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Validation of the Distress Thermometer in a Mexican population with brain tumors: A Diagnostic Accuracy Study

Dan Morgenstern-Kaplan

1. Radiosurgery Unit, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico, dmorgensternk@gmail.com

Sergio Moreno-Jiménez

The American-British Cowdray Medical Center IAP, radioneurocirugia@gmail.com

See next page for additional authors

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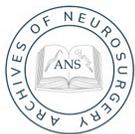
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Abstract

Objective: Mental health in cancer patients must be addressed. This study's main objective was to evaluate the sensitivity and specificity of the DT in a population of patients with brain tumors and determine the optimal cut-off point for the DT. **Methods:** We performed a cross-sectional study at the National Institute of Neurology and Neurosurgery in Mexico City, in a cohort of 110 patients. **Results:** Of the 108 participants with brain tumors that were included in the analysis (2 patients excluded by incomplete DT), 40 had gliomas, 31 had pituitary adenomas, 21 had meningiomas, and 16 had other types of tumors. Mean distress as measured by DT was 5.37 (SD=3), and the mean total problem list score was 21 (SD=9.14), with the most common subtype being physical problems (mean 7.7, SD=4.5) and emotional problems (mean 3.8, SD=1.9). HADS-T score mean was 13.7 (SD=7.3), with the mean HADS-D and HADS-A subsets being 5.8 (SD=4) and 7.85 (SD=4.4) respectively. A Receiver Operating Curve (ROC) analysis was performed to determine the optimal cut-off point of the DT in our population. We obtained an Area Under the Curve (AUC) of 0.71 (CI95%=0.61-0.81, p

Visual Abstract



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VISUAL ABSTRACT

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The Distress Thermometer (DT) is a psycho-oncologic screening tool developed by the NCCN initially published in 1998 [6]. This tool can be used in every cancer patient to screen for emotional distress; it is accompanied by a Problem List (PL) checklist for the patient to fill out the sources of that distress. This tool has been translated to over 21 languages and is broadly used all around the world. There is no paper validating the DT for brain tumors.

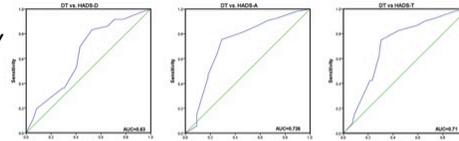


Table 3. Sensitivity, Specificity, Positive and Negative Predictive Values (PPV and NPV), Positive and Negative Likelihood Ratios (LR+, LR-) for each cut-off point of the DT when compared to the HADS-T score as a reference standard test.

DT Cut-Off Value	TP	TN	FP	FN	Sensitivity (CI95%)	Specificity (CI95%)	PPV (CI95%)	NPV (CI95%)	LR+ (CI95%)	LR- (CI95%)
1	51	6	50	1	98% (88–99%)	11% (4–22%)	50% (40–60%)	86% (42–99%)	1.1 (1.0–1.21)	0.18 (0.02–1.44)
2	48	15	41	4	92% (80–97%)	27% (16–40%)	54% (43–64%)	79% (53–93%)	1.26 (1.06–1.5)	0.29 (0.1–0.81)
3	47	19	37	5	90% (78–96%)	34% (22–48%)	56% (44–66%)	79% (57–92%)	1.36 (1.11–1.68)	0.29 (0.11–0.7)
4	47	23	33	7	87% (73–94%)	41% (28–55%)	58% (45–68%)	77% (57–89%)	1.47 (1.15–1.87)	0.32 (0.15–0.7)
5	43	31	25	9	83% (69–91%)	55% (41–68%)	63% (50–74%)	78% (61–88%)	1.84 (1.35–2.54)	0.31 (0.17–0.59)
6	39	39	17	13	75% (60–85%)	70% (55–80%)	70% (56–81%)	75% (60–85%)	2.5 (1.61–3.79)	0.35 (0.22–0.59)
7	32	40	16	20	62% (47–74%)	71% (57–82%)	67% (51–79%)	67% (53–78%)	2.13 (1.35–3.43)	0.53 (0.37–0.79)
8	22	43	13	30	42% (29–56%)	77% (62–86%)	63% (45–78%)	59% (47–70%)	1.82 (1.03–3.23)	0.75 (0.57–0.99)
9	8	51	5	44	15% (7–28%)	91% (80–96%)	62% (32–84%)	54% (43–64%)	1.66 (0.6–4.93)	0.93 (0.81–1.07)
10	4	52	4	48	8% (2–18%)	93% (80–97%)	50% (17–82%)	52% (38–58%)	1.08 (0.28–4.09)	0.99 (0.89–1.11)

We used it in patients with intracranial tumors and found out six as a good cut-off point.

