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A Novel Hybrid Algorithm for Designing a Sustainable Supply Chain of CAR-T Therapy in a Multi-Objective Mode Considering Disease Relapse

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ABSTRACT

This study investigates the sustainable supply chain network design problem in the healthcare sector, where patients with cancer are treated using CAR-T cell therapy. To better reflect real-world conditions, the possibility of disease relapse is incorporated into the problem formulation. The problem is modeled as a multi-objective mixed-integer programming (MIP) problem, aiming to minimize total costs, reduce environmental impacts, and maximize social satisfaction and accessibility. Given the NP-hard nature of the problem, a novel hybrid metaheuristic algorithm is developed to solve large-scale instances. The proposed algorithm is a structured integration of three evolutionary methods: Non-dominated Sorting Genetic Algorithm IV (NSGA-IV) for preserving diversity and Pareto front coverage, S-Metric Selection Evolutionary Multi-Objective Algorithm (SMS-EMOA) for enhancing precision and hypervolume expansion, and the Epsilon-dominance Evolutionary Multi-objective Algorithm (ε-MOEA) for rapid initial convergence. These three were selected as their combined strengths ensure a balanced trade-off between exploration, convergence speed, and final accuracy, which cannot be achieved by any of them individually. The proposed hybrid algorithm employs a two-stage selection mechanism, an adaptive mutation strategy, and a dynamic external archive to generate high-quality solutions across the Pareto front. Numerical experiments across different problem scales confirm its superiority, yielding on average 30% more non-dominated solutions, a 3% reduction in costs, and a 2 to 3% decrease in environmental impacts compared to single algorithms. The findings demonstrate this hybrid approach potential to enhance both strategic and operational decision-making in resilient healthcare delivery networks.

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1) Introduction

Recent years have witnessed transformative advancements in personalized medicine and immunotherapy, fundamentally reshaping the therapeutic landscape for complex, refractory, and relapsing diseases. One of the most prominent achievements in this field is Chimeric Antigen Receptor T-cell (CAR-T) therapy. This approach harnesses the genetic engineering of a patient's own immune cells to confer a remarkable ability to precisely target and eradicate cancerous cells, demonstrating significant success, particularly in relapsed hematological malignancies (Jacoby, 2019). However, the CAR-T therapy supply chain is among the most complex structures in healthcare systems. It encompasses a series of sensitive and interlinked stages: the collection of viable cells, genetic processing, controlled-temperature transportation, secure storage, and ultimate reinfusion into the patient. This process is not only highly time-sensitive and delicate but also demands meticulous coordination of infrastructure across the entire supply network (Bray et al., 2024). The complexity of this chain escalates significantly when a patient experiences disease relapse following initial treatment, as decision-making in such scenarios must be rapid, precise, and sustainable, all while operating within constrained therapeutic resources.

Concurrently, modern healthcare systems face increasing pressure to address the triple dimensions of sustainability. This implies that the design of therapeutic networks must not focus solely on cost or time efficiency; it is imperative to also integrate environmental impacts (such as energy consumption and bio-waste generation) and social consequences (including equitable access to treatment and job creation) into the decision-making process. Attending to these dimensions, particularly for advanced therapies such as CAR-T, constitutes a strategic imperative.

To bridge clinical realities with mathematical modeling, it is essential to clarify how disease relapse scenarios are translated into supply chain design variables and constraints. In practice, relapse generates immediate and additional demand, necessitating rapid resource allocation, the deployment of backup transportation, and the establishment of post-relapse care centers. In the proposed model, these clinical dimensions are represented through parameters for demand at post-relapse care centers, constraints on the capacity of vehicles and mobile medical units, and the location-allocation decisions for these facilities. Furthermore, the time sensitivity inherent in relapse is incorporated by imposing stringent time constraints on manufacturing, transportation, and treatment administration. Therefore, real-world therapeutic requirements are integrated into the model as quantitative variables and constraints, ensuring that the proposed optimization framework is grounded in operational imperatives rather than being a purely abstract theoretical construct.

