



Published in final edited form as:

Ann Vasc Surg. 2023 September ; 95: 80–86. doi:10.1016/j.avsg.2023.03.002.

Depression in Patients with Peripheral Artery Disease: An Underdiagnosis with Increased Mortality

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Abstract

Background: Among patients with peripheral artery disease (PAD), depression is diagnosed in 17–25% and negatively impacts wound healing, quality of life, and survival. We hypothesized that depression is underdiagnosed in patients with PAD. Additionally, given the associations between depression and mortality in PAD patients, there is an increased need to investigate the strength of this relationship. The present analysis includes 2 studies to address the following aims: (1) Investigation of the prevalence of concomitant PAD and depression in a cohort from the Southeastern United States, and (2) Examination of the association between depression and all-cause mortality in a cohort of Canadian patients with PAD.

Methods: STUDY 1: From June–August 2022, the Patient Health Questionnaire Module 9 (PHQ-9) was administered to all patients seeking PAD-related care including medical, wound/podiatric, or vascular interventional/surgical treatment, in the University of North Carolina-Chapel Hill Vascular, Wound, and Podiatry clinics. The PHQ-9 assesses symptoms over 2 weeks and is scored 0–27, with higher scores indicating increasingly severe depression. Demographics, primary diagnosis, depression history, and antidepressant prescription were determined through chart review. We compared the proportion of positive depression screenings (PHQ-9 ≥ 5) to known depression. Among those treated for depression, the PHQ-9 score severity was evaluated. T-tests and χ^2 tests were used to compare means and proportions. STUDY 2: From July 2015 to October 2016, the Geriatric Depression Scale Short Form was administered to adult patients with PAD

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.avsg.2023.03.002>.

undergoing revascularization. The Geriatric Depression Scale Short Form is a self-report measure of depression with a score >5 consistent with depression. The prevalence of depression was determined; primary outcome was all-cause mortality at 6 months.

Results: STUDY 1: In 104 PAD patients (mean age 66.6 ± 11.3 years, 37% female), 37% of respondents scored ≥ 5 on the PHQ-9 survey, indicating at least mild depression. Only 18% of PAD patients had a history of depression, demonstrating a significant difference between the PHQ-9 findings and documented medical history. While depression was underdiagnosed in both men and women, men were more likely to have unrecognized depression (chi-squared statistic = 35.117, $df = 1$, $P < 0.001$). Among those with a history of depression, 74% had a current prescription for antidepressant medication, but 57% still had an elevated PHQ-9 score indicating possible undertreatment. STUDY 2: In 148 patients (mean age 70.3 ± 11.0 years, 39% female) the prevalence of screened depression was 28.4%, but only 3.3% had a documented history of depression suggesting significant underdiagnosis. Patients with depression were significantly more likely to die within 6 months of revascularization (9.5% vs. 0.9%; odds ratio 1.48, 95% confidence interval: 1.08 to 2.29). There was no association between depression and risk of length of stay, reintervention, or readmission.

Conclusions: Depression is underdiagnosed and undertreated among patients with PAD, which has grave consequences as it is associated with 1.5 times the odds of mortality within 6 months of revascularization. There is a critical need for more robust screenings and comprehensive mental health treatment for patients with concomitant depression and PAD.

INTRODUCTION

Peripheral artery disease (PAD) is a common vascular condition with significant effects on morbidity and mortality. In its most severe form, it can lead to ischemic ulcers or gangrene,¹ and chronic limb-threatening ischemia remains a leading cause of lower-limb amputation in the United States and Canada.^{2,3} While patient-centered outcomes, such as the impact of chronic vascular disease on independence, functional status, and mood, have been understudied, there are reports that the quality of life among patients with chronic limb-threatening ischemia is poor.⁴

