BIOLOGY Methods & Protocols

Biology Methods and Protocols, 2022, 1–7

https://doi.org/10.1093/biomethods/bpac006
Advance Access Publication Date: 9 March 2022
Pre-Registered Study Protocols

PRE-REGISTERED STUDY PROTOCOLS

Risk factors and early cardiovascular outcomes in cancer patients treated with anthracycline-based chemotherapy in Tanzania: a protocol for a quasi-experimental study

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Abstract

The objective of this quasi-experimental study is to assess the risk factors and early cardiovascular outcomes in cancer patients treated with anthracycline-based chemotherapy in Tanzania. The study will be conducted at Ocean Road Cancer Institute in Dar es salaam, Tanzania. The study will have three phases: baseline survey, follow-up, and end-line survey. Participants will be newly diagnosed adult cancer patients who are eligible for anthracycline-based chemotherapy. A total of 427 participants will be involved. At baseline, participants will be evaluated for the cardiovascular risk factors before commencing chemotherapy. During follow-up, participants will commence their prescribed anthracycline and the cardiovascular indices monitored throughout until the patient completes the prescribed anthracycline cycles. After completing the prescribed anthracycline cycles, an end line survey will be conducted to evaluate any change in cardiovascular indices. The outcome variable in this study will be the change in biochemical data (high-density lipoprotein, low-density lipoprotein, triglyceride, and troponin I), blood pressure, and electrocardiographic information (heart rate and Bazett QT interval). Independent variables will be demographic characteristics, risk factors for cardiovascular disorders, current dietary practices, and body mass index. Descriptive statistics will be used to describe the participants. Independent and paired *t*-tests will be performed to make comparisons between and within groups. *P*-values <0.05 will be considered statistically significant. The results of this study will help clinicians and policymakers to understand the burden of early cardiovascular outcomes and plan for appropriate preventive strategies.

Keywords: anthracycline; cancer; doxorubicin; epirubicin; cardiovascular risk factors

Received: 8 November 2021; **Revised:** 30 January 2022; **Editorial Decision:** 31 January 2022

Introduction

Advances in the diagnosis and treatment of cancers have resulted in improvement in the survival rates and increased number of cancer survivors, but with increased cardiovascular outcomes. These outcomes are usually unintended, but as adverse effects following the use of anticancer drugs. The cardiovascular outcomes have a profound impact on morbidity and mortality which reduces the net clinical gain and the quality of life during or after treatment [1–5].

The chemotherapeutic agents may cause adverse cardiovascular effects by directly compromising myocardial functioning [4, 6] or by changing vascular hemodynamics [7] or both [8]. The adverse effects may be set or cumulative, predictable or unpredictable, and potentiated or ameliorated by the use of concomitant antineoplastic drugs [2].

Cardiac events commonly observed among cancer patients under chemotherapy may include mild blood pressure changes, electrocardiographic changes, thrombosis, myocarditis, pericarditis, arrhythmias, myocardial infarction, cardiomyopathy, cardiac failure (left ventricular failure), and congestive heart failure [9]. These may occur during or shortly after treatment, within days or weeks after treatment, or may not be apparent until months, and sometimes years, after completion of chemotherapy [9].

Among the anticancer drugs known to have cardiovascular complications are in a group of anthracycline. This group of drugs has the widest spectrum and is commonly exemplified by daunorubicin, doxorubicin (Adriamycin), epirubicin, idarubicin, and valrubicin. The mechanism of anthracycline activity is related to topoisomerase II inhibition, which occurs as a result of intercalation into DNA with consequent disruption of topoisomerase-II-mediated DNA repair, and by the production of hydroxyl-free radicals with both antitumor effects and toxicity to healthy tissues [10, 11]. The notable side effect of anthracycline is anthracycline-induced cardiomyopathy (AIC) which is often irreversible and may lead to clinical congestive heart failure.

Commonly reported risk factors for anthracycline toxicity in addition to cumulative dose are: intravenous bolus administration; higher single doses; concomitant use of other agents known to have cardiotoxic effects such as trastuzumab, cyclophosphamide, and paclitaxel; history of irradiation; female gender; age (young and old age); underlying cardiovascular disease; and increased length of time since anthracycline completion [3, 5]. Others are hypertension, diabetes, African-American ethnicity, very high or very low body weight, and severe co-morbidities [3].

