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Michael M. Halista April 17, 2013

Assessing the Relationship between Depression and Severity of Coronary Artery Disease

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Abstract

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BACKGROUND: The diagnosis of coronary artery disease (CAD) relies on cardiac catheterization to identify occlusions in the arteries that bring blood to heart muscle. Such a test is conducted only if deemed necessary based on the patient's clinical presentation, particularly the severity of a patient's chest pain. Doctors often rely on self-reported patient data to determine the best course of action. The Seattle Angina Questionnaire (SAQ) is a self-reported score that quantifies the severity of a patient's chest pain. This study aimed to elucidate any interaction depression had on the reliability of the SAQ as a prognostic tool.

METHODS: Study participants were enrolled into the Emory University Cardiology Biobank if they were at the hospital for a coronary catheterization. An ROC curve was used to determine the usefulness of the SAQ as a prognostic tool to predict death or myocardial infarction. Univariate and multivariate analysis were performed using patient characteristics provided by an administered questionnaire to determine significant predictors of the primary outcomes. One-way ANOVA was utilized to identify disparities among patients with scores in the upper, middle, or lower tertile of reported SAQ scores. A Kaplan-Meier curve using a Youden's Index to stratify reported SAQ scores according to relative risk of adverse events was created to illustrate the utility of the SAQ as a prognostic tool.

RESULTS: 3915 patients were included in the study. The ROC curve demonstrated that the SAQ's "Quality of Life" was determined to be a statistically-significant predictor of patient outcome with regard to death or myocardial infarction ($p= 0.002$). Multivariate analysis also revealed the "Quality of Life" section to be a significant, independent predictor of the identified primary outcomes ($p = 0.003$). Depression, as scored by the Patient Health Questionnaire- 9 (PHQ-9) was not found to be a predictor of primary outcomes ($p > 0.07$). This study confirmed depression's significant correlation with the severity of a patient's chest pain ($p<0.001$).

CONCLUSIONS: The "Quality of Life" section of the SAQ is a significant, independent predictor of death or myocardial infarctions in patients suffering from CAD and retains its prognostic value despite its correlation with depressive symptoms.

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Assessing the Relationship between Depression and Severity of Coronary Artery Disease

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Introduction

Coronary artery disease

The human heart functions as a pump to supply blood to the rest of the body. Blood acts as a medium to transport essential compounds and nutrients throughout the body via the cardiovascular system. Because of its essential role, the consistent and reliable action of the heart is necessary for the execution of all bodily functions. As a corollary, diseases that significantly affect this regular activity are of paramount importance in patient care. It is unsurprising that cardiac-related disease accounts for the greatest percentage of morbidity out of all causes in the United States.[13]

Like all muscles, the heart requires a significant amount of oxygen and other nutrients to support its metabolic activity. In this capacity the heart is essentially self-sufficient because of its ability to pump blood to itself. A special set of arteries - the vessels that carry blood from the heart - are responsible for supplying heart muscle with the materials it needs to function. Known as coronary arteries, they originate at the base of the aorta and encircle the heart.

One of the most severe and prevalent heart problems involves a blockage of this blood supply. Known as coronary artery disease, (CAD), this condition results in a decreased circulation to heart muscle tissue because of obstructions in the coronary arteries. The most common condition that predisposes people to CAD is a persistently high cholesterol level in the blood. Over time, macromolecules with a large fraction of fat content, known as low-density liproproteins* (LDLs), can become lodged in the interior lining of an artery. Once inside, the fat molecules within the LDLs are exposed to free radicals, such as superoxides and hydroxyl radicals, that otherwise are important for cell signaling and killing bacteria. However, in the presence of large amounts of fat molecules, these radicals

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*These macromolecules are known as “low-density” liproproteins because of the small amount of protein associated with a correspondingly large amount of fat content. Conversely, high-density liproproteins have a greater proportion of protein relative to fat in their composition.

easily donate their extra electrons, thereby oxidizing the fat. In order to counter the accumulation of oxidized fat molecules, a mechanism exists that involves the recruitment of white blood cells called macrophages and T-lymphocytes. At the site of oxidation, these white blood cells absorb oxidized fat molecules in an attempt to prevent them from causing damage to the surrounding tissue. Unfortunately, because the fat molecules have been oxidized, the white blood cells are unable to degrade them. Instead, the oxidized fat molecules collect in the macrophages and lymphocytes and form what are known as "foam cells" due to the appearance of intracellular, foam-like, lipid droplets.[1]

In healthy individuals, circulating macromolecules known as high-density liproproteins, (HDLs), can help recover the function of foam cells by scavenging some of the accumulated fat and cholesterol. Eventually, the function of these white blood cells can be restored and the damage to the blood vessel wall can be repaired. However, when HDL in the blood is low relative to the amount of LDL, this reparative function is inhibited and the foam cells accumulate within the lining of the blood vessel.[2] Over time, the foam cells can die and rupture, releasing cholesterol and oxidized fat content into the surround tissue. The influx of potentially harmful material in the blood vessel lining recruits more white blood cells to the site and restarts the cycle. This reaction, a form of inflammation, can persist and progress over many years.[1]

