A Mathematical Model for The Treatment Cost Estimation of Breast Cancer with Cardiotoxicity

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***Abstract*—Breast cancer is a prevalent and potentially life-threatening disease that requires comprehensive treatment strategies to improve patient outcomes. Cardiotoxicity poses a significant challenge in breast cancer treatment, as it can lead to severe cardiac complications during or after chemotherapy. In this paper, the study presents a stochastic model for estimating breast cancer treatment costs, considering the risk and cost associated with cardiotoxicity. The findings reveal that an increased number of new patients and a higher chance of breast cancer patients experiencing cardiotoxicity increase the total cost of treating all breast cancer patients.**

***Index Terms*—Breast cancer, chemotherapy, cardiotoxicity, treatment cost.**

I. Introduction

ACCORDING to the World Health Organization (WHO), cancer remains a critical global health concern, accounting for 13% of deaths yearly. This figure is predicted to continue increasing in the future. Breast cancer affects millions of women worldwide, and women aged 35-60 years have a six-fold higher risk for breast cancer [1]. Medical advancements have significantly improved the prognosis for breast cancer patients. The factors affecting breast cancer patient's survival are the type of treatment, chemotherapy regimen, and stage of cancer [2].

Various treatment options are available for breast cancer patients, including chemotherapy, hormone therapy, and radiotherapy. Chemotherapy is often recommended as the primary treatment, but it has potential side effects such as cardiotoxicity and neutropenia. Cardiotoxicity is a progressive and usually permanent impairment of diastolic function, followed by left ventricular systolic dysfunction, cardiac arrhythmias, low electrocardiographic voltages, and elevated cardiac troponin levels. It represents a significant adverse effect that may arise during breast cancer treatment for women. Notably, breast cancer survivors suffering from cardiovascular disease face an even higher mortality risk [3]. Fatoni et al. [4] [5] point out that cardiotoxicity is particularly prevalent among patients with stage 3 and stage 4 breast cancer. This side effect is well documented in chemotherapy regimens involving anthracyclines, among the two main drugs employed in breast cancer treatment [6]. Deterministic and stochastic models have been used in research on cancer systems [7] [8]. Furthermore, several mathematical models of the side effects of chemotherapy have been developed. Fathoni [4] discussed a mathematical model of the chemotherapy effect on the heart of breast cancer patients depending on the stage of cancer. Tang [9] showed that the dynamic behavior of the effects of cancer treatment, especially chemotherapy reactions, on the patient's heart can be visualized in a fractional framework.

The financial burden of treatment poses a significant challenge for healthcare providers and patients. Additionally, the potential cardiotoxicity associated with specific chemotherapy regimens adds further complexities to treatment planning and cost estimation [10] [11]. Blumen et al. [12] reported a significant increase in the cost of treating advanced cancer, which is further exacerbated by the additional medications needed to counteract or mitigate the side effects of treatment. Treatment plans and settings influence cancer treatment costs. Moreover, the costs rise as the cancer stage advances and when treatments such as surgery, chemotherapy, radiation therapy, or hormone therapy are repeated. Indirect costs, such as transportation, caregiving, and secondary effects, also contribute to the overall expenses. Therefore, a medical cost model is essential to estimating future financial requirements for successful treatment. Xu et al. [13] utilized a hierarchical generalized linear model (H-GLM) to examine the impact of patient characteristics, cancer type, and therapy on breast cancer treatment costs, revealing significant differences in early cancer care spending. In addition to cancer stage and location, the treatment component also significantly impacts the cost variations [14].

Insurance serves as a financial instrument that provides guarantee and financial protection against future losses. Cancer health insurance emerges as a suitable solution for alleviating the financial burden associated with cancer care and treatment. The hope is that insured patients will be shielded from financial hardships due to medical expenses and hospital care. To determine insurance premiums accurately, insurance companies must estimate the treatment costs incurred by cancer patients.

Cancer prevalence, derived from cancer incidence and survival models, offers a means to predict cancer treatment expenses [15] [16]. Moreover, Bugge et al. [17] utilize the Kaplan-Meier survival model to estimate lifetime and future expenditures for cancer patients. Furthermore, Wahl et al. [18] employ a tumor cell growth-based model to calculate the cost of radiotherapy for cancer treatment. The likelihood of tumor cure significantly impacts the overall cost of the

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provided treatment. This probability follows an exponential pattern determined by the tumor cell measurement, as derived from the mathematical model of tumor growth.

