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Depression among Adult Patients with Primary Brain Tumor: A Cross-Sectional Study of Risk Factors in a Low-Middle Income Country

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Abstract:

OBJECTIVE:
The prevalence of depression among primary brain tumor patients ranges from 15% to 40% globally. Several individual and clinical factors contribute in the development of depression. However, their association with depression in Pakistani setting has not yet been assessed. Thus, we aim to study the factors associated with depression among adult primary brain tumor patients at a tertiary care hospital in Karachi, Pakistan.

METHOD:
This study included 132 patients with biopsy proven primary brain tumor in various stages of treatment at a tertiary care hospital in Karachi, Pakistan. Patients completed a set of pre-structured questionnaire evaluating patient-related, tumor-related, and treatment-related factors. Scores of 10 to 27 on Patient Health Questionnaire-9 (PHQ-9) were indicative of screen positive for depression. Cox algorithm regression assessed association between patient-related, tumor-related, and treatment-related factors and depression. Propensity scores were computed to examine the factors associated with impaired functional status.

RESULTS:
Fifty one (39%) patients in our study screened positive for depression on PHQ-9. There was significant association between depression and KPS scores (Prevalence Ratio: 3.25 and Confidence Interval: 1.87-5.62) after controlling covariates. Propensity scores predicted positive association between KPS (functional status) and unemployment, treatment stage, and tumor recurrence. Tumor-related and treatment related factors including tumor grade, location, type, and hemispheric lateralization were found insignificant.

CONCLUSION:

Depression is common in patients with primary brain tumor. Impaired functional status has direct impact on depression in these patients. Incorporating psychosocial domain earlier in the course of treatment needs to be considered for better neuro-oncology management of primary brain tumor patients.

Strengths and Limitations of this study:

- The major strength of this study is its ability to analyze data using robust statistical techniques.
- To our knowledge, this was the first study conducted in Pakistan to explore depression and its associated factors among primary brain tumor patients.
- A single screening tool to measure depression instead of physician-rated measures or mini-interviews to verify the results of PHQ-9.
- The study included cross-sectional data instead of prospective data which limits both temporality and direction of causation.

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Background:

Although primary brain tumour account for a relatively small percentage of all cancers, it is considered as one of the most devastating types of cancers among adult population [1]. The incidence of primary brain tumor is approximately 9/100,000/year worldwide with higher rates in western countries as compared to low-middle income countries (LMIC) [2]. Interestingly, primary brain tumors rank highest among cancers that cause emotional and psychological burden for patients [3][4].

World Health Organization defines depression as a feeling of sadness, loss of pleasure from daily living activities and lack of self-worth [5]. It is estimated that depression affects about 350 million individuals worldwide and according to the Global Mental Health Survey (2014), nearly 1 in 20 individuals report having at least one episode of depression within a year [6]. Population based researches report a prevalence of clinical depression ranging between 2% to 5% worldwide [7]. The worldwide prevalence of depression in cancer patients is 25% with higher rates among Asian countries [8]. The estimated prevalence of clinically diagnosed depression in Pakistan is approximately 6% out of which 3% are cancer patients [9]. Depression rates among primary brain tumor patients ranges from 15% to 40% with highest rates among glioma patients [10]. However, it is suggested that these rates likely under-represent the true incidence of depression [11]. A systematic review of 42 observational studies reports that the prevalence of depression among glioma patients ranges between 0 to 93% with a median prevalence of 27% [12].

Depression in brain tumor patients is multifactorial and there are several factors contributing to its development, including individual, tumor-related, and disease-related factors [10]. All the studies on this topic to date have been conducted in western population, where the psychosocial circumstances are much different from Pakistani population, for example whereas in UK and US, where most of the data comes from, majority of patients are financially supported by third party payers i.e., state or insurance. In contrast, approximately 85% of patients in Pakistan, and a few other South Asian LMIC countries, are out of pocket payers both for their treatment, and rehabilitation [13]. This we believe, may be the cause of additional psychological burden on the patients. This and several other factors are unknown in the context of settings of low and middle income countries and require a series of researches to establish associations. The aim of this study was to assess association between depression and patient-related, tumor-related, and treatment-related variables among adult primary brain tumor patients in a LMIC.

Methods:

Study Design:

An analytical cross-sectional study design was employed to determine the association between patient related, tumor related and treatment related factors with depression among adult primary brain tumor patients. Non-probability consecutive sampling was used to recruit subjects. All the patients who met eligibility criteria of the study and were willing to give consent were included in the study.

Site and setting

The study was approved by the institution review board (5009-CHS-ERC-17). The recruitment was conducted at tertiary care setting of Karachi, Pakistan and 132 patients with biopsy proven primary brain tumors at various stages of treatment were enrolled. These patients were contacted in neurosurgery wards, neurosurgery and oncology outpatient clinics, and oncology day care suits from November 2017 to July 2018.

Participants

Participants were all adult patients (aged 18 years and above) under treatment at a tertiary care setup. Each patient was enrolled after a written, informed consent. The exclusion criteria for study participants were as follows: diagnosis of depression prior to the diagnosis of brain tumor, confused or incoherent patients and patients with problems with speech or comprehension that prevents them from completing the questionnaire, patients with co-existing systemic malignancies apart from primary brain tumor, and any severe comorbid medical illness such as liver cirrhosis, systemic infections like HIV, and hepatitis which can cause altered mental status.

Procedure

Participant's eligibility was determined by medical record files. Potentially eligible participants were approached by the investigator during a scheduled follow-up visit at neurosurgery and oncology outpatient clinics or during inpatient hospital stay post-surgery. Each patient after the consent were interviewed for 15-20 minutes to fill a pre-structured questionnaire for assessing predictor variables and PHQ-9 scale for screening of depression. The questionnaire was also pilot tested on 10 participants before actual administration.

Measures

We divided all the associated factors into three distinct categories that were patient-related, tumor-related, and treatment-related variables. Patient-related factors comprised of demographic and socio-economic variables including age, gender, marital status, number of dependents, children under 18 years, education, occupation, employment status, residency, travelling cost, care giver support, current smoking status, past/current medical illness, history of psychological dresses, strategies to handle stress (isolation, aggression, prayers, crying, sleeping, addiction, and mind diversions) and functional status. Participant's functional status was assessed using Karnofsky performance score (KPS). KPS scores less than 70 were indicative of impaired functional status. Socio-economic status (SES) was also computed using factorial analysis. Tumor-related and treatment-related variables were assessed by medical record review and included tumor histology, tumor grade, recurrence, hemispheric lateralization, first symptoms, brain structures involved, and cognitive impairment. Treatment related variables included stage of treatment, number of chemotherapy cycles, duration since diagnosis, radiation therapy, current use of steroids and anti-epileptic drugs, and treatment cost. The complete list of variables is mentioned in Table 1.

Depression

Primary brain tumour patients were screened for depression using Urdu version of patient health questionnaire-9 (PHQ-9). The PHQ-9 is a self-rated screening tool which contains 9 items that corresponds to DSM-V criteria of depression and was rated on Likert scale of four points. All the patients were classified into two groups based on the scores on PHQ-9 scale. Participants with a score of ≥ 10 were classified as screened positive for depression.

PHQ-9 score of 10 or above has a sensitivity and specificity of 88% for major depressive symptoms. A recently conducted validation study on Urdu version (national language of Pakistan) of PHQ-9 by Gholizadeh, 2017 [23], reported a specificity of 94% and false positive rate of 6% only.

Statistical Analysis:

Power calculation was derived from previous studies [14, 15]. We calculated sample size using Openepi [16] with a power of 80%, depression to no depression ratio of 1:2, prevalence ratio of 2 and 30% to 70% range of depression for different factors yield a sample size of 108. Adding 20% of attrition rate the final sample size came out to be 130 participants. We used STATA version 12.0 [17] to perform all the analysis. For descriptive data of continuous variables mean and standard deviations were computed. Frequencies and percentages were computed for all qualitative variables. We applied logistic regression cox algorithm to obtain crude and adjusted prevalence ratios. At univariate level, independent variables were considered significant if p-value was ≤ 0.25. We also checked multicollinearity between all the predictor variables. Stepwise model building technique was used for adding up variables. The cut-off for the significance of predictor variable at multivariable analysis was 0.05. Propensity scores were computed to identify factors associated with functional status.

Patient and public involvement

None of the study participants were involved in the design or conduct of this study and no patient opinion regarding the study has been obtained. The results have been reported to head of Mind and brain service line at AKUH in Karachi which primarily deals with neuro-oncology patients.

Results:

Descriptive characteristics of study participants:

The mean age (± SD) of study participants was 43.25 (± 12.28) years, with 86 (65%) males and 46 (35%) female. Fifty one (39%) study participants were screened positive (Scores of 10 and greater on PHQ-9) for depression while 81 participants (61%) were screened negative (Scores less than 10 on PHQ-9) for depression. Table 1 shows descriptive characteristics of study participants.

Table 1: Summary of descriptive characteristic of study participants

PATIENT-RELATED VARIABLES			
S#	Variables	Total N (%)	Screened positive for depression (PHQ-9 ≥ 10) N (%)
1	**Marital Status**		
	Married	117 (89)	43 (37)
	Unmarried/Single/Separated/Divorced	15 (11)	8 (53)
2	**Children under 18 years**		
	Yes	75 (57)	32 (43)
	No	33 (25)	10 (30)
	Unmarried	24 (18)	9 (38)
3	**Current Employment status**		
	Able to work	65 (49)	18 (28)
	Unable to work	24 (18)	13 (54)
	Unpaid (Retired/Student/Housewives)	43 (33)	20 (47)
4	**Residence**		
	In Karachi	49 (37)	19 (39)
	Outside Karachi	83 (63)	32 (39)
5	**Travel Cost for one visit (from hometown to hospital)**		
	5000-10,000	26 (20)	5 (19)
	11,000-20,000	39 (30)	18 (46)
	>20,000	18 (13)	9 (50)
	Not Applicable	49 (37)	19 (39)

6	**Caregiver at Home**		
	Spouse	92 (70)	33 (36)
	Parents	14 (10)	8 (57)
	Others (Kids/Neighbors/Siblings/Self)	26 (20)	10 (38)
7	**Heading Family**		
	Yes	68 (52)	27 (40)
	No	64 (48)	24 (38)
8	**Socio-economic Status** (SES)		
	Low SES	22 (17)	9 (41)
	Middle SES	83 (63)	32 (39)
	High SES	27 (20)	10 (37)
9	**Currently Smoking** (Cigarette, huqa, beeri)		
	Yes	18 (14)	10 (56)
	No	114 (86)	41 (36)
10	**History of Psychological Distress Prior to the Diagnosis of Brain Tumor**		
	Yes	7 (5)	6 (86)
	No	125 (95)	45 (36)
11	**Strategies to Handle Stress**		
	Isolation	26 (20)	10 (38)
	Crying	16 (12)	7 (44)
	Prayers	48 (36)	14 (29)
	Aggression	24 (18)	13 (54)
	Leaves home	1 (0.7)	1 (1.96)
	Sleeping	13 (9)	6 (45)
	Conversation with family/friends	10 (7)	1 (10)
	Addictions (Smoking/drinking)	6 (4)	4 (66)
	Mind diversions (Listening to music/shopping)	2 (1)	0 (00)
12	**Karnofsky Performance Score** (Functional Status)		
	KPS scores >70	102 (77)	27 (26)
	KPS scores ≤ 70	30 (23)	24 (80)
TREATMENT-RELATED VARIABLES			
13	**Overall Treatment Cost during illness**		
	2-8 lac Rupees	45 (34)	17 (38)
	8-12 lac Rupees	47 (36)	20 (43)
	>12 lac Rupees	40 (30)	14 (35)
14	**Treatment Cost Management**		
	Self-support	73 (55)	25 (34)
	Family/relative support	21 (16)	11 (52)
	Welfare from primary treating hospital	28 (21)	13 (46)
	Medical support from workplace/community	10 (8)	2 (20)
15	**Access to Health Insurance**		
	Yes	15 (11)	3 (20)
	No	117 (89)	48 (41)
16	**Treatment Stage at the Time of Interview**		
	Only Surgical procedure done	17 (13)	14 (82)
	Referral given to oncology after surgery	18 (13)	5 (28)
	Oncology treatment started/continued	25 (19)	10 (40)
	Treatment completed/follow-ups	72 (55)	22 (31)
17	**Current Use of Steroids**		
	Yes	22 (17)	13 (59)
	No	110 (83)	38 (35)
18	**Current Use of Antiepileptic Drugs**		
	Yes	48 (36)	17 (35)
	No	84 (64)	34 (40)
19	**Surgical Procedure Performed to Remove Tumor**		
	Craniotomy/craniectomy	96 (73)	41 (43)
	Trans-sphenoidal Resection	36 (27)	10 (28)
20	**Type of surgery**		

