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Relationship between Resilience and Quality of life in patients with Head & Neck Cancer and Brain Tumor in Pakistan; An Analytical Cross Sectional Study Protocol

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Abstract

Background: Cancer is a devastating disease and it has detrimental effect on quality of life (QoL) of cancer survivors. Literature has reported a relationship between QoL and resilience in cancer survivors but there is dearth information regarding this relationship. The aim of study is to assess the relationship between resilience and QoL among cancer survivors and to evaluate the effect of important factors on resiliency and QoL relevant to our local cultural context.

Method and Analysis: A cross-sectional study will be conducted at a tertiary care hospital in Karachi, Pakistan. Around 250 head and neck cancers and 250 brain tumor survivors who have received treatment will be recruited. QoL will be assessed by EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20) and Resilience will be evaluated by Wagnild & Young's 14 item scale. To unfold the locally relevant themes open ended questions will also be administered. Multiple linear regression technique will be applied and β- coefficient with 95% CI will be reported, a *p*-value of <0.05 will be considered as significant.

Ethics and Dissemination: Ethical approval has been obtained by Aga Khan University Karachi's Ethical Review Committee. Written informed consent will be taken from the participants by trained data collectors. Study procedure will be explained to the participants along with potential risks and benefits. On-spot counseling will be given to participants having depression by a trained psychologist and those with severe depression will be referred to a psychiatrist. All study materials containing personal identifiers will be kept in lock and key and the electronic database will be password protected and accessed only by the research staff of this study. The study findings will be disseminated to health care professionals, rehabilitation experts, psychologist and to cancer patients through: 1. Publications 2. Presentations at conferences and workshops. 3. Research briefs.

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Keywords: *Quality of life, Resilience, Cancer Survivors, Life Satisfaction, Post-Cancer Depression, Coping*

Summary:

Strengths and Limitations

- We will use validated measures for evaluating the outcome and independent variables.
- Robust data collection measures will be adopted to increase the overall quality of study, as investigators will randomly assess each data collector's work via spot-checks and at regular bases data collection forms will be reviewed.
- Our study is a single hospital based study therefore, the patients we aim to select may not be similar to those presenting to other centers in Karachi. However, our study results can be generalizable to all those cancer patients presenting to tertiary care private hospitals of Pakistan.
- We do not have any comparative group because it is difficult to compare resilience and QoL of a normal healthy individual with a cancer patient.

Background

Cancer is the second leading cause of death globally. [1] About 70% of the deaths due to cancer are witnessed by Lower Middle Income Countries (LMIC). Globally Head and Neck cancers are one of the most common cancers with nearly 600,000 new cases and 300,000 deaths occurring annually. [2, 3] Moreover, brain tumors are also responsible for approximately 2% of all cancer deaths with an overall incidence of 4-5/100,000 population per year. [4]

Cancer is a potentially life-threatening disease and often leads to psychological distress or trauma. [5] Certainly, a large number of cancer patients suffer from clinically important symptoms of emotional distress such as depression and anxiety. [6] Such emotional distress of cancer patients considerably lowers their QoL and resilience and potentially interferes with treatment compliance. [7] [8]

The broad concept of resilience has been introduced recently stating the protective attributes of an individual in the adaptation to cancer. [5] Resilience of cancer survivors can be accounted on their baseline characteristics or personality traits which enable individuals to thrive in the face of adversity. These baseline characteristics include; basic demographic factors and personal resources, such as; hope (like positive readiness and expectancy), motivation, optimism, sense of coherence (i.e., recognizing world as a meaningful and predictable place), preexisting social support, and spirituality. [9] The other possible factors that might influence ones resiliency is positive adaptation that changes over time and protects one against psychological distress. [10] Lastly the presence of relatively positive psychosocial functioning may help to deal with consequences of traumatic stress. [11] It has been observed that individuals with high resilience have coped up with traumatic events more efficiently than those with low resilience. [12] Moreover, higher resilience has been associated with reduced emotional distress after exposure to the traumatic events.[13] Since the diagnosis and treatment of cancer is potentially a

traumatic event [14], the individual's level of resilience and QoL might influence their emotional problems in response to cancer.

Studies have examined influence of psychological resilience among cancer patients. [15, 16] It indicates that cancer patients with high resilience may be less dependent on psychosocial support to manage their stressful conditions relative to those with low resilience. [15] Resilience has an important impact on QoL of a cancer patient. QoL has two fundamental premises; firstly, a multi-dimensional concept incorporating physical, psychological, social, and emotional functional domains (Figure 1). Secondly it is subjective and must be self-reported, according to the patients' own experiences. Several studies from different parts of the world on cancer survivors suggest that resilience is a protective factor for distress. [5, 17-20] A study reported that resilience was likely to mediate the adverse relationship between cancer symptoms, distress and QoL among cancer survivors, indicating that resilience might play an essential role in protecting them against adverse effects of cancer symptoms. [17]

Resilience and QoL changes over time and may be modifiable towards increased well-being therefore, it is important that before initiating treatment, patients should be referred to a mental health professional for psychological evaluation.

To the best of our knowledge, this will be the first in-depth study to evaluate resilience and QoL among head & neck cancer and brain tumor patients in Pakistan. Moreover, through this study we will be able to identify problems faced by such patients in our setting, enabling us to design interventions in the future to improve resilience and QoL in this population.

Methods

Study Design

To evaluate important factors associated with resilience and QoL after treatment for head & neck cancer and Brain tumor patients an analytical cross sectional study will be conducted. Resilience and QoL will be measured 4 weeks post treatment.

Study Setting

The study will be conducted at Aga Khan University (AKU) which is a JCIA-accredited hospital, in Karachi-Pakistan. Karachi is the largest metropolitan city of Pakistan, a home to all major ethnicities living in Pakistan. AKU is one of the largest private tertiary care hospitals; it consists of multidisciplinary team that provides comprehensive care to cancer patients. AKU caters to different ethnic and socioeconomic groups of Karachi population. The participants will be recruited from surgical clinics at AKU. The proposed duration of data collection will be from 4-6 months.

Study Participants

Men and women greater than 18 years, who have received treatment for brain tumor and head & neck cancer at AKU, fulfilling the below eligibility criteria will be recruited.

Eligibility Criteria

Inclusion Criteria

- Individual aged > 18 years including both male and female.
- Patients with confirmed diagnosis of head and neck cancer and brain tumor by histopathology (evaluated from medical records).
- Patients who had received treatment at AKUH for head & neck cancer and/or brain tumor.
- Cancer survivors living in Pakistan for the last three months.

Exclusion Criteria

- Known cases of any psychiatric illness leading to disability (e.g. manic disorder, schizophrenia etc.) confirmed by medical records will be excluded from the study as they may be on medications, hence may not get the true results.
- Patients on anti-depressants prescribed by a psychiatrist.
- Participant with terminal disease like renal failure and stroke will be excluded because these diseases also have profound effect on QoL and resilience.

Sampling Technique

This study will use purposive sampling technique for selection of the participants. Purposive sampling involves study participants selection criteria based on certain characteristics. The key objective of purposive sampling is to focus on population features that are of interest to the researcher, who can answer the study questions. Our target population i.e. brain tumor and head and neck cancer patients who have received cancer treatment will be approached and they will be screened using our eligibility criteria. Those who will fulfill our eligibility criteria and will be willing to give informed consent will be enrolled in the study (Figure 2)

Sample Size Calculation

Head and Neck Cancer: The Sample size was calculated using one population mean formula. Mean scores for QoL and resilience for head and neck cancer patients were identified from literature. The reported standard deviation (SD) for QoL and resilience ranges from 16.5 to 40.8 at 5 % level of significance, with precision of 2.5 and adjusting the sample size for 10% non-response rate, the minimum sample size estimated was 250 head and neck cancers patients. [21-26]

Brain Tumor: The Sample size was calculated using one population mean formula. Mean scores for QoL and resilience for brain tumor patients were identified from the literature. The

reported standard deviation (SD) for QoL and resilience ranges from 12. 7 to 34.1, at 5 % level of significance, with precision of 2.5 and adjusting the sample size for 10% non-response rate, the minimum sample size estimated was 250 brain tumor patients. [27-30]

Assessment Tools

Resilience (Wagnild & Young's 14 Item)

Resilience is the ability to rebound or spring back, the power of something to resume its original shape or position after compression or bending. [31] Resilience is also defined as the 'capacity of individuals exposed to a negative event to maintain stability, healthy physical and psychological functioning. However, few are of the view that it is a defense mechanism, which permits people to grow in the face of adversity. [32] To measure resilience, we will use Resilience Scale 14 (RS-14) which has been validated in Pakistan. [33] It has two versions, a long 25-item and short 14 item scale, using a 7-point rating likert scale. It comprises of five core characteristics of resilience that includes: purposeful life, perseverance, equanimity, self-reliance and existential loneliness. [34] A high score represents better resilience. The respondent's choice ranges from 1 (Strongly Disagree) to 7 (Strongly Agree). The scale uses total scores rather than scores of individual items.

Quality Of Life (EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20)

Quality of life has been defined by the WHO as "Individual's perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". [35] The QoL of the cancer survivors will be assessed by European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 tool. [36] It is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status QoL scale, and six single items. All of the scales and single-item measures scores range from 0 to 100. A high scale score represents a

higher response level. Specific questionnaires will also be administered to evaluate QoL of patients with brain tumors or Head & Neck Cancer via EORTC QLQ - BN20 and EORTC QLQ-H&N35, respectively. These tools have not been validated in Pakistan. However, in our study we will conduct content validation with a panel of experts and content validity index (CVI) will be calculated.

Socio-demography and Clinical Characteristics

The information will be collected on demographic variables like age, gender, ethnicity, education, family status, number of people actively working, monthly household income, and employment status of the individuals. Socioeconomic determinant factors will include; education, occupation, family income. Moreover comorbid conditions such as; hypertension, diabetes, cardiovascular disease and addiction history such as; use of tobacco (smoked and smokeless) and substance abuse will also be evaluated.

Data on important major recent life events such as: death of child, spouse or any other event that has affected their lives will also be collected. Clinical characteristics and management of brain tumor and head and neck cancer will also be assessed and information will be taken from the patients on; tumor type, site of tumor, type of surgery, type of chemotherapy and/or radiotherapy, etc.

Psycho-Social Characteristics

Depression and anxiety of the participants will be assessed using Hospital and Anxiety Depression Scale (HADS). [37] Moreover, we will also ask about the social support of the participants via Social Support by Enriched Social Support Instrument (ESSI). [38]

Hospital anxiety and depression (HADS)

Hospital Anxiety and Depression Scale (HADS) will be administered to assess the depression and anxiety among the participants. The tool was, developed to assess depression, anxiety and emotional distress among patients who were treated for a variety of clinical problems. [37]

Social support by Enriched Social Support Instrument (ESSI)

Social support can ease the coping process, or help people to overcome or adapt to a stress full event. The ESSI is a 7-item scale which primarily measures functional social support and in particular emotional support. A total score of 18 or less on items 1, 2, 3, 5 and 6 are considered to meet the ENRICHD based on low social support. [38]

Exploratory Questions to Evaluate Culturally Relevant Theme

Lastly, an explanatory questionnaire will be administered to examine the factors that have affected the life of the cancer patient and also to examine the different coping tactics that are used by the patients and their families to combat this disease.

Tool Validation

Since QoL tools: EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20 are not validated according to our cultural context, therefore, content validation will be performed by a panel of experts and content validity index (CVI) will be calculated. A panel of experts comprising of Head and Neck surgeons, neurosurgeons, oncologist, epidemiologist, biostatistician, and psychologist will review the tools and provide their expert suggestions for improvement of the tool according to our cultural context in our local language Urdu. Each and every expert will rate the tool regarding the relevancy and clarity of each question. The responses will be rated on a scale from; not relevant to highly relevant. Based on expert scores CVI will be calculated. CVI quantifies the level of content validity by calculating the percentage agreement between the experts. [39] A CVI of greater than 0.8 indicates high level of agreement

among the experts [40] Permission has been granted by the quality of life tool developers for content validation.

Statistical Analysis

Analysis will be performed using IBM SPSS Statistics version 22. Descriptive statistics will be computed for categorical variables by computing their frequencies and the quantitative variables will be computed by their Mean ± S.D or Median (IQR) as appropriate. Mean scores will be reported for resilience and QoL after treatment. Multiple Linear Regression technique will be applied to evaluate the effect of independent variables on the outcomes - resilience and QoL for head and neck patients and brain tumor patients. Adjusted β-coefficients with their 95% CI will be reported. A p-value of <0.05 will be considered statistically significant. In order to assess the relationship between resilience and QoL, correlation analysis will also be performed using Pearson or Spearman rank correlation coefficients as appropriate.

Ethical Considerations

Ethical approval has been obtained by Aga Khan University Karachi's Ethical Review Committee with ERC # 5154-Sur-ERC-17. Participants will be recruited from surgical clinics AKUH. Written informed consent will be taken from the participants by trained data collectors. Study procedure will be explained in detail to the study participants along with the potential risks and benefits associated in taking part in the study. The data collectors will be trained by the Principal Investigator (PI). In this particular study, there are no possible risks. However, the participants might feel anxious/ uncomfortable during the interview especially when their stress and depression level will be evaluated. To overcome this situation proper training will be provided to the research team for sensitive questions. Participants identified having depression will be counseled on spot by a trained psychologist. However, proper referrals will be made to a psychiatrist for those patients identified with severe depression especially with suicidal

intentions. Strict confidentiality and privacy rules will be followed; and it will be informed to the participants that their information will be kept confidential. Interviews will be conducted in a separate room. All study materials containing personal identifiers will be kept in a locked file cabinet. A unique study identification number will be assigned to each participant. After that data will be entered from hard copy into the electronic database that will be password protected and will be accessible only by the research staff of this study.