A significant accumulation of foam cells and fat within the blood vessel wall forms a hardened structure called an atheromatous plaque. Initially, these plaques narrow the aperture of the artery. Until the occlusion blocks approximately 75% of the artery, however, plaques typically remain asymptomatic. This occlusion can eventually grow so large that it significantly impairs blood flow. A more rapidly progressive problem occurs, however, when the plaque ruptures or erodes. This leads to thrombus formation within the lumen. If the thrombus progresses to total occlusion of the lumen, the heart muscle distally is deprived of blood flow and dies. This event is termed a myocardial infarction and is associated with myocardial (heart muscle) cell death. Alternatively, the thrombus may embolize to the

distal coronary circulation and cause micro infarctions that can become a site of unstable heart rhythms. If ventricular fibrillation ensues, then sudden cardiac death occurs.[1]

Treatment

There are several ways in which CAD can be treated. Depending on the severity of the occlusion(s), different therapies exist. First, medications are prescribed to prevent plaque generation or progression. For example, many of these drugs act by lowering the cholesterol in the blood. Other medications serve to widen the arterial lumen so as to prevent ischemia, or lack of blood flow.[1] If the coronary artery occlusion is already severe, the patient may undergo percutaneous interventions (procedures performed through an insertion in the skin), such as angioplasty or stent implantation, or open surgical procedures, such as a coronary artery bypass graft.[3]

Angioplasty involves the insertion of a catheter into the coronary artery. A deflated balloon is guided into the obstructed artery. When inflated, it forces the obstructive plaque into the walls of the artery which is then opened. A stent is generally implanted after the angioplasty. Stents are mesh, wire devices that can be expanded within an occluded artery to act as a frame or strut to maintain and open channel and prevent future recoil or narrowing.[3]

If medical management and percutaneous intervention are either ineffective or deemed untenable, surgical therapy may be advised. Coronary artery bypass involves the grafting of a vein or artery that is removed from another location in the patient's body to the blocked region. This provides a detour for blood to flow around the blockage and perfuse the affected region of the heart.[3] Unfortunately, all of the above interventions confer heightened risks for the patient and may not be effective in the long-term management of CAD. Therefore, like all diseases, prevention of adverse outcomes is highly preferable.

Catheterization is often used as a tool to assess the severity of a patient's CAD because of its ability to accurately measure coronary artery obstructions. In the current study, patients who were

undergoing cardiac catheterization were recruited before undergoing the procedure. Not all catheterizations are followed by a procedure, angioplasty, or stent implantation, but the need for a catheterization is highly indicative of known or suspected CAD.

Angina as a Symptom and a Tool

The most common symptom of CAD is chest pain, also known as *angina pectoris*. Frequently referred to simply as "angina," this pain often serves as an indication of decreased blood flow to heart muscle tissue. There are two major types of angina with which patients present: stable and unstable angina. Stable angina refers to pain that follows a regular pattern. Patients with stable angina experience discomfort often with exertion due to the increased oxygen demand of the heart outstripping the availability of blood flow that is impeded because of the narrowing of the coronary arteries. Additionally, stable angina can usually be medically managed, although its presence is still indicative of an increased likelihood of adverse cardiac events.[4,9] Unstable angina is chest pain with an atypical frequency of onset, duration, and severity. It can occur at rest and can last longer, and is usually unpredictable. A diagnosis of unstable angina is usually followed by emergency intervention.[10]

Both stable and unstable angina are important warning signs of CAD because of their diagnostic significance. Several studies have shown that the severity of a patient's angina is linked to prognosis.[9,10] These data indicate that more severe pain due to angina is correlated with more frequent adverse cardiovascular events including death. Because the amount of pain experienced by an individual is a subjective measurement, several methods have been established to quantify the severity of a patient's angina. One of the most frequently used methods is the administration of a five-part questionnaire called the "Seattle Angina Questionnaire" (SAQ).

Depression and its Relationship with CAD

Depression frequently occurs concurrently with other serious illnesses.[5] This phenomenon is frequently seen with patients suffering from CAD at least party because of the severity of the diagnosis

and the long-term medical therapy and lifestyle adjustments required.[6,7] Due to the stress-inducing properties of chronic depression, several studies have investigated and discovered serious negative effects of depression on the cardiovascular system.[6,7,8] In fact, these studies have elucidated a positive correlation between depression and the prevalence of CAD as well as the perceived severity of angina symptoms.[6] Because angina severity is linked to patient prognosis, some of these studies have recommended additional screening for depression in patients with CAD.[7,8] The researchers suggest that treating depression may alleviate symptoms of CAD and possibly improve patient prognosis for those diagnosed with both ailments.