	Awake (Local anesthesia/ Scalp block) Conventional (General anesthesia)	37 (28) 95 (72)	12 (32) 39 (41)
21	**External Ventricular Drain Insertion** Yes No	 7 (5) 125 (95)	 5 (71) 46 (37)
22	Time since diagnosis (In months)	Median:9.5 months Range:(1-74 month)	Median: 5 month Range:(1-74 month)
25	Number of chemotherapy cycles	Median: 2.5 cycles Range: (0-33 cycles)	Median: 0 Range:(0-27 cycles)
26	Number of radiation cycles	Median: 3.5 cycles Range: (0-33 cycles)	Median: 0 Range:(0-54 cycles)
TUMOUR-RELATED VARIABLES			
27	**Tumor Histology** Meningioma Pituitary adenoma High grade glioma (Astrocytoma, GBM) Oligodendroglioma Others (Schwannoma, Intraventricular SOLs, CNS lymphoma, Ependymoma, Hemangioblastoma, Craniopharyngioma, Choroid plexus papilloma)	 30 (23) 36 (27) 21 (16) 29 (22) 16 (12)	 16 (53) 9 (25) 9 (43) 8 (28) 9 (56)
28	**Tumor Type** Benign Malignant	 69 (52) 63 (48)	 28 (41) 23 (37)
29	**Hemispheric Lateralization** Left Right Not specified	 60 (45) 35 (27) 37 (28)	 28 (47) 13 (37) 10 (27)
30	**Tumour Grade** Grade I Grade II Grade III Grade IV Not specified	 12 (9) 30 (23) 30 (23) 15 (12) 44 (33)	 5 (42) 14 (47) 13 (43) 7 (47) 12 (27)
31	**Cognitive Impairment** Yes No	 9 (7) 123 (93)	 5 (56) 46 (37)
32	**Tumor Recurrence** Yes No	 23 (17) 109 (83)	 14 (61) 37 (34)
33	**Brain Structures Involved (Tumor location)** Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa Basal ganglia	 53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4) 1 (1) 1 (1)	 23 (43) 13 (43) 10 (38) 1 (20) 9 (25) 3 (60) 6 (85) 0 (00) 0 (00)
34	**First Symptoms Before Brain Tumor Diagnosis** Seizures Headaches Weight loss/gain Mood changes/loss of interest Visual impairment Memory loss Gait instability Nausea/ Vomiting Unconsciousness	 40 (30) 55 (42) 3 (2) 1 (1) 36 (27) 5 (3) 1 (1) 5 (3) 7 (5)	 14 (35) 25 (45) 1 (33) 1 (100) 10 (28) 3 (60) 1 (2) 2 (40) 2 (29)

	Dizziness	1 (1)	0 (00)
	Slurred speech/unable to write & comprehend	3 (2)	1 (33)
	Numbness (arms, legs, body)	2 (1)	1 (50)
	Limb weakness	2 (1)	1 (50)
	Swelling (facial, orbital)	3 (2)	2 (67)
	Sexual dysfunction	1 (1)	0 (00)
	Hearing problems	1 (1)	0 (00)

Univariate analysis:

Univariate analysis showed that impaired functional status (P=<0.001), unemployment (P=0.121), travel cost (P=0.240), current smoking status (P=0.238), history of psychological distress prior to the diagnosis of brain tumour (P=0.073), prayer (strategies to handle stress) (P=0.176), aggression (strategies to handle stress) (P=0.195), health insurance (P=0.178), treatment stage at the time of interview (P=0.041), current use of steroids (P=0.111), surgical intervention performed to remove tumour (P=0.203), external ventricular drain insertion (P=0.196), multiple hospital admissions (P=0.069), number of surgeries (P=0.148), tumour histology (P=0.221), tumour recurrence (P=0.076), tumour involving seller region (brain structure involved) (P=0.106), and tumour involving cerebellum/CP angle (P=0.046) had P-value of ≤ 0.25. After adjusting for the effect of other variables in multivariable model, functional status (KPS) remained the only significant variable with P-value <0.001. Propensity scores for functional status showed three factors that were significantly associated with functional status including employment status, tumour recurrence, and treatment stage at the time of interview. Table 2 shows factors associated with functional status (KPS).

Table 2: Factors associated with functional status determined by using KPS among primary brain tumour patients

S#	Variables	PR & 95% CI	P-value
1	**Current Employment Status** Able to work † Unable to work Unpaid (Student/retired/housewives)	 2.56 (0.95-6.92) 2.66 (1.07-6.66)	
2	**Treatment Stage** Underwent surgery only Referral given to oncology after surgery Oncology treatment started/continued Treatment completed/follow-ups †	 7.17 (2.88-17.89) 1.91 (0.55-6.64) 1.86 (0.59-5.79)	<0.001
3	**Tumor Recurrence** Yes No†	 1.97 (0.89-4.35)	
† Reference Category			

Propensity scores predicted from above model were significantly associated with depression. Table 3 shows models to demonstrate association of functional status (KPS) with depression and propensity scores for functional status (KPS) with depression.

Table 3: Models demonstrating association of functional status (KPS) with depression and propensity scores for functional status (KPS) with depression after adjusting for other covariates.

MODEL 1 (KPS and depression)			MODEL 2 (propensity scores for KPS and depression)		
Variable	PR and 95% CI	P-value	Variable	PR and 95% CI	P-value
KPS scores >70 † KPS scores ≤ 70	3.25 (1.87-5.62)	<0.001	Propensity scores for KPS	1.05 (1.02-1.08)	<0.001

† Reference Category

Model 1 shows that the prevalence of depression among patients with KPS scores ≤ 70 is 3.25 times more as compared to patients with KPS scores > 70 whereas, model 2 shows that with each unit increase in propensity scores for functional status; the depression will increase up to 5%.

Discussion:

The purpose of the present study was to investigate the association between depression and patient-related, tumor-related, and treatment related variables among adult patients with primary brain tumor. Although similar studies have been conducted in different parts of the world, most notably in US and UK, there is no literature from LMIC or even other South Asian countries. We believe that the circumstances for our patients differ from those of the west, for a number of reasons. According to World Health Organization, Pakistan has one of the world's lowest public health expenditure as a percentage of GDP, as well as one of the world highest out of pocket health expenditure, where it shares the top slot with other South Asian LMICs. Thus approximately 85% of our patients are out of pocket payers, in a country already marred with poverty, compared to the high-income countries where majority of patients are financially supported by third party payers i.e., state or insurance. [13] In this setting, the high cost of treatment for brain tumors (surgery, chemotherapy, radiation therapy, rehabilitation, etc.) should theoretically add to the psychological stress of the patients. Although government run hospitals do exist, they cover only a fraction of the overall healthcare and majority of patients have to resort to private hospitals, especially for advanced healthcare. There are also very few state run oncology or rehabilitation centres, and patients have to rely on private healthcare for all these services.

We found that 39% of patients with primary brain tumor treated at AKUH, screened positive for depression on PHQ-9. Impaired functional status was the only significant variable associated with depression and propensity scores for functional status revealed a significant association between impaired functional status and treatment stage at the time of interview, unemployment, and tumour recurrence. We also found that decreasing KPS was directly linked to increased chances of depression, as in with each unit increase in propensity scores for functional status; chances of depression increased by up to 5%. Our findings are consistent with some of the previous studies on the same topic. Rooney (2010) [12] in his systematic review of observational studies concluded that the median prevalence of depression among patients with brain tumor using screening scales was about 27% (range 0%-93%) while clinician-rated measures returned up to 15% (5%-28%). Another meta-analysis conducted by Huang and Colleagues in 2017[18] reported that prevalence of depression in brain tumor patients is nearly 21% using screening scales and 19% with clinician-rated measures, specifically including mini-interviews. A 1-year follow-up study conducted by Mainio (2005) [19] also found functional status as a significant predictor associated with depression among brain tumor patients. Similar findings were observed in observational studies conducted by Anderson (1999) [20], Litofsky (2004) [21], Grant (1994) [22], Fox (2007) [23], Rooney (2013) [24], and Piil (2015) [25] [26].

We found three factors associated with reduced functional status including unemployment, tumor recurrence, and stage of treatment, more specifically, early stage of treatment. Association between employment status and depression has been explored by other investigators too, and there are at least three studies that have included employment status in their primary analysis. A study conducted by Pelletier (2002) [27] found employment status positively associated with depression among patients with brain tumors. However, this association was significant only at univariate level. Another study conducted by Vossen (2014) [28] on cognitive and emotional problems among meningioma patients reported significant association between depression and employment status where depression was assessed by hospital anxiety and depression scale. However, when depression was assessed by other screening tools, no association was found. In contrast, employment status was found to be significantly associated with functional status. A follow-up study conducted by Hickmann (2016) [29] reported a parallel trend

of unemployment as the functional status declines. Though none of the studies have reported any definite association between unemployment and reduced functional status among similar populations but trends and figures explained by previous studies, as well as common sense supports this relationship, especially in countries without unemployment benefits; or without adequate labor laws safeguarding employee rights during illnesses.

We did not find any significant association between tumor recurrence and depression and similar findings were reported by Vossen (2014) [28]. On the other hand, reduced functional status was significantly associated with tumor recurrence, as shown by other investigators as well [30][31]. We included brain tumor patients during different treatment stages after surgical procedure was done. Patients immediately after surgery and in their initial stage of treatment reported highest prevalence of depression (82%). Weitzner (1999) [32], Pringle (1999) [33], and Mainio (2005) [19] also reported higher level of depression during initial stage of treatment that is within first three months after surgery. This variable was also found significantly associated with impaired functional status, that is understandable given the physiological and psychological effects of major surgery and hospitalization. As the treatment progresses and by the time it comes to its end, patients tend to regain their functional status and even resume their jobs. Most brain tumor patients who have transient focal deficits as a result of surgery, by the time they reach the completion of their treatment, also improve in their overall functional status. However, no statistical evidence has been reported by any study on association between functional status and treatment stage.

Conclusion:

Our findings suggest that a high proportion of patients with brain tumor also suffer from depression. Whereas several individual and clinical factors may contribute to the development of depression, patients with reduced functional status should be especially monitored for any signs of psychiatric illness. Given the high proportion of depressed patients in our study population, we would recommend routine psychiatric evaluation, or at the least, the administration of simple self-rated screening tools that will allow healthcare providers to readily identify any prevailing neuropsychiatric ailments, for all patients with brain tumors, at the time of admission and during follow-ups.

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Conflict of interest disclosure:
The authors have no conflicts of interest to declare.

Data availability statement:
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Contribution of Author's:
Anum Sadruddin Pidani: Study design, formulation of questionnaire, data collection, data analysis, manuscript writing
Amna Rehana Siddiqui: Study design, epidemiological expertise in design and implementation phase, manuscript writing and review
Iqbal Azam: Biostatistician (analysis of study data), Manuscript writing and review of study analysis
Muhammad Shahzad Shamim: Design and implementation of study, neurosurgery expert input in the design and analysis phase, manuscript review and writing
Adnan A. Jabbar: Design and implementation of study, Oncology expert input in the design and analysis phase, Manuscript reviewing

Shameel Khan: Design and implementation of study, selection of study tools, Psychology expert input in the design and analysis phase, Manuscript reviewing

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تحقیق کا معلوماتی اجازت نامہ

تحقیق کا عنوان: کراچی پاکستان میں تیسرے درجے کا علاج مہیا کرنے والے ہسپتال میں پچھلے پانچ سالوں کے دوران ابتدائی درجے کے دماغی رسولی (ٹیومر) کی تشخیص کی بدولت نوجوانوں میں نفسیاتی دباؤ اور ملحقہ عناصر کی جانچ۔	
سربراہ تحقیق: ڈاکٹر ریحانہ صدیقی تحقیق کار: انعم صدرالدین پیدانی	تنظیم: شعبہ کمیونٹی ہیلتھ سائنسز، آغا خان یونیورسٹی ہسپتال
دیگر تحقیق کار: ڈاکٹر شہزاد شمیم، ڈاکٹر عدنان جبار، ڈاکٹر شامیل خان، ڈاکٹر اقبال اعظم	

تعارف:

میرا نام محترمہ انعم صدرالدین پیدانی ہے اور میں ایم ایس سی اپیڈ یمیولوجی اینڈ بائیو اسٹیٹسٹک شعبہ کمیونٹی ہیلتھ سائنسز کی طالبہ ہوں۔ میں نوجوانوں میں ابتدائی درجے کے دماغی رسولی (ٹیومر) کی بدولت نفسیاتی دباؤ سے ملحقہ عناصر کی جانچ سے متعلق تحقیق کرنے جارہی ہوں۔

پس منظر معلومات:

تحقیق دستاویز سے معلوم ہوا ہے کہ کسی بھی قسم کے دماغی رسولی (ٹیومر) کے مریضوں میں بیماری کی تشخیص کے بعد اور علاج کے دوران نفسیاتی دباؤ ہوتا ہے۔ کچھ نفسیاتی دباؤ جو کہ بہت کم عرصے کے لئے ہوتا ہے اسے علاج کی ضرورت نہیں ہوتی۔ اگر منفی خیالات لمبے عرصے کے لئے آئیں تو اس صورت میں حمایتی علاج کی بدولت متعلقہ علاج کی کامیابی اور معیار زندگی کو بھی بہتر بنایا جاسکتا ہے۔ اس قسم کی تحقیق پاکستان میں کبھی بھی نہیں ہوئی ہے اس لئے ہم چند عناصر مثلاً علاج کا دورانیہ، ادویات، شعاعی علاج، کیمیائی علاج، نیند کا فقدان، اخراجات اور کوئی بھی دیگر عناصر کی بدولت علاج کے دوران پیدا ہونے والے نفسیاتی دباؤ کی جانچ کرنا چاہتے ہیں۔ وقتی اور موزوں نفسیاتی مدد کی بدولت علاج کے اثرات میں مثبت کردار ادا ہوسکتا ہے۔ ابتدائی درجے کے دماغی رسولی (ٹیومر) کے دوران نفسیاتی دباؤ سے متعلق جاننے کے لئے آپ کے تعاون کی ضرورت ہوگی۔

تحقیق کا مقصد:

