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ANALYZING THE MATHEMATICAL MODEL OF NON-SMALL CELL LUNG CANCER STAGES AND THEIR IMPACT ON HEPATOTOXICITY DURING IMMUNOTHERAPY TREATMENT

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Abstract. Bronchial cancer is considered the leading cause of cancer-related mortality worldwide, in comparison to survival rates of other cancer types. Lung cancer treatments aim to eliminate cancer cells, destroy them, or prevent cancer cell division, using approaches such as immunotherapy. Despite the relatively better effectiveness and tolerability of immunotherapy compared to other treatments, severe side effects related to liver dysfunction, known as hepatotoxicity, can occur in patients. In this study, we evaluated the response of patients with non-small cell lung cancer (NSCLC) to this treatment. These responses are modeled by a system of differential equations based on cancer stage changes, which we analyzed both analytically and numerically. The study methodology encompasses model construction, establishing the existence and uniqueness of the solution, identifying equilibrium points, analyzing stability of equilibrium points using Routh-Hurwitz Criteria, and numerical simulations. The conducted dynamic analysis resulted in determining an asymptotically stable equilibrium point without any prerequisite conditions. The results of the analysis are validated using numerical simulations. This study can serve as an early prediction of cancer progression within a hospital population undergoing immunotherapy. Its objective is to monitor the disease's behavior over time and to visualize the potential impact of this treatment on the incidence of hepatotoxicity in these patients.

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1. INTRODUCTION

Lung cancer, frequently referred to as bronchial cancer, is the leading cause of cancer-related deaths worldwide, where approximatly 85 % of all cases are attributed to smoking as the primary factor [1]. It develops and evolves from cells present in lung tissue. This occurs when abnormal lung cells start to multiply in an unregulated and mutated fashion, leading to the formation of cancerous cells. These cells proliferate uncontrollably and damage the surrounding healthy lung tissue harm. This unregulated expansion has the potential to extend to nearby tissues, lymph nodes, or other remote regions of the body. Broadly, lung cancer can be categorized into two primary groups: non-small cell carcinoma (NSCLC) and small cell carcinoma (SCLC). NSCLC is the most common type accounting for 85 to 90 percent of cases, it is more prevalent and typically exhibits a slow development. On the other hand, SCLC, although less common, tends to progress rapidly, making it a more aggressive form of the disease [2]. In this paper, our focus is on non-small cell lung cancer.

Once the type of lung cancer has been identified, the subsequent phase in the diagnostic process is staging, which involves utilizing a combination of test results and tissue samples (physical exam, blood tests, imaging tests, or a biopsy,...) to accurately determine the stage of lung cancer. Staging is pivotal in formulating the recommended treatment plan. Furthermore, the stage of lung cancer is instrumental in discussing the overall prognosis for recovery. Medical professionals can estimate the prognosis by drawing upon the experiences of individuals with the same type and stage of cancer. It is crucial to recognize that predicting how cancer will respond to treatment is uncertain because each individual responds differently. No doctor can precisely predict the lifespan of a person diagnosed with lung cancer [3]. Different staging systems are used for various types of cancer. The TNM staging system created and managed by the American Joint Committee on Cancer (AJCC) [4] and the Union for International Cancer Control (UICC) [5], is the utilized staging system for NSCLC. T stands for tumor's size and where it's located in the lungs or body. N stands for node involvement, this means whether

or not the cancer has spread to the nearby lymph nodes the lungs. M stands for metastasis, this means whether or not the cancer has spread to distant organs such as the other lung, liver, bones, brain, kidneys, or other parts of the body. The stage of the lung cancer is determined by a combination of all of these factors. The grade is usually assigned a number from 1 to 4. A higher number indicates denotes a faster pace of growth and a larger difference between the appearance of cancer cells and healthy cells [6]. Therefore, the more advanced the stage, the less chance of recovery.

The Treatment of lung cancer depends on the type and spread of the disease. Patients with non-small cell lung cancer can be treated by using diverse therapeutic approaches: surgery, chemotherapy, radiation therapy, targeted therapy, hormone therapy, immunotherapy, or a combination of these treatments. These anticancer therapies are used to eliminate, eradicate, or prevent cancer cells by interfering with their signals for cellular proliferation.

Usually, when our immune system functions properly, it has the ability to detect and destroy cancer cells. However, some cancer cells manage to evade detection by our immune system to avoid elimination. They then undergo transformation, adapt to their environment to exploit it to their advantage, and continue their abnormal and uncontrollable multiplication, leading to the formation of a malignant tumor. Over the past decade, cancer immunotherapy, also known as immuno-oncology, has revolutionized the therapeutic arsenal in oncology by activating and stimulating the patient's immune system, which was paralyzed by the tumor, thereby rendering it active again [7]-[8]. Indeed immunotherapy medications for lung cancer aid the body in identifying the cancer as foreign and harmful, enabling the body to combat it and get rid of the cancer cells.

The notable progress in immunotherapy for lung cancer primarily focus on immune checkpoint inhibitors. Immune checkpoints are molecules located on immune cells that can trigger or halt an immune response. The immune system uses these molecules to differentiate what is normal from what needs to be attacked. In some cases, cancer cells are able to trick the immune system by exposing these checkpoints, thereby protecting them from attack by the body. Immunotherapy drugs are specially designed to counteract this deception of the immune system and encourage a response directed against cancerous cells [9]. Under normal circumstances,

the PD-L1 protein (Programmed cell Death-Ligand 1), present on the surface of cells, can interact with PD-1 (Programmed cell Death-1), a receptor located on the surface of T lymphocytes (immune cells). This PD-L1/PD-1 interaction has a normal regulatory function in the body, preventing excessive or inappropriate immune responses. In the context of cancer, some cancer cells can express the PD-L1 protein. These cells bind to the PD-1 receptors on T lymphocytes, preventing them from activating and destroying tumor cells. Consequently, cancer cells evade recognition by the immune system and can proliferate. This constitutes a mechanism of immune system evasion, as the PD-L1/PD-1 interaction can induce inhibition of T lymphocytes, preventing them from targeting and attacking cancer cells. Many of these drugs, currently approved by the U.S FDA (United States Food and Drug Administration) for lung cancer treatment, block or "inhibit" the interaction between the PD-L1 protein of cancer cells and the PD-1 receptor of immune cells [10]. Disrupting the PD-L1/PD-1 interaction enhances the ability of T lymphocytes to recognize cancer cells and initiate an immune response. This reactivation revitalizes immune cells and fortifies the immune system, aiding in the recognition and combat of cancer cells. Approved medications target either the PD-L1 protein or the PD-1 receptor, citing Pembrolizumab, Nivolumab and Atezolizumab as examples. Regardless of their target, they share the same goal to block or 'inhibit' the interaction between the PD-L1 protein and the PD-1 receptor on T lymphocytes. This reactivates T cells and revitalizes the immune system, helping it to combat cancer [9]-[11].