6. Roth AJ, Kornblith AB, Batel-Copel L, Peabody E, Scher HI, Holland JC. Rapid screening for psychologic distress in men with prostate carcinoma: a pilot study. Cancer 1998;82(10): 1904e8.

Keywords

Depression, Anxiety, Distress Thermometer, Brain tumors, Cancer, STARD, Sensitivity, Specificity

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Authors

Dan Morgenstern-Kaplan, Sergio Moreno-Jiménez, Fernanda Páez-Plascencia, Angel Ruiz-Chow, and Fabiola Flores-Vázquez

Validation of the Distress Thermometer in a Mexican Population with Brain Tumors: A Diagnostic Accuracy Study

Dan Morgenstern-Kaplan ^{a,b}, Sergio Moreno-Jiménez ^{a,e,*}, Fernanda Páez Plasencia ^c, Ángel Ruiz Chow ^{e,f}, Fabiola Flores-Vázquez ^d

^a Radiosurgery Unit, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico

^b Facultad de Ciencias de la Salud, Universidad Anáhuac México Norte, Mexico City, Mexico

^c Neuropsychology Unit, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico

^d Cancer Center, American British Cowdray Medical Center, Mexico City, Mexico

^e Neurological Center, American British Cowdray Medical Center, Mexico City, Mexico

^f Neuropsychiatry Department, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico

Abstract

Objective: Mental health in cancer patients must be addressed. This study's main objective was to evaluate the sensitivity and specificity of the DT in a population of patients with brain tumors and determine the optimal cut-off point for the DT.

Methods: We performed a cross-sectional study at the National Institute of Neurology and Neurosurgery in Mexico City, in a cohort of 110 patients.

Results: Of the 108 participants with brain tumors that were included in the analysis (2 patients excluded by incomplete DT), 40 had gliomas, 31 had pituitary adenomas, 21 had meningiomas, and 16 had other types of tumors. Mean distress as measured by DT was 5.37 (SD = 3), and the mean total problem list score was 21 (SD = 9.14), with the most common subtype being physical problems (mean 7.7, SD = 4.5) and emotional problems (mean 3.8, SD = 1.9). HADS-T score mean was 13.7 (SD = 7.3), with the mean HADS-D and HADS-A subsets being 5.8 (SD = 4) and 7.85 (SD = 4.4) respectively. A Receiver Operating Curve (ROC) analysis was performed to determine the optimal cut-off point of the DT in our population. We obtained an Area Under the Curve (AUC) of 0.71 (CI95% = 0.61–0.81, $p < 0.001$) comparing against HADS-T score; an AUC of 0.726 (CI95% = 0.62–0.82, $p < 0.001$) comparing against the HADS-A subset, and an AUC of 0.63 (CI95% = 0.53–0.74, $p = 0.021$) when comparing against HADS-D subset.

Conclusions: The DT is a psycho-oncologic screening tool applied to cancer patients to screen for emotional distress. We used it in patients with intracranial tumors and found six as a good cut-off point.

Keywords: Depression, Anxiety, Distress thermometer, Brain tumors, Cancer, STARD, Sensitivity, Specificity

1. Introduction

Throughout the world, cancer incidence is growing every year, therefore, arising problems in this group of patients must be addressed, including mental health. The National Comprehensive Cancer Network (NCCN) estimates that 38.4% of the population will develop cancer in their lifetime [1]. Neurological cancers are the 15th most common and have the 10th

highest mortality rate in the United States [2]. In Mexico, it is the 17th most common and the 13th deadliest type of cancer [3]. These patients have a higher rate of mental health pathology; therefore, it must be screened and managed appropriately [4].

