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PAPER

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The Generalized Anxiety Disorder Screener (GAD-7) and the anxiety module of the Hospital and Depression Scale (HADS-A) as screening tools for generalized anxiety disorder among cancer patients

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Abstract

Objective: Anxiety in cancer patients may represent a normal psychological reaction. To detect patients with pathological levels, appropriate screeners with established cut-offs are needed. Given that previous research is sparse, we investigated the diagnostic accuracy of 2 frequently used screening tools in detecting generalized anxiety disorder (GAD).

Methods: We used data of a multicenter study including 2141 cancer patients. Diagnostic accuracy was investigated for the Generalized Anxiety Disorder Screener (GAD-7) and the anxiety module of the Hospital Anxiety and Depression Scale (HADS-A). GAD, assessed with the Composite International Diagnostic Interview for Oncology, served as a reference standard. Overall accuracy was measured with the area under the receiver operating characteristics curve (AUC). The AUC of the 2 screeners were statistically compared. We also calculated accuracy measures for selected cut-offs.

Results: Diagnostic accuracy could be interpreted as adequate for both screeners, with an identical AUC of .81 (95% CI: .79-.82). Consequently, the 2 screeners did not differ in their performance (P = .86). The best balance between sensitivity and specificity was found for cut-offs ≥7 (GAD-7) and ≥8 (HADS-A). The officially recommended thresholds for the GAD-7 (≥ 10) and the HADS-A (≥11) showed low sensitivities of 55% and 48%, respectively.

Conclusions: The GAD-7 and HADS-A showed AUC of adequate diagnostic accuracy and hence are applicable for GAD screening in cancer patients. Nevertheless, the choice of optimal cut-offs should be carefully evaluated.

KEYWORDS

cancer, generalized anxiety disorder, medical psychology, oncology, ROC curve, sensitivity and specificity

1 | BACKGROUND

Given the real threats of malignant diseases, cancer-related anxiety is understandable and may be even considered a normal psychological reaction.[1,2] In some patients, however, anxiety rises to a disproportionately high level, does not resolve, and leads to functional impairments. In such cases, the diagnosis of an anxiety disorder may be justified.[2,3]

Anxiety disorders in somatic patients may lead to higher symptom burden, worse treatment adherence, and poorer health outcomes.[4] Nevertheless, many patients with pathological anxiety in the medical setting remain undetected.[4] Given the availability of effective treatment methods,[5] screening for anxiety disorders in oncological settings seems warranted: Although a recent randomized controlled trial on screening for emotional distress among cancer patients did not find a direct improvement in well-being, screening led to improved referral to psychiatric/psychological care.[6]

Within the anxiety disorders, generalized anxiety disorder (GAD) may be of special interest. The risk of GAD may be heightened after a severe life stressor such as cancer,[2] and the GAD symptomatology including extensive worries about the future may be particularly deteriorated by realistic fears about progression or recurrence of the disease. Other reasons to screen for GAD in cancer patients include its relatively high prevalence and comorbidity with other affective disorders.[3]

Nevertheless, research on the diagnostic accuracy of screeners to detect GAD in oncological settings is limited. Although the American Society for Clinical Oncology recommends the Generalized Anxiety Disorder Screener (GAD-7)[7] with a cut-off ≥10 indicating the need for intervention,[3] no study has tested this cut-off in cancer patients so far. Furthermore, a recent meta-analysis pointed to a considerably lower cut-off (≥8).[8] Another frequently used questionnaire is the anxiety module of the Hospital Anxiety and Depression Scale (HADS-A).[9] To our knowledge, however, only 1 previous study investigated its diagnostic accuracy in detecting GAD among cancer patients, in which the commonly used threshold (≥11) was not considered appropriate.[10]

To enhance applicability of both screeners in oncological settings, we here present a representative sample of 2141 cancer patients to determine the diagnostic accuracy of the GAD-7 and HADS-A in detecting GAD in comparison with a standardized diagnostic interview.

