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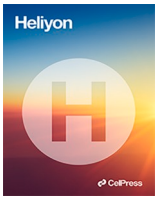

Neurocognitive Dysfunction and predictors in non-CNS cancer patients: Rationale and methods for the neuro-oncology research at a South African academic hospital

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ABSTRACT

Background: The focus on central nervous system (CNS) malignancies has overshadowed scant but substantial research that suggests non-central nervous cancer patients experience cancer-related cognitive impairment (CRCI), which affects higher-order brain function and influences their quality of life. Despite such evidence of the occurrence of CRCI among non-CNS cancer patients, the factors associated with the CRCIs remain a highly debated issue with discrepancies noted. Whether non-CNS cancer itself can affect the brain independent of cancer treatment is an important question to unpack. This necessitates further research, particularly in the sub-Saharan region where the evidence is limited.

Methods: This study aims to assess the effect of chemotherapy-associated cognitive and affective changes in non-CNS cancer patients. A non-experimental, time-series, correlational design will be used, in which a battery of computerized neuropsychological tests will be administered, including the e-MoCA, the CNS Vital Signs, the Patient Health Questionnaire-4, the Center for Epidemiologic Studies Depression Scale, the Hamilton Anxiety Rating Scale, the Functional Assessment of Cancer Therapy-Fatigue, and the Semi-structured Interview Schedule. Descriptive and inferential statistical analysis will be conducted, as well as NVivo thematic analysis of the qualitative data. The scope of the neurocognitive issues and risk factors that may be present in cancer patients and survivors in a developing environment could be determined by this study.

Implications: The study is expected to extend research on the extent at which cancer and cancer treatments are associated with neurocognitive changes among non-CNS cancer patients and their impact on their quality of life in the local context. The results are expected to inform treatment providers to develop treatment guidelines tailored for individuals diagnosed with cancer and who have received cancer treatment, as well as individualized psychosocial interventions aimed at addressing psychological challenges associated with quality of life among cancer survivors.

1. Background

Rigorous efforts to early detection and diagnosis combined with the advancement in cancer treatment modalities has led to better management of, and increase in cancer survivors worldwide [1]. This increased survivorship has garnered attention and interest in

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understanding the long-term effects of both cancer and cancer treatment on cognitive functioning and the health-related quality of life of cancer survivors [2]. According to Monje [3], this growing appreciation has led to an emergent field of cancer survivorship, specifically cancer neuroscience, which is supported by increasing trends in research demonstrating that a significant number of non-central nervous cancer survivors experience acute and prolonged cancer-related cognitive impairment (CRCI) [2,4].

According to The International Cancer and Cognition Task Force (ICCTF), CRCI can be defined as the decline in memory, attention, concentration, and executive function among cancer patients. CRCI has been noted among approximately 30 % of cancer patients prior to commencement of systematic treatment while 70 % and 30 % have been found to experience CRCI during and following treatment [5]. The above impairments have been attributed to both cancer and cancer treatments and have been thought to occur due to diverse neurotoxicity associated with cancer tumors and/or the treatment [2]. The blood-brain barrier (BBB) disruption, DNA damage, oxidative stress, and the ensuing inflammatory response, altered neurotransmission, and hormone alterations are only a few of the many mechanistic hypotheses that have been investigated [5,6].

Evidence of CRCI due to central nervous system (CNS) tumors has been thoroughly established, however, recent research has revealed that patients with non-CNS cancer also experience CRCI through their cancer trajectory [5,7,8]. Several studies have indicated that patients with non-CNS cancer experience neurocognitive deficits on different cognitive domains such as processing speed, attention and concentration, verbal, and short-term memory, as well as executive function before and following treatment [2,5,9–12].

The deficits have been found to present in a subtle manner and through subjective complaints such as slowed mental processing, difficulties attending to things, challenges recalling newly learnt information, finding words, planning, and completing activities, as well as multitasking [8]. Although it has been established that non-CNS cancer patients experience the index complaints throughout their cancer trajectory, the causal factors, and mechanisms of CRCI remains a highly debated issue due to discrepancies in the associations between subjective and objective cognitive impairments in various studies [13]. Existing research has suggested that subjective complaints could be attributed to the psychological distress associated with the cancer diagnosis rather than chemotherapy [5, 13]. Notwithstanding such evidence, there are neuropsychological and neuroimaging studies suggesting evidence of cognitive impairment outside anxiety, depression, fatigue, type of anesthesia or surgery factors [14].