Cancer patients are at increased risk of mental health disorders, including depression and anxiety, which are commonly under-recognized comorbidities. These emotional complications decrease the

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* Corresponding author. Insurgentes Sur 3877 Col. La Fama, Tlalpan, C.P. 14269, Mexico City, Mexico.,
E-mail address: radioneurocirugia@gmail.com (S. Moreno-Jiménez).

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quality of life and can affect the prognosis of cancer patients. Overall, there is a 3-fold risk of having depression in a cancer patient than the general population [5]. Cancer is a pathology that carries a high risk of suicide, which is why the detection of depression and mental health issues is of great importance. According to the current NCCN guidelines screening for distress and emotional complications is required for all patients with cancer [4].

The Distress Thermometer (DT) is a psychoneurologic screening tool developed by the NCCN initially published in 1998 [6]. This tool can be used in every cancer patient to screen for emotional distress; it is accompanied by a Problem List (PL) checklist for the patient to fill out the sources of that distress. This tool has been translated to over 21 languages and is broadly used all around the world. There is no paper validating the DT for brain tumors. The closest paper translated and validated this tool in various types of cancer, comparing it to the Hospital Anxiety and Depression Scale (HADS); they found a cut-off point of 4 to have the best sensitivity [7]. Several cut-off points are used globally depending on the type of cancer; a recent meta-analysis showed that most cut-off points range from 3 to 7 in different types of cancer (breast, lymphoma, prostate, colorectal among others) [8]. Few studies have analyzed the DT in patients with brain tumors, showing cut-offs varying from 4 to 6, but none in a Latin-American population [9,10].

The main objective of this study was to evaluate the sensitivity and specificity of the DT in a population of patients with brain tumors in Mexico and determine the optimal cut-off point for the DT comparing it to the HADS, which can detect depression and anxiety, for its validation. Our central hypothesis was that the DT in our population would behave like other reported studies, with an optimal cut-off point between 4 and 6 and a minimum sensitivity of 75%, for screening purposes.

2. Methods

We performed a cross-sectional study in the National Institute of Neurology and Neurosurgery in Mexico City between July to September 2019.

The study's main goal was to validate the NCCN Distress Thermometer in a population of patients with brain tumors of any kind. This study was modeled and performed after the STARD guidelines for reporting diagnostic accuracy studies [11]. The study was approved by the research and ethics Institutional Review Board of the hospital before starting the study.

Abbreviation list

DT	Distress Thermometer
PL	Problem List
HADS	Hospital Anxiety Depression Scale
AUC	Area Under the Curve
SD	Standard Deviation
ROC	Receiver Operating Characteristic
NCCN	National Comprehensive Cancer Network
STARD	Standards for Reporting of Diagnostic Accuracy Studies
PHQ9	Patient Health Questionnaire
TP	True Positive
TN	True Negative
FP	False Positive
FN	False Negative
PPV	Positive Predictive Value
NPV	Negative Predictive Value
LR	Positive Likelihood Ratio
LR	Negative Likelihood Ratio

Patients were recruited in the outpatient clinic and invited to participate in the study. We used convenience sampling to recruit 110 patients from the outpatient neurosurgery clinic in the hospital. Inclusion criteria were age >18 years, patients with a confirmed histological diagnosis of a brain tumor, the capacity to fill-out self-application forms, and patients who give informed consent to participate in the study. Patients with previous or current psychiatric disorders were excluded as well as those with missing data. Data collection was planned before both the DT and HADS were performed. Standardized protocols of data collection were applied to homogenize data and prevent data loss. Both tests were applied on the same visit. The flow of patients in the study is shown in Fig. 1.

2.1. The NCCN distress thermometer

The DT is a 1-item rapid-screening tool for detecting distress in cancer patients; the patients are asked to fill out their distress (in the past week) in a visual thermometer scale ranging from 0 to 10 (10 being the highest level of distress). The Thermometer is accompanied by a Problem List (PL), where patients need to state whether they had or not any of them (during the past week). The PL consists of 36 items grouped in different categories to establish the source of the patient's distress. The patients self-filled a printed out form of the DT/PL form provided in the neurosurgical follow-up consultation. The physician explained the instructions and answered any questions that arose during this period. The DT version used in the study was the Spanish translation done by Almanza-Muñoz et al. [7].