Discussion

This study protocol presents cross-sectional study regarding the assessment of resilience and QoL of head and neck cancer and brain tumor survivors in Karachi-Pakistan. To the best of our knowledge this will be the first in-depth study to explore the association and the effect of resilience on QoL of head and neck and brain tumor patients'.

Over the last few years, QoL has become an important health related outcome measure relevant to communities and healthcare systems. It is based on multidimensional concept which is difficult to define explicitly. QoL covers the subjective perceptions of positive and negative aspects of cancer patients' symptoms, including; physical, emotional, social and cognitive functions. It also covers the disease symptoms and the side effects of treatment. [41, 42] Around 20 years ago, there was limited literature available on QoL related benefits, however in recent years there has been an uplift in assessment of QoL in studies conducted in different parts of the world. [43] Despite of the fact that QoL plays an imperative role in altering patient's life in chronic diseases such as cancer, there is dearth of information from LMIC countries such as Pakistan, where cancer is becoming a major health issue.

Pakistan is the sixth most populous country in the world. Non-communicable diseases including cancers are taking the form of an epidemic and 150 000 new cases of cancer are reported each year, with 60%-80% deaths each year. The age-standardized ratios for cancers are 172/100

000 for females and 145/100 000 for males. [44] Despite of the graveness of this disease the total per person annual expenditure on health is less than 18$ in Pakistan. [45, 46] Moreover, the health system is not equipped enough to respond to the burden of this chronic disease. The treatment and management of cancer should be given priority however, it is imperative to identify the factors that may decline QoL and also identify strategies that would help in strengthening patients' resiliency mechanisms. [47] Resilience warrants to be targeted from initial phase of cancer diagnosis till the end stage as it represents the survivor's ability to protect their mental well-being when faced with adversity of cancer diagnosis. Resilience modifies over time with each phase of the cancer. Cancer survivors cope with life changes as they go through different phases of cancer diagnosis and treatment and continue to adapt themselves throughout these stages. Furthermore, cancer survivors meet additional challenges with adjusting to their "new normal" and the increased risk of poor physical and psychosocial outcomes. [48] The psychological distress that follows cancer diagnosis and treatment, negatively affects QoL. In this regard it is important to have knowledge of local factors that can affect resilience in Pakistani cancer population. This would help to plan cost effective interventions in the future.

This study will have several important implications such as; we will be to identify important factors that may affect the QoL and resilience among cancer survivors as well as assess the relationship between resilience and QoL. Moreover, this study will provide evidence to design and test intervention in the future to improve resilience, QoL and satisfaction towards life and to reduce depression and anxiety of cancer survivors. This study also aims to inform the healthcare providers and researchers regarding the protective or risk related characteristics for coping with cancer.

List of abbreviations

QoL	Quality of life
AKU	Aga Khan University
AKUH	Aga Khan University Hospital
PTSD	Post-Traumatic Stress Disorder
HR-QoL	Health-related quality of life
LMICs	Low And Middle Income Countries
HNC	head and neck cancers
CD-RISC	Connor–Davidson Resilience Scale
NCCN	National Comprehensive Cancer Network
SD	Standard Deviation

Declarations

Ethics approval and consent to participate

Study protocol is approved by Aga khan university ethical review committee with ERC # 5154-Sur-ERC-17. Written informed consent will be obtained from all the study participants.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors have no conflict of interest to declare. The funders have no role in study, data collection, analysis, decision to publish, or preparation of the manuscript. The content is solely

the responsibility of the authors and does not necessarily represent the official views of the funding body at Aga Khan University.

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Authors' contributions

NZ conceived the study, wrote and critically reviewed the manuscript. WK directly overlooked all aspects of study, wrote and critically reviewed the manuscript. SS and KA intellectually contributed to the study. IA, AJ, NA reviewed the study for overall quality and design robustness. MK and AE assisted as experts and informed aspects of development of the study intellectually. All authors have contributed intellectually to this manuscript. All authors have read and approved the final manuscript.

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Figure Legends

Figure 1: Conceptual Framework Of Resilience And Quality Of Life For Cancer Survivors Adapted From "The Adolescent Resilience Model" [49]

Figure 2: Participants Recruitment Plan Flow Diagram

Figure 1

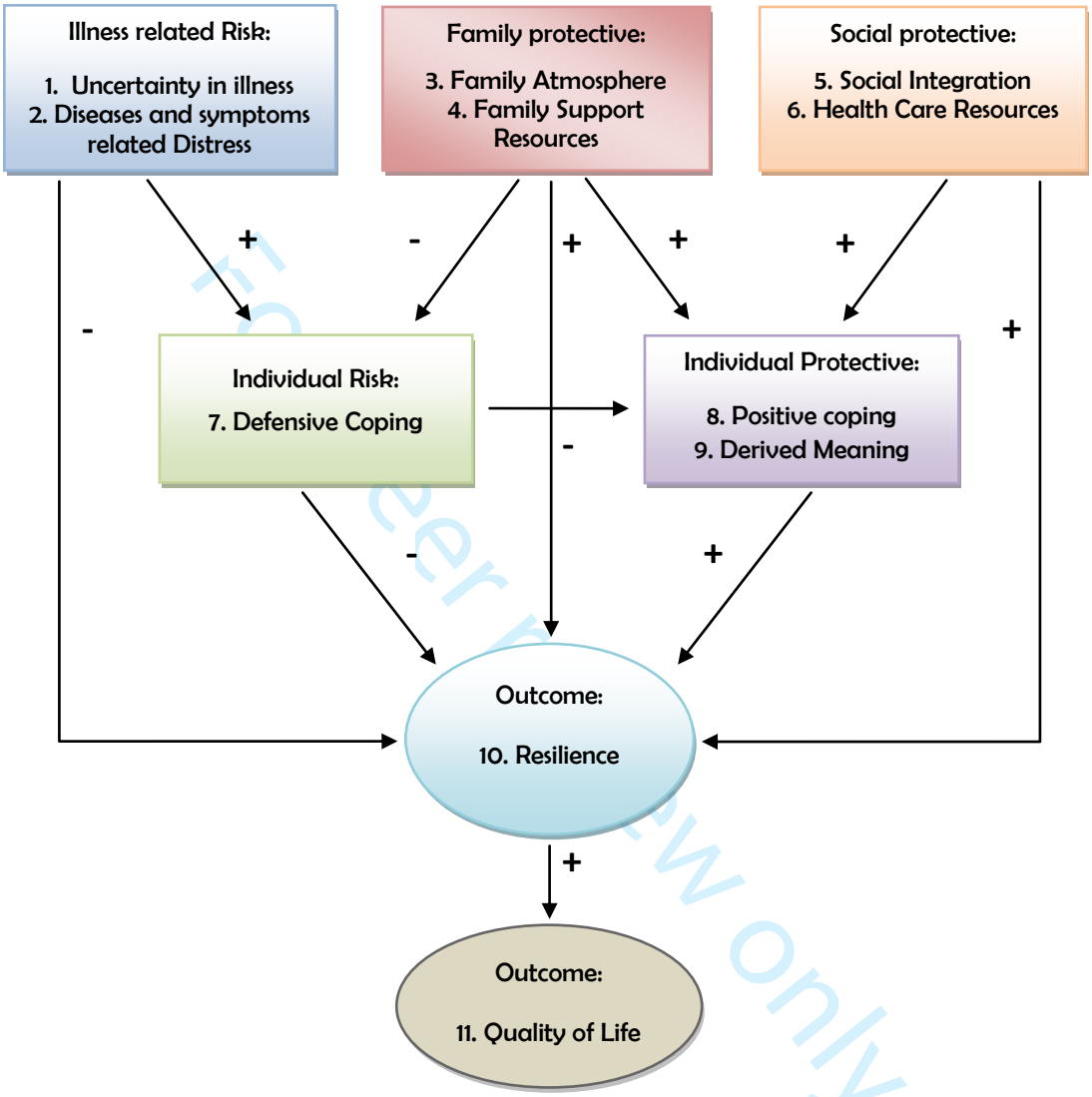
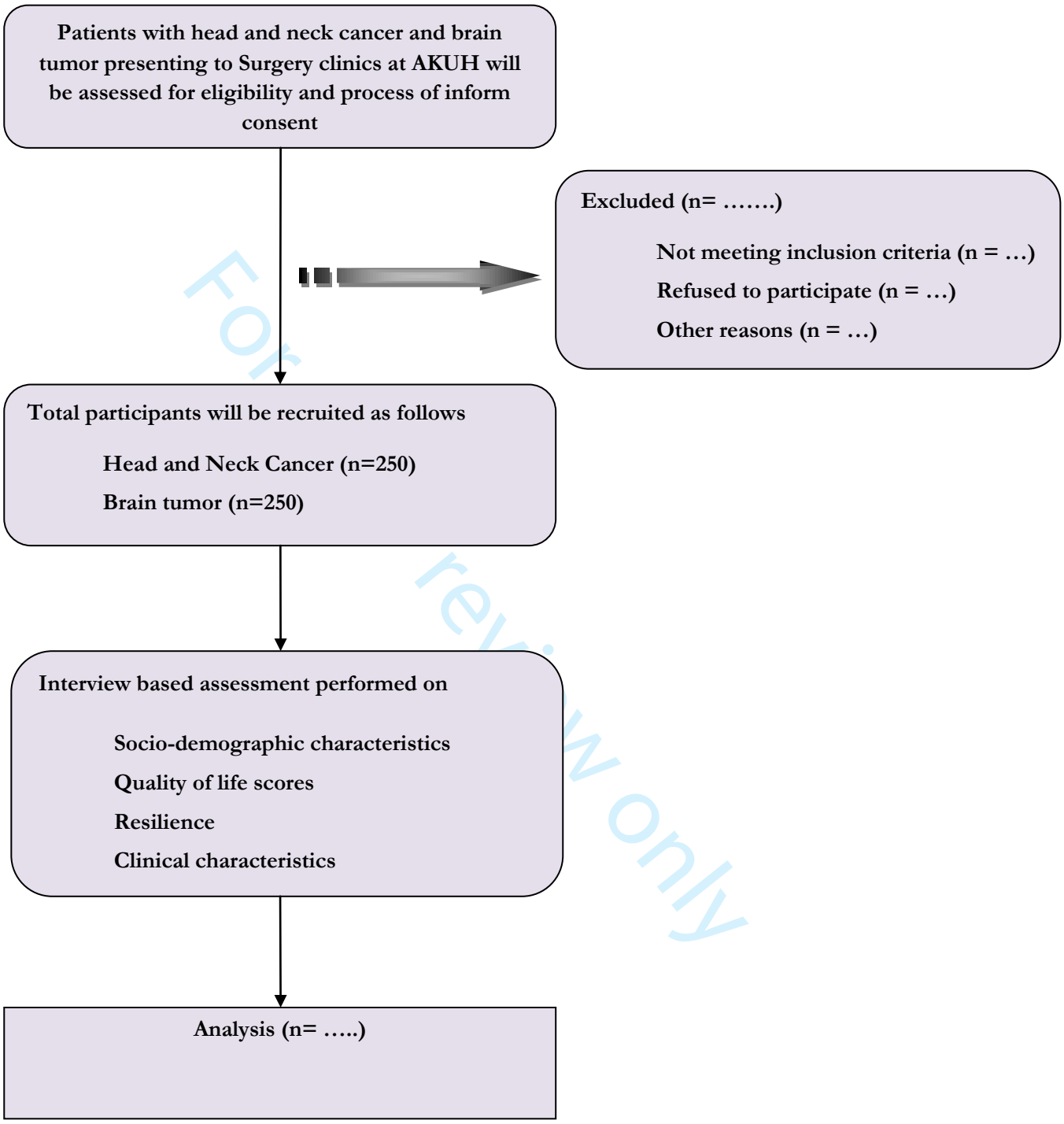


Figure 2



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

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-11
Bias	9	Describe any efforts to address potential sources of bias	*4 in strengths and limitations*
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			N/A
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	4
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*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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Resilience and Quality of life of Head & Neck Cancer and Brain Tumor Survivors in Pakistan; An Analytical Cross Sectional Study Protocol

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Resilience and Quality of life of Head & Neck Cancer and Brain Tumor Survivors in Pakistan; An Analytical Cross Sectional Study Protocol

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Abstract

Background: Cancer is a devastating disease and it has detrimental effect on quality of life (QoL) of cancer survivors. A large number of cancer patients suffer from clinically important symptoms of emotional distress that considerably lowers their QoL and resilience and potentially interferes with treatment compliance. The aim of the study is to assess resilience and QoL among cancer survivors and to evaluate the effect of important factors on resiliency and QoL relevant to our cultural context.

