

Persistent anxiety and in-hospital complications after acute coronary syndrome

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ISSN: 1658-3639

PUBLISHER: Qassim University

ABSTRACT

Objectives: To investigate the effects of pre-event persistent anxiety on in-hospital complications and length of stay (LOS) in patients who experienced acute coronary syndrome (ACS).

Methods: This was a prospective study with patients seeking treatment for ACS events. Anxiety was measured 2 times before the event in 600 patients with pre-existing coronary heart disease (CHD). Patients were followed for 2 years or until they developed an ACS event. 120 patients developed ACS events (rate 20%). Complications and LOS were abstracted from medical records.

Results: Persistently non-anxious patients have lower anxiety scores at 3 months follow-up than baseline (mean [standard deviation (SD)], 6.1 [0.24] vs. 3.9 [0.95], $P < 0.01$). Patients with persistent anxiety had significantly higher complication rates than non-anxious patients (mean [SD], 0.71 [0.12] vs. 0.15 [0.11], $P < 0.05$). In a multiple logistic regression, persistent anxiety was an independent predictor of complications. Patients who were persistently anxious were at 5 times higher risk for developing complications (odds ratio = 5.0, 95% confidence interval: 1.27–38.8, $P < 0.05$).

Conclusion: Anxiety measured up to 2 years before an ACS event was predictive of in-hospital complications. Clinicians caring for patients with CHD need to be as equally aware of the importance of assessing and treating persistent anxiety as clinicians caring for patients hospitalized for an ACS.

Keywords: Anxiety, acute coronary syndrome, complications, length of stay

Introduction

To this moment, cardiovascular disease (CVD) is the number one killer worldwide even with the distinguished improvement in the diagnosis and treatment.^[1,2] In 2013, CVD deaths represented nearly one-third of all global deaths.^[2] More than three-quarters of these deaths occurred in low- and middle-income countries.^[2] In 2013, one of every three deaths in the United States was due to CVD. Each day, 2200 Americans died from CVD, with an average of one death every 40 seconds.^[2]

Coronary heart disease (CHD) is one of the most important CVDs.^[3] The prevalence of CHD is high all over the world including the Middle East and developing countries.^[4] In the Middle East, it is estimated that this prevalence will increase approximately by 175% for men and 150% for women between 1999 and 2020.^[4] As in developed and developing countries, CHD is one of the most important causes of deaths in Jordan.^[5] CHD was responsible for about one-fifth of all deaths in the country in 2012.^[5]

Acute coronary syndrome (ACS), including angina and myocardial infarction, is the primary outcome of CHD. Anxiety is considered one of the earliest psychological responses to ACS events^[3,6,7] and has been shown to affect recovery after the event.^[3,6,7] Anxiety has high prevalence rates after ACS events which might reach up to 80%.^[8,9] Anxiety has been associated with higher rates of complications, mortality and longer length of stay (LOS).^[3,6]

Patients who were anxious early after ACS (first 48 h) events had a higher risk for ventricular complications or recurrent ischemia than patients who were non-anxious.^[7,10,11] Moreover, they were also at 2 times higher risk for atrial complications.^[10,11] Anxiety was related to increased LOS and severity of chest pain early after ACS events.^[3,12-17] Patients who were anxious while hospitalized also have higher long-term complication rates including a higher rate of recurrent myocardial infarction^[18,19] unstable angina,^[20,21] a 54% increase in 3-year all-cause mortality rate^[19] and a three-fold increase in 5 years mortality.^[22]

Anxiety has suitable outcomes when it is transient and produces a drive for action. In patients with ACS, a slight increment in anxiety level might motivate individuals to seek treatment rapidly. However, when anxiety persists or becomes severe, inappropriate consequences may result, including increased (complication rates, risk for acute cardiac events, and LOS), difficulty adhering to prescribed therapies and making suggested lifestyle changes.^[1]

There are two issues regarding the measurement of anxiety in previous studies that partially limit our understanding about the role of anxiety in post-ACS complications. First, all previous studies,^[3,8,18-20,23-26] except for two,^[9,27] measured anxiety after ACS events. Even in one of these two studies,^[27] it has been found that patients were asked following the ACS event (median 4 days) to report how anxious they were 2 h before getting the event. Thus, the effect of anxiety experienced before an ACS event on post-ACS complications is not known. Measuring anxiety before the event can help establish the temporal relationship between anxiety, ACS complications, and LOS. Moreover, this approach will assist with determining the effects of anxiety that are not influenced by stressors associated with the ACS event itself.

