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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: 3

29 Abstract:

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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.

38 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.

47 RESULTS:

⁴⁸ Fifty one (39%) patients in our study screened positive for depression on PHQ-9. There was significant
 ⁴⁹ association between depression and KPS scores (Prevalence Ratio: 3.25 and Confidence Interval: 1.87-5.62) after
 ⁵¹ controlling covariates. Propensity scores predicted positive association between KPS (functional status) and
 ⁵² unemployment, treatment stage, and tumor recurrence. Tumor-related and treatment related factors including
 ⁵³ tumor grade, location, type, and hemispheric lateralization were found insignificant.

CONCLUSION:

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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.

Funding statement:

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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].

30 World Health Organization defines depression as a feeling of sadness, loss of pleasure from daily living activities 31 and lack of self-worth [5]. It is estimated that depression affects about 350 million individuals worldwide and 32 according to the Global Mental Health Survey (2014), nearly 1 in 20 individuals report having at least one episode 33 of depression within a year [6]. Population based researches report a prevalence of clinical depression ranging 34 35 between 2% to 5% worldwide [7]. The worldwide prevalence of depression in cancer patients is 25% with higher 36 rates among Asian countries [8]. The estimated prevalence of clinically diagnosed depression in Pakistan is 37 approximately 6% out of which 3% are cancer patients [9]. Depression rates among primary brain tumor patients 38 ranges from 15% to 40% with highest rates among glioma patients [10]. However, it is suggested that these rates 39 likely under-represent the true incidence of depression [11]. A systematic review of 42 observational studies 40 reports that the prevalence of depression among glioma patients ranges between 0 to 93% with a median 41 42 prevalence of 27% [12]. 43

44 Depression in brain tumor patients is multifactorial and there are several factors contributing to its development, 45 including individual, tumor-related, and disease-related factors [10]. All the studies on this topic to date have been 46 conducted in western population, where the psychosocial circumstances are much different from Pakistani 47 population, for example whereas in UK and US, where most of the data comes from, majority of patients are 48 financially supported by third party payers i.e., state or insurance. In contrast, approximately 85% of patients in 49 50 Pakistan, and a few other South Asian LMIC countries, are out of pocket payers both for their treatment, and 51 rehabilitation [13]. This we believe, may be the cause of additional psychological burden on the patients. This 52 and several other factors are unknown in the context of settings of low and middle income countries and require 53 a series of researches to establish associations. The aim of this study was to assess association between depression 54 and patient-related, tumor-related, and treatment-related variables among adult primary brain tumor patients in a 55 LMIC. 56

Methods:

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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. Nonprobability 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.

10 Site and setting 11

The study was approved by the institution review board (5009-CHS-ERC-17). The recruitment was conducted at 12 tertiary care setting of Karachi, Pakistan and 132 patients with biopsy proven primary brain tumors at various 13 stages of treatment were enrolled. These patients were contacted in neurosurgery wards, neurosurgery and 14 15 oncology outpatient clinics, and oncology day care suits from November 2017 to July 2018. 16

Participants

18 Participants were all adult patients (aged 18 years and above) under treatment at a tertiary care setup. Each patient 19 was enrolled after a written, informed consent. The exclusion criteria for study participants were as follows: 20 diagnosis of depression prior to the diagnosis of brain tumor, confused or incoherent patients and patients with 21 22 problems with speech or comprehension that prevents them from completing the questionnaire, patients with co-23 existing systemic malignancies apart from primary brain tumor, and any severe comorbid medical illness such as 24 liver cirrhosis, systemic infections like HIV, and hepatitis which can cause altered mental status. 25

26 Procedure 27

Participant's eligibility was determined by medical record files. Potentially eligible participants were approached 28 by the investigator during a scheduled follow-up visit at neurosurgery and oncology outpatient clinics or during 29 30 inpatient hospital stay post-surgery. Each patient after the consent were interviewed for 15-20 minutes to fill a 31 pre-structured questionnaire for assessing predictor variables and PHQ-9 scale for screening of depression. The 32 questionnaire was also pilot tested on 10 participants before actual administration. 33

34 Measures 35

We divided all the associated factors into three distinct categories that were patient-related, tumor-related, and 36 37 treatment-related variables. Patient-related factors comprised of demographic and socio-economic variables 38 including age, gender, marital status, number of dependents, children under 18 years, education, occupation, 39 employment status, residency, travelling cost, care giver support, current smoking status, past/current medical 40 illness, history of psychological dresses, strategies to handle stress (isolation, aggression, prayers, crying, 41 sleeping, addiction, and mind diversions) and functional status. Participant's functional status was assessed using 42 Karnofsky performance score (KPS). KPS scores less than 70 were indicative of impaired functional status. Socio-43 economic status (SES) was also computed using factorial analysis. Tumor-related and treatment-related variables 44 45 were assessed by medical record review and included tumor histology, tumor grade, recurrence, hemispheric 46 lateralization, first symptoms, brain structures involved, and cognitive impairment. Treatment related variables 47 included stage of treatment, number of chemotherapy cycles, duration since diagnosis, radiation therapy, current 48 use of steroids and anti-epileptic drugs, and treatment cost. The complete list of variables is mentioned in Table 49 1.

50 51

52 Depression

53 Primary brain tumour patients were screened for depression using Urdu version of patient health questionnaire-9 54 (PHQ-9). The PHQ-9 is a self-rated screening tool which contains 9 items that corresponds to DSM-V criteria of 55 depression and was rated on Likert scale of four points. All the patients were classified into two groups based on 56 the scores on PHQ-9 scale. Participants with a score of ≥ 10 were classified as screened positive for depression. 57

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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 PHO-9 by Gholizadeh, 2017 [23], reported a specificity of 94% and false positive rate of 6% only.

4 Statistical Analysis: 5

6 Power calculation was derived from previous studies [14, 15]. We calculated sample size using Openepi [16] with 7 a power of 80%, depression to no depression ratio of 1:2, prevalence ratio of 2 and 30% to 70% range of 8 depression for different factors yield a sample size of 108. Adding 20% of attrition rate the final sample size came 9 out to be 130 participants. We used STATA version 12.0 [17] to perform all the analysis. For descriptive data of 10 continuous variables mean and standard deviations were computed. Frequencies and percentages were computed 11 for all qualitative variables. We applied logistic regression cox algorithm to obtain crude and adjusted prevalence 12 ratios. At univariate level, independent variables were considered significant if p-value was < 0.25. We also 13 checked multicollinearity between all the predictor variables. Stepwise model building technique was used for 14 15 adding up variables. The cut-off for the significance of predictor variable at multivariable analysis was 0.05. 16 Propensity scores were computed to identify factors associated with functional status. 17

18 Patient and public involvement 19

None of the study participants were involved in the design or conduct of this study and no patient opinion 20 regarding the study has been obtained. The results have been reported to head of Mind and brain service line at 21 22 AKUH in Karachi which primarily deals with neuro-oncology patients. 23

Results:

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26 Descriptive characteristics of study participants: 27

The mean age (\pm SD) of study participants was 43.25 (\pm 12.28) years, with 86 (65%) males and 46 (35%) female. 28 Fifty one (39%) study participants were screened positive (Scores of 10 and greater on PHQ-9) for depression 29 30 while 81 participants (61%) were screened negative (Scores less than 10 on PHO-9) for depression. Table 1 shows 31 descriptive characteristics of study participants. 32

S#	Variables	Total	Screened positive for depressio (PHQ-9 \geq 10)
1	Marital Status	IN (70)	IN (70)
1	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)

Table 1. Summary of descriptive characteristic of study participants

6	Caregiver at Home		
	Spouse	92 (70)	33 (36)
	Darents	$\frac{14}{10}$	8 (57)
	Others (Kids/Naighbors/Siblings/Salt)	26(20)	10(37)
7	Uners (Klus/Ivergnools/Slottings/Sett)	20 (20)	10 (30)
/	Heading Family	(0.(50))	27 (10)
	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		
	Ves	7 (5)	6 (86)
	No	125 (95)	45 (36)
11	Stratagies to Handle Strass	125 (75)	
11	Isolation	26 (20)	10 (28)
		20(20) 16(12)	10(38) 7(44)
		10(12)	/ (44)
	Prayers	48 (50)	14 (29)
	Aggression	24 (18)	15 (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)
TRE	ATMENT-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	10 (30)	
14	Self-support	73 (55)	25 (34)
	Son-support Family/relative support	$\frac{75(55)}{21(16)}$	23 (34) 11 (52)
	Failiny/relative support Walfara from primary tracting heavital	21(10) 28(21)	11(32) 12(46)
	wenare from primary treating hospital		13 (46)
1 -	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		()
1/	Ves	22 (17)	13 (59)
	No	110(83)	38 (35)
19	Current Use of Antionilantia Drugs	110 (03)	
10	Vor	19 (26)	17 (25)
	Y es	48 (50)	1/(35)
10	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		

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	$\mathbf{A}_{1} = \mathbf{A}_{1} + \mathbf{A}_{2} + \mathbf{A}_{1} + \mathbf{A}_{2} $	27 (29)	12 (22)
	Awake (Local anestnesia/ Scalp block)	37 (28)	12(32)
- 1	Conventional (General anesthesia)	95 (72)	39 (41)
21	External Ventricular Drain Insertion		
	Yes	7 (5)	5 (71)
	No	125 (95)	46 (37)
2	Time since diagnosis (In months)	Median:9.5 months	Median: 5 month
		Range:(1-74 month)	Range:(1-74 month)
25	Number of chemotherapy cycles	Median: 2.5 cycles	Median: 0
		Range: (0-33 cycles)	Range:(0-27 cycles)
26	Number of radiation cycles	Median: 3.5 cycles	Median: 0
		Range: (0-33 cycles)	Range:(0-54 cycles)
ΓUΜ	OUR-RELATED VARIABLES		
27	Tumor Histology		
	Meningioma	30 (23)	16 (53)
	Pituitary adenoma	36 (27)	9 (25)
	High grade glioma (Astrocytoma, GBM)	21 (16)	9 (43)
	Oligodendroglioma	29 (22)	8 (28)
	Others (Schwannoma, Intraventricular SOLs, CNS lymphoma,	16(12)	9 (56)
	Ependymoma, Hemangioblastoma, Craniopharvngioma		
	Choroid plexus papilloma)		
28	Tumor Type		
-	Benign \checkmark	69 (52)	28 (41)
	Malignant	63 (48)	23 (37)
29	Hemispheric Lateralization		- (- ')
		60 (45)	28 (47)
	Right	35 (27)	13(37)
	Not specified	37 (28)	10(27)
0	Tumour Grade	57 (20)	
	Grade I	12 (9)	5(42)
	Grade II	$\frac{12}{30}(23)$	14(47)
	Grade III	30(23)	13(43)
	Grade IV	15(12)	7 (47)
	Not specified	$\frac{13}{44}$ (33)	12(27)
1	Cognitive Impairment	++ (55)	
1	Voc	9(7)	5 (56)
	No	(1) 123 (03)	3(30)
27		125 (55)	48 (57)
52	Voc	22 (17)	14 (61)
	No	23(17) 100(83)	17(01) 27(24)
22	NU Drain Structures Involved (Tumor location)	109 (03)	57 (34)
רר ו	DIALIT STRUCTURES HIVOIVED (FUIDOR TOCATION)		
	Frontel John	52 (40)	22(42)
	Frontal lobe	53 (40)	23 (43)
	Frontal lobe Parietal lobe	53 (40) 30 (22) 26 (10)	23 (43) 13 (43) 10 (23)
	Frontal lobe Parietal lobe Temporal lobe	53 (40) 30 (22) 26 (19)	23 (43) 13 (43) 10 (38)
	Frontal lobe Parietal lobe Temporal lobe Occipital lobe	53 (40) 30 (22) 26 (19) 5 (3)	23 (43) 13 (43) 10 (38) 1 (20) 2 (25)
	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region)	53 (40) 30 (22) 26 (19) 5 (3) 36 (27)	23 (43) 13 (43) 10 (38) 1 (20) 9 (25) 2 ((2))
	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4)	23 (43) 13 (43) 10 (38) 1 (20) 9 (25) 3 (60)
	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4)	23 (43) 13 (43) 10 (38) 1 (20) 9 (25) 3 (60) 6 (85)
	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4) 1 (1)	23 (43) 13 (43) 10 (38) 1 (20) 9 (25) 3 (60) 6 (85) 0 (00)
	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	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa Basal ganglia First Symptoms Before Brain Tumor Diagnosis	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	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa Basal ganglia First Symptoms Before Brain Tumor Diagnosis Seizures	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4) 1 (1) 1 (1) 40 (30)	23 (43) 13 (43) 10 (38) 1 (20) 9 (25) 3 (60) 6 (85) 0 (00) 0 (00) 14 (35)
34	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa Basal ganglia First Symptoms Before Brain Tumor Diagnosis Seizures Headaches	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4) 1 (1) 1 (1) 40 (30) 55 (42)	23 (43) 13 (43) 10 (38) 1 (20) 9 (25) 3 (60) 6 (85) 0 (00) 0 (00) 14 (35) 25 (45)
34	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa Basal ganglia First Symptoms Before Brain Tumor Diagnosis Seizures Headaches Weight loss/gain	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4) 1 (1) 1 (1) 40 (30) 55 (42) 3 (2)	23 (43) 13 (43) 10 (38) 1 (20) 9 (25) 3 (60) 6 (85) 0 (00) 0 (00) 14 (35) 25 (45) 1 (33)
34	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa Basal ganglia First Symptoms Before Brain Tumor Diagnosis Seizures Headaches Weight loss/gain Mood changes/loss of interest	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4) 1 (1) 1 (1) 40 (30) 55 (42) 3 (2) 1 (1)	23 (43) 13 (43) 10 (38) 1 (20) 9 (25) 3 (60) 6 (85) 0 (00) 0 (00) 14 (35) 25 (45) 1 (33) 1 (100)
34	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa Basal ganglia First Symptoms Before Brain Tumor Diagnosis Seizures Headaches Weight loss/gain Mood changes/loss of interest Visual impairment	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4) 1 (1) 1 (1) 40 (30) 55 (42) 3 (2) 1 (1) 36 (27)	23 (43) 13 (43) 10 (38) 1 (20) 9 (25) 3 (60) 6 (85) 0 (00) 0 (00) 14 (35) 25 (45) 1 (33) 1 (100) 10 (28)
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34	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa Basal ganglia First Symptoms Before Brain Tumor Diagnosis Seizures Headaches Weight loss/gain Mood changes/loss of interest Visual impairment Memory loss Gait instability	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4) 1 (1) 1 (1) 40 (30) 55 (42) 3 (2) 1 (1) 36 (27) 5 (3) 1 (1)	$\begin{array}{c} 23 \ (43) \\ 13 \ (43) \\ 10 \ (38) \\ 1 \ (20) \\ 9 \ (25) \\ 3 \ (60) \\ 6 \ (85) \\ 0 \ (00) \\ 0 \ (00) \\ \end{array}$ $\begin{array}{c} 14 \ (35) \\ 25 \ (45) \\ 1 \ (33) \\ 1 \ (100) \\ 10 \ (28) \\ 3 \ (60) \\ 1 \ (2) \end{array}$
34	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa Basal ganglia First Symptoms Before Brain Tumor Diagnosis Seizures Headaches Weight loss/gain Mood changes/loss of interest Visual impairment Memory loss Gait instability Nausea/ Vomiting	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4) 1 (1) 1 (1) 40 (30) 55 (42) 3 (2) 1 (1) 36 (27) 5 (3) 1 (1) 5 (3)	$\begin{array}{c} 23 \ (43) \\ 13 \ (43) \\ 10 \ (38) \\ 1 \ (20) \\ 9 \ (25) \\ 3 \ (60) \\ 6 \ (85) \\ 0 \ (00) \\ 0 \ (00) \\ \hline \\ 14 \ (35) \\ 25 \ (45) \\ 1 \ (33) \\ 1 \ (100) \\ 10 \ (28) \\ 3 \ (60) \\ 1 \ (2) \\ 2 \ (40) \\ \hline \end{array}$
34	Frontal lobe Parietal lobe Temporal lobe Occipital lobe Pituitary gland (Seller region) Ventricles Cerebellum/CP angle Posterior fossa Basal ganglia 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	53 (40) 30 (22) 26 (19) 5 (3) 36 (27) 5 (4) 7 (4) 1 (1) 1 (1) 40 (30) 55 (42) 3 (2) 1 (1) 36 (27) 5 (3) 1 (1) 5 (3) 7 (5)	$\begin{array}{c} 23 \ (43) \\ 13 \ (43) \\ 10 \ (38) \\ 1 \ (20) \\ 9 \ (25) \\ 3 \ (60) \\ 6 \ (85) \\ 0 \ (00) \\ 0 \ (00) \\ \hline \\ 14 \ (35) \\ 25 \ (45) \\ 1 \ (33) \\ 1 \ (100) \\ 10 \ (28) \\ 3 \ (60) \\ 1 \ (2) \\ 2 \ (40) \\ 2 \ (29) \end{array}$

