Original Article

Uncertainty, Mood States, and Symptom Distress in Patients With Primary Brain Tumors

Analysis of a Conceptual Model Using Structural Equation Modeling

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BACKGROUND: Patients with primary brain tumors (PBTs) face uncertainty related to prognosis, symptoms, treatment response, and toxicity. The authors of this report examined the direct/indirect relations among patients' uncertainty, mood states, and symptoms. **METHODS:** In total, 186 patients with PBTs were accrued at various points in the illness trajectory. Data-collection tools included an investigator-completed clinician checklist, a patient-completed demographic data sheet, the Mishel Uncertainty in Illness Scale-Brain Tumor Form (MUIS-BT), the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT), and the Profile of Mood States-Short Form (POMS-SF). Structural equation modeling was used to explore correlations among variables. **RESULTS:** Participants were primarily white (80%) men (53%) with a variety of brain tumors. They ranged in age from 19 to 80 years (mean ± standard deviation, 44.2 ± 12.6 years). Lower functional status and earlier point in the illness trajectory were associated with greater uncertainty ($P < .01$ for both). Uncertainty ($P < .05$), except in the model of "confusion," and the 5 negative mood states measured by the POMS-SF were directly associated with symptom severity perceived by patients ($P < .01$ for all). The impact of uncertainty on perceived symptom severity also was mediated significantly by mood states. **CONCLUSIONS:** The results from the study clearly demonstrated distinct pathways for the relations between uncertainty-mood states-symptom severity for patients with PBTs. Uncertainty in patients with PBTs is higher for those who have a poor performance status and directly impacts negative mood states, which mediate patient-perceived symptom severity. This conceptual model suggests that interventions designed to reduce uncertainty or that target mood states may help lessen patients' perception of symptom severity, which, in turn, may result in better treatment outcomes and quality of life. ***Cancer* 2013;119:2796-806.** © *2013 American Cancer Society.*

KEYWORDS: brain tumors; mood; structural equation modeling; symptoms; uncertainty.

INTRODUCTION

Primary brain tumors (PBTs) are a heterogeneous group of tumors that arise from the central nervous system and rarely spread to other parts of the body. Gliomas are the most common class of PBTs, and glioblastoma multiforme (GBM) is the most common and malignant type in adults.[1] Once diagnosed, the overall prognosis for patients remains poor, and their clinical course is complicated and unpredictable because of significant morbidity from both tumor-related neurologic and cognitive symptoms as well as treatment-related toxicity.[2]

Uncertainty, defined as an individual's lack of ability to determine the meaning of illness-related events,[3] may pervade the whole illness trajectory of PBTs. One of our studies demonstrated that patients' uncertainty during active treatment was as high as in the newly diagnosed period.[4] For most patients, treatment consists of maximal safe surgical resection followed by radiation therapy, chemotherapy, or both, with various factors considered when determining treatment options, including tumor type, grade, and patient characteristics like functional status and comorbid conditions. Even after the initial treatment is completed, patients undergo periodic clinical follow-up with magnetic resonance imaging (MRI) to evaluate disease status. Unfortunately, nearly all patients with more malignant tumor types, such as GBM, have disease progression at some point either during or after completing initial therapy. At the time of recurrence, the treatment approach is again varied and may include repeat tumor resection, standard chemotherapy, or participation in a

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clinical trial. Without a treatment protocol that is considered the standard of care, treatment for recurrence is usually continued until the tumor progresses or clinical symptoms mandate a change in therapeutic approach.[1]

Currently, there is no confirmable way, based on clinical, tumor, or imaging characteristics, to predict the survival of individual patients. In addition, we cannot predict when a patient's tumor will recur, and the actual evaluation of response to treatment can be difficult to interpret. For example "pseudoprogression" on MRI, consisting of increased, enhancing tumor size on MRI, is often difficult to distinguish from true progression.[5,6] Typically, this is evaluated further by repeating the MRI 4 to 6 weeks after suspected pseudoprogression while continuing treatment. These treatment and evaluation approaches can result in increased uncertainty for the patient.

Anecdotally, based on the clinical experience of the research team, patients who are surveyed during clinic visits report exacerbation of symptoms and have intrusive thoughts about disease prognosis before the MRI visit. This is similar to breast cancer survivors' experience before the mammogram checkup.[7] Because of the likelihood of disease progression or recurrence, the emotional response to uncertainty, such as anxiety and depression, may be worsened when patients who have symptoms are waiting for MRI results or if they are undergoing clinical follow-up without imaging examination during treatment. Patients may feel uncertain about how to manage symptoms and may worry about the duration of symptoms and their relation to the progression of disease. In turn, patients who experience uncertainty may perceive greater symptom severity and interference with function.

According to Mishel,[8] the erratic nature of symptom onset and disease progression is a significant source of illness-related uncertainty. Our previous study validated the Mishel Uncertainty in Illness Scale-Brain Tumor Form (MUIS-BT) and identified 4 distinct stimuli of uncertainty experienced by patients with PBTs. The 4 factors that can trigger uncertainty are ambiguity or inconsistency of illness-related events, unpredictability of disease prognosis, unpredictability of symptoms or other triggers, and complexity of the disease process.[9] In addition, several studies have demonstrated significant correlations between uncertainty and negative emotional outcomes in patients with other solid tumor types[10] and between symptom distress and both mood disturbance and uncertainty in patients with PBTs.[11] Understanding the nature of the correlations among uncertainty, mood, and symptom can be helpful in designing and evaluating interventions in this patient population.

