- ORIGINAL ARTICLE -

An Agent-Based ”Virtual Clinical Trial” for the Analysis and Evaluation of COPD Patients Cohorts Behavior

Un ensayo clínico virtual basado en agentes para el análisis y evaluación del comportamiento de cohortes de pacientes con EPOC

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a chronic respiratory condition characterized by inflammation and narrowing of the airways, leading to symptoms such as shortness of breath, coughing, and chest tightness. Treatment typically involves lifestyle adjustments, medication, and pulmonary rehabilitation to improve lung function and quality of life. This study presents a model examining COPD patient behavior within cohort-based strategies, focusing on how environmental factors impact vital signs across the entire cohort. We developed a comprehensive virtual clinical trial model that encompasses study protocol design, participant recruitment, virtual data collection, outcome analysis, and conclusions. This includes remote symptom monitoring, virtual healthcare consultations, treatment adherence assessments, and research data collection. Additionally, we explore the influence of external variables such as environmental conditions, comorbidities, and lifestyle factors on chronic disease symptoms and disease stability. We used an Agent-Based Model(ABM) to incorporate these factors to assess COPD progression and treatment efficacy. Individual agents represent COPD patients, each characterized by attributes such as age, smoking history, lung function, comorbidities, and treatment plans.
Keyword: Chronic obstructive pulmonary disease (COPD), Cohort-based strategies, Agent-based modeling, Virtual clinical trial.

Resumen

La Enfermedad Pulmonar Obstructiva Crónica (EPOC) es una afección respiratoria caracterizada por la inflamación y el estrechamiento de las vías respiratorias, lo que provoca síntomas como dificultad para respirar, tos y opresión en el pecho. El tratamiento generalmente implica ajustes en el estilo de vida, medicación y rehabilitación para mejorar la función pulmonar y la calidad de vida. Este estudio presenta un modelo que examina el comportamiento de los pacientes con EPOC dentro de estrategias basadas en cohortes, centrándose en cómo los factores ambientales afectan los signos vitales de los enfermos.

Desarrollamos un modelo integral de ensayo clínico virtual que abarca el diseño del protocolo de estudio, la selección de participantes, la recopilación virtual de datos, el análisis de resultados y las conclusiones. Esto incluye el monitoreo remoto de síntomas, consultas de salud virtuales, evaluaciones de adherencia al tratamiento y la recopilación de datos de investigación. Además, exploramos la influencia de variables externas, como las condiciones ambientales, las comorbilidades y los factores de estilo de vida, en los síntomas de la enfermedad crónica y la estabilidad de la enfermedad. Utilizamos un modelo basado en agentes (MBA) para incorporar estos factores y evaluar la progresión de la EPOC y la eficacia del tratamiento. Los agentes individuales representan a los pacientes con EPOC, cada uno caracterizado por atributos como la edad, el historial de tabaquismo, la función pulmonar, las comorbilidades y los planes de tratamiento.
Palabras claves: Enfermedad pulmonar obstructiva crónica (EPOC), Modelado basado en agentes, Estrategias basadas en cohorts, Ensayo clínico virtual.

1 Introduction

Chronic obstructive pulmonary disease (COPD) stands as a significant contributor to global chronic disease-related morbidity and disability, characterized by a growing prevalence. In Spain, despite being underdiagnosed, epidemiological studies have indicated its impact on approximately 8-10% of the adult population[1]. COPD’s economic and social implications are substantial, with direct costs per patient ranging from 1,712 € to 3,238 € per year, as reported by the Ministry of Health, Social Services, and Equality in Spain[2].

These costs encompass hospital expenses, medication, medical appointments, and tests. [3].

During the COVID-19 pandemic, there has been a surge in patients seeking medical care, exacerbating existing challenges in managing chronic diseases like COPD. One proposed solution to address these challenges is the utilization of the tele-monitoring study, a pioneering investigation in the field of COPD management, shed light on the transformative potential of telemedicine in healthcare delivery. Through meticulous observation and analysis, the study revealed that follow-up care facilitated by telemedicine effectively reduces the necessity for frequent in-person visits with healthcare staff[4]. This paradigm shift in patient monitoring not only streamlines the healthcare process but also offers a host of benefits to both patients and healthcare providers alike. Additionally, the use of Agent-Based Modeling (ABM) in healthcare is another promising approach. ABM allows for the simulation of complex systems by representing individual agents with defined characteristics and behaviors, enabling the exploration of various scenarios and interventions to improve patient outcomes and healthcare delivery efficiency [5]. Using ABM in the simulation of Virtual Clinical Trials can provide some advantages over traditional clinical trials. Firstly, it can reach a larger pool of potential participants, including those in remote areas or with mobility limitations, thus facilitating faster recruitment and enrollment. Secondly, ABM can attract a more diverse participant pool, leading to more representative study results[6]. Thirdly, ABM is often more cost-effective than traditional trials, as it eliminates the need for physical study sites and associated logistical challenges. Traditionally, COPD exacerbations have been identified through patient interviews or manual re- view of healthcare records, which may lead to underreporting[7]. By using the ABM, we improve the identification of exacerbations by incorporating real-time data from various sources, including patient- reported symptoms and healthcare interactions, enhancing the accuracy of diagnosis and management. Effective management of COPD is crucial for improving patient health outcomes and reducing healthcare system burdens. Cohort-based management, which involves grouping patients based on shared characteristics and providing coordinated care, has shown promise in this regard[8]. In this study, we present a novel approach to examining COPD patient behavior within cohort-based strategies using ABM. The primary objective of using the ABM is to simulate a model where the interactions of autonomous agents are assessed to understand their effects on the sys- tem as a whole. In this context, individual agents represent COPD patients, each characterized by distinct attributes such as age, smoking history, lifestyle, comorbidities, and treatment plans. This model al- lows for the simulation of complex interactions and the assessment of how various factors impact disease progression and treatment efficacy [9].