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).

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

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

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 propensityscores for functional status (KPS) with depression after adjusting for other covariates.

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

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† Reference Category

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Model 1 shows that the prevalence of depression among patients with KPS scores \leq 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:

9 The purpose of the present study was to investigate the association between depression and patient-related, tumor-10 related, and treatment related variables among adult patients with primary brain tumor. Although similar studies 11 12 have been conducted in different parts of the world, most notably in US and UK, there is no literature from LMIC 13 or even other South Asian countries. We believe that the circumstances for our patients differ from those of the 14 west, for a number of reasons. According to World Health Organization, Pakistan has one of the world's lowest 15 public health expenditure as a percentage of GDP, as well as one of the world highest out of pocket health 16 expenditure, where it shares the top slot with other South Asian LMICs. Thus approximately 85% of our patients 17 are out of pocket payers, in a country already marred with poverty, compared to the high-income countries where 18 majority of patients are financially supported by third party payers i.e., state or insurance. [13] In this setting, the 19 20 high cost of treatment for brain tumors (surgery, chemotherapy, radiation therapy, rehabilitation, etc.) should 21 theoretically add to the psychological stress of the patients. Although government run hospitals do exist, they 22 cover only a fraction of the overall healthcare and majority of patients have to resort to private hospitals, especially 23 for advanced healthcare. There are also very few state run oncology or rehabilitation centres, and patients have to 24 rely on private healthcare for all these services. 25

27 We found that 39% of patients with primary brain tumor treated at AKUH, screened positive for depression on 28 PHQ-9. Impaired functional status was the only significant variable associated with depression and propensity 29 scores for functional status revealed a significant association between impaired functional status and treatment 30 stage at the time of interview, unemployment, and tumour recurrence. We also found that decreasing KPS was 31 directly linked to increased chances of depression, as in with each unit increase in propensity scores for functional 32 status; chances of depression increased by up to 5%. Our findings are consistent with some of the previous studies 33 on the same topic. Rooney (2010) [12] in his systematic review of observational studies concluded that the median 34 35 prevalence of depression among patients with brain tumor using screening scales was about 27% (range 0%-93%) 36 while clinician-rated measures returned up to 15% (5%-28%). Another meta-analysis conducted by Huang and 37 Colleagues in 2017[18] reported that prevalence of depression in brain tumor patients is nearly 21% using 38 screening scales and 19% with clinician-rated measures, specifically including mini-interviews. A 1-year follow-39 up study conducted by Mainio (2005) [19] also found functional status as a significant predictor associated with 40 depression among brain tumor patients. Similar findings were observed in observational studies conducted by 41 Anderson (1999) [20], Litofsky (2004) [21], Grant (1994) [22], Fox (2007) [23], Rooney (2013) [24], and Piil 42 43 (2015) [25] [26]. 44

45 We found three factors associated with reduced functional status including unemployment, tumor recurrence, and 46 stage of treatment, more specifically, early stage of treatment. Association between employment status and 47 depression has been explored by other investigators too, and there are at least three studies that have included 48 49 employment status in their primary analysis. A study conducted by Pelletier (2002) [27] found employment status 50 positively associated with depression among patients with brain tumors. However, this association was significant 51 only at univariate level. Another study conducted by Vossen (2014) [28] on cognitive and emotional problems 52 among meningioma patients reported significant association between depression and employment status where 53 depression was assessed by hospital anxiety and depression scale. However, when depression was assessed by 54 other screening tools, no association was found. In contrast, employment status was found to be significantly 55 associated with functional status. A follow-up study conducted by Hickmann (2016) [29] reported a parallel trend 56

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 10 stage of treatment reported highest prevalence of depression (82%). Weitzner (1999) [32], Pringle (1999) [33], 11 and Mainio (2005) [19] also reported higher level of depression during initial stage of treatment that is within 12 first three months after surgery. This variable was also found significantly associated with impaired functional 13 14 status, that is understandable given the physiological and psychological effects of major surgery and 15 hospitalization. As the treatment progresses and by the time it comes to its end, patients tend to regain their 16 functional status and even resume their jobs. Most brain tumor patients who have transient focal deficits as a 17 result of surgery, by the time they reach the completion of their treatment, also improve in their overall functional 18 status. However, no statistical evidence has been reported by any study on association between functional status 19 and treatment stage. 20

22 **Conclusion:** 23

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24 Our findings suggest that a high proportion of patients with brain tumor also suffer from depression. Whereas 25 several individual and clinical factors may contribute to the development of depression, patients with reduced 26 functional status should be especially monitored for any signs of psychiatric illness. Given the high proportion of 27 depressed patients in our study population, we would recommend routine psychiatric evaluation, or at the least, 28 the administration of simple self-rated screening tools that will allow healthcare providers to readily identify any 29 30 prevailing neuropsychiatric ailments, for all patients with brain tumors, at the time of admission and during 31 follow-ups. 32

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38 *Conflict of interest disclosure:*

39 The authors have no conflicts of interest to declare. 40

41 Data availability statement: 42

The data that support the findings of this study are available from the corresponding author upon reasonable 43 request. 44

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- 46 Contribution of Author's:
- 47 Anum Sadruddin Pidani: Study design, formulation of questionnaire, data collection, data analysis, manuscript 48 writing 49
- Amna Rehana Siddiqui: Study design, epidemiological expertise in design and implementation phase, manuscript 50 writing and review 51
- 52 Iqbal Azam: Biostatistician (analysis of study data), Manuscript writing and review of study analysis
- 53 Muhammad Shahzad Shamim: Design and implementation of study, neurosurgery expert input in the design and 54 analysis phase, manuscript review and writing 55
- Adnan A. Jabbar: Design and implementation of study, Oncology expert input in the design and analysis phase, 56 Manuscript reviewing 57
- 58
- 59 60