Previous studies have not explored the estimated cost of cancer treatment that encompasses the expenses related to treatment side effects. Subsequently, there is a demand from healthcare providers, policymakers, and insurance companies to estimate the treatment cost of breast cancer while considering the impact of cardiotoxicity in order to optimize healthcare resource allocation and improve the quality of care for breast cancer patients. In this study, a mathematical model is developed to estimate the incidence of cardiotoxicity in breast cancer patients after chemotherapy. Next, this mathematical model is employed to construct a comprehensive medical cost model.

II. Model Formulation

In this section, we constructed a mathematical model that simulates the occurrence of cardiotoxicity in patients undergoing chemotherapy. Among breast cancer patients receiving chemotherapy, various reactions are observed: some succumb to the treatment, some achieve a cure, and others experience cardiotoxicity during or after the treatment. We categorized breast cancer patients into three subgroups: breast cancer patients undergoing chemotherapy (A), patients who have become cancer-free (F), and patients with cardiotoxicity (C). Figure 1 displays a flow chart representing the model, depicting the flow compartments of all variables observed in the population.

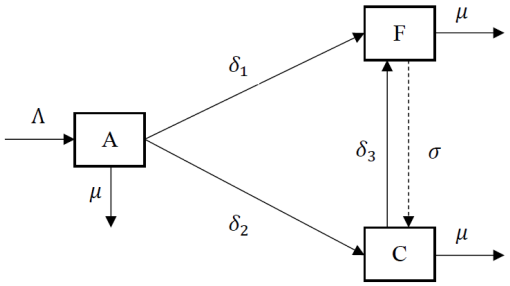

Figure 1: Patient Transfer Chart

Newly diagnosed breast cancer patients receiving chemotherapy are added at a rate of Λ. Among these patients, cardiotoxicity can occur during chemotherapy with a transfer rate of δ_2, and some patients may achieve cancer-free status at a rate of δ_1. Furthermore, all compartments experience natural mortality at an equal rate. This dynamic can be represented by the following equation:

$$\frac{dA}{dt} = \Lambda - (\delta_1 + \delta_2 + \mu)A.$$

The cardiotoxicity compartment is formed by breast cancer patients who develop cardiotoxicity during chemotherapy, and some patients may be declared cancer-free with a rate of δ_3, moving to the cancer-free compartment. The dynamic of the cardiotoxicity compartment is

$$\frac{dC}{dt} = \delta_2 A - (\delta_3 + \mu)C.$$

The cancer-free compartment comprises breast cancer patients who have been declared cancer-free after chemotherapy, including those who did not experience cardiotoxicity during treatment and those who did. The dynamic of the cancer-free patient population is described as follows:

$$\frac{dF}{dt} = \delta_1 A + \delta_3 C - \mu F.$$

Combining all the dynamic equations, we obtain the following system model:

$$\begin{aligned} \frac{dA}{dt} &= \Lambda - (\delta_1 + \delta_2 + \mu)\, A, \\ \frac{dC}{dt} &= \delta_2 A - (\delta_3 + \mu)\, C, \\ \frac{dF}{dt} &= \delta_1 A + \delta_3 C - \mu F, \end{aligned} \tag{1}$$

where the initial condition are

$$A(0) > 0, C(0) > 0, F(0) > 0.$$

Detailed information regarding the parameters can be found in the Table I.