Immunotherapy, is generally better tolerated in comparison to other traditional and classical treatments in terms of adverse sides effects [12]. Nevertheless, the use of immunotherapy treatment of non-small cell lung cancer may still result in various adverse sides effects different from conventional therapies, including hepatotoxicity, which has been observed in a considerable number of patients undergoing this treatment [13]-[14]-[15]-[16]-[17]-[18]-[19].

Mathematical modeling is a versatile computational language employed to depict reality by utilizing mathematical structures and equations. In the context of disease modeling in general, it is frequently utilized to evaluate treatment responses, especially within infectious and oncological scenarios, aiming to predict potential outcomes of specific treatments, offering valuable

insights into the dynamics of diseases and the efficacy of different drugs [20]-[21]–[29]. During recent studies in the mathematical modeling of lung cancer, several research efforts are centered on analyzing tumor growth to enhance and deepen our understanding of the cancer development dynamics, particularly the interplay between cancer cells and immune cells within the tumor microenvironment to define tumor immune dynamics [22]-[23].Furthermore, other studies rely on mathematical modeling of fractional order applied to lung cancer. Several mathematical models have proposed new fractional modeling approaches to describe the growth and spread of cancer [24]-[25]. Other studies also explore fractional methods to examine the effects of chemotherapy on the growth of cancer cells, taking into consideration the interactions between cancer cells, chemotherapy drugs, and immune cells [26]-[27]. At present, the utilization of mathematical modeling for lung cancer is undergoing significant development. This progress reflects the ongoing research efforts aimed at refining and developing mathematical approaches to understand the complex mechanisms involved in the development and progression of lung cancer. These endeavors contribute to enhancing the precision of existing mathematical models and offering new perspectives for a more comprehensive characterization of the different stages of the disease.

Currently, there is no study exploring the mathematical model of immunotherapy in patients with non-small cell lung cancer (NSCLC) at the scale of the population affected by this type of cancer. Taking these considerations into account, in this study, we address a mathematical model of immunotherapy at the population level for non-small cell lung cancer, where patient grouping is based on the stage of cancer detected initially. The cancer can progress from one stage to another as the tumor advances and treatment is administered. In section 2 of the article, we outline the design of the proposed model for non-small cell lung cancer, taking into account the adverse effect of immunotherapy treatment on the liver, thereby introducing a disease known as hepatotoxicity. We describe the movements of patients between compartments and formalize them using ordinary differential equations. In section 3, the proposed lung cancer model undergoes a thorough analysis using mathematical tools. We demonstrate the existence and uniqueness of the solution of the formulated model using the Cauchy-Schwartz theorem. Then, we establish the existence and stability of equilibrium points using the Routh-Hurwitz

criterion. The dynamics of the proposed lung cancer model are further explored by numerically varying different input parameters noted in section 4.

2. Model Formulation

In this model, we consider a population of non-small cell lung cancer patients in a hospital. At the time of the first medical report, the entire patient population is classified into subpopulation corresponding to stage 1, stage 2, stage 3, or stage 4 . In addition, it was assumed that all patients were treated with immunotherapy treatment (Pembrolizumab, Nivolumab, and Atezolizumab), during which patients passed through different phases of treatment, during which some patients recovered, others worsened and others developed hepatotoxicity. The model is represented by a six-subpopulation compartment model, comprising four stages of non-small cell lung cancer compartments represented by the variables A, B, C and D, one compartment for cured patients (disease-free) indicated by E and one compartment containing patients who experienced hepatotoxicity during the immunotherapy process denoted by the variable H. As illustrated in the diagram below in FIGURE 1.

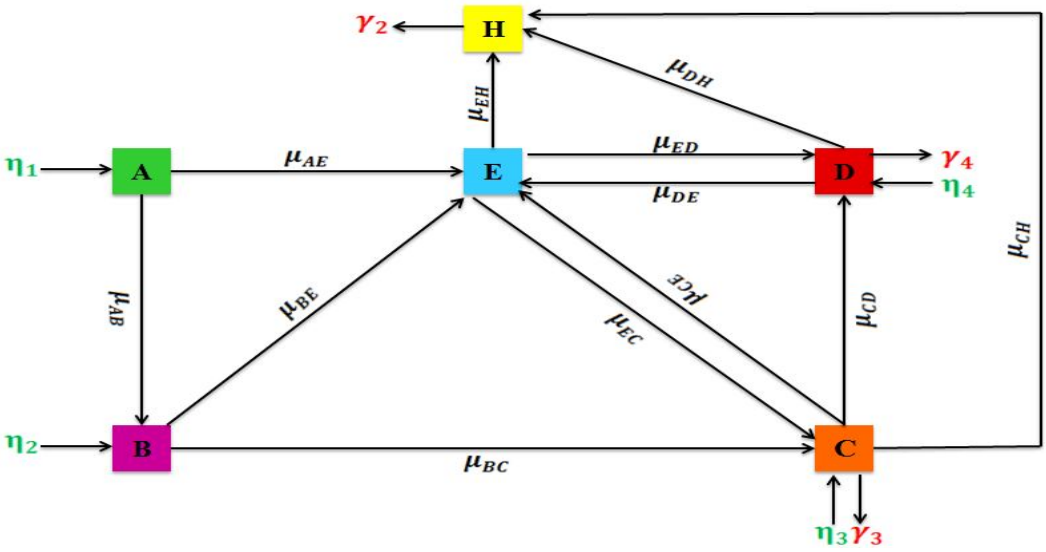

FIGURE 1. Diagram depicting the compartmental model of Non-Small Cell Lung Cancer

Parameter	Meaning
η_i	Number of new patients diagnosed with stage i of lung cancer where i=1,2,3,4
γ_2	Mortality rate of hepatotoxicity patients
γ_3	Mortality rate of stage 3 lung cancer patients
γ_4	Mortality rate of stage 4 lung cancer patients
μ_{AB}	The transition rate from stage 1 to stage 2
μ_{BC}	The transition rate from stage 2 to stage 3
μ_{CD}	The transition rate from stage 3 to stage 4
μ_{AE}	Rate of stage 1 patients achieving a complete response to treatment
μ_{BE}	Rate of stage 2 patients achieving a complete response to treatment
μ_{CE}	Rate of stage 3 patients achieving a complete response to treatment
μ_{DE}	Rate of stage 4 patients achieving a complete response to treatment
μ_{EC}	Rate of disease-free patients returning to stage 3
μ_{ED}	Rate of disease-free patients returning to stage 4
μ_{CH}	Rate of stage 3 cancer immunotherapy patients who presented hepatotoxicity
μ_{DH}	Rate of stage 4 cancer immunotherapy patients who presented hepatotoxicity
μ_{EH}	Rate of disease-free patients with hepatotoxicity

