

Rapid screening for generalized anxiety disorder in patients with migraine

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Keywords

Patient Health Questionnaire; Generalized Anxiety Disorder; Migraine Disorders; Sensitivity and Specificity; Cut-Off Point

Abstract

Background: Generalized anxiety disorder (GAD) often remains undiagnosed in patients with migraine, while comorbidity of GAD with migraine is associated with increased dysfunction and risk of chronic migraine. Generalized Anxiety Disorder Scale 7-item (GAD-7) and Generalized Anxiety Disorder Scale 2-item (GAD-2) are the commonly employed screening measures for generalized anxiety symptoms in different patient groups. The present study aimed to evaluate psychometric properties of the Persian version of GAD-7 and GAD-2 in migraine.

Methods: In this cross-sectional study, patients were diagnosed with migraine headaches according to the International Classification of Headache Disorders, 3rd edition (ICHD-3); then they participated in the psychiatric diagnostic interview, and filled out GAD-7, GAD-2, Beck Anxiety Inventory (BAI), Headache Impact Test-6 (HIT-6), and Migraine-Specific Quality of

Life Questionnaire version 2.1 (MSQv2.1). The psychometric properties of GAD-7 and GAD-2 were examined using SPSS and LISREL.

Results: Final samples were 186 patients with migraine that 83 patients received a diagnosis of GAD. Confirmatory factor analysis (CFA) indicated that the one-factor model of GAD-7 fit the data well. Internal consistency, test-retest, and Guttman split-half reliability of GAD-7 and GAD-2 were good. Significant correlation results, average variance extracted (AVE), and composite reliability (CR) supported the construct validity of the GAD-7. A score of ≥ 10 in GAD-7 and ≥ 3 in GAD-2 achieved satisfactory sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) (GAD-7: 92%, 90%, 88%, and 93%, respectively; GAD-2: 79%, 88%, 71%, and 91%, respectively).

Conclusion: Our findings supported GAD-7 and GAD-2 for assessing GAD in patients with migraine. It seems that GAD-7 and GAD-2 accurately diagnosed GAD in this group of patients.

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Introduction

Headache is one of the frequent pain complaints with high level of dysfunction. International Headache Society divided headache into primary and secondary.¹ Migraine as a primary headache is a neurological disorder that causes excessive pain.² Besides, migraine is one of the most ten prevalent diseases and one of the five leading causes of Years Lived with Disability (YLD); it causes approximately 16.3% of worldwide disability-adjusted life-years (DALYs) across the neurological population.^{3,4} Global Burden of Disease (GBD) 2016 study has considered migraine as an essential medical issue in all ages, especially at the age of 15 to 59 years. It has reported that the majority of migraine sufferers are women.^{5,6} Migraine results in impairment in function and life quality.^{7,8}

The severity of migraine headaches and comorbid conditions are linked together, so that patients with migraine with more headaches and higher levels of pain are more likely to have comorbid conditions such as psychiatric disorders.⁹⁻¹³ On the other side, comorbid conditions contribute to the chronicity of the migraine.¹⁴ The strong association between migraine headaches and anxiety disorders such as generalized anxiety disorder (GAD) has been observed.^{15,16}

From the other side, GAD is one of the most common types of anxiety disorders in the general population, psychiatric clinics, and primary care.¹⁷⁻²⁷ GAD frequently co-occurs with psychiatric disorders or medical conditions,²⁸ but it may be misdiagnosed²⁹⁻³¹ and because of some of the physical symptoms such as irritability and agitation, it is difficult to be recognized.³²⁻³⁴ Some symptoms of anxiety are observed in migraine, and migraine symptoms can also be seen in anxiety.¹⁰

GAD can mainly impact health-related quality of life (HRQOL) and cause impairment in many areas of functioning.³⁵⁻³⁷ These effects are more significant than effects of major depression on quality of life (QOL).³⁷ But, the co-occurrence of migraine and psychiatric disorders such as anxiety disorders leads to marked reduced QOL, more health impairment, and challenges for disease management¹² that affect therapeutic plan and treatment pathway of migraine.¹⁰