The core objective of this research is to evaluate the impact of environmental factors on COPD symptoms and disease stability across an entire cohort of patients. Environmental factors, such as air pollution, and weather conditions are known to exacerbate COPD symptoms and can significantly affect patient outcomes[10]. By incorporating real-world temperature data from the city of Barcelona into our model, we aim to simulate realistic scenarios and explore how these environmental conditions influence COPD management. We developed a comprehensive virtual clinical trial model that encompasses several key components: study protocol design, participant recruitment, virtual data collection, outcome analysis, and conclusions. The model integrates remote symptom monitoring, virtual healthcare consultations, treatment adherence assessments, and research data collection. This multifaceted approach enables a detailed examination of COPD management strategies and their effectiveness in a controlled yet dynamic virtual environment.

Additionally, this study explores the influence of other external variables such as comorbidities and lifestyle factors on COPD progression. Comorbid conditions, such as cardiovascular diseases, diabetes, depression, vaccination, and despondency often coexist with COPD and can complicate its management[11]. Lifestyle factors, including physical activity levels, diet, and adherence to treatment regimens, also play a crucial role in disease outcomes[12]. Our ABM incorporates these variables to provide a holistic view of COPD management and identify potential areas for intervention. By leveraging the capabilities of ABM and telemedicine, this research aims to provide insights into the optimization of COPD management strategies. The findings from this study could inform clinical practice, guiding the development of more effective and personalized treatment plans that consider the multifaceted nature of COPD and the diverse factors influencing its progression.

Finally, this paper presents an innovative framework for modeling COPD patient behavior within cohort-based strategies, focusing on the assessment of environmental impacts and treatment efficacy using an agent-based approach. The integration of real-world data, comprehensive virtual clinical trial design, and the exploration of various external factors provide a robust platform for advancing our understanding of COPD management in a distributed healthcare system. In the following section, a literature review will be presented. In Section III, we describe the agent-based modeling as a case study. Furthermore, in Section IV, we will present the operational variables for both the patient and the healthcare provider. In addition, in Section V, we will present the environment, which includes the simulator with its operational rules, policies, and regulations. Moreover, in Section VI, we will present the discussion and results. Finally, in section VII, we will present the conclusion and future work.

2 Literature Review

Chronic obstructive pulmonary disease (COPD) is a significant global health challenge characterized by airflow limitation and respiratory symptoms like dyspnea, cough, and sputum production[13]. Epidemiological studies highlight its substantial burden worldwide, affecting millions and leading to numerous deaths annually[14]. Mainly caused by long-term exposure to harmful gases and particles, especially cigarette smoke, COPD requires multifaceted management strategies[15]. Understanding its prevalence, risk factors, and the interplay of environmental factors, comorbidities, and lifestyle interventions is crucial. Factors like air pollution, indoor biomass fuel use, and occupational exposures contribute to COPD development[16]. Comorbidities such as cardiovascular disease, diabetes, and depression are common and affect disease management[17]. Lifestyle changes, including smoking cessation and regular physical activity, play a significant role in COPD management, reducing hospital admissions and mortality. Advanced digital health technologies allow for personalized interventions and remote patient monitoring[18]. Virtual clinical trials (VCTs) and agent-based modeling (ABM) have transformed COPD research. VCTs provide a cost-effective method for exploring interventions and tailoring treatment strategies, while ABM offers a dynamic framework for simulating disease progression and patient behavior[19]. ABM involves simulating the actions and interactions of autonomous agents to assess their effects on the system as a whole. Each agent represents an individual with specific characteristics and behaviors, allowing for a detailed simulation of patient populations and their interactions with healthcare systems[20]. In healthcare, ABM has been used to model disease spread, patient behavior, and the impact of healthcare policies. Environmental factors, such as air pollution and weather, significantly influence COPD symptoms. ABM can simulate the effect of these factors on patient health. A study [21] used an agent-based approach to model the impacts of urban air pollution on COPD patients. The model demonstrated that high pollution levels increased the frequency and severity of COPD exacerbations, highlighting the importance of environmental management in COPD care.

3 Agent-Based Modeling: Presentation and Case Study Illustration

We employ Agent-Based Modeling (ABM) as a powerful tool to study complex systems, providing insights into the behavior of individual agents within a larger system. When applied to COPD cohorts, ABM of- fers a dynamic and personalized approach to understanding the disease and its impact on patients. To enhance COPD management and treatment, we turn to innovative methodologies like ABM to gain a deeper understanding of the disease and its effects on patients. In ABM, each individual with COPD is represented as an agent with specific characteristics such as age, smoking history, lung function, comorbidities, and treatment regimen[22]. These agents interact with each other and their environment, enabling us to simulate the complex dynamics of COPD progression within a cohort of patients. By incorporating various factors that influence COPD, such as environmental exposures, lifestyle choices, and treatment adherence, ABM offers us a comprehensive view of how the disease evolves and how different interventions may impact patient outcomes. Typically, the lifestyle of each chronic patient in the cohort impacts health variables, leading to modifications in their quantities. These alterations can shift a patient's stability from unstable to stable or vice versa. Within the cohort, we categorize each chronic patient into distinct classes based on their symptoms and signs[23]. Subsequently, we employ a state ma- chine to illustrate the transitions between different states. Illustrated in Figure 1, each transition captures the behavior of an individual patient, occurring when

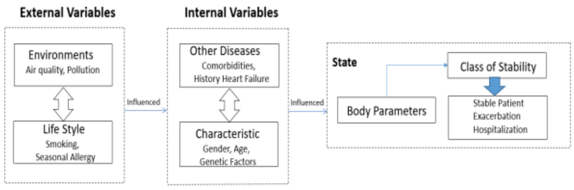


Figure 1: Integrated Framework: Agent-Based Modeling for COPD Patient Management

health variables change due to the influence of external factors on internal variables. This signifies a shift in the patient's state. The array of states represents the various levels of stability exhibited by the patient, encompassing distinct classes of chronic diseases and medically relevant variables. Each shift from one class to another can be visually captured in a diagram depicting the patient's behavior, exemplified in Figure 2 as an extension of Figure 1. The diagram illustrates that our inputs comprise parameters related to the patient's living conditions at a specific time, with these transitions occurring between classes based on the state variable quantities at that particular moment. All modifications occurring over time are visually portrayed in the diagram.