Patients who have received initial treatment and been diagnosed with stage 1 lung cancer are classified in subpopulation A with an η_1 rate. These patients face two possible outcomes: they can either recover with a recovery rate μ_{AE} or encounter the most unfavorable option disease progression, leading them to advance to stage B, governed by μ_{AB} rate. The previously mentioned information is illustrated by the following equation:

$$\frac{dA}{dt} = \eta_1 - \mu_{AB}A - \mu_{AE}A \tag{1}$$

Patients who have been diagnosed with stage 2 lung cancer are bundled to subpopulation B by an η_2 rate. These patients also face two probable scenarios: they can either recover with a recovery rate μ_{BE}, or suffer the most unfavorable course of the disease, which results in a transition to stage C with a rate of μ_{BC}. The discussion above is depicted by the following

equation:

$$\frac{dB}{dt} = \eta_2 + \mu_{AB}A - \mu_{BC}B - \mu_{BE}B \tag{2}$$

Patients diagnosed with stage 3 lung cancer are grouped into subpopulation C with η_3 rate. These patients may face mortality of disease, leading to a γ_3 mortality rate. Following immunotherapy treatment with Pembrolizumab, they have the potential to recover from the disease with an μ_{CE} cure rate. However, they may also experience a deterioration in their state, progressing from stage C to stage D, with a μ_{CD} rate. Due to the severity of stage 3, patients in this category have undergone a more intensive dose Pembrolizumab treatment than those in subpopulations A and B, which can result in hepatotoxicity with a μ_{CH} rate among stage C patients. The previously mentioned discussion can be formulated by the following mathematical equation:

$$\frac{dC}{dt} = \eta_3 + \mu_{BC}B + \mu_{EC}E - \mu_{CD}C - \mu_{CE}C - \mu_{CH}C - \gamma_3 C \tag{3}$$

Patients diagnosed with stage 4 lung cancer are categorised as a part of the group of subpopulation D with a rate of η_4. These individuals may experience disease-related deaths, resulting in a mortality rate of γ_4. The cure of the disease is possible after immunotherapy with pembrolizumab, with a cure rate of μ_{DE}. This group of patient got more intense treatement with Pembrolizumab than the others subpopulations and may have experienced hepatotoxicity with μ_{DH} rate. The differential equation governing the population dynamics in this compartment is provided by:

$$\frac{dD}{dt} = \eta_4 + \mu_{CD}C + \mu_{ED}E - \mu_{DE}D - \mu_{DH}D - \gamma_4 D \tag{4}$$

The rate of disease-free in sub-population E is translated by The augmentation of patients in sub-populations A, B, C, and D. The duration of this disease-free state can be indefinite or short-term. Should this state persist indefinitely, then patients in the sub-population E can return to be sub-populations of B and C with their respective rates μ_{EC} and μ_{ED}. Subsequently, we can express this discussion through the mathematical equation provided below:

$$\frac{dE}{dt} = \mu_{AE}A + \mu_{BE}B + \mu_{CE}C + \mu_{DE}D - \mu_{EH}E \tag{5}$$

Pembrolizumab-induced hepatotoxicity in patients following the treatment may face a risk of hepatic death with γ_2 rate. In view of the fact that the treatment dosage can impact the hepatotoxicity of pembrolizumab, there is an increased likelihood of patients in compartments C, D and E developing hepatic toxicity with rates μ_{CH}, μ_{DH} and μ_{EH} . This is illustrated by the mathematical expression provided by:

$$\frac{dH}{dt} = \mu_{CH}C + \mu_{DH}D + \mu_{EH}E - \gamma_2 H \tag{6}$$

Using equations (1) to (6) which describe the dynamics of patients moving between compartments, a system of differential equations is formed:

$$\begin{cases} \frac{dA}{dt} &= \eta_1 - \mu_{AB}A - \mu_{AE}A \\ \frac{dB}{dt} &= \eta_2 + \mu_{AB}A - \mu_{BC}B - \mu_{BE}B \\ \frac{dC}{dt} &= \eta_3 + \mu_{BC}B + \mu_{EC}E - \mu_{CD}C - \mu_{CE}C - \mu_{CH}C - \gamma_3 C \\ \frac{dD}{dt} &= \eta_4 + \mu_{CD}C + \mu_{ED}E - \mu_{DE}D - \mu_{DH}D - \gamma_4 D \\ \frac{dE}{dt} &= \mu_{AE}A + \mu_{BE}B + \mu_{CE}C + \mu_{DE}D - \mu_{EC}E - \mu_{ED}E - \mu_{EH}E \\ \frac{dH}{dt} &= \mu_{CH}C + \mu_{DH}D + \mu_{EH}E - \gamma_2 H \end{cases} \tag{7}$$

with the non-negative initial conditions:

$$A(0) = A_0; B(0) = B_0; C(0) = C_0; D(0) = D_0; E(0) = E_0 \text{ and } H(0) = H_0.$$

3. Mathematical Analysis of the Model

3.1. Existence and uniqueness: we represent the model (7) in the format provided by:

$$\begin{cases} \frac{dA}{dt} &= \varphi_1(t,A,B,C,D,E,F) \\ \frac{dB}{dt} &= \varphi_2(t,A,B,C,D,E,F) \\ \frac{dC}{dt} &= \varphi_3(t,A,B,C,D,E,F) \\ \frac{dD}{dt} &= \varphi_4(t,A,B,C,D,E,F) \\ \frac{dE}{dt} &= \varphi_5(t,A,B,C,D,E,F) \\ \frac{dH}{dt} &= \varphi_6(t,A,B,C,D,E,F) \end{cases}$$

Note that the above system is a Cauchy problem that we can express in the following form:

$$\begin{cases} x'(t) &= \varphi(t,x(t)) \\ x(0) &= x_0 \end{cases} \tag{8}$$

where:

$$x(t) = \begin{pmatrix} A(t) \\ B(t) \\ C(t) \\ D(t) \\ E(t) \\ H(t) \end{pmatrix} \quad and \quad \varphi(t,x(t)) = \begin{pmatrix} \varphi_1(t,x(t)) \\ \varphi_2(t,x(t)) \\ \varphi_3(t,x(t)) \\ \varphi_4(t,x(t)) \\ \varphi_5(t,x(t)) \\ \varphi_6(t,x(t)) \end{pmatrix}$$

