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FACTORS PREDICTIVE OF PANIC DISORDER IN CARDIOLOGY PATIENTS WITH CHEST PAIN AND NO EVIDENCE OF CORONARY ARTERY DISEASE: A CROSS-VALIDATION

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Abstract—Recent data indicate that a substantial number of cardiology patients with chest pain and no clinical evidence of coronary artery disease suffer from panic disorder. Discriminant function analysis reveals that a self-report anxiety measure alone, or in conjunction with minimal demographic information, can predict whether such patients have panic disorder. Predictive accuracy ranges from 69 to 76% correct classification, significantly improving upon chance predictions alone. A 'split-half' design was used in order to cross-validate predictive equations, and the total sample was also analyzed so as to provide the most stable equation. Clinical and future research implications of these findings are discussed.

INTRODUCTION

SEVERAL recent studies have found that at least one-third of chest pain cardiology patients with normal or near normal coronary arteries have panic disorder [1–4]. These findings may partially explain earlier investigations showing that up to 65% of those pronounced as having normal coronary arteries by a cardiologist continue to experience debilitating symptoms during follow-up periods ranging from 2 to 6 yr [5–11]. Given the extent of panic disorder in this population, along with evidence suggesting that panic disorder is responsive to both chemotherapeutic [12, 13] and psychotherapeutic interventions [14–15], strategies aimed at increasing cardiologists' ability to identify panic disorder patients emerges as an important goal.

A first step in achieving this objective is to identify variables capable of reliably indentifying panic disorder in this population. In this regard, studies cited above documenting panic disorder in cardiology populations have reported classical analyses of variance demonstrating a relation between panic disorder and various self-report measures of psychological functioning. Presumably, these data portend that such measures could be used by cardiologists as an important aid in making clinical decisions regarding individuals in need of more extensive screening and/or referral to a mental health professional.

The general purpose of this study is to develop and validate a predictive model capable of improving the probability with which panic disorder can be identified in cardiology chest pain patients.

(1) In an initial sample (Sample 1), self-report measures of anxiety, depression,

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global psychological symptomatology, phobic avoidance* along with subject sex and age are used to develop a predictive equation which maximises discrimination between subjects with and without panic disorder.

(2) The validity of the predictive equation is evaluated by applying it to a second sample (Sample 2) and assessing its predictive accuracy in this new sample (cross-validation).

(3) Additional data are provided regarding the validity of the predictive model by essentially reversing the procedure described above; i.e. the generation of a second predictive equation from study Sample 2 (initially used to validate the first equation) and the evaluation of its predictive accuracy in Sample 1 ('double' cross-validation).

(4) Generation of a predictive equation derived from the combined samples (Total Sample) in order to obtain a predictive equation that would be maximally stable in future attempts at cross-validation and refinements of the predictive model.

METHOD

Subjects

Over a 2.5 yr data collection period, clinical cardiologists at a university hospital referred 305 consecutive in and out cardiology patients to this study. This group represented consecutive cardiology referrals who were experiencing atypical chest pain and showed no clinical evidence of coronary artery disease (CAD). Atypical chest pain was defined as the presence of one or two but *not* all of the following three symptoms: (1) substernal chest pain; (2) exertional chest pain; or (3) chest pain relieved by rest or nitroglycerine. In keeping with standard clinical practice, absence of CAD was defined by cardiologists who utilised tests available to them for diagnostic work-ups including cardiac catheterisation, treadmills and echocardiography. Of the 305 patients referred to this study, 118 did not provide data for the following reasons: 59 because of scheduling problems for the subject or the interviewer; 43 either could not be reached after agreeing to participate or had changed their minds when they were contacted for scheduling; two had sensory deficits which prohibited them from responding to self-report material. The final subject sample (n = 187) consisted of 68 males (36.4%) and 119 females (66.6%) whose ages ranged from 16 to 86 yr of age (mean = 45.4 yr, SD = 15.5 yr).

