and clinical outcomes. In addition, stress has been affiliated with atherosclerosis, increased left ventricular mass, and the calcification of the coronary artery. It has also been recognized as an acute trigger for adverse outcomes, including myocardial ischemia, malignant arrhythmia, infarction, and sudden cardiac death, in patients with CAD.[30]

In the context of NOCAD, a study involving female patients with symptomatic angina found that those diagnosed with NOCAD experienced greater myocardial ischemia due to mental stress compared to those without NOCAD.[31] In addition, a review focused on the relationship between mental stress and NOCAD emphasized the link between psychological stress and coronary vasomotor disorders, particularly for ischemic patients with NOCAD. The review also pointed out how psychological aspects such as chronic stress, anxiety, depression, and social stressors can significantly influence cardiovascular conditions, highlighting the bidirectional relationship between psychological stress and ischemic heart disease.[32] While these findings underscore the important role of stress in NOCAD, our study found no significant difference in stress levels, as indicated by cortisol levels, between patients with NOCAD and the control group. Moreover, the current study showed that cortisol levels did not differ significantly between patients with OCAD and those with NOCAD, suggesting that both groups experienced similar levels of stress.

However, our study observed no differences in dopamine levels across all participant groups. This discrepancy may be attributed to the intensity of stress experienced by the participants. Most participants scored low on the HADS, falling into the low or non-case categories, while fewer were in the moderate or severe categories. As a result, any noticeable changes in dopamine levels may not have been detectable in this study.

While patients with NOCAD often experience anxiety, it remains unclear whether anxiety contributes to the onset of NOCAD or if it arises as a result of the condition. Interestingly, in this study, based on the logistic regression analysis, we found that anxiety score is associated with NOCAD. However, this finding must be interpreted with caution due to the relatively small number of NOCAD cases, which increases the risk of overfitting and limits generalizability. The wide confidence intervals (1.029, 1.499) further reflect uncertainty in the estimates, underscoring the need for larger, adequately powered studies. In addition, the discriminatory ability of HADS–A was weak (AUC = 0.600), suggesting that anxiety scores alone are insufficient for reliable prediction of NOCAD. Clinically, these finding highlights that while anxiety may be associated with NOCAD, it should not be used in isolation for risk stratification or diagnostic decision-making. Instead, psychosocial measures such as anxiety should be considered

as part of a broader, multidimensional assessment that integrates clinical, demographic, and lifestyle factors. Future research should explore composite models that combine psychological and biomedical predictors to improve accuracy and clinical utility.

Nevertheless, the role of anxiety in the development of NOCAD should not be overlooked. The mechanisms underlying the relationship between anxiety and NOCAD remain unclear. There is no definitive explanation for the association between anxiety and cardiac disease; however, several mechanisms have been proposed to be involved in this complex relationship, including health behavior, inflammation, and dysfunction of the endothelium, platelets, and autonomic nervous system.[33] Regarding endothelial dysfunction, anxiety has exhibited a notable association that may contribute to the development of cardiac disorders, including OCAD and NOCAD. In patients with CAD who also suffer from anxiety or depression, both flow-mediated dilation and the capacity for endothelial progenitor cell-mediated re-reendothelialization were found to be lower compared to CAD patients without anxiety or depression, as well as healthy controls.[34] Anxiety has also been correlated with a low reactive hyperemia index.[35] In terms of NOCAD, a previous study demonstrated a significant association between anxiety and coronary endothelial dysfunction in female patients with NOCAD.[27] Therefore, endothelial dysfunction may be a key factor involved in the symptomatic mechanisms linking anxiety and NOCAD. Furthermore, previous research has shown impaired peripheral microvascular reactivity in patients with NOCAD.[16] This supports the hypothesis that anxiety may contribute to the symptoms observed in NOCAD patients through its association with endothelial dysfunction.

A case study reported that a rare instance of myocardial infarction with NOCAD in a patient who experienced acute chest pain following intense emotional stress due to grief. Despite classic symptoms of myocardial infarction, the coronary angiography revealed no arterial obstruction. This emphasizes that psychological distress can induce myocardial injury even in the absence of CAD.[36] Psychological distress may initiate the development of NOCAD, but it is also possible that this distress arises as a result of the condition. Patients experiencing angina symptoms, frequent hospitalizations, and rising healthcare costs may face increased psychological distress due to their NOCAD. Regardless of whether the distress occurs before or after the onset of NOCAD, studies show a clear association between the two. Currently, guidelines for managing NOCAD primarily focus on relieving symptoms and addressing CVD risk factors to prevent the progression of NOCAD to OCAD.[37] However, with growing evidence highlighting the impact of psychological distress on NOCAD, it may be time to incorporate strategies for managing this distress into the overall treatment plan for NOCAD.

There were understandable limitations in our study. We conducted only a single psychological assessment during the recruitment phase and did not perform any follow-up assessments after the angiogram procedure or at later intervals. Conducting assessments both before and after the angiogram would have provided a broader perspective on the factors that may have influenced the psychological scores of these patients. Another limitation of this study is the small sample size, which may affect the reliability and generalizability of our findings. A limited sample size can reduce statistical power, increase the risk of Type II errors (false negatives), decrease the precision of estimated effects, and poor generalizability which may not represent the larger population. Hence, caution should be exercised when applying these results to larger or more diverse populations. Further research with larger sample sizes is necessary to validate these findings and improve their external validity. Additionally, the use of convenience sampling may introduce selection bias since the control group may not be fully comparable to symptomatic patients in terms of demographic or health-related factors. However, this approach was necessary to ensure feasibility and timely recruitment within the study setting. Meanwhile, the clinically important confounders such as age, sex, diabetes, hypertension, lipid profile, and medication use may have influenced the observed associations between anxiety score and NOCAD. Larger studies with sufficient power to incorporate these covariates are needed to further validate the current findings. While differences in demographic or health-related factors between controls and symptomatic patients may affect comparability and its association, the findings remain informative and contribute valuable insights. Readers should interpret the results with caution, recognizing this limitation alongside the study's overall findings.

CONCLUSION

In patients with NOCAD, the HADS–A score was significantly higher compared to non-symptomatic subjects. This indicates that patients with NOCAD experience considerable emotional distress. Moreover, the HADS–A score is associated with NOCAD. Therefore, addressing anxiety should be a key focus in the treatment and prevention strategies for these patients.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (Approval number:

USM/JEPeM/8010077). All methods were performed in accordance with the relevant guidelines and regulations. All participants signed a written informed consent form approved by the Ethics Committee.

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Conflicts of interest

There are no conflicts of interest.

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