Some guidelines suggest the utilization of standardized scales to screen anxiety disorders and to assess treatment.³⁸ Conducting structured interviews is more expensive in terms of time, money, and required training.^{39,40} Generalized Anxiety Disorder Scale 7-item (GAD-7) was

developed for screening, possible detection, and severity of GAD. The sensitivity and specificity of the GAD-7 were 0.89 and 0.82, respectively, in primary care settings (cut-off point: 10). Furthermore, GAD-7 is brief, time-saving, self-administrated according to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria,⁴¹ and sensitive to clinical improvement;⁴² therefore, it is well qualified for clinical and research purposes.⁴¹

A meta-analysis supported GAD-7 psychometric properties in the adult population.⁴³ In addition, the American Psychological Association (APA) suggested GAD-7 as one of the tools for assessing GAD intensity.⁴⁴ Studies proved the suitability of GAD-7 and GAD-2 for use in non-clinical populations⁴⁵⁻⁵¹ and several clinical populations.⁵²⁻⁶⁵ Acceptable psychometric properties of GAD-7 and GAD-2 were reported in different languages^{45,49,66-71} and versions.^{72,73}

The Korean version of GAD-7 and GAD-2 has been studied in migraine, but the clinical sample was small (n = 32); factor structure, composite reliability (CR), and average variance extracted (AVE) have not been analyzed;⁵⁷ furthermore, cross-cultural bias of GAD-7 and possible subtypes of GAD⁷⁴ were discussed; thus, GAD-7 and GAD-2 should be studied in the context of culture and specific patient groups. The Persian version of GAD has been investigated in a small sample of patients with GAD (n = 24) who did not have a comorbid migraine, and the diagnostic validity of GAD-7 was not studied,⁷⁵ while it is influenced by clinical problems;⁴³ therefore, the present study aimed to investigate the psychometric properties of GAD-7 and GAD-2 as screening tools in a sample of patients with migraine.

Materials and Methods

Study participants: Based on Meyers et al.,⁷⁶ 150 participants were needed; with 20% drop, 188 participants were recruited from the headache clinic of university hospitals and headache specialty centers in Tehran, Iran, by convenience sampling method. They agreed to contribute in the research and gave written informed consent to participate in the study. Finally, 2 cases dropped and 186 participants were analyzed anonymously. Inclusion criteria were as follows: (a) age of at least 18 years, (b) the diagnosis of migraine based on the International Classification of Headache Disorders, 3rd edition (ICHD-3), (c) ability to write and read in Persian, (d) not receiving any

anti-anxiety medications and psychotherapy. Participants who met these criteria were excluded: (a) inability to participate in the interview, (b) inability to perceive self-completion questionnaire due to medical condition, (c) mental defectiveness, (d) or receiving medical treatment that impairs comprehension of the questionnaire.

Procedure: Ethical committee permission was obtained, then sampling was done from August 2019 to February 2020. Relevant study information was provided to the participants. Psychiatric diagnostic interviews [Structured Clinical Interview for DSM-5 (SCID-5)] were conducted with those who received diagnosis of migraine by the professor of neurology according to ICHD-3 criteria, and were interested in participating in the study. Participants filled out the questionnaires privately in the interview room. Psychiatric diagnostic interview was administrated by a trained clinician (PhD candidate in clinical psychology) who answered the participants' questions too. The evaluation tools included GAD-7, Generalized Anxiety Disorder Scale 2-item (GAD-2), Beck Anxiety Inventory (BAI), Headache Impact Test-6 (HIT-6), and Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQv2.1). Retesting of GAD-7 and GAD-2 was performed after 3 weeks. The ethical committee approval number is IR.IUMS.REC.1398.784.