MEASURES

Interview

The Structured Clinical Interview for DSM-III (SCID-UP) [16] was utilised to assess the presence of panic disorder in study subjects. The SCID-UP was specifically developed for the diagnosis of panic disorder, phobic avoidance (agoraphobia), social phobia, simple phobia and major depression. Study subjects were considered positive for panic disorder if they met criteria specified for that disorder by the Work-group to revise the Diagnostic and Statistical Manual of Mental Disorders — third edition (DSM-III) [17] and also had at least one panic attack in each of the previous 3 weeks. This latter criterion ensured that subjects with PD would be experiencing an ongoing series of attacks at the time of interview rather than a single cluster some time in the recent past.

Self-report questionnaires

Each participant was asked to complete the following self-report questionnaires

*These measures are described in detail in the Methods section of this paper.

at the time of the interview: the Zung Self-rating Anxiety Scale (SAS); the Beck Depression Inventory (BDI), the Marks–Mathews Fear Questionnaire (MARKS); and the Brief Symptom Inventory (BSI) ([17–21] respectively). The BSI includes 52 items regarding current psychological symptoms which are rated based on severity using a five point scale. The BSI was designed as a short form of the Symptom Checklist 90 — Revised [22] and provides the same summary measures as that instrument, including the Global Severity Index (GSI). The GSI is a single summary measure of psychological distress representing the mean symptom endorsement for all BSI items. The SAS measures the current intensity of 20 anxiety symptoms on a four point scale. The BDI provides a measure of the current intensity of 21 symptoms of depression on a four point scale. Finally, the 15 items of the MARKS inquire about the degree of fearful avoidance associated with social, blood/injury and agoraphobic situations and stimuli to be rated on an eight point scale.

Procedure

Cardiologists at a university hospital identified consecutive in and outpatient cardiology referrals who were experiencing atypical chest pain yet for whom all clinical evidence indicated that they were free from CAD (see Subjects section for a detailed description of how these subjects were identified). For the individuals who met these criteria and agreed to participate (the Subjects section details information regarding subjects who did not participate), cardiologists contacted a member of our research team who set up an appointment for an interview. Interviews (conducted about 30 min after self-report items were provided) were performed by one of four board eligible psychiatrists trained in the use of the SCID-UP. Twenty-three interviews (12.3%) were conducted in the presence of two interviewers (a primary interviewer and an observer) in order to assess inter-rater reliability. Additionally, all interviewers discussed their findings with the second author after each interview in order to minimise rater drift [23].

RESULTS

Of the 305 individuals who met inclusion criteria, we compared those who did (n = 187) with those who did not go on to participate (n = 118). A chi-square test comparing sex and a t-test contrasting mean age did not reveal significant differences between groups.†

Interview results

The kappa coefficient of agreement for nominal scales [24] was calculated to estimate the inter-rater reliability of the panic disorder diagnosis. The k index obtained for interviews with both a primary interviewer and an observer (n = 23) was 0.89 (z = 4.25, $p < 0.0001$). Cohen [25] suggested that k values over 0.70 indicate satisfactory inter-rater agreement.

†We only had data regarding the sex and age for those who were qualified but did not participate. However, based on the reasons given by qualified subjects for not participating in the study (see Subjects section), along with observations from referring cardiologists we have no reason to believe that this group systematically varied from those who did participate in any clinically meaningful way.

Ninety-one of the 187 study subjects (48.7%) met criteria for panic disorder (PD). PD(+) subjects had a mean age for panic symptom onset of 37.6 yr (SD = 15.2 yr), and a mean duration of panic symptoms of 4.1 yr (SD = 8.5 yr). PD(+) subjects reported experiencing a mean of 6.5 panic attacks (SD = 12.1 panic attacks) in the week prior to the interview, with their last typical panic episodes involving a mean of 7.8 panic symptoms (SD = 2.6 symptoms).

Discriminant function analysis

Cases were randomly assigned to one of two subsamples (Sample 1: $n = 93$, vs Sample 2: $n = 94$). Table I shows mean scores for predictor (independent) variables (i.e. the SAS, BDI, BSI, MARKS, sex and age) by PD(+) vs PD(−) group status (dependent variable) for Sample 1, Sample 2 and the Total (combined) Sample.

Using data From Sample 1, a discriminant function analysis was performed. Two variables contributed significantly to the predictive power of the discriminant function equation; the SAS and subjects' age (Table II). Included in Table II is a 2 × 2 contingency table of correct and incorrect classifications that were generated by using the discriminant function equation.

