January 2015

Symptoms Of Depression Are Linked To Subsequent Recurrent Chest Pain In Patients Admitted To An Emergency Department Chest Pain Unit.

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SYMPTOMS OF DEPRESSION ARE LINKED TO SUBSEQUENT RECURRENT CHEST PAIN IN PATIENTS ADMITTED TO AN EMERGENCY DEPARTMENT CHEST PAIN UNIT.

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

by

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2015

SYMPTOMS OF DEPRESSION ARE LINKED TO SUBSEQUENT RECURRENT CHEST PAIN IN PATIENTS ADMITTED TO AN EMERGENCY DEPARTMENT CHEST PAIN UNIT.

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Prior studies suggest a high prevalence of depression in patients with chest pain, but few US studies have examined depression and recurrent chest pain in the emergency room setting. This study sought to compare symptoms of depression, socio-demographic features, and clinical features between low-moderate-risk emergency room (ER) chest pain center (CPC) patients with and without recurrent chest pain at one-month following enrollment.

This study was a prospective cohort study using convenience sample at a tertiary care hospital emergency room in a semi-urban setting. Patients were recruited from the chest pain center (CPC), and completed baseline surveys that assessed depression, anxiety, stress and chest pain. A one-month follow-up assessed the recurrence of chest pain. Univariate and multivariate statistical analyses were conducted.

Between July 30th 2013 to January 31st 2015 a total of 850 patients were invited to participate in our study, 442 (52.0%) agreed to do so, of which 327 (74.0%) were included in the final analysis. An overall 29% had some evidence of depression, be it

high symptom scores or current treatment for depression. In addition, using the PHQ-8, we identified forty-one (12.5%) new patients with depressive symptoms. More than two-thirds of enrolled patients had chest pain on at least one occasion following discharge from the hospital (n=115; 35.2%). Patients with recurrent chest pain tended to be slightly younger (51 versus 55 years of age; p= .001), more female (64.3%; p= .023) and less Caucasian (63.5% versus 70.3%; p= .154). In general, women had higher rates of recurrent/persistent chest pain (n=74/184; 40.2%) than men (n=41/143; 28.7%). The overall burden of depression was 37.4% of patients with recurrent/persistent chest pain, compared to 24.5% of patients without (p= .018). Regression analysis revealed that for each single point increase in PHQ-8 score, there is an 7.5% increase in the odds of having recurrent chest pain (model 5: OR=1.075; 95% CI=1.005, 1.149; *p*= .035). Gender also had a significant effect in the regression model, and the overall burden of depression was highest among women with recurrent/persistent chest pain (43.2%), and differed significantly from women without recurrent/persistent chest pain (26.4%), (p= .023).

The prevalence of depression is high in ER patients with chest pain, and this is particularly relevant for women with baseline depression and recurrent chest pain at one-month follow-up.

Acknowledgements

Thank you to my thesis mentor Dr. Basmah Safdar, for her support and guidance in this endeavor. Thank you to the Department of Emergency Medicine for the resources available to researchers. Thank you to my Emergency Medicine Thesis Committee for supporting this work. For all their dedication and time, I thank my collaborators Matt Naftilan, Morgan Soffler, James Dziura, Aini Jelani and Yeunjung Kim. This work would not have been possible without the support of the chest pain center staff and administrative assistants. Also thank you to Meredith Young, Matt Turner and Ayesha Muhammad for taking an interest in the project and assisting in the recruiting effort. A special thanks to Tom Adams for teaching me the basics of SPSS.

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Introduction

There are more than 8 million annual visits to U.S. emergency rooms for chest pain. Each time the primary concern is for acute coronary syndrome (ACS), as it is the number one cause of death in the United States. The current standard of care is based on American Heart Association guidelines, and includes a focused history and physical exam, a 12-lead ECG, and serial laboratory studies for cardiac injury markers.[1] However, adverse cardiac events are identified in as few as 15-25% of patients, who are quickly routed down established pathways of cardio-protective care.[1,2] Sadly, there are a reported 2-4% of major adverse cardiac events that are missed, with patients inappropriately discharged from the hospital.[3] Given the high mortality associated with these missed cases, and the threat of litigation, the standard of care is applied rigorously to patients seen in the emergency department, often leading to extensive work-ups. Since the majority of patients will initially test negative, many emergency departments now have dedicated chest pain units (CPUs) for further observation of these patients. In these settings, patients are monitored, and serial cardiac enzymes and repeat ECGs are performed. After a minimum period of time, stress tests and/or imaging studies are performed to rule out ischemia.

After testing fails to reveal ACS or underlying CAD, patients are often discharged with the ambiguous diagnosis of non-cardiac chest pain (NCCP). This heterogeneous diagnosis includes causes such as gastro-esophageal reflux disease, esophageal spasm, musculoskeletal pain, hyperventilation, general anxiety and panic disorder.

In addition, there is growing evidence for unrecognized coronary artery disease (CAD) and microvascular dysfunction, as potential etiologies. Once a certain diagnostic rigor has failed to identify a cause, labels like nonobstructive, non-specific, or unexplained chest pain may seem more appropriate.

Interestingly, psychiatric factors could potentially cause or worsen chest pain in a variety of ways, and it can be unclear whether psychiatric symptoms arise from or produce some of the other causes of chest pain, such as hyperventilation, muscle spasm, and even microvascular disease.[4] Conversely, psychiatric conditions such as depression also increase cardiac mortality in patients.[5] Further complicating matters, psychiatric disease is often associated with non-specific symptoms and co-morbid risk factors, making its effects a challenge to track. This study seeks to explore the relationship between depression and chest pain in patients admitted to an emergency department CPU for cardiac observation.