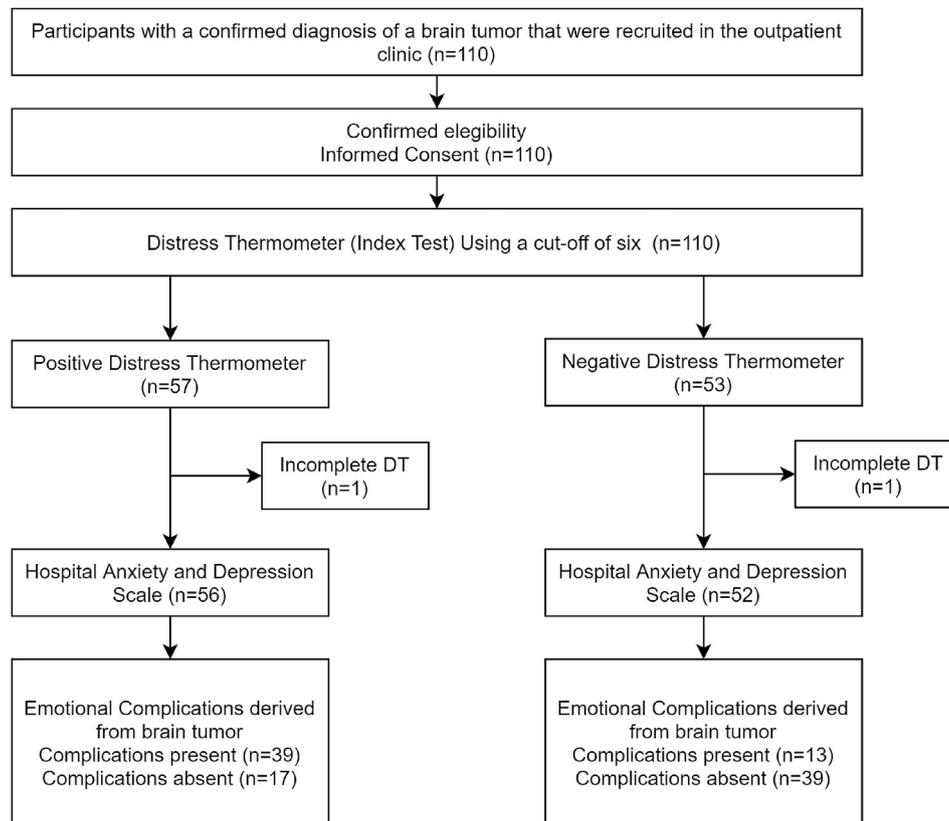


Fig. 1. STARD Flow Diagram showing the flow of patients in our study, including the index and the reference standard used in the study.

The Hospital Anxiety and Depression Scale (HADS) is a self-applied 14-item patient questionnaire to screen for mood disorders in the clinical setting. It is the most studied and validated tool, and it has been validated for its use in cancer patients [12]. It consists of two subsets of questions, one for detecting anxiety (HADS-A) and another for detecting depression (HADS-D); it is graded on a numerical scale, each subset graded from 0 to 21, for a total score (HADS-T) ranging from 0 to 42. The cut-off points for HADS-A and HADS D are >7, and for the HADS-T, it is > 14 for a positive test. Patients were referred to the mental health clinic either if they had a subset or a total score positive test.

HADS was chosen to be the reference standard for the study from other choices, like the Patient Health Questionnaire (PHQ9) because it assesses both anxiety and depression combined in the same test [13] its reliability in various clinical settings and pathologies. A research fellow blindly reviewed answers to the DT/PL and the HADS concerning the personal information and the patient's demographic baseline characteristics. The DT and HADS were applied to the participants the same day in the clinic without time in between.