Method and Analysis: A cross-sectional study will be conducted at a tertiary care hospital in Karachi, Pakistan. The Sample size was calculated using one population mean formula. We will require a minimum sample size of 250 head and neck cancers and 250 brain tumor survivors with 10% inflation for non-response rate, with standard deviation (SD) of QoL and resilience ranging from 16.5 to 40.8 and from 12. 7 to 34.1 for head and neck cancer and for brain tumor respectively, at 5 % level of significance and with a precision of 2.5 . QoL will be assessed by EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20) and resilience will be evaluated by Wagnild & Young's 14 item scale. To unfold the locally relevant themes open ended questions will also be administered. Mean ± SD will be reported for resilience and QoL scores. To assess the association of different factors with the outcomes. unadjusted and adjusted β-coefficient with 95% CI will be reported by using multiple linear regression. Correlation analysis will also be performed using Pearson or Spearman rank correlation coefficients as appropriate. A *p*-value of <0.05 will be considered as significant.

Ethics and Dissemination: Ethical approval has been obtained from Aga Khan University Karachi's Ethical Review Committee. Written informed consent will be taken from the participants by trained research assistants. Study procedure will be explained to the participants along with its potential risks and benefits. On-spot counseling will be given to participants by a trained psychologist and those identified with severe depression will be referred to a psychiatrist. All study materials containing personal identifiers will be kept in lock and key and the electronic database will be password protected and accessed only by the research staff of this study. The study findings will be disseminated to health care professionals, rehabilitation experts, psychologist and to cancer patients through: 1. Publications 2. Presentations at conferences and workshops. 3. Research briefs.

ClinicalTrials.gov Identifier: NCT03466762 https://clinicaltrials.gov/ct2/show/NCT03466762

Keywords: *Quality of life, Resilience, Cancer Survivors, Post-Cancer Depression,*

Summary:

Strengths and Limitations

- I will use validated measures for evaluating the outcome and independent variables.
- The investigators will randomly assess each data collector's work via spot-checks to increase the overall quality of the study
- My study results can be generalizable only to all those cancer patients presenting to tertiary care private hospitals of Pakistan.
- As there is no comparative group therefore, Subgroup analysis will be perfomed by stratification inside the 2 groups to compare the QoL and resilience

Background

Cancer is the second leading cause of death globally. [1] About 70% of the deaths due to cancer are witnessed by Lower Middle Income Countries (LMIC). Globally Head and Neck cancers are one of the most common cancers with nearly 600,000 new cases and 300,000 deaths occurring annually. [2, 3] Moreover, brain tumors are also responsible for approximately 2% of all cancer deaths with an overall incidence of 4-5/100,000 population per year. [4] Pakistan is the sixth most populous country in the world. Non-communicable diseases including cancers are taking the form of an epidemic and 150 000 new cases of cancer are reported each year, with 60%-80% deaths each year. The age-standardized ratios for cancers are 172/100 000 for females and 145/100 000 for males. [5] Despite the graveness of this disease the total per person annual expenditure on health is less than $18 in Pakistan. [6, 7] Moreover, the health system is not equipped enough to respond to the burden of this chronic disease. [8]

Cancer is potentially a life-threatening disease and often leads to psychological distress or trauma. [9] Certainly, cancer patients suffer clinically important symptoms of emotional distress such as depression and anxiety [10] that considerably lowers their QoL and resilience and potentially interferes with treatment compliance. [11] [12]

The broad concept of resilience has been introduced recently stating the protective attributes of an individual in adapting to cancer. [9] Resilience of cancer survivors can be accounted on their baseline characteristics or personality traits which enable individuals to thrive in the face of adversity. These baseline characteristics include; basic demographic factors and personal resources, such as; hope (positive readiness and expectancy), motivation, optimism, sense of coherence (i.e., recognizing the world as a meaningful and predictable place), preexisting social support, and spirituality. [13] The other possible factor that might influence ones resiliency is positive adaptation that changes over time and protects one against psychological distress [14]

and presence of positive psychosocial functioning that may enable a person to deal with traumatic stress. [15] It has been observed that individuals with high resilience have coped up with traumatic events more efficiently than those with low resilience. [16] Moreover, higher resilience has been associated with reduced emotional distress after exposure to traumatic events. [17]

Resilience has an important impact on QoL of a cancer patient. Over the last few years, QoL has become an important health related outcome measure relevant to communities and healthcare systems. It is based on multidimensional concept which is difficult to define explicitly. QoL covers the subjective perceptions of positive and negative aspects of cancer patients' symptoms including; physical, emotional, social and cognitive functions. It also covers the disease symptoms and the side effects of treatment. [18, 19]

QoL has two fundamental premises; firstly, a multi-dimensional concept incorporating physical, psychological, social, and emotional functional domains. Secondly it is subjective and must be self-reported, according to the patients' own experiences. The positive and negative factors that can influence a cancer patient's resilience and QoL are; 1. Illness-related risk: which is perceived illness, ambiguity and complexity, stress of symptoms and severity of illness

2. Family protective factors: which is perceived social support from family and socioeconomic variables, 3. Social protective factors: which is perceived social support from friends, influence of others with similar condition and perceived support from providers 4. Individual risk factors: which is evasive, emotive, and fatalistic coping 5. Individual protective factors: which is confrontive, optimistic, and supportant coping with hope and spiritual perspectives. (Figure 1)

Several studies from different parts of the world suggest that resilience is a protective factor for distress among cancer survivors. [9, 20-23] Studies have examined influence of psychological resilience among cancer patients. [24, 25] which indicates that cancer patients with high

resilience may be less dependent on psychosocial support to manage their stressful conditions relative to those with low resilience. [24] A study reported that resilience was likely to mediate the adverse relationship between cancer symptoms, distress and QoL among cancer survivors, indicating that resilience might play an essential role in protecting them against adverse effects of cancer symptoms. [20] A systematic review of 24 studies on head and neck cancer patients reported that distress-related variables (depression, anxiety, distress) were most oftenly reported to have a negative association with QoL outcomes. [26]

Identifying the association of psychological variables with post-treatment QoL is essential in early identification of those at risk for poorer outcomes and would aid in development of interventions to promote QoL in this population. [26]

Resilience and QoL changes over time and may be modifiable towards increased well-being therefore, it is important that before initiating treatment, patients should be referred to a mental health professional for psychological evaluation. Although QoL plays an essential role in altering patient's life in chronic diseases such as cancer, there is dearth of information from LMIC countries such as Pakistan, where cancer is becoming a major health issue. Hence, it is imperative to understand the local factors that can affect resilience and QoL in Pakistani cancer population. This would help in planning cost effective interventions in the future. To the best of my knowledge, this will be the first in-depth study to evaluate resilience and QoL among head & neck cancer and brain tumor patients in Pakistan. This study will have several important implications such as; I will be able to assess the QoL and resilience of cancer survivors and also identify the important factors that may affect the QoL and resilience among these patients. Moreover, it will also enable me to assess the relationship between resilience and QoL in these patients . This study will provide evidence to design and test intervention in the future to improve resilience and QoL and to reduce depression and anxiety of cancer survivors. This

study also aims to inform the healthcare providers and researchers regarding the protective or risk related characteristics for coping with cancer.

Therefore, in the light of literature the study's research questions/ objectives are as follows:

- To determine resilience and quality of life scores for head & neck cancer and Brain tumor patients at-least 4 weeks post-treatment.
- To evaluate important factors (such as; depression, anxiety, social support etc) associated with resilience and quality of life after treatment for head & neck cancer and brain tumor patients in Pakistan.
- To examine the relationship between resilience and quality of life after treatment for head & neck cancer and Brain tumor patients in Pakistan.

Methods

Study Design

To evaluate resilience and QoL among head & neck cancer and Brain tumor patients and their associated factors, an analytical cross sectional study will be conducted. Resilience and QoL will be measured atleast 4 weeks post treatment.

Study Setting

The study will be conducted at Aga Khan University (AKU) which is a JCIA-accredited hospital, in Karachi-Pakistan. Karachi is the largest metropolitan city of Pakistan, a home to all major ethnicities living in Pakistan. AKU is one of the largest private tertiary care hospitals; it consists of multidisciplinary team that provides comprehensive care to cancer patients. AKU caters to different ethnic and socioeconomic groups of Karachi population. The participants will be recruited from surgical/oncology clinics at AKU. The proposed duration of data collection will be from 4-6 months.

Study Participants

Men and women greater than 18 years, who have received treatment for brain tumor and head & neck cancer at AKU, fulfilling the below eligibility criteria will be recruited.

Eligibility Criteria

Inclusion Criteria

- Individual aged atleast 18 years including both male and female.
- Patients with confirmed diagnosis of head and neck cancer and brain tumor by histopathology (evaluated from medical records).
- Patients who had received treatment (surgery/chemotherapy/radiotherapy) at AKUH for head & neck cancer and/or brain tumor.
- Cancer survivors living in Pakistan for atleast the last three months.

Exclusion Criteria

- Known cases of any psychiatric illness leading to disability (e.g. manic disorder, schizophrenia etc.) confirmed by medical records will be excluded from the study as they may be on medications, hence this might distort the true results.
- Patients on anti-depressants prescribed by a psychiatrist.
- Participant with terminal disease like renal failure and stroke will be excluded because these diseases also have profound effect on QoL and resilience.

Sampling Technique

This study will use purposive sampling technique for selection of the participants. Purposive sampling involves study participants selection criteria based on certain characteristics. The key objective of purposive sampling is to focus on population features that are of interest to the researcher, who can answer the study questions. My target population i.e. brain tumor and head

and neck cancer patients who have received cancer treatment will be approached and they will be screened using our eligibility criteria by trained research assistants. Those who will fulfillthe eligibility criteria and will be willing to give informed consent will be enrolled in the study (Figure 2)

Sample Size Calculation

Head and Neck Cancer: The Sample size was calculated using one population mean formula. Mean scores for QoL and resilience for head and neck cancer patients were identified from literature. The reported standard deviation (SD) for QoL and resilience ranges from 16.5 to 40.8 at 5 % level of significance, with a precision of 2.5 and adjusting the sample size for 10% non-response rate, the minimum sample size estimated was 250 head and neck cancers patients. [27-32]

Brain Tumor: The Sample size was calculated using one population mean formula. Mean scores for QoL and resilience for brain tumor patients were identified from the literature. The reported standard deviation (SD) for QoL and resilience ranges from 12. 7 to 34.1, at 5 % level of significance, with a precision of 2.5 and adjusting the sample size for 10% non-response rate, the minimum sample size estimated was 250 brain tumor patients. [33-36]

Assessment Tools

Resilience (Wagnild & Young's 14 Item)

Resilience is the ability to rebound or spring back, the power of something to resume its original shape or position after compression or bending. [37] Resilience is also defined as the 'capacity of individuals exposed to a negative event, to maintain stability, healthy physical and psychological functioning. However, few are of the view that it is a defense mechanism, which permits people to grow in the face of adversity. [38] It has two versions, a long 25-item and short 14 item scale, using a 7-point rating likert scale. It comprises of five core characteristics of

resilience that includes: purposeful life, perseverance, equanimity, self-reliance and existential loneliness. [39] A high score represents better resilience. The respondent's choice ranges from 1 (Strongly Disagree) to 7 (Strongly Agree). The scale uses total scores rather than scores of individual items. To measure resilience, I will use Resilience Scale 14 (RS-14) which has been validated in Pakistan. It showed moderate negative correlation with the depression and anxiety (r = -0.31), and moderate positive significant correlation with life satisfaction (r = 0.40). The test-retest correlation coefficients and Cronbach's alpha for RS-14 was 0.49 and 0.76 respectively. [40]

Quality Of Life (EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20)

Quality of life has been defined by the WHO as "Individual's perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". [41] The QoL of the cancer survivors will be assessed by European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 tool. [42] It is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status QoL scale, and six single items. All the scales and single-item measures scores range from 0 to 100. A high score of the scale represents a higher response level. Specific questionnaires will also be administered to evaluate QoL of patients with brain tumors or Head & Neck Cancer via EORTC QLQ - BN20 and EORTC QLQ-H&N35, respectively. These tools have not been validated in Pakistan. However, in my study I will conduct content validation with a panel of experts and content validity index (CVI) will be calculated.

Socio-demography and Clinical Characteristics

The information will be collected on demographic variables like; age, gender, ethnicity, education, family status, number of people actively working, monthly household income, and

employment status of the individuals. Socioeconomic determinant factors will include; education, occupation, family income. Moreover comorbid conditions such as; hypertension, diabetes, cardiovascular disease and addiction history such as; use of tobacco (smoked and smokeless) and substance abuse will also be evaluated.

Data on important major recent life events such as: death of child, spouse or any other event that has affected their lives will also be collected. Clinical characteristics and management of brain tumor and head and neck cancer will also be assessed and information will be taken from the patients on; tumor type, site of tumor, type of surgery, type of chemotherapy and/or radiotherapy, etc.