The aims of our study were as follows:

Primary Aim 1: symptom burden of depression in a chest pain unit

Psychiatric conditions have long been associated with chest pain, and this can be one of the first thoughts that comes to mind when someone with few risk factors experiences chest pain. For patients with chest pain, anxiety has received the most attention from the research and medical community. A large number of studies have been performed and agree that the prevalence of anxiety and panic disorders is high

in chest pain populations, and particularly so for non-cardiac chest pain compared to known-cause chest pain. A recently published review of psychological outcomes in patients with non-cardiac chest pain, reported the prevalence of anxiety to be between 21 and 53.5%.[6]

Less studied and less well understood is the relationship between depression and chest pain. Existing studies are limited and have produced inconsistent results when assessing depression in patients with non-cardiac chest pain.[6] For example, comparisons of depression scores in patients with non-coronary chest pain to patients with coronary chest pain, or to the general population, have produced somewhat mixed results. Some studies have reported levels of depression in non-coronary chest pain patients to be similar to, or even lower than, levels seen in coronary chest pain patients,[6-9] while other studies report the high levels of depression in non-coronary chest pain patients.[10,11].[8] Given the conflicting data, the foremost aim of our study is to describe the burden and severity of depressive symptoms in ED chest pain patients. We also wanted to examine the demographic, socio-economic, and clinical patient profiles that are associated with depression in ED chest pain patients and understand its association with recurrent chest pain after discharge. Similar attempts in similar US settings are limited, and there is clinical and scientific benefit to replicating these inquiries at unique sites, as the present work intends to do.

Primary Aim 2: depression and recurrence/persistence of chest pain after ED discharge

The majority of studies evaluating depression in patients with new onset chest pain are cross-sectional, and few U.S. based studies have captured future prognosis of these patients. This stands in contrast to research of coronary heart disease (CHD) and post-myocardial infarct (post-MI), wherein there is a preponderance of valuable prospective evidence linking depression to cardiac morbidity and mortality.[5,12-15] However, some studies have taken the endeavor to follow low-risk chest pain patients from the emergency department onwards. A recent UK publication found anxiety, depression and quality of life to be associated with higher frequency of persistent chest pain, but did not find high levels of depression in their studied population.[16] Our goal was to investigate whether similar relationship is seen in emergency department patients in the US.

Previous studies have suggested that depression interacts with comorbid disease in a non-homogeneous manner, meaning that only certain aspects of depression associate with clinical outcomes.[17-19] Among CAD studies, there is evidence that somatic symptoms may be associated with worsened cardiac prognosis. [18-21] Furthermore, the large NHLBI-funded Women's Ischemia Syndrome Evaluation (WISE) study, found somatic (and not cognitive) symptoms to be associated with cardiovascular mortality and events in women.[22] Likewise, this study seeks to consider cognitive/somatic symptoms separately in a gender-specific model, as potential correlates to recurrent/persistent chest pain.

Secondary Aim 1: depression and chest pain by gender

The literature is mixed regarding the burden of depression for women and men with chest pain. In general, women are more likely to suffer from depression than men, but the implications for chest pain are unclear. Very few studies describing gender differences were based in the emergency setting. One such publication that considered risk factors for chest pain in men and women found an independent association between depression and chest pain, in the case of women only.[23] Yet another study, also a rare prospective investigation into recurrent chest pain, found no differences associated with gender.[16] More observational work is needed to clarify the conflicting relationship. Also, both of these conclusions were drawn outside the U.S. and may not be transferrable to our population. In contrast, a prior pilot study conducted in the same CPU setting as the present work found high levels of depression in women, encouraging further study, but drew no comparisons to men.[4] The paucity of evidence directly relating to this topic make it a goal of the present work to compare the effect of depression on recurrence of chest pain in both men and women.

Ultimately, this work seeks to cast some degree of illumination on the interaction between depressive symptoms and chest pain. For the sake of clarity, references to "chest pain" will signify undifferentiated chest pain with symptoms of discomfort similar-in-nature to those seen in coronary disease. The two primary aims of this work are as follows: 1) to establish the prevalence and symptom burden of depression, and to examine what demographic, socio-economic, and clinical patient

profiles are associated with being an ED chest pain patient with recurrent chest pain; and 2) to evaluate symptoms of depression as possible predictors of recurrent chest pain in patients presenting to the ED with new onset of chest pain. A secondary aim of this work is to compare the symptom burden of depression and role for recurrent chest pain by gender.

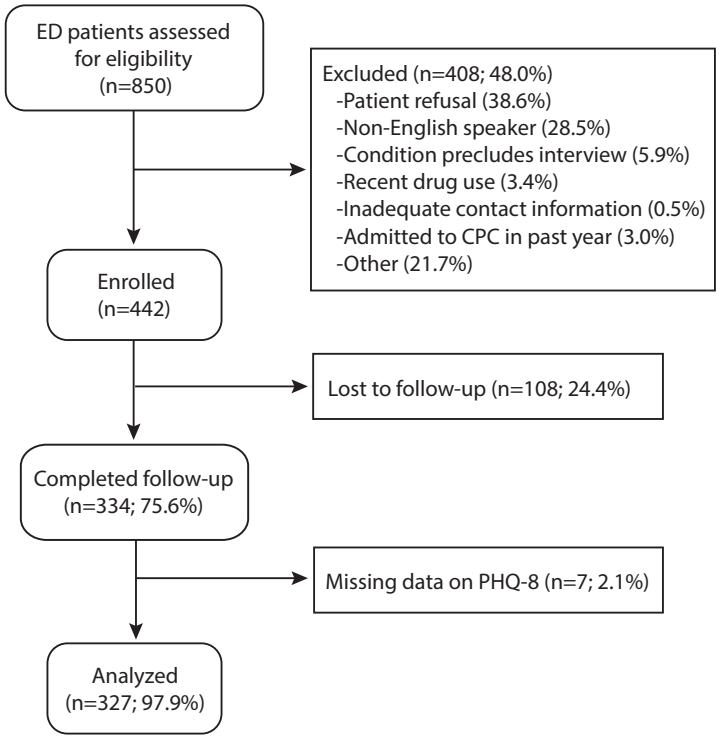
Methods

Overview

We conducted a prospective cohort study using convenience sample at a tertiary care hospital emergency room in a semi-urban setting. We obtained written informed consent from each patient prior to enrollment. The study was approved by the Yale Institutional Review Board. Baseline assessments were collected while the patient was admitted to the CPC. We interviewed patients to collect their socio-demographic and behavioral data, clinical history and risk factors as well measurement of their pain, and psychological assessments using four validated questionnaires. We also collected locator information from them as well as the most convenient number and time to reach them for follow up. We conducted follow-up interviews by telephone, one month following enrollment. Follow-up inquiry began with a yes/no determination of recurrent chest pain, and if patients answered "yes" we assessed frequency of symptoms. Telephone calls were typically made in the early evenings, as most patients indicated this to be the most convenient time. If we

were unable to reach patients after five telephone calls, we mailed reminders, and we continued with five additional telephone attempts. (Figure 1.)