2.2. Statistical analysis

The sample size was calculated before starting the study protocol with the formula described by the PASS software table [14], and the minimum intended sample size was determined to be 61 patients. We performed descriptive statistical analysis in the baseline demographic characteristics in the patients of the study and are reported in frequencies and percentages. The DT and HADS scores were analyzed and reported in means and standard deviations. We compared the DT and HADS scores with a Receiver Operating Characteristic (ROC) analysis to obtain an optimal DT cut-off score that distinguishes clinically significant depression and/or anxiety as defined by HADS. The area under the curve (AUC) was used to establish the discrimination accuracy of the DT in neuro-oncology patients for detection of depression and/or anxiety, defined as a HADS >14. We reported the True Positives, True Negatives, False Positives and False Negatives for each DT score, and calculated the sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and their respective 95% confidence intervals for each possible

DT cut-off score. Missing and indeterminate data were excluded from the statistical analysis. To determine the association between each of the demographic variables, clinical variables, and PL, we performed a chi-squared analysis to categorical variables and t-test for numerical variables, significance was considered as a $p < 0.05$. Associations between the DT and HADS scores and the PL items were explored via Pearson's correlation coefficient. The data were made available in a data repository [15].

3. Results

3.1. Demographic description

Of the 110 patients, two were excluded because of missing data; the final analysis included 108 participants with brain tumors, 40 had gliomas, 31 had pituitary adenomas, 21 had meningiomas, and 16 had other types of tumors, such as vestibular schwannomas, brain metastases, and lymphoma. Other demographic baseline and diagnostic characteristics can be found in Table 1.

3.2. Distress measurement and correlation analysis

Mean distress as measured by DT was 5.37 (SD = 3), and the mean total problem list score was 21 (SD

Table 1. Baseline Demographic and Diagnosis of participants in the study.

Patient Characteristic	n	%
Gender		
Male	58	53.7%
Female	50	46.3%
Mean age in years, (Range)	43.5 (16–72)	
Maximum Academic Level		
Never Studied	18	16.7%
Primary School	21	19.4%
High School	51	47.2%
College	18	16.7%
Marital Status		
Married	60	55.5%
Single	29	26.9%
Partnership	11	10.2%
Widowed	5	4.6%
Divorced	3	2.8%
Type of Tumor		
Meningioma	21	19.4%
Gliomas	40	37%
Pituitary Adenoma	31	28.7%
Other	16	14.8%
Tumor Lateralization		
Right	29	26.9%
Left	40	37%
Other	39	36.1%
Time From Diagnosis		
<1 month	35	32.4%
1–3 months	29	26.9%
>3 months	44	40.7%

= 9.14), with the most common subtype of problems being physical problems (mean 7.7, SD = 4.5) and emotional problems (mean 3.8, SD = 1.9). HADS-T score mean was 13.7 (SD = 7.3), with the mean HADS-D and HADS-A subsets being 5.8 (SD = 4) and 7.85 (SD = 4.4) respectively. The HADS-T scale was positive (score>14) in 52 patients (48% of patients in the sample).

Correlation analysis comparing the DT score and the subsets of the PL show a positive correlation for the total number of problems ($r = 0.41, p < 0.001$), as well as the subsets of emotional problems ($r = 0.51, p < 0.001$), physical problems ($r = 0.26, p = 0.005$) and family-related problems ($r = 0.2, p = 0.036$). A non-significant correlation with practical problems ($r = 0.12, p = 0.19$) was found. DT score was not significantly correlated with the academic level of the patient ($r = -0.066, p = 0.49$). Correlation analysis between the DT and HADS scores resulted in a positive correlation ($r = 0.44, p < 0.001$). Table 2 shows the PL's subset values and their correlation with the DT score, as well as with the HADS score.

3.3. Receiver Operating Characteristic (ROC) analysis

We compared the DT score with HADS-T, taking a score >14 as a positive test; sensitivity, specificity, predictive values, and likelihood ratios were calculated, expressed in Table 3. Receiver Operating Curve (ROC) analysis was performed to determine the optimal cut-off point of the DT in our population. We obtained an Area Under the Curve (AUC) of 0.71 (CI95% = 0.61–0.81, $p < 0.001$) comparing against HADS-T score, an AUC of 0.726 (CI95% = 0.62–0.82, $p < 0.001$) comparing against the HADS-A subset, and an AUC of 0.63 (CI95% = 0.53–0.74, $p = 0.021$) when comparing against HADS-D subset (Fig. 2).