It is for the above reasons that the present study seeks to investigate the objective cognitive functioning (OCF) and subjective cognitive functioning (SCF) changes, as well as the quality of life (QOL) of newly diagnosed non-CNS cancer patients due to receive chemotherapy and a control group with benign condition who do not require chemotherapy. Therefore, objective, and subjective assessments, as well as psychological assessments will be administered shortly after the diagnosis but before, during and following chemotherapy for the test group. The assessments will also be administered to the control group parallel to the test group. We hypothesize that both objective and subjective measures will indicate cognitive deficits while psychological assessments will indicate increased distress levels. In addition to the above, the study will also explore the lived experience of non-CNS cancer patients with self-reported cognitive problems (see Fig. 1).

1.1. Significance of the research study

There is limited research on the extent at which cancer and cancer treatments are associated with neurocognitive changes among cancer patients in developing countries, particularly in the sub-Saharan region, including South Africa. Thus, more research is needed to understand the breadth of neurocognitive impairments among non-CNS cancer patients and their impact on the quality of life, especially in the South African context where there are increasing cases of cancer. In addition, the above knowledge gap reinforces the unavailability of neuropsychological services as the standard care of practice is lacking/limited due to resource constraints. Even more so, a lack of integrated oncology and neuropsychological care poses a challenge to detecting/identifying the magnitude of the problem and importantly, assisting patients who need neuropsychological assessments and specialized neurocognitive rehabilitation.

Considering that cognitive impairments are not only negatively associated with treatment adherence and poor quality of life, but also with dementia and early mortality, the results of this study will inform treatment providers to develop treatment guidelines that are specific to individuals diagnosed with cancer and who have received cancer treatment to curb further deterioration and encourage neurorehabilitation. Additionally, this would provide an opportunity for clinical psychologists to provide personalized psychosocial interventions aimed at addressing challenges such as anxiety, depression, and relationship burdens, as well as the resultant impact on the quality life of the affected cancer survivors.

2. Materials and methods

2.1. Aims and objectives

2.1.1. Study Aim(s)

The study has the following two aims: To evaluate the objective cognitive functioning (OCF), subjective cognitive functioning (SCF) changes and quality of life (QoL) among newly diagnosed non-CNS cancer patients treated with chemotherapy over time in comparison with patients with benign condition who do not require chemotherapy; And to determine the relationship between subjective and objective cognitive functioning changes and psychological factors (depression, anxiety, and fatigue) among non-CNS cancer patients.

Objective(s).

1. To determine the extent of OCF and SCF in non-CNS cancer patients undergoing chemotherapy over time (before, after and following chemotherapy treatment)

2. To determine the impact of chemotherapy associated cognitive changes (OCF and SCF) on the quality of life of non-CNS cancer patients.
3. To determine the relationship between chemotherapy associated cognitive functioning (OCF and SCF) and psychological functioning in non-CNS cancer patients

2.2. Study design

The study will utilize a mixed method research design which involves the combination of both quantitative and qualitative approaches in collecting and analyzing data [15]. This design was adopted to quantitatively investigate the prevalence of chemotherapy associated with cognitive impairment and the parallel lived experiences of patients over different points in time. This method allows for data synthesis at the interpretation phase after analysis [15]. This is known as The Convergent Parallel Mixed Method Research Approach (see Fig. 1).

2.2.1. Quantitative arm

The study is a quasi-experimental time series design. The study will collect data on the objective and subjective functioning, as well as the level of psychological distress of two groups of participants (non-CNS cancer group-Test group and Benign condition group-Control group). The test group will be assessed at comparable time points being before commencing chemotherapy (T0), at 3 months (during chemotherapy) (T1), at 6 months (completion of chemotherapy) (T2), and 12 months after chemotherapy treatment (T3). The same assessment timeline will also be adopted for the control group.