Although using the MUIS-BT offers an opportunity for health care providers to identify the level and sources of patients' uncertainty and further plan for effective information giving or intervention to cope with uncertainty, the underlying triggers of uncertainty may continue throughout the illness trajectory in patients with PBTs. In addition, symptoms may result from permanent brain injury, making amelioration of these symptoms impossible. Evaluating potential mediators (intervening variables) between PBT patients' uncertainty and perceived symptom distress may provide additional targets for interventions that may reduce the impact of symptoms and quality of life.

In the current study, we examined the influences of patients' treatment stage and functional status on uncertainty. We also tested the direct impact of uncertainty on negative mood states and patient-perceived symptom severity as well as the mediating effects of the negative mood states between uncertainty and symptom severity (Fig. 1). In this study, we considered mood states as mediators, and models of 5 negative mood states (tension, depression, anger, fatigue, and confusion) were tested individually. Supported by the significance of the models, we propose that, other than

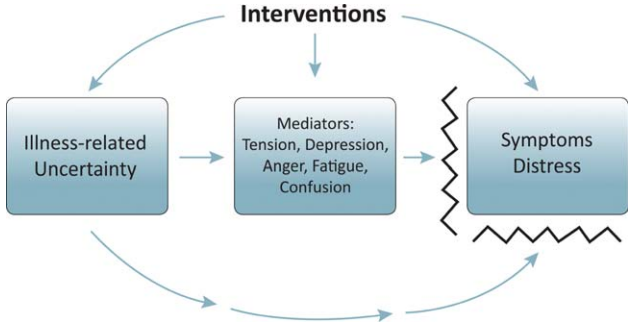

Figure 1. Conceptual framework.

interventions aimed directly at uncertainty and symptoms, decreasing mood disturbance caused by uncertainty also may reduce symptom distress in patients with PBTs and promote positive patient adaptation to the illness experience.

MATERIALS AND METHODS

Participants and Procedure

This study was a secondary data analysis using data collected as part of validation of the MUIS-BT study.[9] To evaluate the feasibility, reliability, and validity of the MUIS-BT, 186 patients with PBTs participated in the original study. The sample size was primarily based on the ability to assess the internal consistency of the MUIS-BT. All participants were recruited from The University of Texas MD Anderson Cancer Center (MDACC) Brain and Spine Center Clinic in Houston, Texas. Approval for the study was obtained from the Institutional Review Board of MDACC before the study. The regulations for protecting confidentiality in the hospital were followed.

Patients who presented for evaluation at the MDACC Brain and Spine Clinic were screened for eligibility. All patients with PBTs who meet eligibility criteria were initially approached about participation. The entry criteria included the following: 1) age $\geq$18 years; 2) the patient was able to speak, read, and write English; 3) the patient was diagnosed with PBT; and 4) the patient was without cognitive deficits, such as aphasia or other alteration in mental status, as determined by the treating physician, that would preclude the ability to self-report uncertainty, mood states, and symptoms or to provide informed consent. Patients could be recruited in different treatment stages during the illness trajectory and were categorized into 1 of the 3 treatment groups: 1) newly diagnosed before the initiation of chemotherapy and/or radiation treatment, 2) receiving treatment at the time of the clinical visit with or without MRI evaluation, and 3) in follow-up without active treatment.

A trained data collector recruited a convenience sample at MDACC and approached potentially eligible individuals in the clinic. Patients answered the questionnaires before they were examined by the physician/nurse practitioner or before results of the MRI examination or other tests were reported on the day consent was provided. The data collector then completed the clinical assessment tool, obtaining clinical information, such as tumor type, tumor location, and treatment history.

Instruments

Five instruments were used in this study: The MUIS-Brain Tumor Form, the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT), the Profile of Mood States-Short Form (POMS-SF), a demographic information sheet, and a clinician checklist.

The Mishel Uncertainty in Illness Scale-Brain Tumor Form

The MUIS-BT,[9] which is the modified, 33-item Mishel Uncertainty in Illness Scale (MUIS),[12] was used to measure uncertainty. The original MUIS has been used extensively with cancer patients. Reports on its validity and reliability have been published.[12-14] The MUIS-BT has acceptable psychometric integrity when completed by patients with PBTs.[9] MUIS-BT employs a 5-point Likert scale in which 1 indicates "strongly disagree" and 5 indicates "strongly agree." Each item asks about illness-related uncertainty that patients feel on the day they are in the clinic. After reverse scoring appropriate items, a total score is calculated by summing all items, and higher scores indicate greater perceived uncertainty.

The MD Anderson Symptom Inventory-Brain Tumor Module

The MDASI-BT consists of 22 symptoms rated on an 11-point scale (from 0 to 10) to indicate the presence and severity of the symptom, with 0 indicating "not present" and 10 indicating "as bad as you can imagine." Symptoms that are included on the instrument are those generally associated with cancer treatment and the neurocognitive symptoms observed in patients with PBTs. Each symptom is rated at its worst in the last 24 hours. The MDASI-BT also includes ratings of how much symptoms interfered with different aspects of a patient's life in the last 24 hours, but those items were not included in the model testing for the current study. The average time to complete the MDASI-BT is 5 minutes. The scale demonstrates validity and reliability in patients with PBTs.[15]

The Profile of Mood States-Short Form

Mood was assessed using the POMS-SF. The original 65-item Profile of Mood States was developed by McNair et al[16] to assess transient distinct mood states. The scale consists of 6 factors: tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, vigor-activity, and confusion-bewilderment. The 37-item short form (POMS-SF) of the POMS was developed by Shacham[17] for physically ill individuals, as patients with cancer. The short form retains the 6 subscales, and the validity and 6-subscale structure and internal consistency have been examined.[17,18] For the current study, we used only the 5 subscales that measured negative moods, which means that

data for vigor-activity were not included in our model testing.