The prevalence of depression in the general U.S. population is 8.4%, with chronic diseases being associated with higher rates of depression.⁵ There is substantial evidence to support the burden of depression in cardiac disease,^{6,7} and patients with depression undergoing coronary bypass surgery have an increased risk of death, postoperative cardiac events, and readmission.⁸⁻¹⁰ On the whole, the risk of depression in patients with PAD may even exceed that of coronary disease,^{11,12} but its prevalence has been poorly defined in the literature, with rates of concomitant PAD and depression ranging from 3–48%.¹³ Although the role of depression in PAD treatment and outcomes is not yet fully understood, several studies have found an increased risk of mortality in PAD patients with depression, ranging from 17–24% greater than the 11.3% risk among their nondepressed peers.¹⁴⁻¹⁶ Age at PAD diagnosis, female gender, and symptom severity have been associated with higher rates of depression.^{17,18} Other mediating factors may include social support, family income, alcohol consumption, and hypertension.^{11,19,20}

It is essential to understand the prevalence of depression in patients with PAD. Appropriate screening and mental health treatment are imperative to achieve better treatment outcomes within this population. Furthermore, given the associations between depression and mortality in PAD patients, there is an increased need to investigate the strength of this relationship. The present analysis includes 2 studies to address the current gap in the literature: (1) An investigation of the prevalence of concomitant PAD and depression in a cohort from the Southeastern United States, and (2) The examination of the association between depression and all-cause mortality in a cohort of Canadian patients with PAD undergoing revascularization.

STUDY 1: DEPRESSION IS UNDERDIAGNOSED IN PATIENTS WITH PAD

Methods

Study Design.—From June to August 2022, the Patient Health Questionnaire Module 9 (PHQ-9) screening was offered to all patients seeking PAD-related care, including medical, wound/podiatric, or vascular interventional/surgical treatment, in the University of North Carolina–Chapel Hill Vascular, Wound, and Podiatry clinics. Patients were allowed to opt out of the mental health survey, and a total of 28 patients declined to participate. The survey was read aloud to patients with vision or literacy challenges. Patients completed the questionnaire, we accessed the electronic health record to manually extract demographic data, medications, comorbidities, history of depression, and details of their PAD symptoms, including Rutherford score and wound details. This study was approved by the institutional review board at the University of North Carolina at Chapel Hill.

Depression Screening Test.—The PHQ-9 assesses depression symptoms and is routinely used as a screening tool due to its high sensitivity and specificity across multiple patient populations (88% and 88%, respectively).²¹ The PHQ-9 surveys symptoms over the past 2 weeks and consists of 9 questions scored from 0 to 3, with 3 indicating greater frequency and intensity of symptoms (see Supplementary Materials). The total is therefore scored from 0–27, with higher scores indicating greater symptom severity. Scores were recorded directly in the electronic health record. The clinician was notified if patients scored 15, indicating moderately severe symptoms. These patients were offered mental health resources and connected with primary care providers for follow-up assessments and support.

Participants.—In the 2-month study period, 106 adult patients attended clinic appointments for evaluation and treatment of PAD. Two new patients who presented for evaluation of PAD were excluded due to no evidence of arterial disease on hemodynamic testing.

Statistical Analysis.—Among the final 104 participants, we compared the proportion of positive screenings (PHQ-9 ≥ 5) to known depression history using a χ^2 test. Among those previously treated for depression, the percentage of PHQ-9 scores ≥ 5 severity was calculated. T-tests and χ^2 tests were used to compare means and proportions. All analyses were conducted using SAS 9.4 statistical software (Cary, NC).

Results

The cohort of 104 patients with PAD was 37% female, 35% non-White, and had an average age of 66.6 ± 11.3 years (Table I). The average time lived with PAD was 4.2 ± 3.1 years and an average Rutherford score of 2.7 ± 2.0 . Women with PAD were more likely than men to have a history of depression [34% vs. 9%, Difference (95% CI) = 25% (9%, 42%)].

For all PAD patients, the average PHQ-9 score was 4.4 ± 4.4 (Table II). Across all PAD patients, 37% of respondents scored ≥ 5 on the PHQ-9 survey, indicating at least mild depression. Only 18% of patients with PAD had a history of depression, demonstrating a significant difference between the PHQ-9 findings and documented medical history [Difference (95% CI) = 18% (6%, 30%)].