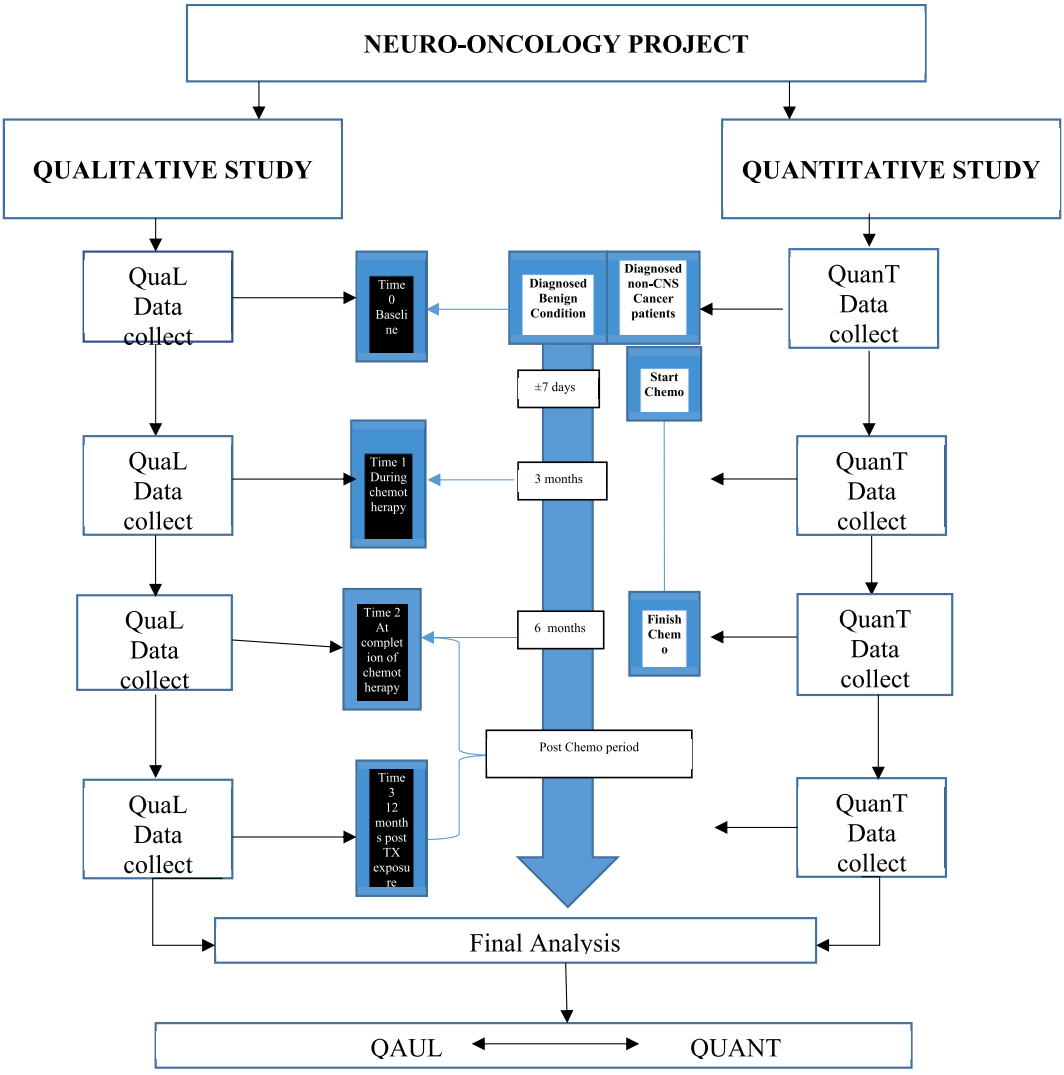

Fig. 1. Diagram representing the study design: Convergent Parallel Mixed Method Design.

2.2.2. Qualitative arm

The study will conduct face to face individual interviews and focus groups to gather the lived experiences of the patients. Individual interviews will be conducted at T0, T1, T2 and T3 while Focus groups will be conducted only at T3.

2.2.3. Setting

Participants will be recruited from a tertiary hospital in Gauteng, South Africa. South Africa is a sub-Saharan country with a population of approximately 60 million people, with majority of the people residing in Gauteng province. The latest cancer incidence rates recorded in the country was 108,168 in 2019 [16].