اس تحقیق کا بنیادی مقصد یہ معلوم کرنا ہے کہ کیا ابتدائی درجے کے دماغی رسولی (ٹیومر) کی بدولت نفسیاتی دباؤ کی مثبت نشانیاں موجود ہیں۔ اس کے ساتھ ساتھ اس بات کی بھی جانچ کی جائے گی کہ کیا علاج کا طویل دورانیہ، ادویات، شعاعی علاج، نیند میں کمی، اخراجات، حیثیت، پھوڑے کی جگہ، پھوڑے کا درجہ، اور دیگر عناصر کا ابتدائی درجے کے دماغی رسولی (ٹیومر) کے مریضوں میں نفسیاتی دباؤ کے ساتھ تعلق ہے۔

طریقہ کار:

اس تحقیق میں آپ کی شرکت کے فیصلے کی بنیاد پر ہم آپ سے خفیہ طریقے سے مشاورت کریں گے۔ سوالات مالی اور ذاتی معلومات، معیار زندگی، دیگر بیماریوں کے ساتھ لگنے والی بیماری، تاریخی اور موجودہ طبی حالت، اور علاج سے متعلق معلومات پر منحصر ہونگے۔ مشاورت کے لئے آپ کے ۲۰ سے ۳۰ منٹ درکار ہونگے۔ آپ کے ڈاکٹر کی اجازت کے بعد میں آپ کے ماضی کے طبی ریکارڈ بیماری کی تشخیص اور علاج سے متعلق معلومات حاصل کرنے کے لئے جانچ کروں گی۔

ممکنہ خطرات اور فوائد:

اس تحقیق میں، آپ کے قیمتی وقت کے علاوہ کسی بھی قسم کے براہ راست خطرات لاحق نہیں ہیں۔اس میں آپ کے ۲۰ سے ۳۰ منٹ درکار ہونگے لیکن اگر آپ سوالات کے جوابات نہیں دینا چاہتے ہیں تو ہم آپ کی سہولت کے مطابق کسی اور دن اسے ترتیب کر سکتے ہیں۔

آپ کو براہ راست کوئی بھی فائدہ نہیں ہوگا۔اس کے باوجود، اس تحقیق کے نتائج کی بدولت ہمیں دماغی رسولی (ٹیومر) کے مریضوں کے علاج سے قبل اور علاج کے دوران نفسیاتی دباؤ کی جانچ کے لئے منصوبہ بندی کرنے میں مدد فراہم ہوگی تا کہ ہم دماغی رسولی (ٹیومر) کے مریضوں کے معیار زندگی کو بہتر بنانے میں مدد فراہم کر سکیں۔

پوشیدگی:

آپ سے حاصل کردہ معلومات کو خفیہ رکھا جائے گا۔میں، ہمارے کمیٹی ممبران اور آپ کے ڈاکٹر کے علاوہ کسی کو بھی اس معلومات تک رسائی حاصل نہیں ہوگی۔آپ کے نام اور پہچان کو کسی بھی ظاہر نہیں کیا جائے گا کیونکہ تمام تر مریضوں کو انوکھا شناختی نمبر مقرر کیا جائے گا اور تجزیے کے لئے بھی اسی انوکھے شناختی نمبر کا استعمال کیا جائے گا۔تمام تر سوالناموں اور جانچ کے آلے کو شعبہ کمیونٹی ہیلتھ سائنسز، آغا خان یونیورسٹی ہسپتال کے دراز میں تالا لگا کر محفوظ کیا جائے گا۔اس کے باوجود، تحقیق سے حاصل کردہ معلومات کو اخلاقی جانچ کی کمیٹی معائنہ کر سکتی ہے اور اسے آپ کے نام اور شناخت کو ظاہر کئے بغیر شمارے میں شائع بھی کر سکتی ہے۔

شرکت سے علیحدگی اور شرکت نہ کرنے کے اختیارات:

آپ کو اس تحقیق میں شرکت کرنے یا نہ کرنے کی مکمل آزادی حاصل ہوگی۔آپ بصورت دیگر حاصل کردہ فوائد کے نقصان کے بغیر تحقیق میں شرکت سے انکار کر سکتے ہیں۔تحقیق میں آپ کی شرکت کرنے یا نہ کرنے کے باوجود بھی آپ کو معیاری علاج مہیا کیا جائے گا۔آپ بصورت دیگر حاصل کردہ فوائد کے نقصان یا کسی بھی قسم نا موافق اثرات کے بغیر کسی بھی وقت اس تحقیق سے علیحدگی اختیار کر سکتے ہیں۔اگر آپ کسی سوال کا جواب دینے کے لئے مطمئن نہیں ہیں تو آپ جواب دینے سے انکار بھی کر سکتے ہیں۔

معلومات کے موجودہ ذرائع:

اس تحقیق سے متعلق کسی بھی قسم کے دیگر سوالات کے آپ تحقیق کار محترمہ انعم صدرالدین پیدانی کو کسی بھی وقت رابطہ کر سکتے ہیں۔آپ ان کو اپنے سوالات anumpidani@gmail.com پر ای میل بھی کر سکتے ہیں۔

اجازت نامہ:

میں نہ یہ اجازت نامہ پڑھ اور سمجھ لیا ہے اور میں رضا کارانہ طور پر اس تحقیق میں شرکت کرنے کیلئے رضامند ہوں۔میں یہ سمجھتا ہوں کہ مجھے اس فارم کی ایک نقل بھی فراہم کی جائے گی۔میں نے رضا کارانہ طور پر شرکت کی ہے، لیکن میں یہ سمجھتا ہوں کہ میرے اس اجازت نامے کو تحقیق سے ملحقہ کسی بھی فرد کی قانونی غلطی یا کوتاہی کے طور پر استعمال نہیں کیا جائے گا۔

شرکت کار کا نام: ----------

شرکت کار کے دستخط یا انگوٹھے کا نشان: ----------

اجازت نامہ پر کرنے والے کا نام:----------

اجازت نامہ پر کرنے والے کے دستخط:----------

تاریخ: ----------

تحقیق کا عنوان: کراچی پاکستان میں تیسرے درجے کا علاج مہیا کرنے والے ہسپتال میں پچھلے پانچ سالوں کے دوران ابتدائی درجے کے دماغی رسولی (ٹیومر) کی تشخیص کی بدولت نوجوانوں میں نفسیاتی دباؤ اور ملحقہ عناصر کی جانچ۔	
سربراہ تحقیق: ڈاکٹر ریحانہ صدیقی تحقیق کار: انعم صدرالدین پیدانی	تنظیم: شعبہ کمیونٹی ہیلتھ سائنسز، آغا خان یونیورسٹی ہسپتال
دیگر تحقیق کار: ڈاکٹر شہزاد شمیم، ڈاکٹر عدنان جبار، ڈاکٹر شامیل خان، ڈاکٹر اقبال اعظم	
مشاورت کا مقام: ---------- فارم پر کرنے والے کا نام: ---------- فارم کی جانچ اور ترمیم کرنے والے کا نام: ---------- فارم درج کرنے والے کا نام: ----------	تاریخ: ----/----/-------- تاریخ: ----/----/-------- تاریخ: ----/----/--------
تحقیق کا شناختی نمبر: ---------- مریض کا نام: ---------- پتہ: ---------- ---------- شناختی نمبر: ----------	

اہلیت کے معیار کا تحقیقاتی آلہ

نمبر	سوال	جواب	اختیار
1	مشاورت کے وقت گلاس گوکوما اسکور (GCS) کا پیمانہ	1) ۱۵ 2) ۱۵ سے کم	اگر ۱۵ سے کم ہے تو یہیں روک دیں۔
2	کیا آپ عرصہ قبل سے ذہنی یا نفسیاتی دباؤ کی ادویات استعمال کر رہے ہیں؟	1) ہاں 2) نہیں	اگر ہاں تو اگلے سوال پر جائیں۔ اگر نہیں تو سوال ۴ کو چھوڑ دیں۔
3	آپ کتنے عرصے سے یہ ادویات استعمال کر رہے ہیں؟	1) دماغی رسولی (ٹیومر) کی تشخیص سے قبل 2) دماغی رسولی (ٹیومر) کی تشخیص کے بعد	اگر دماغی رسولی (ٹیومر) کی تشخیص سے قبل تو یہیں روک دیں اور تحقیق میں مریض کا اندراج نہ کریں۔
4	کیا آپ دماغی رسولی (ٹیومر) سے قبل دیگر دیرینہ بیماریاں (ایچ آئی وی/ایڈز، ایچ سی وی) یا ہارمونل خرابی (ہائپو تھائرویڈیزم) جس کے لئے آپ دوا بھی لیتے ہیں یا پھر جگر یا جلد کی بیماری میں بھی مبتلا ہیں؟	1) ہاں 2) نہیں	اگر ہاں تو یہیں روک دیں اور مریض کو تحقیق کے لئے اندراج نہ کریں۔

انکشاف کی جانچ کے لئے سوالنامہ

سیکشن A: مریض سے متعلق سوالات

نمبر	سوالات	کوڈ	اسکیپ	جوابات
1	آپ کی جنس کیا ہے؟	1- مرد 2- عورت		
2	آپ کی عمر سالوں میں کتنی ہے؟		مکمل سالوں میں بیان کریں۔	----------سالوں میں
3	آپ کی تعلیمی حیثیت کیا ہے؟ (ایک جواب)	1- جماعت ا سے ۹ 2- جماعت ۱۰/O-level 3- کالج ڈگری/A-level 4- بیچلرز ڈگری 5- ماسٹرز ڈگری 6- ڈاکٹریٹ ڈگری		
4	آپ کی ازدواجی حیثیت کیا ہے؟ (ایک جواب)	1- شادی شدہ 2- بیوہ 3- طلاق شدہ 4- علیحدہ 5- غیر شادی شدہ	اگر کبھی بھی شادی نہیں ہوئی تو سوال 8 پر جائیں۔	
5	آپ کے کتنے بچے ہیں؟		اگر نہیں تو سوال 7 پر جائیں۔	
6	کیا آپ کے ۱۸ سال سے کم عمر بچے بھی ہیں؟	1- ہاں 2- نہیں		
7	کیا آپ اس وقت اپنے خاوند/ بیوی کے ساتھ رہتے ہیں؟	1- ہاں 2- نہیں		
8	آپ کی مادری زبان کیا ہے؟ (ایک جواب)	1- اردو 2- پنجابی 3- سندھی 4- پشتو 5- بلوچی دیگر		
9	آپ کا پیشہ کیا ہے؟			---------- ----------

10	آپ کی موجودہ ملازمت کی حیثیت کیا ہے؟ (ایک جواب)	1- تنخواہ کے لئے کام 2- اپنا کام 3- کام سے علیحدہ اور کام کی تلاش 4- طالب علم 5- ریٹائرڈ 6- چھٹیوں پر 7- کام نہیں کر سکتے دیگر	اگر کام نہیں کر سکتے تو سوال 11 پر جائیں ورنہ سوال 11 کو چھوڑ دیں۔	
11	آپ کتنے عرصے سے کام نہیں کر پا رہے ہیں؟ (ایک جواب)	1- تین ماہ سے کم 2- ۴ سے ۶ ماہ 3- ۷ سے ۱۲ ماہ 4- ۱۲ ماہ سے زائد		
12	آپ کہاں رہتے ہیں؟	1- کراچی میں 2- کراچی سے باہر	جگہ بتائیں جہاں سے شرکت کار کا تعلق ہے۔ اگر مریض کراچی سے باہر قیام پزیر ہے تو سوال 13 پر جائیں۔ اگر مریض کراچی میں قیام پزیر نہیں ہے تو سوال 19 پر جائیں۔	جگہ کا نام ---------- ----------
13	علاج کے دوران آپ کہاں رہتے ہیں؟	1- کراچی میں 2- گھر میں (شہر/ضلع/قصبہ)		
14	آپ کراچی میں کہاں رہتے ہیں؟ (ایک جواب)	1- ہوٹل 2- رشتے دار کے گھر 3- کرائے کے گھر میں 4- ذاتی گھر میں دیگر		
15	آپ اپنے شہر/ضلع/ قصبے سے کتنے گھنٹے کا سفر کر کے آغا خان یونیورسٹی ہسپتال تک پہنچتے ہیں؟ (ایک جواب)	1- ۲ سے ۴ گھنٹے 2- ۵ سے ۸ گھنٹے 3- ۹ سے ۱۶ گھنٹے 4- ۱۷ سے ۲۴ گھنٹے 5- ۲۴ گھنٹے سے زائد		

16	آپ کراچی کا سفر کیسے کرتے ہیں؟ (ایک جواب)	1- جہاز سے 2- ٹرین سے 3- بس یا کار سے		
17	آپ کراچی آنے کے لئے کیا استعمال کرتے ہیں؟ (ایک جواب)	1- عوامی ٹرانسپورٹ میں 2- ذاتی ٹرانسپورٹ میں 3- دونوں		
18	آغا خان یونیورسٹی ہسپتال تک ایک مرتبہ سفر پر تقریباً کتنے اخراجات ہوتے ہیں؟		اخراجات روپیوں میں بیان کریں۔	روپیوں میں: ----------
19	گھر میں آپ کی دیکھ بھال کون کرتا ہے؟ (ایک جواب)	1- خاوند/ بیوی 2- والدین 3- بچے 4- رشتے دار 5- دوست 6- دیگر		
20	کیا آپ اپنے خاندان کے سربراہ ہیں؟	1- ہاں 2- نہیں		
21	آپ کے گھر میں کتنے افراد رہتے ہیں؟		نمبروں میں بیان کریں	----------