The combined modifiable risk factors for both cardiovascular diseases and cancer may account for the differences in cardiovascular toxicity among patients using anthracycline [12]. Smoking is a recognized shared risk factor for cancer and cardiovascular disease [13, 14] and one of the causes of about one-third of first myocardial infarctions [14]. In addition to coronary disease, smoking increases the risk of stroke, hypertensive heart diseases, aortic aneurysms, and other cardiovascular conditions [13]. Other studies have linked smoking to cancers of about 14 different body sites including the breast and prostate cancer [13, 14]. Therefore, a cancer patient due to smoking, or who smokes, or with a history of smoking, may potentially have an increased risk for cardiovascular diseases even before commencing chemotherapy, or at lower doses of anthracycline.

Both total obesity, measured by central obesity and body mass index, are associated with an increased risk of cardiovascular death [15], which may also confound the cardiovascular toxicity due to chemotherapy.

A nonprudent diet rich in fat, red meat, and sugar common in western countries has an increased risk for cardiovascular disorders and cancer. Dietary patterns such as the Mediterranean diet are high in fruits and vegetables, whole grains, and unsaturated fat and are associated with improved cardiovascular outcomes [12, 16].

Meta-analysis suggests a dose–response relationship for the effectiveness of exercise in reducing coronary mortality [17]. Compared with being sedentary, 150 and 300 min of week activity reduces mortality by 14% and 20%, respectively [17]. A similar dose–response relationship has been established for exercise in the prevention of heart failure, with the highest levels of physical activity reducing heart failure risk by 30% [18].

In addition, there is an evidence for genetic predispositions to the development of anthracycline-induced cardiotoxicity in some patients. In a study of patients with non-Hodgkin's lymphoma, the evaluation of single-nucleotide polymorphisms in 82 candidate genes hypothesized to be associated with the development of anthracycline cardiotoxicity [19, 20] and identified polymorphisms in genes encoding three proteins: NAPD (H) oxidase, implicated in reactive oxygen species (ROS) generation, and the doxorubicin efflux transporters MRP1 and MRP2. In survivors of high-risk childhood acute lymphocytic leukemia (ALL), the risk of doxorubicin-associated myocardial damage was particularly elevated in the patients with a C282Y mutation, associated with hereditary hemochromatosis [21].

Therefore, the appropriate risk modification prevention strategies begin with early identification of the burden of risk factors and the appropriate timing for executing prevention strategies before the occurrence of a clinically overt cardiovascular complication.

Problem statement

The cardiovascular system consists of many cells that have limited regenerativity. This incurs potential for increased susceptibility to long-term adverse effects from various chemotherapeutic agents due to their no-selective toxicity.

Patients receiving anthracycline are five times more riskier of developing heart failure than patients treated with other chemotherapeutic agents [22]. The mortality rate associated with DXR-induced congestive heart failure is estimated to be at least 20% [23].

The risk for cardiovascular toxicity due to anthracycline use increases with increased risk factors for cardiovascular disorders. However, little is known about the magnitude of risk factors for cardiovascular diseases in cancer patients before and after treatment initiation in Tanzania. As the result, baseline information for establishing prevention strategies is lacking.

While there are very limited studies regarding the cardiovascular complications of chemotherapy in Africa and Tanzania in particular, the existing studies elsewhere provide contradicting conclusions regarding the effect of anthracycline on some cardiovascular diseases such as hypertension. In some studies, increased level of ROS due to anthracycline use affects the blood vessel endothelial cells in a complex manner resulting in hypertension. In contrast, other studies have documented a clinically significant hypotension associated with anthracycline due to some complex changes in the autonomic nervous system [9, 24]. Therefore, there is a compelling need for more studies regarding the cardiovascular complications of anthracycline chemotherapy.

Study objectives

The general objective of this quasi-experimental study is to assess the cardiovascular risk factors and early cardiovascular outcomes among cancer patients treated with anthracycline chemotherapy in Tanzania.

Specific objectives

1. To determine the prevalence of cardiovascular disorders among cancer patients treated with anthracycline-based chemotherapy.
2. To determine the risk factors for cardiovascular disorders among cancer patients treated with anthracycline before and after treatment initiation.
3. To examine the change in systolic blood pressure after anthracycline chemotherapy.
4. To examine the change in diastolic blood pressure among cancer patients after anthracycline chemotherapy.
5. To evaluate the change in level of serum biomarkers to cardiovascular diseases after anthracycline treatment.
6. To determine the change in QT interval after anthracycline chemotherapy.