Table I: Model parameters

Parameter	Description
Λ	The number of new patients diagnosed with breast cancer
δ_1	The rate at which patients diagnosed with breast cancer will recover
δ_2	The rate at which breast cancer chemotherapy patients will experience cardiotoxicity
δ_3	The rate at which breast cancer patients who experience cardiotoxicity will be recover from cancer
μ	The death rate of breast cancer patients

Based on clinical practice reports, long-term breast cancer survivors risk developing cardiotoxicity due to their treatment regimen, typically occurring around ten years after being declared cancer-free [19]. This cardiac issue has become a persistent side effect for breast cancer patients [20]. Moreover, these survivors are also susceptible to developing a second breast cancer [21]. Consequently, in this study, we extended the deterministic system (1) by introducing a stochastic noise parameter in the rate of survivors who experience cardiotoxicity.

$$\begin{cases} dA = (\Lambda - (\delta_1 + \delta_2 + \mu)\, A)\, dt, \\ dC = (\delta_2 A - (\delta_3 + \mu)\, C)\, dt + \sigma F dB(t), \\ dF = (\delta_1 A + \delta_3 C - \mu F)\, dt - \sigma F dB(t). \end{cases} \tag{2}$$

where σ is the intensity of the white noise and $B(t)$ is a standard Brownian motion. A detailed explanation of the remaining parameters in the stochastic model (2) can be found in Table I.

Theorem 2.1: Given

$$\Gamma = \left\{ (A, C, F) \in \mathbb{R}^3_+ : 0 < A \leq \frac{\Lambda}{\alpha}, \right. \\ \left. 0 < C + F \leq (\delta_1 + \delta_2) \left(\frac{\Lambda}{\alpha \mu} \right) \right\},$$

then Γ is positively invariant and bounded for System (2) for every $t \geq 0$.

Proof: Based on System (2), take $\alpha = \min\{\delta_1, \delta_2, \mu\}$ then we have

$$\begin{aligned} dA &= (\Lambda - (\delta_1 + \delta_2 + \mu)A)\, dt \\ &\leq (\Lambda - \alpha A)\, dt. \end{aligned}$$

Hence we get

$$A(t) \leq \frac{\Lambda}{\alpha} + \left(A(0) - \frac{\Lambda}{\alpha}\right) e^{-\alpha t}$$

and for $t \to \infty$, $A(t) \leq \dfrac{\Lambda}{\alpha}$.

Next, by taking $N(t) = C(t) + F(t)$ as the number of patients who are either declared cancer-free or suffer from cardiotoxicity at time t, we obtain

$$\begin{aligned} dN &= dC + dF, \\ &= ((\delta_1 + \delta_2)A - \mu(F + C))\, dt, \\ &= ((\delta_1 + \delta_2)A - \mu N)\, dt, \end{aligned}$$

and since $A(t) \leq \dfrac{\Lambda}{\alpha}$, it holds

$$dN \leq \left((\delta_1 + \delta_2)\left(\frac{\Lambda}{\alpha}\right) - \mu N\right) dt.$$

Thus

$$\begin{aligned} N(t) &\leq (\delta_1 + \delta_2)\left(\frac{\Lambda}{\alpha\mu}\right) \\ &+ \left(N(0) - (\delta_1 + \delta_2)\left(\frac{\Lambda}{\alpha\mu}\right)\right) e^{-\mu t}. \end{aligned}$$

For $t \to \infty$, we obtain $N(t) \leq (\delta_1 + \delta_2)\left(\dfrac{\Lambda}{\alpha\mu}\right)$.

On the other hand, we have

$$\begin{aligned} dA &= (\Lambda - (\delta_1 + \delta_2 + \mu)A)\, dt, \\ &\geq -(\delta_1 + \delta_2 + \mu)A dt, \end{aligned}$$

and thus

$$A(t) \geq A(0) e^{-(\delta_1 + \delta_2 + \mu)t}.$$

Since $A(0) > 0$, then for $t \geq 0$, $A(t) > 0$.

Analogously, we obtain

$$\begin{aligned} dN &= ((\delta_1 + \delta_2)A - \mu N)\, dt, \\ &\geq -\mu N dt, \end{aligned}$$

and the solution is

$$N(t) \geq N(0) e^{-\mu t}.$$

Since $C(0) > 0$ and $F(0) > 0$, we obtain $N(0) > 0$ and thus $N(t) > 0$.

Therefore, it is proved that $A(t) \in (0, \frac{\Lambda}{\alpha}]$ and $0 < C(t) + F(t) \leq (\delta_1 + \delta_2)\left(\frac{\Lambda}{\alpha\mu}\right)$ for all $t \in [0, T]$. ■

III. Treatment Cost Model

After being diagnosed with breast cancer, individuals will receive different treatments depending on the stage of cancer determined by their doctor. These treatments involve various considerations, such as the treatment type, plan, and duration. Chemotherapy is one of the most frequent methods for treating cancer.