2 | METHODS

2.1 | Sample and procedure

Data were assessed within an epidemiological study comprising 5 centers (Hamburg, Freiburg, Heidelberg, Leipzig, Würzburg) conducted to provide prevalence rates of mental disorders in a representative sample of cancer patients.[11]

Data collection took place between July 2008 and November 2010. Patients were eligible if they were (1) diagnosed with a malignant tumor, (2) between 18 and 75 years old, (3) able to speak and read the German language, and (4) able to give informed consent for study participation.

Eligible patients were consecutively approached by study research assistants. At first, participants filled in the PHQ-9[12] to measure their level of emotional distress. Then, they were given a set of questionnaires including the GAD-7 and the HADS. A subsample of the participants was additionally assessed with the diagnostic interview. Thereby, the interview participants were selected according to their level of emotional distress (PHQ-9 sum score). This 2-stage approach has been shown to be valid in previous research.[13] In detail, all patients with a PHQ-9 sum score ≥9 were assigned to the interview (Figure 1, modified from Hartung et al[14]), but only a random sample of those with a PHQ-9 sum score <9. This different sampling probability was later compensated by weighting. The interviews were conducted within the first weeks after study inclusion. Interviewers were blind to the results of the screeners.

The study was performed in accordance with the Declaration of Helsinki and approved by all local ethics committees (file numbers—Hamburg: 2768; Schleswig-Holstein: 61/09; Freiburg: 244/07; Heidelberg: S-228/2007-50155039; Würzburg: 107/07; Leipzig: 200-2007). Prior to participation, all patients provided written informed consent. Further study details are reported elsewhere.[15]

2.2 | Measures

2.2.1 | Sociodemographic and medical information

Sex and age were assessed via self-report. Clinical data (see Table 1) was obtained from the medical records.

2.2.2 | Index tests (screeners)

The GAD-7 contains 7 items assessing core symptoms of GAD.[7,16] Patients rate their frequency of symptoms within the last 2 weeks on a 4-point scale ranging from "not at all" to "almost every day." Scores can take values from 0 to 21, with higher scores indicating higher GAD symptomatology.

The HADS-A is the anxiety module of the Hospital Anxiety and Depression Scale (HADS)[9,17] and contains 7 items assessing anxious symptomatology on a 4-point scale ranging from "not at all" to "most of the time." Scores range between 0 and 21, with higher scores indicating higher symptomatology.

2.2.3 | Reference standard

Diagnoses were made by using the Composite International Diagnostic Interview for Oncology (CIDI-O), a standardized interview for cancer patients assessing mental disorders based on DSM-IV and ICD-10 criteria.[18] For our purpose, we used the 4-week prevalence rates of GAD. Even though the CIDI-O has not been psychometrically tested so far, the assessment of GAD does not differ from the standard CIDI, which showed high objectivity and interrater-reliability.[18,19] Standardization was verified via extensive interviewer training and regular checks of the conducted interviews by an experienced CIDI-O editor.[19]

2.3 | Statistical analyses

We compared participants (ie, all patients with full PHQ-9 data; see Figure 1) with nonparticipants as well as interview completers with