Psycho-Social Characteristics

Depression and anxiety of the participants will be assessed using Hospital and Anxiety Depression Scale (HADS). [43] Moreover, we will also ask about the social support of the participants via Social Support by Enriched Social Support Instrument (ESSI). [11]

Hospital anxiety and depression (HADS)

Hospital Anxiety and Depression Scale (HADS) will be administered to assess the depression and anxiety among the participants. The tool was, developed to assess depression, anxiety and emotional distress among patients who were treated for a variety of clinical problems. The HADS encompasses 14 items, equally subdivided into two scales measuring anxiety and depression. For instance, the item 'Worrying thoughts go through my mind' assesses anxiety, whereas the item 'I have lost interest in my appearance' evaluates the level of depression. All items need to be answered on an ordinal four-point response scale. [43] To measure anxiety and depression I will use urdu version of HADS that has been translated and evaluated in urdu . [44]

Social support by Enriched Social Support Instrument (ESSI)

Social support can ease the coping process, or help people overcome or adapt to a stress full event. The ESSI is a 7-item scale which primarily measures functional social support and in particular emotional support. A total score of 18 or less on items 1, 2, 3, 5 and 6 are considered to meet the ENRICHD based on low social support. [11] To assess social support I will use this tool that has been validated in Pakistan with, content validity index (CVI) for relevance and clarity of 0.95 and 0.97 respectively and cronbach-alpha 0.82 [45]

Exploratory Questions to Evaluate Culturally Relevant Theme

Lastly, an explanatory questionnaire will be administered to examine the factors that have affected the life of the cancer patient and also to examine the different coping tactics that are used by the patients and their families to combat this disease.

Tool Validation

Since QoL tools, EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20 are not validated according to our cultural context, therefore, content validation will be performed by a panel of experts and content validity index (CVI) will be calculated. A panel of experts comprising of Head and Neck surgeons, neurosurgeons, oncologist, epidemiologist, biostatistician, and psychologist will review the tools and provide their expert suggestions for improvement of the tool according to our cultural context in our local language Urdu. Each and every expert will rate the tool regarding the relevancy and clarity of each question. The responses will be rated on a scale from; not relevant to highly relevant. Based on expert scores CVI will be calculated. CVI quantifies the level of content validity by calculating the percentage agreement between the experts. [46] A CVI of greater than 0.8 indicates high level of agreement among the experts [47] Permission has been granted by the quality of life tool developers for content validation.

Statistical Analysis

Analysis will be performed using IBM SPSS Statistics version 22. Descriptive statistics will be computed for categorical variables by computing their frequencies and the quantitative variables will be computed by their Mean ± S.D or Median (IQR) as appropriate. Mean scores will be reported for resilience and QoL after treatment. Multiple Linear Regression technique will be used to evaluate the effect of independent variables on the outcomes - resilience and QoL for head and neck patients and brain tumor patients. Adjusted β-coefficients with their 95% CI will be reported. A p-value of <0.05 will be considered statistically significant. To assess the relationship between resilience and QoL, correlation analysis will also be performed using Pearson or Spearman rank correlation coefficients as appropriate.

Ethical Considerations

Ethical approval has been obtained by Aga Khan University Karachi's Ethical Review Committee with ERC # 5154-Sur-ERC-17. Participants will be recruited from surgical clinics AKUH. Written informed consent will be taken from the participants by trained data collectors. Study procedure will be explained in detail to the study participants along with the potential risks and benefits associated in taking part in the study. The data collectors will be trained by the Principal Investigator (PI). In this particular study, the participants might feel anxious/ uncomfortable during the interview especially when their stress and depression level will be evaluated. To overcome this situation proper training will be provided to the research team for sensitive questions. Participants identified having depression will be given on spot counseling by a trained psychologist. However, proper referrals will be made to a psychiatrist for those patients identified with severe depression especially with suicidal intentions. Strict confidentiality and privacy rules will be followed; and it will be informed to the participants that their information will be kept confidential. Interviews will be conducted in a separate room. All study materials

containing personal identifiers will be kept in a locked file cabinet. A unique study identification number will be assigned to each participant. The data will entered into an electronic database that will be password protected and will be only accessible by the PI and the research staff of this study.

The Patient and Public Involvement:

It will be a cross sectional study design and the partcipants will be interviewed regarding their; sociodemographic factors, anxiety, depression , resilience and quality of life by trained research assistants .

The study findings will be disseminated to different stakeholders such as health care professionals, rehabilitation experts, psychologist and to cancer patients through : 1. Publications at local, national and international journals 2. Presentations at conferences and workshops. 3. Research briefs.

List of abbreviations

QoL	Quality of life
AKU	Aga Khan University
AKUH	Aga Khan University Hospital
PTSD	Post-Traumatic Stress Disorder
HR-QoL	Health-related quality of life
LMICs	Low And Middle Income Countries
HNC	head and neck cancers
CD-RISC	Connor–Davidson Resilience Scale
NCCN	National Comprehensive Cancer Network
SD	Standard Deviation
CVI	Content validity Index

Declarations

Ethics approval and consent to participate

Study protocol is approved by Aga khan university ethical review committee with ERC # 5154-Sur-ERC-17. Written informed consent will be obtained from all the study participants.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors have no conflict of interest to declare. The funders have no role in study, data collection, analysis, decision to publish, or preparation of the manuscript. The content is solely

the responsibility of the authors and does not necessarily represent the official views of the funding body at Aga Khan University.

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Authors' contributions

NZ conceived the study, wrote and critically reviewed the manuscript. WK directly overlooked all aspects of study, wrote and critically reviewed the manuscript. SS and KA intellectually contributed to the study. IA, AJ, NA reviewed the study for overall quality and design robustness. MK and AE assisted as experts and informed aspects of development of the study intellectually. All authors have contributed intellectually to this manuscript. All authors have read and approved the final manuscript.

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Figure Legends

Figure 1: Conceptual Framework Of Resilience And Quality Of Life For Cancer Survivors Adapted From "The Adolescent Resilience Model" [48]

Figure 2: Participants Recruitment Plan Flow Diagram

Figure 1

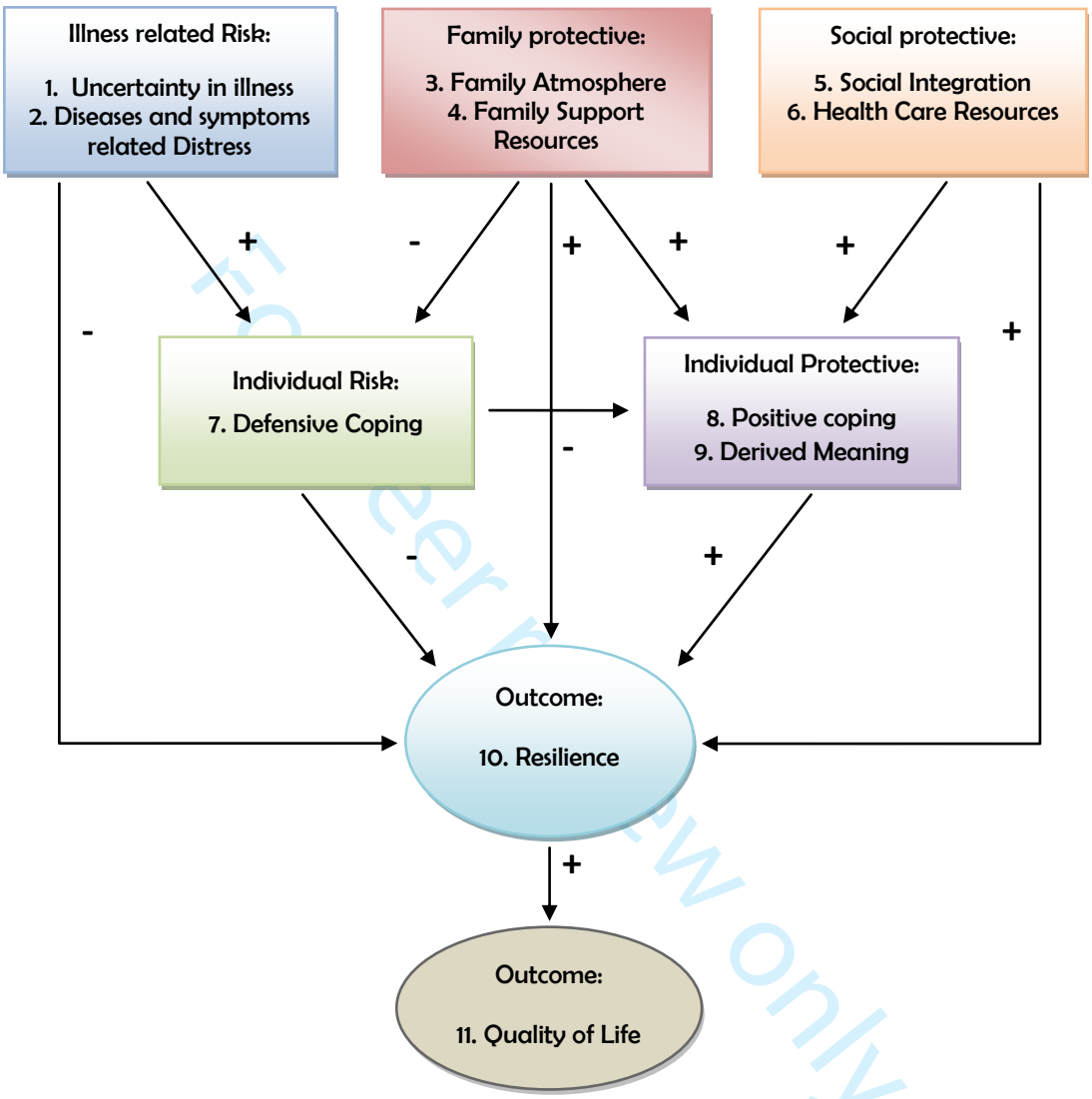
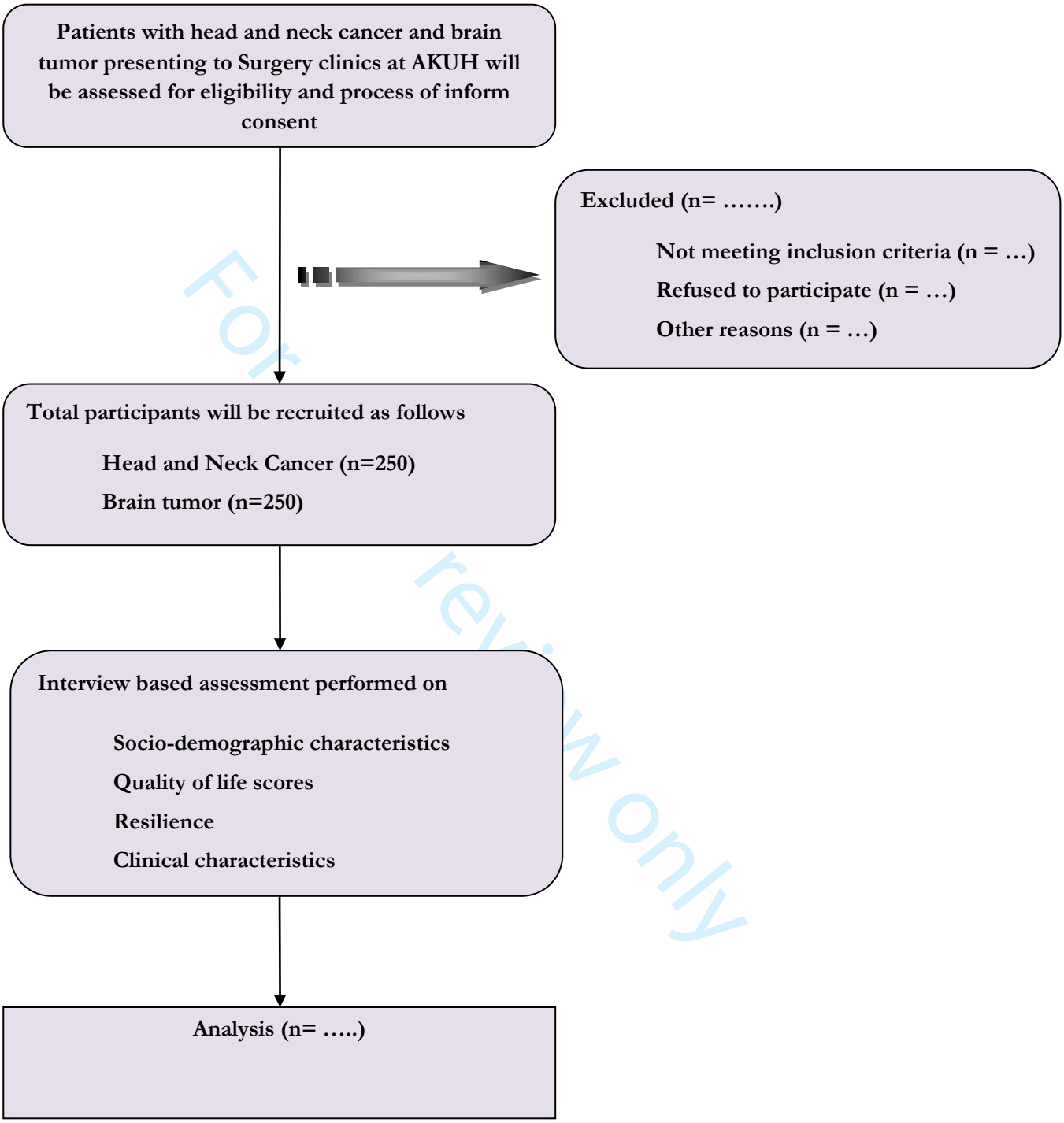


Figure 2



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

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-11
Bias	9	Describe any efforts to address potential sources of bias	*4 in strengths and limitations*
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			N/A
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	4
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*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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Resilience and Quality of life of Head & Neck Cancer and Brain Tumor Survivors in Pakistan; An Analytical Cross Sectional Study Protocol

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Resilience and Quality of life of Head & Neck Cancer and Brain Tumor Survivors in Pakistan; An Analytical Cross Sectional Study Protocol

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Abstract

Background: Cancer is a devastating disease and has detrimental effect on quality of life (QoL) of cancer survivors. Cancer patients suffer from clinically important symptoms of emotional distress that significantly reduces their QoL and resilience and interferes with their treatment compliance. The aim of the study is to assess resilience and QoL among cancer survivors and to evaluate the important factors affecting their resilience and QoL relevant to our cultural context.