Demographic information sheet

The demographic Information Sheet collected study participant sex, ethnicity, age, level of education, marital status, religious background, and employment status. This form was adapted from a similar tool that was used in the validation study of the MDASI-BT.[15] Data collected in this form were used to determine potential variables that may have an impact on uncertainty, mood, and symptom distress in patients with PBTs.

Clinical assessment tool

The clinical assessment tool included information on tumor type, disease status (newly diagnosed, on treatment with or without MRI evaluation, or on follow-up and not on active treatment), tumor location, bidimensional tumor measurement, concurrent medications (steroids, anticonvulsants, analgesic agents, antidepressants), type of visit (clinical evaluation or MRI visit), and functional status measured by the Karnofsky performance status (KPS) scale, which is considered an index of disease severity.[15] Data collected in this form also were used to determine potential variables that may have an impact on uncertainty, mood, and symptom experience.

Statistical Analyses

The obtained data were analyzed using the statistical software package IBM SPSS Statistics 19 (SPSS, Inc., Chicago, Ill). The total scores for each scale and subscale were calculated after some items with reverse scores had been recoded. Missing scale items were replaced using the mean of the nonmissing items on the same scale for each individual as long as at least 75% of the items were nonmissing. The descriptive statistics of central tendency, such as means, standard deviations, and ranges, were calculated. Demographic and clinical data were analyzed to describe the sample. Means, standard deviations, and ranges were calculated to describe the distribution of scores on continuous variables and frequencies, and percentages were used to describe scores on categorical variables.

To determine the relations among uncertainty, mood states, symptom severity, and patients' treatment stage and functional status in terms of KPS score, structural equation modeling (SEM) was conducted to indicate the strength of influence among variables by getting an overall fit of model with the data. One major benefit of SEM is its ability to deal with intervening variables (mediators), which allows for statistical testing on both direct and indirect effects simultaneously. In this study, we considered mood states as mediators, and the models of 5 negative mood states (ie, tension, depression, anger, fatigue, and confusion) were tested independently. Another advantage of using SEM is that it allows the fit of latent variables into the models. In this study, we viewed uncertainty as a latent concept that can be explained by 4 factors: the 4 subscales of the MUIS-BT.[9]

In the current study, models were analyzed using Mplus software version 5.1 (Muther & Muthen, Los Angeles, Calif).[19] SEM was used to test the significance of direct and indirect relations among uncertainty, mood states, and symptom severity. Furthermore, the influence of patients' functional status and treatment stage was estimated by entering these variables into the model at the same time. Model parameters were estimated using maximum likelihood methods. Data that were missing at the variable level were ignored (ie, treated as "missing at random"). All observed data were included when fitting the models.

For this study, we were interested in testing the hypothesis that uncertainty is directly and indirectly correlated to symptom severity (Fig. 1). Thus, SEM can be an inclusive statistical approach to testing correlations for the path model and the measurement model simultaneously. The first step was to specify the measurement model with confirmatory factor analysis that would represent the latent variable (ie, uncertainty). This allowed for an examination of an a priori measurement model corresponding to the latent variable indicators. After it was confirmed that uncertainty could be significantly explained by its 4 factors, structured models were defined and accomplished by indicating the relations between each of the variables in the models.

The model fit was evaluated using various criteria. The chi-square statistic is a test that indicates the closeness of the covariance matrix suggested by the model to the sample covariance matrix.[20] A significant test result ($P < .05$) indicates a poor fit. After this test, the fit of the models was assessed using several values, including the root mean square error of approximation (RMSEA), along with a 90% confidence interval, the Comparative Fit Index (CFI), the Tucker-Lewis Fit Index (TLI), and the standard root mean square residual (SRMR). For the RMSEA, the general rule of thumb is that values $<.05$ indicate close fit, values between .05 and .10 indicate marginal fit, and values $>.10$ indicate poor fit.[21] For both the CFI and the TLI, a value of 1 indicates perfect fit, and the general rule of thumb is that values $>.90$ indicate

adequate fit.[22,23] Also, SRMR values <.08 indicate a very good fit between the model and the data.

RESULTS

Demographics

In total, 186 patients with PBTs were recruited for this study. Participants were primarily white (80%) men (53%). Glioblastoma was the most common pathologic diagnosis. Participating patients ranged in age from 19 years to 80 years (mean age, 44.2 years). Thirty-two of 186 patients (17%) were newly diagnosed with PBTs, 85 (46%) were currently receiving treatment, and 69 (37%) were in follow-up and were not receiving active treatment. The majority of patients (81%) had a KPS score ≥90, and only 19% of patients had a KPS score ≤80. Table 1 lists the demographics and the disease-related characteristics of the patient sample.