Measurements

SCID-5: SCID-5 is a structured diagnostic interview that evaluates psychiatric disorders based on DSM-5 criteria. It contains different common categories of psychiatric disorders, separately. The Persian version of SCID-5 was validated.⁷⁷

GAD-7: GAD-7 as a valid screening tool could be used for clinical practice and research goals. This measure consists of 7 items that examine GAD symptoms and their severity. Participants rated their level of agreement with the statements using a 4-point scale (0 = not at all, 1 = several days, 2 = more than half of the days, 3 = nearly every day). The score range is 0-27; the higher GAD-7 score, the greater symptom severity.⁴¹ The reliability and validity of the Persian version of GAD-7 were supported in 199 students and 24 patients with GAD, but the cut-off point was not studied.⁷⁵

GAD-2: This scale consists of 2 questions. This short form of GAD-7 is scored from 0 to 6. Area under curve (AUC) of GAD-2 has been reported from 0.80 to 0.91 for anxiety disorders.³⁰ The psychometric properties of the Persian version of GAD-2 have not been investigated.

BAI: BAI is a 21-item questionnaire that assesses anxiety symptoms (for example, fear of the worst happening and losing control, inability to relax, nervousness, ...). Each statement is scored from 0 (not at all) to 3 (severely - it bothered me a lot). Final score ranges from 0 to 63. Higher scores reflect more severe anxiety.⁷⁸ Levels of anxiety are categorized into normal, mild, moderate, and severe. The validity and reliability of the Persian version of BAI were confirmed.⁷⁹

HIT-6: HIT-6 consists of 6 Likert-type items. Items focus on impaired function in the job, school, home, and social situation due to headaches. HIT-6 includes various areas such as social, occupational, and intellectual functioning, day job, the severity of pain, and psychological problems. Patients answered to the sentences on a 5-point scale (6 = never, 8 = rarely, 10 = sometimes, 11 = very often, 13 = always). Total scores are 36 to 78 points with higher scores indicating significant influence. It has been shown that HIT-6 is reliable, valid, and sensitive to change.⁸⁰ The Persian version of the HIT-6 was validated in a sample of patients with migraine and tension-type headache.⁸¹

MSQv2.1: The MSQv2.1 examines the impact of migraine on sufferers' activities. This 14-item tool is composed of 3 subscales: role restrictive (RR, seven items), role preventive (RP, four items), and emotion function (EF, three items). The statements are scored from 1 (none of the time) to 6 (all of the time), then were reversed and standardized 0 to 100. Higher scores reflect better QOL. The validity and reliability of MSQv2.1 have been investigated and approved.⁸² MSQv2.1 showed good reliability and validity in the Persian-speaking people.

In this cross-sectional study, test-retest reliability of GAD-7 and GAD-2 was measured with an interval of 3 weeks by using correlation and interclass correlation coefficient (ICC), and Cronbach's alpha was used to assess internal consistency. To check the construct validity of GAD-7, confirmatory factor analysis (CFA) was performed. CR and AVE were computed using LISREL output. The correlation between GAD-7, GAD-2, and BAI as well-established tests was examined for concurrent validity. As criterion concurrent validity, the relation between MSQv2.1, HIT-6, GAD-7, and GAD-2 was computed to investigate whether higher scores in GAD-7 and GAD-2 were related to more significant function and migraine-specific QOL impairments or not. Independent samples t-test was administrated to compare GAD-7 and GAD-2 scores in patients

with migraine with and without GAD diagnosis based on SCID-5. Convergent, concurrent, concurrent criterion, and discriminant validity were checked as construct validity.⁸⁴ The accuracy and ability of GAD-7 and GAD-2 to differentiate GAD-positive and negative patients were analyzed using receiver operating characteristic (ROC) curve. Sensitivity, specificity, and predictive power were calculated as diagnostic accuracy estimates of these scales.

All statistical analyses except for the CFA were conducted using SPSS software (version 21, IBM Corporation, Armonk, NY, USA). CFA was performed using LISREL.