2.3. Sampling procedure

A purposive sampling method will be employed to sample the participants from the study site until reaching a final sample of 80. This would involve the intentional selection of participants based on a defined set of characteristics [17]. The participants will be recruited into both the quantitative and qualitative arm of the study albeit not all participants will be enrolled in the qualitative arm. Participants who are proficient in English, >18 years, who are diagnosed with non-CNS cancer who have not received cancer treatment (surgery or neoadjuvant treatment) will be invited to participate in the study. Patients with CNS cancer or advanced cancer, who have received chemotherapy, CNS surgery and have a history of encephalopathy or have a significant and untreated psychiatric illness will be excluded. The same inclusion and exclusive criteria will be applied to both the test group and control group. Participants who are scheduled to receive chemotherapy will be allocated to the test group while those who do not require chemotherapy will be allocated to the control group.

Research assistants (postgraduate student in psychology or trained psychologist) will provide information about the purpose and procedure of the study to all participants, as well as screen the participants to exclude those with existing cognitive deficits from taking part in the study with the assistance of the treating doctor. Those interested in participating in the study will provide the researcher with their contact details and will be contacted to set up an appointment to complete a screening assessment and the test battery should they meet the inclusion criteria.

2.4. Sample size

The sample size: Is estimated to detect the difference between the rate of abnormal MoCA before (p0 = 60 %) and after (p1 = 90 %) the intervention with a 95 % level of confidence (α error = 5 %), and a study power of 80 % (β error = 20 %). Using the equation for the difference between two proportions (Epi-Info 6.04), the estimated sample size is 39 subjects per group. After adjustment for a dropout rate of about 5 %, the sample size is 40 per group. The following equation was utilized to obtain the sample through the EPI software:

Where α represents the probability of type I error (significance level) is the probability of rejecting the true null hypothesis; β-the probability of type II error (1 - power of the test) is the probability of failing to reject the false null hypothesis; P_0-the proportion of disease in population 1; P_1-the proportion of disease in population 2; r-the ratio of population 2 to population 1 (r population 2 to 1 population 1); N_{Kelsey}-required sample size for the population 1 group using Kelsey formula; N_{Fleiss}-required sample size for the population 1 using Fleiss formula; $N_{Fleiss\text{-}cc}$- required sample size for the population 1 group using Fleiss formula with continunity correction.

2.5. Data collection

The study will utilize a blended approach of data collection using an electronically administered assessment battery consisting of sociodemographic variables, a neuropsychological battery consisting of objective and subjective neuropsychological tests and self-report psychological distress measures. Additionally, the study will also utilize a semi-structured interview guide informed by the Interpretive Phenomenological Analysis (IPA) to explore the participants 'lived experience. Data will be collected at T0, T1, T2 and T3 for all the tests and interviews except for group interviews which will be conducted at T3 only.

2.5.1. Approved data collection procedures

The study's blended method of collecting data is sensitive to COVID-19 protocols. Thus, it will involve scheduled in-person visits and online methods of data collection to minimize the risk of covid-19 infection between the researchers and the patients who are considered an at-risk population. The participants will be requested to come for an in-person assessment upon consenting which will involve the following conditions.

a) The in-person visits will be by appointment only, with appropriate spacing to avoid overcrowding.
b) Completion of SMU COVID-19 app that screens for COVID-related symptoms to enter the campus.
c) All the participants coming for the in-person visits will be requested to wear a face mask.
d) Both the participants and the assessment instruments (iPad and Laptop) will be sanitized before and after every assessment.

Furthermore, the assessments will be administered through a double-view mirror in order to minimize infections. The researcher will administer the assessment to the participant in the test room from the observation room using a microphone.

2.5.2. Assessment battery

2.5.2.1. Sociodemographic data. The sociodemographic information will be collected using a computer at T0 and this will include age, gender, race, highest level of education, employment status and occupation, relationship status, family, and support system, as well as medical information. The medical information will be obtained from the participant's medical file with the permission of the participants. This will involve information regarding their diagnosis, comorbid medical conditions, and treatment information.

2.5.2.2. Neuropsychological battery. The battery consists of neuropsychological tests used to measure objective and subjective cognitive functioning. The choice of the measures was based on previous neuropsychological studies with cancer patients which provide guidelines in this area [18,19]. The authors recommended the integration of both objective and subjective assessments to detect cognitive changes in cognitive domains and self-report measures to assess the psychological functioning and quality of life of patients to understand the functional site, severity, and duration of cognitive impairment in cancer patients [18]. The neuropsychological tests included in the battery have been validated and found reliable in a wide variety of studies. In addition, all the tests have been widely used in clinical neuropsychological practice in South Africa, thus they are validated for use in the local context, have an acceptable reliability and are available per the authors recommendations [20,19].