Descriptive Statistics of the Measures

Only 6 eligible patients refused to participate when approached by the research assistant. There was no single item in the measures that was not answered by more than 4 participants. All participants answered >75% of the questions on each questionnaire. Because all participants met our criterion answered at least 75% of the items, we did not drop data from any participant.

The mean, standard deviation, and potential score range for all measures are presented in Table 2. We also examined the internal consistency of the 4 MUSI-BT subscales and the 5 POMS-SF subscales by calculating the coefficient α values. Overall, these results indicated a high

TABLE 1. Demographic and Clinical Characteristics

Demographic Characteristics, N = 186	No. (%)	Clinical Characteristics, N = 186	No. (%)
Age: Mean [range], years	44.2 [19-80]	Patient group	
Sex		Newly diagnosed	32 (17.2)
Women	87 (46.8)	On treatment	85 (45.7)
Men	99 (53.2)	Follow-up/no active treatment	69 (37.1)
Marital status		Recurrence	
Divorced, separated, widowed	19 (10.2)	Yes: First time	57 (30.6)
Married	139 (74.7)	Yes: Repeated	17 (9.1)
Single	28 (15.1)	No	112 (60.2)
Employment status		Diagnosis	
Employed: Part-time, full-time, homemaker	94 (50.5)	Astrocytoma	44 (23.7)
Employed: Sick leave, disability	24 (12.9)	Oligodendroglioma	38 (20.4)
Retired	18 (9.7)	Oligoastrocytoma	8 (4.3)
Unemployed because of diagnosis of tumor	31 (16.7)	Ependymoma	4 (2.2)
Unemployed: Prior to diagnosis, student	13 (7)	Glioblastoma and gliosarcoma	81 (43.5)
Missing	6 (3.2)	Other	11 (5.9)
Hispanic		Tumor Grade	
Yes	172 (92.5)	1	3 (1.6)
No	13 (7)	2	38 (20.4)
Missing	1 (0.5)	3	59 (31.7)
Ethnic background		4	84 (45.2)
Asian or Pacific Islander	11 (6)	Missing	2 (1.1)
Black	10 (5.4)	Tumor location	
Native American or Alaska Native	3 (1.6)	Infratentorial	8 (4.3)
White	149 (80.1)	Supratentorial	178 (95.7)
Missing	13 (7)	Left side	103 (55.4)
Level of education		Right side	78 (41.9)
Some high school	6 (3.2)	Midline	5 (2.7)
High school graduate	28 (15.1)	Surgery type	
Some college	46 (24.7)	Biopsy	52 (28)
College graduate	53 (28.5)	Partial resection	63 (33.9)
Postgraduate/advanced degree	53 (28.5)	Gross total resection	70 (37.6)
Household income		Missing	1 (0.5)
≥$100,000	59 (31.7)	Results of MRI	
$50,000 to $99,999	51 (27.4)	Response	4 (2.2)
$30,000 to $49,999	27 (14.5)	Stable	116 (62.4)
<$30,000	27 (14.5)	Progression	27 (14.5)
Missing	22 (11.8)	Newly diagnosed	37 (19.9)
		Missing	2 (1.1)
		KPS	
		≤80	36 (19.4)
		≥90	150 (80.6)

Abbreviations: KPS, Karnofsky performance status; MRI, magnetic resonance imaging.

TABLE 2. Descriptive Statistics of the Measures

Measure	No. of Items	Range	Mean ± SD	Cronbach α
MDASI-BT	22	0-7.4	1.68 ± 1.48	.92
POMS				
Anger	7	0-26	3.78 ± 5.49	.92
Confusion	5	0-18	4.75 ± 4.16	.81
Depression	8	0-28	4.34 ± 6.07	.92
Fatigue	5	0-20	5.98 ± 5.02	.91
Tension	6	0-23	5.80 ± 5.42	.90
Uncertainty (MUIS-BT)				
Ambiguity or inconsistency	16	16-66	34.03 ± 10.84	.90
Unpredictability of disease prognosis	7	7-32	17.97 ± 5.33	.77
Unpredictability of symptoms or other triggers	6	6-27	16.63 ± 4.77	.75
Complexity	4	4-20	7.35 ± 2.53	.65

Abbreviations: MDASI-BT, MD Anderson Symptom Inventory-Brain Tumor Module; MUIS-BT, Mishel Uncertainty in Illness Scale-Brain Tumor Form; POMS, Profile of Mood States.