The results from this study will help program planners and policy makers to plan for effective intervention strategies for reducing the burden of cardiovascular morbidity and mortality after cancer treatment in Tanzania in order to improve quality of life during and after treatment. The findings of this study will also serve as the baseline information for future scholars.

Methods

This study will be a one-group pretest–posttest quasi-experimental study [25] that will involve cancer patients using anthracycline-based chemotherapy at Ocean Road Cancer Institute (ORCI) in Dar es salaam, Tanzania. ORCI is a comprehensive specialized facility for cancer care in Tanzania. The institute is located along the Indian Ocean about 200 m from the beach. Currently, the Institute serves more than 50,000 patients that include about 28,000 cancer patients, 10,000 cancer screening patients, and 12,000 non-cancer patients. In addition, the Institute attends to over 15,000 clients in the outreach programs in the Tanzania regions.

The participants will be conveniently selected based on the following eligibility criteria: (1) diagnosed as cancer patient by histopathological examination; (2) stages I–III cancer; and (3) treated with surgery followed by chemotherapy. The exclusion criteria will be: (1) lack of laboratory data; (2) receiving neoadjuvant therapy; (3) pre-existing primary tumors; (4) abnormal cardiopulmonary, liver, or kidney function; (5) patients with diseases affecting serum lipids or taking related drugs that affect serum lipids, and (6) patients with known cardiovascular diseases.

All willing patients will be provided with informed consent for their clinical data to be reviewed by us. This study will comply with the Declaration of Helsinki and will be approved by the Ethics Committee of the University of Dodoma and the Hospital Research Committee of the ORCI. The study design has been summarized in Fig. 1.

Sample size will be estimated using the following formula:

$N = z^2 p\,(100-p)/d^2$

N = desired sample size.

Z = percentage of standard normal distribution corresponding to 95% of confidence interval which is 1.96.

D = marginal error (absolute precision of P which is 5%).

P = the estimated proportion of patients using anthracycline. Because no P was available for Tanzania, an estimate of 50% was used.

$N = 1.96 \times 1.96 \times 50 \times 50/5 \times 5 = 384$. After adjusting for 10% non-response,

$R = 90\%$

$1/R \times 384$

$= 100 \times 384/90 = 426.666 \approx 427$.

Data collection

This study will be divided into three phases: baseline study, follow-up, and end-line survey.

Baseline survey

A cross-sectional survey will be conducted at ORCI. Data will be collected by using a developed semi-structured questionnaire. The questionnaire has been adapted from World Health Organization (WHO, 2008) and modified to suit this study objective (see Supplementary File).

The questionnaire consists of six parts, namely,

Part 1: *Demographic information* (age, sex, marital status, occupation, education, type of cancer, and any drug used).

Part 2: Cardiovascular risk factors (history of diabetes, hypertension and other cardiovascular diseases, alcohol, diet, physical activity, tobacco use, and current dietary practices).

Part 3: *Biochemical data* (HDL, LDL, triglyceride, and troponin I).

Part 4: Physical measurements (blood pressure, weight, height, and body mass index [BMI]).Part 5: Electrocardiographic information (heart rate, Bazett's QT interval).

Data collection will be conducted by researchers and research assistants through face-to-face interviews using the developed questionnaire. Researchers and research assistants will consist of the following professionals: A critical care Nurse Specialist and a Ph.D. candidate, a professor of critical care Nursing, a medical oncologist, a cardiologist, registered nurses, and a quality control specialist.

A critical care nurse specialist and registered nurses will administer the questionnaire and take physical measurements of the participants, a medical cardiologist and oncologist will be responsible for collecting biochemical and electrocardiographic information in collaboration with cardiovascular laboratory technicians, a quality control specialist will be monitoring the completeness and quality of data collected, and a professor of critical care will be the overall supervisor on every step of the study.

Prior to the interview, researchers/research assistants will explain the purpose of the study to the study participants. Written or verbal informed consent will be taken from participants.

Participants found to have cardiovascular diseases or are at higher risk for cardiovascular diseases will be attended by the cardiologist or given a referral letter to a cardiovascular facility for further management.