Figure 1. Study Overview



Distribution of roles in conducting this thesis work

The original study was designed by Drs. Basmah Safdar and Morgan Soffler, to understand the relationship between perceived stress and recurrent chest pain. For the purposes of my thesis research, I utilized the same data set to explore a secondary analysis to answer my related hypothesis that symptoms of depression correlate independently with recurrent chest pain. Dr Basmah Safdar served as my

research advisor throughout the study. I was primarily responsible for enrollment during the first year of the study, and other team members contributed as their schedules allowed. After this time, I trained research associate Matt Naftilan, MS, to conduct enrollment, and he took over enrollment moving forward. I also trained two undergraduate students, who participated briefly as members of our team. Additionally, Matt created and managed our electronic research database. All researchers, including myself, shared the duty of making follow-up calls. Follow-up letters were mailed by Senior Administrative Assistant, Jaydale Codrington-Poyotte, who also organized team meetings. I wanted to be directly involved in the statistical analysis, and was trained in SPSS by a research colleague, Thomas Adams, PhD, who is affiliated with Yale's Psychiatry department. Tom has extensive experience with SPSS and has taught statistics at the graduate level. James Dizuria, a faculty biostatistician in the department of emergency medicine and a co-investigator on this study, also provided consultation and interpretation of statistics and methods. Additional team members and collaborators not mentioned here are referenced in the acknowledgements and authors sections of this report.

Study Participants

We enrolled patients in the Chest Pain Center (CPC) unit of the Yale-New Haven Hospital Emergency Department, usually between the hours of 9 a.m. to 2 p.m., while patients awaited their stress tests. Patients admitted to the CPC, have typically presented to the Emergency Department with symptoms concerning for an acute coronary syndrome, and been immediately assessed by medical staff. With an initial

work-up negative for an acute coronary syndrome, they may be considered for further observation and testing in the CPC. Our study inclusion criteria were in accord with criteria for CPC admission, based on American Heart Association low-intermediate risk profile, negative initial serum troponin, and a normal or non-ischemic ECG.[24] Also, as a voluntary study, patient consent to participate was required. Specific exclusion criteria were as follows:

- Patient seen in CPC within the past year
- Non-English speaking
- Suffering from a condition that precludes interview (i.e. cognitive or communication impairment)
- Acute Coronary Syndrome (positive EKG and/or cardiac enzymes)
- Known pregnancy
- Unable to provide contact number for follow-up study
- Active psychiatric condition (psychosis or suicidal ideation)
- Used heroin, cocaine or alcohol in the past 72 hours
- In police custody at the time of presentation

Measures

The following questionnaires were filled out by patients, and on some occasion were administered by research staff.

The eight-item Patient Health Questionnaire (PHQ-8) was used to assess depressive symptoms. It is a self-administered instrument that is based on DSM criteria for

major depressive disorder, and is a validated tool for detection of depressive disorder and depression severity.[25-27] Items present statements, such as "little interest or pleasure in doing things" and "feeling tired or having little energy," and the patient assigns a frequency using a Likert-type scale, ranging from zero (not at all) to 3 (nearly everyday), with final scores ranging from 0 to 24.

The PHQ is a screening tool for both diagnosis and assessment of symptom severity. We used a cutoff score ≥10, which is highly sensitive and specific for diagnosis of major depressive disorder. A large population-based study showed a PHQ-8 cutoff score ≥10 to have a sensitivity and specificity for major depressive disorder of 100% and 95%, respectively. For any depressive disorder, the sensitivity and specificity were 70% and 98%, respectively.[28] We defined depression severity by previously described PHQ-8 score intervals: 0-4(none), 5-9(mild), 10-14(moderate), 15-19(moderately severe), 20-24(severe).[27,28]

Somatic and cognitive dimensions of PHQ depressive symptoms have been validated previously with high Cronbach α statistics of 0.77 and 0.84, respectively.[17,21,29] *Somatic symptoms* include sleep, energy level, appetite and psychomotor agitation, and *cognitive symptoms* include interest, depressed mood, concentration, negative feelings toward self and suicidal ideation. Of note, the PHQ-8 differs from the PHQ-9 in that it lacks an item to assess suicidal ideation. However, the value of this item in the general population has been questioned, and a large study of patients with CAD concluded the item of suicidal ideation to be of questionable accuracy, and of no

benefit when assessing depression in this patient population.[30] Moreover, the PHQ-8 and PHQ-9 correlate strongly, and have comparable operating characteristics and validity.[27,31] We preferred the PHQ-8 also because patients with active suicidal ideation were automatically excluded from CPC admission prior to being considered for study enrollment.

The Clinical Anxiety Scale (CAS) was used to assess anxiety. The CAS is a 25-item self-administered tool, designed to distinguish between anxious and non-anxious states. [32] Each item presents a statement, such as "I feel calm" or "I am free from senseless or unpleasant thoughts," and the patient selects the frequency at which they identify with the statement on a scale ranging from 1(rarely or none of the time) to 5(most or all of the time). Final scores range from twenty-five to one hundred twenty-five, and a score of thirty is considered to be the clinical cutting score that discriminates between clinically anxious and non-anxious patients. The CAS has high reliability and high validity, compared to numerous alternative anxiety scales. [32]

The ten-item Perceived Stress Scale (PSS-10) was used to assess psychological stress. Based on its properties and past performance, the PSS is suggested for use in studies investigating factors that influence or are influenced by stress appraisal.[33,34] It was designed to assess global stress appraisal in all aspects of life over the past month, and is not limited to appraisal of particular situations.[34] The PSS-10 has demonstrated internal reliability and validity[33-35]. The PSS-10 has ten items formatted as questions, such as "In the last month, how often have you felt

difficulties were piling up so high that you could not overcome them?" The patient selects an answer on a 5-point scale ranging from 0(never) to 4(very often), with final scores ranging from zero to forty.

Follow-up Survey

To survey prospective outcomes, we called each patient one-month following the date of enrollment. To assess any recurrence of chest pain, we asked the following question: "in the past four weeks did you have any discomfort in your chest." The patient was then asked to rate the persistence of their symptoms on a five-point scale: 0(none), 1(1-2 times), 2(>3 times per week), 3(1-3 times per day), and 4(>4 times per day). We also asked about follow-up doctors visits and repeat visits to the emergency room.