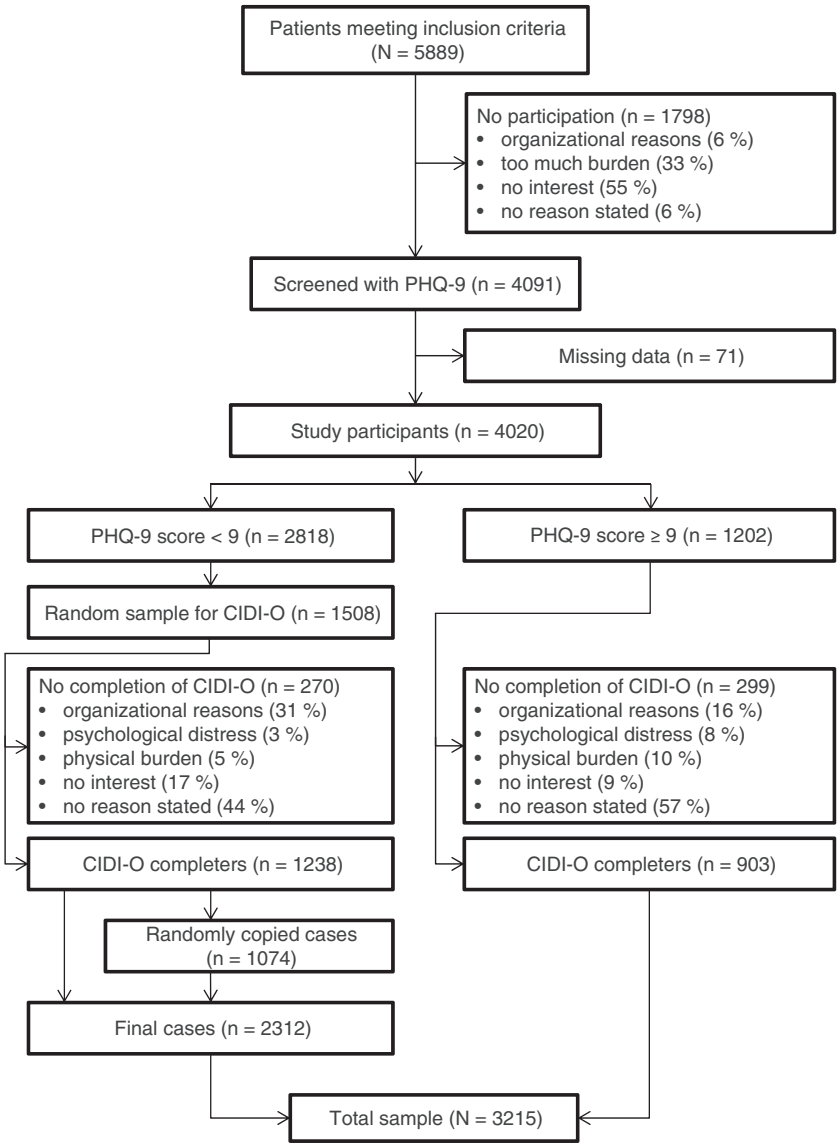

FIGURE 1 Flowchart illustrating the steps leading to the final sample composition (reproduced by kind permission of Wiley from Hartung et al[14])

noncompleters in age, sex, education, treatment setting, study center, and tumor entity via multiple logistic regression models.

Using raw data of the interview participants, ie, after listwise deletion of all cases with at least 1 GAD-7 or HADS-A sum score missing (N = 1961), we calculated the severity of the screeners by diagnosis of the CIDI-O (noncase vs subclinical vs definite). The mean time between questionnaires and the interview was calculated among 1771 patients: this group included all patients with available dates of both assessments and excluded patients with dates containing obvious entry errors or implausibly long time delays between assessments (>100 d). Patients with subclinical GAD (n = 24) were rated as noncases.

Since only a subgroup of participants with a PHQ-9 score <9 was assigned to the interview (Figure 1), the sample was biased. Because measures of diagnostic accuracy need real data to be calculated, we could not include a simple weighting factor to compensate for this disproportion. We therefore weighted the data by the following procedure: We first calculated the ratio of those with a PHQ-9 score < 9 who had been excluded to those with a PHQ-9 score < 9 who had been selected for the interview (1310/1508 = 0.87). We then used this ratio as the weight to randomly select patients from the 1238 with a PHQ-9 score < 9 who completed the interview (n = 1074). Finally, we copied and added this random selection to the original cases with CIDI-O data (n = 2141), leading to the final sample of N = 3215.

In total, 180 interview completers had at least 1 sum score (GAD-7 or HADS-A) missing. Missing sum scores (both 8%) were imputed via the expectation maximization method (EM).[20] In detail, missing values were imputed via maximum likelihood estimation, based on the respective distribution of the observed questionnaire data conditional to the CIDI-O diagnoses of GAD, AAD, and any mental disorder. The application of EM was appropriate given that missing values were not related to the variables used for the imputation process (Little Test: $\chi^2 = 8.13$, df = 11, $P = .70$). All imputed scores were rounded to integers.

Internal consistency of both scales was assessed via Cronbach's alpha.

