Original Article

A Novel Scheme for Optimal Control of a Nonlinear Delay Differential Equations Model to Determine Effective and Optimal Administrating Chemotherapy Agents in Breast Cancer

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Abstract

Background: Determining the optimal and effective scheme for administrating the chemotherapy agents in breast cancer is the main goal of this scientific research. The most important issue here is the amount of drug or radiation administrated in chemotherapy and radiotherapy for increasing patient's survival. This is because in these cases, the therapy not only kills the tumor cells, but also kills some of the healthy tissues and causes serious damages. In this paper we investigate optimal drug scheduling effect for breast cancer model which consist of nonlinear ordinary differential time-delay equations.

Methods: In this paper, a mathematical model of breast cancer tumors is discussed and then optimal control theory is applied to find out the optimal drug adjustment as an input control of system. Finally we use Sensitivity Approach (SA) to solve the optimal control problem.

Results: The goal of this paper is to determine optimal and effective scheme for administering the chemotherapy agent, so that the tumor is eradicated, while the immune systems remains above a suitable level. Simulation results confirm the effectiveness of our proposed procedure.

Conclusion: In this paper a new scheme is proposed to design a therapy protocol for chemotherapy in Breast Cancer. In contrast to traditional pulse drug delivery, a continuous process is offered and optimized, according to the optimal control theory for time-delay systems.

Key words: Breast Neoplasm; Chemotherapy; Immune system; Optimal control

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Introduction

Cancer is one of the most dangerous illnesses, which causes many deaths every year. In a study done by the National Cancer Institute, there is approximately 40% chance for average individuals to develop cancer in their lifetime. This figure includes male and female of all races [1]. Among cancers, breast cancer is one of the most common ones. Near one in eight US women have been diagnosed with breast cancer in their life time [2]. In Iran, Similar to other part of the world breast cancer is the most prevalent malignancy among the women [3]. Surgery is the effective approach to control the disease but chemotherapy (CT) as an adjuvant or neoadjuvant pathway will help the patients and can improve the survival rate (OS= Overall Survival or DFS= Disease free Survival) [4,5]. Selecting the chemotherapy agents and combination with or without radiation therapy remained a scientific problem for oncologist, because of effectiveness of the medicine and complications of chemotherapy. So determining the optimal and effective scheme for

administrating the CT agents in breast cancer cases is the main goal of this scientific research. Although new medical techniques are developed by scientists who are interested in gene therapy and immunotherapy, these techniques are still in the beginning. Therefore traditional treatment regimes, such as chemotherapy and radiotherapy are still being practiced. The most important issue here is the amount of drug or radiation administrated in chemotherapy and radiotherapy for patient's survival. This is because in these cases, the therapy does not only kill the tumor cells; but also kills some of the healthy tissues and may result in serious damage; so the dosage of the therapy must be carefully adjusted in order to minimize damage of healthy tissue and maximize killing of tumor cells [6]. The interaction between the body's immune system, drugs, and a tumor is very complex. In order to obtain a manageable model, we briefly review some key details about this system. Like all eukaryotic cells, tumor cells have four distinct cell cycles: G1 (pre-synthetic) phase, S (synthetic) phase, G2 (post-synthetic) phase, and mitosis. The phases G1, S, and G2 are collectively known as the interphase stage which either the cell prepares for division or some cells have an additional stage known as the G0 (or quiescent phase). At this stage the cell refrains from dividing for a long period of time. A quiescent cell will need some stimuli to enter the cell cycle [7]. Some cells may never enter the quiescent phase, while others same as many nerve cells, may stay in it for their entire life cycle.

In recent years, several papers have been devoted to the problems of modeling and analysis of the interaction between cycle specific drugs, the immune system, and tumor cells. Swanson, et al. [8] modeled glioblastoma multiform (a malignant type of brain tumour) tumour growth using partial differential equations (PDE). Some researchers also investigated the tumour growth model by using cellular automata, which can include very specific characteristics of tumour, patient, and drug effectively in the model [9-11]. Anderson and Chaplain [12] and Enderling et al. [13] also used both PDE's and the cellular automata approach to the tumour growth model, angiogenesis, and metastasis. Another different approach is the work of de Pillis and Radunskaya [14] who constructed a general tumour growth model using ordinary differential equations showing the dynamics of tumour growth by means of numbers of tumours, healthy, and immune cells. They also included chemotherapy effect in the model and applied bang-bang type optimal control to adjust the amount of drug while trying to constrain the normal and immune cell populations above some level. In further works of de Pillis et al. [15, 16], new cancer models were proposed and the effect of chemotherapy and immunotherapy were investigated. Also, in breast cancer model some studies has been done by researchers [17, 18] based on Ordinary Differential Equations.