Current Study

The severity of a patient's angina has been shown to be directly related to their prognosis. In both stable and unstable angina, the severity of chest pain that a patient reports is positively correlated with the occurrence of adverse events such as myocardial infarction and death.[9,10] Importantly, there is also a positive correlation between depression and perceived angina in patients with CAD.[12] As a result, depression has been indicated as a comorbidity for patients with CAD. Studies have shown that treating concurrent depression in patients with CAD can significantly reduce both angina and adverse events, such as myocardial infarction (MI), stroke, congestive heart failure, or death.[8] It has been concluded that patients with CAD who are suspected of suffering from depression should be screened for the latter and monitored more closely regarding adherence to a medical plan and worsening of symptoms.[7]

The characteristics of a patient's angina are measured by using tools such as the Seattle Angina Questionnaire (SAQ). These questionnaires, although completed by the patients, are useful as tools to predict the likelihood of future adverse events. Because of the significance of the information provided to physicians by questionnaires like the SAQ, it is important that these tests maintain their prognostic value in the presence of potentially confounding factors such as depression. The SAQ contains questions that could be influenced by feelings of depression, particularly in the section titled, "Quality of Life."

Although the patients' respective quality of life should correlate with the limitations they face due to their angina, it cannot be assumed that depression does not influence the perspective with which they view their condition.

Little work has been done to assess the validity of self-reported data in patients with depression. The SAQ provides an excellent opportunity to do so because of its use in predicting patient outcomes. This study aims to utilize a large patient base of people (n=3915) suspected of having CAD or having confirmed CAD to test the prognostic value of the SAQ in light of depression ranging from mild to severe (n=3915). Depression was measured by the Patient Health Questionnaire 9 (PHQ-9), a nine-question survey frequently used to identify the existence and magnitude of a patient's depression. The Emory Clinical Cardiovascular Research Institute's (ECCRI) Cardiology Biobank serves as a source of patient data from which information regarding depression, severity of CAD, angina, and quality of life will be obtained. There were approximately 5,500 patients enrolled in the Emory Cardiology Biobank, all of whom had undergone cardiac catheterization and completed a comprehensive questionnaire. This included the Patient Health Questionnaire 9 and the SAQ. Patients were enrolled in the current study based on the availability of data from relevant sections of the questionnaire, including the PHQ-9, the SAQ, and questions pertaining to quality of life. The primary outcome that was analyzed was whether or not the existence of depression affects the predictive value of SAQ in assessing risk of experiencing a myocardial infarction or death by any cause. If interference is found between the PHQ-9 and SAQ scores, the reliability of the SAQ as a diagnostic tool may be of limited use in patients suffering from depression.

Materials and Methods

Cardiology Biobank

The Cardiology Biobank is an ongoing project started in 2003 that catalogues patients who have undergone cardiac catheterization. Sponsored by Emory University, the study enrolls patients from

Emory University Hospital, Emory University Midtown Hospital, Grady Memorial Hospital, and the Atlanta Veteran's Association Hospital. Blood is drawn from patients who choose to enroll during their catheterization. Before or after the procedure, these individuals also complete a detailed questionnaire regarding family history of cardiac disease, medications, and quality of life. The data from the questionnaire, the catheterization, and the initial blood analysis are recorded anonymously in the online registry. The remaining blood, serum, and plasma samples are stored for further analysis.

PHQ-9

The PHQ-9 scale is a nine-question survey included within the questionnaire administered to all enrolled patients. This is a diagnostic tool used by physicians to assess a patient's mental state for signs of depression and consists of questions in which the patient ranks the frequency with which he or she encounters depressive symptoms. Each question is rated on a four point scale – from 0 to 3 – which are summed to assign the patient an aggregate score out of a possible 27 points. The scores are graded to approximate the severity of the patient's depression from "minimal depression," which correlates to a combined score from 1-4, to severe depression, which has a range of 20-27 (See Appendix A).

Gensini Score

The Gensini score is a measurement that reflects the severity of a patient's CAD demonstrated by cardiac catheterization. The score involves measuring arterial occlusion in several regions of the main coronary arteries. A number is assigned relative to the amount of arterial occlusion found within a region. The values for occlusion are the following: 1 for ≤25% narrowing, 2 for 26-50% narrowing, 4 for 51-75% narrowing, 8 for 76-90% narrowing, 16 for 91-99% narrowing, and 32 for total occlusion, (the geometric increase in numeric value for the progression of vessel occlusion reflects the added risk of adverse events due to significant blockage). This number is then multiplied by another value that reflects the relative importance of the occluded vessel based on the functional importance of the area it serves. The left main coronary artery is assigned a value of 5; the proximal left anterior descending and

proximal left circumflex are scored as 2.5; the mid-region is 1.5; and the distal left anterior descending, mid-distal region of the left circumflex, and the right coronary artery are given a score of 1. The calculated values for the total occlusion of the three arteries are summed to form the Gensini score.[12]