Simultaneously, formulating a multi-objective mathematical model that combines these clinical realities with economic, environmental, and social criteria results in a complex problem characterized by conflicting objectives and a non-linear solution space. Under such conditions, classical optimization methods are insufficient, necessitating the use of metaheuristic algorithms (Javadi Gargari et al., 2021). In response to this need, the present study aims to develop a multi-objective mathematical model for the sustainable design of a CAR-T therapy supply chain under conditions of disease relapse. Furthermore, it introduces a novel hybrid algorithm based on the integration of NSGA-IV, ε-MOEA, and SMS-EMOA, designed to effectively balance convergence speed, solution diversity, and final Pareto front precision.

2) Literature Review

Papathanasiou et al. (2020) discuss the production and supply chain challenges of CAR T-Cell therapy, including increasing demand, complex product and process nature, and intricate logistics. Their research focuses specifically on commercial supply chain challenges and presents risks associated with other contributing factors. Karakostas et al. (2020) designed a patient-centric, decentralized supply chain model for Chimeric T-Cell therapy, formulating it as a Mixed-Integer Linear Programming (MILP) model. Hospitals were considered coordinators, and local clinics were designated as treatment administration centers. Jemai et al. (2020) integrated environmental concepts into supply chain management to form a dynamic green supply chain management model. They implemented this concept for blood platelets, a highly perishable product. Their primary objective was to minimize redundancies in blood facility location allocation and create an efficient network for blood platelet collection and distribution. Lam et al. (2021) proposed a discrete-event simulation model to compare the operational feasibility and manufacturing costs of CAR T products between centralized and decentralized settings. They evaluated this simulation regarding resource allocation, cost per treatment, and system resilience level using a hypothetical UK system with three demand levels: low, predicted, and high. Their results indicated that individual facilities in decentralized systems could share facility costs at high treatment volumes. Goodarzian et al. (2021) designed a model to address gaps in the pharmaceutical industry mathematical models, incorporating the production-distribution-inventory-allocation-location framework in a sustainable medical supply chain. They also considered medicines for COVID-19 patients and production/delivery periods according to their perishability, designing a multi-objective, multi-echelon, multi-product, multi-period model for their sustainable supply chain network. Torrado and Barbosa (2022) conducted a review of sustainability in blood supply chains. They examined articles published in the past 10 years, categorizing their analysis into three distinct groups: the description of stages, strategic-tactical and strategic-operational perspectives, and the examination of sustainability dimensions. They pursued three objectives: reviewing literature related to sustainability goals, addressing unanswered research questions, and identifying challenges related to modeling, uncertainty, and risk. Lam et al. (2022) proposed a framework for commercializing autologous cell therapies and, using a illustrative UK example, demonstrated the impact of rapid regulatory approval on capacity planning and investment decisions. They proposed a MILP approach to better understand capacity and portfolio planning decisions for autologous cell therapies. Mansur et al. (2023) considered a multi-level MILP model for a sustainable blood supply chain. Aiming to increase profit by considering multiple blood groups, they accounted for total revenue versus total costs, including purchase, transportation, production, blood bag shelf-life, and carbon emission. They applied their model to a real-world case study. Shayannia (2023) designed a mathematical model incorporating sustainability and a new political sustainability objective. Focusing on an agile supply chain strategy, they considered a four-echelon network of supplier, wholesaler, retailer, and customer. Fallahi et al. (2024) developed a sustainable supply chain network for convalescent plasma during the COVID-19 pandemic. They presented a hybrid multi-objective optimization model to minimize total carbon emissions alongside supply chain costs. Kargar et al. (2024) developed an agent-based COVID-19 simulation model to record disease transmission and predict the number of susceptible individuals and infections. They then created a sustainable vaccine supply chain (VSC) considering greenhouse gas impact.