The theory of optimal control has been already applied to the cancer. For example Acharya et al. [19] discussed about optimal drug delivery. Swan [20] gives a review of the ways in which optimal control theory is applied to growth kinetic models, cell cycle models, and a classification of other models together suggesting better chemotherapy strategies. De Pillis et al. [21] also faced problems of administration of chemotherapy but considering the interesting question of immune resistance; similar works have been previously published [22-27].

In this paper we investigate optimal drug scheduling effect for breast cancer model, which consist of nonlinear ordinary differential equations with time-delay [28]. Similar works has been done using heuristic methods but with ignoring quiescent cells [17].

Materials and Methods

The Model proposed here comes from [28] the two previous models [17, 18] with small changes in the method of adding the effect of drug to the equations. This model, divides the population of tumor cells into interphase cells, mitosis cells, and quiescent cells, which are represented by $T_I(t)$, $T_M(t)$ and $T_Q(t)$ respectively. The term $I(t)$ represents the population of immune cells which are the cytotoxic T-cells. Also $u_1(t), u_2(t), u_3(t)$ are the effects of chemotherapy drug concentration in the tissue or blood, which are proportional amount of drug dose given to the patient by oral, injection, or in the future technology by some kind of portable pumps or straps which can supply drug continuously

to blood circulation. The resulting model is described by the following nonlinear delay differential equations:

$$\begin{cases} \dot{x}(t) = A_0 x(t) + A_1 x(t-\tau) + g(x,u) & , \quad t > 0 \\ x(t) = \phi(t) & , \quad -\tau \le t \le 0 \end{cases} \tag{1}$$

$$x(t) = [T_Q(t)\ T_I(t)\ T_M(t)\ I(t)]^T \ , \ u(t) = [u_1(t)\ \ u_2(t)\ \ u_3(t)]^T$$

$$\phi(t) = [0.01\ \ 0.015\ \ 0.01\ \ 0.01]^T$$

$$A_0 = \begin{bmatrix} -a_6 - d_4 & 0 & 0 & 0 \\ a_6 & -d_2 & 2a_4 & 0 \\ 0 & 0 & -d_3 - a_4 & 0 \\ 0 & 0 & 0 & -d_1 \end{bmatrix} \quad A_1 = \begin{bmatrix} 0 & 0 & 0 & 0 \\ a_5 & -a_5 - a_1 & a_1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$g(x,u) = \begin{bmatrix} -c_5 I(t) T_Q(t) - u_1(t) T_Q(t) \\ -c_5 T_I(t) I(t) \\ -c_3 T_M(t) I(t) - T_M(t) u_2(t) \\ k + \dfrac{\rho I(t) \left(T_Q(t) + T_I(t) + T_M(t)\right)^n}{\alpha + \left(T_Q(t) + T_I(t) + T_M(t)\right)^n} - c_2 I(t) T_I(t) - c_4 T_M(t) I(t) - c_6 T_Q(t) I(t) - I(t) u_3(t) \end{bmatrix}$$

All parameter values are in fractional amounts per day. Parameter τ is the resident time of cells that is considered 0.92 as the same in [28]. The constants a_1 and a_4 represent the fraction of cells, which change from interphase to mitosis and from mitosis to interphase, respectively. Both of these constants need to be between 0.2 and 1.0 per day. It is typical for these values to be between 0.7 and 1.0. The constants d_1, d_2 and d_3 represent fractions of natural cell death (apoptosis) and should be between 0.1 and 0.3. The constants c_i model represents the losses of cells due to an encounter with other cells. For immune cells, these numbers are usually around 0.1. When an immune cell and a cancer cells bind, approximately 10% of the time the immune cell is lost. For cancer cells this loss is somewhere around 20% to 30%.