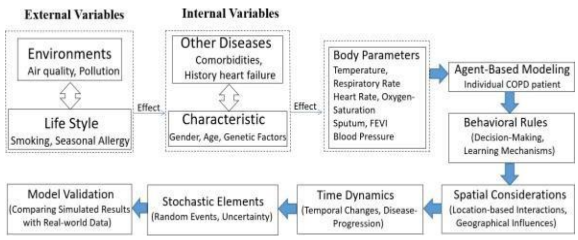


Figure 2: Summary of Patients Characteristics and Trajectory in COPD Cohort

4 Operational Variables: Patients and Healthcare Providers in the COPD Cohort

In our agent-based model (ABM) study, we identify key operational variables for patients and healthcare providers within the COPD cohort. For patients, these variables include demographic factors such as age, gender, and socio-economic status, as well as health-related aspects like smoking history, lung function, and comorbidities. For healthcare providers, variables focus on resource availability, patient interaction frequency, and adherence to clinical guidelines for COPD management. By incorporating these variables, the model simulates real-world interactions between patients and healthcare providers, enhancing our understanding of how these factors influence treatment efficacy and patient outcomes.

4.1 Agents

Within modeling the COPD cohort, we delineate between two pivotal categories of agents: operational and administrative. Operational agents encompass patients and healthcare providers directly involved in COPD management, while administrative agents include individuals and software tasked with overseeing the operation of the simulated healthcare system tailored to COPD care. To effectively model the COPD cohort, it is imperative to initially identify and categorize these agents based on their roles and pertinent attributes. Subsequently, defining the objectives and behaviors of each agent becomes paramount in accurately simulating the dynamics of COPD care within the cohort.

4.2 Patients

Patients serve as the primary beneficiaries within the healthcare system and are integral components of care delivery processes, particularly in the context of managing COPD. They play a crucial role in the cohort strategies tailored to address their specific healthcare needs. Within the COPD cohort, patients can be categorized based on several criteria relevant to modeling objectives, facilitating a comprehensive understanding of their healthcare requirements:
A. Demographic Attributes: Age, gender, occupation, and other demographics serve as recognized risk factors. B. Patient Type: Classification into regular and new patients enables tailored interventions. C. Hierarchy Within the System: Patients may be classified based on criticality levels like routine, urgent, or critical. D. Medical Requirements: Encompassing required services, therapy type, diagnostic procedures, and medical conditions. E. Patient Pathway Features: Includes the mode of arrival and departure within the healthcare system. F. Patient Admission Protocols: Cover scheduling procedures, policies regarding tardiness and missed appointments, and the presence of accompanying individuals.

4.3 Healthcare Professionals

Medical professionals within the COPD cohort encompass all individuals involved in delivering medical care to COPD patients within the healthcare setting. These professionals play a critical role in managing COPD and are typically distinguished by their expertise and qualifications[24]. They undertake various roles within the organization based on their designated function, each entailing specific responsibilities that the individual is obligated to fulfill, Table 1 shows the characteristics present by the patient and the corresponding values they can adopt.

Table 1: Patient Characteristics in the COPD Cohort as case study

Characteristic	Options/Description
Working Place	Occupational dust and chemicals, Indoor air pollution, Outdoor air pollution, Home and office
History of Heart Failure	Yes/No
Vaccination	Yes/No
Depression	Yes/No
Status of Dependency Level	Dependent, Independent
Location	Barcelona
Type of the Patient	Already diagnosed with COPD (Yes/No), History of heart failure (Yes/No), Main symptoms and signs (e.g., Morning cough, Chronic cough, Phlegm cough, Wheeze), Sputum (Normal, Purulent), History of Diabetes (Yes/No), History of Cardiovascular (Yes/No)
Priority within the system	Criticality levels (Stable, Semi-Stable, Non-Stable), COPD Severity Level (Mild, Moderate, Severe, Very Severe)
Patient Trajectory	Transfer to Primary Care (PC), Back to cohort, Transfer to Emergency Department (ED)

Within the COPD cohort, the primary classifications of healthcare professional agents include: A. COPD Specialists: Pulmonologists and respiratory therapists diagnose and treat COPD, with a primary healthcare provider overseeing treatment; B. Healthcare Extenders: Nurse practitioners and other professionals support COPD specialists in providing care; C. Respiratory Care Team: Specialists offer respiratory services like breathing exercises and pulmonary rehabilitation; D. Supplementary Healthcare Providers: Pharmacists, dietitians, and physical therapists provide specialized support; E. Clinical Technicians: Technicians conduct diagnostic tests and procedures for monitoring patients; F. Inpatient and Discharge Team: Professionals manage hospital admissions, coordinate care, and facilitate discharge planning; G. Patient Care Support Staff: Administrative and support staff aid patients with tasks and logistics for a seamless healthcare experience.