Rekabi et al. (2024) solved a responsive, sustainable, and resilient blood supply chain network considering density using a regression method. They presented an innovative multi-period, multi-objective nonlinear mixed-integer model for an efficient and responsive Green Blood Supply Chain (GBSC) incorporating resilience measures. Ala et al. (2024) designed a blood supply chain network with lateral transportation for robust probabilistic optimization. Their objectives included minimizing fixed and temporary facility costs, blood product transfer costs, and shortage levels. Dada et al. (2025) investigated the challenges of the essential medicine supply chain in the United States during the COVID-19 pandemic. Findings revealed that flaws in demand forecasting systems, inventory management, and supply chain transparency led to drug shortages and increased costs. This research was based on the analysis of real crisis-period data and interviews with key stakeholders. The results indicated that novel technologies, such as Artificial Intelligence (AI) and Blockchain, could significantly improve drug supply chain resilience. AI, through accurate demand forecasting, and Blockchain, by creating transparency and traceability in the supply chain, were among the solutions proposed in the study. Camacho-Villalón et al. (2025) presented the METAFOR software framework which uses auto-configuration tools to automatically generate hybrid continuous optimization algorithms. Their results show that these automatically generated hybrid algorithms generally outperform single-method, human-knowledge-based algorithms. Herdianto et al. (2025) presented a hybrid model for the Capacitated Vehicle Routing Problem (CVRP) based on Graph Neural Networks (GNN), which reduces the search space guided by a Large Neighborhood Search (LNS) operator. This method, without requiring retraining for different problem sizes, leads to improved solution quality and scalability of up to 30,000 nodes.

Table 1) Literature Review

Authors	**Evaluation Component**	**Innovation**	**Evaluation Approach**	**Research Method**	**Evaluation Environment**	**Field/Context**
Herdianto et al. (2025)	Computational Efficiency, Scalability	Integration of Machine Learning with LNS in a Hybrid Metaheuristic	Performance Analysis on Large Datasets	Algorithm Design & Simulation	Non-Deterministic	Logistics & Transportation, Hybrid Metaheuristics
Camacho-Villalón et al. (2025)	Solution Quality, Convergence Speed	Automated Design of Hybrid Metaheuristics with PSO, DE, CMA-ES Modules	Empirical Comparison with Baseline Algorithms	Software Framework Development & Numerical Testing	Deterministic	Hybrid Optimization
Dada et al. (2025)	Supply Chain Resilience, Crisis Management	Combination of AI and Blockchain for Drug Traceability	Analysis of Systemic Failures during the Pandemic	Analytical Case Study	Non-Deterministic	Drug Supply Chain Management
Fallahi et al. (2024)	Cost, Carbon Emissions	-	Mathematical Modeling	Case Study	Deterministic	Blood Plasma
Kargar et al. (2024)	Location, Cost, Environmental Impact	-	Mathematical Modeling, Simulation	Case Study	Deterministic	Vaccines
Rekabi et al. (2024)	Green, Responsive, Sustainable, Resilient, Queueing Theory	-	Mathematical Modeling	Case Study	Non-Deterministic	Blood
Ala et al. (2024)	Cost, Shortage, Transshipment	-	Mathematical Modeling, Lexicographic	Random Sample	Probabilistic	Blood
Mansur et al. (2023)	Sustainability	-	Mathematical Modeling	Case Study	Deterministic	Blood
Shayannia (2023)	Sustainability, Political	-	Mathematical Modeling	Case Study	Deterministic	Pharmaceuticals
Lam et al. (2022)	Maximizing Net Present Value	-	Mathematical Modeling	Case Study	Deterministic	Cell Therapy
Torrado et al. (2022)	Sustainability	-	-	Systematic Literature Review	Non-Deterministic	Blood

Goodarzian et al. (2021)	Sustainability, Production, Distribution, Inventory, Allocation, Location	-	Mathematical Modeling	Case Study	Deterministic	Pharmaceuticals
Lam et al. (2021)	Resource Allocation, Cost, Resilience	-	Discrete Event Simulation	Case Study	Deterministic	CAR T-Cell
Papathanasiou et al. (2020)	-	-	-	-	-	CAR T-Cell
Jemai et al. (2020)	Sustainability, Dynamism	-	Mathematical Modeling	Case Study	Deterministic	Blood
Karakostas et al. (2020)	Cost Reduction	-	Mathematical Modeling	20 Random Samples	Deterministic	CAR T-Cell

blood and vaccine supply chains—valuable for sustainability, location, or inventory management—they do not fully address the stochastic conditions and highly time-sensitive constraints of CAR-T therapy. In blood or vaccine chains, demand is often managed collectively over predictable horizons, while in CAR-T therapy, each patient has a unique treatment process where even minor delays can impact clinical efficacy. Furthermore, the occurrence of relapse leads to immediate and uncertain demand surges that are not well-represented in traditional models.