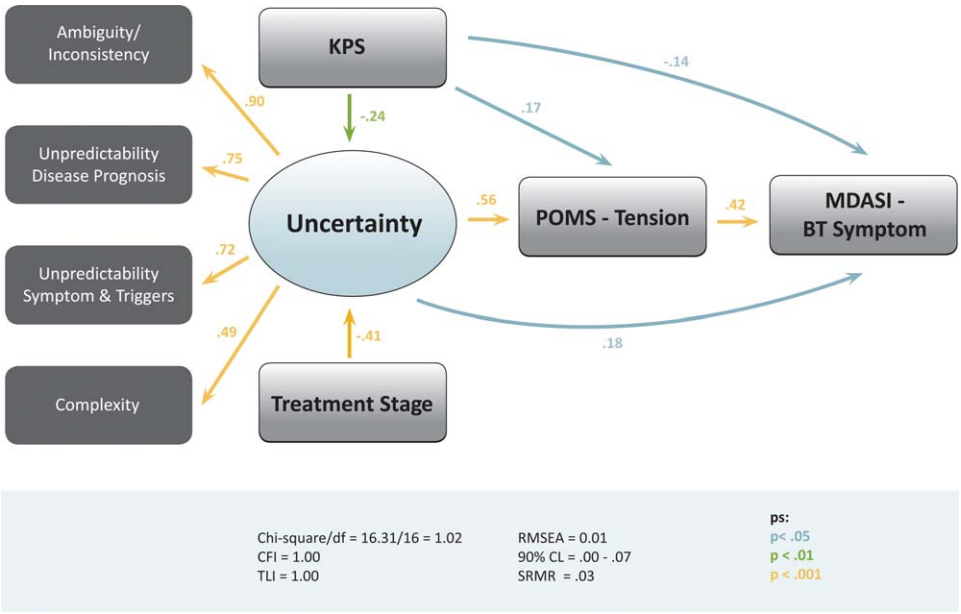

Figure 2. Uncertainty - tension - symptom model. KPS indicates Karnofsky performance status; n.s., nonsignificant; POMS, Profile of Mood States; MDASI-BT, MD Anderson Symptom Inventory-Brain Tumor Module; df, degrees of freedom; CFI, Comparative Fit Index; TLI, Tucker Lewis Fit Index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; CI, confidence interval.

level of reliability for the MDASI-BT, the MUIS-BT, and the POMS-SF (see Table 2).

Model Testing

Five separate models of each negative mood state measured by the POMS-SF (ie, tension, depression, anger, fatigue, and confusion) were created. These models included paths from functional status to uncertainty, from treatment stage to uncertainty, from uncertainty to mood, from functional status to mood, from mood to symptom severity, from functional status to symptom severity, and from uncertainty to symptom severity (Figs. 2-6).

Each model was tested for the fit of the data using model fit statistics, and we observed that the models fit the data adequately. All proposed paths were significant ($P < .05$) for the model of tension (Fig. 2); however, for the models of anger, depression, and fatigue, the paths from KPS to mood and from KPS to symptom were not significant (Figs. 3-5), indicating no direct correlation between KPS and either negative mood states or

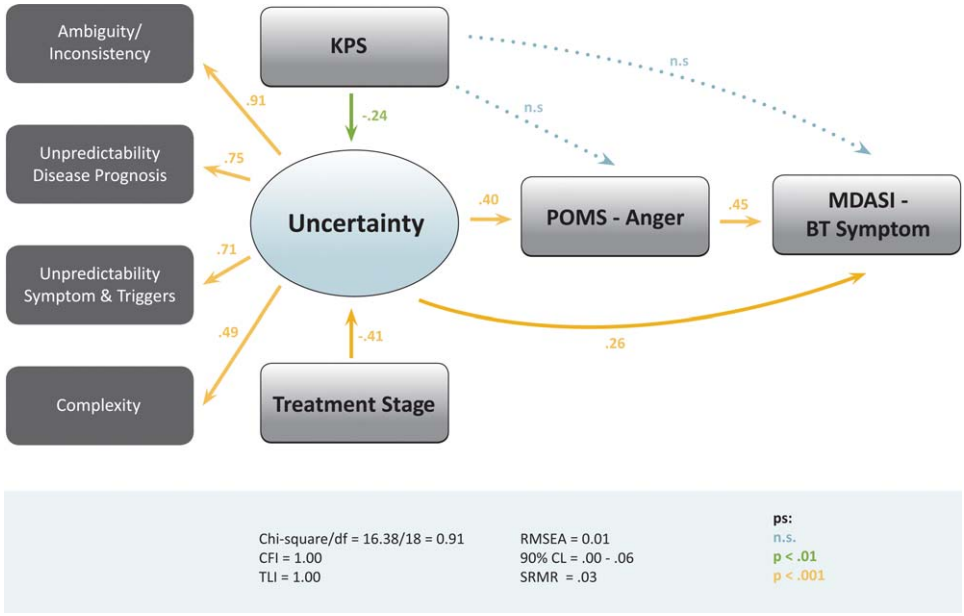

Figure 3. Uncertainty - anger - symptom model. KPS indicates Karnofsky performance status; n.s., nonsignificant; POMS, Profile of Mood States; MDASI-BT, MD Anderson Symptom Inventory-Brain Tumor Module; df, degrees of freedom; CFI, Comparative Fit Index; TLI, Tucker Lewis Fit Index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; CI, confidence interval.