Data Collection and Processing

Patients provided information on demographics, past medical history, medication use, and contact information on initial interview. A small gift of chocolate was provided as a token of gratitude, and sugar-free chocolate was available to patients with a history of diabetes. All data entries were made directly in FileMaker Pro installed on a password protected, encrypted, backed up research iPad. When not in use, this iPad was kept locked in a research locker in the emergency department. We scored surveys on completion and entered raw scores into the database. Hard copies were retained in a secured hospital location for future cross-reference. The

same database was used for follow-up completion. We conducted chart reviews through Epic to fill in any missing information, where appropriate.

Statistical Analysis

Recurrent chest pain was defined as any occurrence of chest discomfort after discharge noted on one-month follow-up telephone call. Current depression for this manuscript was defined by PHQ-8 score ≥10. Burden of depression was considered as the number of patients with PHQ-8 score ≥10 and/or receiving ongoing treatment with anti-depressant medications. Unrecognized depression was the burden of depression minus the patients who were receiving anti-depressant medication.

For descriptive purposes, categorical data were characterized as frequency/total sample size (%) and continuous data were characterized as mean (Standard Deviation). Age was considered skewed data and characterized by median (IQR). Independent sample t tests were used to compare means for sample sizes greater than thirty, and equal variance of standard deviations was applied if significance of Levene's test was less than .05. Univariate group wise comparisons of categorical data were carried out using the Pearson chi square test (χ^2), and univariate interactions between ordinal and continuous data were tested using Spearman's rank correlation coefficient (r_s).

Multivariate binary logistic regression analysis was used to test for independent correlations between depression as measured by PHQ-8 scores and recurrence of chest pain. For our analysis, we treated PHQ-8 scores as continuous numerical variables. Additional covariates chosen for modeling were selected *a-priori* based on our clinical impression of their possible confounding effect on the relationship between depression and chest pain. Cardiac risk factors (hypertension, dyslipidemia, diabetes, smoking, history of coronary heart disease, pertinent family history of coronary heart disease) were considered binary and determined through patient report. Race was considered Caucasian/non-Caucasian, marital status was considered married/non-married, employment was yes/no, and high school degree was yes/no. When patients were unable to answer questions, or interview time did not allow completion of survey topics, chart review was used to complete the data. Five stepwise models were constructed to observe the effects of different categories of covariates.

Where applicable, all tests used 95% confidence intervals (95% CI), and the level of significance was at the level of $p\ value < .05$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS for Macintosh, Version 22.0).

Results

On days when enrollment was carried out, all patients who met eligibility criteria were approached. Between July 30th 2013 to January 31st 2015 a total of 850

patients were invited to participate in our study and 442 (52.0%) agreed to do so. The majority of exclusions were made on the basis of language and patient refusal to participate, and further details of excluded patients can be seen in Figure 1. Of the enrolled patients, 334 completed follow-up, for a rate of 75.6%. Of these patients, seven were excluded for missing or aberrant PHQ-8 survey data, leaving a final sample of 327 patients for analysis. The median age of the analytic sample was fifty-three years, and the majority were women (n=184; 56.3%), Caucasian (n=222; 67.9%), married/cohabiting (n=209; 63.9%), employed (n=224; 68.5%), and had a high school degree or more (94.8%). (Table 1.) Majority of the patients had at least one cardiac risk factor; 46.8% had hypertension, 40.4% had dyslipidemia and 17% had diabetes. Personal and family history of coronary heart disease, as well as high-risk behaviors -cigarette smoking and alcohol consumption- were also reported in Table 1.

Baseline psychological assessments can be seen in Table 1. More than two-thirds of enrolled patients had chest pain on at least one occasion following discharge from the hospital (n=115; 35.2%). Compared to patients without recurrent symptoms, these patients tended to be slightly younger (51 versus 55 years of age), more female (64.3%), less Caucasian (63.5% versus 70.3%) and less partnered (55.7% versus 68.4%). Hypertension and dyslipidemia were less present in the patients with recurrent/persistent chest pain (38.3% and 34.8% versus 51.4% and 43.4%), but other cardiac risk factors were comparable between the two groups.

Table 1: Baseline Demographics of Patients Enrolled in the Study.

	Overall n = 327	Patients w/o recurrent or persistent CP n = 212	Patients with recurrent or persistent CP n = 115	p Value*
Socio-Demographics				
Age, median (IQR), yrs	53 (15.0)	55 (17.5)	51 (12.3)	
Gender				.023
Female, n (%)	184 (56.3)	110 (51.9)	74 (64.3)	
Male, n (%)	143 (43.7)	102 (48.1)	41 (35.7)	
Race				
White, n (%)	222 (67.9)	149 (70.3)	73 (63.5)	.154
Black, n (%)	68 (20.8)	40 (18.9)	28 (24.3)	.269
Hispanic, n (%)	23 (7.0)	12 (5.7)	11 (9.6)	.199
Other, n (%)	14 (4.3)	11 (5.2)	3 (2.6)	
Relationship Status				
Married/cohabiting, n (%)	209 (63.9)	145 (68.4)	64 (55.7)	.015
Single, n (%)	66 (20.2)	37 (17.5)	29 (25.2)	.058
Divorced, n (%)	40 (12.2)	18 (8.5)	22 (19.1)	.006
Widowed, n (%)	12 (3.7)	12 (5.7)	0 (0.0)	.009
Highest Degree of Education				
Did not complete H.S., n (%)	17 (5.2)	9 (4.2)	8 (7.0)	.305
H.S. diploma or GED, n (%)	164 (50.2)	109 (51.4)	55 (47.8)	.615
College degree, n (%)	146 (44.6)	94 (44.3)	52 (45.2)	.961
Employment Status				
Employed, n (%)	224 (68.5)	142 (67.0)	82 (71.3))	.379
Retired, n (%)	54 (16.5)	42 (19.8)	12 (10.4)	.026
Student/homemaker, n (%)	10 (3.1)	6 (2.8)	4 (3.5)	.761
Unemployed, n (%)	39 (11.9)	22 (10.4)	17 (14.8)	.379
Insurance Coverage				
Uninsured, n (%)	15 (4.6)	11 (5.2)	4 (3.5)	.465
Cardiac Risk Factors				
CHD, n %	21 (6.4)	12 (5.7)	9 (7.8)	.465
HTN, n (%)	153 (46.8)	109 (51.4)	44 (38.3)	.032
Dyslipidemia, n (%)	132 (40.4)	92 (43.4)	40 (34.8)	.108
Diabetes, n (%)	56 (17.1)	35 (16.5)	21 (18.3)	.513
Smoker, n (%)	52 (15.9)	32 (15.1)	20 (17.4)	.623
Family history, n %	88 (26.9)	58 (27.4)	30 (26.1)	.751
Regular Alcohol, n (%)	25 (7.6)	19 (9.0)	6 (5.2)	.212
Psychological Assessments				
Anti-depression Rx, n (%)	54 (16.5)	29 (13.7)	25 (21.7)	.033
Anti-anxiety Rx, n (%)	58 (17.7)	32 (15.1)	26 (22.6)	.052
CAS score, mean (SD)	43.19 (14.03)	41.51 (12.52)	46.29 (16.07)	.004
PSS-10 score, mean (SD)	16.69 (8.41)	16.21 (7.88)	17.57 (9.29)	.141

