Review Article

Recognition of depression/anxiety-complicated coronary diseases and evaluation of commonly used scales

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ABSTRACT

With the transformation of the medical model to a bio – psycho – social medical model, people are becoming more and more concerned about psychological and social factors in the development, prognosis and treatments of cardiovascular diseases. Some prospective studies have shown that depression/anxiety may be one of the risk factors for coronary diseases; it can accelerate the progression of the disease and may also be a risk factor for poor prognosis. However, depression/anxiety-complicated coronary diseases is rarely recognized by non-psychiatrists; therefore, these patients often fail to receive timely diagnosis and treatment and may even undergo further psychological and economic burden because of excessive examination and treatment. Identification and intervention of coronary diseases associated with depression/anxiety as early as possible is yet to be achieved. This article reviews how to identify coronary diseases patients with depression/anxiety and how the common depression/anxiety scales are used and evaluated nowadays.

Key words: Anxiety, coronary diseases, depression, medical model

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INTRODUCTION

For patients with depression/anxiety-complicated coronary diseases, their symptoms were usually quantified and evaluated by some scales in clinical assessment. Scale is a useful tool for clinical practice, teaching and scientific research, and the greatest advantage is its standardization and quantification. However, it cannot be used to replace clinical examination or to substitute the medial history and other medical records; furthermore, the symptom scales used for evaluating symptom severity cannot be used as a diagnostic tool. There are various scales that can be mainly divided into self-rating scales and others-rating scales. Currently, the most frequently used self-rating scales mainly include Hospital Anxiety and Depression Scale, Self-rating Depression Scale and Self-rating Anxiety Scale, Beck Depression Inventory and Beck Anxiety Inventory, Geriatric Depression Scale, General Anxiety Disorder Scale-7, Patient Health Questionnaire and Cardiologic Depression Scale; others-rating scales include Hamilton Rating Scale for Depression and Hamilton Rating Scale for Anxiety. The others-rating scales are generally operated by medical staff with certain professional knowledge of mental psychology, such that the applications of others-rating scales in non-psychiatric fields are limited to some extent. Therefore, self-rating scales are more widely used in non-psychiatric fields.

SELF-RATING SCALES

Hospital anxiety and depression scale (HADS)

This scale includes total scale HADS-t, anxiety subscale HADS-a and depression sub-scale HADS-d. The subscales consist of one item in each subscale; in total 14 items with each item containing four grades (0, 1, 2, 3), and the scores of subscales were calculated accordingly. The adopted critical values in individual studies are different according to the recommended criteria, the scores in subscales indicate: 0-7 scores indicating absence of manifestation;

8-10 scores indicating suspected; 11-12 scores indicating response; 12-21 scores indicating the confirmed presence of symptoms.

Strik *et al*.[1] evaluated the application value of HADS in 206 post-myocardial infarction patients by taking SCID-I as the gold standard and using ≥8 scores as the cut-off point, the sensitivity and specificity were 75% and 77.6%, respectively; positive predictive value (PPV) and negative predictive value (NPV) were 32.1% and 98.4%, respectively. Wang Xuelai[2] reported that the correlations of HADS-t and HADS-d with the clinical diagnosis were 0.723 and 0.732, the cut-off points were respectively adopted at 14 and 7, and the generated sensitivities were both 88.9%; the specificities were 85.7% and 90.5%, respectively; the PPV and NPV of these two scales were 80% and 95% *vs*. 72.7% and 94.7%, respectively; it was considered that HADS can be used for the screening of depression and anxiety in Chinese patients with coronary diseases; BDI (Beck Depression Inventory), HADS-t and HADS-d had similar validity in depression screening, but HADS-d was more sensitive for patients with mild depression compared with BDI. While in anxiety screening, Leung *et al*. thought that the total scale had higher validity than the subscales, and suggested that the total scale should be given priority for anxiety testing in the comprehensive population; this situation had also been verified in the Chinese population with coronary artery disease. Under the situation of same sensitivity (83.3%), the specificity and PPV of HADS-t and HADS-a showed significant differences (91.7% *vs*. 79.2%, 80% *vs*. 50%); thus, HADS-t was more effective than HADS-a in anxiety screening. Stafford *et al*.[3] analyzed the value of HADS in patients with percutaneous coronary intervention (PCI) or coronary artery bypass grafting, regarding depression screening; when the cut-off point was set at 5 scores, the sensitivity, specificity, PPV and NPV were 77.8%, 80.6%, 60.9% and 90.3%, respectively; when taking 8 scores as the cut-off point, the sensitivity, specificity, PPV and NPV were 38.9%, 94.2%, 72.4% and 79.9%, respectively. Soares-Filho *et al*.[4] used HADS to screen depression and anxiety situations in the chest pain unit and found a high prevalence of depression and anxiety; therefore, it was believed that the regular application of HADS screening in the chest pain unit was helpful for the differential diagnosis of chest pain and saving medical resources.