$$\frac{\rho I(t) \left(T_Q(t) + T_I(t) + T_M(t)\right)^n}{\alpha + \left(T_Q(t) + T_I(t) + T_M(t)\right)^n} \tag{2}$$

As above, the term (2) represents the nonlinear

Table 1. Parameters used in the model

parameter	a_1	a_4	a_5	a_6	c_1	c_2	c_3
value	0.98	0.8	0.0001	0.00015	0.9	0.085	0.9
parameter	c_4	c_5	c_6	d_1	d_2	d_3	d_4
value	0.085	0.05	0.00085	0.029	0.11	0.11	0.11

growth of the immune population due to the presence of a tumor. The constant a_4 and a_5 are transition rate of the proliferating cells to the quiescent cells and the quiescent cells to the proliferating cells, respectively. The constant d_4 represent the natural death rate of the quiescent tumor cells. Table 1 summarizes all parameter values in this model.

By linearization of the above system around its initial nominal condition ϕ, the linear state space model can be achieved as follows:

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) + A_1 x(t-\tau) \quad , \quad t > 0 \\ x(t) = \phi(t) \quad , \quad -\tau \le t \le 0 \end{cases} \tag{3}$$

$$A = A_0 + \left.\frac{\partial g(X,u)}{\partial X}\right|_{(X,u)=(\phi,0)} \qquad B = \left.\frac{\partial g(x,u)}{\partial u}\right|_{(x,u)=(\phi,0)}$$

It has been assumed that $n = 2$ in (2).

Optimal Control Design Using Sensitivity Approach

In this section, we will use the optimal control theory for linear systems with state time-delay. Although the system is linear, but time-delay in the model leads to two point boundary value problem (TPBVP), by not only time- delay terms but also time-advance terms [29]. Consequently, solving the optimal control problem is very difficult even for simple time delay systems, either exact solutions or numeral solutions. [28] An efficacious approach (Sensitivity Approach) was proposed to solve optimal control of linear systems with state time-delay. In this approach TPBVP was obtained from necessary conditions of optimality containing time-delay and time-advance terms and then translating into infinite TPBVPs without time- delay and time-advance terms. Through intercepting frontal finite terms of the optimal series solution, a suboptimal control law is obtained; the number of the terms intercepted is dependent on the size of the time-delay. The method is especially suitable for the synthesis of small time-delay systems. For better understanding of the method, consider the linear system (3) with the following cost functional:

$$J = \frac{1}{2} x^T(t_f) S\, x(t_f) + \frac{1}{2}\int_0^{t_f} [x^T(t) Q\, x(t) + u^T(t) R\, u(t)]dt \tag{4}$$

Where Q and S are positive semi-definite, and R is a positive definite matrices of appropriate dimensions, respectively. If $t \to \infty$, the cost functional is as follow:

$$J = \frac{1}{2}\int_0^{\infty} [x^T(t) Q\, x(t) + u^T(t) R\, u(t)]dt \tag{5}$$

The optimal control problem is to find out an optimal control law $u^*(t)$; the cost functional (4) is minimized while the dynamic equality constraint (3) is satisfied. According to the Pontryagin's maximum principle, the optimality condition is obtained as the following nonlinear TPBVP:

$$\begin{cases} \dot{x}(t) = Ax(t) + A_1 x(t-\tau) + B - R^{-1}B^T p(t) \quad , \quad 0 \le t \le t_f \\ \dot{p}(t) = \begin{cases} -Q\,x(t) - A^T p(t) - A_1^T p(t+\tau) \quad , \quad 0 \le t \le t_f - \tau \\ -Q\,x(t) - A^T p(t) \quad , \quad t_f - \tau \le t \le t_f \end{cases} \end{cases} \tag{6}$$

With the boundary conditions:

$$\begin{cases} x(t) = \phi(t) \quad , \quad -\tau \le t \le 0 \\ p(\infty) = Sx(t_f) \end{cases} \tag{7}$$

Then the control law can be expressed as follow:

$$u^*(t) = -BR^{-1}B^T p(t) \tag{8}$$

The TPBVP (6)-(7) concludes not only time-delay term but also time-advance term. It is difficult to solve this problem even numerical. In the sequel the TPBVP (6)-(7) is translated into a sequence of linear TPBVPs without time-delay and time-advance terms. By solving that sequence recursively and through intercepting frontal N terms of infinite series solution parts in the expression of the optimal control law $u^*(t)$; we obtain a suboptimal control law in the form of state feedback, which increases robustness of the solution.