CP, chest pain; IQR, interquartile range; HS, high school; GED, general educational development; CHD, coronary heart disease; HTN, hypertension; Rx, medication; CAS, clinical anxiety scale; PSS, perceived stress scale. *Statistical significance at $p < .05$ for Pearson Chi square test or independent T test, as appropriate.

Primary Aim 1: Depressive symptom burden in CPC patients

A heavy burden of depression was present in patients admitted to the cardiac observation unit. (Table 2.) An overall 29% had some evidence of depression, be it high symptom scores or current treatment for depression. The mean PHQ-8 score was M=5.58 (SD=5.43), but nearly one fifth had PHQ-8 scores ≥10 (n=64; 19.6%). Sixteen and a half percent had pre-existing diagnosis of depression and were on treatment. Comparing PHQ-8 scores to treated depression, we identified forty-one (12.5%) patients with new or unrecognized depressive symptoms. Men and women had similar PHQ-8 mean scores (M=5.62, SD=5.12 and M=5.54, SD=5.05, respectively) and similar proportions of PHQ-8 scores ≥10 (18.2% and 20.7%, respectively). However, there were more women receiving treatment for depression (22.3% versus 9.1%), leading to higher estimates of overall depressive burden for women (33.2% versus 23.8%).

Primary Aim 2: Depressive symptom burden and recurrent/persistent chest pain

The symptom burden of depression was significantly higher in patients with recurrent/persistent chest pain, compared to those without. (Table 2.) This was reflected in mean PHQ-8 scores, in PHQ-8 scores ≥10, and in the proportion of patients receiving treatment for depression. Patient with recurrent/persistent chest pain were significantly more likely to have higher average PHQ-8 scores (M=6.94, SD=5.58) than patients without recurrent chest pain (M=4.84, SD=4.63) (p= .001). Interestingly, cognitive and somatic symptom dimensions both contributed to this relationship. The proportion of patients with PHQ-8 scores ≥10 was 27.8% when

presenting with recurrent/persistent chest pain, compared to 15.1% in patients without recurrence of chest pain. In addition, more than one fifth (21.7%) of patients with recurrent/persistent chest pain reported ongoing treatment of depression with anti-depressant medications, compared to 13.7% of asymptomatic patients. For clinical context, the overall burden of depression was 37.4% of patients with recurrent/persistent chest pain, compared to 24.5% of patients without symptoms ($\chi^2(1, N=327)=5.61$, $p= .018$).

PHQ-8 scores can be used to further describe the distribution of depressive symptoms. The majority of patients (57.5%) without recurrent/persistent chest pain had very low PHQ-8 scores indicating 'no depression,' while less than half (43.5%) of patients with recurrent/persistent chest pain had scores in this low range. The two groups were nearly matched with about 27-29% percent of patients having 'mild depression,' and higher scores were more prevalent in patients with recurrent/persistent chest pain.

Patients with more severe depression experienced chest pain more frequently than those with milder depressive symptoms, and Spearman testing of this relationship revealed a significant low positive correlation ($r_s=0.222$, n=327, $p= .000$). Similar results were seen for depressive symptom dimensions. Cognitive symptoms showed a very low positive correlation ($r_s=0.196$, n=321, $p= .000$), and somatic scores also fell to a very low positive correlation ($r_s=0.179$, n=321, $p< .001$), both statistically significant.

Table 2. Descriptive overview of comorbid depression (history and baseline severity) in patients with and without recurrent/persistent chest pain, and by gender.