Seattle Angina Questionnaire (SAQ)

The Seattle Angina Questionnaire is a five-section survey included within the questionnaire administered to patients enrolled in the present study. Each section assesses different aspects of a patient's angina with specific regard to the following: anginal stability, anginal frequency, physical limitation due to angina, treatment satisfaction, and quality of life. In addition, each of these five parts is scored separately. The answers to the questions are assigned numerical values, with 1 being the score for the lowest functional ability of the patient. The aggregate score for each section is then subtracted by the lowest possible score, divided by the maximum possible score for that section, and finally multiplied by 100. A higher score indicates a better quality of life.[4] In the current study, only three of the five sections were assessed: "anginal frequency," "physical limitation due to angina," and "quality of life."

Exclusion Criteria

Exclusion criteria for enrollment in the Emory Biobank are the following: congenital heart disease, recent blood transfusion, moderate to severe anemia, active cancer, and physician request for patient not to be included in the study.

Data Analysis

Patient characteristics were tabulated and included in Table 1 to identify basic information regarding participants. An ROC curve was then used, based on patients' "Quality of Life" SAQ score, to discriminate between patients who were at higher myocardial infarction and those at lower risk. This also was intended to demonstrate how accurate the "Quality of Life" section is at predicting adverse

outcomes. A Youden's Index was then determined from the ROC curve to determine the numerical cutoff value between high and low risk patients based on this particular characteristic (SAQ "Quality of Life" score). The Univariate Cox regression was used to indicate patient characteristics that contributed to an adverse outcome on follow-up. The primary endpoint used was myocardial infarction or death experienced by the patient. The characteristics that were calculated to be most closely associated with death or myocardial infarction (with $p < 0.2$) were then screened by backward stepwise multivariate analysis to indicate which factors were most independently correlated with death by myocardial infarction. From this analysis, it was determined that the Youden's Index calculated from the "Quality of Life" section of the SAQ was an independent predictor of death or myocardial infarction. A one-way ANOVA was performed with the patients divided into tertiles with regard to SAQ "Quality of Life" score to identify the characteristics of patients among the three groups and show any bias among them. The patients were divided evenly into the three groups; "Group 1" consisted of patients that scored low (<41.7) on the "Quality of Life" questionnaire, "Group 2" represented those with intermediate scores (41.7 – 66.6), and "Group 3" consisted of patients with the highest score (>66.6). Finally, a Kaplan-Meier survival curve was created to assess the relationship between SAQ scores and the time-to-death by myocardial infarction to indicate its usefulness as a prognostic tool. The two groups in the Kaplan-Meier curve were established based on their relationship to the Youden's Index of the score of 45.83 from the "Quality of Life" section of the SAQ (out of a possible score of 100).

Results

Patient Characteristics

There are 3915 patients enrolled in this study. Table 1 summarizes the characteristics of those included with regard to physical tests, medical history, and medications. Although the patient

population is almost 66% male and 82% white, univariate analysis (Table 2) demonstrated no correlation between sex (p = 0.553) nor race (p = 0.668) and death or myocardial infarction, the primary outcome.

ROC Analysis

An ROC curve was created to determine the Youden's Index for the "Quality of Life" score of the SAQ. The Youden's Index would be indicative of when this particular characteristic of a patient profile is predictive of adverse outcomes. The calculated Youden's Index was a score of 45.83. In the univariate and multivariate analysis of characteristics and their correlations with the primary outcome, the calculated Youden's Index was used as a cutoff score to stratify patient groups based on their "Quality of Life" score.

Variables Linked to Death by Myocardial Infarction

All recorded characteristics from Table 1, (i.e. BMI, gender, etc.), were initially tested to assess their relationship with the defined primary outcomes, death or myocardial infarction.

Table 1.Characteristics of Participants	(n=3915)
Variables	Mean (Standard Deviation)
Demographics	
Age (years)	63 (12)
Gender (%)	
Male	65.9
Female	34.1
Race (%)	
Black	18
White	82
Medical History	

Body Mass Index (mass/height^2)		30 (6)
Creatinine (mg/dL)		1.2 (0.9)
Ejection Fraction Estimate (%)		54 (12)
Cholesterol (mg/dL)		170 (44)
LDL (mg/dL)		98 (37)
CRP (mg/L)		7.0 (12.5)
Gensini		42.5 (65)
Acute MI (%)*	Yes	10.7
*(n= 3840)	No	89.3
Diabetes (%)	Yes	32.3
	No	67.7
Hypertension (%)		
	Yes	72.3
	No	27.7
Dyslipidemia (%)	Yes	30.5
	No	69.5
PHQ9 Depressive Category (%)*		
*(N= 2988)	Mild (score of ≤10)	86.8
	Moderate (11-20)	12
	Severe (>20)	1.2
SAQ Categories (%)		
	Physical Limitation*	66 (25)
	*(n=2211)	