While depression was underdiagnosed in both men and women, men were more likely to have unrecognized depression. The positive depression screening to history of depression ratio was 3.8 and 1.2 for men and women, respectively (chi-squared statistic = 35.117, df = 1, $P < 0.001$). Among PAD patients with a history of depression, 74% had a current prescription for antidepressant medication, and 57% had an elevated PHQ-9 score.

STUDY 2: DEPRESSION IS ASSOCIATED WITH MORTALITY IN PAD PATIENTS

Methods

Study Design.—This was a subanalysis from the FRailty Assessment in Lower Extremity Arterial Disease prospective study,²² and protocols were approved by the Jewish General Hospital (Montreal, QC, Canada). Data were collected at 2 tertiary centers in Montreal, Quebec, Canada. Questionnaires were available in English and French languages. The methods and primary results of the primary study were recently reported²²; briefly, patients completed a preprocedural assessment of frailty, disability, comorbidity, cognitive function, and mood and subsequently completed a follow-up interview at 6 and 12 months.

Depression Screening Tool.—Depressive symptoms were evaluated with the 15-item Geriatric Depression Scale Short Form (GDS-SF). A GDS-SF score of ≥ 5 is indicative of clinically relevant depression (see Supplementary Materials). The GDS-SF is a validated screening instrument for depression and has a sensitivity of 72% and a specificity of 78%.²³ The GDS-SF was administered at baseline, 6 months and 12 months postprocedure. Patients were stratified according to their screened depression status based on the GDS-SF.

Participants.—Adult patients undergoing endovascular or open interventions for PAD were consecutively enrolled between October 2015, and August 2016. Patients with PAD with Rutherford class III or higher were recruited. Patients were excluded from the study if they had emergency surgery or unstable vital signs, severe neuropsychiatric impairment, or a prohibitive language barrier.

Statistical Analysis.—In this substudy of FRailty Assessment in Lower Extremity Arterial Disease, the prevalence, correlates, and prognostic impact of depressive mood

symptoms were examined. The primary end point studied was all-cause mortality at 6 months. The secondary outcomes were readmission, vascular reintervention, and length of stay. Continuous variables were summarized with the sample mean and standard deviation. Depression status was analyzed as a continuous variable (GDS-SF scores of 0–15 points). Univariate analysis was performed to assess the association of all relevant clinical covariates with the study end points. Multivariable logistic regression was used to estimate the association between 6-month all-cause mortality, reintervention, and vascular readmission with the predictor variable of screened depression using the GDS-SF. Multivariable linear regression was used to estimate the association between length of stay and our predictor variable. Regression models were adjusted for baseline covariates, including age, sex, body mass index, surgical approach, and the revised cardiac risk index. Survival curves were generated with the Kaplan – Meier method. Statistical analyses were performed with the R studio software package (version 0.99.491, Boston, MA) and STATA software package (version 14.1, College Station, Texas).

Results

The cohort consisted of 148 patients undergoing endovascular or open interventions for PAD, with a mean age of 70.3 ± 11.0 and 39% females (Table III). Patients received either an endovascular intervention (54.7%) or an open intervention (45.3%), and there was no clinically relevant difference in the proportion who had depression in each group (27.2% and 29.9% for endovascular interventions and open interventions). Overall, the prevalence of positive depression screening was 28.4% ($N = 42$), whereas the documented prevalence in the clinical chart was only 3.3%

At 6 months, 4 deaths (9.5%) were observed in the depressed group compared to 1 death (0.9%) in the nondepressed group (Table IV, Fig. 1). On multivariable analysis, the association between depression and 6-month all-cause mortality was statistically significant (odds ratio [OR] 1.48, 95% confidence interval [CI]: 1.08 to 2.29). Depression did not significantly predict vascular reintervention (OR 1.11, 95% CI: 0.99 to 1.26), readmission (OR 1.16, 95% CI 0.96 to 1.39), or length of stay (OR 1.16, 95% CI 0.96 to 1.39).