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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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1 2	تى اجازت نامه	فتحقيق كامعلوما
3 4 5		شخقیق کاعنوان:
6 7	وں کے دوران ابتدائی درج کے دماغی رسولی (ٹیومر) کی تشخیص کی بد دلت نوجوانوں	کراچی یا کستان میں تیسرےدر جے کاعلاج مہیا کرنے والے ہیپتال میں چھلے پانچ سال
8 9		میں نفسیاتی د باؤادرملحقہ عناصر کی جانچ ۔ میں نفسیاتی د باؤادرملحقہ عناصر کی جانچ ۔
10 11	تنظیم: شعبه کمیونٹ ہیلتھ سائنسز، آغاخان یو نیور سٹی ہیپتال	سربراه تحقيق: ڈاکٹرر یحانہ صدیقی
12 13		تحقيق کار: الغم صدرالدين پيدانی
14 15		ديگر شخفيق كار: دْاكىرْشْهْرادشيم،دْاكىرْعدىنان جبار،دْاكىرْشامىل خان،دْاكىرْا قبال اعظم
16 17		
18 19		تعارف:
20 21	ل شعبہ کمیونٹی ہیلت _ق سائنسز کی طالبہ ہوں۔ میں نوجوا نوں میں ابتدائی درج کے د ماغی	میرانام محترمهانع صدرالدین بیدانی یےاور میں ایم ایس سی اپیڈیولو جی ابنڈیا ئیواسٹیٹ
22 23	بى ہوں۔	رسولی (ٹیومر) کی بدولت نفساتی دباؤ سے ملحقہ عناصر کی جانج سے متعلق تحقیق کرنے جار
24 25		
26 27		پې منظرمعلومات:
28 29	بیاری کی تشخیص کے بعداد رعان? کے دوران نفساتی دیاؤہوتا ہے۔ کچرنفساتی دیاؤجو کہ	تحقیق دستادین به سرمعلوم ہوا ہے کہ کسی بھی قشم کے دیاغی رسو لی (ٹیوم) کے م یضوں میں
30 31	ر صبے کے لئے آ ^س ن تو اس صورت میں جہاتی علاج کی بدولت متعلقہ علاج کی کامیاتی اور	بہت کم عر <u>صے کے لئے ہوتا ہے</u> ا سےعلاج کی ضرورت نہیں ہوتی۔اگرمنفی خیالات کیے
32 33	۔ اس لئے ہم چندعناصر مثلاً علاج کا دورانیہ،ادوہات، شعاعی علاج، کیمائی علاج، نیند کا	، معارزندگی کوبھی بہتر بنایا حاسکتا ہے۔اس قتم کی تحقیق یا کستان میں کبھی بھی نہیں ہوئی ہے
34 35	سیاتی د باؤ کی جانچ کرنا جاہتے ہیں۔وقتی اورموز وں نفسیاتی مدد کی بدولت علاج کے اثر ات سیاتی د باؤ کی جانچ کرنا جاہتے ہیں۔وقتی اورموز وں نفسیاتی مدد کی بدولت علاج کے اثر ات	فقدان،اخراجات اورکوئی بھی دیگر عناصر کی بدولت علاج کے دوران پیدا ہونے والے نف
36 37) دباؤے متعلق جاننے کے لئے آپ کے تعاون کی ضرورت ہوگی۔	میں مثبت کردارادا ہوسکتا ہے۔ابتدائی درج کے دماغی رسولی (ٹیومر) کے دوران نفسیاتی
38 39	·	
40 41		شخقيق كارة ورب
42 43	ا ن از برک شنده به معرف بر کار از از بر کار	یں جمعد . پیر تحقق میں برید میں معامی میں میں ایر اور کی میں ایک میں کار کار کی ک
44 45 46)بدونت نفسیان دباوی منبت تشانیان موجود جن ۱۰ نے ساتھ ساتھا ک بات کی جن اید چینہ میں تھی کی گھر میں کاری کھریٹ کاردیہ ایک کر عناصر کاریں لائی دید ہے کہ داغی	ال یک کابلیادی معصد مید صعوم کرنا ہے کہ لیا ابتدائی درجے کے دما می رسومی کر یومر) د انچ کر این گر کی ادار جرکاط مل بدیداد و ارد این شراع مدارج کے ذما میں ملز کموں خ
40 47 49	ہات، سیبیت، چورےں جلبہ، چنورے ۵ درجہ،اورد پر معما سر ۵ ابتدان درجے دما ن	چان کی جانے کی لہ کیا علان کا عولی دورائیہ،ادوپات، شعا کی علان، سیلریں کی،ا ٹراچ سدلی(ٹیدم) کرم لضدی میں زفہ آتی دیائہ کر اتحاقیق یہ
40 49 50		ر دون (يو ۲) سے (یا دون یا کشتیان دباد سے مالا کا ہے۔
50 51 52		
52 53 54		طريقة كار:
55 56	۔ یں گے۔سوالات مالی اور ذاتی معلومات ،معیار زندگی ،دیگر بیاریوں کے ساتھ لگنےوالی 	ا ^{س ح} قیق میں آپ کی شرکت کے فیصلے کی بنیاد پرہم آپ سے خفیہ طریقے سے مشاورت کر بند
57 58	ت کے لئے آپ کے ۲ سے ۲ ۰ منٹ درکار ہو نگ <mark>ے ۔</mark> آپ کے ڈاکٹر کی اجازت کے بعد بیسین	بیاری، تاریخی اورموجود د طبی حالت ،اورعلاج سے متعلق معلومات پر منحصر ہو نگے ۔مشاور بیاری ، تاریخی اور موجود د طبی حالت ،اور علاج سے متعلق معلومات پر منحصر ہو نگے ۔مشاور
59 60	نے کے لئے جاچ کروں کی۔ For peer review only - http://bmiope	میں آپ کے ماضی کے طبی ریکارڈ بیاری کی سخیص اورعلاج سے منعلق معلومات حاصل کر n.bmj.com/site/about/guidelines.xhtml
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	open		
فقيق) کاعنوان:		
راچی	پاکستان میں تیسرےدرج کاعلاج مہیا کرنے والے ہیپتال میں پچھلے پانچ سا	لوں کے دوران ابتدائی درجے کے دماغی رسول) (ٹیومر) کی تشخیص کی بدولت نوجوانوں
يسفن	إتى د باؤاورملحقه عناصر کی جان ^خ _		
براه ^خ	قيق: دْاكْتْرْرِيجانەصدىقى	تنظيم: شعبه کمیونگ ہیلتھ سائنسز، آغاخان یو	نيورسٹی جسپتال
نی ن ک	کار: الغم صدرالدین پیدانی		
رخقيون	ت کار: ڈاکٹر شہرادشیم،ڈاکٹر عدینان جبار،ڈاکٹر شامیل خان،ڈاکٹرا قبال اعظم		
اورين	تكامقام:		
م پر که	رنے والے کانام: ۔۔۔۔۔	זוניי:/	
م کی . م کی .	جانچ اورتر میم کرنے والے کا نام: ۔۔۔۔۔	זוניל:ל	
م در,	ج کرنے والے کا نام: ۔۔۔۔۔	تاريخ:/	
نی ت ک	ما شاختی نمبر:		
يض ً	كانام:كانام:		
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ختی نم	······································		
	اہلیت کے معہ	إركاتحقيقاتي آله	
		•	
	سوال	جواب	اختيار
	سوال مشاورت کے وقت گلاس گوکو مااسکور (GCS) کا پیانہ	جواب 1) ۵۱	اختیار اگر۵اہے کم ہےتو نیمیں روک دیں۔
	سوال مشاورت کے وقت گلاس گوکو مااسکور (GCS) کا پیانہ	جواب 1) ۱۵ 2) ۱۵سے کم	اختیار اگر۵اہے کم ہےتو نیہیں روک دیں۔
	سوال مشاورت کے وقت گلاس گوکو مااسکور (GCS) کا پیانہ کیا آپ عرصہ قبل سے ذہنی یا نفسیاتی دباؤ کی ادویات استعال کررہے ہیں؟	جواب 1) ۱۵ 2) ۱۵سے کم 1) ہاں	اختیار اگر ۵۱ ہے کم ہےتو یہیں روک دیں۔ اگر ہاں توا گلے سوال پر جا کیں۔اگر نہیں تو
)	سوال مشاورت کے وقت گلاس گوکو مااسکور (GCS) کا پیانہ کیا آپ عرصة جمل سے ذہنی یا نفسیاتی د باؤکی ادومات استعال کررہے ہیں؟	جواب جواب 1) ۱۵ 2) ۵۱سے کم 1) ہاں 2) نہیں	اختیار اگر ۵۱ سے کم ہےتو نیہیں روک دیں۔ اگر ہاں توا گلے سوال پر جا ^ک یں۔اگرنہیں تو سوال مہ کو چھوڑ دیں۔
	سوال مشاورت کے وقت گلاس گوکو مااسکور (GCS) کا پیانہ کیا آپ عرصة قبل سے ذہنی یا نفسیاتی دباؤ کی ادویات استعال کررہے ہیں؟ آپ کتنے عرصے سے بیا دویات استعال کررہے ہیں؟	جواب جواب 2) ۵۱ <i>یے کم</i> 1) ہاں 2) نہیں 1) دماغی رسولی(ٹیومر) کی تشخیص سے	اختیار اگر ۵۱ سے کم ہے تو یہیں روک دیں۔ اگر ہاں توا گلے سوال پر جا ئمیں۔اگر نہیں تو سوال م کو چھوڑ دیں۔ اگر د ماغی رسو لی (ٹیومر) کی تشخیص یے قبل
	سوال مشاورت کے وقت گلاس گوکو مااسکور (GCS) کا پیانہ کیا آپ عرصة قبل سے ذہنی یا نفسیاتی دباؤ کی ادومیات استعال کررہے ہیں؟ آپ کتنے عرصے سے بیا دومیات استعال کررہے ہیں؟	جواب جواب 2) ۵۱سے کم 1) ہاں 2) نہیں 1) دماغی رسولی(ٹیومر) کی شخیص سے قبل	اختیار اگر ۵۱ ہے کم ہےتو سیمیں روک دیں۔ اگر ہاں توا گلے سوال پر جا ئیں۔اگر نہیں تو سوال مہ کو چھوڑ دیں۔ اگر د ما فی رسولی (ٹیومر) کی تشخیص یے قبل تو سیمیں روک دیں اور تحقیق میں مریض کا
,	سوال مشاورت کے وقت گلاس گوکو مااسکور (GCS) کا پیانہ کیا آپ عرصة جمل سے ذہنی یا نفسیاتی د باؤ کی ادویات استعال کررہے ہیں؟ مآپ کتنے عرصے سے میدادویات استعال کررہے ہیں؟	جواب جواب 2) ۵۱ سے کم 1) ہاں 2) نہیں 1) دماغی رسولی(ٹیومر) کی تشخیص سے قبل 2) دماغی رسولی(ٹیومر) کی تشخیص سے	اختیار اگر ۵۱ سے کم ہےتو یہیں روک دیں۔ اگر ہاں توا گلے سوال پر جا ئیں۔اگرنہیں تو سوال ۴ کو چھوڑ دیں۔ اگر دماغی رسو لی (ٹیومر) کی تشخیص یے قبل تو یہیں روک دیں اور تحقیق میں مریض کا اندراج نہ کریں۔
	سوال مشاورت کے وقت گلاس گوکو مااسکور (GCS) کا پیانہ کیا آپ عرصة قبل سے ذہنی یا نفسیاتی دباؤ کی ادویات استعال کررہے ہیں؟ آپ کتنے عرصے سے بیا دویات استعال کررہے ہیں؟	جواب 1) ۵۱ 2) ۵۱ سے کم 1) ہاں 2) نہیں 1) دماغی رسولی(ٹیومر) کی تشخیص سے قبل 2) دماغی رسولی(ٹیومر) کی تشخیص کے بعد	اختیار اگر ۵۱ سے کم ہے تو یہیں روک دیں۔ اگر ہاں تو الحطے سوال پر جائیں۔ اگر نہیں تو سوال م کو چھوڑ دیں۔ اگر د ماغی رسو لی (ٹیومر) کی تشخیص یے قبل تو یہیں روک دیں اور تحقیق میں مریض کا اندراج نہ کریں۔
	سوال مشاورت کے دقت گلاس گوکو مااسکور (GCS) کا پیانہ کیا آپ عرصة قبل سے ذہنی یا نفسیاتی دباؤ کی ادومیات استعال کررہے ہیں؟ آپ کتنے عرصے سے روادویات استعال کررہے ہیں؟ کیا آپ دماغی رسولی (ٹیومر) یے قبل دیگر دیرینہ بیماریاں (ایچ آئی	جواب جواب 2) ۵۱ سے کم (1) ہاں 2) نہیں 1) دماغی رسولی(ٹیومر) کی تشخیص سے قبل 2) دماغی رسولی(ٹیومر) کی تشخیص کے بعد (1) ہاں	اختیار اگر ۵۱ ہے کم ہےتو یہیں روک دیں۔ اگر ہاں توا گلے سوال پر جا ئیں۔ اگر نہیں تو سوال مہ کو چھوڑ دیں۔ اگر دما غی رسولی (ٹیومر) کی تشخیص یے قبل تو یہیں روک دیں اور تحقیق میں مریض کا اندراج نہ کریں۔ اگر ہاں تو یہیں روک دیں اور مریض کو
	سوال مشاورت کے دفت گلاس گوکو مااسکور (GCS) کا پیانہ کیا آپ عرصة قبل سے ذہنی یا نفسیاتی د باؤ کی ادویات استعال کرر ہے ہیں؟ آپ کتنے عرصے سیدادویات استعال کرر ہے ہیں؟ کیا آپ د ماغی رسولی (ٹیومر) سے قبل دیگر دیرینہ بیماریاں (آپچ آئی وی/ ایٹرز، ایچ سی دی) یا ہار مونل خرابی (ہائیچ قعائر ویڈیزم) جس کے لئے	جواب جواب 2) ۵۱ سے کم 2) ۵۱ سے کم 1) ہاں 2) نہیں تبل 2) دماغی رسولی (ٹیومر) کی تشخیص سے تبل 2) دماغی رسولی (ٹیومر) کی تشخیص سے بعد 2) نہیں 2) نہیں 2) نہیں 2) نہیں	اختیار اگر ۵۱ سے کم ہےتو یہیں روک دیں۔ اگر ہاں توا گلے سوال پر جا ئیں۔ اگر نہیں تو سوال مہ کو چھوڑ دیں۔ اگر دما غی رسو لی (ٹیومر) کی تشخیص یے قبل اندراج نہ کریں۔ اگر ہاں تو یہیں روک دیں اور مریض کو شخصی تے لئے اندراج نہ کریں۔