4. Discussion

In this study, we validated the DT in a Mexican population of patients with brain tumors, a population with historically high levels of distress. Regarding demographic characteristics, our study provides a sample size following other studies in patients with the same pathology with roughly the same sex distribution and marital status; however, larger studies that use the DT exist in other more common types of cancer [16]. Our sample's mean age was younger than other reported series, and our time from diagnosis was more evenly distributed between <1 month, 1–3 months, and >3 months, which could have contributed to their levels of distress [9,17]. We

Table 2. Distribution of the Problem Categories and Correlation Analysis of each PL category and the DT score, as well as the HADS-T Score and the DT Score.

Problem List Category	Mean	Standard Deviation	Correlation coefficient (r)	P value
Physical	7.7	9.14	0.26	0.005
Emotional	3.8	1.9	0.51	0.001
Practical	2.6	1.4	0.12	0.19
Family	0.4	0.7	0.2	0.036
Total Problems	21	9.1	0.41	0.001
HADS-T Score	13.7	7.3	0.44	0.001

measure the academic study level to determine its association with levels of distress, which did not yield a significant correlation in the statistical analysis.

Many studies have tried to determine distress levels in patients with brain tumors, using the DT as a screening tool [9,17–22]. The diagnosis distribution of the different brain tumors characterizes our series in that we included malignant and benign tumors as well (meningiomas, pituitary adenomas) compared to previously published series. We proceed this way because we believe that a brain tumor, no matter the type, is a significant source of distress in any person; however, it is also a limitation of the study since the DT was intended to be used in cancer patients only. Due to this, another study, with a sub-analysis of distress in different brain tumors, would be useful to determine the distress levels divided by this variable.

The prevalence of depression in brain cancer patients has been estimated to be 21.7% in a recent meta-analysis [23]. Depression carries an inherent risk of suicide; in cancer patients, it has been described to increase (RR = 13.6) in the first week after diagnosis and to persist after (3.1) the first year [24]. It demonstrates, once again, the importance of correct screening and management of mental health disorders in these patients. It has been demonstrated that preoperative depression decreases the overall survival of patients in the first year after surgery (from 41% to 15%) [25].

In our study, mean distress levels were similar to other studies done in brain cancer patients [9,17], which range from 5.5 to 5.7, but higher than other types of cancer, such as breast [26], gynecologic and colorectal [27,28]. The PL sources of distress also behaved similarly, with physical problems being the most common source of distress [20], followed by emotional problems. However, in our study, the (PL) emotional problems have the highest correlation with the distress levels. In this sample, 48% of the patients presented with a positive screening test (using HADS), which shows that levels of depression and anxiety are higher in patients with brain tumors than other oncologic diseases (range 25–34%), depending on the type of cancer and time since diagnosis [21,26–28].

The main difference of all the studies in different types of cancer is that of the optimal cut-off score of the DT for the best sensitivity and specificity, but the most common cut-off is 4 [16]. In our analysis, the DT performed as a tool with moderate discrimination abilities compared with the HADS-T (AUC = 0.71), with slightly better discrimination for anxiety than for depression. The optimal cut-off score for a screening test should be the one with high sensitivity, an acceptable specificity, and the highest positive likelihood ratio. Therefore, the best cut-off in our sample of patients with brain tumors was 6, which yields a sensitivity of 75% and a specificity of 70% with a positive likelihood ratio of 2.5. The cut-off of six is similar to other studies, and since the DT is a

Table 3. Sensitivity, Specificity, Positive and Negative Predictive Values (PPV and NPV), Positive and Negative Likelihood Ratios (LR+, LR-) for each cut-off point of the DT when compared to the HADS-T score as a reference standard test.