In summary, HADS is mainly used in the screening of anxiety and depression in patients at comprehensive hospitals; it is a reliable tool of good reliability and validity to discover emotional disturbance.

Self-rating depression scale (SDS) and self-rating anxiety scale (SAS)

SDS is applied for measuring the severity of depression status and its changes during treatment. The evaluation time range was the recent 1 week. The scoring method: Each item is scored in four grades, ranging from 1 to 4, mainly evaluating the frequency of occurred symptoms. Analysis index: Original score and standard score: The original score (also known as raw score) is derived by summing the individual item scores; the standard total score is derived by multiplying the raw score with 1.25, the integer part is the standard total score, it can be also transferred by table search, which is more convenient. The boundary score of SDS total raw score depression symptoms is 41 and the standard score is 53.

SAS is a considerably convenient clinical tool for analyzing patients' subjective symptoms; it is a frequently used scale in the psychological counseling clinic for understanding anxiety symptoms. The main statistical index of SAS is the total score. The raw score is derived by summing individual scores of 20 items; the standard score is derived by multiplying the raw score by 1.25, the integer part is taken as the standard score and the same transfer can be conducted by table search. According to the evaluation results of American subjects, Zung specified that the total raw score of 40 and the standard score of 50 in SAS as the critical values of anxiety symptom.

Zhang Ming[5] studied the diagnostic effect of SDS in coronary diseases, 169 patients with suspected coronary diseases with the chief compliant of chest pain and 40 healthy subjects were recruited. The results suggested that SDS accumulated scores were significantly increased in patients without high-risk factors whose ECG examination results were normal, and its detection rate of depression was higher than that of the other groups; while the detection rate of coronary diseases was lower than that of the other groups expect for healthy control group, the correlation analysis showed that there was no correlation between SDS accumulated scores and coronary diseases accumulated scores, the detection rate of depression in patients with coronary diseases was higher than that in the non-coronary artery disease group, indicating that SDS was a useful measurement in the differential diagnosis of coronary diseases, especially for ruling out of chest pain caused by depression.

Beck depression inventory (BDI) and beck anxiety inventory (BAI)

There are several versions of BDI, and the early version was a 21-item scale. However, it was found in clinical practice that some depression patients, especially the patients with severe depression, could not accomplish the 21-item assessment. Therefore, Beck developed a new version with only 13 items in 1974, which had good quality by practice, and the correlation coefficient with the 21-item version was as high as 0.96. BSI II, introduced by King-May, revised

by US Harcourt Inc. in 1996. Compared with the previous Beck Depression Inventory (BDI), the second version of the BDI had a higher validity reaching 0.92. The individual items in BDI scale were with four-grade scores ranging from 0 to 3, i.e. 0 indicated absence of this symptom, 1 indicated mild symptom, 2 indicated moderate symptom, 3 indicated severe symptom. Beck suggested that the total score can be used to determine the absence or presence of depression symptoms and its severity by BDI-13 items: 0-4 indicated essentially absence of symptom, 5-7 indicated mild symptom, 8-15 indicated moderate symptom, 16 and above indicated severe; BDI-21 items: 10-18 indicated mild to moderate symptom, 19-29 indicated moderate to severe symptom, 30-63 indicated severe symptom.