Sensitivity Approach

First, we introduce a sensitivity parameter ε in TPBVP (6)-(7) and obtain the following TPBVP including sensitivity coefficient ε

$$\begin{cases} \dot{x}(t,\varepsilon) = Ax(t,\varepsilon) + \varepsilon A_1 x(t-\tau,\varepsilon) - BR^{-1}B^T p(t,\varepsilon) \quad , \quad 0 \le t \le t_f \\ \dot{p}(t,\varepsilon) = \begin{cases} -Q\,x(t,\varepsilon) - A^T p(t,\varepsilon) - \varepsilon A_1^T p(t+\tau,\varepsilon) \quad , \quad 0 \le t \le t_f - \tau \\ -Q\,x(t,\varepsilon) - A^T p(t,\varepsilon) \quad , \quad t_f - \tau \le t \le t_f \end{cases} \\ x(t,\varepsilon) = \phi(t) \quad , \quad -\tau \le t \le 0 \\ p(\infty,\varepsilon) = Sx(t_f) \end{cases} \tag{9}$$

where $0 \le \varepsilon \le 1$ is a scalar. In the following discussion, we always assume that the solution of TPBVP (9) is uniquely existed, and $x(t,\varepsilon)$, $p(t,\varepsilon)$ with parameter ε are infinitely differentiable with respect to the ε around $\varepsilon = 0$, and their Maclaurin series expansions are convergent at $\varepsilon = 1$; obviously when $\varepsilon = 1$, TPBVP (9) is equivalent to original problem (6).

According to this assumption, we can write:

$$\begin{cases} x(t,\varepsilon) = \sum_{i=0}^{\infty} \dfrac{\varepsilon^i x^{(i)}(t)}{i!} \\ p(t,\varepsilon) = \sum_{i=0}^{\infty} \dfrac{\varepsilon^i p^{(i)}(t)}{i!} \end{cases} \tag{10}$$

Now by substituting (10) into (9) and equating terms with the same order of ε on each side we have:

$$\begin{cases} \dot{x}^{(0)}(t) = Ax^{(0)}(t) - BR^{-1}B^T p^{(0)}(t) \\ \dot{p}^{(0)}(t) = -Qx^{(0)}(t) - A^T p^{(0)}(t) \\ x^{(0)}(0) = \phi(t) \ , \ p^{(0)}(\infty) = Sx(t_f) \end{cases} \tag{11}$$

$$\vdots$$

$$\begin{cases} \dot{x}^{(i)}(t) = Ax^{(i)}(t) - BR^{-1}B^T p^{(i)}(t) + A_1 x^{(i-1)}(t-\tau) \\ \dot{p}^{(i)}(t) = \begin{cases} -Qx^{(i)}(t) - A^T p^{(i)}(t) - A_1^T p^{(i-1)}(t+\tau) & , \quad 0 \le t < t_f - \tau \\ -Qx^{(i)}(t) - A^T p^{(i)}(t) & , \quad t_f - \tau < t \le t_f \end{cases} \\ x^{(i)}(0) = 0 \ , \ p^{(i)}(\infty) = 0 \\ i = 1,2,3,... \end{cases} \tag{12}$$

It should be noted that in (12) $x^{(i-1)}(t-\tau)$ and $p^{(i-1)}(t+\tau)$ are known from previous iteration so (11)-(20) is a sequence of inhomogeneous linear TPBVPs without time-delay and time-advance terms in each iteration.
After determining $x^{(i)}(t)$ and $p^{(i)}(t)$ for $i \ge 0$, $x(t,\varepsilon)$ and $p(t,\varepsilon)$ can be determined as the solution of TPBVP (9) by using (10). Consequently, at $\varepsilon = 1$, (9) and (8) are equivalent, so we have:

$$\begin{cases} x(t) = x(t,1) = \sum_{i=0}^{\infty} \dfrac{x^{(i)}(t)}{i!} \\ p(t) = p(t,1) = \sum_{i=0}^{\infty} \dfrac{p^{(i)}(t)}{i!} \end{cases} \tag{13}$$