Numerous research studies have been conducted to identify the potential adverse effects of cancer therapy. One potential consequence arising from the medications administered during chemotherapy is cardiotoxicity [26]. This adverse reaction can occur either while the patient is undergoing treatment or even after they have been declared cancer-free. It is important to emphasize that not all patients experience this side effect.

Cancer therapy is undoubtedly expensive. Every breast cancer patient requires comprehensive treatment, which includes the use of specialized drugs. When patients experience treatment-related side effects, additional measures are needed to reduce or eliminate these adverse effects, leading to a prolonged treatment period and increased costs.

The financial burden associated with cancer treatment comprises direct medical, direct non-medical, and indirect costs. Direct medical expenses encompass payments made for medical services such as physician consultations, medications, medical supplies, and hospitalization fees. On the other hand, non-medical costs are not directly related to medical services, such as transportation, household assistance, wigs, and other miscellaneous expenses. Variations in treatment type, treatment duration, and the number of medications and procedures received by the patient can contribute to fluctuations in overall treatment costs.

The estimated cost of treating breast cancer patients experiencing cardiotoxicity side effects per treatment period comprises planned and additional treatment costs. The planned medical costs encompass expenses for medical services and oral drugs administered during each scheduled treatment period. Additional medical costs are attributed to cardiotoxic conditions arising during or after chemotherapy. This paper assumes that all breast cancer patient's average costs remain constant in each treatment period.

Let t represent the chemotherapy period, with the average time between treatments for each patient at three weeks. At period t, patients who have not yet achieved cancer-free status will receive chemotherapy and additional treatment for their side effects, specifically cardiotoxicity. Then, the total cost of treating the entire population of breast cancer patients can be formulated as follows:

$$T_{cost} = C_{plan}(A + C) + C_{car}C \tag{3}$$

where A and C, defined in System (2), are breast cancer patients undergoing chemotherapy and patients with cardiotoxicity; respectively, C_{plan} is the planned treatment cost, and C_{car} is the cardiotoxicity treatment cost.

Equation (3) can be expressed in a stochastic differential equation as

$$\begin{aligned} dT_{cost} &= C_{plan}dA + (C_{plan} + C_{car})dC, \\ &= C_{plan}\left(\Lambda - (\delta_1 + \delta_2 + \mu)A\right) dt + (C_{plan} \\ &\quad + C_{car})\left((\delta_2 A - (\delta_3 + \mu)C)\, dt + \sigma F dB(t)\right) \\ &= (C_{plan}(\Lambda - (\delta_1 + \mu)A - (\delta_3 + \mu)C) \\ &\quad + C_{car}(\delta_2 A - (\delta_3 + \mu)C))\, dt \\ &\quad + (C_{plan} + C_{car})\sigma F dB(t) \end{aligned} \tag{4}$$

where σ is the intensity of the white noise, $B(t)$ is a standard Brownian motion, and other parameters are defined in Table I.

IV. Numerical Simulation

In this section, we carried out numerical simulations to explore the outcomes of our proposed system and medical cost model. We take the parameter values $\Lambda = 36$, $\delta_1 = 0.36$, $\delta_2 = 0.3$, $\delta_3 = 0.2$, and $\mu = 0.56$ and the initial values are $A(0) = 64$ patients, $C(0) = 10$ patients, and $F(0) = 10$ patients [4].

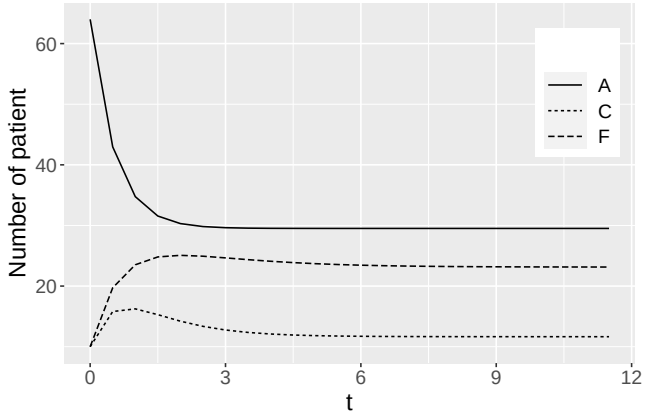

Figure 2: The trajectory solution of the System (1)