Method and Analysis: A cross-sectional study will be conducted at a tertiary care hospital in Karachi, Pakistan. The Sample size was calculated using one population mean formula. We will require a minimum sample size of 250 head and neck cancers and 250 brain tumor survivors with 10% inflation for non-response rate, with standard deviation (SD) of QoL and resilience ranging from 16.5 to 40.8 and 12.7 to 34.1 for head and neck cancer and for brain tumor respectively, at 5 % level of significance, with a precision of 2.5. QoL will be assessed by EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20) and resilience will be evaluated by Wagnild & Young's 14 item scale. To unfold the locally relevant themes open ended questions will also be administered. Mean ± SD will be reported for resilience and QoL scores. Unadjusted and adjusted β- coefficient with 95% CI will be reported by using multiple linear regression to assess the association of different factors with the outcomes. Correlation analysis will also be performed using Pearson or Spearman rank correlation coefficients as appropriate. A *p*-value of <0.05 will be considered as significant.

Ethics and Dissemination: Ethical approval has been obtained from Aga Khan University Karachi's Ethical Review Committee. Written informed consent will be taken from the participants by trained research assistants. Study procedure and its potential risks and benefits will be explained to the participants. Trained psychologist will provide on-spot counseling to the participants and those identified with severe depression will be referred to a psychiatrist. The study materials and the electronic data base will be kept in lock and key and will be password protected and only accessed by the research team. The study findings will be disseminated to health care professionals, rehabilitation experts, psychologist and to cancer patients through: 1. Publications 2. Presentations at conferences and workshops. 3. Research briefs.

ClinicalTrials.gov Identifier: NCT03466762 https://clinicaltrials.gov/ct2/show/NCT03466762

Keywords: *Quality of life, Resilience, Cancer Survivors, Post-Cancer Depression,*

Summary:

Strengths and Limitations

- We will use validated measures for evaluating the outcome and independent variables.
- The overall quality of the study will be maintained by random spot-checks.
- Our study results can be generalized on all cancer patients presenting to private tertiary care hospitals of Pakistan.
- To compare the QoL and resilience within these two groups of patients subgroup analysis will be performed by stratification.

Background

Globally cancer is the second leading cause of death. [1] Approximately 70% of the deaths witnessed by Lower Middle Income Countries (LMIC) is due to cancer. Head and Neck cancers are one of the most common cancers with nearly 600,000 new cases and 300,000 deaths occurring annually. [2, 3] While, approximately 2% of all cancer deaths with an overall incidence of 4-5/100,000 population per year occurs due to brain tumor. [4] Pakistan is the sixth most populous country in the world. Annually about 150 000 new cases of cancer are reported, with 60%-80% deaths. The age-standardized ratios for cancers of females and males are 172/100000 and 145/100000 respectively. . [5] However, despite of the graveness of the disease, in Pakistan the total annual expenditure on health per person is less than $18. [6, 7] Moreover, the health systems are not well-equipped to tackle the burden of this chronic disease. [8]

Cancer is a life-threatening disease and often leads to psychological distress or trauma. [9] Cancer patients suffer clinically important symptoms of emotional distress such as depression and anxiety [10] that reduces their QoL and resilience and interferes with their treatment compliance. [11] [12]

The concept of resilience from a range of disciplinary perspectives has been recently introduced [9] Resilience among cancer survivors enables them to promote a resilient disposition towards life stressors and can be accounted on their baseline characteristics or personality traits. These baseline characteristics include; basic demographic factors and personal resources, such as; hope (positive readiness and expectancy), motivation, optimism, sense of coherence (i.e., recognizing the world as a meaningful and predictable place), preexisting social support, and spirituality. [13] The other possible factor that might influence ones resiliency is positive adaptation that changes over time and protects one against psychological distress [14] and

presence of positive psychosocial functioning that may enable a person to deal with traumatic stress. [15] Individuals with high resilience cope up more efficiently to traumatic events as compared to those with low resilience. [16] Moreover, higher resilience is associated with reduced emotional distress after exposure to traumatic events. [17]

Resilience has an important impact on QoL of a cancer patient. QoL has become an important health related outcome measure relevant to communities and healthcare systems over the last few years. . It is based on multidimensional concept and it incorporates: the subjective perceptions of positive and negative aspects of cancer symptoms including; physical, emotional, social and cognitive functions, the disease symptoms and the side effects of treatment. [18, 19]

QoL has two fundamental premises; firstly, a multi-dimensional concept incorporating physical, psychological, social, and emotional functional domains. Secondly it is subjective and must be self-reported, according to the patients' own experiences. The positive and negative factors that can influence a cancer patient's resilience and QoL are; 1. Illness-related risk: which is perceived illness, ambiguity and complexity, stress of symptoms and severity of illness

2. Family protective factors: which are perceived social support from family and socioeconomic variables, 3. Social protective factors: which include; perceived social support from friends, influence of others with similar condition and perceived support from providers 4. Individual risk factors: which are evasive, emotive, and fatalistic coping 5. Individual protective factors: which include confrontive, optimistic, and supportant coping with hope and spiritual perspectives. (Figure 1)

Several studies from different parts of the world suggest that resilience is a protective factor for distress among cancer survivors. [9, 20-23] Studies have examined influence of psychological resilience among cancer patients. [24, 25] which indicates that cancer patients with high

resilience need less psychosocial support to manage their stressful conditions relative to those with low resilience. [24] A study reported that resilience mediates adverse relationship between cancer symptoms, distress and QoL among cancer survivors. Hence, resilience plays an imperative role in protecting them against adverse effects of cancer symptoms. [20] A systematic review of 24 studies on head and neck cancer patients reported that distress-related variables (depression, anxiety and distress) have a negative association with QoL outcomes. [26]

Early identification of psychological variables associated with post-treatment QoL is essential among those at increased risk of poorer outcomes as it would aid in development of interventions to improve their QoL. [26]

Resilience and QoL changes over time and may be modifiable towards increased well-being therefore, before initiating treatment, patients should be referred to mental health professionals for psychological evaluation. Although QoL plays an imperative role in altering patient's life in chronic diseases such as cancer, there is dearth of information from LMIC countries such as Pakistan, where cancer is becoming a major health issue. Hence, it is imperative to understand the factors that can affect resilience and QoL in Pakistani cancer population. This would enable us in planning cost effective interventions in the future. To the best of our knowledge, this will be the first in-depth study to evaluate resilience and QoL among head & neck cancer and brain tumor patients in Pakistan. This study will have several important implications such as; we will be able to assess the QoL and resilience of cancer survivors and also identify the important factors that may affect the QoL and resilience among these patients. Moreover, it will also enable us to assess the relationship between resilience and QoL in these patients . This study will also provide evidence to design and test intervention in the future to improve resilience and QoL and reduce depression and anxiety among cancer survivors. This study also aims to

inform the healthcare providers and researchers regarding the protective or risk related characteristics for coping with cancer.

Therefore, in the light of literature the study's research questions/ objectives are as follows:

- To determine resilience and quality of life scores for head & neck cancer and Brain tumor patients at-least 4 weeks post-treatment.
- To evaluate important factors (such as; depression, anxiety, social support etc) associated with resilience and quality of life after treatment for head & neck cancer and brain tumor patients in Pakistan.
- To examine the relationship between resilience and quality of life after treatment for head & neck cancer and Brain tumor patients in Pakistan.

Methods

Study Design

To evaluate resilience and QoL among head & neck cancer and Brain tumor patients and their associated factors, an analytical cross sectional study will be conducted. Resilience and QoL will be measured atleast 4 weeks post treatment.

Study Setting

The study will be conducted at Aga Khan University (AKU) which is a JCIA-accredited hospital, in Karachi-Pakistan. Karachi is the largest metropolitan city of Pakistan, a home to all major ethnicities living in Pakistan. AKU is one of the largest private tertiary care hospitals; it consists of multidisciplinary team that provides comprehensive care to cancer patients. AKU caters to different ethnic and socioeconomic groups of Karachi population. The participants will be recruited from surgical/oncology clinics at AKU. The proposed duration of data collection will be 4-6 months.

Study Participants

Men and women greater than 18 years, who have received treatment for brain tumor and head & neck cancer at AKU, fulfilling the below eligibility criteria will be recruited. The reason why we are studying these two groups in our study is firstly, according to a recent data the prevalence of head and neck tumor is increasing in Pakistan and there is limited information on QoL in these patients from our context. Secondly, brain tumor is an understudied area in Pakistan and there is dearth of information regarding QoL in these patients. However, to maintain internal validity these two groups will be studied on assumptions pertained to the respective group i.e the tools we will use are exclusive to each cancer type. The sample size was calculated based on assumption for both the groups separately and they will also be analyzed separately.

Eligibility Criteria

Inclusion Criteria

- Individual aged atleast 18 years including both male and female.
- Patients with confirmed diagnosis of head and neck cancer and brain tumor by histopathology (evaluated from medical records).
- Patients who had received treatment (surgery/chemotherapy/radiotherapy) at AKUH for head & neck cancer and/or brain tumor.
- Cancer survivors living in Pakistan for atleast three months.

Exclusion Criteria

- Known cases of any psychiatric illness leading to disability (e.g. manic disorder, schizophrenia etc.) confirmed by medical records will be excluded from the study as they may be on medications, that might distort our true results.
- Patients on anti-depressants prescribed by a psychiatrist

- We will exclude participants with physical comorbidities, stroke and renal failure because these are debilitating diseases that will distort our results. The reasons for not excluding CVD/heart failure, diabetes, COPD are; firstly, these are not debilitating diseases and secondly, around 1 in 4 Pakistani suffers from cardiovascular risk factors, therefore ,excluding these conditions will make majority of the participants ineligible and we will not be able to achieve our sample size. However, we can adjust these co-morbid conditions on analysis

Sampling Technique

This study will use purposive sampling technique for selection of the participants. Our target population i.e. brain tumor and head and neck cancer patients who have received cancer treatment will be approached by research assistants who will be responsible for data collection. The nurse at the clinic will hand over the list of appointments one day prior, to the research assistants who will identify the participants with head and neck cancer and/or brain tumor. On the day of appointment they will screen the participants for eligibility by administering a screening tool, if they fulfill our eligibility criteria and give consent to participate, they will be enrolled in the study. (Figure 2)

Sample Size Calculation

Head and Neck Cancer: The Sample size was calculated using one population mean formula. Mean scores for QoL and resilience for head and neck cancer patients were identified from literature. The reported standard deviation (SD) for QoL and resilience ranges from 16.5 to 40.8 at 5 % level of significance, with a precision of 2.5 and adjusting the sample size for 10% non-response rate, the minimum sample size estimated was 250 head and neck cancers patients. [27-32]

Brain Tumor: The Sample size was calculated using one population mean formula. Mean scores for QoL and resilience for brain tumor patients were identified from the literature. The reported standard deviation (SD) for QoL and resilience ranges from 12. 7 to 34.1, at 5 % level of significance, with a precision of 2.5 and adjusting the sample size for 10% non-response rate, the minimum sample size estimated was 250 brain tumor patients. [33-36]

Assessment Tools

Resilience (Wagnild & Young's 14 Item)

Resilience is the ability to rebound or spring back, the power of something to resume its original shape or position after compression or bending. [37] Resilience is also defined as the 'capacity of individuals exposed to a negative event, to maintain stability, healthy physical and psychological functioning. However, few are of the view that it is a defense mechanism, which permits people to grow in the face of adversity. [38] The resilience tool has two versions, a long 25-item and short 14 item scale, using a 7-point rating likert scale. It comprises of five core characteristics of resilience that includes: purposeful life, perseverance, equanimity, self-reliance and existential loneliness. [39] A high score represents better resilience. The respondent's choice ranges from 1 (Strongly Disagree) to 7 (Strongly Agree). The scale uses total scores rather than scores of individual items. To measure resilience, we will use validated urdu version of the resilience Scale 14 (RS-14) which indicates moderate negative correlation of resilience with depression and anxiety (r = -0.31), and moderate positive significant correlation of resilience with life satisfaction (r = 0.40). The test-retest correlation coefficients and Cronbach's alpha for RS-14 was 0.49 and 0.76 respectively. [40]

Quality Of Life (EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20)

Quality of life is defined by the WHO as “Individual’s perceptions of their position in life in the context of the culture and value systems and their goals, expectations, standards and concerns”. [41] The QoL of the cancer survivors will be assessed by European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 tool. [42] It is composed of multi-item scales and single-item measures. These include; five functional scales, three symptom scales, a global health status QoL scale, and six single items. All the scales and single-item measures scores range from 0 to 100. A high score of the scale represents a higher response level. Specific questionnaires will also be administered to evaluate QoL of patients with brain tumors or Head & Neck Cancer via EORTC QLQ - BN20 and EORTC QLQ-H&N35, respectively. Since the tool has not been validated in urdu therefore, in our study we will conduct content validation with a panel of experts and content validity index (CVI) will be calculated.