Results

The final samples were 186 patients with migraine: 55 men (30%) and 131 women (70%), 49 of whom were asked to complete GAD-7 and GAD-2 again after three weeks. The average age of the participants was 37 ± 9 years. Most patients were married (n = 130, 69%) and unemployed (n = 97, 52%). The level of education of the completers ranged from high school education (n = 67, 36%) to PhD (n = 11, 5.9%); the most common level of education was university graduate (n = 79, 42%). 44% (n = 83) of patients with migraine fulfilled the criteria of DSM-5 for GAD according to diagnostic interview (SCID-5). The participants with GAD and migraine compared to participants with migraine demonstrated higher anxiety level obtained with BAI [GAD-7: t(182) = -15.00, P < 0.001; GAD-2: t(182) = -15.27, P < 0.001], higher HIT-6 scores [GAD-7: t(180) = -5.00, P < 0.001; GAD-2: t(180) = -5.46, P < 0.001], and lower QOL when using the MSQv2.1 score [GAD-7: t(184) = 7.00, P < 0.001; GAD-2: t(184) = 8.63, P < 0.001].

Reliability: The results demonstrated that GAD-7 and GAD-2 possessed high internal consistency based on the approval threshold.⁸⁵ Additionally, Guttman split-half reliability and test-retest reliability after 3 weeks by using correlation and ICC have also been found to be satisfactory (Tables 1 and 2).

Construct validity: CFA was used to check the

unidimensionality of GAD-7 (Table 3, Figure 1). The results showed that the model fit values were good [χ^2 (14) = 40.07, P = 0.0002, root mean square error of approximation (RMSEA) = 0.100, comparative fit index (CFI) = 0.97, goodness of fit index (GFI) = 0.94, adjusted GFI (AGFI) = 0.88]. This one-factor model had 7 items, with factor loadings ranging from 0.64 to 0.80.

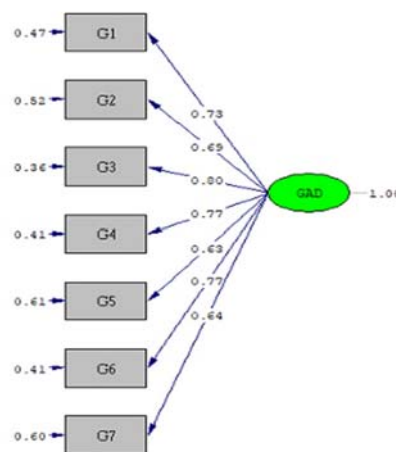


Figure 1. One-factor model of the Generalized Anxiety Disorder Scale 7-item (GAD-7)

AVE derived from CFA results was identified as one of the convergent validity indexes, that measures the construct's amount of variance in proportion to the variance of measurement error. In this study, AVE index was desirably accordant with the conventional threshold⁸⁴ (AVE = 0.51). CR was also called construct reliability;⁸⁴ values of 0.7 and above were introduced as a high degree of CR.⁸⁶ The results showed that CR was 0.88, indicating that all of the items represent a hidden structure.

The correlation between GAD-7, GAD-2, and BAI was significant (n = 186, P < 0.001). Increase in GAD-7 and GAD-2 scores was correlated with an increase in BAI scores, that shows strong concurrent validity. The relationship between GAD-7, GAD-2, MSQv2.1, and HIT-6 as the concurrent criterion validity was also significant.