	Angina Frequency*	69 (24.5)
	*(n=2266)	
	Quality of Life*	53 (24)
	*(n=2098)	
Medication Use		
Aspirin (% use)		80.4
Beta Blocker (%)		63.3
Plavix (%)		44.9
Statins (%)		72.6

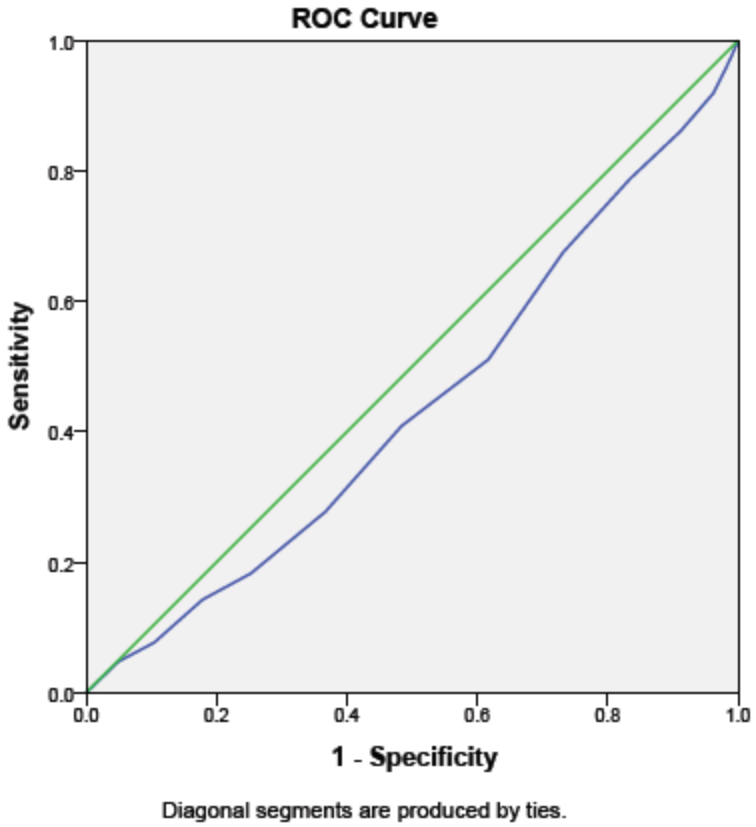


Figure 1. This ROC curve is demonstrating the sensitivity and specificity of the "Quality of Life" section of the SAQ with regard to indicating risk of myocardial infarction or death. The distance of the blue line from the green line (the line of "no discrimination") and the subsequent area between the two indicates the utility of the "Quality of Life" score in determining a patient's risk for the predefined outcomes.

Univariate analysis identified several variables that were linked to adverse outcomes. Among those were age ($p < 0.001$); BMI ($p = 0.012$); serum creatinine levels ($p < 0.001$); previous acute myocardial infarction ($p < 0.001$); diabetes mellitus ($p < 0.001$); hypertension ($p < 0.001$); ejection fraction estimate ($p < 0.001$); LDL levels ($p < 0.001$); cholesterol levels ($p < 0.001$); Gensini score ($p < 0.001$); CRP levels ($p < 0.001$); and

the categories from both the PHQ-9 and the SAQ (all p values ≤0.223). These endpoints were then analyzed by multivariate analysis to identify independent predictors of outcome to yield eight variables that were significantly linked to death by myocardial infarction.

There were three sections of the SAQ included in this study: "Angina Frequency," "Physical Limitation," and "Quality of Life." Of the three groups, only the "Quality of Life" section of the SAQ was identified as an independent predictor of death by myocardial infarction ($p < 0.001$, odds ratio: 0.661).

PHQ-9 scores were divided into two categories related to the severity of the patient's depression. A score of 0-14 was considered mild-to-moderate depression whereas a score of 15 or above was considered to be moderate-to-severe depression. Both depressive categories were shown to be only slightly linked to death or myocardial infarction by univariate analysis, ($p = 0.075$ for mild-moderate depression; $p = 0.223$ for moderate-severe depression) (Table 2). Although they were both included in the multivariate analysis, both PHQ-9 categories were demonstrated to be uncorrelated with the primary outcomes.

Other variables that were shown to be independent predictors of death by myocardial infarction in participants were typical of those suffering from heart disease. They included age ($p = 0.005$), occurrence of acute myocardial infarction ($p < 0.001$), diabetes mellitus ($p = 0.047$), hypertension ($p= 0.019$), ejection fraction estimate ($p < 0.001$), cholesterol levels ($p = 0.005$), and Gensini score ($p < 0.001$) (Table 2).