DISCUSSION

The results of these 2 studies demonstrate that depression is underdiagnosed among patients with PAD in diverse cohorts and that the presence of depression was significantly associated with mortality. Regardless of the depression screening tool used, depression was frequently identified in patients undergoing treatment for PAD. Depression is underdiagnosed by up to 19–25%. Our results suggest that depression underdiagnosis occurs across different centers and regions, considering that our work was conducted in 2 different countries with distinct PAD population characteristics. Together, these results indicate that the underdiagnosis of depression holds true across the spectrum of PAD disease severity and is consistent between the PHQ-9 and GDS-S scales and across American and Canadian cohorts.

Furthermore, our results indicate that even among patients with known depression, 57% still had elevated depression symptom scores, suggesting that these patients are undertreated. This is of particular significance because the results of the second study indicate that among

Canadian adults presenting for PAD intervention, depression is associated with increased all-cause mortality. This supports prior research, which found that, among U.S. veterans, a comorbid diagnosis of depression at the time of PAD diagnosis was associated with a 17% greater mortality risk over 5 years than patients without depression.¹⁴ Additionally, a recent meta-analysis found that depression was associated with a 24% increase in mortality, making it a significant clinical factor in PAD management.¹⁵

These findings indicate that identifying and treating depression is a crucial target to improve the care for patients with PAD. In addition to increased mortality, depression has been associated with a decline in patients' quality of life: Depressed patients have shorter pain-free and total walking distances and experience more significant annual declines in functioning relative to their nondepressed counterparts.^{24,25} Depression severity is also associated with higher inflammation in PAD patients,²⁶ and depressed patients have a greater risk of recurrent and debilitating symptoms.²⁷ Therefore, it is imperative to intervene in PAD patients with depressive symptoms to improve quality of life and reduce mortality risk.

Past research has found an increased risk of depression among women with PAD.¹⁷ Similarly, our study found that women were more likely to have a history of depression; however, we found that men were more likely to be underdiagnosed with depression. These results suggest the importance of considering the role of depression in all patients presenting with PAD and may be an important avenue for future research to investigate the influence of gender on depression symptom presentation within this population. This is especially salient given the scarcity of research on the underdiagnosis of depression in men and even fewer investigations into depression in men with PAD.

Several studies have demonstrated that treating depression in PAD patients is feasible. Garnefski et al. found that adjustments in cognitive coping strategies were related to improvement in depressive symptoms in a cohort of patients with PAD.²⁸ Similarly, a small trial of a cognitive-behavioral self-help program for patients with depression and PAD found significantly improved depression symptom scores at posttest and follow-up.²⁹ These findings indicate that treating depression is a reachable target in patients with PAD and should be an important component of the care plan. Given our findings of underdiagnosed depression in PAD patients, a collaborative approach between vascular and primary care providers may benefit the identification and treatment of depression in the setting of PAD.

There are several limitations to consider. The first is that the PHQ-9 and GDS-S are screening tools rather than diagnostic tools. While both are well-studied and widely used to assess depression symptom severity, elevated scores are not necessarily diagnostic of major depressive disorder or other psychiatric illnesses. While the generalizability of results is improved by assessing both cohorts, the datasets could not be combined to improve the power of the study since different depression screening tools are used at each of the institutions. Additionally, the patient populations served in North Carolina and Quebec are heterogeneous with different access to health insurance, public health policies, and ultimately different mental health screening protocols and procedures. Nonetheless, the reproducibility of our findings in these heterogeneous settings is compelling evidence that

a relationship exists between depression and PAD. Both studies are limited by modest sample size; however, it is noteworthy that both study sites found similar results indicating underdiagnosis of depression, despite the differences between the methodologies. Regarding the findings on depression and mortality, the number of total deaths (5) was low within the 6 months and this association may have been strengthened with more data at the 1-year and 3-year benchmark. Additionally, we did not specifically assess how depression impacts limb loss and amputation-free survival, which may be of interest in future analysis as limb preservation is an important clinical target in PAD. Finally, due to small sample size, we do not have enough power to report on the association between severity of depression and severity of PAD; however, this is an important avenue for future research and intervention.