Wang Xuelai[2] analyzed and compared the validities of BDI, BAI and HADS scales in Chinese patients with coronary diseases, and found that the correlation of BAI and clinical diagnosis was not significant, indicating that it was not suitable for screening anxiety in the population with coronary artery disease. While the analysis and comparison of BDI II, BAI and HADS scales[2] showed that the correlation of BDI II, HADS-t and HADS-d were 0.669, 0.723 and 0.732, respectively, the cut-off point of 12 was adopted in BDI II and the sensitivity and specificity were found to be 88.9% and 85.7%, respectively; by comparing the areas under Receiver – Operator Curve plots, no statistically significant difference was found between BDI II and HADS-d in validity of depression screening; however, by comparing the score distribution of these two scales, HADS-d was found to be closer to normal distribution, indicating that BDI II was less sensitive than HADS-d in the screening of mild depression in patients with coronary diseases, while BDI II was more accurate and effective in the screening of severe depression. Moreover, BDI II showed a unique advantage as the incidence rate of severe depression in coronary diseases was 20%. Therefore, it was recommended that the cardiologic medical staff should pay more attention that different scales should be selected according to the patients' clinical symptoms; HADS-d was suitable for screening, while BDI was suitable for auxiliary diagnosis.

Geriatric depression Scale (GDS)

The elderly usually have many physical chief complaints, which are common during this age period; however, these physical complaints may be misdiagnosed as depression. GDS with more sensitivity was designed to detect the specific physical symptoms in elderly patients with depression. The formulary answers of "yes" and "no" in GDS were easier to be mastered than the other grading scales. Its 30 items represented the key factors of elderly depression. Ten of the 30 items were scored in reverse order (the answer of "no" indicated the presence of depression) and 20 were scored in natural order (the answer of "yes" indicated the presence of depression). Each answer indicating depression made 1 point. GDS is suitable for the elderly over 56 years old. It was a depression scale created specifically for the elderly and had been standardized; at this point, it has undeniable superiority. The following criteria can be adopted: 0-10 scores, normal; 11-20 scores, mild depression; 21-30 scores, moderate to severe depression. GDS-SF is the simplified version of GDS, developed by Yesavage and Sheikh in 1986, in which 15 items were selected from GDS. They conducted a small sample study in 1986 and found that the correlation coefficient of the scale was as high as 0.84. The general cut-off point was 6, and a score more than 10 indicated severe depression.

Low *et al*.[6] evaluated the practice of BDI and GDS in a cardiovascular monitoring center and found that when a cut-off point of ≥11 was adopted, the sensitivity, specificity, PPV and NPV of GDS was 100%, 85%, 29% and 100%, respectively. In recent years, GDS-SF has been widely used. Haworth *et al*.[7] investigated the value of GDS-SF in patients with heart failure: The sensitivity, specificity, PPV and NPV were found to be 81.8%, 83.3%, 62.1% and 93.2%, respectively, when a cut-off point of 5 was adopted. The value of cardiologic depression scale (CDS) was studied in a cardiac rehabilitation center where a total of 222 subjects in the subgroup completed GDS-SF. The results suggested a moderate to high correlation between CDS and GDS-SF, with a correlation coefficient of 0.77, higher than the correlation of CDS and BDI. The number of patients with mild to moderate depression screened from the patients with cardiovascular diseases with the two scales accounted for 17% and 18% of the total patients, respectively; however, the patients with severe depression screened by CDS was 21%, which was 7% by GDS-SF.[8] This difference was due to the fact that CDS was designed in a scoring manner of each item including 1-7 scores, while GDS was answered merely by "yes" or "no"; the former could better screen different degrees of depression.

In summary, GDS is valuable in screening depression in patients with cardiovascular disease, and is more appropriate to assess the depression degree of the elderly patients in view of the large proportion of the elderly in coronary diseases patients. For the GDS-SF developed in recent years, most related studies were conducted in the Department of Neurology and the data about patients with cardiovascular diseases were limited; therefore, further studies are needed to evaluate GDS-SF.