If we stop the procedure at this step, by using (8) and (13) we can find the optimal control law which is an open loop control; but for obtaining a close loop control in the form of state feedback, we continue our discussion by assuming that i th-order terms of $p(t)$ in (12) be

$$p^{(i)}(t) = Kx^{(i)}(t) + g_i(t) \tag{14}$$

where K is the unique positive solution of the Riccati matrix equation

$$A^T K + KA - KBR^{-1}B^T K + Q = 0 \tag{15}$$

And $g_0(t) = 0$. Substituting (14) into (12) yields

$$\begin{cases} \dot{x}^{(0)}(t) = (A - BR^{-1}B^T K)x^{(0)}(t) \\ x^{(0)}(0) = \phi(t) \\ p^{(0)}(t) = Kx^{(0)}(t) \end{cases}$$

$$\vdots$$

$$\begin{cases} \dot{x}^{(i)}(t) = (A - BR^{-1}B^T K)x^{(i)}(t) - BR^{-1}B^T g_i(t) + A_1 x^{(i-1)}(t-\tau) \quad , \quad 0 \le t \le t_f \\ \dot{g}_i(t) = \begin{cases} Mx^{(i)}(t) + Zg_i(t) + w_i(t) \quad , \quad 0 \le t < t_f - \tau \\ Mx^{(i)}(t) + Zg_i(t) - A_1 x^{(i-1)}(t-\tau) \quad , \quad t_f - \tau \le t \le t_f \end{cases} \\ x^{(i)}(0) = 0 \quad , \quad g_i(\infty) = 0 \\ i = 1,2,3,... \end{cases} \tag{16}$$

where

$$M = -(KA - KBR^{-1}B^T K + Q + A^T K) \tag{17}$$

$$Z = BR^{-1}B^T - A^T \tag{18}$$

$$w_i(t) = (A_1 - A_1^T K)x^{(i-1)}(t+\tau) - A_1^T g_{i-1}(t+\tau) \tag{19}$$

and $g_0(t) = 0$ for $-\tau \le t < 0$. After solving (16), we can obtain $x^{(i)}(t), g_i(t)$ and consequently, $p^{(i)}(t)$ according to (14) for $i = 0,1,2,...$ by using, (13) the optimal state trajectory $x(t)$ and optimal co-state vector $p(t)$ can be determined. Optimal control law would be:

$$u^*(t) = -R^{-1}B^T\left(Kx(t) + \sum_{i=1}^{\infty}\frac{g_i(t)}{i!}\right) \tag{20}$$

It should be noted that the state feedback term in (20) is the exact solution. In practice, calculating infinite terms of series in (16) is almost impossible, intercepting N terms of the series, we obtain a suboptimal solution

$$u(t) = -R^{-1}B^T\left(K\sum_{i=0}^{N}\frac{x^{(i)}(t)}{i!} + \sum_{i=1}^{N}\frac{g_i(t)}{i!}\right) \tag{21}$$

Results

It is known that at the early stages of carcinogenesis, immune cells fight against the tumor cells. Depending on the aggressiveness of the tumor and strength of the patient's immune system, carcinogenesis can be avoided, meaning the system goes to an equilibrium corresponding to a zero tumors level. However, if the immune system of the patient is weak, the tumor cells population cannot be inhibited and the system goes to a large tumor equilibrium point, causing patient's death. It is desired that the immune cells are kept in a specific range above the tumor cells level. For this, we should define $I_{new}(t) \overset{\Delta}{=} I(t) - r$ as a new state variable in (1), in which r represents a constant desired value of immune cells level. In this simulation, we take $R = 1$, $S = 0$ and Q as a unity matrix of dimension four. After simulation, it is clear that the optimal control functions, which show the effect of drug concentration in the blood, can effectively control the system. In 20 days time, the population of tumor cells decreases to zero whereas immune cells remain at the upper level. Also, in figure 2 the effects of the drug using chemotherapy agents can be seen. Constructing an agent of this concentration with this effect in the blood is beyond the paper's goal. Also