CONCLUSIONS

Depression is underdiagnosed and undertreated among patients with PAD and is a significant predictor of all-cause mortality among PAD patients undergoing revascularization. This may carry significant implications for the success of complex treatment strategies, outcomes, disease progression, and quality of life. Our findings indicate a strong need for more robust screenings and comprehensive mental health treatment for patients with PAD and depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding sources:

This work was supported by the Carolina Medical Student Research Program (CMSRP).

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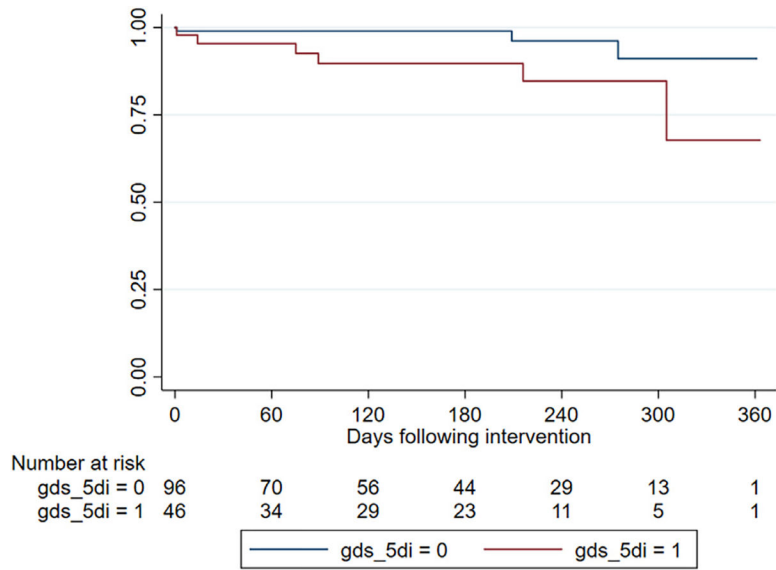


Fig. 1. Kaplan–Meier Survival Curve. Kaplan–Meier Survival Curve of PAD patients undergoing open or endovascular interventions. Patients with concomitant depression have a worse survival rate at 6 months compared to patients who do not suffer from depression.

Table 1.

Study 1 Demographics and PHQ-9 questionnaire data

	Total (n = 104)	Prior depression (n = 19)	No prior depression (n = 85)	Difference (95% CI)
Age (years)	66.6 ± 11.3	64.7 ± 12.5	67.0 ± 11.1	-2.3 (-8.0, 3.4)
Sex (female)	38 (36.5%)	13 (68.4%)	25 (29.4%)	39.0% (14.3%, 57.4%)
Race				
White/Caucasian	68 (65.4%)	14 (73.7%)	54 (63.5%)	10.2% (-14.2%, 28.2%)
Black/African American	33 (31.7%)	5 (26.3%)	28 (32.9%)	6.6% (-17.6%, 24.5%)
Other	3 (2.9%)	0 (0.0%)	3 (3.5%)	3.5% (-13.5%, 9.8%)
Hypertension	95 (91.3%)	16 (84.2%)	79 (92.9%)	8.7% (-4.0%, 30.8%)
Dyslipidemia	91 (87.5%)	16 (84.2%)	75 (88.2%)	4.0% (-9.4%, 26.4%)
Obesity	47 (45.2%)	13 (68.4%)	34 (40.0%)	28.4% (3.6%, 47.3%)
Diabetes	69 (66.3%)	13 (68.4%)	56 (65.9%)	2.5% (-21.7%, 21.9%)
Coronary artery disease	51 (49.0%)	10 (52.6%)	41 (48.2%)	4.4% (-19.0%, 26.9%)
Cerebrovascular disease	21 (20.2%)	3 (15.8%)	18 (21.2%)	5.4% (-17.6%, 19.6%)
Chronic obstructive pulmonary disease	23 (22.1%)	6 (31.6%)	17 (20.0%)	11.6% (-7.3%, 35.1%)
Congestive heart failure	32 (30.8%)	6 (31.6%)	26 (30.6%)	1.0% (-18.3%, 25.1%)
Smoker				
Current	25 (24.0%)	7 (36.8%)	18 (21.2%)	15.6% (-4.6%, 38.9%)
Former	54 (51.9%)	8 (42.1%)	46 (54.1%)	12.0% (-12.1%, 33.5%)
Never	25 (24.0%)	4 (21.1%)	21 (24.7%)	3.6% (-20.1%, 19.7%)
Wound	49 (47.1%)	10 (52.6%)	39 (45.9%)	6.7% (-16.7%, 29.2%)
Revascularization	78 (75.0%)	14 (73.7%)	64 (75.3%)	1.6% (-16.1%, 25.4%)

