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Clinical depression among patients after acute coronary syndrome: a prospective single-tertiary centre analysis

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INTRODUCTION Clinical depression is a known consequence of acute coronary syndrome (ACS) and is associated with an adverse outcome among these patients, although this is often under-recognised. Through this study, we investigated the incidence of depression in post-ACS patients and its associated factors.

METHODS We conducted a prospective cohort study in 95 patients with ACS admitted to University Malaya Medical Centre, Malaysia. Clinical depression was assessed during the index admission and at 30 days after discharge, using the Patient Health Questionnaire-9 (PHQ-9). Data was analysed using IBM SPSS Statistics, and binary logistic regression was used to determine the independent factors associated with depression, after adjusting for significant demographic variables and clinical characteristics. The strength of this association was presented as odds ratio and 95% confidence interval, and the significance level was set at 0.05.

RESULTS The mean age of the study population was about 60 years, and 72.6% of the patients were male. Symptoms of depression were present in 88.4% of the patients at baseline. Depression at 30 days was more likely in female patients, patients with diabetes mellitus and patients on dialysis ($p = 0.024$, $p < 0.001$, $p = 0.008$, respectively). Patients with baseline moderate to severe depression were more likely to have moderate to severe depression at 30 days ($p < 0.001$). Baseline depression was the strongest predictor of depression at 30 days. An increment of one unit in PHQ-9 baseline score increased the risk of developing severe depression at 30 days by 31%.

CONCLUSION Depression was prevalent in our post-ACS patients. The associated factors were female gender, diabetes mellitus and dialysis treatment.

Keywords: ACS, depression, NSTEMI, screening outcome, STEMI

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide. Out of all global deaths in 2016, an estimated 17.9 million (31%) occurred from cardiovascular disease.[1] Patients with coronary artery disease (CAD) may present with acute coronary syndrome (ACS) or stable angina. ACS includes conditions such as ST-elevation myocardial infarction, non-ST-elevation myocardial infarction and unstable angina. Cardiomyocyte necrosis is observed in non-ST-elevation myocardial infarction, while myocardial ischaemia without cell loss is observed in unstable angina.[2]

Depression is prevalent among patients with cardiovascular disease. It affects about 20% of patients with CAD[3] and has a significant negative impact on various outcomes in patients with cardiovascular disease. The association between ACS and depression has been extensively reported and studied. This relationship is bidirectional – cardiovascular disease has been shown to increase the risk of depression, while depression is found to be associated with higher rates of cardiovascular mortality and morbidity.[4] The presence of depression in patients with coronary disease has been linked to lower rates of compliance with treatment and lifestyle modification; it is, thus, important to detect depression among patients in this group.[5] However, recent data from the American College of Cardiology suggests no benefit of detecting depression in these patients.[6]

Following an ACS event, patients often experience psychological stress. This may account for the prevalence of depression in this patient group.[7] However, depression is frequently under-recognised in patients with cardiac disease. Untreated depression can have a significant impact on the patient's quality of life and increase the burden on family members.[8] Patients with CAD who experience depression show elevated levels of cytokines and interleukin. Inflammatory cytokines cause atherosclerotic plaques to become unstable and subsequently rupture, resulting in thrombosis.[9]

Owing to the negative impact of depression on patient outcomes, professional societies have recommended screening for depression in patients with coronary heart disease and appropriate referral to specialty care.[10] Early treatment and intervention in patients with cardiac disease are crucial to prevent untoward cardiovascular outcomes. The current study investigated the incidence and effect of depression among patients admitted with ACS, to explore whether the effects reported in other studies were observed in our patient population.

METHODS

A prospective study was conducted involving all patients diagnosed with ACS who were admitted to the cardiology ward of University Malaya Medical Centre, Malaysia, from July 2017 to February 2019. Both male and female patients aged > 18 years who presented with a diagnosis of ST-elevation myocardial infarction, non-ST-elevation myocardial infarction or unstable angina and who were able to complete the validated English

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or Bahasa Melayu Patient Health Questionnaire-9 (PHQ-9) were included. Patients who presented with Type 2 myocardial infarction or heart failure, and those who had underlying depression or had previously been admitted for psychiatric illness were excluded. Patients with ACS who met the inclusion criteria were selected using the consecutive sampling technique.

The statistical power of the study was determined using the OpenEpi software (www.openepi.com). Based on our calculation, a sample size of 68 was required to provide 80% power to estimate an odds ratio of 10 for having depression at 30 days after discharge, with 95% confidence.[11] Considering a potential loss to follow-up of 20%, we required at least 82 participants at the baseline of the study.