Second, anxiety was measured at 1 time point in all^[3,8,18,19,23-26] but two^[9,20] of the previous studies examining the association between anxiety and cardiac complications. Measuring anxiety at 2 time points can decrease the risk of erroneously categorizing patients who are experiencing transient anxiety as persistently anxious. It is possible that early recognition of persistent anxiety before ACS events will identify a critical group of patients at high risk for poor outcomes. Therefore, the purpose of this study was to investigate the effects of persistent anxiety measured at 2 time points before an ACS event on complications of patients hospitalized for an ACS.

Research hypotheses

Hypothesis 1: Patients who have high anxiety scores at both time points (persistently anxious) will have longer LOS in the critical care unit and in the hospital than patients who have high anxiety scores at only 1 time point (transiently anxious) or patients who have low anxiety scores at both time points (persistently non-anxious). Hypothesis 2: Patients who are persistently anxious will have more in-hospital complications than patients who are transiently anxious or patients who are persistently non-anxious. Hypothesis 3: Anxiety scores will be independent predictors of in-hospital complications after controlling for demographic and clinical variables.

Methods

Design, sample, and setting

This was a prospective observational study for patients with a pre-existing diagnosis of CHD. Patients were followed for

2 years or until they developed ACS event. 700 patients with pre-existing CHD was approached at the outpatients clinics of the selected hospitals. Among them, 600 agreed to participate and filled the questionnaires. These 600 people composed the sample that was followed for 2 years or till the patient develop ACS event.

A total of 120 patients who met the following inclusion criteria were included in the final analyses: (1) Hospitalization with chest pain or symptoms suggestive of ACS lasting for more than 15 min with new transient or persistent ST-segment ischemic ECG changes with disposition as (a) acute myocardial infarction (AMI) including non-Q wave infarction, and Q-wave infarction; (b) unstable or stable angina; (c) post-infarction angina; (d) angina requiring revascularization; (e) dysrhythmias causing ischemia or hemodynamic compromise (systolic blood pressure <90 mm Hg), and attributed to ischemic heart disease, (2) free of terminal illness such as AIDS, cancer, or chronic renal failure, and (3) ACS occurred outside of a hospital.

Patients were excluded from this study if they (a) had a confirmed diagnosis of psychiatric disorder or if they were on anti-anxiety or anti-depressant medications, (b) had a previous ACS event or treated for an ACS event before enrollment in the study, (c) developed ACS event or death between the baseline measure and the 3 months follow-up. Patients were treated in the critical care and telemetry units of five hospitals located in Amman, Jordan. Two hospitals were governmental, and three were private. There were no differences in the incidence of patients who were persistently anxious or in complication rates among the hospitals.

Measurement of variables

Demographic and clinical characteristics

During the meeting with the patients in the outpatients clinics, a sociodemographic questionnaire was given to the patients to collect information on age, gender, marital status, and smoking status. These variables were used as covariates in the analyses. The following clinical data were collected or confirmed from the medical record review: Admission vital signs (pulse, systolic and diastolic blood pressure), Killip classification (which classify the risk of developing heart failure following AMI to predict risk of mortality; Class I no signs of heart failure, Class II shows rales or crackles in the lungs and S₃, Class III shows pulmonary edema, and Class IV shows cardiogenic shock), β -blocker administration, use of anxiolytics and pain medication, LOS in the hospital and in the critical care units, worst chest pain on 0–10 scale, history of diabetes mellitus, hypertension, and heart failure.