For each of the screeners, we assessed diagnostic accuracy at selected cut-offs via (1) *sensitivity* (SEN) as the probability of a positive screening result in patients with GAD, (2) *specificity* (SPE) as the probability of a negative screening result in patients without GAD, (3) *positive predictive value* (PPV) as the probability that patients with a positive screening result have GAD, and (4) *negative predictive value* (NPV) as

TABLE 1 Patient characteristics for the 2141 completers of the CIDI-O

	N (%)
Sex, women	1103 (52)
Age, y (M, SD)	58 (11)
Time since current diagnosis, mo (M, SD)[a]	14 (25)
Tumor entity (ICD-10)	
Breast (C50)	442 (21)
Prostate (C61)	318 (15)
Colon/rectum (C17-21)	293 (14)
Lung (C34)	189 (9)
Female genital organs (C51-57)	183 (9)
Hematological (C81-C96. D46-47. D60)	172 (8)
Stomach/esophagus (C15-16)	86 (4)
Kidney/urinary tract (C64-66)	74 (4)
Head and neck (C02-14. C31-32)	69 (3)
Bladder (C67)	54 (3)
Pancreas (C25)	52 (2)
Skin (C43-44)	39 (2)
Soft tissue (C45-49)	38 (2)
Brain (C71)	36 (2)
Hepatobiliary (C22-23)	26 (1)
Testis (C62)	22 (1)
Thyroid (C73)	14 (1)
Others[b]	34 (2)
Tumor stage (UICC TNM)[a]	
I	280 (20)
II	372 (26)
III	292 (21)
IV	480 (34)
Current disease status[a]	
In remission	829 (40)
Not in remission	1262 (60)
Treatment intention[a]	
Curative	1278 (60)
Palliative	502 (23)
Current or completed treatment[a]	
Surgery	1537 (74)
Radiation	930 (45)
Chemotherapy	1123 (54)
Hormone therapy	222 (11)
Others	179 (9)
Treatment setting	
Inpatients	932 (44)
Outpatients	640 (30)
Rehabilitation	569 (27)
ECOG performance status[a]	
0: Asymptomatic	986 (47)
1: Symptomatic, but completely ambulatory	757 36)
2: Symptomatic, <50% in bed during the day	260 (13)
3: Symptomatic, >50% in bed, but not bedbound	76 (4)
4: Bedbound	3 (<1)

Abbreviations: CIDI-O, Composite International Diagnostic Interview for Oncology; UICC, International Union Against Cancer; ECOG, Eastern Cooperative Oncology Group.

[a]Fewer cases due to missing data.

[b]Including bone (C40-41; n = 9) and thymus (C37, n = 4).

the probability that patients with a negative screening result do not have GAD. Additionally, we calculated the *Youden Index* (YI)[21] that takes equally into account SEN and SPE: a value of 0 indicates the same proportion of positive tests in cases and noncases, a value of 1 indicates no false classification.

For each of the screeners, overall diagnostic performance was assessed via *receiver operating characteristics (ROC) curve analyses*. The curves are created by plotting SEN against SPE—1 for each threshold. The area under the ROC curve (AUC) provides the probability that a randomly selected GAD case scores higher on the screener than a randomly selected noncase.[22]

We compared the AUC of both screeners using a nonparametric approach.[23]

We performed sensitivity analyses to assess the impact on AUC and maximum YI by the following factors: data preparation (raw data vs weighting and imputation), time between questionnaire and interview, previous psychotherapeutic treatment, and treatment setting.

Alphas were 2-sided and set at .05. Analyses were performed using SPSS 24 (2011, IBM Corporation, Armonk, New York) and MedCalc (2016, MedCalc Statistical Software, Ostend, Belgium).

3 | RESULTS

We contacted 5889 patients, of which 4020 provided full PHQ-9 data and hence were included in the study (response rate: 68%) (Figure 1).

Compared with nonparticipants, participants were younger, higher educated, and more likely to be recruited from rehabilitation centers (all $P < .001$). Differences were also found between study centers and tumor entities (both $P < .001$), with the lowest risk of nonparticipation in Würzburg and among patients with cancer of the male genital organs, respectively. No differences were found in gender ($P < .10$).