4.4 Administrative managers

COPD cohort encompasses personnel managers who oversee various administrative functions within the healthcare system. These professionals are responsible for managing staff and resources efficiently to ensure optimal patient care and operational effectiveness. This group includes healthcare administrators and professionals involved in finance, accounting, human resources management, operations, procurement and logistics, facility maintenance, and related areas, all of whom play a crucial role in supporting the management and operation of COPD care facilities.

4.5 Administrative Database

It serves as an essential repository for storing various types of information relevant to patient care and research. These databases may include physical forms of data storage, such as protocol manuals, reference materials, and patient files, as well as digital repositories like electronic health records, scanned images, and patient databases [25]. Table 2 provides an overview of the types and features of databases used in COPD management within the COPD cohort. Given the complexity

Table 2: Forms and Databases for COPD Management

Forms	Databases
Telephonic follow-up form for COPD patients	Patient clinical record
Direct Assessment	Patient Trajectory to Primary Care or Hospital
Modify medicine and diet	COPD clinical monitoring of entire the cohort
Referring to the primary care	Education of the patient in the cohort

of COPD management and research, these databases must be regularly consulted through search features to access relevant information. Additionally, they require ongoing updates to accommodate additions, deletions, and modifications to existing data, ensuring that the information remains accurate and up-to-date. Furthermore, secure access controls are necessary to safeguard patient privacy and ensure that only authorized personnel can retrieve sensitive information from these databases.

4.6 Datasets

Data processing in this context involves managing time-specific captured information. The project primarily deals with two types of data: baseline data and environmental variables. The raw data can be categorized into various groups, with each category specifically indicating numerical and string variables. Table 3 presents 130 virtual patients from the cohort with diverse characteristics demonstrating four grades of COPD Gold (Mild, moderate, severe, and very severe). Each patient is uniquely identifiable by their assigned ID number, facilitating easy data access. Patient characteristics include gender, with some studies suggesting that women may have a higher predisposition to chronic obstructive pulmonary disease (COPD) than men.[26]

Table 3: Patient Characteristics in the COPD Cohort Patient Dataset Entire the Cohort

Characters	Mild	Mod	Severe	V. Severe	Total
Patients	53	36	25	16	130
Age	63.6	65.2	73.7	67.6	67.5
Women	22	16	14	5	57
Men	31	20	11	11	73
Heart Failure	5	9	13	9	36
Height	1.74	1.76	1.70	1.72	1.73
Location	Barcelona				
Work Field	I: 1 II: 14 III: 4 IV: 35	I: 4 II: 10 III: 10 IV: 12	I: 8 II: 3 III: 11 IV: 3	I: 10 II: 0 III: 5 IV: 0	I: 23 II: 27 III: 30 IV: 50
COPD GOLD	53	36	25	16	130
Vaccination	15	9	13	4	41
Depression	9	16	6	4	35
Dependent	9	6	10	2	27
mMRC	>1	1 <2	2 <3	3 >4	130

We consider several variables such as the Body Mass Index (BMI) to play a crucial role in evaluating the amount of accumulated body fat, with research indicating that individuals with a lower BMI may face an increased risk of COPD compared to those with a higher BMI. Height generally, taller individuals might have larger lung volumes and potentially better respiratory mechanics, which can be somewhat beneficial in managing respiratory conditions. In COPD patients, the disease's impact on lung function and respiratory muscles can diminish the advantages associated with height. Regardless of height, the severity of COPD and the associated lung damage are crucial factors in determining respiratory health and function. According to the Global Initiative for Chronic Obstructive Lung

Disease (GOLD), which categorizes COPD based on symptom severity, airflow limitation, and exacerbation risk, patients are classified into four levels: Mild (GOLD 1), Moderate (GOLD 2), Severe (GOLD 3), and Very Severe (GOLD 4). COPD, a condition that can be exacerbated by prior ailments such as heart failure, diabetes, and depression is strongly influenced by smoking status, which is the primary cause of the disease. Therefore, patients are categorized into three groups: 1. Current smokers; 2. Ex-smokers; and 3. Never-smokers. The mMRC scale, an internationally recognized self-management tool, is widely used to assess dyspnea in COPD patients. Respiratory Rate is classified as (<11, 12-19, >20), Heart Rate is categorized as Normal, Higher, or Lower, and Sputum is evaluated based on color and quantity, classified as Normal (white) or Purulent. Oxygen saturation (SpO_2) is categorized into four groups: (96% or more), (95%), (93-94%), and 92% or less. Additionally, FEV1 measures the volume of air forcefully exhaled from the lungs within one second[27].

5 Environment

We employed a simulator named the Supervised Identification Exacerbation Level (SIEL) to implement a self-management program for remote monitoring in a cohort of COPD patients, enabling research and interventions in a virtual setting. The main target of this research is to analyze external variables such as environmental factors. In this context, 'environmental' refers to various elements or conditions within the simulated environment that influence the behavior and interactions of these agents. These factors can include physical attributes such as terrain, weather, and resources, as well as social, economic, or regulatory conditions.

5.1 Process

The process modeling within an agent-based model entails delineating a sequence of interrelated activities and tasks crucial for effectively managing COPD among the patient population.