انکشاف کی جانچ کے لئے سوالنامہ

			A: مریض سے متعلق سوالات	سيش
جوابات	اسكيپ	كوژ	سوالات	نمبر
		1- مرد	آپ کی جنس کیا ہے؟	1
		2- عورت		
مالوں میں	مکمل سالوں میں بیان کریں ۔		آپ کی عمر سالوں میں کتنی ہے؟	2
		1- جماعت اسے9	آپ کې تعليمې حيثيت کيا ہے؟	3
		2- جماعت•ا/O-level	(ایک جواب)	
		3- كالح ڈ گرى/A-level		
	6	4- بيچكرزد گرى		
		5- ماسٹرزڈگری		
		6- ڈاکٹریٹڈ گری		
	اگربھی بھی شادی نہیں ہوئی تو	1- شادی شده	آپ کی از دواجی حیثیت کیا ہے؟	4
	سوال8 پرجائیں۔	2- يوه	(ا یک جواب)	
		3- طلاق شده		
		4- عليحده		
	· · · · · · · · · · · · · · · · · · ·	5- غیرشادی شدہ		
	ا کر ہیں تو سوال 7 پر جا تکیں ۔		أپ کے لینے بچے ہیں؟	5
		1- <i>پا</i> ں	کیا آپ کے ۱۸سال سے کم عمر بچے بھی ہیں؟	6
		2- مېين		
		1- ہاں د	کیا آپ اس دقت اپنے خادند/ ہیوی کے ساتھ رہتے	7
		2- مہيں	ېيں؟	
		1- اردو	آپ کی مادری زبان کیا ہے؟ ب	8
		2- پنچابی س	(ایک جواب)	
		3- سندلطی		
		4- پسو - با ج		
		5- بو پی ا		
		<i>دیگر</i>		
	For peer review only - h	ittp://bmjopen.bmj.com/sit	ا پکاپیشرلیا ہے؟ e/about/guidelines.xhtml	9
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$\begin{array}{c c c c c c c c c c c c c c c c c c c $	2 3		پرجائیں درنہ سوال 11 کو چھوڑ	2- اپناکام	(ایک جواب)	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	4 5		دیں۔ دیں۔	3- كام يے عليحدہ اور كام كى تلاش		
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$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	17			1- تثين ماہ سے کم	آپ کتنے عرصے سے کا مہیں کر پار ہے ہیں؟	11
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	23	جگه کا نام	جگه بتائیں جہاں سے شرک ت ک ار	1- كراچى ي ي	آپ کہاں رہتے ہیں؟	12
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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	31		پڑ <i>بر ہے و</i> شوال 13 ا پر جا یں۔ بالہ نہ کہ جہ میں	4.		
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$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	38			1- ڪراچي ميں	علاج کے دوران آپ کہاں رہتے ہیں؟	13
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	39 40			2- گھر میں(شہر/ضلع/قصبہ)		
43 ب کار	41 42			1- ہوٹل	آپ کراچی میں کہاں رہتے ہیں؟	14
45 45 47 48 49 -3 44 49 49 50 <t< td=""><td>43 44</td><td></td><td></td><td>2- رشتےدار کے گھر</td><td>پ په ۲۰ ۲ ، <u>۲</u>۰ (ایک <u>ج</u>واب)</td><td></td></t<>	43 44			2- رشتےدار کے گھر	پ په ۲۰ ۲ ، <u>۲</u> ۰ (ایک <u>ج</u> واب)	
47 48 49 50 50 51 52 51 52 53 54 53 54 55 56 56 56 56 56 56 56 57 58 58 59 60 For peer review only - http://bmja/bind.com/Site/about/guidelines.xhtml	45 46			3- کرا نز کرگھ میں	× - · · · · · · · · · · · · · · · · · ·	
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52 آپ اچ شبر/طنع / قصبے سے گنے گھنے کا سفر کر کے آغا 1- ۲ سے ۳ کھنے 53 54 55 54 خان یو نیور ٹی می پینچ میں ؟ 2- ۵ سے ۸ گھنے 55 56 56 56 56 56 57 56 57 58 58 59 60 For peer review only - http://bmja/dambid/mbid/2007/5ite/about/guidelines.xhtml	50 51			ډير س		
54 54 55 55 56 57 57 58 58 59 60 For peer review only - http://bmjapde.mbd.ap.com/Site/about/guidelines.xhtml	52 53			1- ۲ <u>س</u> ے کھنٹے	آپاپن شہ(صلع/ قصبے سے کتنے کھنٹےکا سفر کر کے آغا	15
55 56 57 57 58 59 60 For peer review only - http://bmjaple.about/guidelines.xhtml	55 54			2- ۵ سے ۸ گھنٹے	خان يو نيور ٿي ہي تال تک پنهنچة ٻي؟	
57 58 59 60 For peer review only - http://bmjøper.big/com/5ie/about/guidelines.xhtml	55 56			3- 9 سے الگھنٹے	(ایک جواب)	
59 For peer review only - http://bmjøpeجه المعرفة ا	57 58			4- 2اسے۲۴ گھنٹے		
	59 60		For peer review only - h	ttp://bmjøþen.þr∰.com/5it	e/about/guidelines.xhtml	

		1- جہازسے	آپ کراچی کاسفر کیسے کرتے ہیں؟	16
		2- ٹرین سے	(ایک جواب)	
		3- بسن پاکارسے		
		1- عوامی ٹرانسپورٹ میں	آپ کراچی آنے کے لئے کیااستعال کرتے ہیں؟	17
		2- ذاتی ٹرانسپورٹ میں	(ایک جواب)	
		3- دونوں		
رو پيوں ميں:	اخراجات رو پیوں میں بیان		آغاخان يونيور شي سپتال تك ايك مرتبه سفر پرتقريباً كتنے	18
	کریں۔		اخراجات ہوتے ہیں؟	
	0	1- خاوند/ بیوی	گھر میں آپ کی دیکھ بھال کون کرتا ہے؟	19
		2- والدين	(ایک جواب)	
		<i>چ</i> -3		
		4- رشتےدار		
		5- دوست		
		6- دیگر		
		1- باں	کیا آپ اپنے خاندان کے سربراہ میں؟	20
		2- خبين		
	نمبروں میں بیان کریں	1	آپ کے گھرمیں کتنے افرادر بتے ہیں؟	21
			B: ساجی ومالیاتی حیثیت	سيثن
جوابات	اسكيپ	كوژ	سوالات	نمبر
	اگرہاں تو سوال2 پر جائیں ۔	1- ہاں	کیا آپ گھر کے مالک ہیں؟	1
		2- نہیں		
	نمبروں میں بیان کریں۔	,	آپ کے گھر میں کل کتنے کمرے ہیں؟	2
	نمبروں میں بیان کریں۔	,	آپ کے کتنے موبائل فون ہیں؟	3
	اگرنہیں تو سوال5 کو چھوڑ دیں۔	1- ہاں	کیا آپ کے ہل خانہ میں کسی کے پاس اپنی گاڑی ہے؟	4
		2- نہیں		
	نمبروں میں بیان کریں۔		آپ کے پاس کتنی گاڑیاں ہیں؟	5
	اگرنہیں تو سوال7 کو چھوڑ دیں۔	1- ہاں	کیا آپ کے اہل خانہ میں کسی کے پاس اپنی موٹر سائیکل	6
	For peer review only - h	ېېر http://bmjopen.br h/ :con <mark>/</mark> /si	te/about/guidelines.xhtml	
	نمبروں میں بیان کریں۔		آپ کے پاک تنی موڑ سائیکلیں ہیں؟	7
			÷ •	

				· -
		1- ہاں	کیا آپ کےاہل خانہ میں کسی کے پاس زرعی زمین موجود	8
		2- نہیں		
		5000-10000 -1	آپ کی ماہانہ آمدنی کنٹی ہے؟	9
		11000-20000 -2	(ایک جواب)	
		21000-30000 -3		
		31000-40000 -4		
		41000-50000 -5		
		>50000 -6		
	اگر ہاں تو سوال 11 پر جا ئیں	1- ہاں	کیا آپ کے خانہ میں سے کوئی دوسرار کن کما تاہے؟	10
	O,	2- نہیں		
	0	5000-10000-1	آپ کے خانہ کی ماہانہ آمدنی کتنی ہے؟	11
		11000-20000 -2	(ایک جواب)	
		21000-30000 -3		
		31000-40000 -4		
		41000-50000 -5		
		>50000-6		

م داقعات	سیشنC: انفرادی چوری، نشه کااستعال،اورزندگی کے ا	,

35			کے ، ہم واقعات	نC: الفرادي چوري، سے کا استعال،اورزندي-	٣.
36 37	جوابات	اسكيپ	كوڈ	سوالات	نمبر
38 39 40		مکمل داقعہ بیان کریں۔	1- ہاں	ابتدائی درج کے دماغی رسولی (ٹیومر) کےعلاوہ کیا آپ کی	1
40			2- نہیں	زندگی میں دیگراہم واقعات بھی رونماہوئے ہیں جیسے کہ کسی	1
42 43 44				اہل خانہ کا وفات پانا یا بڑی عمر میں اپنی نو کری سے فارغ ہونا؟	
45					L
46 47 48				آپاپنے نفسیاتی دباؤ کو کیسے کم کرتے ہیں؟	2
48 49 50					
50 51 52					
53					1
54 55			1- ہفتے میں ایک مرتبہ سے	آپاپناہل خانہ یا دوستوں کے ساتھ کتنی مرتبہ سیر وتفریح	3
56 57			زياده	کے لئے جاتے ہیں؟	
58 59			2- ہفتے میں کم از کم ایک مرتبہ	(ایک جواب)	
60		For peer review only - ht	tp://bmjopen.bmj.com/s 3- مجلى لبھار	ite/about/guidelines.xhtml	
			4- تىجىمى ئېيىں		1

$\begin{array}{c c c c c c c c c c c c c c c c c c c $					—
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	-	اگرنہیں تو سوال5 کو چھوڑ دیں	1- ہاں	کیا آپٹلیویژن بھی دیکھتے ہیں؟	4
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			2- نہیں		
$\begin{array}{c c} \frac{1}{2} \frac{1}{$			1- روزانه	چچلےسات دنوں کے دوران ، آپ نے کتنی کثر ت سے	5
$ \begin{array}{c c} (1 \sum_{i} \pi_{i}(i)) \\ (1 \sum_{i} \pi_{i}(i)) \\$			2- ہفتے میں کم از کم ایک مرتبہ	ٹیلیویژن کے پروگرام دیکھے؟	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			3- ملجعى كبھار	(ایک جواب)	
6 $\lambda_2 \overline{1} \overline{\psi}_c e(i l_{icc} l_c^{\dagger} \overline{J} - \underline{x}_1 \overline{y})^2$ 1 - $\overline{y} \overline{y}$ 7 $\lambda_2 \overline{1} \overline{\psi}_c \overline{y}_c e(i \Delta_g \partial_g \partial_g e_1 \partial_g x_1 \partial_g e_1 \partial_g \partial_g \partial_g e_1^{\dagger} e_2 \partial_g \partial_g e_1^{\dagger} e_2 \partial_g \partial_g e_1^{\dagger} e_2 \partial_g \partial_g \partial_g e_1^{\dagger} e_2 \partial_g \partial_g \partial_g \partial_g \partial_g \partial_g \partial_g \partial_g \partial_g \partial_g$			4- شمجني تبين		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $			1- باں	کیا آپ دوزانہ ورزش کرتے ہیں؟	6
$\begin{array}{c c} 7 & \begin{array}{c} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 $			2- نہیں		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	-	ا گرنہیں تو سوال8 کو چھوڑ دیں	1- ہاں	کیا آپ کی روز مرہ کی خوراک میں کمی واقع ہوئی ؟	7
8 $\frac{1}{2}$ $\frac{3}{2}$ $\frac{3}{2}$ 8 9 $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ 1- $\frac{1}{2}$ $\frac{1}{2}$ 9 $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ 1- $\frac{1}{2}$ $\frac{1}{2}$ 10 $\frac{1}{2}$		0	2- نہیں		
$\begin{array}{c c} \hline & & & & & & & & & & \\ \hline & & & & & & &$)		کتنے عرصے سے آپ کی روز مرہ کی خوراک میں کمی داقع	8
9 $\lambda_{2}(e(x_{0}, e_{2})) \wedge \lambda_{2}(e(x_{2}, e_{2}))$ 1- η_{1} $-\gamma^{2}$ 2- $\gamma_{2}y_{1}$ 2- $\gamma_{2}y_{1}$ 10 λ_{2} (7) 1- η_{1} $\lambda_{1}^{2}(e_{2}) + e_{2} + e_{2}^{2}$ 10 λ_{2} (7) 2- $\gamma_{2}y_{2}$ 10 11 $\gamma_{2}^{2}(e_{2}) + e_{2}^{2}(e_{2}) + e_{2}$				ہوئی؟	
$\begin{array}{c c} -\gamma & 2-i $			1- بإن	کیاروزمرہ کےکام کرنے میں آپ کومدد کی ضرورت پڑتی	9
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$			2- نہیں	? <u>~</u> ?	
2- نہیں 2- نہیں 11 آپ کتنے کر صے سے تمبا کونو ٹی کرر ہے ہیں؟ 11 12 آپ کتنی مرتبہ سگریٹ پیتے ہیں؟ 1- روزانہ 12 آپ کتنی مرتبہ سگریٹ پیتے ہیں؟ 1- روزانہ 12 آپ کتنی مرتبہ سگریٹ پیتے ہیں؟ 13 آپ کتنی مرتبہ سگریٹ پیتے ہیں؟ 14 12 15 12 16 12 17 12 18 12 19 12 10 12 11 12 12 12 13 12		ا گرنہیں تو سوال 14 پر جائں ۔	1- ہاں	کیا آپ نے بھی سگریٹ،حقہ یا بیڑی پی ہے؟	10
11 آپ کتنے عرصے سے تمبا کونوشی کررہے ہیں؟ سالوں میں بیان کریں۔ 11 12 آپ کتنی مرتبہ سگریٹ پیتے ہیں؟ 1- روزانہ 12 12 آپ کتنی مرتبہ سگریٹ پیتے ہیں؟ 1- روزانہ 12 (ایک جواب) 2- ہفتہ وار 2- ہفتہ وار			2- نہیں		
12 آپ کتنی مرتبه سگریٹ پیتے ہیں؟ (ایک جواب) 2- ہفتہ وار	سال	سالوں میں بیان کریں۔	0	آپ کتنے عرصے سے تمبا کونوشی کررہے ہیں؟	11
(ا یک جواب) 			1- روزانه	آپكتىمرىتەبىىگرىيە بىيتے بىي؟	12
:44 -3			2- ہفتہوار	(ايک جواب)	
			3- مابانہ	5.	
4- مابانہ سے کم			4- ماہانہ سے کم		
13 آپ دن میں کتنی سگریٹ پیتے ہیں؟	يوميسكريك			آپ دن میں کتنی سگریٹ پیتے ہیں؟	13
14 کیا آپ پان/تمباکو/ چھالیہ/ سپاڑی/شراب/ ڈرگ کا 1- ہاں			1- بإن	کیا آپ پان/تمبا کو/ چھالیہ/ سپاڑی/شراب/ ڈرگ کا	14
استعال کرتے ہیں؟ 2- نہیں			2- نہیں	استعال کرتے ہیں؟	
15 آپ <i>کتنے جرہے</i> ا	سال	سالوں میں بیان کریں۔		آپ کٽنے عرصے سے	15
پان/تمباکو/چھالیہ/سپاڑی/شراب/ ڈرگ کااستعال کررہے				پان/تمباکو/چھالیہ/سپاڑی/شراب/ڈرگ کااستعال کررہے	
<u>ب</u> ن؟				یں؟	