Patient health questionnaire (PHQ)

PHQ is a convenient, self-rating tool that has been widely used in the diagnosis of mental disorders in primary

medical units. Different from the other diagnostic tools, it was revised according to the diagnostic criteria of DSM-IV. PHQ-9 includes two parts: The first part consists of nine items, i.e. nine depression symptoms; the second part only includes one item, which is a survey about social function injury. Each item scores from 0 to 3, and, generally, 10-19 points indicate mild to moderate depression while 20 or above indicate severe depression.

Stafford[3] evaluated the PHQ-9 in screening depression in 193 patients with proposed PCI or coronary artery bypass surgery, DSM-IV was used as the gold standard for the diagnosis of depression, the cut-off point was 5, the sensitivity and specificity reached 81.5% and 80.6%, respectively and PPV and NPV were 62% and 91.8%, respectively. Recently, the Prevention Committee of American Heart Association published recommendations for screening, referral and treatment of depression-complicated coronary artery disease.[9] PHQ-2 was recommended firstly to be used for assessment. PHQ-2 includes two core symptom evaluation of depression: Whether the patient has been bothered by the following things frequently during the past 1 month: (1) hardly have interest in doing anything and (2) feel gloomy, depressed or despair. If the patients answered yes to either of the above two questions, PHQ-9 would be used as the next step to conduct further assessment. Then, different treatments should be adopted according to different scores.

Cardiologic depression Scale (CDS)

CDS, established by Hare-Davis,[10] was initially applied in Italian subjects, specially used for the survey of depression in patients with cardiovascular diseases. CDS can distinguish whether the physical symptoms were caused by cardiovascular diseases or by depression. CDS is two-dimensional, the first dimension includes sleep (two items), hesitant (six items), affection (five items), despair (three items) and reduced activity (three items); the second dimension includes anhedonia (three items) and cognition (four items). There are a total of 26 items, and each item is scored by adopting the Richter Scale 7 grades. Seven of the 26 items are reversely scored; higher score indicated a greater level of depression. When ≥95 points was adopted as the cut-off point, the sensitivity of screening severe depression was up to 100% and specificity was 81%; when taking ≥85 points as the cut-off point, the sensitivity for screening all types of depression was 97% and the specificity was 76%.

Frances *et al*.[8] studied the reliability of CDS in a population participating in a cardiac rehabilitation program, and found that CDS had a good internal consentience (Cronbach's, $\alpha = 0.92$) and was highly related to a simplified version of geriatric depression scale ($r = 0.77$, $P = 0.000$). The cut-off point of ≥90 was mainly used in the screening of mild to moderate depression (sensitivity 84%, specificity 78%), while ≥100 was used in the screening of more severe depression. Mirella *et al*.[11] compared CDS and BDI in patients with acute coronary syndrome, and the results showed a good correlation between CDS and BDI ($r = 0.69$), affirming the usefulness of these two scales in screening relatively severe depression; moreover, CDS was more valuable in screening of relatively mild or untypical depression in patients with cardiovascular problems. Wenru[12] conducted a psychometric study on the Chinese Cardiologic Depression Scale (C-CDS) in which the 26th item (i.e., whether the patient worries about his/her sexual ability) was removed according to the cultural difference. As the results suggested that C-CDS had very good internal consistency (Cronbach's, $\alpha = 0.91$) and reliability of repeated measurement ($r = 0.94$), the authors believed that C-CDS was suitable for the Chinese population suffering from cardiovascular diseases. In conclusion, CDS is valuable in the screening of both mild depression and severe depression as a scale established in a population suffering from cardiovascular disease; CDS not only has good correlations with previously widely used BDI and GDS scales but is also better than BDI in the screening of untypical mild depression.

Generalized anxiety disorder Scale-7 (GAD-7)

GAD-7 scale was established by Robert *et al*. in 2006 who selected seven of 13 items that constituted the currently widely used GAD-7 scale. The main contents includes: Whether the patients have experienced the following seven anxiety-related problems in the past 2 weeks:

1. Feeling nervous, anxious or on edge;
2. Becoming easily annoyed or irritable;
3. Feeling afraid as if something awful might happen;
4. Worrying too much about different things;
5. Being so restless that it's hard to sit still;
6. Not being able to stop or control worrying;
7. Trouble relaxing. The highest score for each question was 3.