Figure 2 shows the trajectory solution of system (1) (where $\sigma = 0$). This figure shows that the number of patients diagnosed with breast cancer is decreasing until it finally stabilizes around 29 patients. As for patients who recovered after completing a series of chemotherapy, there are 10 patients at $t = 0$, and there are about 23 patients at $t \to \infty$. It is also seen that the number of patients suffering from cardiotoxicity after chemotherapy was ten at the beginning of the period and approximately 11 at $t \to \infty$. It is also clear that for every $t_1, t_2 \in [0, \infty)$, where $t_1 < t_2$, $A(t_1) \geq A(t_2)$. However, for every $t_1, t_2 \in [2, \infty)$, $C(t_1) \geq C(t_2)$ and $F(t_1) \geq F(t_2)$. It indicates that the function of classes A, C, and F is monotonically descending for $t \in [2, \infty)$.

Afterward, we utilize the Euler-Maruyama Method to determine the solution of the system (2). The discretized version of the system (2) is as follows:

$$\begin{cases} A_{i+1} = A_i + (\Lambda - (\delta_1 + \delta_2 + \mu)\, A_i)\, \Delta t, \\ C_{i+1} = C_i + (\delta_2 A_i - (\delta_3 + \mu)\, C_i)\, \Delta t + \sigma F_i \sqrt{\Delta t} Z, \\ F_{i+1} = F_i + (\delta_1 A_i + \delta_3 C_i - \mu F_1)\, \Delta t - \sigma F_i \sqrt{\Delta t} Z, \end{cases}$$

where $t \in [t_0, t_N]$, $\Delta t = \frac{t_N - t_0}{N}$, and Z is normally distributed $N(0, 1)$. Figure 3 shows the value distribution for each class in the system (2), with $\sigma = 0.05$ and 10 paths. Moreover, the discretization form of the cost model (4) is given as

$$\begin{aligned} T_{cost(i+1)} \quad = \quad & T_{cost(i)} + (C_{plan}(\Lambda - (\delta_1 + \mu)A_i \\ & -(\delta_3 + \mu)C_i) + C_{car}(\delta_2 A_i - (\delta_3 + \mu)C_i)) \\ & \Delta t + (C_{plan} + C_{car})\sigma F_i \sqrt{\Delta t} Z. \end{aligned}$$

As reported in [14], individuals without health insurance might face a minimum monthly expense of $290 for breast cancer treatment during the first 12 months following diagnosis. Patients are typically charged an average extra $289.67 for cardiotoxicity-related direct expenses, encompassing primary care, outpatient care, inpatient care, prehospital emergency and ambulatory care, and pharmaceutical costs [27]. Based on these findings, the total cost estimate for breast cancer treatment in the initial period is $T_{cost}(0) = (A(0) + C(0))C_{plan} + C(0)C_{car}$. Figure 4 illustrates that the average total treatment cost decreases each treatment period. Nevertheless, it tends to stabilize at approximately $15,000 after the fifth period.

Figures 4-6 illustrate the outcomes of simulations related to the overall treatment expenses under various σ (standard deviation) levels. These figures demonstrate that as σ approaches zero, the expected total costs become more uniform and steady. Nevertheless, for all σ values, the confidence intervals expand as time (t) progresses. Simply put, the variability in total treatment costs increases as time increases.