SAQ and Depression

Although univariate analysis demonstrated a correlation between both PHQ-9 scores and SAQ scores, only one category of the SAQ was found to be a significant predictor of adverse events after multivariate analysis. The "Quality of Life" portion of the SAQ demonstrated correlation with death and myocardial infarction ($p < 0.001$, odds ratio = 0.661). In order to further investigate the prognostic value

of this SAQ section, the "Quality of Life" scores were divided into three groups whose characteristics were assessed (Table 3). There were several features that varied among the groups. For example, age ($p<0.001$), the PHQ raw score ($p<0.001$), and both other sections of the SAQ, "Angina Frequency" ($p<0.001$) and "Physical Limitation" ($p<0.001$), were also all significantly different among the tertiles.

In order to determine the extent to which the SAQ's "Quality of Life" section is related to patient outcomes, a Kaplan-Meier survival curve was created (Figure 2). To create the graph, patients were divided into two groups based on the Youden's Index. Those at or above the Index score of 45.83, (indicating a better reported quality of life), were assigned to group "1," (shown in black in Figure 2), while those who reported lower than the Youden's Index were placed in group "2" (red in Figure 2). It was found that patients in group 1 had a significntly better prognosis when compared to patients in group 2 ($p< 0.001$) and lived an average of almost 100 days longer (Figure 2).

Table 2. Univariate and Multivariate Associations Between Measures of Health Status and Death or MI

Bolded Rows Indicate Significance after Multivariate Analysis

Characteristics	Univariate		Multivariate	
	Odds Ratio (95% CI)	p value	Odds Ratio (95% CI)	p value
Age	**1.026 (1.018 - 1.035)**	**<0.001**	**1.014 (1.001 - 1.028)**	**0.033**
Male Gender	1.059 (0.877 - 1.278)	0.553		

Race (Caucasian)	0.952(0.747 - 1.213)	0.668		
BMI	0.981 (0.966 - 0.996)	0.012	0.98 (0.956 - 1.004)	0.099
Creatinine	1.203 (1.150 - 1.258)	<0.001		
Acute MI	**1.944 (1.545 - 2.446)**	**<0.001**	**1.84 (1.315 - 2.575)**	**<0.001**
Diabetes Mellitus	**1.555 (1.300 - 1.861)**	**<0.001**	**1.391 (1.040 - 1.860)**	**0.026**
Hypertension	**1.443 (1.176 - 1.771)**	**<0.001**	**1.414 (1.014 - 1.972)**	**0.041**
Dyslipidemia	1.045 (0.865 - 1.262)	0.648		
Ejection Fraction Estimate	**0.974 (0.968 - 0.980)**	**<0.001**	**0.978 (0.968 - 0.989)**	**<0.001**
Aspirin	0.923 (0.668 - 1.277)	0.63		
Beta Blockers	1.807 (1.342 - 2.433)	<0.001		
Plavix	1.646 (1.274 - 2.126)	<0.001	**1.324 (0.979 - 1.790)**	**0.069**
Statin Use	1.083 (0.884 -	0.442		

	1.326)			
LDL	0.993 (0.990 - 0.995)	<0.001		
Cholesterol	**0.995 (0.993 - 0.998)**	**<0.001**	**0.996 (0.993 - 1.000)**	**0.032**
Gensini	**1.004 (1.003 - 1.005)**	**<0.001**	**1.003 (1.001 - 1.005)**	**<0.001**
CRP	1.017 (1.013 - 1.022)	<0.001		
SAQ Categories				
Physical Limitation	0.994 0.990 - 0.999)	0.017		
Angina Frequency	0.996 (0.991 - 1.000)	0.065		
Quality of Life (Score >45.83)	**0.991 (0.986 - 0.996)**	**<0.001**	**0.661 (0.502 - 0.872)**	**0.003**
PHQ Categories				
Mild - Moderate Depression	1.274 (0.976 - 1.663)	0.075		
Moderate - Severe Depression	1.533 (0.759 - 3.093)	0.233		

Discussion

Depression has been linked to a worse health status in patients suffering from CAD.[6,7,8] These reports, however, focus primarily on the effects of depression on other self-reported scores rather than physical manifestations of worsening CAD. One of the primary goals of this study was to elucidate depression's effects on patients with CAD in terms of its effect on outcome. As the multivariate analysis suggests, depression is not linked to adverse outcomes, such as death or myocardial infarction (Table 2). Neither mild-to-moderate ($p= 0.075$) nor moderate-to-severe ($p = 0.223$) depression was an independent predictor of death or myocardial infarction. Although depression may increase symptom burden, a relationship not measured in this study, it was unclear whether depression presented in any serious physical manifestation in CAD over time such as Gensini score. However, worsening depression was seen to be significantly linked ($p<0.001$) to a lower score on the "Quality of Life" section of the SAQ, an independent predictor of adverse outcomes. Despite this link with a true predictor of death or myocardial infarction, depression alone is not indicative of a risk of adverse outcomes. Other typical measures of cardiac health, such as hypertension and blood cholesterol levels, were found to be correlated with death or myocardial infarction over time (Table 2).