سیکشن B: سماجی و مالیاتی حیثیت

نمبر	سوالات	کوڈ	اسکیپ	جوابات
1	کیا آپ گھر کے مالک ہیں؟	1- ہاں 2- نہیں	اگر ہاں تو سوال 2 پر جائیں۔	
2	آپ کے گھر میں کل کتنے کمرے ہیں؟		نمبروں میں بیان کریں۔	----------
3	آپ کے کتنے موبائل فون ہیں؟		نمبروں میں بیان کریں۔	----------
4	کیا آپ کے اہل خانہ میں کسی کے پاس اپنی گاڑی ہے؟	1- ہاں 2- نہیں	اگر نہیں تو سوال 5 کو چھوڑ دیں۔	
5	آپ کے پاس کتنی گاڑیاں ہیں؟		نمبروں میں بیان کریں۔	----------
6	کیا آپ کے اہل خانہ میں کسی کے پاس اپنی موٹر سائیکل ہے؟	1- ہاں 2- نہیں	اگر نہیں تو سوال 7 کو چھوڑ دیں۔	
7	آپ کے پاس کتنی موٹر سائیکلیں ہیں؟		نمبروں میں بیان کریں۔	----------

8	کیا آپ کے اہل خانہ میں کسی کے پاس زرعی زمین موجود ہے؟	1- ہاں 2- نہیں		
9	آپ کی ماہانہ آمدنی کتنی ہے؟ (ایک جواب)	1- 5000-10000 2- 11000-20000 3- 21000-30000 4- 31000-40000 5- 41000-50000 6- >50000		
10	کیا آپ کے خانہ میں سے کوئی دوسرا رکن کماتا ہے؟	1- ہاں 2- نہیں	اگر ہاں تو سوال 11 پر جائیں	
11	آپ کے خانہ کی ماہانہ آمدنی کتنی ہے؟ (ایک جواب)	1- 5000-10000 2- 11000-20000 3- 21000-30000 4- 31000-40000 5- 41000-50000 6- >50000		

سیکشن C: انفرادی چوری، نشے کا استعمال، اور زندگی کے اہم واقعات

نمبر	سوالات	کوڈ	اسکیپ	جوابات
1	ابتدائی درجے کے دماغی رسولی (ٹیومر) کے علاوہ کیا آپ کی زندگی میں دیگر اہم واقعات بھی رونما ہوئے ہیں جیسے کہ کسی اہل خانہ کا وفات پانا یا بڑی عمر میں اپنی نوکری سے فارغ ہونا؟	1- ہاں 2- نہیں	مکمل واقعہ بیان کریں۔	---------- ---------- ---------- ----------
2	آپ اپنے نفسیاتی دباؤ کو کیسے کم کرتے ہیں؟			---------- ---------- ---------- ----------
3	آپ اپنے اہل خانہ یا دوستوں کے ساتھ کتنی مرتبہ سیر و تفریح کے لئے جاتے ہیں؟ (ایک جواب)	1- ہفتے میں ایک مرتبہ سے زیادہ 2- ہفتے میں کم از کم ایک مرتبہ 3- کبھی کبھار 4- کبھی بھی نہیں		

4	کیا آپ ٹیلیویژن بھی دیکھتے ہیں؟	1- ہاں 2- نہیں	اگر نہیں تو سوال 5 کو چھوڑ دیں۔	
5	پچھلے سات دنوں کے دوران، آپ نے کتنی کثرت سے ٹیلیویژن کے پروگرام دیکھے؟ (ایک جواب)	1- روزانہ 2- ہفتے میں کم از کم ایک مرتبہ 3- کبھی کبھار 4- کبھی بھی نہیں		
6	کیا آپ روزانہ ورزش کرتے ہیں؟	1- ہاں 2- نہیں		
7	کیا آپ کی روزمرہ کی خوراک میں کمی واقع ہوئی؟	1- ہاں 2- نہیں	اگر نہیں تو سوال 8 کو چھوڑ دیں۔	
8	کتنے عرصے سے آپ کی روزمرہ کی خوراک میں کمی واقع ہوئی؟			
9	کیا روزمرہ کے کام کرنے میں آپ کو مدد کی ضرورت پڑتی ہے؟	1- ہاں 2- نہیں		
10	کیا آپ نے کبھی سگریٹ، حقہ یا بیڑی پی ہے؟	1- ہاں 2- نہیں	اگر نہیں تو سوال 14 پر جائیں۔	
11	آپ کتنے عرصے سے تمباکو نوشی کر رہے ہیں؟		سالوں میں بیان کریں۔	---------- سال
12	آپ کتنی مرتبہ سگریٹ پیتے ہیں؟ (ایک جواب)	1- روزانہ 2- ہفتہ وار 3- ماہانہ 4- ماہانہ سے کم		
13	آپ دن میں کتنی سگریٹ پیتے ہیں؟			---------- یومیہ سگریٹ
14	کیا آپ پان/تمباکو/ چھالیہ/ سپاڑی/شراب/ ڈرگ کا استعمال کرتے ہیں؟	1- ہاں 2- نہیں		
15	آپ کتنے عرصے سے پان/تمباکو/ چھالیہ/ سپاڑی/شراب/ ڈرگ کا استعمال کر رہے ہیں؟		سالوں میں بیان کریں۔	---------- سال

سیکشن D: طبی تاریخ

نمبر	سوالات	کوڈ	اسکپ	جوابات

1	کیا آپ کے اہل خانہ میں کبھی کسی کو کینسر کی بیماری ہوئی ہے؟	1-ہاں 2-نہیں	کینسر کا نام بیان کریں۔	----------
2	کیا آپ کے اہل خانہ میں کبھی کسی کو بنیادی درجے کا دماغی رسولی (ٹیومر) کی بیماری ہوئی ہے؟	1-ہاں 2-نہیں		
3	کیا آپ نے کبھی کسی علم نفسیات کے ڈاکٹر کے پاس معائنہ کروایا ہے؟	1-ہاں 2-نہیں	اگر نہیں تو سوال 5 پر جائیں۔	
4	معائنے کی وجہ کیا تھی؟			---------- ---------- ----------
5	کیا آپ کبھی نفسیاتی بیماری کا شکار ہوئے ہیں؟	1-ہاں 2- نہیں	اگر نہیں تو سوال 9 پر جائیں۔	
6	کیا آپ نے اس بیماری کے علاج کے لئے کوئی نفسیاتی بیماری کی دوا استعمال کی ہے؟	1-ہاں 2- نہیں		
7	آپ نے کتنے عرصے تک وہ دوا استعمال کی تھی؟			----------
8	دوا کے علاوہ، آپ نے اپنی نفسیاتی بیماری کے علاج کے کیا دیگر اقدامات اٹھائے؟			---------- ---------- ---------- ---------- ----------
9	کیا آپ نے بنیادی درجے کے دماغی رسولی (ٹیومر) کی تشخیص کے بعد کسی علم نفسیات کے ڈاکٹر کے پاس معائنہ کروایا ہے؟	1-ہاں 2-نہیں	اگر نہیں تو سوال 11 پر جائیں۔	
10	معائنے کی وجہ کیا تھی؟			---------- ---------- ----------
11	آپ کو دیگر کونسی بیماری ہے؟			---------- ---------- ---------- ----------

سیکشن E: دماغی رسولی (ٹیومر) اوراس کے علاج سے متعلق سوالات

نمبر	سوالات	کوڈ	اسکیپ	جوابات
1	بنیادی درجے کے دماغی رسولی (ٹیومر) کی تشخیص سے قبل ابتدائی علامت کونسی تھی؟ (ایک سے زیادہ جواب)	1- اچانک دورہ 2- سردرد 3- وزن میں کمی 4- مزاج میں تبدیلی دیگر		
2	آپ کے دماغی رسولی (ٹیومر) کی تشخیص کب ہوئی؟ (ایک جواب)	1- تین ماہ سے کم 2- تین سے بارہ ماہ 3- تیرہ سے چوبیس ماہ 4- چوبیس ماہ سے زائد		
3	پچھلے ۱۲ ماہ کے دوران، آپ نے کتنی مرتبہ ہسپتال میں داخلہ کروایا؟			
4	مکمل بیماری کے علاج کے دوران تشخیص کی جانچ، آپریشن، دوبارہ معائنے، کیمیائی علاج، شعاعی علاج وغیرہ پر تقریباً کتنے اخراجات ہوئے؟ (ایک جواب)	1- دولاکھ سے کم 2- دو سے چار لاکھ 3- پانچ سے آٹھ لاکھ 4- آٹھ سے بارہ لاکھ 5- بارہ لاکھ سے زائد		
5	آپ نے آغا خان یونیورسٹی ہسپتال میں اخراجات کس طرح برداشت کئے؟			
6	کیا آپ کے پاس کوئی صحتی انشورنس ہے؟	1- ہاں 2- نہیں	اگر ہاں تو سوال 7 پر جائیں	
7	آپ کے صحتی بیمے کا ذریعہ کیا ہے؟	1- نوکری میں طبی فوائد 2- انشورنس کی قسط دیگر		

نوٹ: تمام تر علاج اور دماغی رسولی (ٹیومر) سے متعلق معلومات کی جانچ میڈیکل ریکارڈ فائل سے کی جائے گی۔

سیکشن F: کارآمد حیثیت

نمبر	سوالات	کوڈ	اسکیپ	جوابات
1	کیا آپ روزمرہ کی عام سرگرمیاں اکیلے ہی کر سکتے ہیں یا پھر آپ کو مدد کی ضرورت پڑتی ہے؟ آپ کو کس حد تک مدد کی ضرورت پڑتی ہے؟	1- KPS scores > 70 2- KPS scores <= 70	اسکور کو مندرجہ ذیل KPS پیمانے کے مطابق حساب لگائیں۔	اسکور: ----------

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes Page no 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes Page 1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes Page 2
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Yes Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes Page 3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes Page 3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes Page 3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes Page 3
Bias	9	Describe any efforts to address potential sources of bias	Yes Page 4
Study size	10	Explain how the study size was arrived at	Yes Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes Page 4

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes Page 4
		(*b*) Describe any methods used to examine subgroups and interactions	Yes Page 4
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes Page 3
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes Page 5
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	Yes Page 4- 5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes Page 7
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes Page 7
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes Page 8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes Page 2
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes Page 8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes

			Page 9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA Page 2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Depression among Adult Patients with Primary Brain Tumor: A Cross-Sectional Study of Risk Factors in a Low-Middle Income Country

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Depression among Adult Patients with Primary Brain Tumor: A Cross-Sectional Study of Risk Factors in a Low-Middle Income Country

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Running title: Factors associated with depression
Word count excluding references: 3749
Tables: 3

Abstract:

OBJECTIVE:
The prevalence of depression among primary brain tumor patients ranges from 15% to 40% globally. Several individual and clinical factors contribute in the development of depression. However, their association with depression in Pakistani setting has not yet been assessed. Thus, we aim to study the factors associated with depression among adult primary brain tumor patients at a tertiary care hospital in Karachi, Pakistan.

METHOD:
This study included 132 patients with MRI confirmed primary brain tumor in various stages of treatment at a tertiary care hospital in Karachi, Pakistan. Patients completed a set of pre-structured questionnaire evaluating patient-related, tumor-related, and treatment-related factors. Scores of 10 to 27 on Patient Health Questionnaire-9 (PHQ-9) were indicative of screen positive for depressive symptoms. Cox algorithm assessed association between patient-related, tumor-related, and treatment-related factors and depression. Propensity scores were computed to examine the factors associated with impaired functional status.

RESULTS:
Fifty one (39%, CI: 33.33-46.94) patients in our study screened positive for depressive symptoms on PHQ-9. There was significant association between depressive symptoms and KPS scores (Prevalence Ratio: 3.25 and Confidence Interval: 1.87-5.62) after controlling covariates. Propensity scores predicted positive association between KPS (functional status) and unemployment, treatment stage, and tumor recurrence. Tumor-related and treatment related factors including tumor grade, location, type, and hemispheric lateralization were found insignificant.

CONCLUSION:

Depression is common in patients with primary brain tumor. Impaired functional status has direct impact on depression in these patients. Incorporating psychosocial domain earlier in the course of treatment needs to be considered for better neuro-oncology management of primary brain tumor patients.

Strengths and Limitations of this study:

Strengths:

- To our knowledge, this was the first study conducted in Pakistan to explore depression and its associated factors among primary brain tumor patients.
- The study have assessed those associations which were not assessed in any of the previous studies on similar population including treatment stage, EVD insertion, number of admissions, stressful events, strategies use to handle stress, and first symptoms. Moreover, relation of different costs including travelling cost and overall treatment cost with depression was also evaluated in this study.

Limitations:

- A single screening tool to measure depression instead of physician-rated measures or mini-interviews to verify the results of PHQ-9.
- The study included cross-sectional data instead of prospective data which limits both temporality and direction of causation.

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Background:

Although primary brain tumour account for a relatively small percentage of all cancers, it is considered as one of the most devastating types of cancers among adult population [1]. The incidence of primary brain tumor is approximately 9/100,000/year worldwide with higher rates in western countries as compared to low-middle income countries (LMIC) [2]. Interestingly, primary brain tumors rank highest among cancers that cause emotional and psychological burden for patients [3][4].