These processes encompass various aspects such as disease progression, treatment interventions, interactions with healthcare providers, lifestyle modifications, and the influence of environmental factors on COPD outcomes [28]. By simulating these processes at the individual patient level within the cohort, we can glean valuable insights into how diverse factors and interventions influence the overall management of COPD in a personalized and dynamic manner. Activities between the network are performed by agents either directly or remotely using telemedicine techniques. These activities may or may not necessitate the presence of the patient. For instance, examining a patient requires the patient to be present, while analyzing test results does not mandate the patient's presence. As demonstrated in Figure 3, we can categorize the processes in healthcare as follows: a) Transfer Processes involve moving patients within a healthcare network or between different services. b) Communication Processes: These are crucial for structuring the exchange of information between healthcare providers and patients. c) Administrative Processes: These include operational rules, policies, and regulations that govern healthcare facilities. d) Care Processes: These often adhere to standardized proto- cols such as clinical practice guidelines. Typically, they begin with patient admission and end with discharge. Care processes are usually divided into sequential phases. e) Evaluation Processes: These involve collecting and analyzing data, often through dashboards, to assess healthcare performance and outcomes. Processes define the typical, intended, or likely ways of functioning and serve as action guidelines. However, since the agents in the system are intelligent and proactive, they may not always strictly follow these processes. Modelers can design agents with strict adherence to these processes, or allow them to exhibit some degree of behavioral deviation. Additionally, the simulation environment can include events or crises (refer to the scenario component in a later subsection) that may impact the normal progression of one or more processes [29].

5.2 Trial Design

By enrolling COPD patients in a virtual trial, Figure 4, we investigated the potential impacts of external factors, such as fluctuations in environmental temperature, smoking status, seasonal allergies, and lifestyle changes, on the COPD patient cohort. The patients in the cohort are located in the city of Barcelona, each with distinct characteristics. To achieve this, we segmented the runtime of the simulator into three intervals in March 2024, covering specific date ranges (1-11, 12-19, and 20-28), based on the real-time ambient temperature of Barcelona.

This study was structured as a pragmatic trial involving a cohort of 130 patients, each with unique baseline data states.

Depending on various factors, the patients were categorized into a control group and a monitored group. The control group typically comprises patients in stable condition falling under COPD GOLD 1 and 2. As per the definitions and protocols in this study, the control group can seek medical assistance directly from primary care for non-critical conditions or from the hospital in emergencies. On the other hand, the monitored group consists of patients in an unstable condition with higher-risk profiles falling under COPD GOLD 3 and 4. This design aims to reduce the workload for healthcare professionals and enhance the potential for self-management for individuals with COPD, thereby improving the applicability of the findings to other healthcare settings.

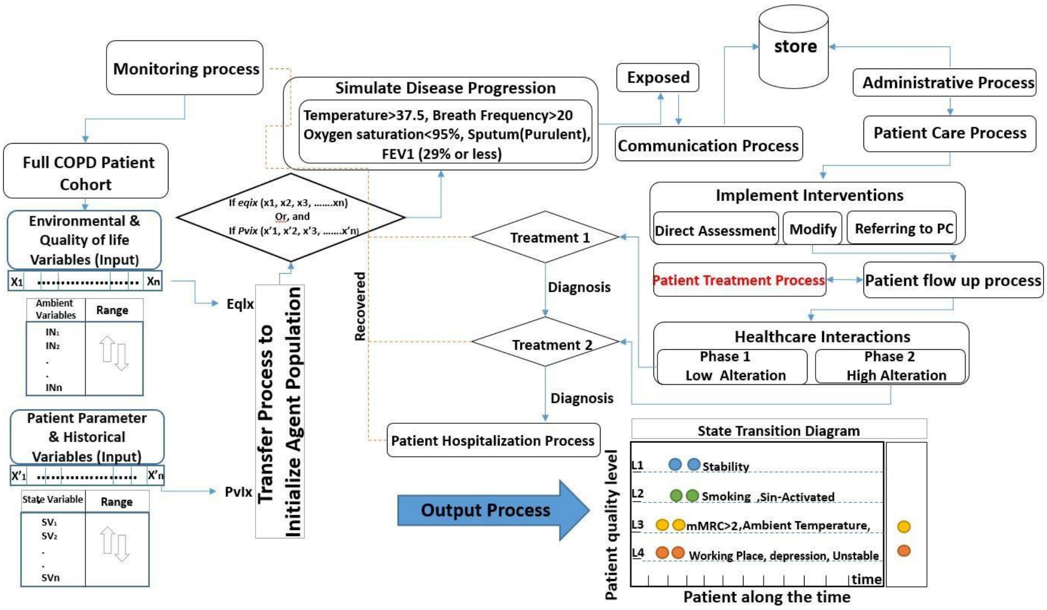


Figure 3: General structural overview of the COPD network and agents modeling

6 Discussion and Results

At this stage, we have randomized 56 patients from the monitored group, Figure 4. The objective was to enhance focus and better demonstrate with fewer patients for improved validation and calibration of the simulator. During the initial run of the simulator from March 1st to March 11th, 2024, the temperature ranged approximately from 2°C to 18°C, and the Air quality index (AQI) was 45 US AQI. Despite variations in environmental conditions, the study yielded promising results for the COPD patient cohort.

We meticulously analyzed internal patient variables and seven vital physiological parameters, presenting our findings in Table 3. Additionally, we explored the impact of lifestyle factors on these variables, acknowledging smoking and pollution as significant contributors to COPD severity, as depicted in Figure 5. Patients exposed to these factors faced more challenges compared to those in cleaner environments or who abstained from smoking. Influenza infections significantly risk exacerbations and complications in COPD patients, while exposure to air pollutants worsens respiratory symptoms and disease progression. Smoking, the primary cause of COPD, accelerates lung function decline and increases the risk of exacerbations and comorbidities. Additionally, seasonal allergies like pollen allergies can worsen COPD symptoms and cause respiratory distress. During the second simulator run from March 12th to March 19th, 2024, with temperatures ranging from 2°C to 25°C and an AQI of 65 US AQI indicating poor air quality, we also factored in additional variables such as depression and dependency. Figure 6 highlights two critical patient variables: body temperature and oxygen saturation. Interestingly, during this run, 13 non-smoker and ex-