Follow-up survey

Participants will start their scheduled anthracycline-based chemotherapy and followed up throughout their anthracycline

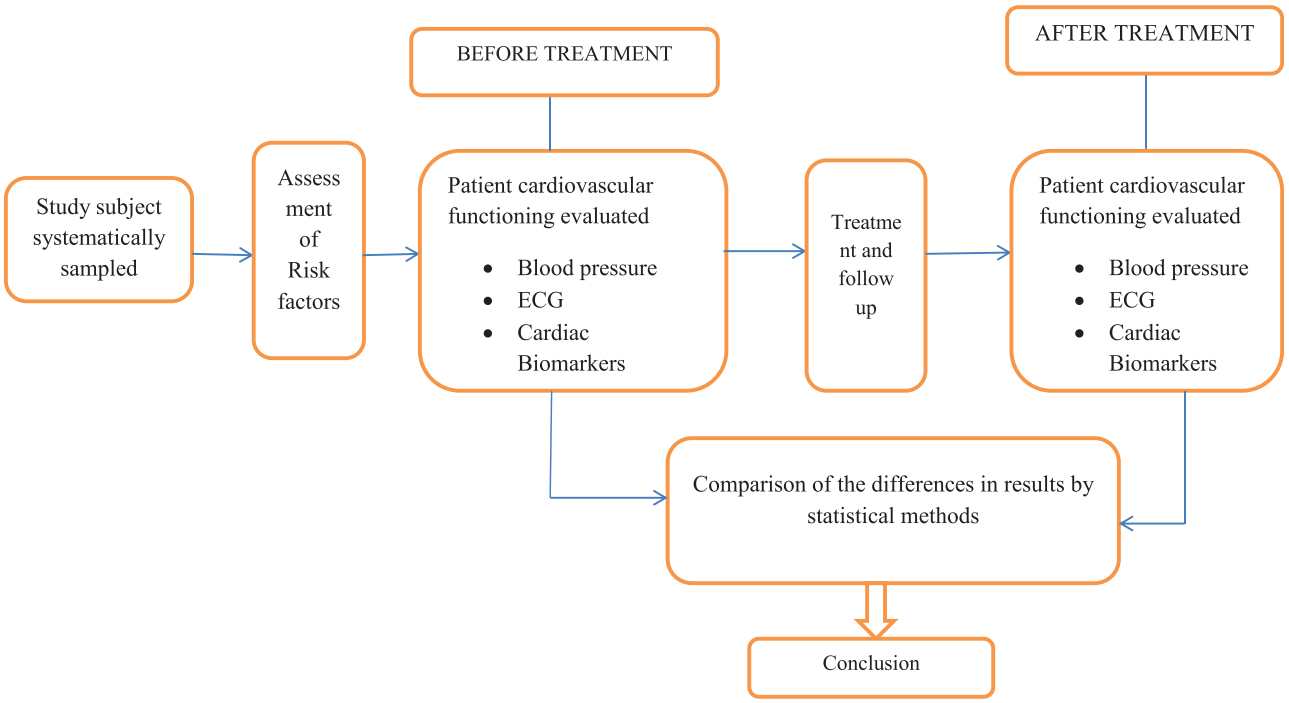

Figure 1: Study design and flow chart.

treatment period. Participants will be evaluated for any signs and symptoms of cardiovascular diseases every time they come for the next anthracycline cycle, by checking blood pressure and taking a cardiovascular history.

End-line survey

An end-line survey will be conducted using a similar questionnaire as in the baseline survey.

Measurement of variables

Dependent variable

Dependent variable in this study will be change in biochemical data (HDL, LDL, triglyceride, and troponin I), blood pressure, and electrocardiographic information (heart rate and Bazett QT interval).

For the collection of biochemical samples for fasting blood sugar (FBS) and lipid, participants will be requested to fast overnight for 12 h. Venous blood samples (4 mL of blood) will be collected in a cardiovascular laboratory for analysis.

Diabetes will be defined as having FBS level (of plasma venous value) of 7 mmol/L, (equivalent to 126 mg/dL) or higher or currently taking any anti-diabetic medications.