Of all patients selected for the interview, 79% completed the interview. Compared with noncompleters, completers were younger and higher educated (both $P \leq .01$). We also found differences in tumor entities, with the highest noncompletion rate among breast cancer patients (30%). No differences were found in gender and treatment setting.

Among raw data after listwise deletion of all cases with at least 1 missing sum score (n = 1961), means and standard deviations of the GAD-7 and the HADS-A were 5.3 (4.1) and 6.2 (4.0) for the 1892 noncases, 11.3 (4.8) and 12.0 (4.2) for the 24 subclinical cases, and 11.3 (4.9) and 11.2 (3.6) for the 45 definite cases, respectively. The absolute mean time between the screeners and the CIDI-O was 8.7 days (SD = 15.0).

Among the weighted plus imputed sample (N = 3215), 1.7% were diagnosed with GAD (n = 56).

Internal consistency was good for both scales, with Cronbach's alpha of .83 (HADS-A) and .88 (GAD-7).

The overall diagnostic performance (AUC) for diagnosing GAD was .81 (95% CI, .79-.82) for both screeners. This means that with a probability of 81%, a randomly selected patient with GAD would score higher in the screeners than a randomly selected patient without GAD. The 2 screeners did not differ in their performance ($P = .86$). The best balance between SEN and SPE was found for cut-offs ≥7 (GAD-7) and ≥8 (HADS-A), with maximum YI of .51 and .49, respectively (Table 2). The recommended thresholds for the GAD-7 (≥10)

TABLE 2 Operating characteristics of the GAD-7 and the HADS-A for identifying patients with generalized anxiety disorder (GAD) according to the CIDI-O at selected cut-offs

	Sensitivity % (95% CI)	Specificity % (95% CI)	Youden Index % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
GAD-7					
≥4	96 (92-100)	40 (38-42)	.36 (.32-.38)	3 (2-3)	100 (100-100)
≥5	84 (74-94)	50 (48-52)	.34 (.28-.38)	3 (2-4)	99 (99-100)
≥6	79 (68-89)	66 (65-68)	.45 (.38-.49)	4 (3-5)	99 (99-100)
≥7[a]	**77 (66-88)**	**74 (73-76)**	**.51 (.44-.56)**	**5 (4-6)**	**99 (99-100)**
≥8	64 (52-77)	81 (80-83)	.46 (.39-.51)	6 (4-8)	99 (99-100)
≥9	63 (50-75)	85 (84-87)	.48 (.41-.54)	7 (5-9)	99 (99-100)
≥10[b]	**55 (42-68)**	**89 (88-90)**	**.44 (.38-.51)**	**8 (5-11)**	**99 (99-99)**
HADS-A					
≥5	96 (92-100)	39 (37-40)	.35 (.31-.37)	3 (2-3)	100 (100-100)
≥6	89 (81-97)	48 (46-50)	.37 (.32-.40)	3 (2-4)	100 (99-100)
≥7	84 (74-94)	64 (62-65)	.48 (.42-.52)	4 (3-5)	100 (99-100)
≥8[a]	**77 (66-88)**	**72 (71-74)**	**.49 (.43-.54)**	**5 (3-6)**	**99 (99-100)**
≥9	68 (56-80)	79 (78-81)	.47 (.41-.53)	6 (4-7)	99 (99-100)
≥10	57 (44-70)	84 (83-86)	.41 (.35-.48)	6 (4-8)	99 (99-99)
≥11[c]	**48 (35-61)**	**88 (87-89)**	**.36 (.30-.43)**	**7 (4-9)**	**99 (99-99)**

Abbreviations: CI, confidence interval; Youden Index, accuracy measure equally taking into account sensitivity and specificity; PPV, positive predictive value; NPV, negative predictive value.

[a]Cutoff score with maximum Youden Index (i.e., best trade off between sensitivity and specificity).

[b]Cutoff score officially recommended by the American Society for Clinical Oncology.

[c]Cutoff score officially recommended by the HADS.

and the HADS-A (≥11) showed relatively low sensitivities of 55% and 48%, respectively. Across cut-offs, PPV ranged from 3% to 8%.