	Overall	Patients w/o recurrent or persistent CP	Patients with recurrent or persistent CP	p Value*
All patients	**n = 327**	**n = 212**	**n = 115**	
Treated depression, n (%)	54 (16.5)	29 (13.7)	25 (21.7)	.061
PHQ-8 score ≥10, n (%)	64 (19.6)	32 (15.1)	32 (27.8)	.006
Burden of depression, n (%)	95 (29.1)	52 (24.5)	43 (37.4)	.018
Unrecognized depression, n (%)	41 (12.5)	24 (11.3)	17 (14.8)	.391
PHQ-8 levels of depression, n (%)				.003
no depression	172 (52.6)	122 (57.5)	50 (43.5)	
mild depression	91 (27.8)	58 (27.4)	33 (28.7)	
moderate depression	40 (12.2)	23 (10.8)	17 (14.8)	
moderately severe depression	17 (5.2)	6 (2.8)	11 (9.6)	
severe depression	7 (2.1)	3 (1.4)	4 (3.5)	
PHQ-8 total score, mean (SD)	5.58 (5.08)	4.84 (4.63)	6.94 (5.58)	.001
PHQ-8 cognitive score, mean (SD)	2.19 (2.89)	1.84 (2.60)	2.84 (3.28)	.006
PHQ-8 somatic score, mean (SD)	3.40 (2.73)	3.07 (2.60)	4.00 (2.86)	.003
Women	**n = 184**	**n = 110**	**n = 74**	
Treated depression, n (%)	41 (22.3)	22 (20.0)	19 (25.7)	.364
PHQ-8 score ≥10, n (%)	38 (20.7)	14 (12.7)	24 (32.4)	.001
Burden of depression, n (%)	61 (33.2)	29 (26.4)	32 (43.2)	.023
Unrecognized depression, n (%)	20 (10.9)	8 (7.3)	12 (16.2)	.064
PHQ-8 levels of depression, n (%)				.000
no depression	98 (53.3)	70 (63.6)	28 (37.8)	
mild depression	48 (26.1)	26 (23.6)	22 (29.7)	
moderate depression	25 (13.6)	10 (9.1)	15 (20.3)	
moderately severe depression	9 (4.9)	3 (2.7)	6 (8.1)	
severe depression	4 (2.2)	1 (0.9)	3 (4.1)	
PHQ-8 total score, mean (SD)	5.54 (5.05)	4.44 (4.60)	7.19 (5.27)	.000
PHQ-8 cognitive score, mean (SD)	2.11 (2.85)	1.62 (2.56)	2.82 (3.11)	.007
PHQ-8 somatic score, mean (SD)	3.47 (2.78)	2.93 (2.68)	4.25 (2.75)	.002
Men	**n = 143**	**n = 102**	**n = 41**	
Treated depression, n (%)	13 (9.1)	7 (6.9)	6 (14.6)	.144
PHQ-8 score ≥10, n (%)	26 (18.2)	18 (17.6)	8 (19.5)	.798
Burden of depression, n (%)	34 (23.8)	23 (22.5)	11 (26.8)	.587
Unrecognized depression, n (%)	21 (14.7)	16 (15.7)	5 (12.2)	.594
PHQ-8 levels of depression, n (%)				.986
no depression	74 (51.7)	52 (50.1)	22 (53.7)	
mild depression	43 (30.1)	32 (31.4)	11 (26.8)	
moderate depression	15 (10.5)	13 (12.7)	2 (4.9)	
moderately severe depression	8 (5.6)	3 (2.9)	5 (12.2)	
severe depression	3 (2.1)	2 (2.0)	1 (2.4)	
PHQ-8 total score, mean (SD)	5.62 (5.12)	5.28 (4.64)	6.49 (6.13)	.258
PHQ-8 cognitive score, mean (SD)	2.30 (2.94)	2.07 (2.63)	2.88 (3.60)	.203
PHQ-8 somatic score, mean (SD)	3.30 (2.67)	3.21 (2.52)	3.55 (3.03)	.491

CP, chest pain; Treated depression, patients taking anti-depressant medications; PHQ, patient health questionnaire; Burden of depression, number of treated depression and/or PHQ-8 score ≥10; Unrecognized depression, Burden of depression minus patients with Treated depression. *Statistical significance at $p < .05$ for Pearson Chi square test, independent T test, or Spearman rank correlation, as appropriate.

Independent relationship of depressive symptoms and recurrent/persistent chest pain

Multivariate logistic regression analysis established an independent relationship between depressive symptom severity and recurrence of chest pain. (Table 3.) The Hosmer-Lemeshow goodness-of-fit test indicated that the logistic model suitably fit the data (Chi-square 9.064, df 8, p= .337). Stepwise addition of covariates, including demographics, cardiac risk factors and psychological test scores altered the OR for recurrent chest pain, but the relationship remained significant. The PHQ-8 is a continuous variable with a maximum score of 24, and the OR observed for the most complete model indicates that for each single point increase in PHQ-8 score, there is an 7.5% increase in the odds of having recurrent chest pain (model 5: OR=1.075; 95% CI=1.005, 1.149; p= .035).

Table 3. Multiple logistic regression modeling for the relationship between PHQ-8 scores and recurrent chest pain.

Model Number	**Odds Ratio for recurrent or persistent chest pain (95% CI)**	**p Value**	**Covariates Included in the Model**
1	1.084 (1.036, 1.134)	.000	**PHQ-8**
2	1.074 (1.025, 1.125)	.003	PHQ-8, **age, gender, race**
3	1.069 (1.020, 1.122)	.006	PHQ-8, age, gender, race, **marital status, education level, employment status**
4	1.078 (1.026, 1.132)	.003	PHQ-8, age, gender, race, marital status, education level, employment status, **cardiac risk factors (HTN, diabetes, dyslipidemia, smoking, family history, prior CHD)**
5	1.075 (1.005, 1.149)	.035	PHQ-8, age, gender, race, marital status, education level, employment status, cardiac risk factors (HTN, diabetes, dyslipidemia, smoking, family history, prior CHD), **CAS, PSS**

PHQ, patient health questionnaire; HTN, hypertension; CHD, coronary heart disease; CAS, clinical anxiety scale; PSS, perceived stress scale. Statistical significance at $p < .05$ and 95% CI, Confidence Interval.

Secondary aim 1: Depressive symptom burden, recurrent/persistent chest pain and gender

As shown in Table 1, the depressive symptom burden was higher in women with recurrent/persistent chest pain across all measures, compared to men. In general, women had higher rates of recurrent/persistent chest pain (n=74/184; 40.2%) than men (n=41/143; 28.7%). Mean PHQ-8 scores were higher for both men and women with recurrent/persistent chest pain compared to those without, however this was only statistically significant for women. Comparing women with recurrent/persistent chest pain to those without revealed a significant upward shift in levels of depressive symptom severity. For men with recurrent/persistent chest pain this shift was not consistent across levels of PHQ-8 depression, and strangely there were fewer than expected with moderate level depression scores (4.9%, N=2/41). The rate of currently treated depression was higher for both men and women with recurrent/persistent chest pain versus those without, but the numbers were small for men. Of both men and women using antidepressants, more than 40% had recurrent/persistent chest pain (6/13 men and 19/41 women). The overall burden of depression was highest among women with recurrent/persistent chest pain (43.2%), and differed significantly from women without recurrent/persistent chest pain (26.4%), ($\chi^2(1, N=184)=5.17$, p= .023). In contrast, men with and without recurrent/persistent chest pain had more similar rates of burden of depression (26.8% vs. 22.5%, respectively), and no statistical different was present ($\chi^2(1, N=143)=0.296$, p= .587). Interestingly, our study revealed an equal number of men and women with unrecognized depression. However, the majority of these women

went on to have recurrent chest pain (12 out of 20 (60%)), compared to men (5 out of 21 (24%)).