Similarly, a total cholesterol level of ≥240 mg/dL (equivalent to 6.2 mmol/L), LDL-C of ≥160 mg/dL, and triglycerides ≥200 mg/dL will be defined as high, whereas high-density lipoprotein (HDL-C) <50 mg/dL for men and <40 mg/dL for women (equivalent to 1.3 mmol/L for men and 1.0 mmol/L for women) will be considered normal.

Independent variables

The independent variables include: demographic characteristics, risk factors for cardiovascular disorders, current dietary practices, and BMI. Information on the demographic factors, lifestyle, psychosocial factors, personal and family history of cardiovascular disoders (CVD) and risk factors (hypertension and diabetes mellitus) will be obtained through the use of a structured questionnaire. Height and weight will be measured when subjects are wearing light indoor clothing without shoes and a BMI calculated using the following formula: BMI = weight (kg)/height^2.

Physical activity

A person not meeting any of the following criteria is considered being physically inactive and therefore at risk of chronic cardiovascular diseases: three or more days of vigorous-intensity activity of at least 20 min per day; odds ratio (OR) 5 or more days of moderate-intensity activity or walking of at least 30 min per day; OR 5 or more days of any combination of walking, moderate- or vigorous intensity activities achieving a minimum of at least 600 metabolic equivalent-minutes per week [26].

Tobacco use

Data related to the pattern of tobacco use (smoking and smokeless), including the age of initiation and frequency of use will be collected from current, past, and daily users.

Current smokers will be defined as those who had smoked or used smokeless tobacco products in the last 30 days [27]. Participants who reported smoking at least 100 cigarettes in their lifetime and who, at the time of the survey, did not smoke were defined as past smokers [27].

Alcohol consumption

Participants will be required to report the status of their alcohol consumption. Standard drinks and frequency of drinking in the last 30 days will be obtained from current alcohol users [27]. Pictorial cards featuring different kinds of glasses and bowls that are most commonly used in Tanzania will be displayed to

the participants to help them recall the amount of drinking. The self-reported amount will then be used to determine the number of standard drink of alcohol consumed (one standard drink is equal to 10 g of ethanol) [27]. In the same way, current episodic heavy drinking will be considered as five or more drinks on any day in the past 30 days [27].

Diet

The dietary recall method will be used to collect information on the types, amount, and servings of vegetables and fruit consumed in the last three days. Measurement of the amount of fruit and vegetables will be aided by pictorial show cards and measuring cups (one standard serving of fruit or vegetables is equal to 80 g). Less than 400 g of fruit and vegetables intake in three days will be considered insufficient intake.

Anthropometric measurement

Height will be measured in centimeters with a portable standard stature scale with foot and head-wear off, and hair untied. Later, the height will be converted in meters for appropriate calculation of BMI. Weight will be recorded in kilograms with a portable digital scale by placing on a firm, flat surface. BMI will be calculated and categorized below normal ($<18.5\,kg/m^2$), normal (18.5–25.0 kg/m^2), overweight (25.0–$<30.0\,kg/m^2$), or obese ($\geq 30.0\,kg/m^2$) [26].

Clinical examination

A total of three readings of the systolic and diastolic blood pressure will be taken using an aneroid sphygmomanometer. Participants will be allowed to take a rest for 3 min between each reading. The participant will be required to wait for at least 30 min in case of any history of acute smoking or drinking a caffeinated drink. An average of the second and third readings was used as the final measurement for the analysis. Hypertension was defined as having a systolic blood pressure level of $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg or taking any antihypertensive medication.

The anthracycline-based chemotherapy regimens and dose will be determined in accordance with the standard treatment guidelines and national essential medicines list for Tanzania mainland.

Data processing and analysis

Data will be cleaned, edited, and coded before data analysis. Statistical Package for Social Sciences version 25.0 will be used to analyze the data. Descriptive statistics will be used to generate frequency distribution, mean, standard deviation, and cross tabulation to describe the characteristics of the study participants.

The comparisons between the pre-treatment and post-treatment levels of HDL, LDL, triglycerides, troponin, blood pressure, and change in QT intervals will be determined using independent *t*-tests.

Regression analysis will be conducted to determine the predictors of change in the outcome variables. The $P < 0.05$ will be considered statistically significant.

Dissemination of results

The findings of this study will be presented at the Central South University in China and to the University of Dodoma. Further, the findings will be communicated to the ORCI where this study will be conducted.