Anxiety

To decrease the risk of erroneously categorizing patients who were experiencing transient anxiety (which occurs over a short momentary period due to a certain situation or an

event, i.e., ACS) as persistently (steadily) anxious, anxiety was measured at enrollment and at 3 months follow-up. The maximal timeline between anxiety measurement and ACS event was 2 years. Anxiety was defined as the total score of the anxiety subscale of Hospital Anxiety and Depression Scale (HADS). Because the participants of this study were Arabic speakers, this instrument has many advantages. It is a short, easy to use and interpret, translated into Arabic, valid, and reliable.^[28-31]

The psychometric properties of the Arabic version were established.^[28,30,31] The Cronbach's α reliability coefficient was 0.78 indicating a very good internal consistency. Moreover, this version has a high sensitivity and the specificity at 86% and 87%, respectively.^[28,30,31] This subscale consists of seven-items in which the participants rated each item on a 0–3 scale, with 3 indicating higher symptom frequency and severity. The total score can range from 0 to 21, with higher scores indicating higher levels of anxiety. The scores were categorized as the following: 0–7, normal; 8–10, mild; 11–14, moderate; and 15–21, severe anxiety.^[28,30,31] For the purposes of this study, patients were considered non-anxious if they have a score from 0 to 7, and anxious if they have a score 8–21.

Complications

The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria^[32] was used to define in-hospital complications. These criteria have been used in previous studies^[3,8,9,10] to define complications associated with ACS. Complications were defined as the presence of any of the following: (1) Acute recurrent ischemia evidenced by new onset of chest pain, ST-segment depression or systolic blood pressure < 90 mm Hg, (2) development of AMI confirmed by elevated cardiac enzymes and standard ECG changes for anginal patients, (3) sustained ventricular tachycardia (>15 s), or any ventricular tachycardia requiring pharmacological and/or electrical intervention due to hemodynamic instability or chest pain, (4) ventricular fibrillation, or (5) in-hospital death.

Procedure

Institutional Review Board approval was received from Applied Science Private University, Amman, Jordan, and from each site before data collection. Informed consent obtained at enrollment including permission to review medical records of patients were admitted to the hospital. Patients were interviewed by the research nurse at baseline and completed the HADS and a sociodemographic questionnaire. The HADS was completed again after 3 months.

Patients, spouses, or significant others were asked to contact the investigator after they were discharged from an admission for an ACS event. It was recognized that not all patients and family members would remember to call. Therefore, patients were followed up at 3, 6, 12, and 24 months. During

these phone calls, patients were queried about whether they experienced any hospital admissions in the intervening period. If the patient has developed ACS event or death before the 3 months follow-up, he/she was excluded from the study. If the patients have been hospitalized for ACS events after the 3 months, the medical records were obtained and reviewed by research nurses who were critical care specialists and blinded to the participants' anxiety levels.

The nurses received specialized training sessions in medical record abstraction using standardized criteria. Inter-rater reliability of medical record abstraction data was tested. Research nurses were asked to collect the needed information from 10 trial charts. After they finished the first half of these charts, the principal investigator checked the data and differences were resolved. The percentage of agreement was >95%.

Data analysis

Data were analyzed using SPSS version 21.0. Data examination showed no violation of the normality assumptions or presence of multicollinearity. Patients were classified as (1) persistently anxious if they had high anxiety scores (≥ 8) at both time points, (2) transiently anxious if they had a low anxiety score (≤ 7) at 1 time point and high score at the other time point, and (3) persistently non-anxious if they had low anxiety scores at both time points. Based on this classification, 38 patients were persistently anxious, 38 patients were transiently anxious, and 44 patients were persistently non-anxious. A series of analysis of variance (ANOVA) were run to determine whether groups differed on key clinical and demographic characteristics at baseline. There were no differences between groups. An alpha of 0.05 was set a priori.