The correlation between depressive symptom severity and frequency of chest pain was strongest in women, and Spearman analysis showed a significant fairly positive result (r_s=0.355, n=184, *p*= .000). The same relationship was evident for cognitive symptoms (r_s=0.286, n=179, *p*= .000), and to a slightly greater extent, somatic symptoms (r_s=0.311, n=179, *p*= .000). In contrast, Spearman analysis of men's depression scores and symptom frequency produced very low strength relationships, and did not achieve statistical significance. Gender also had a significant effect on recurrent chest pain in all models shown in Table 3., where included (model 5: female-weighted OR= 1.717; 95% CI= 1.041, 2.831; *p*= .034), indicating women to have seventy one percent higher odds of having recurrent/persistent chest pain compared to men while adjusting for socio-demographic, clinical and psychological factors.

Missing data

About one fourth of enrolled patients were lost to follow-up (n=108). These patients were compared to the analytic sample, to account for potential disparities, as shown in Table 4. No meaningful differences were observed for baseline demographic information, including age, gender and race. Interestingly, the group lost to follow-up had a higher rate of PHQ-8 scores ≥10 (26.9% vs. 19.6%), indicating a potential loss of depressed patients. This loss was evident for both genders, and particularly

pronounced for men, with a 28.3% rate of depression among men lost to follow-up, compared to 18.2% of men in the analytic sample. Also contributing to missing data: seven patients who had not properly completed the PHQ-8 survey were excluded from the overall analysis, and six patients with absent hard-copy (itemized) PHQ-8 data were excluded from the cognitive/somatic symptom portion of the analysis.

Table 4. Characterization and comparison between patients lost to follow-up and analytic sample.

	Lost to Follow Up (n = 108)	**Patients that Completed Follow Up (n = 327)**
Age, mean, yrs (SD)	51.9 (10.98)	53 (15.0)
Gender		
Female, n (%)	62 (57.4)	184 (56.3)
Male, n (%)	46 (42.6)	143 (43.7)
Race		
White, n (%)	73 (67.6)	222 (67.9)
Black, n (%)	23 (21.3)	68 (20.8)
Hispanic, n (%)	7 (6.5)	23 (7.0)
Other, n (%)	5 (4.6)	14 (4.3)
PHQ-8 score ≥10, n (%)	28 (26.9)	64 (19.6)
Women, n (%)	15 (25.9)	38 (20.7)
Men, n (%)	13 (28.3)	26 (18.2)

Discussion

This is the first U.S. based ED study to show that depressive symptoms in the emergency department patients predict recurrence of chest pain. We report three key findings. First, we demonstrated a high prevalence of depression in our low-risk cardiac observation unit population. Second, we found that depression was independently associated with recurrent chest pain post-discharge. And finally, these effects preferentially impacted women as opposed to men.

We found that about *3*0% of low-risk ED cardiac observation patients screened positive for depression, and 12.5% received this as a new diagnosis. These figures likely underestimate the true burden of depression, yet are comparable to the 20-25% in post-MI patients, and far surpass depression in the general population. This is also consistent with our prior report from five years ago that demonstrated similar high rates of depression using a different screening tool in the ED chest pain population. According to a 2009-2012 CDC household report, 9.8% of Americans aged 40-59 were moderately to severely depressed.[36] An important clinical reminder, the CDC found the most depression occurs in the 40-59 age group, which corresponds with the demographics of our study population.[36] Existing literature on depression in low-risk ED cardiac observation units is limited, has produced conflicting findings, and has been conducted mostly outside the US. Here in the US, depression in non-cardiac chest pain is primarily studied in primary care settings, and a paucity of these studies in acute care settings may reflect a lost opportunity

for preventative care. The rates in our study are consistent with a 2011 BMJ systematic review of psychological outcomes in patients with acute non-cardiac chest pain, that found the prevalence of probable depression from 9% to 40%.[6] A Turkish study of similar size to our study, found more than half of ED patients with chest pain to be depressed, regardless of the cause of the chest pain.[9] However, this study used the Hospital Anxiety and Depression Scale (HADS) with cut-off scores validated in Turkey, making it difficult to compare with our methods. A much lower prevalence of depression (less than 10%) was found among ED chest pain patients in an Australian study.[37] Yet another study done in the UK -and more similar to ours in its CPU setting- found a 13% prevalence of depression, but noted this to be lower than the 25% reported in previous UK studies.[38] The lack of literature produced in US ED settings and the wide variability produced in other countries, leaves little for comparison to our current findings of prevalence of depression. This underscores the importance of the present study to the body of US-based, ED-based inquiries.

We considered the effect of depressive symptoms on recurrence of chest pain and found there to be small, but significant effect. Patients with recurrent/persistent chest pain tended to be younger, female, divorced, and non-white than their counterparts without recurrent/persistent chest pain. Prospective studies tracking continued chest pain in ED patients are scarce. Our study confirms the findings of a UK based report that showed almost half of patients to have recurrent chest pain.[16] Similar to our findings, they found baseline depression to correlate with the frequency of recurrent chest pain.[16] However, although we found a striking amount

of recurrent chest pain, we did not find it to approach fifty percent. Several explanations are possible for the difference in our rates of recurrent chest pain. One is that their study used mail-in follow-up survey, which may have introduced a bias toward people who had pain to report. Whereas, our study had a similar rate of follow-up completion, but used multiple-attempt telephone follow-ups, decreasing the dependence on the patient to initiate report. Also, although our sample populations were well matched, it is possible that differences in ED utilization by patients in the UK and the US may have contributed to our lower rate of recurrent chest pain.

Our findings of high prevalence of depression and associated recurrence of chest pain were significant for women and not necessarily for men. There is evidence that women may be especially vulnerable to cardiovascular consequences of depression, including mortality post-MI, and young women may be especially vulnerable.[39-41] We are extending the work to pre-MI patients with cardiac risk factors. High levels of depression in women with non-coronary chest pain are also found in previous studies.[4,23] Our findings of a significant correlation between depressive symptoms and recurrent/persistent chest pain in women support a potential role for greater psychological screening and perhaps brief interventions in the emergency department for these patients. However, our lack of significant findings for men may be attributed to the limited number of men with recurrent/persistent chest pain, and warrant further investigation.