سیشنD: طبی تاریخ نمبر سوالات

بر سوالات For peer review السكي المعرفة المعرفة

1 2	 کینسرکانام بیان کریں۔	1-پا <i>ل</i>	کیا آپ کے اہل خانہ میں بھی کسی کو کینسر کی بیاری ہوئی ہے؟	1
3 4 5		2- ين 1-پال	کیا آپ کے اہل خانہ می ^{ں ب} ھی کسی کو بنیا دی در جے کا د ماغی	2
6 7		2- نہیں	رسولی(ٹیومر) کی بیاری ہوئی ہے؟	
8 9 10	اگرنہیں توسوال5 پر جائیں۔	1-پاں	کیا آپ نے بھی سی علم نفسات کے ڈاکٹر کے پاس معائنہ	3
11 12		2- نہیں	كروايا ہے؟	
12 13 14			معائنے کی وجہ کیاتھی؟	4
15 16 17				
18 19 20	اگرنہیں تو سوال9 پر جائیں۔	1-بإں	کیا آپ ^{مب} ھی نفسیاتی بیاری کا شکارہوئے ہیں؟	5
21 22 23	0	2- نہیں		
24 25	(1-پاں	کیاآپ نے اس بیاری کےعلاج کے لئے کوئی نفسیاتی بیاری	6
26 27		2- نہیں	کی دوااستعال کی ہے؟	
28 29 30 31		C.	آپ نے کتن <i>ے صح</i> تک وہ دوااستعال کی تھی؟	7
32 33 34		0	دوا کےعلاوہ، آپ نے اپنی نفسیاتی یہاری کےعلاج کے کیا	8
35 36		le l	ديگراقدامات اللهائ؟	
37 38			0	
39 40			7/	
41 42	 بالمنبعين أستريب		کاتر زنای جرک افخ الرف کا	
43 44	ا کرنیں تو شوال ۲۱ پر جا یں۔	۱-با <i>ل</i> چېنېد	کیا آپ نے بلیادی درج نے دمانی رسوں (یومر) می تشخص س کسرعلدن کے دمانی رسوں (یومر) می	9
45 46		2- ئىل	سیس کے بعد کی م تفسیات کے ڈاکٹر کے پاک معاہد کرواہاہے؟	
47 48 49			معائنے کی وجہ کیاتھی؟	10
50 51				
52 53				
54 55 56			آپ کودیگر کونسی بیماری ہے؟	11
50 57 58				
59 60	 For peer review only - h	ttp://bmjopen.bmj.com/s	ite/about/guidelines.xhtml	

1			^{ىل} ق سوالات	نE: دماغی رسولی(ٹیومر)اوراس کےعلاج سے مت	سيكش
3 4	جوابات	اسکیپ	كوژ	سوالات	نمبر
5 6			1- اچانک دوره	بنیادی درج کے دماغی رسولی (ٹیوم) کی شخیص سے تبل	1
7 8			2- זיק כנפ	ابتدائى علامت كونسى تقى؟	
9 10			3- وزن میں کمی	(ایک سےزیادہ جواب)	
11 12			4- مزاج میں تبدیلی		
13 14			دیگر		
15 16			1- تثين ماه يسيحكم	آپ کے دماغی رسولی (ٹیومر) کی شخیص کب ہوئی ؟	2
17 18			2- تتين سےبارہ ماہ	(ایک جواب)	
19 20			3- تيره سے چوبيس ماه		
21 22			4- چوبیس ماہ سےزائد		
23 24			P	بچھلے ا اماہ کے دوران، آپ نے کتنی مرتبہ سپتال میں داخلہ	3
25 26				كروايا؟	
27 28			1- دولا کھتے کم	کمل بیاری کےعلاج کےدوران تشخیص کی جائج ،آ پریشن،	4
29 30			2- دوسے چارلا کھ	دوباره معائنه، کیمیائی علاج، شعاعی علاج وغیرہ پر تقریباً کتنے	
31 32			3- پانچ سے آٹھلاکھ	اخراجات ہوئے؟	
33 34			4- أثه ي باره لاكھ	(ایک جواب)	
35 36			5- بارەلاكھسےزائد	2	
37 38				آپ نے آغاخان یو نیور شی ہیپتال میں اخراجات کس طرح	5
39 40				برداشت كئي؟	
41 42		اگر ہاں تو سوال7 پر جائس	1- بإن	کیا آپ کے پاس کوئی صحتی انشورنس ہے؟	6
43 44			2- نہیں		
45 46			1- نو کری میں طبی فوائد	آپ کصحتی بیمےکا ذریعہ کیا ہے؟	7
47 48			2- انشورکس کی قسط		
49 50			ديگر		
51 52		ئے گی۔	نچ میڈیکلریکارڈ فائل سے کی جائے	: تمام تر علاج اوردما غی رسو کی (ٹیومر) سے متعلق معلومات کی جا	نو ٹ سر
53 54				نF: کارآ مدحیثیت	سيكثثر
55 56	جوابات	اسكيپ	كوژ	سوالات	نمبر
57 58	اسکور:	اسكوركومندرجهذيل KPS	KPS scores > 70 -1	کیا آپ روزمرہ کی عام سرگرمیاں ا کیلے ہی کر سکتے ہیں یا پھر	1
59 60		For peer Kevievio Kily -	К.₽. \$/,869888.5 . .7.8.7.	آپ کومدد کی ضرورت پڑتی hards کو hards کو کامان کو کردار ite/bourd guldel hards	
		لگائىي-		ضرورت پڑتی ہے؟	

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Section/Topic	ltem #	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	Yes
		collection	Page 3
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Yes
		06.	Page 3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if	Yes
		applicable	Page 3
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe	Yes
measurement		comparability of assessment methods if there is more than one group	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	Yes
		why	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,	Yes
		confirmed eligible, included in the study, completing follow-up, and analysed	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	Yes
		confounders	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	Yes
		interval). Make clear which confounders were adjusted for and why they were included	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	Yes
		magnitude of any potential bias	Page 2
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from	Yes
		similar studies, and other relevant evidence	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	NA
		which the present article is based	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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BMJ Open

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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Manuscript ID	bmjopen-2019-032748.R1
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Date Submitted by the Author:	07-Feb-2020
Complete List of Authors:	Pidani, Anum; Aga Khan University, Community Health Sciences Siddiqui, Amna Rehana; Aga Khan University, Community Health Sciences Azam, Iqbal; Aga Khan University, Community Health Sciences shamim, Muhammad Shahzad ; Aga Khan University, Surgery Jabbar, Adnan; Aga Khan University Medical College Pakistan Khan, Shameel; Aga Khan University, Psychiatry
Primary Subject Heading :	Epidemiology
Secondary Subject Heading:	Mental health, Oncology
Keywords:	Adult, Brain tumor, Depression, Neurosurgery < SURGERY, Psychosocial Factors





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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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Tables: 3

- 2829 Abstract:
- 30 31

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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.

38 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.

47 RESULTS:

⁴⁸ Fifty one (39%, CI: 33.33-46.94) patients in our study screened positive for depressive symptoms on PHQ-9.
 ⁴⁹ There was significant association between depressive symptoms and KPS scores (Prevalence Ratio: 3.25 and
 ⁵⁰ Confidence Interval: 1.87-5.62) after controlling covariates. Propensity scores predicted positive association
 ⁵² between KPS (functional status) and unemployment, treatment stage, and tumor recurrence. Tumor-related and
 ⁵³ treatment related factors including tumor grade, location, type, and hemispheric lateralization were found
 ⁵⁴ insignificant.

56 57 CONCLUSION:

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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.

Funding statement:

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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].

37 Diagnostic and Statistical Manual-V defines depression as a feeling of sadness, loss of pleasure from daily living 38 activities, body weight changes, reduction in physical activity, fatigue, failure to think or concentrate, lack of self-39 worth and recurrent suicidal ideations [5]. It is estimated that depression affects about 350 million individuals 40 worldwide and according to the Global Mental Health Survey (2014), nearly 1 in 20 individuals report having at 41 least one episode of depression within a year [6]. Population based researches report a prevalence of clinical 42 43 depression ranging between 2% to 5% worldwide [7]. The worldwide prevalence of depression in cancer patients 44 is 25% with higher rates among Asian countries [8]. The estimated prevalence of clinically diagnosed depression 45 in Pakistan is approximately 6% out of which 3% are cancer patients [9]. Depression rates among primary brain 46 tumor patients ranges from 15% to 40% with highest rates among glioma patients [10]. However, it is suggested 47 that these rates likely under-represent the true incidence of depression [11]. A systematic review of 42 48 observational studies reports that the prevalence of depression among glioma patients ranges between 0 to 93% 49 with a median prevalence of 27% [12]. 50

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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 treatmentrelated variables among adult primary brain tumor patients in a LMIC.

Methods:

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Study Design:

An analytical cross-sectional study design was employed to determine the association between patient related, 12 tumor related and treatment related factors with depression among adult primary brain tumor patients. Non-13 14 probability consecutive sampling was used to recruit subjects. All the patients who met eligibility criteria of the 15 study and were willing to give consent were included in the study. 16

17 Site and setting 18

The study was approved by the institution review board (5009-CHS-ERC-17). The recruitment was conducted at 19 tertiary care setting of Karachi, Pakistan and 132 patients with biopsy proven primary brain tumors at various 20 stages of treatment were enrolled. These patients were contacted in neurosurgery wards, neurosurgery and 21 22 oncology outpatient clinics, and oncology day care suits from November 2017 to July 2018. 23

Participants

25 Participants were all adult patients (aged 18 years and above) under treatment at a tertiary care setup. Each patient 26 was enrolled after a written, informed consent. The exclusion criteria for study participants were as follows: 27 diagnosis of depression for about one prior to the diagnosis of brain tumor, confused or incoherent patients and 28 patients with problems with speech or comprehension that prevents them from completing the questionnaire, 29 30 patients with co-existing systemic malignancies apart from primary brain tumor, and any severe comorbid medical 31 illness such as liver cirrhosis, systemic infections like HIV, and hepatitis which can cause altered mental status. 32

33 Procedure 34

Participant's eligibility was determined by medical record files. Potentially eligible participants were approached 35 by the investigator during a scheduled follow-up visit at neurosurgery and oncology outpatient clinics or during 36 37 inpatient hospital stay post-surgery. Each patient after the consent were interviewed for 15-20 minutes to fill a 38 pre-structured questionnaire for assessing predictor variables and PHQ-9 scale for screening of depression. The 39 questionnaire was also pilot tested on 10 participants before actual administration. 40

41 Measures 42

We divided all the associated factors into three distinct categories that were patient-related, tumor-related, and 43 treatment-related variables. Patient-related factors comprised of demographic and socio-economic variables 44 45 including age, gender, marital status, number of dependents, children under 18 years, education, occupation, 46 employment status, residency, travelling cost, care giver support, current smoking status, past/current medical 47 illness, history of psychological dresses, strategies to handle stress (isolation, aggression, prayers, crying, 48 sleeping, addiction, and mind diversions) and functional status. Participant's functional status was assessed using 49 Karnofsky performance score (KPS). KPS scores less than 70 were indicative of impaired functional status. Socio-50 economic status (SES) was also computed using factorial analysis. Tumor-related and treatment-related variables 51 52 were assessed by medical record review and included tumor histology, tumor grade, recurrence, hemispheric 53 lateralization, first symptoms, brain structures involved, and cognitive impairment. Treatment related variables 54 included stage of treatment, number of chemotherapy cycles, duration since diagnosis, radiation therapy, current 55 use of steroids and anti-epileptic drugs, and treatment cost. The complete list of variables is mentioned in Table 56 1.