Hypothesis 1: ANOVA was used to test the hypothesis that patients who were persistently anxious had a longer LOS in the critical care unit and in the hospital than patients who were transiently anxious or persistently non-anxious.

Hypothesis 2: ANOVA was used to test the hypothesis that patients who were persistently anxious had more in-hospital complications than patients who were transiently anxious or persistently non-anxious. A *post hoc* analysis was performed using least significant difference test to determine which group differences were responsible for the significant main effect.

Hypothesis 3: A logistic regression was done in three blocks to test the hypothesis that HADS scores were an independent predictor of in-hospital complications after controlling for demographic and clinical variables. In the first block, age and gender were entered to control for their effects on complications. In the second block history of diabetes mellitus, hypertension, smoking history, use of anxiolytics, beta blockers, peak chest pain in the emergency department, admission systolic and diastolic blood pressure, and admission

Killip classification was entered to control for the effects of these variables on complications. In the third block, HADS scores at baseline were entered. Two additional regressions were run using the same first and second blocks. One included 3 months HADS scores in the third block. The other regression included patient classification as persistently anxious and persistently non-anxious in the third block. The transiently anxious category was excluded from the final regression based on the results of data analyses for Hypothesis 2.

Results

Characteristics of the sample

The clinical and demographic characteristics of the three anxiety groups based on the HADS scores are presented in Table 1. There were no significant differences in any of the demographic or clinical characteristics among the groups. Although a higher percentage of women experienced persistent anxiety than men, this difference was not statistically significant.

Anxiety scores

Table 2 summarizes baseline and 3 months anxiety scores for the three groups. The only difference within the groups is that

persistently non-anxious have lower anxiety scores at 3 months follow-up than baseline.

Hypothesis 1: The means \pm standard deviation (SD) for hospital LOS for non-anxious, transiently anxious, and persistently anxious were (5.7 \pm 5.2), (7.8 \pm 5.0), and (5.0 \pm 4.4), respectively. For the LOS in CCU, the means \pm SD were, (3.1 \pm 2.9), (5.4 \pm 5.1), and (4.3 \pm 4.0), respectively. There were no significant differences among groups in either CCU or hospital LOS.

Hypothesis 2: The means \pm SD for complication rates non-anxious, transiently anxious, and persistently anxious were (0.15 \pm 0.11), (0.45 \pm 0.15), and (0.71 \pm 0.12), respectively. There was a significant difference in a mean number of complications among the groups ($F_{(2,117)} = 3.47, P < 0.05$). *Post hoc* analysis showed that only the persistently anxious and persistently non-anxious groups differed from each other ($P < 0.05$). The mean complication rate of the transiently anxious group did not differ from either of the other groups.

Hypothesis 3: Table 3 summarizes the results of the first logistic regression when the baseline HADS scores were entered alone in the third block. Only HADS scores and Killip class were predictive of in-hospital complications. Based

Table 1: Clinical and demographic characteristics of the groups

Characteristics	Persistently non-anxious <i>n</i> =44 (36.6)	Transiently anxious <i>n</i> =38 (31.7)	Persistently anxious <i>n</i> =38 (31.7)
Sex			
Male	26 (59)	18 (41)	24 (63)
Female	18 (41)	12 (32)	26 (68)
Marital status			
Married	22 (50)	22 (50)	11 (29)
Single/divorced/widowed	22 (50)	11 (29)	27 (71)
Age (years)	71 \pm 8	67 \pm 11	68 \pm 10
Peak chest pain (0–10 scale)	6 \pm 3	5 \pm 2	6 \pm 2
Peak CK-MB (ng/ml)	26 \pm 35	19 \pm 11	12 \pm 18
Admission diagnosis			
Angina	33 (75)	32 (84)	34 (89)
AMI	11 (25)	6 (16)	4 (11)
Admission Killip class			
I	35 (80)	30 (79)	33 (87)
II/III/IV	9 (20)	8 (21)	5 (13)
Admission systolic blood pressure (mmHg)	141 \pm 23 145 \pm 26 146 \pm 29	145 \pm 26 77 \pm 15	72 \pm 157 77 \pm 15 76 \pm 17
Admission diastolic blood pressure (mm Hg)	72 \pm 15	77 \pm 15	76 \pm 17
Admission pulse (beats/min)	79 \pm 22	73 \pm 20	77 \pm 19
History of hypertension	23 (52)	30 (79)	32 (84)
History of diabetes	15 (34)	14 (37)	13 (34)
Smoker	8 (19)	8 (21)	7 (19)