In this study, we also investigated the influence of each parameter on the overall cost of breast cancer treatment

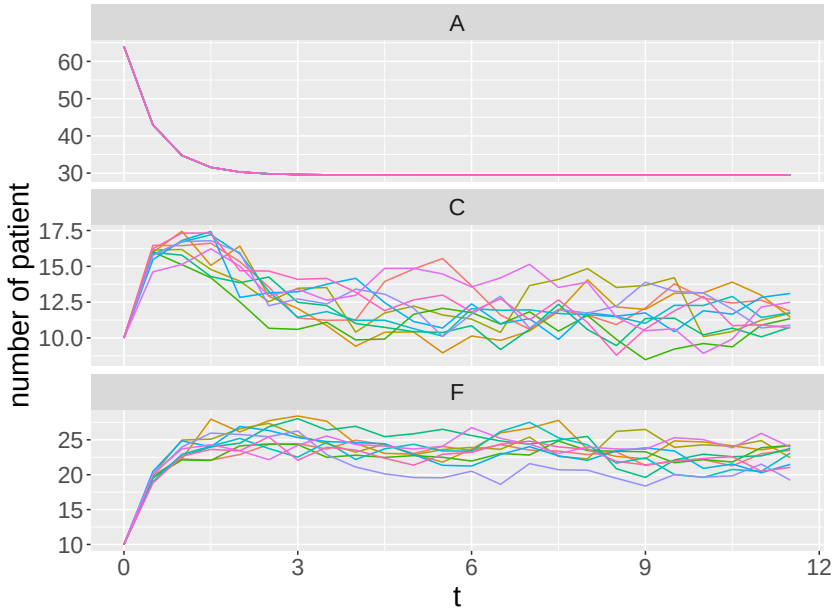

Figure 3: The solution of the System (2) with $\sigma = 0.05$, 10 paths

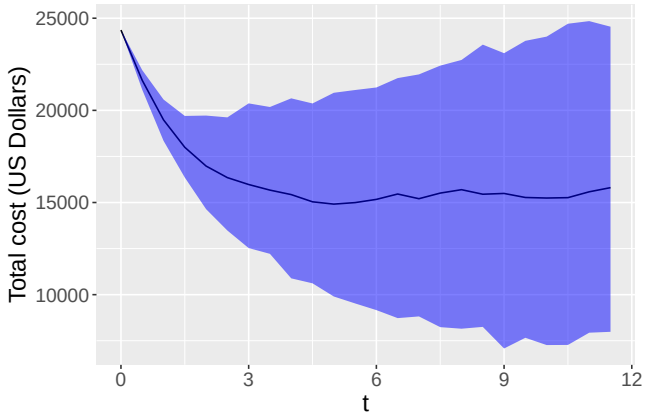

Figure 4: Simulation Result for Cost of Treatment with a confidence interval of 95 % and $\sigma = 0.05$

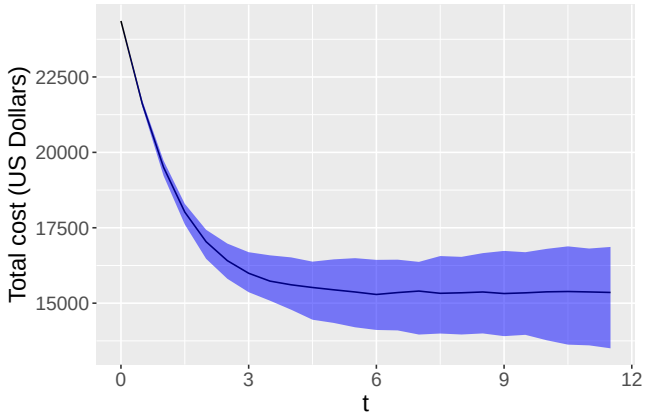

Figure 5: Simulation Result for Cost of Treatment with a confidence interval of 95 % and $\sigma = 0.01$

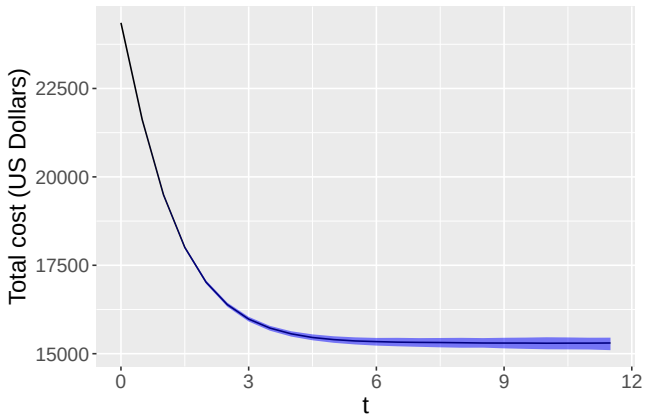

Figure 6: Simulation Result for Cost of Treatment with a confidence interval of 95 % and $\sigma = 0.001$