Socio-demography and Clinical Characteristics

The information will be collected on demographic variables like; age, gender, ethnicity, education, family status, number of people actively working, monthly household income, and employment status of the individuals. Socioeconomic determinant factors will include; education, occupation, family income. Moreover comorbid conditions such as; hypertension, diabetes, cardiovascular disease and addiction history such as; use of tobacco (smoked and smokeless) and substance abuse will also be evaluated.

Data on important major recent life events such as: death of child, spouse or any other event that has affected their lives will also be collected. Clinical characteristics and management of brain tumor and head and neck cancer will also be assessed and information will be taken from the patients on; tumor type, site of tumor, type of surgery, type of chemotherapy and/or radiotherapy, etc.

Psycho-Social Characteristics

The participant's depression and anxiety will be assessed using Hospital and Anxiety Depression Scale (HADS). [43] and social support will be determined via Social Support by Enriched Social Support Instrument (ESSI). [11]

Hospital anxiety and depression (HADS)

Hospital Anxiety and Depression Scale (HADS) will be administered to assess depression and anxiety among the participants. The tool was, developed to assess depression, anxiety and emotional distress among patients who were treated for a variety of clinical problems. HADS encompasses 14 items, equally subdivided into two scales measuring anxiety and depression. For instance, the item 'Worrying thoughts go through my mind' assesses anxiety, whereas the item 'I have lost interest in my appearance' evaluates depression. All the responses are on an ordinal four-point scale. [43] To measure anxiety and depression we will use urdu version of HADS. [44]

Social support by Enriched Social Support Instrument (ESSI)

Social support can ease the coping process, or help people overcome or adapt to a stressful event. The ESSI is a 7-item scale which primarily measures functional social support and emotional support. A total score of 18 or less on items 1, 2, 3, 5 and 6 is considered as low social support. [11] To assess social support we will use validated urdu version of ESSI with a content validity index (CVI) for relevance and clarity of 0.95 and 0.97 respectively and cronbach-alpha 0.82 [45]

Exploratory Questions to Evaluate Culturally Relevant Theme

Lastly, an explanatory questionnaire will be administered to examine the factors that have affected the life of the cancer patient and also to examine the different coping tactics that are used by the patients and their families to combat this disease.

Tool Validation

Since QoL tools, EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20 are not validated in urdu content validation will be performed by a panel of experts and content validity index (CVI) will be calculated. The panel of experts will comprise of Head and Neck surgeons, neurosurgeons, oncologist, epidemiologist, biostatistician, and psychologist. They will provide their expert suggestions for improvement of the tool according to our cultural context in Urdu. Each and every expert will rate the tool regarding the relevancy and clarity of each question. The responses will be rated on a scale from not relevant to highly relevant. Based on expert scores CVI will be calculated. CVI quantifies the level of content validity by calculating the percentage agreement between experts. [46] A CVI of greater than 0.8 indicates high level of agreement among the experts. [47] Permission has been granted by the quality of life tool developers for content validation.

Statistical Analysis

Analysis will be performed using STATA version 12. Descriptive statistics will be computed for categorical variables by computing their frequencies and percentages and the quantitative variables will be computed by their Mean ± S.D/ Median (IQR) as appropriate. Mean scores will be reported for resilience and QoL after treatment. Multiple Linear Regression technique will be used to evaluate the effect of independent variables on the outcomes - resilience and QoL for head and neck patients and brain tumor patients. Adjusted β-coefficients with their 95% CI will be reported. A p-value of <0.05 will be considered statistically significant. To assess the

relationship between resilience and QoL, correlation analysis will also be performed using Pearson or Spearman rank correlation coefficients as appropriate.

Ethical Considerations

Ethical approval has been obtained by Aga Khan University Karachi's Ethical Review Committee with ERC # 5154-Sur-ERC-17. Participants will be recruited from surgical/oncology clinics AKUH. Written informed consent will be taken from the participants by trained research assistants. Study procedure and its potential risks and benefits will be explained to the study participants. The research assistants will be trained by the Principal Investigator (PI). In this particular study, the participants might feel anxious/ uncomfortable during interview especially when their stress and depression level will be evaluated. To overcome this proper training will be given to the research team for sensitive questions. On spot counseling by a trained psychologist will be provided to the participants identified having depression. However, proper referrals will be made to a psychiatrist for those patients identified with severe depression especially with suicidal intentions. Strict confidentiality and privacy rules will be maintained and the participant's information will be kept confidential. Interviews will be conducted in a separate room. All study materials containing personal identifiers will be kept in a locked file cabinet. A unique study identification number will be assigned to each participant. Data will be entered in a password protected electronic database only accessible by the research team.

The Patient and Public Involvement:

It will be a cross sectional study design and the participants will be interviewed regarding their; socio-demographic factors, anxiety, depression, resilience and quality of life by trained research assistants.

The study findings will be disseminated to different stakeholders such as health care professionals, rehabilitation experts, psychologist and to cancer patients through: 1.

Publications at local, national and international journals 2. Presentations at conferences and workshops 3. Research briefs.

List of abbreviations

QoL	Quality of life
AKU	Aga Khan University
AKUH	Aga Khan University Hospital
PTSD	Post-Traumatic Stress Disorder
HR-QoL	Health-related quality of life
LMICs	Low And Middle Income Countries
HNC	head and neck cancers
CD-RISC	Connor–Davidson Resilience Scale
NCCN	National Comprehensive Cancer Network
SD	Standard Deviation
CVI	Content validity Index

Declarations

Ethics approval and consent to participate

Study protocol is approved by Aga khan university ethical review committee with ERC # 5154-Sur-ERC-17. Written informed consent will be obtained from all the study participants.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors have no conflict of interest to declare. The funders have no role in study, data collection, analysis, decision to publish, or preparation of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding body at Aga Khan University.

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Authors' contributions

NZ conceived the study, wrote and critically reviewed the manuscript. WK directly overlooked all aspects of study, wrote and critically reviewed the manuscript. SS and KA intellectually contributed to the study. IA, AJ, NA reviewed the study for overall quality and design robustness. MK and AE assisted as experts and informed aspects of development of the study intellectually. All authors have contributed intellectually to this manuscript. All authors have read and approved the final manuscript.

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Figure Legends

Figure 1: Conceptual Framework Of Resilience And Quality Of Life For Cancer Survivors Adapted From "The Adolescent Resilience Model" [48]

Figure 2: Participants Recruitment Plan Flow Diagram

Figure 1

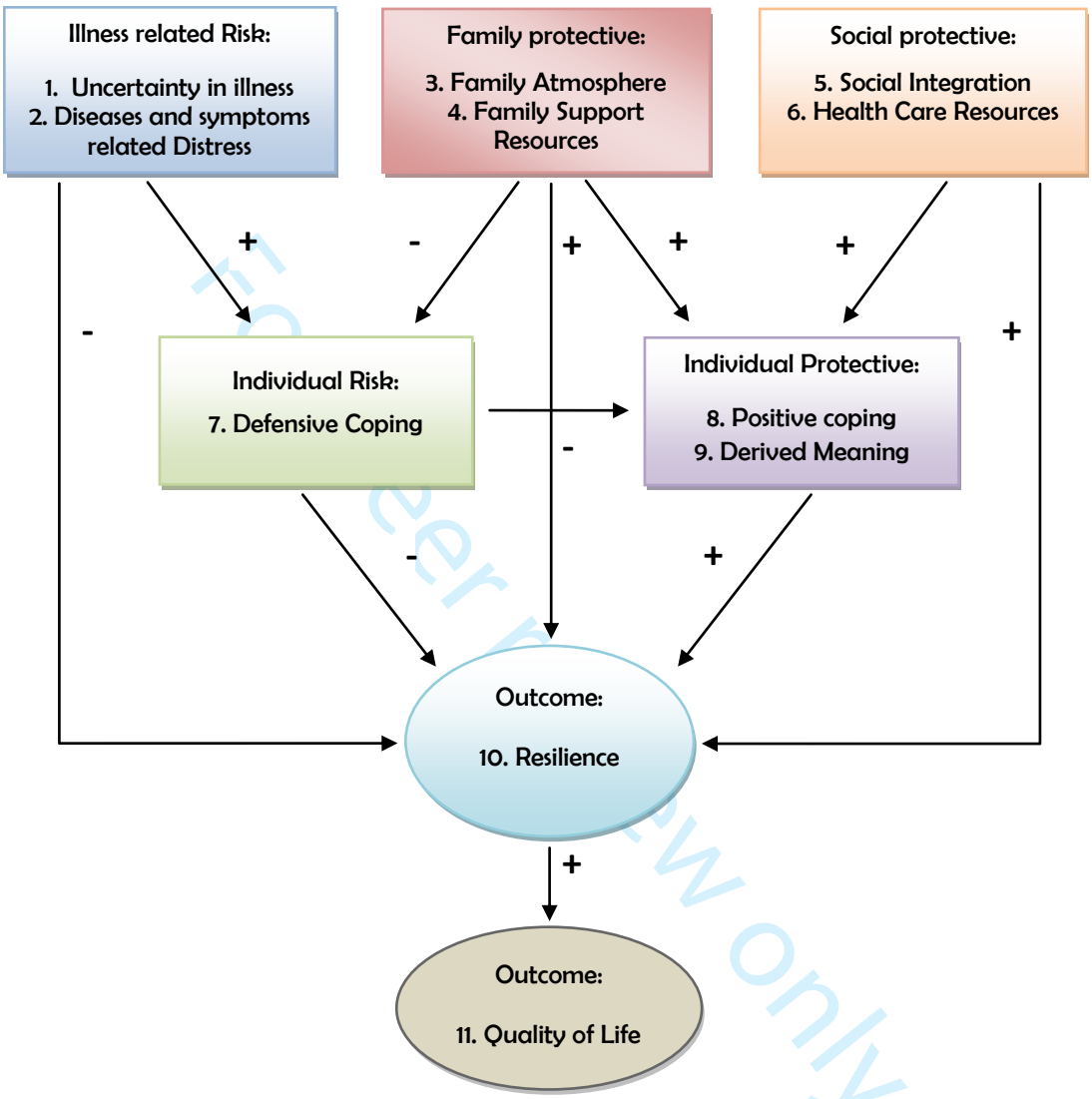
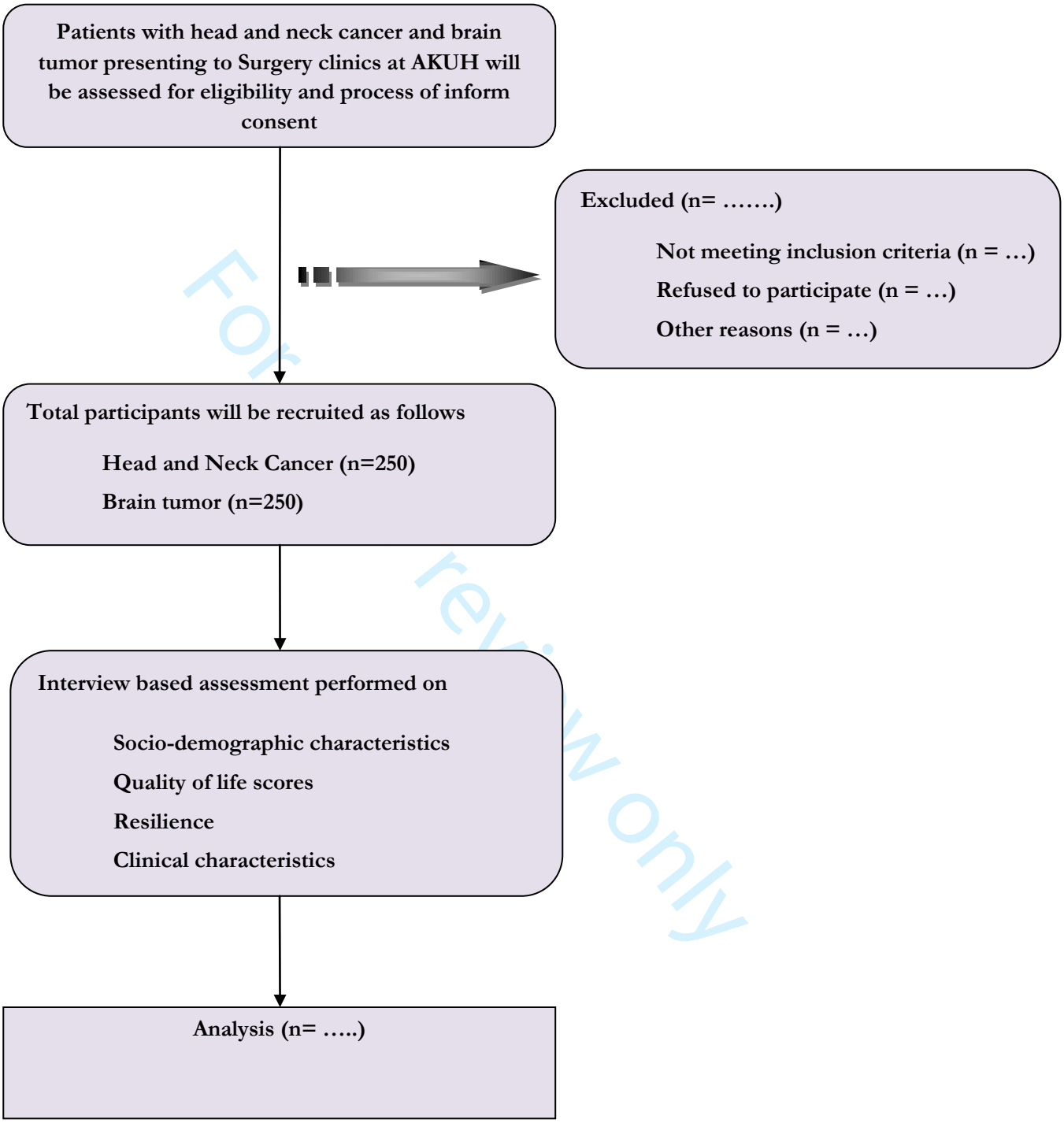


Figure 2



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

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-11
Bias	9	Describe any efforts to address potential sources of bias	*4 in strengths and limitations*
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	8
		(*e*) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			N/A
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	4
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*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.