Table 1. Reliability of Generalized Anxiety Disorder Scale 7-item (GAD-7) and Generalized Anxiety Disorder Scale 2-item (GAD-2) (n = 186)

	Internal consistency	Guttman reliability	Test-retest reliability	ICC
GAD-7	0.87	0.85	0.66*	0.79*
GAD-2	0.62	0.62	0.60*	0.65*

*P < 0.001

GAD-7: Generalized Anxiety Disorder Scale 7-item; GAD-2: Generalized Anxiety Disorder Scale 2-item; ICC: Interclass correlation coefficient

Table 2. Item-total statistics of Generalized Anxiety Disorder Scale 7-item (GAD-7) (n = 186)

Item	Scale mean if item deleted	Scale variance if item deleted	Corrected item-total correlation	Cronbach's alpha if item deleted
1	8.08	26.66	0.67	0.86
2	8.53	25.31	0.63	0.86
3	8.00	25.15	0.75	0.85
4	8.58	25.04	0.70	0.85
5	9.22	27.65	0.60	0.86
6	8.40	24.72	0.70	0.85
7	8.56	25.67	0.58	0.87

Table 3. Factor loadings of the Generalized Anxiety Disorder Scale 7-item (GAD-7) items in the one-dimensional model (n = 186)

Item	Unstandardized	Standardized	T-value
1	0.73	0.73	11.06*
2	0.69	0.69	10.28*
3	0.80	0.80	12.52*
4	0.77	0.77	11.84*
5	0.63	0.63	9.06*
6	0.77	0.77	11.84*
7	0.64	0.64	9.21*

*P < 0.001

GAD-7 and GAD-2 scores were significantly and negatively correlated with MSQv2.1, reflecting that the higher the GAD-7 and GAD-2 scores, the poorer the QOL (P < 0.001). Furthermore, higher GAD-7 and GAD-2 values were associated with more significant functional impairment and higher rates of psychological distress due to headache (P < 0.001) (Table 4).

To evaluate discriminant validity, an independent samples t-test was conducted to compare mean GAD-7 and GAD-2 scores in patients with migraine with and without GAD (Table 4). The significant difference was observed between patients with migraine with and without GAD conditions [GAD-7: $t(184) = -18.55, P = 0.01$; GAD-2: $t(184) = -13.82, P = 0.001$]. The results indicated that the co-occurrence of GAD and migraine could result in increase in GAD-7 and GAD-2 scores.

Sensitivity and specificity: To test the diagnostic accuracy of GAD-7 and GAD-2 for

detecting patients with GAD, ROC curve analysis was done. Diagnosis of GAD based on SCID-5 was considered as the gold standard (state variable).

The area under the ROC curve indicates that the correct differentiation of the diseased group from non-diseased group was functional and highly accurate in GAD-7 and GAD-2 (0.96 and 0.90, respectively).⁸⁷ These values were exceedingly near 1, which means that GAD-7 and GAD-2 were highly accurate screening measures based on proposed values.^{87,88} Besides, the nearer ROC curve to the top left corner is, the better the measure will be. Figures 2 and 3 met this design criterion.

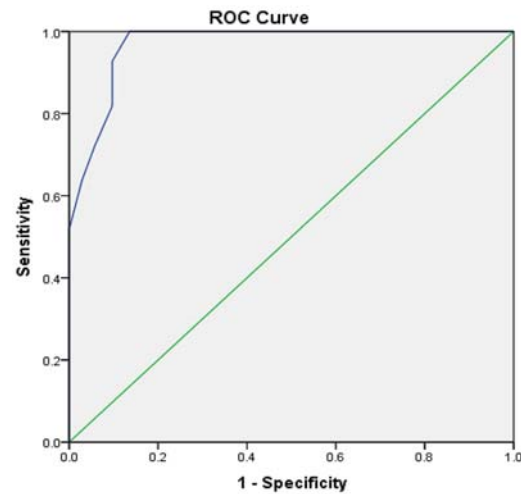


Figure 2. Receiver operating characteristic (ROC) curve of Generalized Anxiety Disorder Scale 7-item (GAD-7)

Table 4. Construct validity of Generalized Anxiety Disorder Scale 7-item (GAD-7) and Generalized Anxiety Disorder Scale 2-item (GAD-2) (n = 186)

	Convergent validity		Concurrent validity	Concurrent criterion validity		Discriminant validity
	CR	AVE	BAI	MSQv2.1	HIT-6	T-test
GAD-7	0.88	0.51	0.79**	-0.66**	0.40**	-18.55*
GAD-2	-	-	0.67**	-0.59**	0.39**	-13.82**