Moreover, although some studies have used metaheuristic approaches to solve complex problems in therapeutic chains, the combined application of advanced algorithms, particularly under relapse-sensitive conditions, has not been reported. Recent works on hybrid metaheuristics and robust optimization in healthcare supply chains also show that single-stage approaches cannot simultaneously meet the needs for solution diversity, convergence speed, and resilience to uncertainty. This gap is particularly evident in CAR-T supply chain design, where existing models primarily focus either on cost/location dimensions or on deterministic constraints. In contrast, relapse conditions require the simultaneous consideration of demand dynamics, stringent time constraints, and the triple-bottom-line of sustainability. Accordingly, this study aims to fill this void by presenting a multi-objective optimization model coupled with an advanced hybrid metaheuristic algorithm capable of addressing the real-world needs of the CAR-T treatment chain under uncertainty and relapse. In response to these gaps, the present study offers two key innovations:

1. Development of a dedicated multi-objective modeling framework specifically designed for CAR-T therapy supply chain design under relapse conditions, incorporating sustainability criteria.
2. Introduction of a novel, advanced hybrid metaheuristic algorithm that leverages a three-stage integration of NSGA-IV, ε-MOEA, and SMS-EMOA. Employing the Taguchi experimental design method for systematic parameter tuning, this algorithm uniquely ensures three key features simultaneously: high Pareto front quality, solution diversity, and convergence speed for complex therapeutic problems.

This novel approach not only addresses theoretical gaps in the literature but also provides practical solutions for optimizing the supply chain of advanced cell therapies under real-world conditions. The unique combination of advanced mathematical modeling with hybrid optimization algorithms enables more efficient decision-making in the face of dynamic healthcare system challenges.

3) Methodology

Chimeric Antigen Receptor T-cell (CAR-T) therapy is a highly personalized and time-sensitive treatment that requires a precise and coordinated therapeutic supply chain. The process begins with a patient visiting a specialized hospital for initial examination and eligibility confirmation. Upon approval, two blood samples are collected from the patient via leukapheresis. These samples are subsequently transported by specialized blood transport vehicles, subject to scheduling and capacity constraints, to therapy manufacturing centers. Each vehicle must deliver the samples within a specified time window and geographical radius, provided that the total input volume to any center does not exceed its operational capacity (Hayden et al., 2022). The activation of a manufacturing center is determined by its operational capacity, the spatial distribution of demand, and its proximity to hospitals and infusion sites. Each active center is allocated to a specific set of hospitals and infusion sites to maximize the efficiency of the manufacturing and delivery process.

Following the completion of manufacturing and final approval, the produced therapy is transported to the infusion site by a mobile medical unit accompanied by a specialist physician. Infusion sites are selected based on proximity to the manufacturing center and transportation constraints. If the patient chooses their residence as the infusion site, a mobile unit is dispatched to their home. Alternatively, if a local clinic is preferred, vehicle allocation is based on availability and the aggregated demand for that time period. To ensure timely delivery, only one mobile unit is assigned to each infusion site per service period. To cover patients in case of disease relapse, a backup vehicle is allocated to each infusion site. These vehicles are responsible for transporting relapsed patients to post-relapse care centers. The allocation of these care centers is based on demand patterns at each infusion site. The entire supply chain structure is designed to meet all therapeutic demands, ensuring that manufacturing, delivery, and infusion processes occur within clinically acceptable timeframes. Furthermore, each infusion site is linked to a dedicated post-relapse care center to guarantee comprehensive treatment services and follow-up.