The second goal of this study was to assess the utility of the Seattle Angina Questionnaire in predicting adverse outcomes in patients suffering from CAD. Surprisingly, only one of the sections of the SAQ, ("Quality of Life," $p = 0.003$), showed significance in its correlation with death or myocardial infarction. Although all three scores are related to the severity of the angina from which a patient suffers, that which affects the overall quality of a person's life is also the most significant gauge as to how likely that individual is to experience an adverse outcome. By using an ROC curve and deducing a Youden's Index for the "Quality of Life" scores reported, the true prognostic value of the SAQ became evident. Although the ROC curve showed that the "Quality of Life" score demonstrated a limited ability to distinguish between high- and low-risk patients with CAD, the significance of the test's sensitivity and

specificity was very good ($p<0.001$). This suggests that the "Quality of Life" score can be relied upon to accurately indicate the health status of a patient. At the very least, a very low "Quality of Life" score could indicate the need for a cardiac catheterization to assess a patient for possible coronary artery occlusions.

The primary goal of this study was to determine the effect of depression as an independent variable on the prognostic value of the SAQ to predict the severity and prognosis of CAD. Because angina severity and frequency is correlated with the likelihood of adverse outcomes, the SAQ was tested against the outcomes of death or myocardial infarction using univariate and multivariate analysis. Both the overall SAQ score and the scores of the 3 individual sections included in this study's questionnaire were found to be highly linked with patient outcomes up to over five years from enrollment at the time of catheterization by univariate analysis (Table 2). This finding further emphasized the link between a patient-reported score of chest pain and individual outcome. However, when assessed by multivariate analysis, only the "Quality of Life" portion of the SAQ proved to be an independent predictor of patient outcomes.

Table 3. Characteristics Within Tertiles of Scores for SAQ: Quality of Life (Bolded Features are Significantly Different Among Groups)

	Group: SAQ "Quality of Life" Score:	**1** <41.7	**2** 41.7-66.6	**3** >66.6	
Characteristics		Mean (Standard Deviation) (95% CI)	Mean (Standard Deviation)(95% CI)	Mean (Standard Deviation)(95% CI)	p value

Age		60.4 (13) (59.55 - 61.26)	62.9 (11) (62.11 - 63.73)	63.6 (12)(62.56 - 64.62)	>0.001
BMI		30.4 (7) (29.9 - 30.9)	29.8 (6) (29.4 - 30.3)	28.8 (6) (28.3 - 29.3)	>0.001
Creatinine		1.13 (0.917) (1.07 - 1.20)	1.15 (0.849) (1.09 - 1.21)	(0.818) (0.04) (1.08 - 1.22)	0.944
HDL		40.6 (12) (39.8 - 41.4)	41.3 (13) (40.4 - 42.2)	43.0 (14) (41.8 - 44.2)	0.003
Dyslipidemia		178.6 (127) (170 - 187)	160.6 (112) (153 - 169)	151.4 (104.0) (142 - 160)	>0.001
LDL		97.8 (38.6) (95 - 100.4)	98.9 (35.5) (96.4 - 101.5)	99.2 (37.9) (95.9 - 102.5)	0.752
Cholesterol		171.8 (45.2) (169 - 175)	171.6 (42.7) (169 - 175)	168.6 (43.7) (165 - 173)	0.396
CRP		7.71 (13.3) (6.8 - 8.61)	6.99 (12.7) (6.09 - 7.9)	5.77 (9.6) (4.94 - 6.6)	0.02
Gensini		47.8 (69.7) (43 - 53)	43.2 (67.8) (38.4 - 48)	40.3 (63.4) (34.7 - 45.38)	0.119
SAQ: Physical Limitation		57.6 (28.3) (55.7 - 59.6)	71.6 (20.8) (70.1 - 73.2)	73.7 (16.8) (72.1 - 75.3)	>0.001
SAQ: Angina Frequency		54.6 (23.7) (52.9 - 56.3)	71.6 (19.3) (70.2 - 73)	81.5 (20.1) (79.7 - 83.3)	>0.001

PHQ9: Raw Score	7.32 (5.6) (6.9 - 7.7)	3.94 (4.3) (3.6 - 4.3)	2.68 (3.5) (2.4 - 3)	>0.001
Ejection Fraction Estimate	53.4 (12.6) (52.5 - 54.3)	54.4 (11.4) (53.5 - 55.2)	55.4 (10.3) (54.5 - 56.3)	0.008

The SAQ is known to have prognostic value when assessing patients with CAD.[4,6] Because depression affects patients' perception of their respective health status, it is important to assess the relationship between depression and the SAQ. Multivariate analysis demonstrated the significance of the "Quality of Life" section of the SAQ and its relationship to patient outcomes independent of other, potentially confounding variables. At the same time, the multivariate analysis showed that depression is not significantly correlated with the primary outcomes defined in this study. Regardless of depression's effects on patient perception of health status, which was confirmed again in this study (Table 3), the SAQ retained its use as a prognostic tool and its ability to predict patient outcomes. This implies that the SAQ is still a reliable measure of the severity of a patient's angina even if the person suffers from severe depression. The information provided by the "Quality of Life" section of the SAQ can be used to help doctors decide the best course of intervention for a patient that also suffers from depression.