during each treatment phase. The impact is presented in Table II. The total cost of treatment demonstrates a positive correlation with Λ. This suggests that a higher number of recently diagnosed breast cancer patients lead to an elevation in the overall cost of breast cancer treatment for each treatment phase. Conversely, fluctuations in cancer recovery rates, both for patients without cardiotoxicity and those experiencing cardiotoxicity, have an adverse effect on the total treatment expenses for each session. The overall treatment expense diminishes when δ_1 or δ_3 values rise. The parameter μ, which signifies the mortality rate, demonstrates a comparable trend. A heightened mortality rate reduces total treatment costs because fewer patients necessitate ongoing therapy. Furthermore, as illustrated in Table II, an elevated patient growth rate with cardiotoxicity resulting from chemotherapy (δ_2) results in a rise in the overall treatment expenditure.

Table II: Total cost simulation with $\sigma = 0.001$ and 100 paths

Parameter	$T_{cost}(t)$				
	$t=1$	$t=2$	$t=3$	$t=4$	$t=5$
Λ					
24	16,551	12,784	11,217	10,602	10,362
30	18,018	14,903	13,601	13,085	12,883
36	19,494	17,027	15,987	15,577	15,413
δ_1					
0.30	20,263	17,875	16,812	16,380	16,211
0.36	19,494	17,027	15,987	15,577	15,413
0.42	18,751	16,243	15,227	14,832	14,672
δ_2					
0.2	18,312	15,830	14,845	14,463	14,303
0.3	19,494	17,027	15,987	15,577	15,413
0.4	20,580	18,042	16,944	16,511	16,336
δ_3					
0.1	20,146	18,077	17,123	16,688	16,488
0.2	19,494	17,027	15,987	15,577	15,413
0.3	18,872	16,115	15,067	14,703	14,585
μ					
0.44	21,860	20,132	19,220	18,775	18,563
0.50	20,654	18,501	17,486	17,043	16,852
0.56	19,494	17,027	15,987	15,577	15,413

V. Discussion

Cancer insurance providers necessitate an estimation of treatment costs (3) and its variability. These estimates play a crucial role in determining insurance premiums and benefits. The more costly cancer treatment becomes, the larger the insurance claim becomes. Increased variability and standard deviation in medical expenses raise the risk for insurance companies to pay more for insurance benefits.

Insurance companies might implement restrictions on insurance benefits to address the issue of high expenses and fluctuations in cancer treatment costs. For instance, the maximum benefit offered in each period is $\mu_{cost} + k\sigma_{cost}$, where μ_{cost} represents the average medical cost per period, k is a constant, and σ_{cost} signifies the standard deviation of medical costs per period. It is evident that $k\sigma_{cost}$ reflects a company's capacity to cover expenses that surpass the average medical cost.

VI. Conclusion

In this study, we formulated a mathematical model to represent the dynamics of breast cancer patients undergoing chemotherapy, particularly those experiencing cardiotoxicity as a side effect. Furthermore, we have introduced a stochastic

model incorporating fluctuations in the number of breast cancer survivors encountering cardiotoxicity. Through this stochastic model, we can estimate the population of breast cancer patients undergoing chemotherapy and the number of patients who develop heart-related issues due to chemotherapy. This estimation allows us to predict the overall cost of breast cancer treatment for each treatment cycle.

According to the constructed cost model, two primary factors influence the total cost of cancer treatment: the number of newly diagnosed breast cancer patients and the likelihood of chemotherapy patients experiencing cardiotoxicity. An increase in these parameters leads to higher treatment costs for breast cancer. Additionally, these factors significantly impact changes in the overall cost of breast cancer treatment in each period. Furthermore, the overall expected treatment cost decreases with the duration of treatment, eventually stabilizing at a specific value. However, the variance in total treatment costs increases over time.

This developed model is a valuable tool for healthcare professionals, policymakers, and researchers to estimate the cost of breast cancer treatment while considering the effects of cardiotoxicity. By offering more accurate cost projections, this model contributes to optimizing healthcare resource allocation and enhances the quality of care provided to breast cancer patients.

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