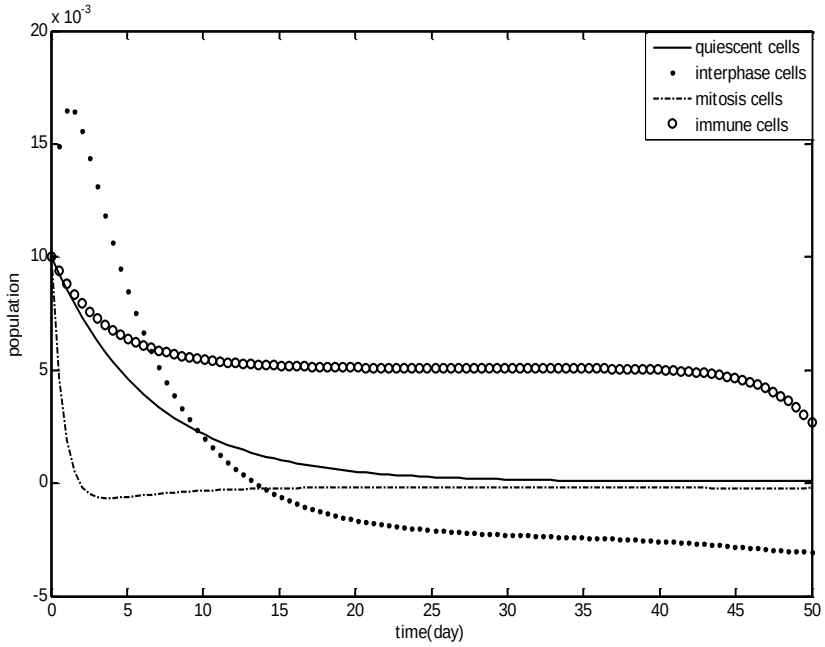

Figure 1. Population of cells during therapy

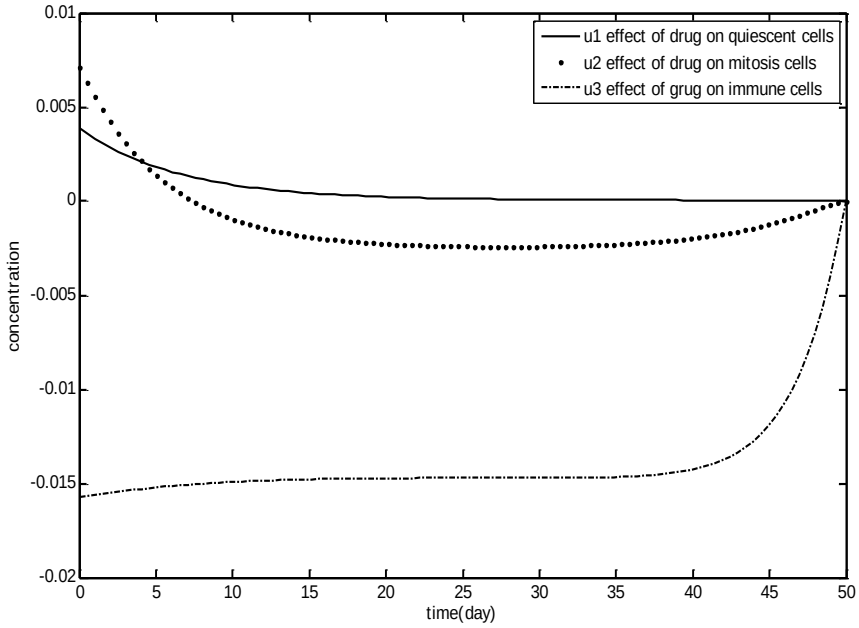

Figure 2. Drug effect on cells

we just offered a new therapy protocol. This computational approach may not prove to be practical and requires further experiment for validation of its approach.

Conclusion

In this paper a new scheme is proposed to design a chemotherapy protocol in breast cancer. In contrast to traditional pulse drug delivery, a continuous process is offered and optimized according to the optimal control theory for time-delay systems. The results are in a research stage and there is no guarantee for real cases to use this procedure. Experimental works are needed to validate this scheme.

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Conflict of Interest

The authors have no conflict of interests in this article.

Authors' Contribution

RHR conceived, designed the study, interpreted the results, draft the manuscript and carried out the data analyses. SS participated in writing and revising the manuscript, while AME revised the final manuscript. All authors read and approved the final manuscript.

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