Data was collected using the PHQ-9, a diagnostic tool for assessing depression that is easy to administer and has good sensitivity and specificity. There were two sets of questionnaires – an English version and a validated Bahasa Melayu version. The questionnaire was answered by participants in a face-to-face interview during the index admission and via a telephone call at 30 days after discharge.[12] To avoid bias, only one interviewer administered the questionnaire. Data was collected by a designated medical officer, and a pilot study was performed in five patients. The dependent variable was depression at baseline and at 30 days after discharge.

The PHQ assesses eight diagnoses, divided into threshold disorders and subthreshold disorders. Threshold disorders are those that correspond to specific diagnoses in the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV): major depressive disorder, panic disorder, other anxiety disorder and bulimia nervosa. The PHQ-9 is the nine-item depression module from the full PHQ,[13] and the questions are based on the diagnostic criteria for depression from the DSM-IV.

For the current study, the PHQ-9 sought information about the patient's experience in the past two weeks. Major depression was defined as the presence of five or more of the nine depressive symptom criteria at least 'more than half the days' in the past two weeks, with one of the symptoms being depressed mood or anhedonia. The nine questions from the PHQ-9 were scored using a scale of 0 to 3: not at all (score: 0), several days (score: 1), more than half the days (score: 2) and nearly every day (score: 3). The total PHQ-9 score ranged from 0 to 27, and depression was classified as: none to minimal (score: 0–4), mild (score: 5–9), moderate (score: 10–14), moderately severe (score: 15–19) and severe (score: 20–27).[13] Depression scores were dichotomised into two groups: none to mild depression (PHQ-9 < 10) and moderate to severe depression (PHQ-9 ≥ 10). For regression analysis, patients who scored < 10 were coded as '1' and those who scored ≥ 10 were coded as '2'. In this study, we used a cut-off score of ≥ 10. This cut-off score was found to be optimal for maximising sensitivity without the loss of specificity.[13]

The independent variables were sociodemographic characteristics (age, gender, ethnicity) and clinical characteristics (cardiovascular risks, smoking history, premorbid condition and diagnosis of ACS). Data was cleaned, coded and analysed using IBM SPSS Statistics version 24.0 (IBM Corp, Armonk, NY, USA). Crude odds ratios with 95% confidence interval were estimated using binary logistic regression analysis to assess the association between each independent variable and the outcome variable. Variables with a value < 0.25 in the bivariable logistic regression analysis were considered in the multivariable logistic regression analysis.[14] Adjusted odds ratios with 95% confidence interval were estimated to assess the strength of the association, and variables with a p-value < 0.05 were considered significant factors.

Table I. Sociodemographic and clinical characteristics of recruited patients (n = 95).

Variable	No. (%)
Mean age (yr)	59.97 ± 11.28
Age (yr)	
< 60	42 (44.2)
≥ 60	53 (55.8)
Ethnicity	
Malay	53 (55.8)
Chinese	14 (14.7)
Indian	28 (29.5)
Gender	
Male	69 (72.6)
Female	26 (27.4)
Cardiovascular risk	
Diabetes mellitus	52 (54.7)
Hypertension	66 (69.5)
Dyslipidaemia	38 (40.0)
Smoking status	
Non-smoker	42 (44.2)
Ex-smoker	26 (27.4)
Active smoker	27 (28.4)
Premorbid condition	
Chronic kidney disease	24 (25.3)
Stroke	5 (5.3)
Pre-existing CAD	45 (47.4)
Dialysis	10 (10.5)
Diagnosis of ACS	
STEMI	26 (27.4)
NSTEMI	34 (35.8)
Unstable angina	35 (36.8)

ACS: acute coronary syndrome; CAD: coronary artery disease; NSTEMI: non-ST-elevation myocardial infarction; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation; STEMI: ST-elevation myocardial infarction

RESULTS

Of the 139 recruited patients, 95 met the inclusion criteria. Seven patients were lost to follow-up and seven patients died during the course of the study, leaving 81 patients for the PHQ-9 reassessment at 30 days after discharge. The mean age of the patients was 59.97 ± 11.28 (range 25–80) years. Patients were predominantly male (72.6%) and Malay (55.8%). The majority had hypertension and were non-smokers. Their cardiovascular risks were similar to those listed in the National Cardiovascular Disease Database Malaysia. Participants were distributed equally among the three subgroups of ACS (Table I). Following an ACS

event, at least 88.4% of patients reported depression, with 46.3% of them having moderate to severe depression (Table II).