Theorem 3.1. *For any non-negative initial condition, the system (7) has a unique solution for all time $t>0$.*

Proof. To establish the existence and uniqueness of the solution to the differential system (7), we rely on the Cauchy-Lipschitz theorem. Initially, the $(\varphi_i)_{i=1,..,6}$ functions exhibit local continuity on $\mathbb{R}$, and they are lipcshitizian. Indeed:

$$|\varphi_1(t,A_1,B,C,D,E,H) - \varphi_1(t,A_2,B,C,D,E,H)| \leq \delta_1 |A_1 - A_2|$$

$$|\varphi_2(t,A,B_1,C,D,E,H) - \varphi_2(t,A,B_2,C,D,E,H)| \leq \delta_2 |B_1 - B_2|$$

$$|\varphi_3(t,A,B,C_1,D,E,H) - \varphi_3(t,A,B,C_2,D,E,H)| \leq \delta_3 |C_1 - C_2|$$

$$|\varphi_4(t,A,B,C,D_1,E,H) - \varphi_4(t,A,B,C,D_2,E,H)| \leq \delta_4 |D_1 - D_2|$$

$$|\varphi_5(t,A,B,C,D,E_1,H) - \varphi_5(t,A,B,C,D,E_2,H)| \leq \delta_5 |E_1 - E_2|$$

$$|\varphi_6(t,A,B,C,D,E,H_1) - \varphi_6(t,A,B,C,D,E,H_2)| \leq \delta_6 |H_1 - H_2|$$

Where:

$$\delta_1 = \mu_{AB} + \mu_{AE}; \quad \delta_2 = \mu_{BC} + \mu_{BE}; \quad \delta_3 = \mu_{CD} + \mu_{CE} + \mu_{CH} + \gamma_3$$

$$\delta_4 = \mu_{DE} + \mu_{DH} + \gamma_4; \quad \delta_5 = \mu_{EC} + \mu_{ED} + \mu_{EH}; \quad \delta_6 = \gamma_2 \tag{9}$$

The associated proof establishes that φ satisfies the conditions of the Cauchy-Lipschitz theorem; thereby ensuring the existence of a unique solution for the model (7).

3.2. Equilibrium Point.

Theorem 3.2. *For all positive initial conditions, the equilibrium points of the system of non small cell lung cancer exist without any specific condition.*

Proof. The equilibrium points are determined by equating the system's equations (7) to zero:

$$\begin{cases} \eta_1 - \delta_1 A = 0 \\ \eta_2 + \mu_{AB} A - \delta_2 B = 0 \\ \eta_3 + \mu_{BC} B + \mu_{EC} E - \delta_3 C = 0 \\ \eta_4 + \mu_{CD} C + \mu_{ED} E - \delta_4 D = 0 \\ \mu_{AE} A + \mu_{BE} B + \mu_{CE} C + \mu_{DE} D - \delta_5 E = 0 \\ \mu_{CH} C + \mu_{DH} D + \mu_{EH} E - \delta_6 H = 0 \end{cases} \tag{10}$$

Where the parameters δ_1, δ_2, δ_3, δ_4, δ_5, and δ_6 are defined in (9) above.

After performing calculations by eliminating certain terms and substituting others, we result a unique equilibrium point $P_{eq} = (A_{eq}, B_{eq}, C_{eq}, D_{eq}, E_{eq}, H_{eq})$. Where:

$$A_{eq} = \frac{\eta_1}{\delta_1}, \quad B_{eq} = \frac{\alpha}{\delta_1 \delta_2}, \quad C_{eq} = \frac{\beta}{\delta_1 \delta_2 \delta_3} + \frac{\mu_{EC}}{\delta_3} E_{eq}$$

$$D_{eq} = \frac{\nu}{\delta_1 \delta_2 \delta_3 \delta_4} + \left(\frac{\sigma}{\delta_3 \delta_4} \right) E_{eq}, \quad E_{eq} = \frac{\theta}{\rho}, \quad H_{eq} = \frac{\rho}{\delta_1 \delta_2 \delta_3 \delta_4 \delta_6} + \left(\frac{\xi}{\delta_3 \delta_4 \delta_6} E_{eq} \right) \tag{11}$$

And,

$\alpha = \delta_1 \eta_2 + \mu_{AB} \eta_1$

$\beta = \delta_1 \delta_2 \eta_3 + \mu_{BC}(\delta_1 \eta_2 + \mu_{AB} \eta_1)$

$\nu = \delta_1 \delta_2 \delta_3 \eta_4 + \mu_{CD}(\delta_1 \delta_2 \eta_3 + \mu_{BC}(\delta_1 \eta_2 + \mu_{AB} \eta_1))$

$\sigma = \mu_{CD} \mu_{EC} + \delta_3 \mu_{ED}$

$\theta = \delta_2 \delta_3 \delta_4 \mu_{AE} \eta_1 + \delta_3 \delta_4 \mu_{BE}(\delta_1 \eta_2 + \mu_{AB} \eta_1) + \delta_4 \mu_{CE}(\delta_1 \delta_2 \eta_3 + \mu_{BC}(\delta_1 \eta_2 + \mu_{AB} \eta_1)) + \mu_{DE}(\delta_1 \delta_2 \delta_3 \eta_4 + \mu_{CD}(\delta_1 \delta_2 \eta_3 + \mu_{BC}(\delta_1 \eta_2 + \mu_{AB} \eta_1)))$

$\rho = \delta_1 \delta_2 \mu_{DE} \mu_{EC}(\mu_{CH} + \gamma_3) + \delta_1 \delta_2 \mu_{EC}(\mu_{DH} + \gamma_4)(\mu_{CD} + \mu_{CH} + \gamma_3) + \delta_1 \delta_2 \delta_3 \mu_{ED}(\mu_{DH} + \gamma_4) + \delta_1 \delta_2 \delta_3 \delta_4 \mu_{EH}$

$\rho = \mu_{CH} \delta_4(\delta_1 \delta_2 \eta_3 + \mu_{BC}(\delta_1 \eta_2 + \mu_{AB} \eta_1)) + \mu_{DH}(\delta_1 \delta_2 \delta_3 \eta_4 + \mu_{CD}(\delta_1 \delta_2 \eta_3 + \mu_{BC}(\delta_1 \eta_2 +$

$\mu_{AB}\eta_1)))$

$\xi = \delta_4\mu_{CH}\mu_{EC} + \mu_{DH}(\mu_{CD}\mu_{EC} + \delta_3\mu_{ED}) + \delta_3\delta_4\mu_{EH}$

When examining the system from the perspective of equilibrium points, it is evident that the values of A_{eq}, B_{eq}, C_{eq}, D_{eq}, and H_{eq} are all positive, with some of these values containing the value of E_{eq},which is also positive. Consequently, the existence of equilibrium points is confirmed without imposing any conditions.