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¹ Depression

2 Primary brain tumour patients were screened for depression using Urdu version of patient health questionnaire-9 3 (PHQ-9). The PHQ-9 is a self-rated screening tool which contains 9 items that corresponds to DSM-V criteria of 4 depression and was rated on Likert scale of four points. All the patients were classified into two groups based on 5 6 the scores on PHQ-9 scale. Participants with a score of ≥ 10 were classified as screened positive for depression. 7 PHQ-9 score of 10 or above has a sensitivity and specificity of 88% for major depressive symptoms. A recently 8 conducted validation study on Urdu version (national language of Pakistan) of PHQ-9 by Gholizadeh, 2017 [14], 9 reported a specificity of 94% and false positive rate of 6% only. 10

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12 Statistical Analysis:

Sample size was calculated from previous studies [15] using Openepi [16] with a power of 80%, depression to no 13 depression ratio of 1:2, prevalence ratio (PR) of 2 and 30% to 70% range of depression for different factors yield 14 15 a sample size of 108. Adding 20% of attrition rate the final sample size came out to be 130 participants. We used 16 STATA version 12.0 [17] to perform all the analysis. For descriptive data of continuous variables mean and 17 standard deviations were computed. Frequencies and percentages were computed for all qualitative variables. We 18 applied cox algorithm to obtain crude and adjusted prevalence ratios. At univariate level, independent variables 19 were considered significant if p-value was ≤ 0.25 . We also checked multicollinearity between all the predictor 20 variables. To assess Multicollinearity, three different tests were used. Pearson's correlation was used for two 21 22 normally distributed continuous variables, ETA was used for one qualitative and one quantitative variable 23 whereas; Cramer's V was used for two qualitative variables. Moreover, the cut-off for Multicollinearity was 0.8. 24 After Multicollinearity, multivariable analysis was performed using cox algorithm to obtained adjusted 25 prevalence ratio. The cut-off for the significance of predictor variable at multivariable analysis was ≤ 0.05 . We 26 also calculated Propensity scores for the only significant variable left after performing multivariable model 27 building (functional status). The purpose of computing propensity scores was to identify factor associated with 28 the functional status and understand the viscous pathway of associations between explanatory variables and 29 30 depression. To predict propensity scores, functional status was kept as dependent variable and was regress with 31 other explanatory variables. After the final model was obtained for functional status, propensity scores were 32 computed. At last, Propensity scores were regress against depression (dependent variable in the study) to see its 33 association with depression. The cut-off for significance of propensity scores was ≤ 0.05 . 34

36 *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:

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Descriptive characteristics of study participants:

The mean age (\pm SD) of study participants was 43.25 (\pm 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 characterist	tic of study participants
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PATIENT-RELATED VARIABLES						
S#	Variables	Total	Screened positive for depressive symptoms (PHQ-9 \ge 10)			
		N (%)	N (%)			
1	Marital Status					

	Married	117 (89)	43 (37)
	Unmarried/Single/Senarated/Divorced	15(11)	-45(57) 08(53)
2	Children under 19 meers	15(11)	08 (55)
2	Children under 18 years		22 (12)
	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)
1	Basidanca		
t	In Verschi	40 (27)	10 (20)
		49 (37)	19 (39)
	Outside Karachi	83 (63)	32 (39)
	Travel Cost for one visit (from hometown to hospital)		
	5000-10,000 Rupees	26 (20)	05 (19)
	11,000-20,000 Rupees	39 (30)	18 (46)
	>20,000 Rupees	18 (13)	09 (50)
	Not Applicable	49 (37)	19 (39)
<u>í</u>	Caregiver at Home		
-	Snouse	92 (70)	33 (36)
	Derente	14(10)	
	Others (Vide/Neighborg/Siblings/Self)	26(20)	10(37)
_	Others (Kids/Neighbors/Siblings/Seif)	26 (20)	10 (38)
7	Heading Family		
	Yes	68 (52)	27 (40)
	No	64 (48)	24 (38)
3	Socio-economic Status (SES)		
	Low SES	22 (17)	09 (41)
	Middle SES	83 (63)	32 (39)
	High SES	27(20)	10(37)
)	Currently Smoking (Cigarette huga beeri)		
,	Vog	18 (14)	10 (56)
		10(14)	10(50)
		114 (80)	41 (30)
0	History of Psychological Distress Prior to the Diagnosis o)T	
	Brain Tumor		
	Yes	07 (05)	6 (86)
	No	125 (95)	45 (36)
1	Strategies to Handle Stress		
	8		10 (20)
	Isolation	26 (20)	10 (38)
	Isolation Crying	26 (20)	10 (38) 07 (44)
	Isolation Crying Prayers	26 (20) 16 (12) 48 (36)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \end{array} $
	Isolation Crying Prayers Aggression	26 (20) 16 (12) 48 (36) 24 (18)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \end{array} $
	Isolation Crying Prayers Aggression	26 (20) 16 (12) 48 (36) 24 (18)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.00) \end{array} $
	Isolation Crying Prayers Aggression Leaves home	26 (20) 16 (12) 48 (36) 24 (18) 01 (0.7) 12 (20)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.96) \\ 05 (45) \end{array} $
	Isolation Crying Prayers Aggression Leaves home Sleeping	26 (20) 16 (12) 48 (36) 24 (18) 01 (0.7) 13 (09)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.96) \\ 06 (45) \\ \end{array} $
	Isolation Crying Prayers Aggression Leaves home Sleeping Conversation with family/friends	26 (20) 16 (12) 48 (36) 24 (18) 01 (0.7) 13 (09) 10 (07)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.96) \\ 06 (45) \\ 01 (10) \end{array} $
	Isolation Crying Prayers Aggression Leaves home Sleeping Conversation with family/friends Addictions (Smoking/drinking)	26 (20) 16 (12) 48 (36) 24 (18) 01 (0.7) 13 (09) 10 (07) 06 (04)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.96) \\ 06 (45) \\ 01 (10) \\ 04 (66) \end{array} $
	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)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.96) \\ 06 (45) \\ 01 (10) \\ 04 (66) \\ 0 0(00) \end{array} $
12	Isolation Crying Prayers Aggression Leaves home Sleeping Conversation with family/friends Addictions (Smoking/drinking) Mind diversions (Listening to music/shopping) Karnofsky Performance Score (Functional Status)	26 (20) 16 (12) 48 (36) 24 (18) 01 (0.7) 13 (09) 10 (07) 06 (04) 02 (01)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.96) \\ 06 (45) \\ 01 (10) \\ 04 (66) \\ 0 0(00) \end{array} $
12	Isolation Crying Prayers Aggression Leaves home Sleeping Conversation with family/friends Addictions (Smoking/drinking) Mind diversions (Listening to music/shopping) Karnofsky Performance Score (Functional Status) KPS scores >70	26 (20) 16 (12) 48 (36) 24 (18) 01 (0.7) 13 (09) 10 (07) 06 (04) 02 (01) 102 (77)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.96) \\ 06 (45) \\ 01 (10) \\ 04 (66) \\ 0 0(00) \\ \end{array} $
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12 TRE. 13	Isolation Crying Prayers Aggression Leaves home Sleeping Conversation with family/friends Addictions (Smoking/drinking) Mind diversions (Listening to music/shopping) Karnofsky Performance Score (Functional Status) KPS scores >70 KPS scores ≤ 70 ATMENT-RELATED VARIABLES Overall Treatment Cost during illness 200,000-800,000 Rupees 800,000-1,200,000 Rupees >1,200,000 Rupees Treatment Cost Management Self-support Ensity/relating summent	26 (20) 16 (12) 48 (36) 24 (18) 01 (0.7) 13 (09) 10 (07) 06 (04) 02 (01) 102 (77) 30 (23) 45 (34) 47 (36) 40 (30) 73 (55) 21 (16)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.96) \\ 06 (45) \\ 01 (10) \\ 04 (66) \\ 0 0 (00) \\ \hline 27 (26) \\ 24 (80) \\ \hline 17 (38) \\ 20 (43) \\ 14 (35) \\ \hline 25 (34) \\ 11 (52) \\ \hline \end{array} $
12 <u>TRE</u> 13 14	Isolation Crying Prayers Aggression Leaves home Sleeping Conversation with family/friends Addictions (Smoking/drinking) Mind diversions (Listening to music/shopping) Karnofsky Performance Score (Functional Status) KPS scores >70 KPS scores ≤ 70 ATMENT-RELATED VARIABLES Overall Treatment Cost during illness 200,000-800,000 Rupees 800,000-1,200,000 Rupees >1,200,000 Rupees Treatment Cost Management Self-support Family/relative support W block	26 (20) 16 (12) 48 (36) 24 (18) 01 (0.7) 13 (09) 10 (07) 06 (04) 02 (01) 102 (77) 30 (23) 45 (34) 47 (36) 40 (30) 73 (55) 21 (16) 20 (21)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.96) \\ 06 (45) \\ 01 (10) \\ 04 (66) \\ 0 0 (00) \\ \hline 27 (26) \\ 24 (80) \\ \hline 17 (38) \\ 20 (43) \\ 14 (35) \\ \hline 25 (34) \\ 11 (52) \\ 12 (46) \\ \hline \end{array} $
12 <u>TRE</u> 13 14	Isolation Crying Prayers Aggression Leaves home Sleeping Conversation with family/friends Addictions (Smoking/drinking) Mind diversions (Listening to music/shopping) Karnofsky Performance Score (Functional Status) KPS scores >70 KPS scores ≤ 70 ATMENT-RELATED VARIABLES Overall Treatment Cost during illness 200,000-800,000 Rupees 800,000-1,200,000 Rupees >1,200,000 Rupees Treatment Cost Management Self-support Family/relative support Welfare from primary treating hospital	26 (20) 16 (12) 48 (36) 24 (18) 01 (0.7) 13 (09) 10 (07) 06 (04) 02 (01) 102 (77) 30 (23) 45 (34) 47 (36) 40 (30) 73 (55) 21 (16) 28 (21) 10 (0)	$ \begin{array}{c} 10 (38) \\ 07 (44) \\ 14 (29) \\ 13 (54) \\ 01 (1.96) \\ 06 (45) \\ 01 (10) \\ 04 (66) \\ 0 0 (00) \\ \hline 27 (26) \\ 24 (80) \\ \hline 17 (38) \\ 20 (43) \\ 14 (35) \\ \hline 25 (34) \\ 11 (52) \\ 13 (46) \\ 0 (20) \\ \hline \end{array} $

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15	Access to Health Insurance		
	Ves	15 (11)	3 (20)
	No	117 (80)	$\frac{3}{48} (20)$
17		117 (89)	40 (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	12 (33)	
1/		00 (17)	12 (50)
	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 Desection	36 (27)	10(28)
20		30 (27)	10 (28)
20	1 ype 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)
<u></u>	Time since diagnosis (In months)	Median: 0.5 months	Median: 5 month
<i>LL</i>	i nine since diagnosis (in monuis)	Den equil 74 months	$\frac{1}{2} \frac{1}{2} \frac{1}$
		Range:(1-/4 month)	Range:(1-/4 month)
25	Number of chemotherapy cycles	Median: 2.5 cycles	Median: 0
		Range: (0-33 cycles)	Range:(0-27 cycles)
26	Number of radiation cycles	Median: 3.5 cycles	Median: 0
		Range: (0-33 cycles)	Range:(0-54 cycles)
TUM	IOUR-RELATED VARIABLES		
27	Tumor Histology		
21	Meningioma	30 (23)	16 (53)
	Dituitary adaption	26 (27)	10(33) 00(25)
	Pituitary adeitoina	30 (27)	09 (23)
	High grade glioma (Astrocytoma, GBM)	21 (16)	09 (43)
	Oligodendroglioma	29 (22)	08 (28)
	Others (Schwannoma, Intraventricular SOLs, CNS lymphoma,	16 (12)	09 (56)
	Ependymoma, Hemangioblastoma, Craniopharyngioma,		
	Choroid plexus papilloma)		
28	Tumor Type		
	Benign	69 (52)	28 (41)
	Malignant	(32)	20 (11)
• •	wangnant	03 (48)	23 (57)
29	Hemispheric Lateralization		
	Left	60 (45)	28 (47)
	Right	35 (27)	13 (37)
	Not specified	37 (28)	10 (27)
30	Tumour Grade		
20	Grade I	12 (9)	05 (42)
	Grada II	$\frac{12}{20}$ (22)	14 (47)
		50 (25) 20 (22)	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)
20	Титок Водинионос	123 (95)	
32	I umor Kecurrence	22 (17)	
	Yes	23 (17)	14 (61)
	No	109 (83)	37 (34)
33	Brain Structures Involved (Tumor location)		
	Frontal lobe	53 (40)	23 (43)
		· ·	· ·
			6

		Parietal lobe	30 (22)	13 (43)	
l		Temporal lobe	26 (19)	10 (38)	
2		Occipital lobe	05 (3)	01 (20)	
3		Pituitary gland (Seller region)	36 (27)	09 (25)	
1		Ventricles	05 (4)	03 (60)	
5		Cerebellum/CP angle	07 (4)	06 (85)	
5		Posterior fossa	01 (1)	00 (00)	
7		Basal ganglia	01 (1)	0 0(00)	
3	34	First Symptoms Before Brain Tumor Diagnosis			
)		Seizures	40 (30)	14 (35)	
0		Headaches	55 (42)	25 (45)	
1		Weight loss/gain	3 (2)	1 (33)	
2		Mood changes/loss of interest	1(1)	1 (100)	
13		Visual impairment	36 (27)	10 (28)	
14		Memory loss	5 (3)	3 (60)	
15		Gait instability	1 (1)	1 (2)	
16		Nausea/ Vomiting	5 (3)	2 (40)	
17		Unconsciousness	7 (5)	2 (29)	
12		Dizziness	1 (1)	0 (00)	
10		Slurred speech/unable to write & comprehend	3 (2)	1 (33)	
00		Numbness (arms, legs, body)	2 (1)	1 (50)	
20		Limb weakness	2 (1)	1 (50)	
21		Swelling (facial, orbital)	3 (2)	2 (67)	
<u> </u>		Sexual dysfunction	1 (1)	0 (00)	
23		Hearing problems	1 (1)	0 (00)	
24					

²⁵ *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 \leq 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 braintumour 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	-	
† Re	ference Category which was kept as reference in	n 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].