BMJ Open

Resilience and Quality of life of Head & Neck Cancer and Brain Tumor Survivors in Pakistan; An Analytical Cross Sectional Study Protocol

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Resilience and Quality of life of Head & Neck Cancer and Brain Tumor Survivors in Pakistan; An Analytical Cross Sectional Study Protocol

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Abstract

Background: Cancer is a devastating disease and has detrimental effects on the quality of life (QoL) of cancer survivors and interferes with their treatment compliance. The aim of the study is to assess resilience and QoL among cancer survivors and to evaluate the important factors affecting their resilience and QoL, with respect to the Pakistani cultural context.

Method and Analysis: A cross-sectional study will be conducted at a tertiary care hospital in Karachi, Pakistan. A minimum sample size of 250 head and neck cancers and 250 brain tumor survivors with 10% inflation for non-response rate will be required. The standard deviation (SD) of QoL and resilience will range from 16.5 to 40.8 for head and neck cancer, and 12.7 to 34.1 for brain tumor, at 5 % level of significance, with 2.5 precision. QoL will be assessed by EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20) and resilience will be evaluated by Wagnild & Young's 14 item scale.

Mean ± SD will be reported for resilience and QoL scores. Unadjusted and adjusted β-coefficients, with 95% CI, will be reported by using multiple linear regression analysis. Correlation analysis will also be performed using Pearson or Spearman rank correlation coefficients. A *p*-value of <0.05 will be considered significant.

Ethics and Dissemination: Ethical approval has been obtained from the Aga Khan University Pakistan's Ethical Review Committee. Written informed consent will be taken from the participants by trained research assistants. A trained psychologist will provide on-spot counseling to the participants and those identified with severe depression will be referred to a psychiatrist. The study materials will be kept under lock and key and the electronic data base will be password protected and will only be accessed by the research team. The study findings will be disseminated through publications conferences and workshops and research briefs.

ClinicalTrials.gov Identifier: NCT03466762 https://clinicaltrials.gov/ct2/show/NCT03466762

Keywords: *Quality of life, Resilience, Cancer Survivors, Post-Cancer Depression*

Summary:

Strengths and Limitations

- Validated measures will be used for evaluating the outcomes and the independent variables.
- The overall quality of the study will be maintained through random spot-checks.
- The study results can be generalized to all cancer patients presenting at private tertiary care hospitals in Pakistan.
- To compare the QoL and resilience within the two groups of patients, subgroup analysis will be performed by stratification.

Background

Globally, cancer is the second leading cause of death. [1] Approximately 70% of the deaths from cancer occur in the Lower Middle Income Countries (LMIC). Head and neck cancers are the 6th most common cancers worldwide, with nearly 630,000 new cases diagnosed annually, causing 350,000 deaths. [2] [3] Globally, brain tumors are also a significant source of cancer-related morbidity and mortality, with an overall incidence of 4-5/100,000 cases annually, contributing to 2% of all cancer deaths . [4]And in Pakistan approximately 150,000 new cases of cancer are diagnosed annually, causing 60%-80% deaths. [5]

Conventionally, the endpoints of medical care for cancer patients are focused on survival rate, local control rate, or complication rate. [6] These assessments do not capture the patients' mental and emotional wellbeing [6] although the diagnosis of cancer considerably affects a patient's emotional and psychological status [7]

Cancer patients suffer clinically important symptoms of emotional distress such as depression and anxiety [8] that reduces their QoL and resilience and interferes with their treatment compliance. [9] [10] Studies have found that cancer patients with similar diseases and treatment status have significantly different QoLs [11] [12]. It is believed that resilience is the main factor that causes patients with similar situations to have different perceptions about their QoL [13] [14].

Resilience is an important trait that contributes to a person's mental and physical well-being. Evidence suggests that resilience is related to motivation. This motivation to recover from physical or psychological traumatic events [15] [16] minimizes the impact of risk factors, thus increasing a person's ability to deal with challenges of life [17]. Resilience, thus protects against psycho-social health related issues, such as depression, anxiety, fear and helplessness, and helps to reduce their associated negative effects [18].

Resilience has an important impact on the QoL of a cancer patient. Hence, over the last few years, QoL has become an important health related outcome measure with regard to communities and healthcare systems. This outcome measure is based on multidimensional concept that incorporates: the subjective perceptions of positive and negative aspects of cancer

symptoms, physical, emotional, social,cognitive functions, the disease symptoms and the side effects of treatment. [7 19]

There are several positive and negative factors that can influence a cancer patient's resilience and QoL. These are: Illness-related risk, which include perceived illness, ambiguity and complexity, stress of symptoms, severity of illness,

Family protective factors, which include perceived social support from family and socio-economic variables, Social protective factors, which include perceived social support from friends, influence of others with similar conditions, and perceived support from providers, Individual risk factors including evasive, emotive, and fatalistic coping measures/strategies, Individual protective factors, which include confrontive, optimistic, and supportant coping, along with hope and spiritual factors. (Figure 1)

Studies have examined the influence of psychological resilience among cancer patients. [20 21] These studies from different parts of the world suggest that resilience is a protective factor against distress among cancer survivors [22-26] which indicates that cancer patients with high resilience require less psychosocial support to manage their stressful conditions, as compared to those with low resilience. [20] One study reports that resilience mediates between cancer symptoms and distress and QoL among cancer survivors. Hence, resilience plays an important role in protecting them against the adverse effects of cancer symptoms. [22] A systematic review of 24 studies on head and neck cancer patients reports that distress-related variables (depression, anxiety, and distress) have a negative association with QoL outcomes. [27]

Moreover, resilience is a critical component for QoL at all stages; during diagnosis, treatment, survivorship, and palliative care. It is an important trait for promoting positive psycho-social well-being. Early identification of psychological factors associated with post-treatment QoL is essential among those at increased risk of poorer outcomes, as this can aid in the development of interventions to improve their QoL. [27]

Limited evidence is available from the Pakistani context regarding resilience and QoL among cancer patients. To the best of the researchers' knowledge, this will be the first in-depth study to evaluate resilience and quality of life among head and neck cancer and brain tumor patients in Pakistan. Resilience and QoL among them changes over time and may be modifiable towards

increased well-being. This study will, therefore, enable designing of interventions in the future to improve resilience and QoL. In the light of literature, the objectives of this study are:

- To determine the resilience and the quality of life scores for head and neck cancer and brain tumor patients, at least four weeks post-treatment.
- To evaluate important factors associated with resilience and quality of life among head and neck cancer and brain tumor patients, at least four weeks post-treatment.
- To examine the relationship between resilience and the quality of life for head & neck cancer and brain tumor patients, at least four weeks post-treatment.

Methods

Study Design

To evaluate resilience and QoL among head and neck cancer and brain tumor patients and their associated factors an analytical cross sectional study will be conducted. Resilience and QoL will be measured at least four weeks post treatment.

Study Setting

The study will be conducted at the Aga Khan University Hospital (AKU) which is a JCIA-accredited hospital, in Karachi-Pakistan. Karachi is the largest metropolitan city of Pakistan, a home to all major ethnicities living in this country. AKUH is one of the largest private tertiary care hospitals that cater to different ethnic and socio-economic groups of population in Karachi. The participants will be recruited from the surgical/oncology clinics at AKU. It has a multidisciplinary team that provides comprehensive care to cancer patients. The proposed duration of data collection will be 4-6 months.

Study Participants

Men and women aged 18 years and above , who have received treatment for brain tumor and head and neck cancer at AKUH, fulfilling the below eligibility criteria, will be recruited. According to recent data, the prevalence of head and neck cancer is escalating in Pakistan and limited information is available about their QoL brain tumor also is an understudied area in

Pakistan and there is dearth of information regarding their QoL. To maintain internal validity, the participants will be studied based on assumptions pertaining to their respective group.

Eligibility Criteria

Inclusion Criteria

- Individuals aged 18 years and above, who have received treatment at AKUH for head and neck cancer or brain tumor.
- Cancer survivors living in Pakistan for at least three months.
- Patients who will give consent to participate in the study.

Exclusion Criteria

- Known cases of any psychiatric illness leading to disability (e.g. manic disorder, schizophrenia etc.) as confirmed by medical records, will be excluded from the study as they may be on medications that might distort the results.
- Patients on anti-depressants prescribed by a psychiatrist
- Participants with physical comorbidities, stroke, and renal failure, will be excluded because these are debilitating diseases that will distort the results. Patients with CVD/heart disease, diabetes or COPD will not be excluded as every th Pakistani suffers from cardiovascular risk factors. If patient with these conditions are excluded, the majority of the participants will be ineligible and the required sample size will not be achieved. However, these co-morbid conditions will be adjusted during analysis

Sampling Technique

Purposive sampling technique will be used for selecting the participants. The target population, i.e. brain tumor and head and neck cancer patients who have received cancer treatment, will be approached by trained research assistants. The research assistants will be informed about the possible study participants who will be coming in for their appointment, by the nurse. On the day of appointment the participants will be screened for eligibility and if they fulfill the eligibility criteria and give consent to participate, they will be enrolled in the study. (Figure 2)

Sample Size Calculation

Head and Neck Cancer: The Sample size has been calculated based on mean QoL and resilience scores for head and neck cancer patients from previous studies. It has been calculated using one population mean formula, based on a standard deviation range of 16.5 to 40.8, 5 % level of significance with precision of 2.5, and by adjusting the sample size for 10% non-response rate. The minimum sample size has been estimated to be 250. [6 14 28-31].

Brain Tumor: The Sample size has been calculated based on previously reported estimates for QoL and resilience among patients with brain tumors. It has been calculated using one population mean formula, based on a standard deviation range of 12.7- 34.1, 5 % level of significance with precision of 2.5, and by adjusting the sample size for 10% non-response rate. The minimum sample size has been estimated to be 250**.** [32-35].

Assessment Tools

Resilience (Wagnild & Young's 14 Items)

Resilience is the ability to rebound or spring back, the power of something to resume its original shape or position after compression or bending. [36] Resilience is also defined as the 'capacity of individuals exposed to a negative event, to maintain stability and healthy physical and psychological functioning. It is a defense mechanism, which permits people to grow in the face of adversity. [37] The resilience tool that will be used has two versions; a long 25-item and short 14 item scale, using a 7-point rating likert scale. It comprises the five core characteristics of resilience, which include: purposeful life, perseverance, equanimity, self-reliance, and existential loneliness. [38] A high score represents better resilience. The respondent's choice ranges from 1 (Strongly Disagree) to 7 (Strongly Agree). The scale uses total scores rather than scores of individual items. To measure resilience, the validated Urdu version of the resilience Scale 14 (RS-14), which indicates moderate negative correlation of resilience with depression and anxiety (r = -0.31), and moderate positive significant correlation of resilience with life satisfaction (r = 0.40) will be used. The test-retest correlation coefficients and Cronbach's alpha for RS-14 are 0.49 and 0.76 respectively. [39]

Quality of Life (EORTC QLQ-C30, EORTC QLQ-H&N35 & EORTC QLQ-BN20)

Quality of life is defined by the WHO as "Individual's perceptions of their position in life in the context of the culture and value systems and their goals, expectations, standards and concerns". [40] The QoL of the cancer survivors will be assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 tool. [41] It is composed of multi-item scales and single-item measures. These include: five functional scales, three symptom scales, a global health status QoL scale, and six single items. All the scales and single-item measures scores range from 0 to 100. A high score on the scale represents a higher response level. Specific questionnaires will also be administered to evaluate the QoL of patients with brain tumors and head and neck cancer via EORTC QLQ - BN20 and EORTC QLQ-H&N35, respectively. Since the tool has not been validated in Urdu, therefore, in this study content validation will be conducted through a panel of experts and the content validity index (CVI) will be calculated. The panel of experts will comprise head and neck surgeons, neurosurgeons, an oncologist, an epidemiologist, a biostatistician, and a psychologist. They will be asked to provide their expert suggestions for improving the tool according to the Pakistani cultural context, in Urdu. Each and every expert will rate the tool regarding the relevancy and clarity of each question. The responses will be rated on a scale from not relevant to highly relevant. Based on expert scores, the CVI will be calculated. CVI quantifies the level of content validity by calculating the percentage agreement between experts. [42] CVI of greater than 0.8 indicates high level of agreement among the experts. [43] Permission has been granted by the quality of life tool developers for content validation.