3.3. Equilibrium Point's Stability.

Theorem 3.3. *The equilibrium points of the system of lung cancer is locally asymptotically stable without any condition.*

Proof. In this demonstration, we employ the Routh-Hurwitz Criterion [30] to analyse the stability of the equilibrium point. To accomplish this, we represent the corresponding equation in matrix form:

$$\mathscr{J} = \mathscr{K}\mathscr{L} + \Phi$$

With,

$$\mathscr{J} = \begin{bmatrix} \dot{A} \\ \dot{B} \\ \dot{C} \\ \dot{D} \\ \dot{E} \\ \dot{H} \end{bmatrix}; \mathscr{K} = \begin{bmatrix} -\delta_1 & 0 & 0 & 0 & 0 & 0 \\ \mu_{AB} & -\delta_2 & 0 & 0 & 0 & 0 \\ 0 & \mu_{BC} & -\delta_3 & 0 & \mu_{EC} & 0 \\ 0 & 0 & \mu_{CD} & -\delta_4 & \mu_{ED} & 0 \\ \mu_{AE} & \mu_{BE} & \mu_{CE} & \mu_{DE} & -\delta_5 & 0 \\ 0 & 0 & \mu_{CH} & \mu_{DH} & \mu_{EH} & -\delta_6 \end{bmatrix}; \mathscr{L} = \begin{bmatrix} A \\ B \\ C \\ D \\ E \\ H \end{bmatrix}; \Phi = \begin{bmatrix} \eta_1 \\ \eta_2 \\ \eta_3 \\ \eta_4 \\ 0 \\ 0 \end{bmatrix}$$

The characteristic polynomial associated to the matrix $\mathscr{K}$ is

$$P(\lambda) = \det(\mathscr{K} - \lambda I) = \begin{vmatrix} -\delta_1 - \lambda & 0 & 0 & 0 & 0 & 0 \\ \mu_{AB} & -\delta_2 - \lambda & 0 & 0 & 0 & 0 \\ 0 & \mu_{BC} & -\delta_3 - \lambda & 0 & \mu_{EC} & 0 \\ 0 & 0 & \mu_{CD} & -\delta_4 - \lambda & \mu_{ED} & 0 \\ \mu_{AE} & \mu_{BE} & \mu_{CE} & \mu_{DE} & -\delta_5 - \lambda & 0 \\ 0 & 0 & \mu_{CH} & \mu_{DH} & \mu_{EH} & -\delta_6 - \lambda \end{vmatrix}$$

We get,

$$P(\lambda) = (\lambda+\delta_1)(\lambda+\delta_2)(\lambda+\delta_6)\left(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3\right) \tag{12}$$

where,

$$a_1 = \delta_3 + \delta_4 + \delta_5 \ ;$$
$$a_2 = \delta_3\delta_5 + \delta_3\delta_4 + \delta_4\delta_5 - \mu_{ED}\mu_{DE} - \mu_{EC}\mu_{CE};$$
$$a_3 = \delta_3\delta_4\delta_5 - \delta_3\mu_{ED}\mu_{DE} - \delta_4\mu_{EC}\mu_{CE} - \mu_{EC}\mu_{CD}\mu_{DE}$$

It's clear that characteristic polynomial equation possesses six eigenvalues $\lambda_1 = -\delta_1 < 0$, $\lambda_2 = -\delta_2 < 0$, $\lambda_3 = -\delta_6 < 0$, the reality of an eigenvalue is negative, and the rest of eigenvalues are the roots of the following equation given by:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$$

By using Routh-Hurwitz criterion's stability, the three other eigenvalues have a strictly negative real part if and only if $a_1 >$, $a_3 > 0$ and $a_1a_2 - a_3 > 0$. Obtained by:

$$\begin{aligned}
a_1 &= \delta_3 + \delta_4 + \delta_5 > 0 \\
a_3 &= \delta_3\delta_4\delta_5 - \delta_3\mu_{ED}\mu_{DE} - \delta_4\mu_{EC}\mu_{CE} - \mu_{EC}\mu_{CD}\mu_{DE} \\
&= \mu_{DE}\mu_{EC}(\mu_{CH}+\gamma_3) + \mu_{EC}(\mu_{DH}+\gamma_4)(\mu_{CD}+\mu_{CH}+\gamma_3) + \delta_3\mu_{ED}(\mu_{DH}+\gamma_4) \\
&\quad + \delta_3\delta_4\mu_{EH} > 0 \\
a_1a_2 - a_3 &= (\delta_3+\delta_4)(\delta_3\delta_4 + \mu_{CE}(\mu_{ED}+\mu_{EH}) + \delta_5(\mu_{CD}+\mu_{CH}+\gamma_3) + \mu_{DE}(\mu_{EC}+\mu_{EH}) \\
&\quad + \delta_5(\mu_{DH}+\gamma_4)) + \delta_5(\mu_{CE}(\mu_{ED}+\mu_{EH}) + \delta_5(\mu_{CD}+\mu_{CH}+\gamma_3) + \mu_{DE}(\mu_{EC}+\mu_{EH}) \\
&\quad + \delta_5(\mu_{DH}+\gamma_4)) + \delta_3\mu_{ED}\mu_{DE} + \delta_4\mu_{EC}\mu_{CE} + \mu_{EC}\mu_{CD}\mu_{DE} > 0
\end{aligned}$$

Therefore, the system is locally asymptotically stable without any conditions.

4. NUMERICAL SIMULATION

In this section of the article, we conduct numerical simulations using MATLAB to obtain a more precise understanding of patients and to investigate the dynamics of the proposed model (7) for non-small cell lung cancer.This includes consideration of the undesired complication of hepatotoxicity associated with immunotherapy treatment. The numerical simulations conducted

are obtained from the medical article [28] and the following specified parameters: $\eta_1 = 20$; $\eta_2 = 150$; $\eta_3 = 200$; $\eta_4 = 500$; $\mu_{AB} = 0.5$; $\mu_{AE} = 0.6$; $\mu_{BC} = 0.46$; $\mu_{BE} = 0.57$; $\mu_{CD} = 0.6$; $\mu_{CE} = 0.3$; $\mu_{CH} = 0.35$; $\mu_{DE} = 0.2$; $\mu_{DH} = 0.42$; $\mu_{EC} = 0.52$; $\mu_{ED} = 0.6$, $\mu_{EH} = 0.4$; $\gamma_2 = 0.3$; $\gamma_3 = 0.23$; $\gamma_4 = 0.87$.