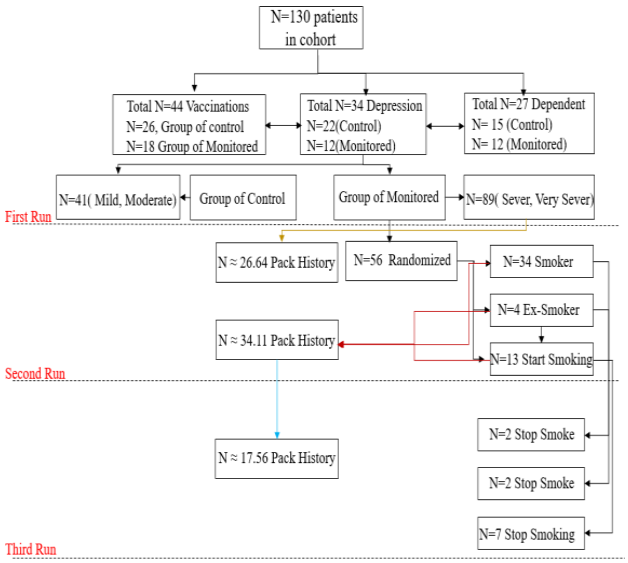


Figure 4: Exploring External Factors and Patient Stratification in a Pragmatic Trial

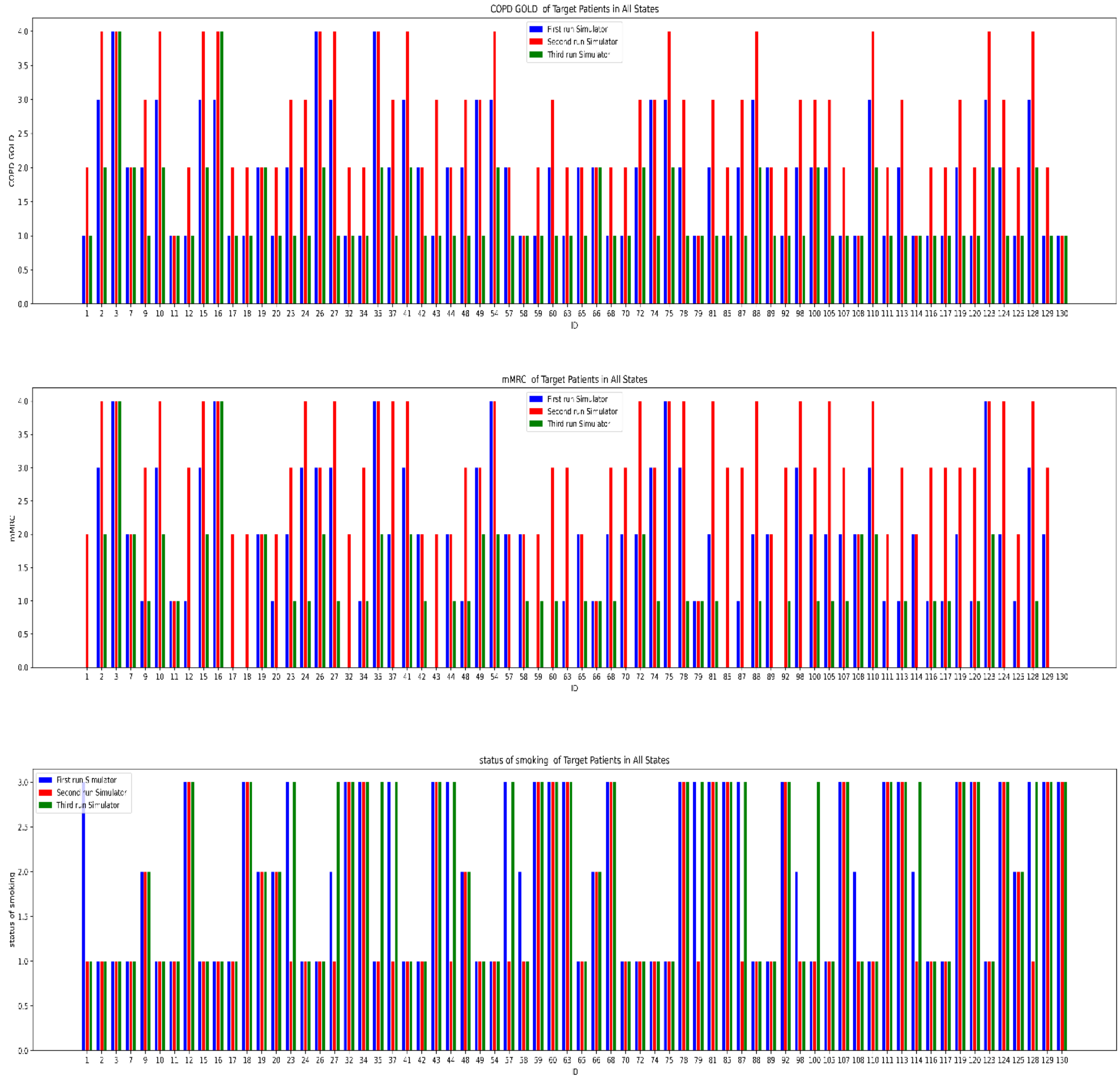
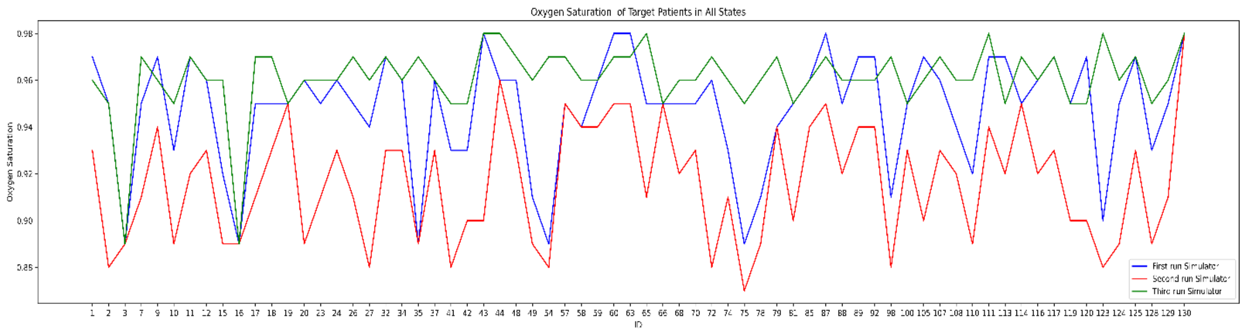