Diagnostic and Statistical Manual-V defines depression as a feeling of sadness, loss of pleasure from daily living activities, body weight changes, reduction in physical activity, fatigue, failure to think or concentrate, lack of self-worth and recurrent suicidal ideations [5]. It is estimated that depression affects about 350 million individuals worldwide and according to the Global Mental Health Survey (2014), nearly 1 in 20 individuals report having at least one episode of depression within a year [6]. Population based researches report a prevalence of clinical depression ranging between 2% to 5% worldwide [7]. The worldwide prevalence of depression in cancer patients is 25% with higher rates among Asian countries [8]. The estimated prevalence of clinically diagnosed depression in Pakistan is approximately 6% out of which 3% are cancer patients [9]. Depression rates among primary brain tumor patients ranges from 15% to 40% with highest rates among glioma patients [10]. However, it is suggested that these rates likely under-represent the true incidence of depression [11]. A systematic review of 42 observational studies reports that the prevalence of depression among glioma patients ranges between 0 to 93% with a median prevalence of 27% [12].

Depression in brain tumor patients is multifactorial and there are several factors contributing to its development, including individual, tumor-related, and disease-related factors [10]. All the studies on this topic to date have been conducted in western population, where the psychosocial circumstances are much different from Pakistani population, for example whereas in UK and US, where most of the data comes from, majority of patients are financially supported by third party payers i.e., state or insurance. In contrast, approximately 85% of patients in

Pakistan, and a few other South Asian LMIC countries, are out of pocket payers both for their treatment, and rehabilitation [13]. This we believe, may be the cause of additional psychological burden on the patients. This and several other factors like social support, family setup, and social status are unknown in the context of settings of low and middle income countries and require a series of researches to establish associations. The aim of this study was to assess association between depression and patient-related, tumor-related, and treatment-related variables among adult primary brain tumor patients in a LMIC.

Methods:

Study Design:
An analytical cross-sectional study design was employed to determine the association between patient related, tumor related and treatment related factors with depression among adult primary brain tumor patients. Non-probability consecutive sampling was used to recruit subjects. All the patients who met eligibility criteria of the study and were willing to give consent were included in the study.

Site and setting
The study was approved by the institution review board (5009-CHS-ERC-17). The recruitment was conducted at tertiary care setting of Karachi, Pakistan and 132 patients with biopsy proven primary brain tumors at various stages of treatment were enrolled. These patients were contacted in neurosurgery wards, neurosurgery and oncology outpatient clinics, and oncology day care suits from November 2017 to July 2018.

Participants
Participants were all adult patients (aged 18 years and above) under treatment at a tertiary care setup. Each patient was enrolled after a written, informed consent. The exclusion criteria for study participants were as follows: diagnosis of depression for about one prior to the diagnosis of brain tumor, confused or incoherent patients and patients with problems with speech or comprehension that prevents them from completing the questionnaire, patients with co-existing systemic malignancies apart from primary brain tumor, and any severe comorbid medical illness such as liver cirrhosis, systemic infections like HIV, and hepatitis which can cause altered mental status.

Procedure
Participant's eligibility was determined by medical record files. Potentially eligible participants were approached by the investigator during a scheduled follow-up visit at neurosurgery and oncology outpatient clinics or during inpatient hospital stay post-surgery. Each patient after the consent were interviewed for 15-20 minutes to fill a pre-structured questionnaire for assessing predictor variables and PHQ-9 scale for screening of depression. The questionnaire was also pilot tested on 10 participants before actual administration.

Measures
We divided all the associated factors into three distinct categories that were patient-related, tumor-related, and treatment-related variables. Patient-related factors comprised of demographic and socio-economic variables including age, gender, marital status, number of dependents, children under 18 years, education, occupation, employment status, residency, travelling cost, care giver support, current smoking status, past/current medical illness, history of psychological dresses, strategies to handle stress (isolation, aggression, prayers, crying, sleeping, addiction, and mind diversions) and functional status. Participant's functional status was assessed using Karnofsky performance score (KPS). KPS scores less than 70 were indicative of impaired functional status. Socio-economic status (SES) was also computed using factorial analysis. Tumor-related and treatment-related variables were assessed by medical record review and included tumor histology, tumor grade, recurrence, hemispheric lateralization, first symptoms, brain structures involved, and cognitive impairment. Treatment related variables included stage of treatment, number of chemotherapy cycles, duration since diagnosis, radiation therapy, current use of steroids and anti-epileptic drugs, and treatment cost. The complete list of variables is mentioned in Table 1.

Depression

Primary brain tumour patients were screened for depression using Urdu version of patient health questionnaire-9 (PHQ-9). The PHQ-9 is a self-rated screening tool which contains 9 items that corresponds to DSM-V criteria of depression and was rated on Likert scale of four points. All the patients were classified into two groups based on the scores on PHQ-9 scale. Participants with a score of ≥ 10 were classified as screened positive for depression. PHQ-9 score of 10 or above has a sensitivity and specificity of 88% for major depressive symptoms. A recently conducted validation study on Urdu version (national language of Pakistan) of PHQ-9 by Gholizadeh, 2017 [14], reported a specificity of 94% and false positive rate of 6% only.

Statistical Analysis:

Sample size was calculated from previous studies [15] using Openepi [16] with a power of 80%, depression to no depression ratio of 1:2, prevalence ratio (PR) of 2 and 30% to 70% range of depression for different factors yield a sample size of 108. Adding 20% of attrition rate the final sample size came out to be 130 participants. We used STATA version 12.0 [17] to perform all the analysis. For descriptive data of continuous variables mean and standard deviations were computed. Frequencies and percentages were computed for all qualitative variables. We applied cox algorithm to obtain crude and adjusted prevalence ratios. At univariate level, independent variables were considered significant if p-value was ≤ 0.25. We also checked multicollinearity between all the predictor variables. To assess Multicollinearity, three different tests were used. Pearson's correlation was used for two normally distributed continuous variables, ETA was used for one qualitative and one quantitative variable whereas; Cramer's V was used for two qualitative variables. Moreover, the cut-off for Multicollinearity was 0.8. After Multicollinearity, multivariable analysis was performed using cox algorithm to obtained adjusted prevalence ratio. The cut-off for the significance of predictor variable at multivariable analysis was ≤0.05. We also calculated Propensity scores for the only significant variable left after performing multivariable model building (functional status). The purpose of computing propensity scores was to identify factor associated with the functional status and understand the viscous pathway of associations between explanatory variables and depression. To predict propensity scores, functional status was kept as dependent variable and was regress with other explanatory variables. After the final model was obtained for functional status, propensity scores were computed. At last, Propensity scores were regress against depression (dependent variable in the study) to see its association with depression. The cut-off for significance of propensity scores was ≤0.05.

Patient and public involvement

None of the study participants were involved in the design or conduct of this study and no patient opinion regarding the study has been obtained. The results have been reported to head of Mind and brain service line at AKUH in Karachi which primarily deals with neuro-oncology patients.

Results:

Descriptive characteristics of study participants:

The mean age (± SD) of study participants was 43.25 (± 12.28) years, with 86 (65%) males and 46 (35%) female. Fifty one (39%) study participants were screened positive (Scores of 10 and greater on PHQ-9) for depression while 81 participants (61%) were screened negative (Scores less than 10 on PHQ-9) for depression. Table 1 shows descriptive characteristics of study participants.

Table 1: Summary of descriptive characteristic of study participants

PATIENT-RELATED VARIABLES			
S#	Variables	Total N (%)	Screened positive for depressive symptoms (PHQ-9 ≥ 10) N (%)
1	**Marital Status**		

	Married Unmarried/Single/Separated/Divorced	117 (89) 15 (11)	43 (37) 08 (53)
2	**Children under 18 years** Yes No Unmarried	 75 (57) 33 (25) 24 (18)	 32 (43) 10 (30) 9 (38)
3	**Current Employment status** Able to work Unable to work Unpaid (Retired/Student/Housewives)	 65 (49) 24 (18) 43 (33)	 18 (28) 13 (54) 20 (47)
4	**Residence** In Karachi Outside Karachi	 49 (37) 83 (63)	 19 (39) 32 (39)
5	**Travel Cost for one visit (from hometown to hospital)** 5000-10,000 Rupees 11,000-20,000 Rupees >20,000 Rupees Not Applicable	 26 (20) 39 (30) 18 (13) 49 (37)	 05 (19) 18 (46) 09 (50) 19 (39)
6	**Caregiver at Home** Spouse Parents Others (Kids/Neighbors/Siblings/Self)	 92 (70) 14 (10) 26 (20)	 33 (36) 08 (57) 10 (38)
7	**Heading Family** Yes No	 68 (52) 64 (48)	 27 (40) 24 (38)
8	**Socio-economic Status** (SES) Low SES Middle SES High SES	 22 (17) 83 (63) 27 (20)	 09 (41) 32 (39) 10 (37)
9	**Currently Smoking** (Cigarette, huqa, beeri) Yes No	 18 (14) 114 (86)	 10 (56) 41 (36)
10	**History of Psychological Distress Prior to the Diagnosis of Brain Tumor** Yes No	 07 (05) 125 (95)	 6 (86) 45 (36)
11	**Strategies to Handle Stress** Isolation Crying Prayers Aggression Leaves home Sleeping Conversation with family/friends Addictions (Smoking/drinking) Mind diversions (Listening to music/shopping)	 26 (20) 16 (12) 48 (36) 24 (18) 01 (0.7) 13 (09) 10 (07) 06 (04) 02 (01)	 10 (38) 07 (44) 14 (29) 13 (54) 01 (1.96) 06 (45) 01 (10) 04 (66) 0 0(00)
12	**Karnofsky Performance Score** (Functional Status) KPS scores >70 KPS scores ≤ 70	 102 (77) 30 (23)	 27 (26) 24 (80)
TREATMENT-RELATED VARIABLES			
13	**Overall Treatment Cost during illness** 200,000-800,000 Rupees 800,000-1,200,000 Rupees >1,200,000 Rupees	 45 (34) 47 (36) 40 (30)	 17 (38) 20 (43) 14 (35)
14	**Treatment Cost Management** Self-support Family/relative support Welfare from primary treating hospital Medical support from workplace/community	 73 (55) 21 (16) 28 (21) 10 (8)	 25 (34) 11 (52) 13 (46) 02 (20)

15	**Access to Health Insurance**		
	Yes	15 (11)	3 (20)
	No	117 (89)	48 (41)
16	**Treatment Stage at the Time of Interview**		
	Only Surgical procedure done	17 (13)	14 (82)
	Referral given to oncology after surgery	18 (13)	5 (28)
	Oncology treatment started/continued	25 (19)	10 (40)
	Treatment completed/follow-ups	72 (55)	22 (31)
17	**Current Use of Steroids**		
	Yes	22 (17)	13 (59)
	No	110 (83)	38 (35)
18	**Current Use of Antiepileptic Drugs**		
	Yes	48 (36)	17 (35)
	No	84 (64)	34 (40)
19	**Surgical Procedure Performed to Remove Tumor**		
	Craniotomy/craniectomy	96 (73)	41 (43)
	Trans-sphenoidal Resection	36 (27)	10 (28)
20	**Type of surgery**		
	Awake (Local anesthesia/ Scalp block)	37 (28)	12 (32)
	Conventional (General anesthesia)	95 (72)	39 (41)
21	**External Ventricular Drain Insertion**		
	Yes	7 (5)	5 (71)
	No	125 (95)	46 (37)
22	Time since diagnosis (In months)	Median:9.5 months Range:(1-74 month)	Median: 5 month Range:(1-74 month)
25	Number of chemotherapy cycles	Median: 2.5 cycles Range: (0-33 cycles)	Median: 0 Range:(0-27 cycles)
26	Number of radiation cycles	Median: 3.5 cycles Range: (0-33 cycles)	Median: 0 Range:(0-54 cycles)
TUMOUR-RELATED VARIABLES			
27	**Tumor Histology**		
	Meningioma	30 (23)	16 (53)
	Pituitary adenoma	36 (27)	09 (25)
	High grade glioma (Astrocytoma, GBM)	21 (16)	09 (43)
	Oligodendroglioma	29 (22)	08 (28)
	Others (Schwannoma, Intraventricular SOLs, CNS lymphoma, Ependymoma, Hemangioblastoma, Craniopharyngioma, Choroid plexus papilloma)	16 (12)	09 (56)
28	**Tumor Type**		
	Benign	69 (52)	28 (41)
	Malignant	63 (48)	23 (37)
29	**Hemispheric Lateralization**		
	Left	60 (45)	28 (47)
	Right	35 (27)	13 (37)
	Not specified	37 (28)	10 (27)
30	**Tumour Grade**		
	Grade I	12 (9)	05 (42)
	Grade II	30 (23)	14 (47)
	Grade III	30 (23)	13 (43)
	Grade IV	16 (12)	07 (47)
	Not specified	44 (33)	12 (27)
31	**Cognitive Impairment**		
	Yes	09 (07)	05 (56)
	No	123 (93)	46 (37)
32	**Tumor Recurrence**		
	Yes	23 (17)	14 (61)
	No	109 (83)	37 (34)
33	**Brain Structures Involved (Tumor location)**		
	Frontal lobe	53 (40)	23 (43)

	Parietal lobe	30 (22)	13 (43)
	Temporal lobe	26 (19)	10 (38)
	Occipital lobe	05 (3)	01 (20)
	Pituitary gland (Seller region)	36 (27)	09 (25)
	Ventricles	05 (4)	03 (60)
	Cerebellum/CP angle	07 (4)	06 (85)
	Posterior fossa	01 (1)	00 (00)
	Basal ganglia	01 (1)	0 0(00)
34	**First Symptoms Before Brain Tumor Diagnosis**		
	Seizures	40 (30)	14 (35)
	Headaches	55 (42)	25 (45)
	Weight loss/gain	3 (2)	1 (33)
	Mood changes/loss of interest	1 (1)	1 (100)
	Visual impairment	36 (27)	10 (28)
	Memory loss	5 (3)	3 (60)
	Gait instability	1 (1)	1 (2)
	Nausea/ Vomiting	5 (3)	2 (40)
	Unconsciousness	7 (5)	2 (29)
	Dizziness	1 (1)	0 (00)
	Slurred speech/unable to write & comprehend	3 (2)	1 (33)
	Numbness (arms, legs, body)	2 (1)	1 (50)
	Limb weakness	2 (1)	1 (50)
	Swelling (facial, orbital)	3 (2)	2 (67)
	Sexual dysfunction	1 (1)	0 (00)
	Hearing problems	1 (1)	0 (00)

Univariate analysis:

Univariate analysis showed that impaired functional status (P=<0.001), unemployment (P=0.121), travel cost (P=0.240), current smoking status (P=0.238), history of psychological distress prior to the diagnosis of brain tumour (P=0.073), prayer (strategies to handle stress) (P=0.176), aggression (strategies to handle stress) (P=0.195), health insurance (P=0.178), treatment stage at the time of interview (P=0.041), current use of steroids (P=0.111), surgical intervention performed to remove tumour (P=0.203), external ventricular drain insertion (P=0.196), multiple hospital admissions (P=0.069), number of surgeries (P=0.148), tumour histology (P=0.221), tumour recurrence (P=0.076), tumour involving seller region (brain structure involved) (P=0.106), and tumour involving cerebellum/CP angle (P=0.046) had P-value of ≤ 0.25. After adjusting for the effect of other variables in multivariable model, functional status (KPS) remained the only variable found associated with depressive symptoms among primary brain tumor patients with P-value <0.001.