Table II.

Study 1 depression and PHQ-9 scores

	Total (n = 104)	Prior depression (n = 19)	No prior depression (n = 85)	Difference (95% CI)
PHQ-9 categories				
Minimal (0–4)	66 (63.5%)	9 (47.4%)	57 (67.1%)	19.7% (–3.7%, 41.7%)
Mild (5–9)	27 (26.0%)	7 (36.8%)	20 (23.5%)	13.3% (–7.0%, 36.7%)
Moderate (10–14)	9 (8.7%)	2 (10.5%)	7 (8.2%)	2.3% (–8.6%, 23.6%)
Moderate-severe (15–19)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (–16.8%, 4.3%)
Severe (20+)	2 (1.9%)	1 (5.3%)	1 (1.2%)	4.1% (–2.7%, 23.5%)
Average PHQ-9 score	4.4 ± 4.4	6.2 ± 4.9	3.9 ± 4.2	2.3 (0.1, 4.5)
Antidepressant prescription	27 (26.0%)	14 (73.7%)	13 (15.3%)	58.4% (34.1%, 74.1%)

Table III.

Study 2 baseline characteristics of cohort of patients stratified by depression status

	Total N = 148	Depressed N = 42 (28.4%)	Not depressed N = 106 (71.6%)	P value
Demographics				
Age (years)	70.3 ± 11.0	69.5 ± 11.2	70.6 ± 11.0	0.5861
Male (%)	90 (60.8%)	25 (59.5%)	65 (59.6%)	0.5381
Endovascular (%)	81 (54.7%)	22 (52.4%)	59 (55.7%)	0.7919
Open (%)	67 (45.3%)	20 (47.6%)	47 (44.3%)	0.8053
Patient Characteristics				
Critical limb ischemia (%)	65 (43.9%)	24 (54.1%)	41 (38.7%)	0.2314
Smoking (%)	111 (75%)	34 (81.0%)	77 (72.6%)	0.3472
Hypertension (%)	106 (71.6%)	33 (78.6%)	73 (68.9%)	0.3058
Dyslipidemia (%)	92 (62.2%)	29 (69.0%)	63 (59.4%)	0.3797
Coronary artery disease (%)	45 (30.4%)	14 (33.3%)	31 (29.2%)	0.7844
Chronic kidney disease (%)	14 (9.5%)	7 (16.7%)	7 (6.6%)	0.5703
Cerebrovascular disease (%)	11 (7.4%)	4 (10.0%)	7 (6.6%)	0.8474
Chronic obstructive pulmonary disease (%)	20 (13.5%)	6 (14.3%)	14 (13.2%)	0.9488

Table IV.

Outcome variables

Outcome variables	Total N = 148	Depressed N = 42 (28.3%)	Not depressed N = 106 (71.6%)
Primary end point			
All-cause mortality at 6 months (%)	5 (3.4%)	4 (9.5%)	1 (0.9%)
Secondary end points			
Length of stay (days)	3.1 [0–52]	4.9 [0–52]	2.6 [0–49]
Reintervention (%)	50 (33.8%)	16 (38.1%)	34 (32.1%)
Readmission (%)	46 (31.1%)	15 (35.7%)	31 (29.2%)