The *sensitivity* of the equation (i.e. ability of the equation to correctly identify those subjects who have panic disorder) is displayed in the upper left cell of the contingency table (70.7%). The *specificity* of the equation (i.e. ability of the equation to correctly identify those patients who do not have panic disorder) is displayed in the lower right cell of the contingency table (76.2%). These indices taken together reveal an overall 'hit-rate' (cases correctly classified) of 74.4%.

TABLE I.—STUDY PREDICTOR VARIABLES BY PANIC DISORDER GROUP STATUS FOR SAMPLE 1, SAMPLE 2, AND THE TOTAL (COMBINED) SAMPLE

	Sample 1		Sample 2		Total sample	
Predictor variables	PD(+) $n = 41$	PD(−) $n = 42$	PD(+) $n = 44$	PD(−) $n = 42$	PD(+) $n = 85$	PD(−) $n = 84$
Zung Anxiety Scale (SAS)						
Mean	41.8	35.0	40.7	33.5	41.2	34.3
SD	7.7	6.5	8.0	7.1	7.8	6.8
Beck Depression Inventory (BDI)						
Mean	13.7	8.8	12.3	7.5	13.0	8.1
SD	9.9	5.7	8.9	5.0	9.0	5.4
Marks–Mathews Fear/Injury Questionnaire (MARKS)						
Mean	32.9	25.1	31.8	23.9	32.4	24.1
SD	20.3	15.3	17.8	17.8	18.9	16.5
Brief Symptom Inventory (BSI)						
Mean	52.2	29.3	48.7	26.1	50.4	27.7
SD	30.2	24.2	33.4	20.0	31.9	22.2
Age						
Mean	39.5	47.0	42.1	52.8	40.9	49.9
SD	15.0	14.9	16.1	14.8	15.5	15.1
Sex						
Males	17(18%)	17(18%)	14(15%)	20(21%)	31(17%)	37(20%)
Females	28(30%)	31(33%)	32(34%)	28(30%)	60(32%)	59(32%)

PD(+) indicates subjects with panic disorder, and PD(−) indicates subjects without panic disorder.

TABLE II.—PREDICTIVE EQUATION DERIVED FROM SAMPLE 1 AND APPLIED TO BOTH SAMPLE 1 AND SAMPLE 2

Step	Variable	Cumulative variance accounted for
1	Zung Anxiety Scale (SAS)	0.18
2	Age	0.20

Sample 1 equation applied to Sample 1 data

	Actual condition: Panic disorder	Actual condition: No panic
Predicted group		
Panic disorder	29 (70.7%)[a]	10 (23.8%)
No panic	12 (29.3%)	32 (76.2%)[b]
Percent correctly classified	74.4%*	

Sample 1 equation applied to Sample 2 data

	Actual condition: Panic disorder	Actual condition: No panic
Predicted group		
Panic disorder	27 (61.4%)[a]	6 (14.3%)
No panic	17 (38.6%)	36 (85.7%)[b]
Percent correctly classified	73.4%*	

*$p < 0.0001$.

Note. Superscript 'a' = the *sensitivity* of the equation (i.e. ability of the equation to identify those subjects who have panic disorder). Superscript 'b' = the *specificity* of the predictive equation (i.e. ability of the equation to identify those patients who do not have panic disorder).

In terms of statistical significance, Huberty [26] describes the *proportional chance criterion* which asks 'Is the number of units correctly classified by the equation significantly greater than the number of correctly classified by chance?' (p. 166). As outlined by Huberty [26], correct classifications were evaluated against the expected chance classification utilising a standardised normal statistic. The results of this analysis revealed that the degree of predictive information gained over chance by utilising the predictive equation is highly significant ($z = 4.17$, $p < 0.0001$).

Importantly, the predictive power of the discriminant function when applied to the sample from which it is derived is inflated [27]. In order to obtain a more unbiased assessment of the equation's predictive power we applied the equation derived from Sample 1 to predict group membership in Sample 2. Included in Table II is the 2 × 2 contingency table of correct and incorrect classifications resulting from this analysis. Note that 73.4% of the cases were correctly classified. Classification analysis as described above revealed that the information provided by the Sample 1 predictive equation increased correct classification significantly when applied to Sample 2 ($z = 4.09$, $p < 0.0001$).