Table 2: Summary of final reduced multivariate models using Cox Algorithm to predict prevalence of depressive symptoms and its association with functional status

Variable	PR and 95% CI	P-value
KPS scores >70 †	1	-
KPS scores ≤ 70	3.25 (1.87-5.62)	<0.001
†Reference Category which was kept as reference in Analysis		

Table 2 shows that the prevalence of depression among patients with KPS scores ≤ 70 is 3.25 times more as compared to patients with KPS scores > 70

Propensity scores for functional status showed three factors that were significantly associated with functional status including employment status, tumour recurrence, and treatment stage at the time of interview. Table 3 shows factors associated with functional status (KPS).

Table 3: Factors associated with functional status determined by using KPS among primary brain tumour patients

S#	Variables	PR & 95% CI	P-Value (z)	P-value (F)
1	**Current Employment Status**			
	Able to work †	1	-	
	Unable to work	2.56 (0.95-6.92)	0.063	
	Unpaid (Student/retired/housewives)	2.66 (1.07-6.66)	0.034	
2	**Treatment Stage**			
	Underwent surgery only	7.17 (2.88-17.89)	<0.001	
	Referral given to oncology after surgery	1.91 (0.55-6.64)	0.306	<0.001
	Oncology treatment started/continued	1.86 (0.59-5.79)	0.282	
	Treatment completed/follow-ups †	1	-	
3	**Tumor Recurrence**			
	Yes	1.97 (0.89-4.35)	0.090	
	No†	1	-	
† Reference Category which was kept as reference in Analysis				

Propensity scores predicted from above model were significantly associated with depression. Table 3 shows models to demonstrate association of propensity scores for functional status (KPS) with depression after controlling for current employment status, treatment stage, and tumor recurrence.

Table 4: Summary of association between propensity scores for functional status (KPS) with depressive symptoms after adjusting for current employment status, treatment stage, and tumor recurrence.

Variable	PR and 95% CI	P-value
Propensity scores for KPS	1.05 (1.02-1.08)	<0.001

Table 4 shows that with each unit increase in propensity scores for functional status; the depression will increase up to 5%.

Discussion:

The purpose of the present study was to investigate the association between depression and patient-related, tumor-related, and treatment related variables among adult patients with primary brain tumor. Although similar studies have been conducted in different parts of the world, most notably in US and UK, there is no literature from LMIC or even other South Asian countries. We believe that the circumstances for our patients differ from those of the west, for a number of reasons. According to World Health Organization, Pakistan has one of the world's lowest public health expenditure as a percentage of GDP, as well as one of the world highest out of pocket health expenditure, where it shares the top slot with other South Asian LMICs. Thus approximately 85% of our patients are out of pocket payers, in a country already marred with poverty, compared to the high-income countries where majority of patients are financially supported by third party payers i.e., state or insurance. [13] In this setting, the high cost of treatment for brain tumors (surgery, chemotherapy, radiation therapy, rehabilitation, etc.) should theoretically add to the psychological stress of the patients. Although government run hospitals do exist, they cover only a fraction of the overall healthcare and majority of patients have to resort to private hospitals, especially for advanced healthcare. There are also very few state run oncology or rehabilitation centres, and patients have to rely on private healthcare for all these services.

We found that 39% of patients with primary brain tumor treated at AKUH, screened positive for depression on PHQ-9. Impaired functional status was the only significant variable associated with depression and propensity scores for functional status revealed a significant association between impaired functional status and treatment stage at the time of interview, unemployment, and tumour recurrence. We also found that decreasing KPS was directly linked to increased chances of depression, as in with each unit increase in propensity scores for functional status; chances of depression increased by up to 5%. Our findings are consistent with some of the previous studies

on the same topic. Rooney (2010) [12] in his systematic review of observational studies concluded that the median prevalence of depression among patients with brain tumor using screening scales was about 27% (range 0%-93%) while clinician-rated measures returned up to 15% (5%-28%). Another meta-analysis conducted by Huang and Colleagues in 2017[18] reported that prevalence of depression in brain tumor patients is nearly 21% using screening scales and 19% with clinician-rated measures, specifically including mini-interviews. A 1-year follow-up study conducted by Mainio (2005) [19] also found functional status as a significant predictor associated with depression among brain tumor patients. Similar findings were observed in observational studies conducted by Anderson (1999) [20], Litofsky (2004) [21], Grant (1994) [22], Fox (2007) [14], Rooney (2013) [23], and Piil (2015) [24] [25].

We found three factors associated with reduced functional status including unemployment, tumor recurrence, and stage of treatment, more specifically, early stage of treatment. Association between employment status and depression has been explored by other investigators too, and there are at least three studies that have included employment status in their primary analysis. A study conducted by Pelletier (2002) [26] found employment status positively associated with depression among patients with brain tumors. However, this association was significant only at univariate level. Another study conducted by Vossen (2014) [27] on cognitive and emotional problems among meningioma patients reported significant association between depression and employment status where depression was assessed by hospital anxiety and depression scale. However, when depression was assessed by other screening tools, no association was found. In contrast, employment status was found to be significantly associated with functional status. A follow-up study conducted by Hickmann (2016) [28] reported a parallel trend of unemployment as the functional status declines. Though none of the studies have reported any definite association between unemployment and reduced functional status among similar populations but trends and figures explained by previous studies, as well as common sense supports this relationship, especially in countries without unemployment benefits; or without adequate labor laws safeguarding employee rights during illnesses.

We did not find any significant association between tumor recurrence and depression and similar findings were reported by Vossen (2014) [27]. On the other hand, reduced functional status was significantly associated with tumor recurrence, as shown by other investigators as well [29][30]. We included brain tumor patients during different treatment stages after surgical procedure was done. Patients immediately after surgery and in their initial stage of treatment reported highest prevalence of depression (82%). Weitzner (1999) [31], Pringle (1999) [32], and Mainio (2005) [19] also reported higher level of depression during initial stage of treatment that is within first three months after surgery. This variable was also found significantly associated with impaired functional status that is understandable given the physiological and psychological effects of major surgery and hospitalization. As the treatment progresses and by the time it comes to its end, patients tend to regain their functional status and even resume their jobs. Most brain tumor patients who have transient focal deficits as a result of surgery, by the time they reach the completion of their treatment, also improve in their overall functional status. However, no statistical evidence has been reported by any study on association between functional status and treatment stage.

This study had few limitations. Firstly, we conducted a cross-sectional study which by default doesn't conclude any temporal relationship between explanatory variables and the outcome. Though our study provides new insight to the psychological burden brain tumor patients may experience along with its associated factors but results of this study must be interpreted with caution. However, future studies with larger sample size and different prospective designs are required to hypothesize any specific association. Secondly, we used a single screening tool to measure depression. We did not use physician-rated measures or mini-interviews to verify the results of PHQ-9. This might have over-estimated the prevalence of depression among study participants. However, our study aimed to screen patients for depressive symptoms and not to diagnose thus, one screening tool was used only. Moreover, to prevent excessive fatigue to the patients, we decided to take less time of our participants. Therefore, screening tool was considered best to screen for depressive symptoms instead of interviews which could have taken longer time. Thirdly, this study was a single center study and thus results cannot be generalized

to entire population of brain tumor patients. Though we included diversified group of patients with different ethnic and cultural background but there is a possibility that patients who presented to government and semi-government sectors for the treatment of brain tumor might have different socio-economic backgrounds and other demographic characteristics. There is a possibility that patients presented to other care settings apart from AKUH might have different predisposing factors which leads to depression. Therefore, we cannot generalize our results to all brain tumor patients. However, our findings does represent group of brain tumor patients presented to private tertiary care settings in Pakistan.

Conclusion:

Our findings suggest that a high proportion of patients with brain tumor also suffer from depression. Whereas several individual and clinical factors may contribute to the development of depression, patients with reduced functional status should be especially monitored for any signs of psychiatric illness. Given the high proportion of depressed patients in our study population, we would recommend routine psychiatric evaluation, or at the least, the administration of simple self-rated screening tools that will allow healthcare providers to readily identify any prevailing neuropsychiatric ailments, for all patients with brain tumors, at the time of admission and during follow-ups.

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Conflict of interest disclosure:
The authors have no conflicts of interest to declare.

Data availability statement:
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Contribution of Author's:
Anum Sadruddin Pidani: Study design, formulation of questionnaire, data collection, data analysis, manuscript writing
Amna Rehana Siddiqui: Study design, epidemiological expertise in design and implementation phase, manuscript writing and review
Iqbal Azam: Biostatistician (analysis of study data), Manuscript writing and review of study analysis
Muhammad Shahzad Shamim: Design and implementation of study, neurosurgery expert input in the design and analysis phase, manuscript review and writing
Adnan A. Jabbar: Design and implementation of study, Oncology expert input in the design and analysis phase, Manuscript reviewing
Shameel Khan: Design and implementation of study, selection of study tools, Psychology expert input in the design and analysis phase, Manuscript reviewing

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes Page no 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes Page 1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes Page 2
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Yes Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes Page 3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes Page 3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes Page 3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes Page 3
Bias	9	Describe any efforts to address potential sources of bias	Yes Page 4
Study size	10	Explain how the study size was arrived at	Yes Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes Page 4

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes Page 4
		(*b*) Describe any methods used to examine subgroups and interactions	Yes Page 4
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes Page 3
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes Page 5
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	Yes Page 4- 5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes Page 7
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes Page 7
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes Page 8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes Page 2
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes Page 8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes

			Page 9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA Page 2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Depression among Adult Patients with Primary Brain Tumor: A Cross-Sectional Study of Risk Factors in a Low-Middle Income Country

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Depression among Adult Patients with Primary Brain Tumor: A Cross-Sectional Study of Risk Factors in a Low-Middle Income Country

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Running title: Factors associated with depression
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Tables: 4

Abstract:

OBJECTIVE:
The prevalence of depression among primary brain tumor patients ranges from 15% to 40% globally. Several individual and clinical factors contribute to the development of depression. However, their association with depression in Pakistani setting has not yet been assessed. Thus, we aim to study the factors associated with depression among adult primary brain tumor patients at a tertiary care hospital in Karachi, Pakistan.

STUDY DESIGN:
A prospective cross-sectional study

SETTING:
This study was conducted at a tertiary care hospital of Karachi, Pakistan

PARTICIPANTS:
This study included 132 patients with confirmed diagnosis of primary brain tumor (initially diagnosed on MRI brain with contrast and later confirmed on histology of surgical specimen) in various stages of treatment.

PRIMARY OUTCOME:
The primary outcome of this study was to assess depression and its associated factors among adult primary brain tumor patients. Depression was assessed using a validated screening tool (Patient Health Questionnaire-9). Scores of 10 to 27 on Patient Health Questionnaire-9 (PHQ-9) were indicative of screen positive for depressive symptoms. A set of the structured pre-tested questionnaire was used to evaluate patient-related, tumor-related, and treatment-related factors.

RESULTS:
Fifty-one (39%, CI: 33.33-46.94) patients in our study screened positive for depressive symptoms on PHQ-9. There was a significant association between depressive symptoms and Karnofsky Performance Scores (KPS) (Prevalence Ratio: 3.25 and Confidence Interval: 1.87-5.62) after controlling covariates. Propensity scores predicted a positive association between

KPS (functional status) and unemployment, treatment stage, and tumor recurrence. Tumor-related and treatment-related factors including tumor grade, location, type, and hemispheric lateralization were found insignificant.

CONCLUSION:
Depression is common in patients with a primary brain tumor. Impaired functional status has a direct impact on depression in these patients. Incorporating the psychosocial domain earlier in the course of treatment needs to be considered for better neuro-oncology management of primary brain tumor patients.