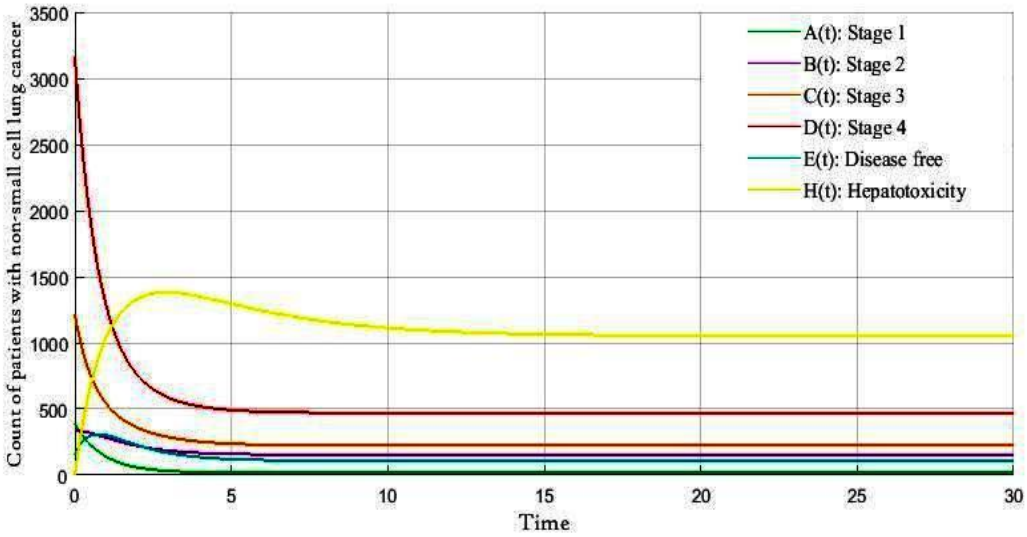

FIGURE 2. Model simulations with initial conditions

FIGURE 2. These simulation is conducted with the initial conditions (A_0, B_0, C_0, D_0, E_0, H_0) = (386, 338, 1217, 3157, 157,0). Analyzing the graph reveals fluctuations in the population over time, ranging from 0 to 13th. After time 13th, the population stabilizes at the endemic equilibrium point (A_{eq}, B_{eq}, C_{eq}, D_{eq}, E_{eq}, H_{eq}) = (18.18, 154.5, 224.6, 470.1, 109.4, 1076). This graph illustrates the occurrence of equilibrium conditions from the 13th time period. In equilibrium conditions, the stage 1 subpopulation, starting with an initial condition of 386 patients, decreased to 18 patients. Similarly, the stage 2 subpopulation, originating from the initial condition of 338 patients, declines to 154 in equilibrium conditions.The stage 3 subpopulations initially at 1217 patients decrease to 224 in the steady state. The stage 4 subpopulation witnessed a decrease from 3157 to 470.The Disease-Free subpopulation remains relatively stable, displaying minimal changes in population from the initial condition to equilibrium, decreasing from 157 to 109. In contrast to the hepatotoxic subpopulation, which exhibited a substantial

increase from the initial 0 patients to 1380 patients before stabilizing at 1052 patients in equilibrium conditions.

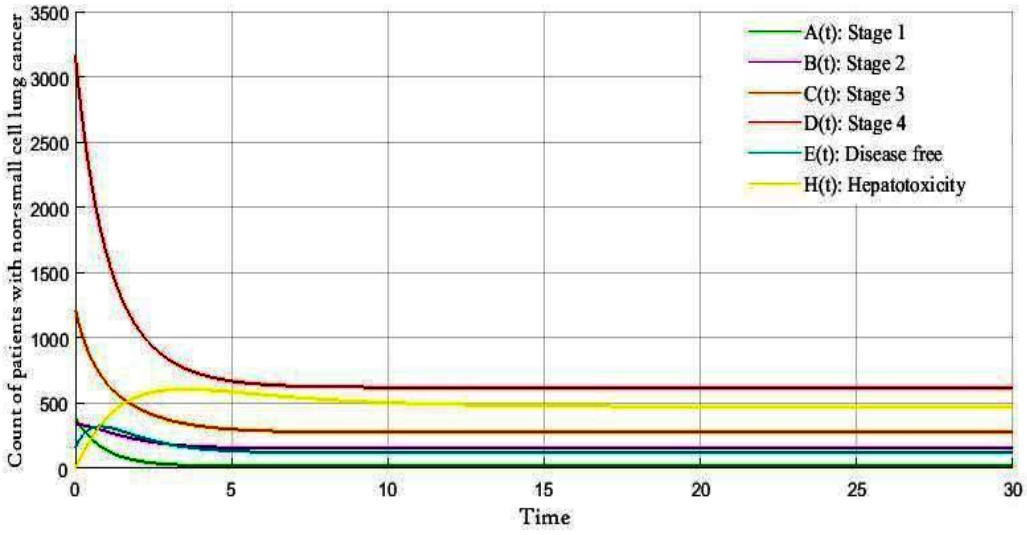

FIGURE 3. Model simulation with reduced hepatotoxicity rates

FIGURE 3 is obtained by reducing the hepatotoxicity rates μ_{CH} and μ_{DH} to 0.1 for both. The graph shows a significant decrease in the hepatotoxic sub-population to 495 patients at the time of equilibrium, which is considered a positive outcome for NSCLC patients. Regarding the sub-populations at stage 3, stage 4, and disease-free, they have slightly increased compared to the initial simulation, while the other sub-populations remain relatively stable compared to the first simulation. All these changes can be clearly observed by using different decreasing values of hepatotoxicity rates, as illustrated in the figures [4-5-6-7] below.

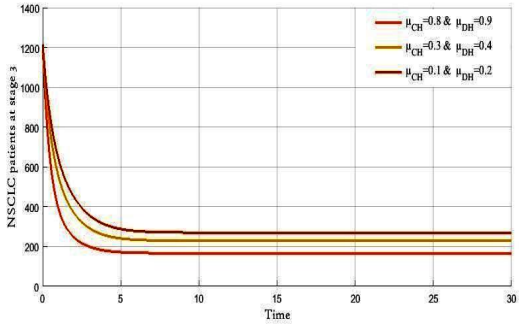

FIGURE 4.