The score of 0 means the patient does not have those symptoms at all; 1 indicates the symptoms have lasted for several days; 2, over half the days; 3, nearly every day. The authors suggested that the cut-off points of 5, 10 and 15 represent mild, moderate and severe anxiety, respectively.

Robert *et al*.[13] investigated the value of GAD-7 in 2740 adult patients by taking clinical diagnosis in the psychiatric department as the gold standard. There were mainly three conclusions: (1) GAD-7 was a very useful tool, which was very valuable for screening potential anxiety; by taking 10 as the cut-off point, the sensitivity, specificity, PPV and NPV were 89%, 82%, 29% and 99%, respectively; (2) GAD-7

had great advantages in evaluating the degree of anxiety, as it was closely related to social function injury and disability days; (3) even if many patients were with co-existence of depression and anxiety, the factor analysis confirmed that GAD-7 only had one dimension. Lowe *et al*.[14] evaluated GAD-7 in the general population; a total of 5030 subjects were enrolled and the results found that it was with good internal consistency, suggesting GAD-7 was a reliable tool for screening anxiety in the general population. Kroenke *et al*.[15] thought that GAD-7 had good sensitivity and specificity for the screening of generalized anxiety and panic disorders.

The majority of psychological health and primary healthcare personnel are too busy to comply with the strict questions required in DSM-IV standard to diagnose generalized anxiety. The GAD-7 scale is a fast, reliable and effective tool, which can diagnose the presence or absence of anxiety when the patients are only manifested with symptoms of anxiety or combined depression. However, further evaluation is needed to determine whether GAD-7 can be applied to the patients with anxiety-complicated coronary artery disease.

OTHERS-RATING SCALES

The most commonly used scales are Hamilton Rating Scale for Depression (HAMD) and Hamilton Rating Scale for Anxiety (HAMA). HAMD is the most widely used scale in clinical practice for depression status evaluation. Most of the items in its 24-item version adopt a 5-grade scoring method ranging from 0 to 4, the criteria for each grade is: 0, none;1, mild; 2, moderate; 3, severe; 4, extremely severe. A few items adopt a 3-grade scoring method ranging from 0 to 2, the criteria for each grade were: 0, none; 1, mild to moderate; 2, severe. According to Davis's cut-off score, if the total score is more than 35, the patient is possibly suffering from severe depression; if more than 20, it is possibly mild or moderate depression; less than 8 indicates absence of depression symptoms.

HAMA is one of the commonly clinically used scales in the psychiatric department that includes 14 items. All items in HAMA adopt a 5-grade scoring method ranging from 0 to 4, the criteria of each grade is as follows: 0, no symptom; 1, mild; 2, moderate; 3, severe; 4, extremely severe. According to the data provided by the National Scale Cooperation group, if the total score is more than 29, it is possibly severe anxiety; if more than 21, there must be significant anxiety; if more than 14, anxiety certainly exists; if more than 7, anxiety possibly exists; if less than 6, the patients are absent of anxiety symptoms.

Although HAMD and HAMA are the most commonly used depression/anxiety rating scales in psychiatric department, and serve as standard depression/anxiety scales, they cannot well distinguish depression from anxiety; moreover, the requirement of special training and the problem of time-consuming rating relatively limit their application in general practitioners.

Psychological scale is a very effective and important measurement for the detection of psychological disorders; however, the main psychological scales currently used in China were all introduced from abroad. Thombs *et al*. systemically retrospectively analyzed the application values of BDI and HADS scales in post-myocardial infraction patients. The authors found that the most widely used scales were BDI and HADS-d; however, most of the experimental studies were of low quality and none of these scales was absolutely superior to the others in application. Further studies are needed to weigh BDI/HADS and PHQ-9 against each other. In conclusion, the traditional scales met various challenges; more studies should be conducted focusing on the scales of PHQ-9, GDS, CDS, GAD-7 and GAI.