The second leg of the double cross-validation was begun by reversing the roles Sample 1 and Sample 2 played in the analyses described above. Discriminant analysis of data from Sample 2 revealed that three variables (SAS score, age, and sex) made significant contributions to the predictive power of the equation. Table III shows the cumulative variance accounted for at each step of the predictive equation, along with a 2 × 2 contingency table of correct and incorrect classifications; 76.4% of the Sample 2 cases were correctly classified ($z = 4.64$, $p < 0.0001$).

TABLE III.—PREDICTIVE EQUATION DERIVED FROM SAMPLE 2 AND APPLIED TO BOTH SAMPLE 1 AND SAMPLE 2

Step	Variable	Cumulative variance accounted for
1	Zung Anxiety Scale (SAS)	0.19
2	Age	0.29
3	Sex	0.32

Sample 2 equation applied to Sample 2 data

	Actual condition: Panic disorder	Actual condition: No panic
Predicted group		
Panic disorder	33 (75.0%)[a]	9 (21.4%)
No panic	11 (25.0%)	33 (78.6%)[b]
Percent correctly classified	76.4%‡	

Sample 2 equation applied to Sample 1 data

	Actual condition: Panic disorder	Actual condition: No panic
Predicted group		
Panic disorder	33 (80.5%)[a]	18 (42.9%)
No panic	17 (19.5%)	24 (57.1%)[b]
Percent correctly classified	68.7%*	

*$p < 0.001$.
‡$p < 0.0001$.
Note. Superscript 'a' = the *sensitivity* of the equation (i.e. ability of the equation to identify those subjects who have panic disorder). Superscript 'b' = the *specificity* of the predictive equation (i.e. ability of the equation to identify those patients who do not have panic disorder).

In order to complete the double cross-validation procedure, the predictive equation derived from Sample 2 was applied to Sample 1. Table III shows the correct and incorrect predictions of group membership resulting from that procedure. As can be seen in Table 3, 68.7% of Sample 1 subjects were correctly classified ($z = 3.51$, $p < 0.001$).

In order to determine the most stable predictive equation available from the current data, a discriminant function analysis was performed on the Total Sample. Two variables (SAS score and age) contributed significantly to the predictive equation. Table IV shows the cumulative variance accounted for by these variables and a 2 × 2 contingency table of correct and incorrect classifications; 69.8% of the cases were correctly classified ($z = 5.12$, $p < 0.0001$).

Because the SAS score accounted for the overwhelming amount of predictive variance in all analyses, a final discriminant function analysis was performed on the Total Sample using only the SAS score as a predictor variable. The bottom of Table IV shows a 2 × 2 contingency table of correct and incorrect classifications resulting from this analysis. Note that 70.1% ($z = 5.42$, $p < 0.0001$) of the cases were correctly classified using a predictive equation based on the SAS score alone.

Because the final equation has only one predictor variable, a single value for that variable can be derived which predicts the presence or absence of PD. This value is found by algebraically solving for the predictor score, where the discriminant score cut-off and the constant are determined by the discriminant analysis. Utilising this procedure, a raw SAS value of 38 was found to be the cut off point. That is,

TABLE IV.—PREDICTIVE EQUATION DERIVED FROM TOTAL SAMPLE

Step	Variable	Cumulative variance accounted for
1	Zung Anxiety Scale (SAS)	0.18
2	Age	0.23

Total sample equation applied to total sample data

	Actual condition: Panic disorder	Actual condition: No panic
Predicted group		
Panic disorder	56 (65.9%)[a]	22 (26.2%)
No panic	29 (34.1%)	62 (73.8%)[b]
Percent correctly classified	69.8%*	

Total sample equation applied to total sample data (SAS only)

	Actual condition: Panic disorder	Actual condition: No panic
Predicted group		
Panic disorder	59 (69.4%)[a]	23 (27.4%)
No panic	26 (30.6%)	61 (72.6%)[b]
Percent correctly classified	70.1%*	

*$p < 0.0001$.