Sensitivity analyses (Table A1) showed that measures of diagnostic accuracy were only slightly affected by any of the investigated factors, with maximum deviations from the final sample of .02 (AUC) and .06 (maximum YI). For some subsamples, however, optimal cut-offs differed from those of the final sample, eg, for the GAD-7 among inpatients (≥11) or patients from rehabilitation centers (≥9).

4 | DISCUSSION

4.1 | Main findings

This study showed identical and adequate overall diagnostic performance of the GAD-7 and the HADS-A in identifying GAD among cancer patients. At the recommended cut-offs, SEN was relatively low for both screeners.

4.2 | Comparison with previous research

With AUC in previous studies ranging from .65 to .96,[8] the overall diagnostic performance of the GAD-7 ranks in the midrange. As for the HADS-A, the only comparable study among cancer patients did not report AUC[10]; nevertheless, a study among patients with coronary heart disease (n = 523) found a largely similar AUC of .85.[24]

At the recommended cut-off of the GAD-7, 2 previous large studies[7,25] and a recent meta-analysis[8] found better SEN (74%-89%), but equal or even lower SPE (52%-83%) when compared with our findings. At the officially recommended cut-off of the HADS-A, the only comparison study among cancer patients reported SEN of 24% and SPE of 97%, which is similar to our results finding high SPE in combination with relatively low SEN.

The PPV for both screeners were considerably lower when compared with previous findings at the recommended cut-offs, eg, 29%[7] and 44%[25] for the GAD-7 and 89%[10] for the HADS-A.

The question arises whether the differences between our and previous findings are caused by distinct features of cancer patients. For example, the low PPV in our study may be due to the low prevalence of GAD in our study.[26] The relatively low SEN at the recommended thresholds may alternatively be explained by the fact that SEN improves when the target condition in the diseased patients is more severe.[27,28] In fact, our GAD-7 mean score among GAD cases (11.3) was lower than in the comparison studies (12.8[25] and 14.4[7]), which may indicate relatively mild GAD cases and thus might have worsened our SEN. Apart from such considerations, given that even high degrees of anxiety among cancer patients are understandable and hence do not necessarily reflect a pathological GAD,[1-3] it seems plausible that diagnostic accuracy and optimal cut-offs in oncological populations may be different. In this context, future diagnostic accuracy studies may also take into account cancer-specific constructs that may resemble symptoms of GAD, such as fear of recurrence.[29]

4.3 | Clinical implications

Given the lack of previous studies, our results need to be replicated to draw clear conclusions. Nevertheless, our study is in line with previous studies on the HADS-A[10,24] and the GAD-7[8] in identifying GAD, which pointed to thresholds below the officially recommended cut-offs. One study explicitly recommended to lower the cut-offs of the HADS (total score) when used in oncological settings.[30]

In an undesirable setting where a screener is the only assessment, one should apply the cut-off point with maximum YI representing the best trade-off between SEN and SPE.[31] In a 2-step process where all positively screened patients are subsequently interviewed, an even lower cut-off might be considered to miss as few potential GAD cases as possible. Irrespective of the assessment procedure, the low SEN of both screeners represents an argument in favor of lowering current cut-offs to improve detection of cases in need of psycho-oncological intervention.

Nevertheless, even at the optimal cut-offs, the classification rate of the YI for both screeners is only mediocre. Furthermore, the PPV across cut-offs was 8% or even lower. This means that among 100 patients with positive screening result, only 8 or fewer will in fact have GAD. Given these results, one may wonder whether screening for GAD in cancer patients is warranted at all. In fact, it seems problematic to use these screeners as sole assessment tool; nevertheless, they may be usefully applied in settings where positively screened patients are further explored by an interview. The effort of a such 2-stage process seems warranted compared with the detrimental medical effects of anxiety among cancer patients,[4] the indirect costs of patients with undetected mental disorders,[32] and the subjective burden of untreated patients. In combination with screening for depression,[3] detection of patients of GAD may considerably improve the management of patients' distress. For example, patients with pathological anxiety may need more medical information and clinicians should avoid simple reassurance and rather focus on the patients' interpretation of disease-related symptoms.[2]