*P < 0.01; **P < 0.001

GAD-7: Generalized Anxiety Disorder Scale 7-item; GAD-2: Generalized Anxiety Disorder Scale 2-item; BAI: Beck Anxiety Inventory; MSQv2.1: Migraine-Specific Quality of Life version 2.1; HIT-6: Headache Impact Test-6; CR: Composite reliability; AVE: Average variance extracted

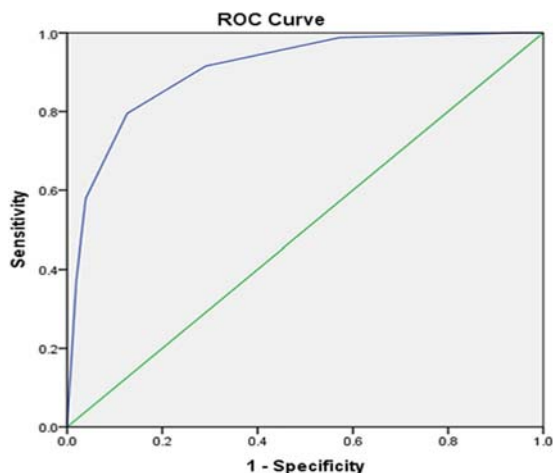


Figure 3. Receiver operating characteristic (ROC) curve of Generalized Anxiety Disorder Scale 2-item (GAD-2)

A series of sensitivity/specificity pairs in proportion to the entire range of cut-off points was produced by ROC curve; best cut-off points of GAD-7 and GAD-2 according to an optimal balance between sensitivity and specificity were 10 and 3, respectively. The sensitivity estimates the positive cases that are properly detected and the specificity estimates the negative cases that are properly detected. In other words, 92% and 79% of migraine patients with GAD would be recognized positive by GAD-7 and GAD-2, respectively, and 90% and 88% of migraine patients without GAD would be recognized as negative by GAD-7 and GAD-2, respectively. Positive predictive value (PPV) and negative predictive value (NPV) of GAD-7 and GAD-2 were good (Table 5). PPV indicates the likelihood that people will be positively diagnosed with a screening tool when they actually have the disease. NPV indicates the likelihood that people will be negatively diagnosed with a screening tool when they actually do not have the disease.

Discussion

Psychiatric comorbidity including GAD with migraine is associated with poor prognosis, greater disability, less satisfaction with drug treatment, and increased frequency of headache;^{89,90} which is a risk

factor for chronicity of migraine¹⁴ and medication overuse headache;⁹¹ therefore, psychiatric comorbidity in migraine must be considered. Thus, the scales should be studied in the context of culture and groups of patients, and the self-report questionnaires are cost-effective, so the present study supports the psychometric properties of Persian version of GAD-7 and GAD-2 in migraine.

Our finding showed that GAD-7 and GAD-2 were valid and reliable measures for detecting GAD in patients with migraine. Satisfactory consistency over three weeks, internal consistency, and split-half reliability of GAD-7 and GAD-2 were confirmed; Cronbach's alpha value of GAD-7 is similar to another study in patients with migraine,⁵⁷ patients with epilepsy,^{52,53} psychiatric patients,^{63,92} and patients with chronic obstructive pulmonary disease (COPD).⁵⁶ Internal consistency of GAD-2 was similar to other researches.^{57,68}

One-dimensionality hypothesis of GAD-7 was evaluated by CFA or exploratory factor analysis (EFA) method in different studies. The CFA finding demonstrated that all seven items of GAD-7 had robust loadings to the general factor. Our finding is in line with the previous studies that showed that one-factor model of GAD-7 could fit the data well;^{31,71} in some studies, the modified one-factor model was accepted.^{63,74} Other studies claimed that the two-factor structure was better.^{65,93}