Depression/anxiety-complicated coronary artery disease has become a key issue of concern in the cardiovascular department; early identification and intervention of depression/anxiety complications in patients with coronary diseases is meaningful for the improvement of patients' survival and their recovery of social function. With the development of medical science and update of concepts, many physicians have recognized that the current phenomenon of "treating diseases but ignoring patients' specific needs" should be changed. The cardiovascular physicians must develop a diagnosis and treatment habit concerning the patients' psychological behaviors, and receive appropriate training of psychological skills so as to further improve the ability of recognizing psychological diseases. Consultation-liaison psychiatry (CLP), known as liaison psychiatry or general hospital psychiatry, is an important branch of clinical psychiatry. It focuses on the clinical practice, teaching and scientific researches developed in general hospitals by psychiatric physicians, explores the relationship among psychological, social factors, physical diseases and mental disorders and advocates to diagnose and treat patients from psychological, social and biomedicine aspects. It is very helpful for improving the psycho – mental technique of physicians in general hospitals and can be the tendency of further development.

REFERENCES

1. Strik J, Honig A, Lousberg R, Denollet J. Sensitivity and specificity of observer and self-report questionnaires in major and minor depression following myocardial infarction. Psychosomatics 2001;42:423-8.

2. Xue-lai W. Validity analysis and comparison of BDI, BAI and HAD scales in Chinese patients with coronary heart diseases // Hu Da-yi. Mental health training course for patients with heart disease. Beijing: People's Military Medical Press; 2006. p. 242-50.
3. Stafford L, Berk M, Jackson HJ. Validity of the Hospital Anxiety and Depression Scale and patient health questionnaire-9 to screen for depression in patients with coronary artery disease. Gen Hosp Psychiatry 2007;29:417-24.
4. Soares-Filho GL1, Freire RC, Biancha K, Pacheco T, Volschan A, Valença AM, *et al*. Use of the Hospital Anxiety and Depression Scale (HADS) in a Cardiac Emergency Room-Chest Pain Unit. Clinics 2009;64:209-14.
5. Zhang Ming. Study on the role of SDS in Diagnosing Coronary Artery Disease. Prog Mod Biomed 2006;6:43.
6. Thombs BD1, de Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, Mitchell AJ, *et al*. Depression screening and patient outcomes in cardiovascular care: A systematic review. JAMA 2008;300:2161-71.
7. Haworth JE, Moniz-Cook E, Clark AL, Wang M, Cleland JG. An evaluation of two self-report screening measures for mood in an out- patient chronic heart failure population. Int J Geriatr Psychiatry 2007;22:1147-53.
8. Frances MW. Validation of the Cardiac Depression Scale in a cardiac. J Psychosom Res 2006;60:177-83.
9. Lichtman JH, Bigger JT Jr, Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lespérance F, *et al*; American Heart Association Prevention Committee of the Council on Cardiovascular Nursing; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Epidemiology and Prevention; American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research; American Psychiatric Association. Depression and coronary heart disease. Recommendations for screening, referral and treatment: A science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: Endorsed by the American Psychiatric Association. Circulation 2008;118:1054-9.
10. Hare DL, Davis CR. Cardiac depression scale: Validation of a new depression scale for cardiac patients. J Psychosom Res 1996;40:379-86.
11. Di Benedetto M1, Lindner H, Hare DL, Kent S. Depression following acute coronary syndromes a comparison between the Cardiac Depression Scale and the Beck Depression Inventory II. J Psychosom Res 2006;60:13-20.
12. Wang W, Thompson DR, Chair SY, Hare DL. A psychometric evaluation of a Chinese version of the cardiac depression scale. J Psychosom Res 2008;65:123-9.
13. Spitzer RL1, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: The GAD-7. Arch Intern Med 2006;166:1092-7.
14. Löwe B1, Decker O, Müller S, Brähler E, Schellberg D, Herzog W, *et al*. Validation and standardization of the GAD-7 in the general population. Med Care 2008;46:266-74.
15. Skapinakis P. The 2-item Generalized Anxiety Disorder scale had high sensitivity and specificity for detecting GAD in primary care. Evid Based Med 2007;12:149.

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