11 We found three factors associated with reduced functional status including unemployment, tumor recurrence, and 12 stage of treatment, more specifically, early stage of treatment. Association between employment status and 13 14 depression has been explored by other investigators too, and there are at least three studies that have included 15 employment status in their primary analysis. A study conducted by Pelletier (2002) [26] found employment status 16 positively associated with depression among patients with brain tumors. However, this association was significant 17 only at univariate level. Another study conducted by Vossen (2014) [27] on cognitive and emotional problems 18 among meningioma patients reported significant association between depression and employment status where 19 depression was assessed by hospital anxiety and depression scale. However, when depression was assessed by 20 other screening tools, no association was found. In contrast, employment status was found to be significantly 21 22 associated with functional status. A follow-up study conducted by Hickmann (2016) [28] reported a parallel trend 23 of unemployment as the functional status declines. Though none of the studies have reported any definite 24 association between unemployment and reduced functional status among similar populations but trends and 25 figures explained by previous studies, as well as common sense supports this relationship, especially in countries 26 without unemployment benefits; or without adequate labor laws safeguarding employee rights during illnesses. 27

29 We did not find any significant association between tumor recurrence and depression and similar findings were 30 reported by Vossen (2014) [27]. On the other hand, reduced functional status was significantly associated with 31 tumor recurrence, as shown by other investigators as well [29][30]. We included brain tumor patients during 32 different treatment stages after surgical procedure was done. Patients immediately after surgery and in their initial 33 stage of treatment reported highest prevalence of depression (82%). Weitzner (1999) [31], Pringle (1999) [32], 34 and Mainio (2005) [19] also reported higher level of depression during initial stage of treatment that is within 35 first three months after surgery. This variable was also found significantly associated with impaired functional 36 37 status that is understandable given the physiological and psychological effects of major surgery and 38 hospitalization. As the treatment progresses and by the time it comes to its end, patients tend to regain their 39 functional status and even resume their jobs. Most brain tumor patients who have transient focal deficits as a 40 result of surgery, by the time they reach the completion of their treatment, also improve in their overall functional 41 status. However, no statistical evidence has been reported by any study on association between functional status 42 and treatment stage. 43

45 This study had few limitations. Firstly, we conducted a cross-sectional study which by default doesn't conclude 46 any temporal relationship between explanatory variables and the outcome. Though our study provides new insight 47 to the psychological burden brain tumor patients may experience along with its associated factors but results of 48 this study must be interpreted with caution. However, future studies with larger sample size and different 49 prospective designs are required to hypothesize any specific association. Secondly, we used a single screening 50 tool to measure depression. We did not use physician-rated measures or mini-interviews to verify the results of 51 52 PHQ-9. This might have over-estimated the prevalence of depression among study participants. However, our 53 study aimed to screen patients for depressive symptoms and not to diagnose thus, one screening tool was used 54 only. Moreover, to prevent excessive fatigue to the patients, we decided to take less time of our participants. 55 Therefore, screening tool was considered best to screen for depressive symptoms instead of interviews which 56 could have taken longer time. Thirdly, this study was a single center study and thus results cannot be generalized 57

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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.

⁹₁₀ Conclusion:

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11 Our findings suggest that a high proportion of patients with brain tumor also suffer from depression. Whereas 12 several individual and clinical factors may contribute to the development of depression, patients with reduced 13 14 functional status should be especially monitored for any signs of psychiatric illness. Given the high proportion of 15 depressed patients in our study population, we would recommend routine psychiatric evaluation, or at the least, 16 the administration of simple self-rated screening tools that will allow healthcare providers to readily identify any 17 prevailing neuropsychiatric ailments, for all patients with brain tumors, at the time of admission and during 18 follow-ups. 19

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 all the residents and consultants who assisted in this project.

²⁵₂₆ *Conflict of interest disclosure:*

The authors have no conflicts of interest to declare.

29 Data availability statement:

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

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34 *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
- ³⁹ 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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Section/Topic	ltem #	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	Yes
		collection	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	Yes
		applicable	Page 3
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe	Yes
measurement		comparability of assessment methods if there is more than one group	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	Yes
		why	Page 4

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

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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,	Yes
		confirmed eligible, included in the study, completing follow-up, and analysed	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	Yes
		confounders	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	Yes
		interval). Make clear which confounders were adjusted for and why they were included	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	Yes
		magnitude of any potential bias	Page 2
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from	Yes
		similar studies, and other relevant evidence	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	NA
		which the present article is based	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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26 Abstract: 27

28 **OBJECTIVE:** 29

The prevalence of depression among primary brain tumor patients ranges from 15% to 40% globally. Several individual 30 and clinical factors contribute to the development of depression. However, their association with depression in Pakistani 31 setting has not yet been assessed. Thus, we aim to study the factors associated with depression among adult primary brain 32 tumor patients at a tertiary care hospital in Karachi, Pakistan. 33

35 STUDY DESIGN:

36 A prospective cross-sectional study 37

38 SETTING:

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39 This study was conducted at a tertiary care hospital of Karachi, Pakistan 40

41 **PARTICIPANTS:**

42 This study included 132 patients with confirmed diagnosis of primary brain tumor (initially diagnosed on MRI brain with 43 contrast and later confirmed on histology of surgical specimen) in various stages of treatment. 44

45 PRIMARY OUTCOME: 46

The primary outcome of this study was to assess depression and its associated factors among adult primary brain tumor 47 patients. Depression was assessed using a validated screening tool (Patient Health Ouestionnaire-9). Scores of 10 to 27 on 48 Patient Health Questionnaire-9 (PHQ-9) were indicative of screen positive for depressive symptoms. A set of the structured 49 pre-tested questionnaire was used to evaluate patient-related, tumor-related, and treatment-related factors. 50

51 **RESULTS:** 52

53 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 54 and Confidence Interval: 1.87-5.62) after controlling covariates. Propensity scores predicted a positive association between 55

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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 PHO-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:

32 Although primary brain tumors account for a relatively small percentage of all cancers, it is considered one of the most 33 devastating types of cancers among the adult population [1]. The incidence of primary brain tumors is approximately 34 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 36 patients [3-4].

38 Diagnostic and Statistical Manual-V defines depression as a feeling of sadness, loss of pleasure from daily living activities, 39 body weight changes, reduction in physical activity, fatigue, failure to think or concentrate, lack of self-worth, and recurrent 40 suicidal ideations [5]. It is estimated that depression affects about 350 million individuals worldwide and according to the 41 Global Mental Health Survey (2014), nearly 1 in 20 individuals report having at least one episode of depression within a 42 43 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 44 45 estimated prevalence of clinically diagnosed depression in Pakistan is approximately 6% out of which 3% are cancer 46 patients [9]. Depression rates among primary brain tumor patients range from 15% to 40% with the highest rates among 47 glioma patients [10]. However, it is suggested that these rates likely under-represent the true incidence of depression [11]. 48 A systematic review of 42 observational studies reports that the prevalence of depression among glioma patients ranges 49 between 0 to 93% with a median prevalence of 27% [12]. 50

51 Depression in brain tumor patients is multifactorial and there are several factors contributing to its development, including 52 individual, tumor-related, and disease-related factors [10]. All the studies on this topic to date have been conducted in the 53 western population, where the psychosocial circumstances are much different from the Pakistani population, for example 54 whereas in the UK and US, where most of the data come from, the majority of patients are financially supported by third 55 party payers i.e., state or insurance. In contrast, approximately 85% of patients in Pakistan, and a few other South Asian 56 LMIC countries are out of pocket payers both for their treatment, and rehabilitation [13]. This we believe, maybe the 57

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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 patientrelated, tumor-related, and treatment-related variables among adult primary brain tumor patients in an LMIC.

Methods:

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Study Design:

The analytical cross-sectional study design was employed to determine the association between patient-related, tumorrelated, 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 28 participants were as follows: diagnosis of depression for about one year prior to the diagnosis of primary brain tumor, 29 confused or incoherent patients and patients having problems with speech or comprehension that prevents them from 30 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 32 mental status. 33

Procedure

37 Participant's eligibility was determined by medical record files. Potentially eligible participants were approached by the 38 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

45 We divided all the associated factors into three distinct categories that were patient-related, tumor-related, and treatment-46 related variables. Patient-related factors comprised of demographic and socio-economic variables including age, gender, 47 marital status, number of dependents, children under 18 years, education, occupation, employment status, residency, 48 traveling cost, caregiver support, current smoking status, past/current medical illness, history of psychological distress, 49 strategies to handle stress (isolation, aggression, prayers, crying, sleeping, addiction, and mind diversions) and functional 50 status. The participant's functional status was assessed using the Karnofsky performance score (KPS). KPS scores less than 51 52 70 were indicative of impaired functional status. Socio-economic status (SES) was also computed using factorial analysis. 53 Tumor-related and treatment-related variables were assessed by medical record review and included tumor histology, tumor 54 grade, recurrence, hemispheric lateralization, first symptoms, brain structures involved, and cognitive impairment. 55 Treatment-related variables included stage of treatment, number of chemotherapy cycles, duration since diagnosed, 56

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

Depression

5 Primary brain tumor patients were screened for depression using the Urdu version of patient health questionnaire-9 (PHQ-6 9). The PHQ-9 is a self-rated screening tool which contains 9 items corresponds to DSM-V criteria of depression and rated 7 on Likert scale of four points. All the patients were classified into two groups based on the scores on the PHO-9 scale. 8 Participants with a score of ≥ 10 were classified as screened positive for depression. PHQ-9 score of 10 or above has a 9 sensitivity and specificity of 88% for major depressive symptoms. A recently conducted validation study on Urdu version 10 (the national language of Pakistan) of PHQ-9 by Gholizadeh, 2017 [15], reported a specificity of 94% and a false-positive 11 12 rate of 6% only. 13

Statistical Analysis:

16 Sample size was calculated from previous study [16] using Openepi [17] with a power of 80%, depression to no depression 17 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. 18 Adding 20% of the attrition rate the final sample size came out to be 130 participants. We used STATA version 12.0 [18] 19 to perform all the analyses. For descriptive data of continuous variables mean and standard deviations were computed. 20 Frequencies and percentages were computed for all qualitative variables. We applied the cox algorithm to obtain crude and 21 adjusted prevalence ratios [19]. At the univariate level, independent variables were considered significant if the p-value was 22 ≤ 0.25 [20]. We also checked multicollinearity between all the predictor variables. To assess Multicollinearity, three 23 different tests were used. Pearson's correlation was used for two normally distributed continuous variables, ETA was used 24 for one qualitative and one quantitative variable whereas; Cramer's V was used for two qualitative variables. Moreover, the 25 26 cut-off for Multicollinearity was 0.8. After Multicollinearity, multivariable analysis was performed using the cox algorithm 27 to obtained adjusted prevalence ratio. The cut-off for the significance of the predictor variable at multivariable analysis was 28 <0.05. We also calculated Propensity scores for the only significant variable left after performing multivariable model 29 building (functional status). The purpose of computing propensity scores was to identify the factor associated with the 30 functional status and understand the vicious pathway of associations between explanatory variables and depression. To 31 predict propensity scores, functional status was kept as a dependent variable and was regress with other explanatory 32 variables. After the final model was obtained for functional status, propensity scores were computed. At last, Propensity 33 scores were regressed against depression (dependent variable in the study) to see its association with depression. The cut-34 off for the significance of propensity scores was ≤ 0.05 . 35

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:

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Descriptive characteristics of the study participants:

The mean age (\pm SD) of study participants was 43.25 (\pm 12.28) years, with 86 (65%) males and 46 (35%) female. Fiftyone (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