Figure 5: Results of randomized patients during the first run of the simulator, including COPD GOLD, mMRC, and smoking status variables.



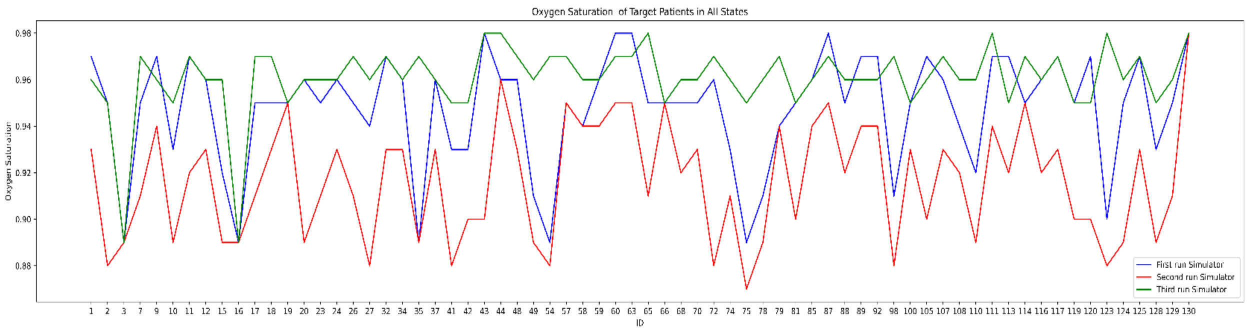


Figure 6: The results of the second run of the simulator observed among randomized patients during the first run of the simulator. Included body temperature and oxygen saturation.

smoker patients from the cohort resumed smoking, influenced by other factors. The coexistence of depression and dependency in COPD patients presents a significant challenge with implications for patient well-being and treatment outcomes. Depression often stems from COPD's chronic nature, causing emotional distress, reduced motivation, and treatment adherence issues. Dependency due to declining physical function can exacerbate feelings of loss of independence and caregiver burden. Addressing these psychosocial factors is crucial for optimizing COPD management and improving patient outcomes. Interventions for depression may include counseling, psychotherapy, and medication, while strategies for dependency could focus on promoting self- management skills and providing support services. We conducted a third simulation run from March 20th to March 28th, 2024. Throughout this timeframe, temperatures fluctuated between approximately 5°C and 23°C, while the Air Quality Index (AQI) remained at 43 US AQI, indicating substandard air quality. The evidence suggests that most patients receive treatment through direct assessment, medication adjustments, or hospital referrals. Figure 7 illustrates COPD GOLD and mMRC Scale variables from different simulator runs, highlighting a notable difference between run times. This approach was guided by the stability observed among patients in the third simulation run, leading to interventions focused on optimizing treatment regimens, adjusting medications, and providing specialized care when needed to ensure ongoing patient well-being. Furthermore, the third simulation run shows notable changes in the patient's smoking habits Some patients reduced their smoking history, while others opted to quit smoking entirely. This trend is illustrated in Figure 8, underscoring the dynamic nature of smoking behavior among COPD patients within the cohort.

7 Conclusion and Future Work

This paper describes a model for agent-based simulation in distributed healthcare systems. We discuss modeling each component using a real-world case study, incorporating actual temperature data from the city of Barcelona. Unlike other healthcare frameworks that concentrate on the technical aspects of designing and implementing agent-based simulation systems, Our proposal addresses conceptual issues related to the development of healthcare models. It provides a reference guideline for executing this process independently of specific technical decisions.

Applying this generic model accelerates the development of agent-based simulations in distributed healthcare systems while also reducing the likelihood of omitting essential elements, concepts, or interactions. By incorporating agent-based modeling, we simulated