Values are *n* (%) or mean \pm SD. SD: Standard deviation, CK: Creatine kinase-MB, AMI: Acute myocardial infarction

on the odds ratio, patients with high baseline HADS scores were 4.1 times higher risk developing complications than patients with low scores. Patients in Killip Class II, III, or IV were at approximately 8.0 times higher risk for developing complications than patients in Killip Class I.

Table 4 summarizes the second logistic regression when HADS scores at 3 months were entered in the third block. In contrast to baseline anxiety scores, 3 months anxiety scores were not an independent predictor of complications. In this regression Killip class remained an independent predictor of the complications.

Table 5 summarizes the regression in which persistently anxious and persistently non-anxious were entered in the final block. Persistently anxious patients were at 5 times higher risk for developing complications than persistently non-anxious patients. Killip class remained an independent predictor of the complications in this model also.

Discussion

The results of this study supported the hypothesis that patients with persistent anxiety would have more complications than

patients in which anxiety was not persistent. These results are consistent with other studies in which an association between anxiety and complications in patients hospitalized for ACS was reported.^[3,8,10,20,21,33] Thus, this study provides further evidence that anxiety plays a key role in increasing susceptibility to complications associated with ACS.

An important difference between this study and previous research is that anxiety was measured up to 2 years before an ACS event. All previous studies, except for one,^[9] measured anxiety after ACS events. Patients with ACS may be anxious due to fear of death, strange intensive care unit environment, loss of personal control, unpredictable consequences, diagnostic or therapeutic procedures, cost of treatment, and potential inability to return to work.^[6,10] Measuring anxiety after ACS events makes it difficult to differentiate between anxiety associated with the event itself and persistent anxiety before the event. Therefore, measuring anxiety before an ACS event provides a further understanding of the role of anxiety, specifically, anxiety that is independent of the event itself. This anxiety can affect complications in the same manner as anxiety that is presumably affected by the ACS event.

Measurement of anxiety pre-event also assisted in demonstrating the temporality aspect between anxiety and complications. Most of the life-threatening complications such as ventricular tachycardia and ventricular fibrillation occurs within the first 24–72 h after the event, which coincides with when anxiety has been measured in previous studies.^[3,8,10] In these cases it is not possible to conclude that anxiety preceded complications, we can only conclude that it coexisted with complications.

The association between anxiety and complications is explained through the activation of the sympathetic nervous system by anxiety.^[3] This activation stimulates a flow of physiological responses that increase myocardial oxygen consumption^[34,35] augment cardiac vascular reactivity^[36] and platelet adherence,^[37] and lower the dysrhythmic threshold.^[34,35] These responses to anxiety should precede the complications to be considered as their risk factor. Previous studies measured anxiety after the event or during the occurrence of these complications which might cover the actual effect of anxiety on these complications.