4.4 | Study limitations

Even though our sample is large, the number of GAD cases in our study was small (n = 56 in the final sample). Therefore, our results should be interpreted carefully. Nevertheless, it should be noted that the study that was used by the American Society for Clinical Oncology to choose the optimal GAD-7 cut-off was based on a sample with a similarly large number of GAD cases (n = 73).[7]

Given the lack of reliable information about the number of patients who had previously been diagnosed with GAD, our results may not be applicable for previously undiagnosed cases.[33] Nevertheless, our sensitivity analyses showed that excluding patients with previous psychotherapeutic treatment (who may also have received a diagnosis) only minimally affected diagnostic accuracy measures. The impact of data preparation or extensive time between the questionnaire and the interview was also shown to be minimal. Nevertheless, for some subsamples such as inpatients and patients in rehabilitation centers, optimal cut-offs differed from those found for the final sample. Even though the small number of GAD cases in each of these subgroups does not allow to draw clear conclusions, this finding is important for 2 reasons. First, it indicates that the broad range of different patients in our sample may have limited the reliability of our results. Second, further studies should evaluate whether optimal cut-offs should be chosen according to treatment setting. Finally, neither weighting nor imputation directly biased measures of diagnostic accuracy, since none of these techniques altered the already existing relation between questionnaire scores and GAD diagnosis.

5 | CONCLUSIONS

Our data suggest that GAD-7 and HADS-A may be applied among cancer patients for identifying GAD. Cut-offs should be carefully applied to ensure detection of as many patients in need for psychological intervention as possible.

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CONFLICTS OF INTEREST

None declared.

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APPENDIX

TABLE A1 Sensitivity analyses investigating the impact of data preparation, time between measurement points, previous psychotherapeutic treatment, and treatment setting on diagnostic accuracy measures of the GAD-7 and HADS-A in identifying cancer patients with generalized anxiety disorder (95% CI in brackets)

		GAD-7		HADS-A	
	N	AUC	Maximum YI	AUC	Maximum YI
Reference (final weighted and imputed sample)	3215	.81 (.79-.82)	≥7: .51 (.44-.56)	.81 (.80-.82)	≥8: .49 (.43-.54)
Data preparation					
Imputation only	2141	.82 (.80-.84)	≥7: .52 (.46-.57)	.82 (.80-.83)	≥8: .51 (.44-.55)
Weighting only	2947	.82 (.80-.83)	≥7: .53 (.47-.57)	.82 (.80-.83)	≥8: .51 (.45-.56)
Raw data[a]	1961	.83 (.81-.84)	≥7: .54 (.47-.57)	.82 (.80-.84)	≥8: .52 (.45-.55)
Other factors[b]					
Acceptable interval[c]	2283	.81 (.80-.83)	≥7: .53 (.46-.58)	.81 (.80-.83)	≥8: .51 (.44-.56)
Without previous treatment[d]	2484	.82 (.81-.85)	≥7: .50 (.41-.56)	.82 (.80-.83)	≥7: .48 (.39-.54)
Inpatients/acute care only	1398	.83 (.81-.85)	≥11: .53 (.40-.64)	.80 (.78-.82)	≥8: .45 (.31-.54)
Rehabilitation only	840	.82 (.80-.84)	≥9: .48 (.35-.57)	.83 (.80-.85)	≥9: .55 (.42-.62)
Outpatients only	977	.79 (.77-.82)	≥7: .55 (.46-.61)	.80 (.77-.83)	≥8: .51 (.42-.57)

Abbreviations: AUC, area under the receiver operating curve; CI, confidence interval; YI, Youden Index.

[a]N after deletion of all cases with at least 1 missing GAD-7 or HADS-A sum score.

[b]To improve comparability with the main results, subsamples were drawn from the final, ie, weighted and imputed sample.

[c]Results for patients with available assessment dates for the questionnaires and the CIDI-O who completed the questionnaires less than 28 days before or 7 days after the interview (|M| = 4; SD = 6).

[d]Excluding all patients previously treated with psychotherapy.