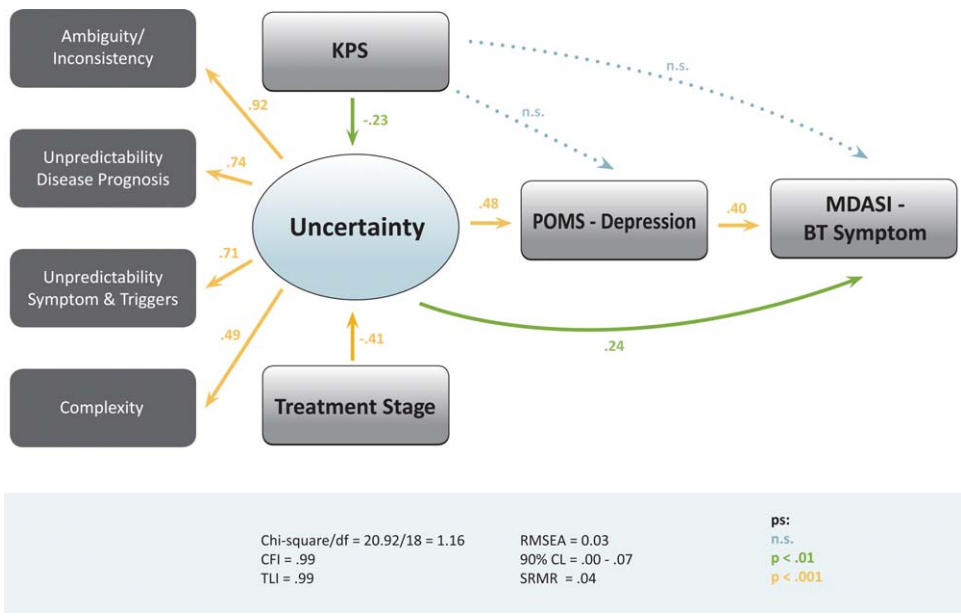

Figure 4. Uncertainty - depression - symptom model. KPS indicates Karnofsky performance status; n.s., nonsignificant; POMS, Profile of Mood States; MDASI-BT, MD Anderson Symptom Inventory-Brain Tumor Module; df, degrees of freedom; CFI, Comparative Fit Index; TLI, Tucker Lewis Fit Index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; CI, confidence interval.

symptom severity. For the model of confusion (Fig. 6), the paths from KPS to mood and symptom severity and from uncertainty to symptom severity were not significant, indicating that symptom severity only indirectly influenced by uncertainty through the mood state of confusion.

For the final model fit, the nonsignificant paths were deleted (ie, the coefficients of all nonsignificant paths

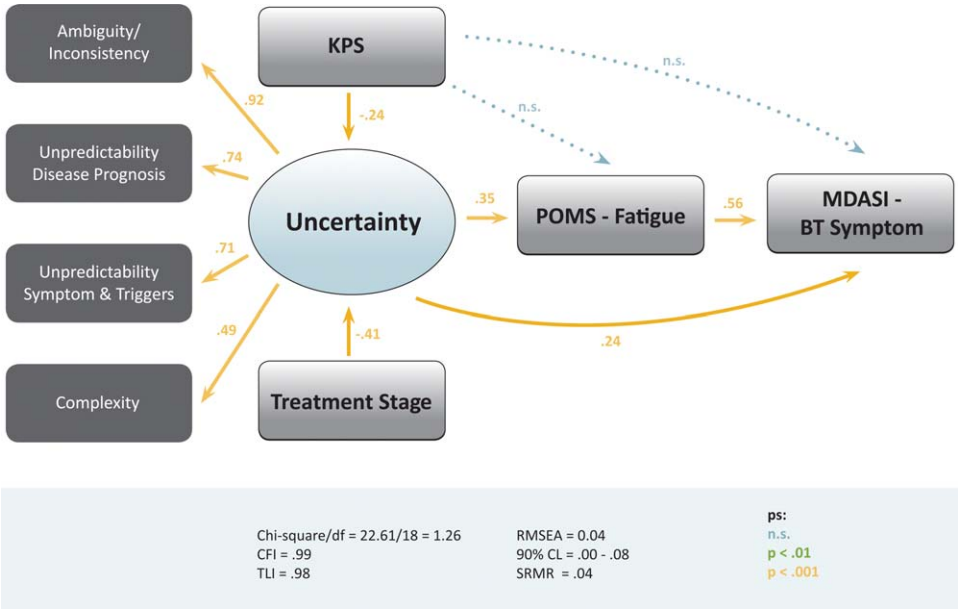

Figure 5. Uncertainty - fatigue - symptom model. KPS indicates Karnofsky performance status; n.s., nonsignificant; POMS, Profile of Mood States; MDASI-BT, MD Anderson Symptom Inventory-Brain Tumor Module; df, degrees of freedom; CFI, Comparative Fit Index; TLI, Tucker Lewis Fit Index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; CI, confidence interval.