2.5.2.2.1. Quantitative arm. An assessment battery consisting of computerized objective neuropsychological tests, subjective neuropsychological tests, and self-report measures, will be administered to the test group before (T0) receiving chemotherapy, during treatment (T1), after completing the treatment cycle (T2) and 12 months following treatment (T3) in tandem with a control group. For participants that are not conversant with computer tests, paper-based tests will be administered. The administration time is estimated to be 1.3 h to 2 h depending on the participant's response speed.

2.5.2.2.2. Objective cognitive functioning (OCF). The International Cognition and Cancer Task Force (ICCTF) recommends evaluating learning, memory, processing speed and executive functioning [21,22]. Therefore, a blended approach of evaluation involving administration of either a battery of computerized (electronic Montreal Cognitive Assessment & Central Nervous System Vital signs) or paper-and-pencil based objective tests developed to assess a wide range of cognitive domains will be utilized.

2.5.2.2.3. Computerized neuropsychological tests. The Montreal cognitive assessment (MoCA) is a test that is used to detect mild cognitive impairment. The e-MoCA is a digital version of the paper and pencil MoCA which assesses the following domains: Executive functioning, visuospatial abilities, attention, memory, concentration, language, and orientation [23]. The test is scored out of 30 and has a cut off score of 26 with a low score suggesting cognitive deficiency [24].

The CNS Vital signs is a computerized neurocognitive assessment battery that evaluates the neurocognitive status of patients. The Battery consists of 7 neuropsychological tests which assess the following basic domains: Executive functioning, processing speed, memory (composite, verbal & visual memory), psychomotor speed, reaction time, attention (Complex & visual), and cognitive flexibility (see http://www.cnsvitalsigns.com). The domain scores contribute towards a total Neurocognitive Index (NCI) score, wherein lower scores indicate possible cognitive impairment while higher scores indicate a higher cognitive functioning based on normative data [25].

2.5.2.2.4. Paper-and-pencil neuropsychological tests. The following are paper based tests of the above electronic tests and the domains they assess. To assess for *general cognitive functioning*, the paper based MoCA which is used to detect mild cognitive impairment will be used. For *Visual spatial functioning,* the Draw-A-Clock test (DAC) and the Rey Complex Figure test RCFT) which assesses visuoconstructive abilities will be used. In addition, to assess the ability to plan, recognize rules, reason and engage in decision-making (*Executive functioning*), a Stroop test, Trail-making (alternating) B test, and Backward Digit Span test will be used.

Moreover, to assess for *Complex Attention*, which is the ability to track and respond to information over long periods of time and/or perform mental tasks while excluding other stimuli [26], the Stroop test, Digit Span test, Digit Symbol test and the Trail-making test will be utilized. Concerning the speed at which one is able to recognize and process information (*Processing speed*), the Stroop and Digit Symbol test will be used. Psychomotor *functioning*, which is the ability to perceive, attend, respond to visual-perceptual information, motor speed and fine motor coordination, the Digit Symbol test, and the Finger-tapping test will be utilized.

In addition, *Learning and Memory* which consists of *Visual memory*, *Verbal memory a*nd *Working memory*, will be assessed through the following tests; the Rey Complex Figure and the Bender-Gestalt-II, which assesses the patient's ability to recall visual information (Figures) shortly after presentation and after a long period of time; The Rey auditory Verbal Learning Test, which assesses the ability to recognize and recall words presented earlier in a word list-learning task; And the Stroop test, which assess an individual's mental flexibility and the ability to manipulate information in the immediate awareness.

2.5.2.2.5. Subjective cognitive functioning (SCF). To assess the patient's subjective cognitive functioning, the Functional Assessment of Cancer Therapy (FACT-Cog) will be utilized. The FACT-Cog is a 37-item scale that was developed to assess cognitive complaints in cancer patients. The FACT-Cog yields a total score and four subscale scores including 1) perceived cognitive impairment (PCI), 2) perceived impairment in quality of life (QoL), 3) perception and comments from others (PCO), and perceived cognitive ability) (PCA). The FACT- Cog has been widely used and validated in numerous studies with patients with breast cancer and other types of cancer. It was found to have a Cronbach alpha ranging from 0.77 to 0.86 in breast cancer studies, which is acceptable.