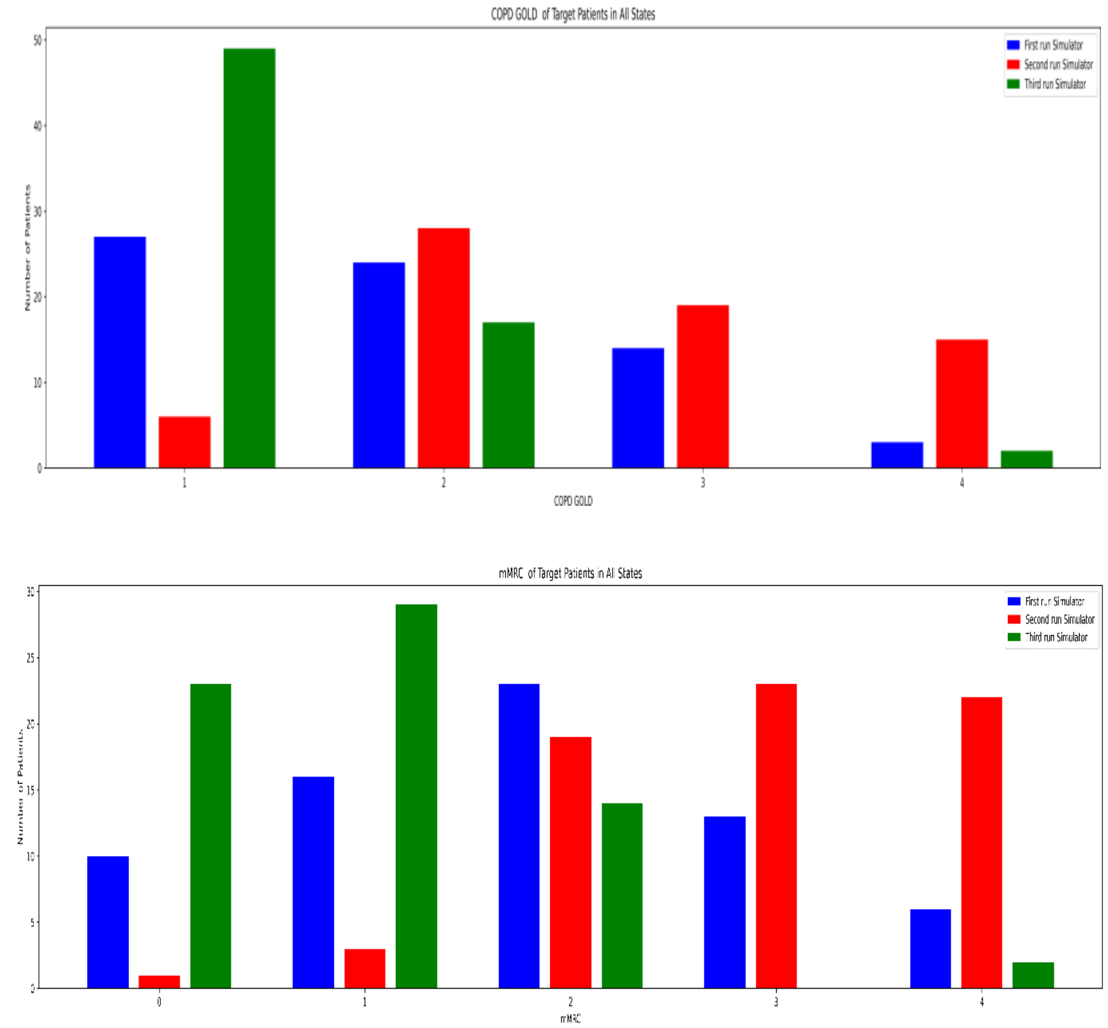


Figure 7: Demonstrate the three runs of the simulator over time and compare the results.

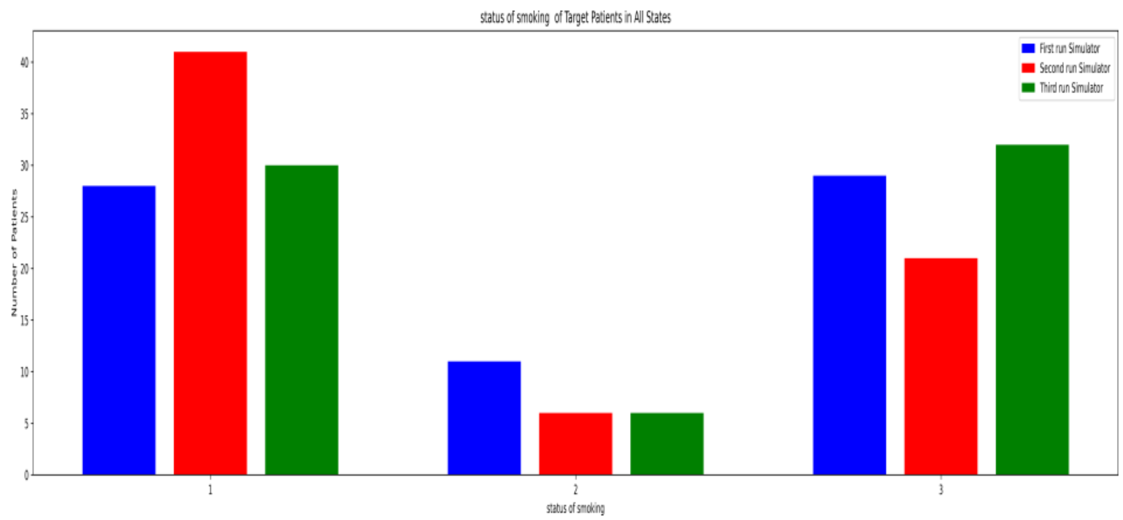


Figure 8: The difference between smokers, non-smokers, and never-smokers during the three runs of the simulator.

COPD progression and treatment efficacy. The findings underscore the potential of virtual clinical trial models to advance COPD research and improve patient outcomes through personalized treatment strategies. Future research should validate and refine the model for enhanced accuracy in predicting COPD progression and treatment outcomes. Advanced environmental monitoring technologies will improve assessment. Exploring personalized treatment algorithms and validating them across diverse populations is crucial. Efforts to translate findings into clinical practice are essential for improving patient outcomes and healthcare efficiency.

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Competing Interests

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Authors' Contributions

The authors confirm contribution to the paper as follows: M.H.A: Conceptualization, Methodology, Software, Writing Original draft preparation. A.W: Writing- Software, Data curation, Investigation. M.T: Reviewing and Editing, Funding acquisition Writing-Reviewing and Editing. D.R and E.L: Supervision, Software, Validation, Reviewing and Editing, Funding acquisition. F.E: Investigation, Validation. All authors reviewed the results and approved the final version of the manuscript.

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