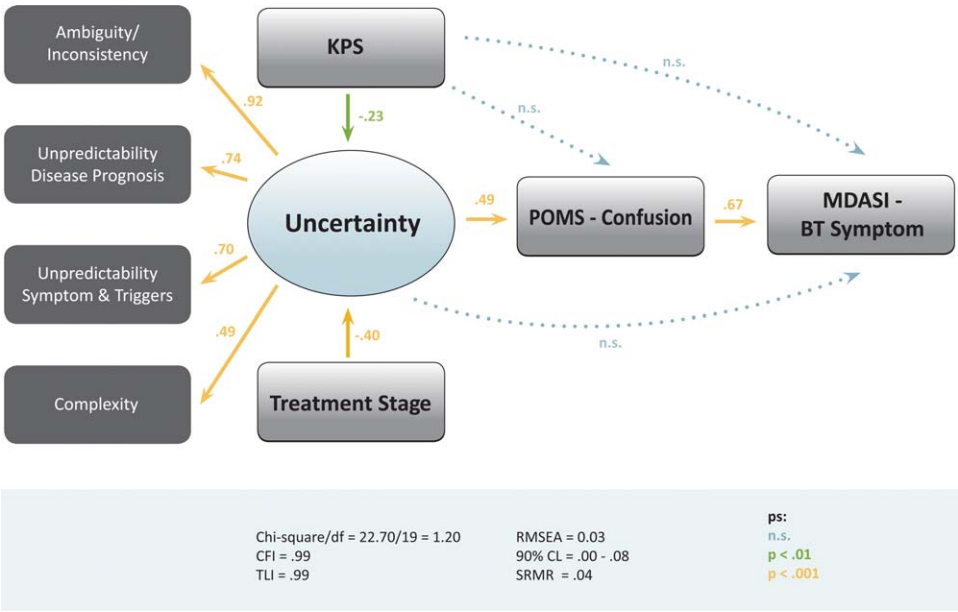

Figure 6. Uncertainty - confusion - symptom model. KPS indicates Karnofsky performance status; n.s., nonsignificant; POMS, Profile of Mood States; MDASI-BT, MD Anderson Symptom Inventory-Brain Tumor Module; df, degrees of freedom; CFI, Comparative Fit Index; TLI, Tucker Lewis Fit Index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; CI, confidence interval.

were restricted to equal zero because of the small ratio of estimated error to standard error). Subsequent analyses demonstrated that the fit indices of the 5 modified models all provided strong evidence of a close fit with an RMSEA $<.05$, an SRMR $<.08$, a CFI close to 1.0, and a TLI close to 1.0 (see Table 3). Therefore, all 5 of the final models were considered significant and were not rejected by the data, suggesting potential paths for the correlations

TABLE 3. Model Fit Statistics

Model	Chi-Square/df	*P*	CFI	TLI	SRMR	RMSEA	
						Estimate	90% CI
Tension	1.02	.43	1.00	1.00	0.03	0.01	0.00-0.07
Anger	0.91	.57	1.00	1.00	0.03	0.01	0.00-0.06
Depression	1.16	.28	0.99	0.99	0.04	0.03	0.00-0.07
Fatigue	1.26	.21	0.99	0.98	0.04	0.04	0.00-0.08
Confusion	1.20	.25	0.99	0.99	0.04	0.03	0.00-0.08

Abbreviations: CFI, Comparative Fit Index; CI, confidence interval; df, degrees of freedom; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; TLI, Tucker Lewis Fit Index.

TABLE 4. Standardized Parameter Estimate of the Correlations in the Final Models

Model	KPS to Uncertainty	TX Stage to Uncertainty	Uncertainty to POMS	KPS to POMS	POMS to Symptom	KPS to Symptom	Uncertainty to Symptom
Tension (Fig. 2)	−.24[a]	−.41[b]	.56[b]	.17[c]	.42[b]	−.14[c]	.18[c]
Anger (Fig. 3)	−.24[a]	−.41[b]	.40[b]	NS	.45[b]	NS	.26[b]
Depression (Fig. 4)	−.23[a]	−.41[b]	.48[b]	NS	.40[b]	NS	.24[a]
Fatigue (Fig. 5)	−.24[b]	−.41[b]	.35[b]	NS	.56[b]	NS	.24[b]
Confusion (Fig. 6)	−.23[a]	−.40[b]	.49[b]	NS	.67[b]	NS	NS

Abbreviations: KPS, Karnofsky performance status; NS, not significant; POMS, Profile of Mood States; TX, treatment.
[a] $P < .01$.
[b] $P < .001$.
[c] $P < .05$.

among uncertainty, mood states, and symptom severity. Thus, uncertainty not only has a direct impact on symptoms but also results in mood disturbances, which influence patients' perception of the severity of symptoms.

Significant Direct and Indirect Effects

After confirmation that all working models were significant, the next analysis determined whether each component had a direct or an indirect effect on the others. Standardized estimates of all significant paths in the 5 models are presented in Table 4. Also, uncertainty is significantly represented by 4 factors: ambiguity or inconsistency of illness-related events, unpredictability of disease prognosis, unpredictability of symptoms or other triggers, and complexity of the disease process. The standardized factor loading of the measurement models are presented in Table 5. The coefficients of significant paths are also presented in Figures 2 through 6.

In all 5 models, patients' KPS scores had a significantly negative impact on uncertainty ($P < .01$), indicating that lower functional status was associated with greater uncertainty. In addition, patients' treatment stage had a significantly negative effect on uncertainty ($P < .001$), indicating that an earlier stage in the illness trajectory was associated with greater uncertainty.

For the model of tension (Fig. 2), KPS also had a significant negative impact on tension ($P < .05$) and symptom severity ($P < .05$). For the other 4 mood states (Figs. 3-6), there was no significant correlation either between KPS and the specific mood state (Figs. 3-6, dotted arrows) or between KPS and the severity of symptoms (Figs. 3-6, dotted arrows). Although KPS had a direct impact on uncertainty in these models, its effect on mood and symptom severity only occurred indirectly through uncertainty.

Uncertainty had a significant direct impact on all negative mood states ($P < .001$), and those negative mood states had a significant, direct impact on symptom severity ($P < .001$), with higher levels of uncertainty associated with worse negative mood states and symptom severity. In all models (except uncertainty-confusion-symptom), uncertainty had an impact not only directly on symptom severity but also indirectly through negative mood states (Figs. 2-5).