Univariate analysis showed differences in characteristics between patients with and without depression. Using male gender as the reference group, female patients had a four-fold increased risk of having depression. In terms of ethnicity, Malays had a higher rate of depression, although this was not statistically significant. Patients with diabetes mellitus had a five-fold increased risk of developing depression. An association between smoking status and the odds of depression was also observed; at baseline, active smokers were 82% less likely to develop depression compared with non-smokers. In addition, patients undergoing dialysis were found to have significant depression. However, no significant relationship was observed between chronic kidney disease/stroke/dyslipidaemia and depression at baseline, and between the subgroups of ACS and depression at baseline (Table III).

At 30 days after discharge, female patients had a three-fold increased risk of developing depression. Patients with diabetes mellitus and those undergoing dialysis also had increased odds of having depression. Patients who had moderate to severe depression (PHQ-9 score ≥ 10) at 30 days after discharge had a significantly higher baseline PHQ-9 score compared with those with none to mild depression at 30 days after discharge. In the moderate to severe depression group, an additional increase in one unit of PHQ-9 score from the baseline would lead to 34% increased odds of developing worsening depression at 30 days after discharge (Table IV).

There was no significant difference in mortality outcome between the group of patients with none to mild depression (PHQ-9 < 10) and the group with moderate to severe depression (PHQ-9 ≥ 10). The severity of depression did not change the in-hospital and 30-day mortality outcomes of patients, and it had no influence on readmission rates (Table V). After controlling for all

Table II. Prevalence of depression in post-acute coronary syndrome patients on admission (n = 95).

Severity of depression	PHQ-9 score	No. (%)
None	0	11 (11.6)
Minimal depression	1–4	17 (17.9)
Mild depression	5–9	23 (24.2)
Moderate depression	10–14	13 (13.7)
Moderately severe depression	15–19	12 (12.6)
Severe depression	20–27	19 (20.0)

PHQ-9: Patient Health Questionnaire-9

Table III. Univariate analysis of depression with sociodemographic and clinical characteristics on admission (n = 95).

Variable	PHQ-9 total score*		χ^2	p-value	OR	95% CI
	< 10	≥ 10				
Gender			10.31	0.001		
Male	44 (63.8)	25 (36.2)			1.00	
Female	7 (26.9)	19 (73.1)			4.78	1.77–12.93
Age (yr)			1.11	0.291		
< 60	20 (39.2)	22 (50.0)			1.00	
≥ 60	31 (60.8)	22 (50.0)			0.65	0.29–1.46
Ethnicity			5.39	0.068		
Malay	23 (43.4)	30 (56.6)			1.00	
Chinese	10 (71.4)	4 (28.6)			0.31	0.09–1.10
Indian	18 (64.3)	10 (35.7)			0.43	0.17–1.10
Cardiovascular risk						
Diabetes mellitus	19 (37.3)	33 (75.0)	13.58	< 0.001	5.05	2.08–12.27
Hypertension	32 (62.7)	34 (77.3)	2.35	0.125	2.02	0.82–4.99
Dyslipidaemia	20 (39.2)	18 (40.9)	0.03	0.867	1.07	0.47–2.44
Smoking status			10.87	0.004		
Active smoker	21 (41.2)	6 (13.6)			0.18	0.06–0.53
Ex-smoker	14 (27.5)	12 (27.3)			0.53	0.20–1.42
Non-smoker	16 (31.4)	26 (59.1)			1.00	
Premorbid condition						
Chronic kidney disease	11 (21.6)	13 (29.5)	0.80	0.372	1.53	0.60–3.86
Stroke	2 (40.0)	3 (60.0)	0.40	0.528	1.79	0.29–11.25
Pre-existing CAD	21 (41.2)	24 (54.5)	1.69	0.193	1.71	0.76–3.87
Dialysis	1 (2.0)	9 (20.5)	8.58	0.003	12.86	1.56–106.12
Type of ACS on admission			2.61	0.106		
Unstable angina	15 (29.4)	20 (45.5)			1.00	
Myocardial infarction†	36 (70.6)	24 (54.5)			0.50	0.22–1.17

*Data presented as no. (%). †Includes both ST- and non-ST-elevation myocardial infarction. ACS: acute coronary syndrome; CAD: coronary artery disease; CI: confidence interval; OR: odds ratio; PHQ-9: Patient Health Questionnaire-9

Table IV. Univariate analysis of depression at 30 days after discharge with sociodemographic/clinical characteristics and baseline PHQ-9 scores (n = 95).