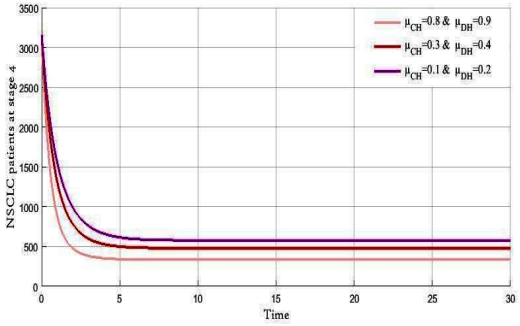

FIGURE 5.

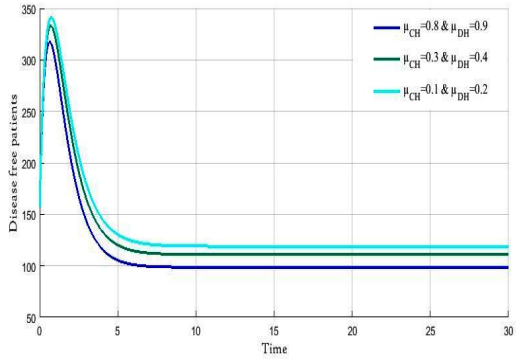

FIGURE 6.

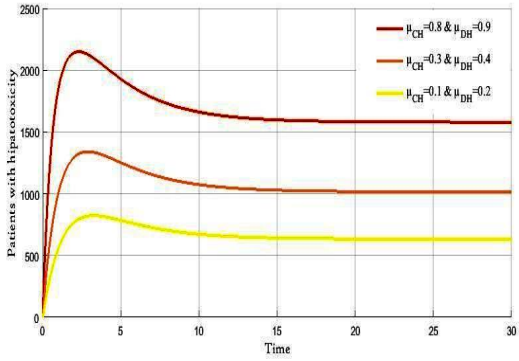

FIGURE 7.

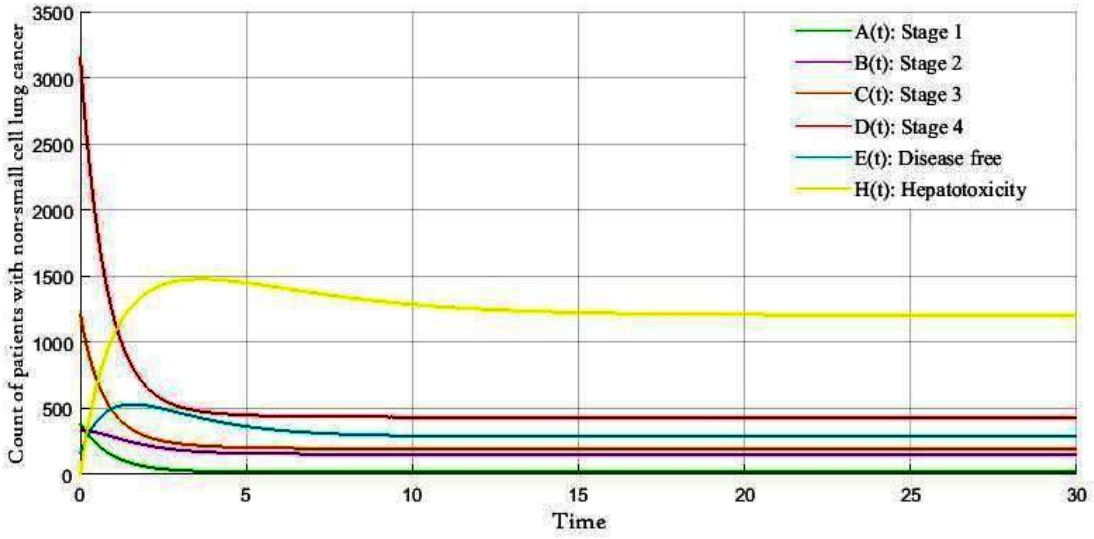

FIGURE 8. Model simulation with reduced replase rates

FIGURE 8. For this numerical simulation, we suggest to reduce the relapse rates at stages 3 and 4, μ_{EC} and μ_{ED}, to 0.1 for both. The numerical results indicate a slight increase in the hepatotoxic sub-population, reaching 1204 patients in a stable state. Similarly, the disease-free sub-population shows a favorable increase, reaching 286 patients at equilibrium. The sub-populations of patients at stages 1 and stage 2 exhibit no significant changes compared to the initial simulation, while the sub-populations of patients at stages 3 and 4 decreased by 195 and 433 patients, respectively, at equilibrium.

5. Conclusion

Research in mathematical modeling has played a crucial role in supporting and advancing progress in the field of oncology for several decades. This contribution is enabled by monitoring and comprehending the intricate dynamic interactions between tumors and treatments, coupled with notable advancements in computational science. The mathematical modeling employed in this study aimed to predict the progression of non-small cell lung cancer following immunotherapy treatment over time and assess the likelihood of hepatotoxicity in these patients. The dynamic analysis conducted in this study resulted in an asymptotically stable equilibrium point without any condition. This stability originates from the system forming without any interaction, exclusively involving the movement of the population from one stage to another based on the patients' responses to immunotherapy. The cancer response to immunotherapy can manifest as a complete response, stabilization at a certain stage, no change, complications of hepatotoxicity due to therapy, or even malignant intensification, resulting in an increase in cancer after immunotherapeutic treatment.

Conflict of Interests

The authors declare that there is no conflict of interests.

References

[1] World Health Organization, Lung Cancer. https://www.who.int/news-room/fact-sheets/detail/lung-cancer.

[2] Cancer Research UK, Types of Lung Cancer. https://www.cancerresearchuk.org/about-cancer/lung-cancer/stages-types-grades/types.

[3] American Lung Association, Lung Cancer Staging. https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/symptoms-diagnosis/lung-cancer-staging.

[4] American Joint Committee on Cancer, Cancer Staging Systems. https://www.facs.org/quality-programs/cancer-programs/american-joint-committee-on-cancer/cancer-staging-systems/.

[5] Union for International Cancer Control, UICC and the TNM Classification of Malignant Tumours. https://www.uicc.org/who-we-are/about-uicc/uicc-and-tnm.

[6] Canadian Cancer Society, Stage and Grade. https://cancer.ca/en/cancer-information/what-is-cancer/stage-and-grade.

[7] Canadian Cancer Society, Immunotherapy. https://cancer.ca/en/treatments/treatment-types/immunotherapy.