Concurrent validity of GAD-7 in patients with migraine was supported by strong positive correlation with BAI ($r = 0.79$); this finding is comparable to another study in migraine population ($r = 0.75$),⁵⁷ original study ($r = 0.72$),⁴¹ a study in heterogeneous psychiatric sample ($r = 0.69$),⁶³ and Korean version of study ($r = 0.78$).⁶⁸

The present finding of correlation between GAD-2 and BAI ($r = 0.67$) was in line with the Korean version of GAD-2 in patients with migraine⁵⁷ and in nonclinical and psychiatric samples.⁶⁸

In our sample, the t-test analysis indicated that the means of GAD-7 and GAD-2 were significantly different in patients with and without GAD; this statistical evidence proved discriminant validity. In some samples, GAD-7 discriminated between GAD and control groups too.^{63,65,68,71,92}

Table 5. Operational characteristic of Generalized Anxiety Disorder Scale 7-item (GAD-7) and Generalized Anxiety Disorder Scale 2-item (GAD-2) (n = 186)

	Cut-off point	Sensitivity	Specificity	PPV	NPV
GAD-7	≥ 10	0.92	0.90	0.88	0.93
GAD-2	≥ 3	0.79	0.88	0.71	0.91

GAD-7: Generalized Anxiety Disorder Scale 7-item; GAD-2: Generalized Anxiety Disorder Scale 2-item; PPV: Positive predictive value; NPV: Negative predictive value

In line with the previous study,⁵⁷ GAD severity by GAD-7 and GAD-2 was negatively associated with QOL in patients with migraine and positively associated with headache intensity. As expected, the severity of general anxiety was related to impaired function and QOL in patients with migraine, that supports criterion concurrent validity.

CR and AVE which were calculated using factor loadings in CFA confirmed the internal consistency of the GAD-7 construct. Both values were above advocated thresholds⁸⁴ and acceptable. To our knowledge, compared to previous studies, these indexes present new evidence of construct validity.

Similar to the original study findings⁴¹ and some studies in different patient groups,^{64,66,70,71,92} the best possible sensitivity (0.92), specificity (0.90), and cut-off point ≥ 10 were suggested in GAD-7, but these findings are not in line with the Korean version in migraine.⁵⁷ Cut-off point ≥ 3 suggested in GAD-2 is in line with other samples in some studies,^{21,54,68} but the cut point of Korean version in migraine was 7,⁵⁷ and this value is 4 in web-based version of GAD-2.⁷²

Therefore, clinicians could use the GAD-7 and GAD-2 as cost-effective measures for rapid screening of GAD in patients with migraine. According to GAD-7, patients with migraine who received GAD diagnosis and truly had GAD (sensitivity), were recognized better than patients with migraine who did not receive GAD diagnosis and did not truly have GAD (specificity).

The less studied assessment of the construct validity of GAD-7 (CR and AVE) and administrating diagnostic interviews (SCID) by the trained clinician are the strengths of the present study. Besides, to our knowledge, the psychometric properties of the Persian version of

GAD-2 and diagnostic validity of the Persian version of GAD-7 were studied for the first time.

The findings of this research should be given in view of the following limitation. The ability of GAD-7 and GAD-2 to precisely measure changes caused by the intervention in patients with migraine was not evaluated, while the responsiveness of the questionnaire is so helpful for clinical studies. The present findings may not apply to different kinds of headaches.

Conclusion

GAD-7 as a measure should be used primarily in the context of culture due to cultural bias and in specific groups, because its diagnostic accuracy is influenced by clinical problems, so our study focused on patients with migraine. Generally, our finding confirmed that this measure could detect GAD rapidly and relatively correct in patients with migraine, and the Persian version of GAD-7 and GAD-2 has yielded good results in this sample. For quick screening, GAD-7 and GAD-2 were supported in patients with migraine, but the diagnostic interview is suggested for important screening and intervention.

Conflict of Interests

The authors declare no conflict of interest in this study.

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