DT Cut-Off Values										
DT Cut-Off value	TP	TN	FP	FN	Sensitivity (CI95%)	Specificity (CI95%)	PPV (CI95%)	NPV (CI95%)	LR+ (CI95%)	LR- (CI95%)
1	51	6	50	1	98% (88–99%)	11% (4–22%)	50% (40–60%)	86% (42–99%)	1.1 (1.0–1.21)	0.18 (0.02–1.44)
2	48	15	41	4	92% (80–97%)	27% (16–40%)	54% (43–64%)	79% (53–93%)	1.26 (1.06–1.5)	0.29 (0.1–0.81)
3	47	19	37	5	90% (78–96%)	34% (22–48%)	56% (44–66%)	79% (57–92%)	1.36 (1.11–1.68)	0.29 (0.11–0.7)
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5	43	31	25	9	83% (69–91%)	55% (41–68%)	63% (50–74%)	78% (61–88%)	1.84 (1.35–2.54)	0.31 (0.17–0.59)
6	39	39	17	13	75% (60–85%)	70% (55–80%)	70% (56–81%)	75% (60–85%)	2.5 (1.61–3.79)	0.35 (0.22–0.59)
7	32	40	16	20	62% (47–74%)	71% (57–82%)	67% (51–79%)	67% (53–78%)	2.13 (1.35–3.43)	0.53 (0.37–0.79)
8	22	43	13	30	42% (29–56%)	77% (62–86%)	63% (45–78%)	59% (47–70%)	1.82 (1.03–3.23)	0.75 (0.57–0.99)
9	8	51	5	44	15% (7–28%)	91% (80–96%)	62% (32–84%)	54% (43–64%)	1.66 (0.6–4.93)	0.93 (0.81–1.07)
10	4	52	4	48	8% (2–18%)	93% (80–97%)	50% (17–82%)	52% (38–58%)	1.08 (0.28–4.09)	0.99 (0.89–1.11)