A second important difference is that anxiety was measured at 2 time points. To date, only two studies^[9,20] measured anxiety at multiple time points. Many people who experience an anxiety-producing event (~50%) are able to respond appropriately using their internal coping abilities which would result in transient anxiety.^[38-40] In others, the coping responses are inadequate and anxiety persists. Measuring anxiety at 1 time point may result in classifying about half of these patients erroneously as either anxious or non-anxious. If we used the baseline scores alone in this study, 20 patients would have been erroneously classified as non-anxious and 12 as anxious. If we used only the 3 months follow-up scores, 20 patients would have been erroneously

Table 2: Baseline and 3 months anxiety scores among groups

Group	Baseline	3 months follow-up
Persistently non-anxious	6.1±0.24	3.9±0.95*
Persistently anxious	8.3±2.1	10.2±1.9
Persistently non-anxious	14.1±0.8	15.2±1.6

Values are mean ± SD, *P < 0.01. SD: Standard deviation

Table 3: Independent predictors of in-hospital complications, baseline HADS scores entered alone

Predictor	OR	95% CI	B	SE	Wald	P
Killip class	8.0	1.8–39.1	2.2	0.82	6.8	0.01
HADS scores	4.1	1.2–14.7	1.6	0.67	5.87	0.02

OR: Odds ratio, CI: Confidence interval, B: Beta, SE: Standard error of the mean, P: P value, HADS: Hospital Anxiety and Depression Scale

Table 4: Independent predictors of in-hospital complications, 3 months HADS scores entered alone

Predictor	OR	95% CI	B	SE	Wald	P
Killip class	9.1	3.0–42.9	2.9	0.83	8.9	0.005
HADS scores	2.0	0.68–6.9	0.77	0.59	1.9	0.21

OR: Odds ratio, CI: Confidence interval, B: Beta, SE: Standard error of the mean, P: P value, HADS: Hospital Anxiety and Depression Scale

Table 5: Independent predictors of in-hospital complications, when patients' classification entered

Predictor	OR	95% CI	B	SE	Wald	P
Killip class	8.1	1.71–39.0	2.1	0.79	6.9	0.008
HADS scores	5.0	1.27–38.8	2.4	0.93	5.7	0.02

OR: Odds ratio, CI: Confidence interval, B: Beta, SE: Standard error of the mean, P: P value, HADS: Hospital Anxiety and Depression Scale

classified as anxious and 12 classified as non-anxious. This potential misclassification may limit the ability to reach a definite conclusion about the relationship between anxiety and complications. The number of complications in the transiently anxious group did not differ from either the persistently anxious or persistently non-anxious groups. Inclusion of these people in either group would have diminished the differences observed between the other two groups.

Even though, the previous studies that checked the persistence of anxiety showed conflicting results. The first study^[20] enrolled 913 patients with unstable angina and myocardial infarction from 12 coronary care units and showed that persistent anxiety has negative effects on the outcome (increase complication rates) following ACS events. This result is consistent with our findings and giving further support to our hypothesis that persistent anxiety negatively affects patients with ACS events. However, the second study^[9] did not show any correlation between persistent anxiety and the prediction of complications. The explanation for these results might be the nature of the samples of the three studies. In the study^[20] that showed a significant association between persistent anxiety and negative outcomes and this study, the samples are relatively homogenous. However, in the study^[9] that did not show this correlation, the sample is heterogeneous from five different hospitals in three countries (USA, Australia, and New Zealand). Further studies are warranted to give further support to this hypothesis.

Anxiety levels had no effect on the LOS in the CCU or in the hospital in this study. Higher anxiety levels were related to longer LOS in one larger previous study.^[3] Anecdotal evidence suggests that in the current health-care climate, patients are often transferred from critical care units or discharged from the hospitals based as much on shortage of hospital beds for incoming patients or insurance restrictions as on their medical condition. This limits the validity of LOS as an outcome measure. Larger sample sizes are needed to overcome the effect of confounding factors on LOS. For example, to reach 80% power for the ANOVA with a medium effect size and an alpha of 0.05, the sample size in each group for our study would have been 52 patients, with a total sample size of 156.^[41]

Conclusion and Clinical Implication

Previous research demonstrated that higher anxiety levels measured after an ACS are related to increased complications. The present study demonstrated that anxiety levels measured up to 2 years before an ACS event are also related to higher complication rates. Combined, these results suggest that clinicians caring for patients with CHD need to be as equally aware of the importance of assessing and treating anxiety as clinicians caring for patients hospitalized for an ACS.

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