Furthermore, the findings will be presented with the Ministry of Health, Community Development, Gender, Elderly, and Children. In addition, we aim to publish the findings in a suitable peer-reviewed academic journal and present these at local and international conferences.

Ethical clearance and consent to participate

This study was submitted to the Directorate of Research, Publications, and Consultancy of the University of Dodoma and to the ethical committee for assessment and ethical approval.

Permission to conduct this study will be sought from the ORCI. This study is voluntary to participants. The participants will have the absolute right and freedom to withdraw from the study at any time with no effect to them.

To ensure confidentiality and anonymity, code numbers on the questionnaire will be used for identification rather than names. Participants found to have any cardiovascular or other life-threatening conditions will be assisted by research assistants to seek appropriate medical interventions.

Discussion

This will be the first study designed to evaluate the early cardiovascular outcomes of anthracycline-based chemotherapy in Tanzania. The results of this study will establish a need and a baseline for reference in designing various interventions to reduce cardiovascular morbidity and mortality among cancer patients in Tanzania.

Randomized controlled trials (RCTs) regarding the causal effect of cardiovascular disorders in cancer patients treated with anthracycline-based chemotherapy are limited. Although our study is not a full RCT, using the pre-/post-test design is likely to provide useful information regarding the causal effect of cardiovascular disorders in cancer patients treated with anthracycline-based chemotherapy. Such information may lay grounds for future RCTs.

Although anthracycline has been helpful in the treatment of several solid and blood cancers, the after-treatment cardiovascular complications raise several concerns regarding its use. The notable side effect of anthracycline is AIC which is often irreversible and may lead to clinical congestive heart failure [10]. Other toxicities of the anthracycline, including stomatitis, nausea and vomiting, and alopecia which are generally reversible.

Anthracycline-induced cardiotoxicity may be reduced or prevented by an administration schedule that produces low peak plasma drug concentrations, and by administration of dexrazoxane to provide cardioprotection. In Tanzania, while dexrazoxane is not yet authorized as a routine drug in preventing cardiotoxicity, administration schedules have been adjusted in such a way that bolus administration is avoided. Instead, short infusions of anthracycline mixed in 500 mL of normal saline running between 45 min to 1 h are preferred to produce a low peak plasma concentration. Modification of CVD risk factors remains the most effective strategy for primary prevention and/or management of CVDs in cancer patients [28]. At present, an educational program that focuses on risk modification is provided to each individual patient. However, its effectiveness in preventing early cardiovascular outcomes is ill known. Furthermore, cardiovascular management by a cardiologist to cancer patients is usually done when the patient begins to reveal features of cardiovascular deterioration. Therefore, this

study will reveal a burden of cardiovascular risk factors and post-treatment cardiovascular complications that guide early strategies for prevention.

Additionally, cancer and the use of anthracycline chemotherapy have been associated with increased prevalence of metabolic disorders which have an indirect influence on CVDs. For example, global estimate of cancer patients with diabetes mellitus, ranges between 8% and 18% [29], which is higher than the general population in high-, mid-, and low-income countries for women and men [15]. The shared risk factors between cancer and diabetes such as older age, male sex, obesity, and tobacco smoking [30] are also the risk factors for myocardial infarction and other cardiovascular complications of chemotherapy. Therefore, strengthening early identification programs and modification of risk factors may be more important in improving the overall morbidity and mortality due to cardiovascular and non-cardiovascular diseases.

The follow-up study will enable participants to report any early cardiovascular signs and symptoms that will lead to early seeking of appropriate management before developing severe cardiovascular diseases.

Supplementary data

Data not publically available, but may be accessed upon request.

Acknowledgments

Authors would like to acknowledge the University of Dodoma, Tanzania, Central South University, China, and the Chinese Scholarship committee for their commitment to support this project.

Author contributions

V.B. conceived the study and prepared the first draft for the background section. V.B., M.J., M.N., L.W., and L.Y. designed the study. M.J. and M.N. prepared the first draft for the "Materials and methods" section. L.W. prepared the first draft for the discussion section and M.Y. revised the first draft of the manuscript. All authors have read, approved, and will take the responsibility of any issues that might arise from the publication of this manuscript.

Funding

This work was supported by the Chinese Ministry of Education through the Chinese Scholarship Committee and the University of Dodoma. The grant will assist in the data collection process. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest statement. None declared.

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