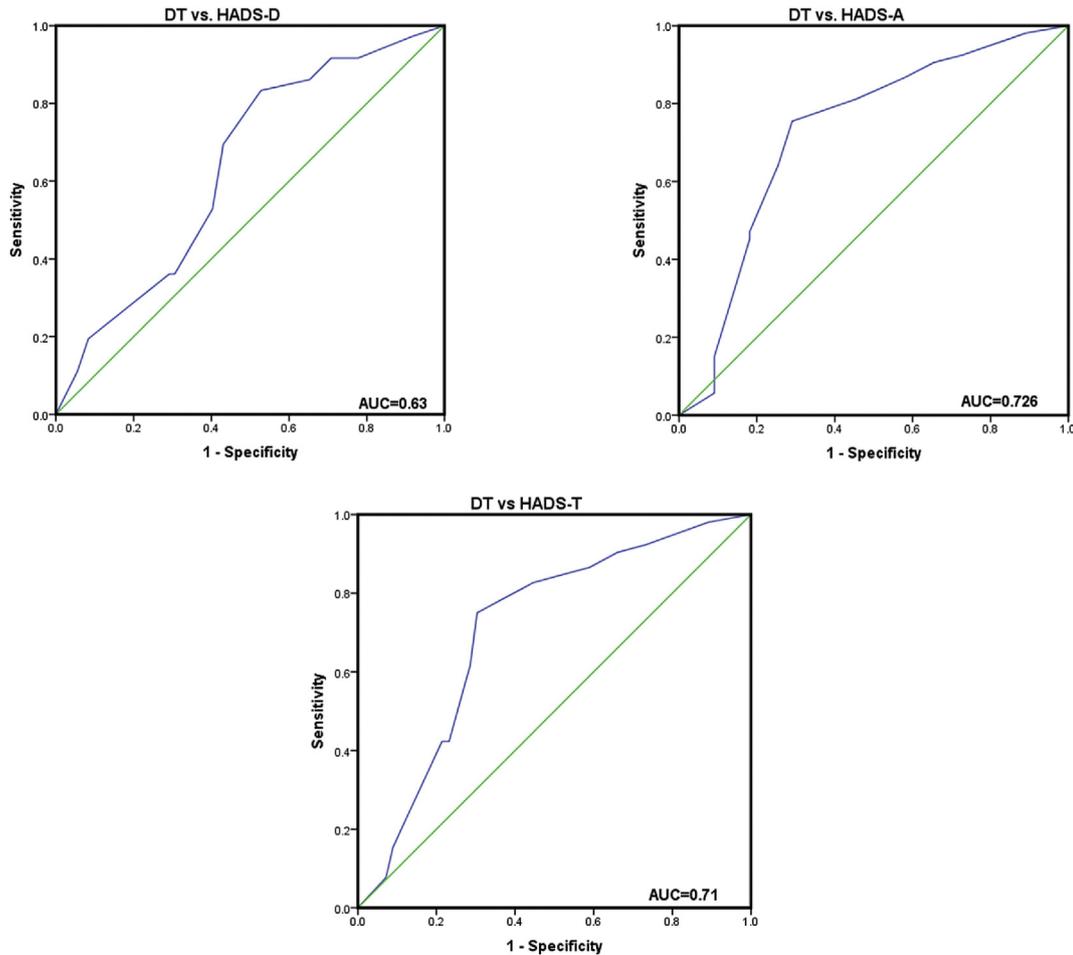


Fig. 2. ROC Curves comparing the DT Scores with the HADS Total Score with its Anxiety and Depression subscales.

screening test, we consider it to be the optimal score to use in patients with brain tumors.

In brain tumors, sometimes, there is a belief that these tools can be ineffective due to the cognitive and functional damage that neurological conditions cause in the patients; however, in several studies with brain tumors, the DT has been correctly validated. Moreover, a higher risk for mental health conditions has been described due to the risk of functional, neurologic, and cognitive sequelae that can result from brain cancer [20], concordant with the results of the present study.

The NCCN defines distress as a “multifactorial, unpleasant experience of a psychological (i.e., cognitive, behavioral, emotional), social, spiritual, and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment” [4]. In Mexico, and the Spanish language overall population, there is a common misunderstanding and misuse of the word distress, since there exists no word in Spanish that correctly translates distress. Therefore, it has been used as a word to describe a combination of

depression and anxiety, but these words are not the same as the definition of distress in English. We found the DT and HADS scores have a significant but moderate correlation coefficient, probably explaining they measure different concepts (as referred above), the one being depression or anxiety, and the other being distress. This fact provides a clue for many other factors that may have a significant effect on brain tumors' emotional complications.

5. Limitations

One of the main limitations of our study is the relatively small sample size. We included tumors of different lineages, which can make more challenging the interpretation of the results. Single-lineage studies will have to be done in future research.

6. Clinical implications

This study may help to encourage the use of tools such as the distress thermometer in patients with brain tumors. We generally focus on assessing their neurological and functional status, but we neglect the

implications in their emotions, which are of utmost importance.

7. Conclusions

The DT is a psycho-oncologic screening tool that is applied to cancer patients to screen for emotional distress and is accompanied by the PL checklist for the patient to fill out the sources of that distress. We used it in patients with intracranial tumors and found out six as a good cut-off point. Larger studies are needed in order to analyze separately between malignant and benign tumors.

Funding

No funding for this research. Not applicable for that section.

Conflicts of interest

The authors state that they do not have any conflict of interest.

Ethics approval

The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the National Institute of Neurology and Neurosurgery. Approval number CB/435/13.

Authors contributions

DMK (statistical analysis, manuscript writing), SMJ (Idea, patient recruitment, manuscript writing), FPP (patient evaluation), FFV (Idea, manuscript review).

Data availability

The data that support the findings of this study are openly available in Mendeley Data at <http://doi.org/10.17632/dsk88krhbk.3>.

Publication comment

Publication comment #1

The authors are making the first approach to validate the Distress Thermometer in a Mexican population, including a wide range of brain tumors. As they state in their work, any kind of brain tumor, regardless of whether it has or not an aggressive behavior, could be a source of distress. Moreover, to have this instrument in the armamentarium to evaluate the emotional status of the Mexican

population will be a useful tool to make psychological interventions that help the patients improve their prognosis and quality of life, and also their adherence to treatment. The authors found that, even though the DT has been validated for oncologic pathologies, brain tumor patients showed a higher percentage of positive screening tests, and this finding enforces the necessity of this kind of instrument to evaluate mental health disorders in neuro-oncologic patients.

Bárbara Nettel Rueda, MD

Specialties Hospital, National Medical Center Century XXI, Mexican Institute of Social Security, Mexico City, Mexico

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