Strengths and Limitations of this study:

STRENGTHS:

- To our knowledge, this was the first study conducted in Pakistan to explore depression and its associated factors among primary brain tumor patients.
- The study has assessed those associations which were not assessed in any of the previous studies on a similar population including treatment stage, extra ventricular drain (EVD) insertion, number of admissions, stressful events, strategies use to handle stress, and first symptoms. Moreover, the relation of different costs including traveling cost and overall treatment cost with depression was also evaluated in this study.

LIMITATIONS:

- A single screening tool to measure depression instead of physician-rated measures or mini-interviews to verify the results of PHQ-9.
- The study design is cross-sectional which limits both temporality and direction of causation

Funding statement:
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

Background:

Although primary brain tumors account for a relatively small percentage of all cancers, it is considered one of the most devastating types of cancers among the adult population [1]. The incidence of primary brain tumors is approximately 9/100,000/year worldwide with higher rates in western countries as compared to low-middle income countries (LMIC) [2]. Interestingly, primary brain tumors rank highest among cancers that cause an emotional and psychological burden for patients [3-4].

Diagnostic and Statistical Manual-V defines depression as a feeling of sadness, loss of pleasure from daily living activities, body weight changes, reduction in physical activity, fatigue, failure to think or concentrate, lack of self-worth, and recurrent suicidal ideations [5]. It is estimated that depression affects about 350 million individuals worldwide and according to the Global Mental Health Survey (2014), nearly 1 in 20 individuals report having at least one episode of depression within a year [6]. Population-based researches report a prevalence of clinical depression ranging between 2% to 5% worldwide [7]. The worldwide prevalence of depression in cancer patients is 25% with higher rates among Asian countries [8]. The estimated prevalence of clinically diagnosed depression in Pakistan is approximately 6% out of which 3% are cancer patients [9]. Depression rates among primary brain tumor patients range from 15% to 40% with the highest rates among glioma patients [10]. However, it is suggested that these rates likely under-represent the true incidence of depression [11]. A systematic review of 42 observational studies reports that the prevalence of depression among glioma patients ranges between 0 to 93% with a median prevalence of 27% [12].

Depression in brain tumor patients is multifactorial and there are several factors contributing to its development, including individual, tumor-related, and disease-related factors [10]. All the studies on this topic to date have been conducted in the western population, where the psychosocial circumstances are much different from the Pakistani population, for example whereas in the UK and US, where most of the data come from, the majority of patients are financially supported by third party payers i.e., state or insurance. In contrast, approximately 85% of patients in Pakistan, and a few other South Asian LMIC countries are out of pocket payers both for their treatment, and rehabilitation [13]. This we believe, maybe the

cause of the additional psychological burden on the patients. This and several other factors like social support, family setup, and social status is unknown in the context of settings of low and middle income countries and requires a series of researches to establish associations. The aim of this study was to assess the association between depression and patient-related, tumor-related, and treatment-related variables among adult primary brain tumor patients in an LMIC.

Methods:

Study Design:

The analytical cross-sectional study design was employed to determine the association between patient-related, tumor-related, and treatment-related factors with depression among adult primary brain tumor patients. Non-probability consecutive sampling was used to recruit subjects. All the patients who met the eligibility criteria of the study and were willing to give consent were included in the study.

Site and setting

The study was approved by the institution review board (5009-CHS-ERC-17). The recruitment was conducted at tertiary care setting of Karachi, Pakistan and 132 patients with confirmed diagnosis primary of brain tumors at various stages of treatment were enrolled. These patients were contacted in neurosurgery wards, neurosurgery and oncology outpatient clinics, and oncology day care suits from November 2017 to July 2018.

Participants

Participants were all adult patients (aged 18 years and above) with a confirmed diagnosis of primary brain tumor (initially diagnosed on MRI brain with contrast and later confirmed on histology of surgical specimen) in various stages of treatment at a tertiary care setup. Each patient was enrolled after written, informed consent. The exclusion criteria for study participants were as follows: diagnosis of depression for about one year prior to the diagnosis of primary brain tumor, confused or incoherent patients and patients having problems with speech or comprehension that prevents them from completing the questionnaire, patients with co-existing systemic malignancies apart from a primary brain tumor, and any severe comorbid medical illness such as liver cirrhosis, systemic infections like HIV, and hepatitis which can cause altered mental status.

Procedure

Participant's eligibility was determined by medical record files. Potentially eligible participants were approached by the investigator during a scheduled follow-up visit at neurosurgery and oncology outpatient clinics and inpatient hospital stay post-surgery. Each patient after the consent were interviewed for 15-20 minutes to fill a structured pre-tested questionnaire [14] for assessing predictor variables and PHQ-9 scale for the screening of depression. The questionnaire was also pilot tested on 10 participants before the actual administration.

Measures

We divided all the associated factors into three distinct categories that were patient-related, tumor-related, and treatment-related variables. Patient-related factors comprised of demographic and socio-economic variables including age, gender, marital status, number of dependents, children under 18 years, education, occupation, employment status, residency, traveling cost, caregiver support, current smoking status, past/current medical illness, history of psychological distress, strategies to handle stress (isolation, aggression, prayers, crying, sleeping, addiction, and mind diversions) and functional status. The participant's functional status was assessed using the Karnofsky performance score (KPS). KPS scores less than 70 were indicative of impaired functional status. Socio-economic status (SES) was also computed using factorial analysis. Tumor-related and treatment-related variables were assessed by medical record review and included tumor histology, tumor grade, recurrence, hemispheric lateralization, first symptoms, brain structures involved, and cognitive impairment. Treatment-related variables included stage of treatment, number of chemotherapy cycles, duration since diagnosed,

radiation therapy, current use of steroids and anti-epileptic drugs, and treatment cost. The complete list of variables is mentioned in Table 1.

Depression

Primary brain tumor patients were screened for depression using the Urdu version of patient health questionnaire-9 (PHQ-9). The PHQ-9 is a self-rated screening tool which contains 9 items corresponds to DSM-V criteria of depression and rated on Likert scale of four points. All the patients were classified into two groups based on the scores on the PHQ-9 scale. Participants with a score of ≥ 10 were classified as screened positive for depression. PHQ-9 score of 10 or above has a sensitivity and specificity of 88% for major depressive symptoms. A recently conducted validation study on Urdu version (the national language of Pakistan) of PHQ-9 by Gholizadeh, 2017 [15], reported a specificity of 94% and a false-positive rate of 6% only.

Statistical Analysis:

Sample size was calculated from previous study [16] using Openepi [17] with a power of 80%, depression to no depression ratio of 1:2, prevalence ratio (PR) of 2 and 30% to 70% range of depression for different factors yield a sample size of 108. Adding 20% of the attrition rate the final sample size came out to be 130 participants. We used STATA version 12.0 [18] to perform all the analyses. For descriptive data of continuous variables mean and standard deviations were computed. Frequencies and percentages were computed for all qualitative variables. We applied the cox algorithm to obtain crude and adjusted prevalence ratios [19]. At the univariate level, independent variables were considered significant if the p-value was ≤ 0.25 [20]. We also checked multicollinearity between all the predictor variables. To assess Multicollinearity, three different tests were used. Pearson's correlation was used for two normally distributed continuous variables, ETA was used for one qualitative and one quantitative variable whereas; Cramer's V was used for two qualitative variables. Moreover, the cut-off for Multicollinearity was 0.8. After Multicollinearity, multivariable analysis was performed using the cox algorithm to obtained adjusted prevalence ratio. The cut-off for the significance of the predictor variable at multivariable analysis was ≤0.05. We also calculated Propensity scores for the only significant variable left after performing multivariable model building (functional status). The purpose of computing propensity scores was to identify the factor associated with the functional status and understand the vicious pathway of associations between explanatory variables and depression. To predict propensity scores, functional status was kept as a dependent variable and was regress with other explanatory variables. After the final model was obtained for functional status, propensity scores were computed. At last, Propensity scores were regressed against depression (dependent variable in the study) to see its association with depression. The cut-off for the significance of propensity scores was ≤0.05.

Patient and public involvement

None of the study participants was involved in the design or conduct of this study and no patient opinion regarding the study has been obtained. The results have been reported to head of Mind and brain service line at AKUH in Karachi which primarily deals with neuro-oncology patients.

Results:

Descriptive characteristics of the study participants:

The mean age (± SD) of study participants was 43.25 (± 12.28) years, with 86 (65%) males and 46 (35%) female. Fifty-one (39%) study participants were screened positive (Scores of 10 and greater on PHQ-9) for depression while 81 participants (61%) were screened negative (Scores less than 10 on PHQ-9) for depression. Table 1 shows the descriptive characteristics of study participants.

Table 1: Summary of the descriptive characteristics of study participants

PATIENT-RELATED VARIABLES

S#	Variables	Total N (%)	Screened positive for depressive symptoms (PHQ-9 ≥ 10) N (%)
1	**Marital Status**		
	Married	117 (89)	43 (37)
	Unmarried/Single/Separated/Divorced	15 (11)	8 (53)
2	**Children under 18 years**		
	Yes	75 (57)	32 (43)
	No	33 (25)	10 (30)
	Unmarried	24 (18)	9 (38)
3	**Current Employment status**		
	Able to work	65 (49)	18 (28)
	Unable to work	24 (18)	13 (54)
	Unpaid (Retired/Student/Housewives)	43 (33)	20 (47)
4	**Residence**		
	In Karachi	49 (37)	19 (39)
	Outside Karachi	83 (63)	32 (39)
5	**Travel Cost for one visit (from hometown to hospital)**		
	5000-10,000 Rupees	26 (20)	5 (19)
	11,000-20,000 Rupees	39 (30)	18 (46)
	>20,000 Rupees	18 (13)	9 (50)
	Not Applicable	49 (37)	19 (39)
6	**Caregiver at Home**		
	Spouse	92 (70)	33 (36)
	Parents	14 (10)	08 (57)
	Others (Kids/Neighbors/Siblings/Self)	26 (20)	10 (38)
7	**Heading Family**		
	Yes	68 (52)	27 (40)
	No	64 (48)	24 (38)
8	**Socio-economic Status** (SES)		
	Low SES	22 (17)	9 (41)
	Middle SES	83 (63)	32 (39)
	High SES	27 (20)	10 (37)
9	**Currently Smoking** (Cigarette, huqa, beeri)		
	Yes	18 (14)	10 (56)
	No	114 (86)	41 (36)
10	**History of Psychological Distress Prior to the Diagnosis of Brain Tumor**		
	Yes	7 (5)	6 (86)
	No	125 (95)	45 (36)
11	**Strategies to Handle Stress**		
	Isolation	26 (20)	10 (38)
	Crying	16 (12)	7 (44)
	Prayers	48 (36)	14 (29)
	Aggression	24 (18)	13 (54)
	Leaves home	1 (0.7)	1 (1.96)
	Sleeping	13 (9)	6 (45)
	Conversation with family/friends	10 (7)	1 (10)
	Addictions (Smoking/drinking)	6 (4)	4 (66)
	Mind diversions (Listening to music/shopping)	2 (1)	0(0)
12	**Karnofsky Performance Score** (Functional Status)		

	KPS scores >70 KPS scores ≤ 70	102 (77) 30 (23)	27 (26) 24 (80)
TREATMENT-RELATED VARIABLES			
13	**Overall Treatment Cost during illness** 200,000-800,000 Rupees 800,000-1,200,000 Rupees >1,200,000 Rupees	 45 (34) 47 (36) 40 (30)	 17 (38) 20 (43) 14 (35)
14	**Treatment Cost Management** Self-support Family/relative support Welfare from primary treating hospital Medical support from workplace/community	 73 (55) 21 (16) 28 (21) 10 (8)	 25 (34) 11 (52) 13 (46) 2 (20)
15	**Access to Health Insurance** Yes No	 15 (11) 117 (89)	 3 (20) 48 (41)
16	**Treatment Stage at the Time of Interview** Only Surgical procedure done Referral given to oncology after surgery Oncology treatment started/continued Treatment completed/follow-ups	 17 (13) 18 (13) 25 (19) 72 (55)	 14 (82) 5 (28) 10 (40) 22 (31)
17	**Current Use of Steroids** Yes No	 22 (17) 110 (83)	 13 (59) 38 (35)
18	**Current Use of Antiepileptic Drugs** Yes No	 48 (36) 84 (64)	 17 (35) 34 (40)
19	**Surgical Procedure Performed to Remove Tumor** Craniotomy/craniectomy Trans-sphenoidal Resection	 96 (73) 36 (27)	 41 (43) 10 (28)
20	**Type of surgery** Awake (Local anesthesia/ Scalp block) Conventional (General anesthesia)	 37 (28) 95 (72)	 12 (32) 39 (41)
21	**External Ventricular Drain Insertion** Yes No	 7 (5) 125 (95)	 5 (71) 46 (37)
22	Time since diagnosis (In months)	Median:9.5 months Range:(1-74 month)	Median: 5 month Range:(1-74 month)
25	Number of chemotherapy cycles	Median: 2.5 cycles Range: (0-33 cycles)	Median: 0 Range:(0-27 cycles)
26	Number of radiation cycles	Median: 3.5 cycles Range: (0-33 cycles)	Median: 0 Range:(0-54 cycles)
TUMOUR-RELATED VARIABLES			
27	**Tumor Histology** Meningioma Pituitary adenoma High grade glioma (Astrocytoma, GBM) Oligodendroglioma	 30 (23) 36 (27) 21 (16) 29 (22)	 16 (53) 9 (25) 9 (43) 8 (28)