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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		
e	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	Caragivar at Home	(57)	17(57)
0	Spouse	02 (70)	22 (26)
	Darants	$\frac{92}{14}(10)$	08 (57)
	Others (Kids/Neighbors/Siblings/Self)	14(10) 26(20)	10(38)
7	Heading Family	20 (20)	10 (58)
/		68 (52)	27 (40)
	I CS No	64(32)	27(40) 24(38)
0	NO Socio coopomia Status (SES)	04 (40)	24 (38)
0	Low SES	22 (17)	0 (41)
	LOW SES	22(17) 92(62)	9(41) 22(20)
	Middle SES	83(03)	32(39) 10(27)
0		27 (20)	10(37)
9	Currently Smoking (Cigarette, huqa, beeri)	10 (14)	10 (56)
	Yes		
10		114 (86)	41 (36)
10	History of Psychological Distress Prior to the		
	Diagnosis of Brain Tumor	7 (5)	
	Yes	/ (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)	
	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)
10	Vannafalm Danfann an as Saans (Eurational Status)		

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	KPS scores >70	102 (77)	27 (26)
	KPS scores ≤ 70	30 (23)	24 (80)
TRE	ATMENT-RELATED VARIABLES		
13	Overall Treatment Cost during illness		
	200,000-800,000 Rupees	45 (34)	17 (38)
	800,000-1,200,000 Rupees	47 (36)	20 (43)
	>1,200,000 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)	37 (28)	12 (32)
	Conventional (General anesthesia)	95 (72)	39 (41)
21	External Ventricular Drain Insertion	4	
	Yes	7 (5)	5 (71)
	No	125 (95)	46 (37)
22	Time since diagnosis (In months)	Median:9.5	Median: 5 month
		months	Range:(1-74 month
		Range:(1-74	
		month)	
25	Number of chemotherapy cycles	Median: 2.5	Median: 0
		cycles	Range:(0-27 cycles
		Range: (0-33	
		cycles)	
26	Number of radiation cycles	Median: 3.5	Median: 0
		cycles	Range:(0-54 cycles
		Range: (0-33	
		cycles)	
TUM	IOUR-RELATED VARIABLES	· · · · · · · · · · · · · · · · · · ·	
27	Tumor Histology		
	Meningioma	30 (23)	16 (53)
	Pituitary adenoma	36 (27)	9 (25)
	High grade glioma (Astrocytoma, GBM)	21 (16)	9 (43)
			/

		Others (Schwannoma, Intraventricular SOLs, CNS	16 (12)	9 (56)
1		lymphoma, Ependymoma, Hemangioblastoma,		
2		Craniopharyngioma, Choroid plexus papilloma)		
3	28	Tumor Type		
4		Benign	69 (52)	28 (41)
5		Malignant	63 (48)	23(37)
6 7	29	Hemispheric Lateralization		20 (01)
/ Q		Left	60 (45)	28 (47)
9		Right	35 (27)	13 (37)
10		Not specified	37 (28)	10 (27)
11	30	Tumour Grade		
12		Grade I	12 (9)	05 (42)
13		Grade II	30 (23)	14 (47)
14		Grade III	30(23)	13 (43)
15		Grade IV	16(12)	7 (47)
16		Not specified	44 (33)	12 (27)
17	31	Cognitive Impairment		
18	51	Ves	9(7)	5 (56)
19		No	123 (93)	46 (37)
20	22	Tumor Doourrongo	125 (75)	+0 (37)
21	52	V _{os}	23 (17)	14 (61)
22		I CS No	23(17) 100(83)	14(01) 27(24)
23	22	Proin Stanatures Involved (Turner leastion)	109 (83)	37 (34)
24	55	Brain Structures Involved (Tumor location)	52 (40)	22(42)
25		Pariotal labo	33 (40) 20 (22)	23(43)
20		Tampanal labo	30(22) 26(10)	13 (43)
27		Consistent lobe	20(19) 5(2)	10(38) 1(20)
20		Dituitory alond (Saller region)	3(3) 2((27))	1(20)
30		Ventrialea	50(27)	9 (23)
31		Ventricles	$ \frac{3(4)}{7(4)} $	3(60)
32		Cerebellum/CP angle	/ (4)	0(83)
33		Posterior Iossa	(1)	0(0)
34	24	Dasai gangna	1 (1)	0(0)
35	34	First Symptoms Before Brain Tumor Diagnosis	10 (20)	14 (25)
36		Seizures	40 (30)	14(35)
37		Headaches Waisht Isra/asia	55 (42) 2 (2)	25 (45)
38		Weight loss/gain	3(2)	1(33)
39		Mood changes/loss of interest	$\begin{array}{c}1\left(1\right)\\2\left(\left(27\right)\end{array}\right)$	1(100)
40		Visual impairment	$\frac{36(27)}{5(2)}$	10(28)
41		Memory loss	5(3)	3 (60)
42		Gait instability	$\begin{pmatrix} 1 \\ 5 \end{pmatrix}$	$\frac{1}{2}$ (2)
43		Nausea/ Vomiting	5(3)	2(40)
44 45			/ (5)	2 (29)
45 16		DIZZINESS	1(1) 2(2)	0(00)
40		Surred speech/unable to write & comprehend	5(2)	1 (55)
-17 48		Numbness (arms, legs, body)	2(1)	1 (50)
49			2(1)	1 (50)
50		Swelling (tacial, orbital)	5(2)	2 (6/)
51		Sexual dystunction		$\mathbf{U}(0)$
52		Hearing problems	1(1)	0(0)

Univariate analysis:

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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 \leq 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	-	
† Ret	ference 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.

VariablePR and 95% CIP-value

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Propensity sc	ores 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:

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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 10 South Asian countries. We believe that the circumstances for our patients differ from those of the west, for a number of 11 reasons. According to World Health Organization, Pakistan has one of the world's lowest public health expenditure as a 12 percentage of GDP, as well as one of the world's highest out of pocket health expenditure, where it shares the top slot with 13 other South Asian LMICs. Thus approximately 85% of our patients are out of pocket payers, in a country already marred 14 with poverty, compared to the high-income countries where the majority of patients are financially supported by third party 15 payers i.e., state or insurance. [13] In this setting, the high cost of treatment for brain tumors (surgery, chemotherapy, 16 radiation therapy, rehabilitation, etc.) should theoretically add to the psychological stress of the patients. Although 17 government-run hospitals do exist, they cover only a fraction of the overall healthcare, and the majority of patients have to 18 resort to private hospitals, especially for advanced healthcare. There are also very few state-run oncology or rehabilitation 19 centers, and patients have to rely on private healthcare for all these services. 20

22 We found that 39% of patients with a primary brain tumor treated at AKUH, screened positive for depression on PHQ-9. 23 Impaired functional status was the only significant variable associated with depression and propensity scores for functional 24 status revealed a significant association between impaired functional status and treatment stage at the time of the interview, 25 unemployment, and tumor recurrence. We also found that decreasing KPS was directly linked to increased chances of 26 depression, as in with each unit increase in propensity scores for functional status; chances of depression increased by up to 27 5%. Our findings are consistent with some of the previous studies on the same topic. Rooney (2010) [12] in his systematic 28 review of observational studies concluded that the median prevalence of depression among patients with brain tumor using 29 screening scales was about 27% (range 0%-93%) while clinician-rated measures returned up to 15% (5%-28%). Another 30 meta-analysis conducted by Huang and Colleagues in 2017[21] reported that the prevalence of depression in brain tumor 31 patients is nearly 21% using screening scales and 19% with clinician-rated measures, specifically including mini-interviews. 32 A 1-year follow-up study conducted by Mainio (2005) [22] also found functional status as a significant predictor associated 33 with depression among brain tumor patients. Similar findings were observed in observational studies conducted by 34 Anderson (1999) [23], Litofsky (2004) [24], Grant (1994) [25], Fox (2007) [26], Rooney (2013) [27], and Piil (2015) [28-35 29]. 36

We found three factors associated with reduced functional status including unemployment, tumor recurrence, and stage of 38 treatment, more specifically, the early stage of treatment. Association between employment status and depression has been 39 40 explored by other investigators too. A study conducted by Pelletier (2002) [30] found employment status positively 41 associated with depression among patients with brain tumors. However, this association was significant only at the 42 univariate level. Another study conducted by Vossen (2014) [31] on cognitive and emotional problems among meningioma 43 patients reported a significant association between depression and employment status where depression was assessed by 44 hospital anxiety and depression scale. However, when depression was assessed by other screening tools, no association was 45 found. In contrast, employment status was found to be significantly associated with functional status. A follow-up study 46 conducted by Hickmann (2016) [32] reported a parallel trend of unemployment as the functional status declines. Though 47 none of the studies have reported any definite association between unemployment and reduced functional status among 48 similar populations but trends and figures explained by previous studies, as well as common sense supports this relationship, 49 especially in countries without unemployment benefits; or without adequate labor laws safeguarding employee rights during 50 illnesses. 51

52 We did not find any significant association between tumor recurrence and depression and similar findings were reported 53 by Vossen (2014) [31]. On the other hand, reduced functional status was significantly associated with tumor recurrence, as 54 shown by other investigators as well [33-34]. We included brain tumor patients during different treatment stages after 55 surgical procedure was done. Patients immediately after surgery and in their initial stage of treatment reported the highest 56 57

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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.

9 This study had few limitations. Firstly, we conducted a cross-sectional study which by default doesn't conclude any temporal 10 relationship between explanatory variables and the outcome. Though our study provides new insight into the psychological 11 burden brain tumor patients may experience along with its associated factors but the results of this study must be interpreted 12 with caution. However, future studies with larger sample size and different prospective designs are required to hypothesize 13 14 any specific association. Secondly, we used a single screening tool to measure depression. We did not use physician-rated 15 measures or mini-interviews to verify the results of PHO-9. This might have over-estimated the prevalence of depression 16 among study participants. However, our study aimed to screen patients for depressive symptoms and not to diagnose thus, 17 one screening tool was used only. Moreover, to prevent excessive fatigue to the patients, we decided to take less time off 18 our participants. Therefore, a screening tool was considered best to screen for depressive symptoms instead of interviews 19 which could have taken a long time. Thirdly, this study was a single-center study and thus results cannot be generalized to 20 the entire population of brain tumor patients. Though we included a diversified group of patients with different ethnic and 21 cultural backgrounds but there is a possibility that patients who presented to government and semi-government sectors for 22 the treatment of brain tumors might have different socio-economic backgrounds and other demographic characteristics. 23 There is a possibility that patients presented to other care settings apart from AKUH might have different predisposing 24 factors that lead to depression. Therefore, we cannot generalize our results to all brain tumor patients. However, our findings 25 do represent a group of brain tumor patients presented to private tertiary care settings in Pakistan. 26

Conclusion:

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30 Our findings suggest that a high proportion of patients with brain tumor also suffer from depression. Whereas several 31 individual and clinical factors may contribute to the development of depression, patients with reduced functional status 32 should be specially monitored for any signs of psychiatric illness. Given the high the proportion of depressed patients in our 33 study population, we would recommend routine psychiatric evaluation, or at the least, the administration of simple self-34 rated screening tools that will allow healthcare providers to readily identify any prevailing neuropsychiatric ailments, for 35 all patients with brain tumors, at the time of admission and during follow-ups. 36

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41 *Conflict of interest disclosure:* 42

The authors have no conflicts of interest to declare. 43

- 45 *Data availability statement:*
- The data that support the findings of this study are available from the corresponding author upon reasonable request. 46 47
- 48 Contribution of Author's:
- 49 Anum Sadruddin Pidani: Study design, formulation of questionnaire, data collection, data analysis, manuscript writing

50 Amna Rehana Siddiqui: Study design, epidemiological expertise in design and implementation phase, manuscript writing 51 and review

- 52 Iqbal Azam: Biostatistician (analysis of study data), Manuscript writing and review of study analysis
- 53 Muhammad Shahzad Shamim: Design and implementation of study, neurosurgery expert input in the design and analysis 54 phase, manuscript review and writing 55
- Adnan A. Jabbar: Design and implementation of study, Oncology expert input in the design and analysis phase, Manuscript 56 reviewing 57
- 58
- 59 60

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

³ *Abbreviations:*

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- ⁴ PHQ-9: Patient Health Questionnaire-9
- AKUH: Aga Khan University Hospital
- 7 KPS: Karnofsky Performance Score
- bSM-V: Diagnostic and Statistical Manual of Mental Disorders-5th Edition
- 9 PR: Prevalence Ratio
- 10 HIV: Human Immunodeficiency Viruses
- 11 LMIC: Low-Middle Income Country
- 12 UK: United Kingdom
- 13 US: United States
- 14 MRI: Magnetic Resonance Imaging
- 15 SES: Socio-economic Status
- 16 EVD: Extra Ventricular Drain17

18 References:19

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Section/Topic	ltem #	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	Yes
		collection	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	Yes
		applicable	Page 3
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe	Yes
measurement		comparability of assessment methods if there is more than one group	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	Yes
		why	Page 4

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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,	Yes
		confirmed eligible, included in the study, completing follow-up, and analysed	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	Yes
		confounders	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	Yes
		interval). Make clear which confounders were adjusted for and why they were included	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	Yes
		magnitude of any potential bias	Page 2
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from	Yes
		similar studies, and other relevant evidence	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	NA
		which the present article is based	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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