In this paper, the conceptual model structure was first designed according to the characteristics of CAR-T therapy. Subsequently, a deterministic optimization model was developed for decision-making across various domains, including facility location, inventory control, production planning, and transportation routing (Kargar et al., 2024). Although the model is formulated with deterministic assumptions, given the inherently uncertain nature of the treatment environment, it can be extended to robust or fuzzy forms. Input data was generated using random number generation methods based on hypothetical yet realistic scenarios, as real-world data is unavailable due to the novelty of the treatment. The definitions of indices, parameters, and model variables are presented in Table 2. To verify the validity and efficiency of the proposed model, it was evaluated using the proposed hybrid metaheuristic algorithm. This algorithm was developed by hierarchically integrating three approaches: NSGA-IV, ε-MOEA, and SMS-EMOA. The computational implementation was performed using the Python programming language (version 3.9), utilizing specialized libraries including DEAP and NumPy.

3.1) Mathematical Modeing

The assumptions of the mathematical model are summarized as follows:

- Intra-center production scheduling of the therapy is not considered.
- All blood samples used are fresh.
- Pre-infusion chemotherapy is administered by mobile units or clinics.
- Each clinic is dependent on only one manufacturing center and one hospital.
- Each infusion site (home or clinic) receives service only once per period.
- Mobile medical units are dispatched from manufacturing centers and return after service.
- Transportation of relapsed patients is performed by dedicated ambulances.
- Post-relapse care centers have specified capacities and fixed stay durations.
- Two units of blood from the patient are required for each CAR-T therapy unit.

Table 2)Definition of Indices, Parameters and Variables of the Mathematical Model

Symbol	Description
H	Set of hospitals for receiving blood, $h \in H$
B	Set of hospitals for transfusion, $b \in B$
K	Set of clinics for transfusion, $k \in K$
P	Set of patients' homes for transfusion, $p \in P$
F	Set of T-cell production centers, $f \in F$
S	Set of post-treatment care centers (SOS), $s \in S$
T	Set of courses, $t \in T$
V	Set of cars for transporting blood, $v \in V$
M	Set of cars for transporting people or sending produced T-cells, $m \in M$
$W = \{B, P, K\}$	Set of hospital, clinic, and patient collections for T-cell transfusion, $w \in W$
Parameter	**Description**
CX_{vt}	Transportation cost per unit distance by vehicle v in period t.
DX_{hf}	Distance between centers h and f.
CZ_{mt}	Transportation cost per unit distance by vehicle m in period t.
DZ_{fw}	Distance between centers f and w.
DG_{ws}	Distance between centers w and s.
FR_f	Fixed cost of establishing production center f.
FL_s	Fixed cost of establishing SOS center s.
CS_{wt}	Service cost at center w in period t.
CO_{st}	Service cost per patient at SOS center s in period t.
PR_{wt}	Probability of patient relapse after treatment at center w in period t.
λ_m	Environmental pollution per unit distance traveled by vehicle m.
λ_v	Environmental pollution per unit distance traveled by vehicle v.
γ_f	Environmental pollution per unit of production at center f.
γ_s	Environmental pollution per patient post-relapse care at center s.
ϕ_f	Personnel required per unit of production at center f.
ϕ_s	Personnel required per patient post-relapse care at center s.
CE_f	Hiring cost per personnel per unit of production at center f.
CE_s	Hiring cost per personnel per patient post-relapse care at center s.
CV_v	Capacity of vehicle v for blood transportation.
CM_m	Capacity of vehicle m for transportation between centers.
BW_s	Maximum capacity for post-relapse patient care at SOS center s.
CG_h	Admission capacity of hospital h for blood sample collection.
CP_f	T-cell production capacity at production center f.
DB_{wt}	Number of patients at center w in period t.
DW_{wt}	Number of patients experiencing relapse after treatment at centers w in period t.
TR_{hfvt}	Transportation time between centers h and f by vehicle v in period t.
TR_{fwmt}	Transportation time between centers f and w by vehicle m in period t.