Note. Superscript 'a' = the *sensitivity* of the equation (i.e. ability of the equation to identify those subjects who have panic disorder). Superscript 'b' = the *specificity* of the predictive equation (i.e. ability of the equation to identify those patients who do not have panic disorder).

subjects scoring below 38 on the SAS were classified by the predictive equation as PD(−) and those scoring equal or above 38‡ were classified as PD(+).

DISCUSSION

Discriminant function equations correctly classified 69–76% of CAD free cardiology patients regarding the presence or absence of panic disorder. As expected, a small reduction in predictive power occurs when moving from the original sample to the cross-validation sample. The major implication of these findings is the potential for substantially improving the identification of cardiology patients with panic disorder; a population which has only recently come to the attention of researchers. Studies cited earlier suggested that from 30 to 50% of cardiology patients with chest pain and no evidence of CAD suffer from panic disorder [1–4]. Because these patients typically go undiagnosed, and are thus not referred for appropriate treatment, information aimed at making this group easier to identify offers important clinical utility.

Not surprisingly, the SAS, a self-report instrument which inquires directly about several panic symptoms, emerged as the most potent discriminator between those with and those without panic disorder. More suprisingly was the finding that once the predictive variance associated with the SAS was accounted for, other predictor variables accounted for only a marginal amount of additional variance. This finding

‡Zung [18] suggests that raw scores from the SAS be represented as a percentage of the maximum possible score (i.e. 80). Employing this transformation on an SAS score of 38 results in an adjusted score of 48.

may suggest that the capacity of other measures of psychological symptoms shown to discriminate PD(+) and PD(−) subjects [2–4] are redundant to and subsumed by the predictive relation associated with the SAS. Future research could address this question.

Also of interest were subjects who fell into the false positive and false negative predictive categories. The former includes a group of subjects who, while showing no evidence of CAD or panic disorder, endorsed a high degree of anxiety symptoms on the SAS. This group may deserve special focus when it is considered that psychiatric problems other than panic have been reported to be common in cardiology patients who are free of CAD but continue to have chest pain [28, 29]. Thus, it seems quite possible that false positives in this study are experiencing mental difficulties other than panic. While this speculation cannot be substantiated in the current investigation, future studies in this area, along with clinical cardiologists, should remain open to the possibility of a wide range of mental problems in this group. Future research should also explore possible differences between panic patients who demonstrate moderate to high anxiety (true positives) vs panic patients reporting relatively low anxiety on the SAS (false negatives). In terms of using an instrument such as the SAS to screen for panic patients, it will be important to determine in what way this process operates selectively.

Limitations to the current study include questions of generalizability (external validity). That is, in spite of added confidence stemming from the cross-validation procedure, the issue of the degree to which current findings will apply to other populations remains open. In this regard, the SAS displays a high degree of face validity as a panic disorder discriminator as 10 of its 20 items inquire directly about panic symptoms. Further, studies investigating mental disorders in cardiology populations [1–4] have consistently found the SAS to discriminate PD(+) and PD(−) groups (i.e. higher SAS scores are associated with panic disorder). These past findings lend confidence to the generalizability of the current findings; however, future replications of this study will be required to address this question more definitively.

In conclusion, the current findings suggest that a predictive equation using the SAS alone, or in conjunction with minimal demographic information, can aid substantially in the identification of individuals presenting to cardiologists with atypical chest pain who are negative for CAD but who may be suffering from panic disorder. As indicated earlier, panic disorder appears to be common in this population, but typically remains undiagnosed. Inasmuch as panic disorder is responsive to a wide range of psychiatric and psychological interventions [12–15] the identification and referral of these individuals emerges as a professional imperative.

Future research in this area needs to replicate and extend the findings of the current study. Confidence in the SAS as an important predictor variable is buttressed by study findings which showed that that measure accounted for the majority of predictive variance for all equations (see Tables 2–4), while remaining quite stable in its relation to the criterion from one equation to the next. In consideration of these findings, along with the easy administration of the SAS (e.g. self-administering, usually taking less than 10 min to complete), this measure stands as a standard against which results from future research can be compared.

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