Published literature has pointed to a distinct association between baseline somatic symptoms of depression and cardiovascular mortality post-MI in women.[21,22] This lead us to hypothesize that the link between somatic symptoms and the heart may also be relevant to undifferentiated chest pain in women. Unexpectedly, we found both cognitive and somatic symptom dimensions to contribute to the relationship between PHQ-8 scores and recurrent/persistent chest pain in women, suggesting that cognitive symptoms also play an important role.

The findings of this study, beg a mechanistic explanation for the link between symptoms of depression and symptoms of the heart. Most of the work in this general area has been done in depressed patients post-MI, as we know that depression predicts poor cardiac outcomes in this group, and also predicts a higher likelihood of having recurrent chest pain in the first six months post-MI.[42] Theories fall into two major camps: biologic and behavioral. Possible biological links can be divided into autonomic dysfunction (reduced heart rate variability and baroreceptor sensitivity), neuroendocrine activation (hypothalamic-pituitary axis dysfunction) and inflammatory responses. Behavioral theory considers depression's association with risk factors such as smoking, obesity, sedentary lifestyle and medication non-compliance, to be indirectly driving the link to heart disease. It is also possible that depression could increase the risk of microvascular disease in these patients and the recurrence of pain is from microvascular angina as opposed to obstructive angina. In the absence of widely available screening tests for microvascular disease, this mechanism still needs to be investigated.

The comorbidity of depression and chronic chest pain has been long recognized by the primary care community. Even in the absence of a proven mechanism to explain the link between depression and chest pain, treatments have been targeted at the interaction. Particularly, therapies that promote neuroplasticity may be most useful. Although few randomized controlled trials exist, cognitive behavioral therapy (CBT) appears to be the most effective psychological therapy at diminishing chest pain.[43] For example, in a 1999 Netherlands study, CBT treatment was found to improve chest pain in 48-50% of patients receiving up to twelve CBT sessions, compared to 6-13% of those receiving standard care.[44] Hypnotherapy also appeared to have marked benefit in decreasing non-cardiac chest pain, as shown in a very small but significant 2006 trial.[45] Systematic review of medication trials has suggested modest evidence that low-dose antidepressants benefit NCCP by reducing symptoms.[46] Interestingly, the five studies that assessed depression found scores were stable over time, suggesting that the pain-modulating effects of the antidepressants is distinct from the measured symptoms of depression.[46] However, the small number and heterogeneity of the existing works limits the drawing of comprehensive conclusions and warrants more rigorous trials.

Our interest in the prospect of cognitive/somatic symptoms dimensions in patients with chest pain was partly inspired by findings of the Enhancing Recovery In Coronary Heart Disease (ENRICHD) study. This work with post-MI patients found treatment with CBT +/- sertraline to decrease cognitive and somatic symptoms of

depression, but found only the decreases in somatic symptoms to be associated with improved cardiac prognosis.[47] In contrast, we found both somatic and cognitive symptoms to be similarly associated with the recurrence/persistence of chest pain, suggesting that future research and/or treatment of pain and associated depression may not benefit from targeting of symptom dimensions of depression.

This study had several limitations. For starters, the original design of the study was intended to assess perceived stress, and the sample population was powered for those conditions. Also, the interim analysis reported here was run prior to achievement of the enrollment goal, in order to make this thesis deadline. However, we scrutinized all of our analyses for statistical significance, and selected tests that were appropriate for our sample size. We intend to use the same aim and analytical techniques upon completion of the study.

Missing data, primarily related to our follow-up rate, was a key weakness of this study. We made concerted efforts to complete follow-ups, however during the study there were random periods when the research team was not available for telephone follow-ups. This can potentially introduce random bias. For example, we know that there was a preferential loss of depressed patients, and depressed men in particular. We acknowledge that the addition of these cases would have strengthened our sample size and could have potentially rendered statistical significance to our findings for men. Fortunately, we suspect that completion of these follow-ups would most likely strengthen our findings, and not the opposite given the positive

relationship between depression and recurrent chest pain. Upon completion of our study, we also intend to do chart reviews for patients who did not complete follow-up.

Due to our inability to accommodate languages other than English, we lost a large number of Spanish speakers. This makes the application of our findings to the Hispanic population a challenge. This is particularly important as our demographic data suggested that recurrent chest pain was more common among Blacks and Hispanics, compared to Caucasians, and our numbers may actually underestimate the burden of this disease in the CPC population. Future studies in these groups may be warranted.

Additional limitations may stem from our assessment of depression. For example, we used the PHQ-8 as a screen for depression, which is less specific than interview-based DSM-based clinical diagnosis. Also, the PHQ-8 is not as commonly used in comparable international research as is the Hospital Anxiety and Depression Scale (HADS). While this does not invalidate our findings, it may make them more difficult to relate to the study designs, methods and results of the existing body of literature. Also, we assessed baseline symptoms of depression and did not reassess on follow-up, but it may be worthwhile for future studies to compare trends in depression scores to trends in chest pain, in the absence or presence of treatment. Moreover, we did not query patients, or obtain collateral, on the psychiatric diagnoses they carried or non-pharmacologic treatments they may have been receiving

(psychotherapy, electroconvulsive therapy, repetitive transcranial magnetic stimulation, etc.). However, addition of these factors would only strengthen our findings of a high burden of depression in this population.

It could also be argued that this study would have benefited from including more variables in the analysis. For example, a quality of life measure may have enhanced our capture of symptom burden, and stress test results may have helped us to interpret our findings. Also, our regression analysis may have deserved more cardiac risk factors, such as an account of obesity, and exercise.

Our findings further confirm the high prevalence of depression and depressive symptoms in patients presenting to the ER with new chest pain. This supports a potential benefit for depression screening in CPC settings. We also uncovered a role for baseline depression in the recurrence of chest pain after discharge. However, we found the association between depression and recurrent chest pain, although independent and significant, to be weak when adjusted for confounders. This may be a function of inadequate numbers. We expect the relationship to change upon completion of the study. Also, we did not distinguish between etiologies of chest pain, and stronger trends might be revealed by including stress test results, post-discharge diagnoses and/or psychological follow-up data into the analysis.

Conclusions

Our study confirms a high prevalence of depression in ED patients with chest pain, and suggests a relationship between depression and recurrence of chest pain, particularly for women.

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