2.5.2.3. Psychosocial functioning: depression, anxiety, and fatigue. The following tests will be used to assess for psychosocial functioning:

CES-D 20. The Center for Epidemiologic Studies Depression (CES-D 20) has shown to be a valid and reliable tool for assessing depressive symptoms among cancer patients. Von Ah and Tallman [27], in their study with cancer patients found the CES-D20 to have

a high Cronbach alpha of 0.89.

HAM-A. The Hamilton Anxiety Rating Scale (HAM-A) will be used to assess anxiety symptoms in the participants. It has been found to be a valid and reliable screen of anxiety in the cancer population.

FACT-F. The Functional Assessment of Cancer Therapy-Fatigue (FACT-F) is a 13-item measure that will be used to assess symptoms of fatigue in the participants. It has also demonstrated consistently good reliability, with a Cronbach alpha ranging from 0.70 to as high as 0.94.

3.5.2.3.1. Qualitative arm. The Semi-structured Interview Schedule (SIS) will be utilized to conduct both individual and focus groups interviews which will be audiotaped. The SIS is a semi-structured interview schedule which provides guidance on conducting individual and focus groups through the Interpretive Phenomenological Analysis (IPA) theory. This interview is used to explore the lived experiences of non-CNS cancer patients with self-reported chemotherapy associated cognitive challenges.

3.5.3. Quality control

Data collected during the study will be stored online. Data collected using google forms will be stored in the study account that is password protected and access limited to the study team. Furthermore, data collected using the e-MoCA and CNS-vital signs test programmes will be temporarily stored remotely on the programme servers which adhere to data protection regulations. Once extracted, the data will be stored in a folder in a password protected computer.

3.6. Data analysis

Sociodemographic and clinical characteristics of the sample will be computed descriptively in the form of mean (M), standard deviations (SD), and frequency distributions. Differences between the non-CNS group and control group will be examined using an independent *t*-test (continuous data) and *Chi-Square* test while changes over time for variables OCF, SCF, and QoL will be examined using mixed between-within subjects' analysis of variance ANOVA. Further, a hierarchical multiple regression analysis will be utilized to determine whether there is a relationship between SCF and OCF and QoL in non-CNS cancer patients. A univariate regression analysis will be utilized to assess the relevance of psychological variables (depression, anxiety, and fatigue) in predicting cognitive functioning and QoL in non-CNS patients. IBM SPSS Statistics version 20 (IBM Corporation, Armonk, NY, USA.) will be used to compute analyses. All statistical tests will be at two-sided with p values ≤ 0.05 considered significant. Regarding the qualitative data, the collected data will be transcribed and anonymized. The data will then be transferred and analyzed using NVivo.

3. Ethical implications

The study was developed and will be implemented according to the ethical principles stipulated by the declaration of Helsinki [28]. Participants will be provided with adequate information about the study in order for them to make an autonomous and voluntary decision about their participation [29]. During this process, they will also be informed about their rights to voluntary participation, withdrawal of participation at any time without repercussions to their healthcare access and confidentiality of their information. The study uses an electronic consent form, therefore, clicking agree and proceeding to the test items implies that the participants have read and given informed consent to participate in the study.

In the unlikely event of them experiencing psychological distress while participating, the participants will have access to the Clinical Psychology Departmental Clinic for free or provided with contact details of other psychological services.

4. Dissemination

The dissemination of the research findings will be at both a participant level (Optional), organizational level and scientific community level. At a participant level, the participants who would like to request their results will be provided with a report indicating their cognitive and psychological functioning. Institutionally, the relevant hospital personnel will be provided with information regarding patient care.

Considering that the exploration of cognitive impairment associated with chemotherapy is a significant area of study yet unexplored in the local context, publication of this study's results will fill in an important neglected research gap. Therefore, the study findings will be published in journal articles and presented in scientific conferences.

Ethics approval and consent to participate

The study has received ethical approval from both the School Research Ethics Committee (SREC) and the Sefako Makgatho Health Science Research Ethics Committee (SMUREC/M/48/2020:IR). Additionally, permission to conduct the study at the hospital site has also been granted by the hospital superintendent.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Disclaimer

The funding agencies had no role in the study design; decision to publish the manuscript; or portion of the manuscript.

Authors' contributions

AGL conceived and designed the experiments. AGL and TBM wrote the paper.

Ethics

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Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

Not applicable.

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