DISCUSSION

The results from the study clearly demonstrated distinct pathways of the correlations between uncertainty, mood states, and symptom severity for patients with PBTs. Because of the severity of the illness and the erratic nature and ambiguity of the symptoms, patients with PBTs continue to experience uncertainty during the illness trajectory. According to Mishel,[3] uncertainty in illness is more

TABLE 5. Standardized Factor Loading of the Measurement Models[a]

Model	Ambiguity/Inconsistency	Unpredictability of Disease Prognosis	Unpredictability of Symptoms/Other Triggers	Complexity
Tension	.90	.75	.72	.49
Anger	.91	.75	.71	.49
Depression	.92	.74	.71	.49
Fatigue	.92	.74	.71	.49
Confusion	.92	.74	.70	.49

[a] Note that the *P* value for all models was $< .001$.

commonly appraised as a danger in Western culture by individuals who are ill and is commonly associated with negative emotional outcomes, such as anxiety and depression.[10] Our previous studies indicated that negative mood states and patient-perceived symptom severity are both significantly correlated with illness-related uncertainty in patients with PBTs.[9,11] This study further illustrated not only that uncertainty and negative mood states have a direct impact on symptom severity perceived by patients with PBTs but also that the mood states mediate the relation between uncertainty and symptom severity (see Figs. 2-6).

The current research finding supports our conceptual framework (Fig. 1), indicating that intervening in negative mood states may help patients with PBTs to relieve perceived symptom distress when their mood is impacted by an elevation in the level of uncertainty. This is critical, because many symptoms may result from brain injury and represent a permanent dysfunction and may not be amendable to interventions to reduce or eliminate the symptoms directly. If a patient's perception of the severity of symptoms can be modified by directed interventions at either uncertainty or mood, then this may have a significant impact on the patient's quality of life despite tumor-related or treatment-related symptoms.

On the basis of the theoretical model proposed in this study, uncertainty is also influenced directly by a patient's functional status and treatment stage. The research findings indicate that having worse functional status and being earlier in the treatment trajectory are associated significantly with greater uncertainty. The significant correlations are consistent with Mishel's[3] theory that the inability to determine the meaning of illness-related circumstances may cause a cognitive state of uncertainty, especially when patients are newly diagnosed with a severe illness. By perceiving that uncertainty may arise from illness-related situations, the level of uncertainty is also more likely to change contextually after alteration of an ill patient's medical condition.

According to the findings of the current study, patients with PBTs feel more uncertain when their functional status is lower. The significant role of functional status validates the importance of considering patient's clinical characteristics when studying uncertainty. We also tested the influence of functional status in terms of KPS on negative mood states and symptom severity. However, the only significant, direct correlation observed was between KPS and tension, suggesting that patients are more anxious when their functional status is lower (Fig. 2). The impact of KPS on other negative mood states was fully mediated by uncertainty in this study, and there was no significant correlation between KPS and symptom severity. Patients with lower functional status may feel angrier, more depressed, fatigued, and confused because of uncertainty triggered by the symptoms of illness itself or the side effects of cancer treatment (Figs. 3-6).

When patients reported higher levels of uncertainty in this study, they felt overwhelmed by illness-related situations that they did not understand or could not control.[9] Several intervention protocols have been developed and have been proven effective for managing uncertainty in patients with breast cancer and patients with localized or advanced prostate cancer.[10] Although the uncertainty in PBTs may not be totally avoided, promoting more positive mood states by stress-relieving interventions, such as relaxation training; cognitive-behavioral therapies, such as improving coping skills; or enhancing patient-provider communication may help patients perceive less symptom distress.

By treating negative mood states as an intervening variable, our findings indicate that mood state mediated the correlation between uncertainty and perceived symptom severity in patients with PBTs. Furthermore, the study demonstrated that uncertainty was well represented by 4 factors: ambiguity or inconsistency, unpredictability of disease prognosis, unpredictability of symptoms or other triggers, and complexity (see Table 5). To develop more individualized interventions that may decrease uncertainty and negative moods, the recognition of these 4 factors help health care providers identify distinct

sources of uncertainty experienced by different patients with PBTs.

Strengths of the current study include the inclusion of patients at multiple points in the disease process and the relatively large sample size with few missing data. Major variables, such as uncertainty and symptom severity, were measured by using questionnaires that have been validated in patients with PBTs. Although the POMS-SF is not specifically validated in patients with PBTs, the internal consistency of each subscale was high in this study (see Cronbach α values, Table 2). This novel study indicated a significant association between levels of uncertainty and both worsened mood and patient-perceived symptom severity using SEM. The findings provide potential targets for developing interventions that may reduce symptom distress perceived by patients with PBTs, thus promoting positive adaptation to the illness experience. Limitations of the study include the homogeneity of the sample (largely white, married, well educated participants) and the nature of the study as a secondary data analysis with a self-selected sample that was recruited at a single hospital.

In conclusion, uncertainty is a significant psychological experience for patients with PBTs. Illness-related uncertainty has a significant influence on patients' mood states and symptoms. Although many studies have demonstrated the significant impact of uncertainty on negative psychological outcomes and symptom severity, the current results support our hypothesis that it may be possible to decrease symptom severity and gain better quality of life for patients with PBTs by reducing their uncertainty and promoting more positive mood states. These findings provide support for the development of guidelines for health care providers in delivering a more individualized symptom-management paradigm and lessening illness-related uncertainty throughout the entire illness trajectory of PBTs.

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CONFLICT OF INTEREST DISCLOSURES

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