Variable	PHQ-9 total score*		χ^2	p-value	OR	95% CI
	< 10	≥ 10				
Gender			5.08	0.024		
Male	36 (85.7)	25 (64.1)			1.00	
Female	6 (14.3)	14 (35.9)			3.36	1.14–9.93
Age (yr)			0.95	0.329		
< 60	17 (40.5)	20 (51.3)			1.00	
≥ 60	25 (59.5)	19 (48.7)			0.65	0.27–1.56
Ethnicity						
Malay	20 (47.6)	25 (64.1)			1.00	
Chinese	9 (21.4)	3 (7.7)			0.27	0.06–1.12
Indian	13 (31.0)	11 (28.2)			0.68	0.25–1.83
Cardiovascular risk						
Diabetes mellitus	15 (35.7)	29 (74.4)	12.17	< 0.001	5.22	2.01–13.59
Hypertension	27 (64.3)	30 (76.9)	1.55	0.213	1.85	0.70–4.92
Dyslipidaemia	15 (35.7)	17 (43.6)	0.53	0.469	1.39	0.57–3.40
Smoking status			3.27	0.195		
Active smoker	16 (38.1)	8 (20.5)			0.38	0.13–1.11
Ex-smoker	11 (26.2)	11 (28.2)			0.75	0.26–2.19
Non-smoker	15 (35.7)	20 (51.3)			1.00	
Pre-morbid condition						
Chronic kidney disease	9 (21.4)	10 (25.6)	0.20	0.655	1.26	0.45–3.54
Stroke	3 (7.1)	2 (5.1)	0.14	0.707	0.70	0.11–4.45
Pre-existing CAD	18 (42.9)	22 (56.4)	1.49	0.223	1.725	0.72–4.16
Dialysis	0 (0)	6 (15.4)	6.98	0.008	UTC	UTC
Invasive PCI	8 (19.0)	11 (28.2)	0.95	0.331	1.67	0.59–4.72
Type of ACS on admission			0.07	0.798		
Unstable angina	15 (35.7)	15 (38.5)			1.00	
Myocardial infarction†	27 (64.3)	24 (61.5)			0.89	0.36–2.19
Total PHQ-9 score at baseline	5.10 ± 5.44	15.95 ± 6.22		< 0.001	1.34	1.19–1.52

*Data presented as no. (%) or mean ± standard deviation. †Includes both ST and non-ST elevation myocardial infarction. ACS: acute coronary syndrome; CAD: coronary artery disease; CI: confidence interval; OR: odds ratio; PCI: percutaneous coronary intervention; PHQ-9: Patient Health Questionnaire-9; UTC: unable to compute

Table V. Univariate analysis of depression with clinical characteristics and mortality outcome (in-hospital and 30-day all-cause mortality rates).

Variable	PHQ-9 total score*		χ^2	p-value	HR	95% CI
	< 10	≥ 10				
Mortality						
30-day	3 (5.9)	4 (9.1)	0.36	0.553	1.60	0.34–7.57
In-hospital	1 (33.3)	1 (25)	0.06	0.810	0.67	0.03–18.06
Readmission	3 (5.9)	2 (4.5)	0.09	0.772	0.76	0.12–4.78

*Data presented as no. (%). CI: confidence interval; HR: hazard ratio; PHQ-9: Patient Health Questionnaire-9

covariates, baseline depression remained the strongest predictor of depression at 30-day follow-up, with an increase in PHQ-9 score of one unit raising the odds of depression by 31% (Table VI).

DISCUSSION

The association between depression and cardiovascular morbidity and mortality has been explored for many years.[5] Several meta-analyses have summarised the findings as a bidirectional association, whereby the presence of depression is an independent risk factor for CAD and vice versa.[15] The presence of depression was shown to confer a negative prognosis in patients with CAD.[16] The mechanism of how depression affects the outcome has been described on many levels, and these include the behavioural, hormonal and endothelial aspects.[17-19] Depression is more likely to be associated with poor lifestyle modifications and lower compliance with therapies. On a more cellular level, various theories such as endothelial stress and platelet activation have been explored.[20]

The current study found that female patients with cardiac disorders were four times more likely to have at least moderate depression during the index admission compared with male patients. This female preponderance has also been reported in other studies.[21] A meta-analysis has shown that the prevalence of major depression in female patients with CAD is higher than that in male patients.[22] It has also been reported that the incidence of depression is two times greater in women than in men.[23] Postulated explanations for gender differences include psychosocial factors

Table VI. Multivariate logistic regression of clinical predictors of depression 30 days after discharge.