SK_{ft}	T-cell production time at center f in period t.
TS_{wt}	Service time for patient injection at center w in period t.
TU_{wt}	Maximum allowable time for T-cell injection to patients at center w in period t.
Positive Variables	**Description**
CA_{ft}	Time to complete T-cell production at center f in period t.
CT_{wmt}	Time to complete T-cell injection at center w provided by vehicle m in period t.
Binary Variables	**Description**
Q_{hfvt}	One if blood is transported from hospital h to production center f by vehicle v in period t, zero otherwise.
E_{fwmt}	One if a connection is established from production center f to center w (hospitals, clinics, patients' homes) for T-cell injection by vehicle m in period t, zero otherwise.
G_{wsmt}	One if a connection is established from center w to SOS center s for post-treatment relapse care by vehicle m in period t, zero otherwise.
R_f	One if production center f is selected, zero otherwise.
L_s	One if SOS center s is selected for post-relapse care, zero otherwise.
Integer Variables	**Description**
Y_{ht}	Number of individuals admitted to hospital h in period t for blood sample collection.
X_{hfvt}	Number of blood samples dispatched from hospital h to production center f by vehicle v in period t.
GX_{wsmt}	Number of patients dispatched from center w to SOS center s for post-treatment relapse care by vehicle m in period t.
Z_{fwmt}	Number of T-cells dispatched from production center f to center w (hospitals, clinics, patients' homes) by vehicle m in period t.

Objective Functions of the Proposed Model:

The objective function F1 involves minimizing the fixed costs of establishing T-cell production centers and SOS centers, transportation between centers, injection services at W centers (hospitals, clinics, and patients' homes), post-relapse care services, and personnel hiring.

$$
\begin{aligned}
&Min(F1) = \sum_{f\in F} R_f \times CR_f + \sum_{s\in S} L_s \times CL_s \\
&+\sum_{h\in H}\sum_{f\in F}\sum_{v\in V}\sum_{t\in T} CX_{vt} \times DX_{hf} \times Q_{hfvt} + \sum_{f\in F}\sum_{w\in W}\sum_{m\in M}\sum_{t\in T} CZ_{mt} \times DZ_{fw} \times E_{fwmt} + \\
&\sum_{w\in W}\sum_{s\in S}\sum_{m\in M}\sum_{t\in T} CZ_{mt} \times DG_{ws} \times G_{wsmt} \\
&+\sum_{t\in T}\sum_{w\in W} CS_{wt} \times \sum_{f\in F}\sum_{m\in M} Z_{fwmt} + \sum_{t\in T}\sum_{s\in S}\sum_{w\in W} CO_{st} \times PR_{wt} \times \sum_{m\in M} GX_{wsmt} \\
&+\sum_{f\in F} CE_f \times \sum_{t\in T}\sum_{w\in W}\sum_{m\in M} Z_{fwmt} + \sum_{s\in S} CE_s \times \sum_{t\in T}\sum_{w\in W}\sum_{m\in M} PR_{wt} \times GX_{wsmt}
\end{aligned} \tag{1}
$$

The objective function F2 aims to minimize environmental pollution emissions generated by transportation vehicles, production centers, and SOS centers.

$$
\begin{aligned}
&Min(F2) = \\
&+\sum_{h\in H}\sum_{f\in F}\sum_{v\in V}\sum_{t\in T} \lambda_v \times DX_{hf} \times Q_{hfvt} + \sum_{f\in F}\sum_{w\in W}\sum_{m\in M}\sum_{t\in T} \lambda_m \times DZ_{fw} \times E_{fwmt} + \\
&\sum_{w\in W}\sum_{s\in S}\sum_{m\in M}\sum_{t\in T} \lambda_m \times DG_{ws} \times G_{wsmt} \\
&+\sum_{t\in T}\sum_{f\in F} \gamma_f \times \sum_{w\in W}\sum_{m\in M} Z_{fwmt} + \sum_{t\in T}\sum_{s\in S} \gamma_s \times \sum_{w\in W}\sum_{m\in M} PR_{wt} \times G_{wsmt}
\end{aligned} \tag{2}
$$

The objective function F3 seeks to maximize employment and job creation within the production centers and post-relapse care facilities.

$$Max\,(F3)=\sum_{f\in F}\varphi_f\times\sum_{t\in T}\sum_{w\in W}\sum_{m\in M}Z_{fwmt}+\sum_{s\in S}\varphi_s\times\sum_{t\in T}\sum_{w\in W}\sum_{m\in M}PR_{wt}\times GX_{wsmt} \tag{3}$$

Constraints:

Constraint (4) specifies the hospitals designated to collect blood from patients.