	Others (Schwannoma, Intraventricular SOLs, CNS lymphoma, Ependymoma, Hemangioblastoma, Craniopharyngioma, Choroid plexus papilloma)	16 (12)	9 (56)
28	**Tumor Type**		
	Benign	69 (52)	28 (41)
	Malignant	63 (48)	23 (37)
29	**Hemispheric Lateralization**		
	Left	60 (45)	28 (47)
	Right	35 (27)	13 (37)
	Not specified	37 (28)	10 (27)
30	**Tumour Grade**		
	Grade I	12 (9)	05 (42)
	Grade II	30 (23)	14 (47)
	Grade III	30 (23)	13 (43)
	Grade IV	16 (12)	7 (47)
	Not specified	44 (33)	12 (27)
31	**Cognitive Impairment**		
	Yes	9 (7)	5 (56)
	No	123 (93)	46 (37)
32	**Tumor Recurrence**		
	Yes	23 (17)	14 (61)
	No	109 (83)	37 (34)
33	**Brain Structures Involved (Tumor location)**		
	Frontal lobe	53 (40)	23 (43)
	Parietal lobe	30 (22)	13 (43)
	Temporal lobe	26 (19)	10 (38)
	Occipital lobe	5 (3)	1 (20)
	Pituitary gland (Seller region)	36 (27)	9 (25)
	Ventricles	5 (4)	3 (60)
	Cerebellum/CP angle	7 (4)	6 (85)
	Posterior fossa	1 (1)	0 (0)
	Basal ganglia	1 (1)	0(0)
34	**First Symptoms Before Brain Tumor Diagnosis**		
	Seizures	40 (30)	14 (35)
	Headaches	55 (42)	25 (45)
	Weight loss/gain	3 (2)	1 (33)
	Mood changes/loss of interest	1 (1)	1 (100)
	Visual impairment	36 (27)	10 (28)
	Memory loss	5 (3)	3 (60)
	Gait instability	1 (1)	1 (2)
	Nausea/ Vomiting	5 (3)	2 (40)
	Unconsciousness	7 (5)	2 (29)
	Dizziness	1 (1)	0 (00)
	Slurred speech/unable to write & comprehend	3 (2)	1 (33)
	Numbness (arms, legs, body)	2 (1)	1 (50)
	Limb weakness	2 (1)	1 (50)
	Swelling (facial, orbital)	3 (2)	2 (67)
	Sexual dysfunction	1 (1)	0 (0)
	Hearing problems	1 (1)	0 (0)

Univariate analysis:

Univariate analysis showed that impaired functional status (P=<0.001), unemployment (P=0.121), travel cost (P=0.240), current smoking status (P=0.238), history of psychological distress prior to the diagnosis of brain tumor (P=0.073), prayer (strategies to handle stress) (P=0.176), aggression (strategies to handle stress) (P=0.195), health insurance (P=0.178), treatment stage at the time of interview (P=0.041), current use of steroids (P=0.111), surgical intervention performed to remove the tumor (P=0.203), external ventricular drain insertion (P=0.196), multiple hospital admissions (P=0.069), number of surgeries (P=0.148), tumor histology (P=0.221), tumor recurrence (P=0.076), tumor involving seller region (brain structure involved) (P=0.106), and tumor involving cerebellum/CP angle (P=0.046) had P-value of ≤ 0.25. After adjusting for the effect of other variables in the multivariable model, functional status (KPS) remained the only variable found associated with depressive symptoms among primary brain tumor patients with P-value <0.001.

Table 2: Summary of final reduced multivariate models using Cox Algorithm to predict prevalence of depressive symptoms and its association with functional status

Variable	PR and 95% CI	P-value
KPS scores >70 †	1	-
KPS scores ≤ 70	3.25 (1.87-5.62)	<0.001
†Reference Category which was kept as reference in Analysis		

Table 2 shows that the prevalence of depression among patients with KPS scores ≤ 70 is 3.25 times more as compared to patients with KPS scores > 70

Propensity scores for functional status showed three factors that were significantly associated with functional status including employment status, tumor recurrence, and treatment stage at the time of the interview. Table 3 shows factors associated with functional status (KPS).

Table 3: Factors associated with functional status determined by using KPS among primary brain tumor patients

S#	Variables	PR & 95% CI	P-Value (z)	P-value (F)
1	**Current Employment Status**			
	Able to work †	1	-	
	Unable to work	2.56 (0.95-6.92)	0.063	
	Unpaid (Student/retired/housewives)	2.66 (1.07-6.66)	0.034	
2	**Treatment Stage**			
	Underwent surgery only	7.17 (2.88-17.89)	<0.001	
	Referral given to oncology after surgery	1.91 (0.55-6.64)	0.306	<0.001
	Oncology treatment started/continued	1.86 (0.59-5.79)	0.282	
	Treatment completed/follow-ups †	1	-	
3	**Tumor Recurrence**			
	Yes	1.97 (0.89-4.35)	0.090	
	No†	1	-	
† Reference Category which was kept as reference in Analysis				

Propensity scores predicted from the above model were significantly associated with depression. Table 3 shows models to demonstrate the association of propensity scores for functional status (KPS) with depression after controlling for current employment status, treatment stage, and tumor recurrence.

Table 4: Summary of association between propensity scores for functional status (KPS) with depressive symptoms after adjusting for current employment status, treatment stage, and tumor recurrence.

Variable	PR and 95% CI	P-value

Propensity scores for KPS	1.05 (1.02-1.08)	<0.001

Table 4 shows that with each unit increase in propensity scores for functional status; the depression will increase up to 5%.

Discussion:

The purpose of the present study was to investigate the association between depression and patient-related, tumor-related, and treatment-related variables among adult patients with primary brain tumors. Although similar studies have been conducted in different parts of the world, most notably in the US and UK, there is no literature from LMIC or even other South Asian countries. We believe that the circumstances for our patients differ from those of the west, for a number of reasons. According to World Health Organization, Pakistan has one of the world's lowest public health expenditure as a percentage of GDP, as well as one of the world's highest out of pocket health expenditure, where it shares the top slot with other South Asian LMICs. Thus approximately 85% of our patients are out of pocket payers, in a country already marred with poverty, compared to the high-income countries where the majority of patients are financially supported by third party payers i.e., state or insurance. [13] In this setting, the high cost of treatment for brain tumors (surgery, chemotherapy, radiation therapy, rehabilitation, etc.) should theoretically add to the psychological stress of the patients. Although government-run hospitals do exist, they cover only a fraction of the overall healthcare, and the majority of patients have to resort to private hospitals, especially for advanced healthcare. There are also very few state-run oncology or rehabilitation centers, and patients have to rely on private healthcare for all these services.

We found that 39% of patients with a primary brain tumor treated at AKUH, screened positive for depression on PHQ-9. Impaired functional status was the only significant variable associated with depression and propensity scores for functional status revealed a significant association between impaired functional status and treatment stage at the time of the interview, unemployment, and tumor recurrence. We also found that decreasing KPS was directly linked to increased chances of depression, as in with each unit increase in propensity scores for functional status; chances of depression increased by up to 5%. Our findings are consistent with some of the previous studies on the same topic. Rooney (2010) [12] in his systematic review of observational studies concluded that the median prevalence of depression among patients with brain tumor using screening scales was about 27% (range 0%-93%) while clinician-rated measures returned up to 15% (5%-28%). Another meta-analysis conducted by Huang and Colleagues in 2017[21] reported that the prevalence of depression in brain tumor patients is nearly 21% using screening scales and 19% with clinician-rated measures, specifically including mini-interviews. A 1-year follow-up study conducted by Mainio (2005) [22] also found functional status as a significant predictor associated with depression among brain tumor patients. Similar findings were observed in observational studies conducted by Anderson (1999) [23], Litofsky (2004) [24], Grant (1994) [25], Fox (2007) [26], Rooney (2013) [27], and Piil (2015) [28-29].

We found three factors associated with reduced functional status including unemployment, tumor recurrence, and stage of treatment, more specifically, the early stage of treatment. Association between employment status and depression has been explored by other investigators too. A study conducted by Pelletier (2002) [30] found employment status positively associated with depression among patients with brain tumors. However, this association was significant only at the univariate level. Another study conducted by Vossen (2014) [31] on cognitive and emotional problems among meningioma patients reported a significant association between depression and employment status where depression was assessed by hospital anxiety and depression scale. However, when depression was assessed by other screening tools, no association was found. In contrast, employment status was found to be significantly associated with functional status. A follow-up study conducted by Hickmann (2016) [32] reported a parallel trend of unemployment as the functional status declines. Though none of the studies have reported any definite association between unemployment and reduced functional status among similar populations but trends and figures explained by previous studies, as well as common sense supports this relationship, especially in countries without unemployment benefits; or without adequate labor laws safeguarding employee rights during illnesses.

We did not find any significant association between tumor recurrence and depression and similar findings were reported by Vossen (2014) [31]. On the other hand, reduced functional status was significantly associated with tumor recurrence, as shown by other investigators as well [33-34]. We included brain tumor patients during different treatment stages after surgical procedure was done. Patients immediately after surgery and in their initial stage of treatment reported the highest

prevalence of depression (82%). Weitzner (1999) [35], Pringle (1999) [36], and Mainio (2005) [22] also reported a higher level of depression during the initial stage of treatment that is within the first three months after surgery. This variable was also found significantly associated with an impaired functional status that is understandable given the physiological and psychological effects of major surgery and hospitalization. As the treatment progresses and by the time it comes to its end, patients tend to regain their functional status and even resume their jobs. Most brain tumor patients who have transient focal deficits because of surgery, by the time they reach the completion of their treatment, also improve in their overall functional status. However, no statistical evidence has been reported by any study on the association between functional status and treatment stage.

This study had few limitations. Firstly, we conducted a cross-sectional study which by default doesn't conclude any temporal relationship between explanatory variables and the outcome. Though our study provides new insight into the psychological burden brain tumor patients may experience along with its associated factors but the results of this study must be interpreted with caution. However, future studies with larger sample size and different prospective designs are required to hypothesize any specific association. Secondly, we used a single screening tool to measure depression. We did not use physician-rated measures or mini-interviews to verify the results of PHQ-9. This might have over-estimated the prevalence of depression among study participants. However, our study aimed to screen patients for depressive symptoms and not to diagnose thus, one screening tool was used only. Moreover, to prevent excessive fatigue to the patients, we decided to take less time off our participants. Therefore, a screening tool was considered best to screen for depressive symptoms instead of interviews which could have taken a long time. Thirdly, this study was a single-center study and thus results cannot be generalized to the entire population of brain tumor patients. Though we included a diversified group of patients with different ethnic and cultural backgrounds but there is a possibility that patients who presented to government and semi-government sectors for the treatment of brain tumors might have different socio-economic backgrounds and other demographic characteristics. There is a possibility that patients presented to other care settings apart from AKUH might have different predisposing factors that lead to depression. Therefore, we cannot generalize our results to all brain tumor patients. However, our findings do represent a group of brain tumor patients presented to private tertiary care settings in Pakistan.

Conclusion:

Our findings suggest that a high proportion of patients with brain tumor also suffer from depression. Whereas several individual and clinical factors may contribute to the development of depression, patients with reduced functional status should be specially monitored for any signs of psychiatric illness. Given the high the proportion of depressed patients in our study population, we would recommend routine psychiatric evaluation, or at the least, the administration of simple self-rated screening tools that will allow healthcare providers to readily identify any prevailing neuropsychiatric ailments, for all patients with brain tumors, at the time of admission and during follow-ups.

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Conflict of interest disclosure:
The authors have no conflicts of interest to declare.

Data availability statement:
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Contribution of Author's:
Anum Sadruddin Pidani: Study design, formulation of questionnaire, data collection, data analysis, manuscript writing
Amna Rehana Siddiqui: Study design, epidemiological expertise in design and implementation phase, manuscript writing and review
Iqbal Azam: Biostatistician (analysis of study data), Manuscript writing and review of study analysis
Muhammad Shahzad Shamim: Design and implementation of study, neurosurgery expert input in the design and analysis phase, manuscript review and writing
Adnan A. Jabbar: Design and implementation of study, Oncology expert input in the design and analysis phase, Manuscript reviewing

Shameel Khan: Design and implementation of study, selection of study tools, Psychology expert input in the design and analysis phase, Manuscript reviewing

Abbreviations:
PHQ-9: Patient Health Questionnaire-9
AKUH: Aga Khan University Hospital
KPS: Karnofsky Performance Score
DSM-V: Diagnostic and Statistical Manual of Mental Disorders-5th Edition
PR: Prevalence Ratio
HIV: Human Immunodeficiency Viruses
LMIC: Low-Middle Income Country
UK: United Kingdom
US: United States
MRI: Magnetic Resonance Imaging
SES: Socio-economic Status
EVD: Extra Ventricular Drain

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes Page no 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes Page 1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes Page 2
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes Page 3
Methods			
Study design	4	Present key elements of study design early in the paper	Yes Page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes Page 3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes Page 3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes Page 3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes Page 3
Bias	9	Describe any efforts to address potential sources of bias	Yes Page 4
Study size	10	Explain how the study size was arrived at	Yes Page 4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes Page 4

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes Page 4
		(*b*) Describe any methods used to examine subgroups and interactions	Yes Page 4
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes Page 3
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes Page 5
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	Yes Page 4- 5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes Page 7
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes Page 7
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes Page 8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes Page 2
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes Page 8-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes

			Page 9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA Page 2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.