Characteristic	β	p-value	OR	95% CI
Gender	0.126	0.904	1.13	0.15–8.70
Ethnicity				
Malay		0.521	1.00	
Chinese	–1.171	0.323	0.31	0.03–3.16
Indian	0.354	0.664	1.43	0.29–7.03
Diabetes mellitus	0.583	0.456	1.79	0.39–8.31
Hypertension	0.047	0.957	1.05	0.19–5.73
Smoking status				
Non-smoker		0.900	1.00	
Ex-smoker	0.387	0.687	1.47	0.22–9.67
Active smoker	0.020	0.985	1.02	0.13–7.79
Pre-existing CAD	0.345	0.681	1.41	0.27–7.32
Dialysis	19.719	0.999	–	–
Baseline PHQ-9 score	0.269	< 0.001	1.31	1.15–1.49

CAD: coronary artery disease; CI: confidence interval; OR: odds ratio; PHQ-9: Patient Health Questionnaire-9

(e.g. role overload) and biological factors (e.g. hormones).[22] One study found that women more often present with internalising symptoms, whereas men present with externalising symptoms.[24] Women who are depressed have also been found to have poorer outcomes than depressed men do.[25] Having less social support as compared to men and an older average age of event in women have been put forward as the causes.

The association between diabetes mellitus and depression is bidirectional.[26] Studies have also shown that overweight and obesity are associated with depression. These patients have an approximately 40% higher risk of developing Type 2 diabetes mellitus.[27] Diabetes mellitus has a considerable impact on patients' quality of life, with possible limitations in physical activities, family relations, social life and leisure activities. Thus, diabetics have an increased risk of developing depression.[28] A meta-analysis reported an 11% prevalence of major depression among patients with diabetes mellitus.[29]

Depression is also common in patients with end-stage renal failure. Patients undergoing dialysis experience a wide range of somatic symptoms and have significantly less involvement in occupational, social and recreational activities. The combination of psychological distress and disturbing physical symptoms results in significantly reduced quality of life, contributing to the development of depression.[30]

In our study, patients who were active smokers at baseline had 82% lower odds of developing significant depression. This might be attributable to smoking being a coping mechanism. Following a cigarette puff, nicotine enters the cerebral circulation and binds to the neuronal nicotinic acetylcholine receptors.[31] Hence, nicotine stimulates dopamine receptors in the brain, causing patients to feel less depressed. However, at 30 days after discharge, smoking was no longer associated with less depression. It is possible that active smokers might have quit smoking after they were discharged from the hospital.

Patients who had significant baseline depression were found to have an increased risk of developing significant depression at 30 days after discharge. However, depression in our patients with ACS was not significantly associated with an increase in in-hospital or out-of-hospital mortality and morbidity. Similarly, no increase in readmission rates was observed. Our findings contrasted with those of other studies,[32-34] which have shown positive associations between depression and all these factors. Our follow-up period was only 30 days compared with most studies, which showed a mortality difference at six months.[35,36] Despite these differences, we feel that this study should be treated as a pilot to a larger study with a longer follow-up duration. This will allow us to ascertain whether depression is a negative prognostic factor in our population. Larger or definitive studies will also enable us to determine whether screening for depression will help our population, like it has in Western practice.

This study has some limitations. An important confounding factor that may limit the generalisability of our study findings was the exclusion of patients with language barriers, namely patients who were unable to read or write English and Malay. Communication problems faced by patients have been found to be a barrier to seeking and accessing mental health services, which could subsequently affect the outcomes that are measured.[37,38] Additionally, the mean age of our patients was lower (60 years) compared to that of patients in developed countries (63.4–68.0 years). However, as the mean age of our cohort was comparable to that of patients with ACS (55.9–59.1 years) in Malaysia (based on the Malaysian National Cardiovascular Disease Database), we opine that this would have little impact on generalisability.[39] Another limitation of the study was its small sample size, resulting in possible selection bias. Also, we recognise that factors such as socioeconomic status, social support, alcohol intake and substance abuse are important confounders that may have an impact on depression;[34] unfortunately, these factors were not explored in our study.

In conclusion, depression was prevalent in our cohort of post-ACS patients. Factors associated with the presence of depression were female gender, diabetes mellitus and dialysis treatment. In addition, we found that severity of depression had no impact on in-hospital and 30-day outcomes in our cohort. Most of our results did not reach statistical significance, possibly owing to the short duration of follow-up. Hence, our findings should be replicated in a larger study with a longer follow-up period, to guide future screening for depression in patients with ACS.

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