[8] L'Institut National de la Santé et de la Recherche Médicale (Inserm), Immunothérapie des Cancers. https://www.inserm.fr/dossier/immunotherapie-cancers.

[9] American Lung Association, Lung Cancer Immunotherapy. https://www.lung.org/lung-health-diseases/lung-disease-lookup/lung-cancer/treatment/types-of-treatment/immunotherapy.

[10] Memorial Sloan Kettering Cancer Center, Immunotherapy for Lung Cancer, https://www.mskcc.org/cancer-care/types/lung/treatment/immunotherapy.

[11] National Cancer Institute City of Hope, Immunotherapy for Lung Cancer. https://www.cancercenter.com/cancer-types/lung-cancer/treatments/immunotherapy.

[12] T.F. Nishijima, S.S. Shachar, K.A. Nyrop, et al. Safety and Tolerability of PD-1/PD-L1 Inhibitors Compared with Chemotherapy in Patients with Advanced Cancer: A Meta-Analysis, The Oncologist 22 (2017), 470–479. https://doi.org/10.1634/theoncologist.2016-0419.

[13] K. Kurokawa, M. Hara, S. Iwakami, et al. Cholestatic Liver Injury Induced by Pembrolizumab in a Patient with Lung Adenocarcinoma, Intern. Med. 58 (2019), 3283–3287. https://doi.org/10.2169/internalmedicine.2591-18.

[14] C. Masetti, N. Pugliese, L. Rimassa, et al. Pembrolizumab-Induced Vanishing Bile Duct Syndrome: A Case Report, SN Compr. Clin. Med. 3 (2021), 906–908. https://doi.org/10.1007/s42399-021-00803-9.

[15] G.A. Osman, A. Marra, D. Iacono, et al. Misleading Impaired Liver Function in a Non-Small-Cell Lung Cancer Patient Treated with Pembrolizumab: A Case Report, Anti-Cancer Drugs 30 (2019), 757–761. https://doi.org/10.1097/CAD.0000000000000764.

[16] B. Calderon, A. Stancu, F.R. Vanel, et al. Pembrolizumab Treatment-Induced Liver Toxicity, Case Rep. Gastroenterol. 15 (2021), 742–750. https://doi.org/10.1159/000518128.

[17] I. Tsung, R. Dolan, C.D. Lao, et al. Liver Injury Is Most Commonly Due to Hepatic Metastases Rather than Drug Hepatotoxicity during Pembrolizumab Immunotherapy, Aliment. Pharmacol. Ther. 50 (2019), 800–808. https://doi.org/10.1111/apt.15413.

[18] V. Mathew Thomas, P. Bindal, S. Ann Alexander, et al. Nivolumab-Induced Hepatitis: A Rare Side Effect of an Immune Check Point Inhibitor, J. Oncol. Pharm. Pract. 26 (2020), 459–461. https://doi.org/10.1177/1078155219837342.

[19] A. Khadilkar, K. Patel, S2686 A Rare Case of Atezolizumab-Induced Hepatotoxicity, Amer. J. Gastroenterol. 115 (2020), S1406–S1406. https://doi.org/10.14309/01.ajg.0000712792.58094.f0.

[20] Y. Xiao, J. Shen, X. Zou, School of Mathematics and Statistics, Wuhan University, Wuhan, 430072, China, Mathematical Modeling and Dynamical Analysis of Anti-Tumor Drug Dose-Response, Math. Biosci. Eng. 19 (2022), 4120–4144. https://doi.org/10.3934/mbe.2022190.

[21] M. Rodriguez Messan, O.N. Yogurtcu, J.R. McGill, et al. Mathematical Model of a Personalized Neoantigen Cancer Vaccine and the Human Immune System, PLOS Comput. Biol. 17 (2021), e1009318. https://doi.org/10.1371/journal.pcbi.1009318.

[22] H. Dritschel, S. Waters, A. Roller, H. Byrne, A Mathematical Model of Cytotoxic and Helper T Cell Interactions in a Tumour Microenvironment, Lett. Biomath. 5 (2018), S36–S68. https://doi.org/10.30707/LiB5.2Dritschel.

[23] S. Tabassum, N.B. Rosli, M.S.A. Binti Mazalan, Mathematical Modeling of Cancer Growth Process: A Review, J. Phys.: Conf. Ser. 1366 (2019), 012018. https://doi.org/10.1088/1742-6596/1366/1/012018.

[24] F. Irshad, N. Kumar, Role of Ordinary and Partial Differential Equations as Mathematical Models in Tumor Growth, in: Book of Abstracts of the 2nd International Conference on Applied Mathematics and Computational Sciences (ICAMCS-2022), AIJR Publisher, (2022).

[25] D. Amilo, B. Kaymakamzade, E. Hincal, A Fractional-Order Mathematical Model for Lung Cancer Incorporating Integrated Therapeutic Approaches, Sci. Rep. 13 (2023), 12426. https://doi.org/10.1038/s41598-023-38814-2.

[26] D. Baleanu, A. Jajarmi, S.S. Sajjadi, D. Mozyrska, A New Fractional Model and Optimal Control of a Tumor-Immune Surveillance with Non-Singular Derivative Operator, Chaos 29 (2019), 083127. https://doi.org/10.1063/1.5096159.

[27] F. Özköse, S. Yılmaz, M. Yavuz, İ. Öztürk, M.T. Şenel, B.Ş. Bağcı, M. Doğan, Ö. Önal, A Fractional Modeling of Tumor–Immune System Interaction Related to Lung Cancer with Real Data, Eur. Phys. J. Plus 137 (2022), 40. https://doi.org/10.1140/epjp/s13360-021-02254-6.

[28] S. Khozin, R.A. Miksad, J. Adami, et al. Real-world Progression, Treatment, and Survival Outcomes during Rapid Adoption of Immunotherapy for Advanced Non–Small Cell Lung Cancer, Cancer 125 (2019), 4019–4032. https://doi.org/10.1002/cncr.32383.

[29] M.I.A. Fathoni, Gunardi, F.A. Kusumo, S.H. Hutajulu, Mathematical Model Analysis of Breast Cancer Stages with Side Effects on Heart in Chemotherapy Patients, AIP Conf. Proc. 2192 (2019), 060007. https://doi.org/10.1063/1.5139153.

[30] M. El Karchani, N.I. Fatmi, K. Mouden, Quantifying the Impact of Immunotherapy Response of Breast Cancer Stages: A Computational Approach for Mathematical Model and Numerical Simulation, Commun. Math. Biol. Neurosci. 2023 (2023), 138. https://doi.org/10.28919/cmbn/8341.