Socio-demography and Clinical Characteristics

The information on demographic variables will be collected on aspects like; age, gender, ethnicity, education, family status, number of people actively working, monthly household income and employment status of the individuals. The Socio-economic determinant will include education, occupation and family income. Information on comorbid conditions such as hypertension, diabetes, cardiovascular disease, addiction history (including smoking and substance abuse)will also be evaluated. Data on important major recent life events, such as death of child, spouse, or any other event that has affected their lives will also be collected. Clinical

characteristics and management of brain tumor and head and neck cancer will also be assessed by taking information from the patients on tumor type, site of tumor, type of surgery, type of chemotherapy and/or radiotherapy.

Psycho-Social Characteristics

The participants' depression and anxiety will be assessed using the Hospital and Anxiety Depression Scale (HADS), [44] and social support will be determined via the Enriched Social Support Instrument (ESSI). [9]

Hospital anxiety and depression (HADS)

The Hospital Anxiety and Depression Scale (HADS) will be administered to assess depression and anxiety among the participants. This tool was developed to assess depression, anxiety, and emotional distress among patients who were treated for a variety of clinical problems. HADS encompasses 14 items, equally subdivided into two scales,one measuring anxiety and the other depression. For instance, the item 'Worrying thoughts go through my mind' assesses anxiety, whereas the item 'I have lost interest in my appearance' evaluates depression. All the responses are on an ordinal four-point scale. [44] To measure anxiety and depression, the Urdu version of HADS will be used. [45]

Social support by Enriched Social Support Instrument (ESSI)

Social support can ease the coping process, or help people overcome or adapt to a stressful event. The ESSI is a 7-item scale that primarily measures functional social support and emotional support. A total score of 18 or less on items 1, 2, 3, 5 and 6 is considered as low social support. [9] To assess social support, the validated Urdu version of ESSI, with a content validity index (CVI) for relevance, and clarity of 0.95 and 0.97, respectively, and cronbach-alpha 0.82 [46] will be used.

Explanatory Questions to Evaluate Culturally Relevant Theme

Lastly, an explanatory questionnaire will be administered to examine the factors that have affected the lives of the cancer patients and also to examine the different coping tactics used by the patients and their families to combat this disease.

Statistical Analysis

Analysis will be performed using the STATA version 12. Descriptive statistics will be computed for categorical variables by computing their frequencies and percentages, and the quantitative variables will be computed by their Mean ± S.D/ Median (IQR), as appropriate. Mean scores will be reported for resilience and QoL. The Multiple Linear Regression technique will be used to evaluate the effect of independent variables on the outcomes - resilience and QoL for head and neck patients and brain tumor patients. Adjusted β-coefficients with 95% CI will be reported. A p-value of <0.05 will be considered statistically significant. To assess the relationship between resilience and QoL, correlation analysis will also be performed, using the Pearson or Spearman rank correlation coefficients as appropriate.

Ethical Considerations

Ethical approval has been obtained from the Aga Khan University Karachi's Ethical Review Committee with ERC # 5154-Sur-ERC-17. Participants will be recruited from the surgical/oncology clinics of AKUH. Written informed consent will be taken from the participants by trained research assistants, after explaining the study procedure and its potential risks and benefits to them.

In this particular study, the participants might feel anxious/ uncomfortable during the interview, especially when their stress and depression level will be evaluated. To overcome this, proper training will be given to the research team for sensitive questions. On spot counseling by a trained psychologist will be provided to the participants identified as having depression. Those patients identified with severe depression especially with suicidal intentions will be referred to a psychiatrist. .

Strict confidentiality and privacy rules will be maintained and the participants' information will be kept confidential. Interviews will be conducted in a separate room. All study materials containing personal identifiers will be kept in a locked file cabinet. A unique study identification number will be assigned to each participant. Data will be entered in a password protected electronic database that will only be accessible by the research team.

Patient and Public Involvement

This will be a cross sectional study design and the participants will be interviewed, regarding their socio-demographic factors, anxiety, depression, resilience, and quality of life, by trained research assistants.

The study findings will be disseminated to different stakeholders, such as health care professionals, rehabilitation experts, psychologists, and cancer patients through: publications at local, national and international journals, presentations at conferences and workshops and through research briefs.

List of abbreviations

QoL	Quality of life
AKU	Aga Khan University
AKUH	Aga Khan University Hospital
PTSD	Post-Traumatic Stress Disorder
HR-QoL	Health-related quality of life
LMICs	Low And Middle Income Countries
HNC	head and neck cancers
CD-RISC	Connor–Davidson Resilience Scale
NCCN	National Comprehensive Cancer Network
SD	Standard Deviation
CVI	Content validity Index

Declarations

Ethics approval and consent to participate

Study protocol is approved by Aga khan university ethical review committee with ERC # 5154-Sur-ERC-17. Written informed consent will be obtained from all the study participants.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors have no conflict of interest to declare. The funders have no role in study, data collection, analysis, decision to publish, or preparation of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding body at Aga Khan University.

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Authors' contributions

NZ conceived the study, wrote and critically reviewed the manuscript. WK wrote and critically reviewed the manuscript. SS and KA intellectually contributed to the study. IA, AJ, NA reviewed the study for overall quality and design robustness. MK and AE assisted as experts and informed aspects of development of the study intellectually. All authors have contributed intellectually to this manuscript. All authors have read and approved the final manuscript.

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Figure Legends

Figure 1: Conceptual Framework Of Resilience And Quality Of Life For Cancer Survivors Adapted From "The Adolescent Resilience Model" [47]

Figure 2: Participants Recruitment Plan Flow Diagram

Figure 1

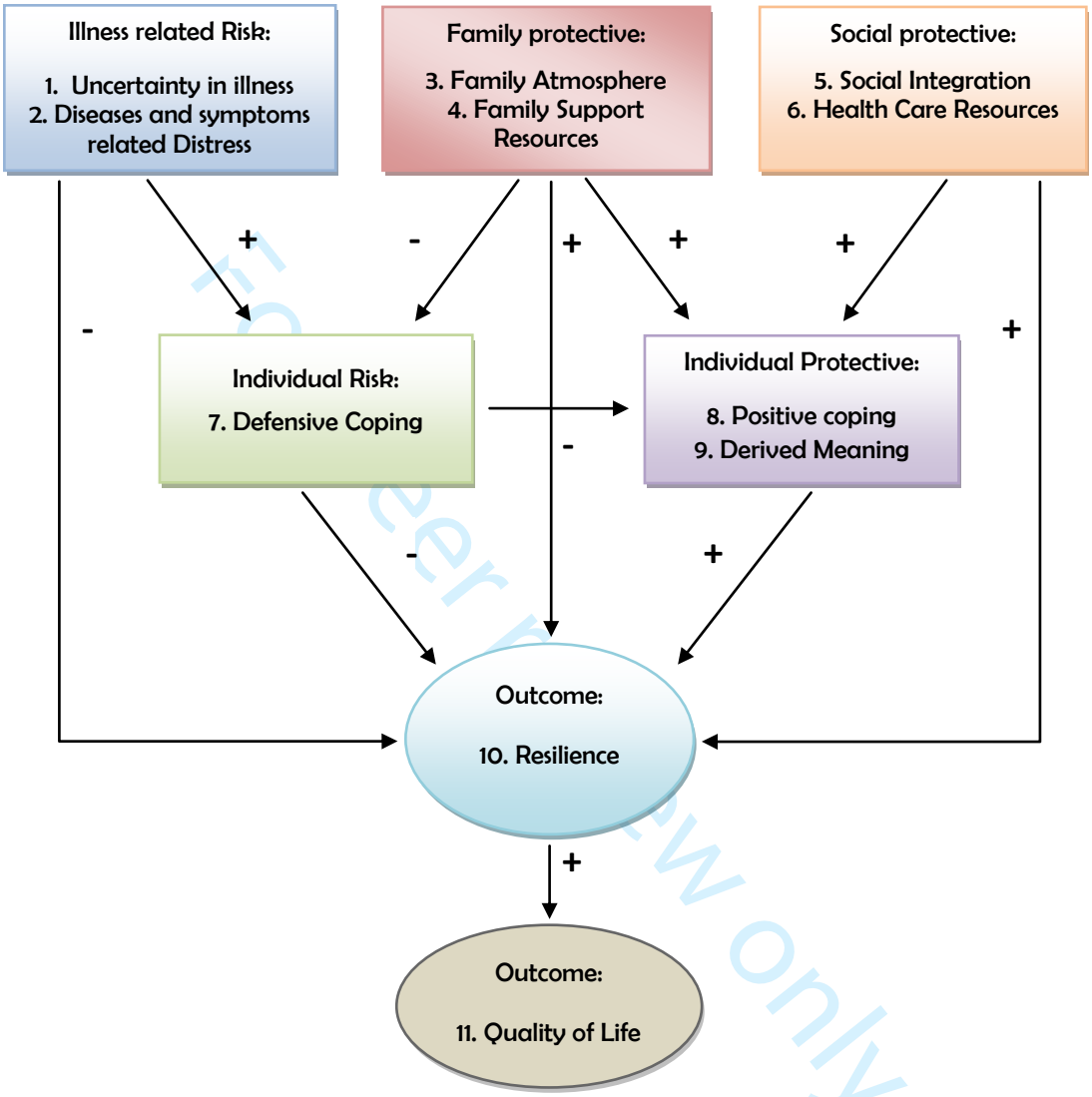
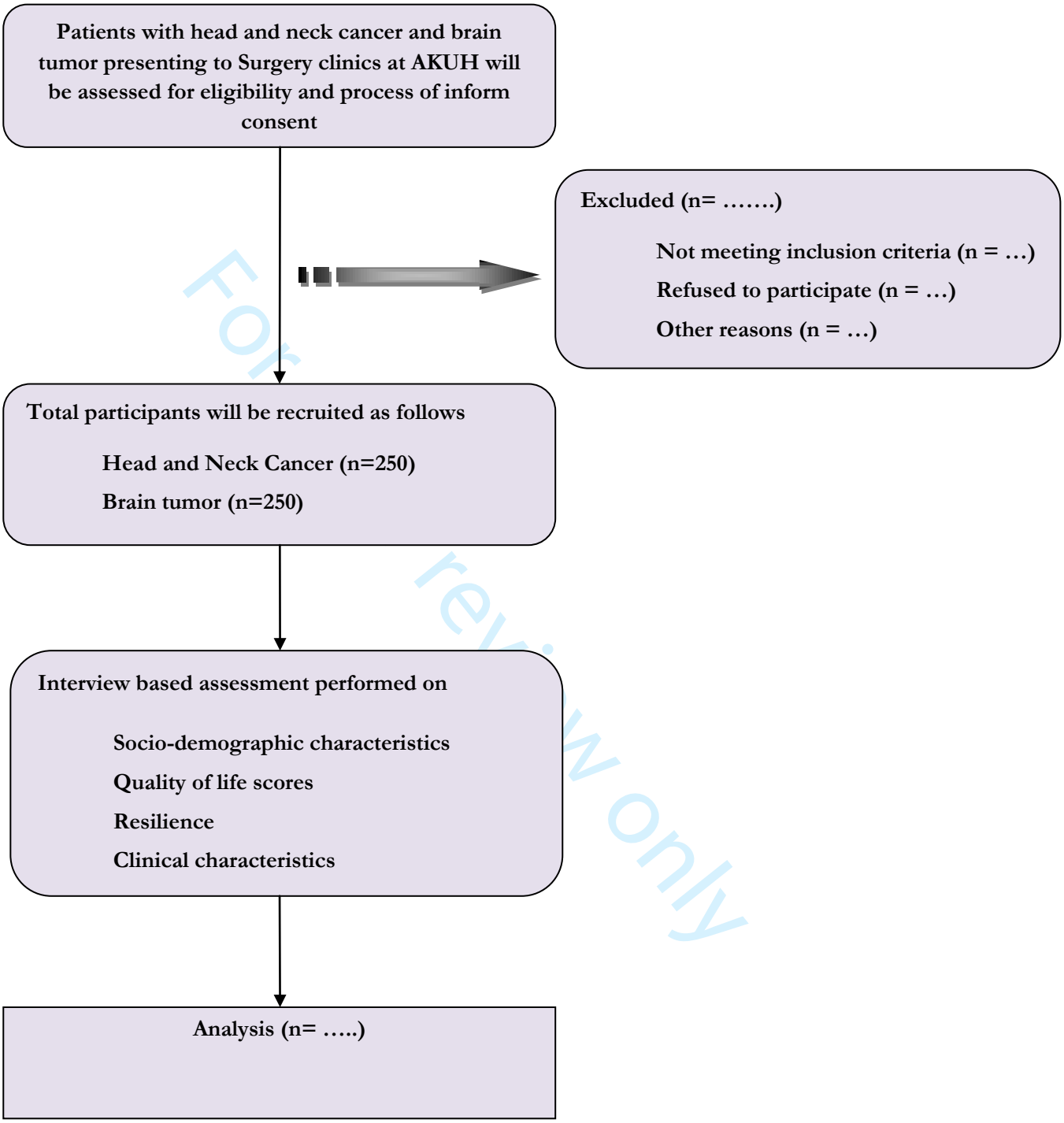


Figure 2



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

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	*4 in strengths and limitations*
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12
		(*b*) Describe any methods used to examine subgroups and interactions	12
		(*c*) Explain how missing data were addressed	12
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			N/A
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	4
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	4
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*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.