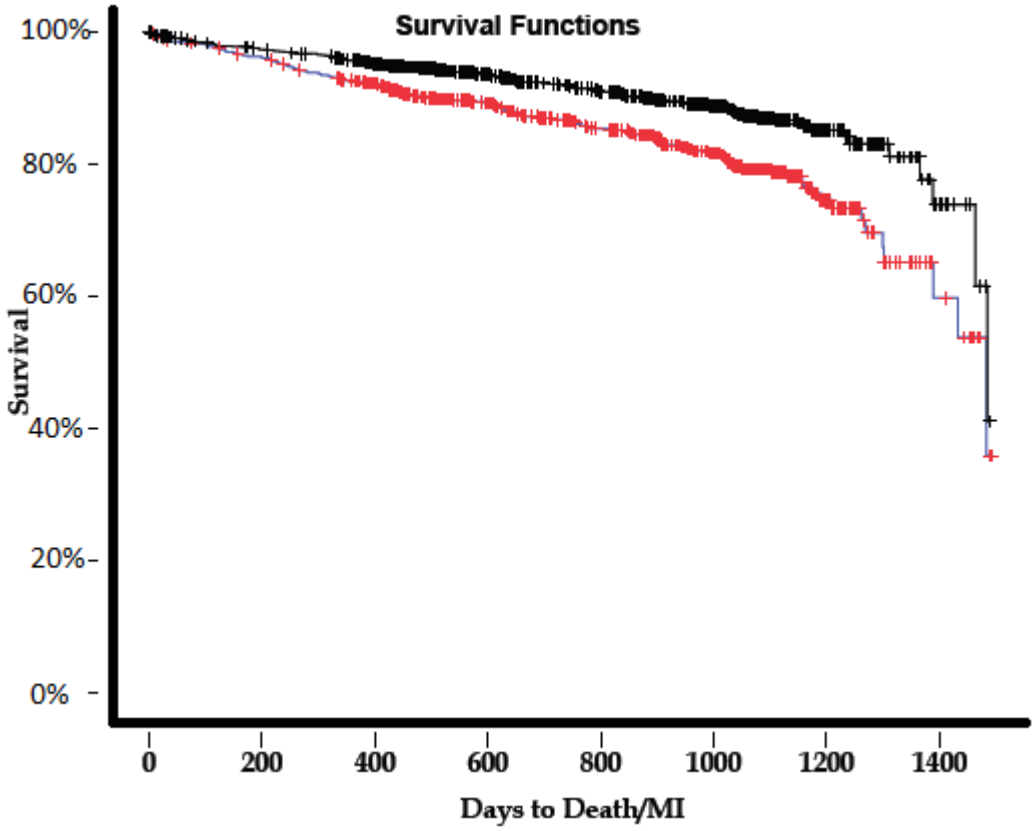
When considering any type of self-reported health score, it is important for doctors to trust the efficacy of the test being performed in light of potentially confounding factors such as depression. The SAQ, and particularly the "Quality of Life," section of the SAQ, have been indicated as useful tools when determining the relative risk of a patient suffering from CAD. Because medical therapy and interventional procedures both carry costs and risks, it is essential that doctors continue to improve their ability to discriminate between those patients who are at significant risk from CAD and those who are not. As demonstrated here, the SAQ is one way, albeit not the only way, doctors can assess a

patient's risk for adverse effects. Despite the limited specificity and sensitivity demonstrated by the "Quality of Life" section as a prognostic device, the significance of the correlation was strong, even when assessed in patients with mild to severe depression.

Although depression was not found to interfere with the prognostic value of the "Quality of Life" section of the SAQ and was not an independent predictor of patient outcomes in CAD, its role in affecting other self-reported patient scores may be more significant. For example, a patient presenting to his/her physician with knee pain may benefit from a diagnostic test such as an X-ray if the pain is severe enough. However, if the patient also suffers from depression, it may be hard to confirm that the patient's description of the pain is unbiased. To confirm the reliability of any diagnostic test with regard to patients suffering from depression, it may be important to study the occurrence of false-positive indications and the concurrence of depressive symptoms. By removing or confirming the possibility of depression as a potentially confounding variable, doctors will be able to more confidently rely on tests that use self-reported patient data.

Figure 2. Kaplan Meier Survival Curve Demonstrating the Relationship Between the "Quality of Life" Section of the SAQ and Patient Death by Myocardial Infarction.

The red line indicates patients with SAQ scores below the Youden's Index Value calculated for the "Quality of Life" section of the SAQ while the black line indicates those patients with SAQ scores above the Youden's Index Value



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