$$\sum_{h\in H}Y_{ht}=\sum_{w\in W}DB_{wt} \qquad \forall t\in T \tag{4}$$

Constraint (5) ensures the maximum blood collection capacity of each hospital is not exceeded.

$$Y_{ht}\le CG_h \qquad \forall h\in H,t\in T \tag{5}$$

Constraint (6) calculates the quantity of blood shipped from hospitals to T-cell producers based on the number of admitted patients.

$$\sum_{f\in F}\sum_{v\in V}X_{hfvt}=Y_{ht} \qquad \forall h\in H,t\in T \tag{6}$$

Constraint (7) enforces the maximum transportation capacity for vehicles shipping materials from hospitals to production centers.

$$X_{hfvt}\le CV_v\times Q_{hfvt} \qquad \forall h\in H,v\in V,f\in F,t\in T \tag{7}$$

Constraint (8) establises a conditional relationship between variables and ensures that if one variable is zero, then the other must also be zero.

$$Q_{hfvt}\le X_{hfvt} \qquad \forall h\in H,v\in V,f\in F,t\in T \tag{8}$$

Constraint (9) ensures that the quantity of blood samples shipped from hospitals to production centers equals the quantity of produced T-cells shipped from production centers to W centers.

$$\sum_{h\in H}\sum_{v\in V}X_{hfvt}=\sum_{w\in W}\sum_{m\in M}Z_{fwmt} \qquad \forall f\in F,t\in T \tag{9}$$

Constraint (10) calculates the shipment quantity of T-cells from production center f to W centers.

$$\sum_{f\in F}\sum_{m\in M}Z_{fwmt}=DB_{wt} \qquad \forall w\in W,t\in T \tag{10}$$

Constraint (11) imposes an upper bound on the maximum T-cell production capacity at the production centers.

$$\sum_{w\in W}\sum_{m\in M}Z_{fwmt}\le CP_f\times R_f \qquad \forall f\in F,t\in T \tag{11}$$

Constraint (12) enforces the maximum transportation capacity for vehicles shipping goods from production centers to W centers.

$$Z_{fwmt}\le CM_m\times E_{fwmt} \qquad \forall f\in F,w\in W,m\in M,t\in T \tag{12}$$

Constraint (13) defines a logical linkage between variables, where if one variable is zero, then the other variable is forced to zero.

$$E_{fwmt}\le Z_{fwmt} \qquad \forall f\in F,w\in W,m\in M,t\in T \tag{13}$$

Constraint (14) calculates the completion time for T-cell production at the production centers.

$$CA_{ft}\ge TR_{hfvt}+SK_{ft}\times X_{hfvt}-MM\times(1-Q_{hfvt}) \qquad \forall h\in H,v\in V,f\in F,t\in T \tag{14}$$

Constraint (15) calculates the arrival time of the required T-cells to patients at home, clinics, and hospitals.

$$CT_{wmt} \geq CA_{ft} + (TS_{wt} \times Z_{fwmt}) + TR_{fwmt} - MM \times (1 - E_{fwmt}) \quad \forall w \in W, m \in M, f \in F, t \in T \quad (15)$$

Constraint (16) determines the maximum allowable arrival time for required blood products to patients at home, clinics, and hospitals.

$$CT_{wmt} \leq TU_{wt} \times \sum_{f \in F} E_{fwmt} \quad \forall w \in W, m \in M, f \in F, t \in T \quad (16)$$

Constraint (17) calculates the number of patients admitted to the SOS center.

$$\sum_{s \in S} \sum_{m \in M} GX_{wsmt} = DW_{wt} \quad \forall w \in W, t \in T \quad (17)$$

Constraint (18) guarantees that the number of admitted patients does not exceed the acceptance capacity of the SOS center.

$$\sum_{w \in W} \sum_{m \in M} GX_{wsmt} \leq BW_s \quad \forall w \in W, t \in T \quad (18)$$

Constraint (19) enforces the maximum transportation capacity for vehicles moving from W centers to the SOS center.

$$GX_{wsmt} \leq CM_m \times G_{wsmt} \quad \forall f \in F, w \in W, m \in M, t \in T \quad (19)$$

Constraint (20) establishes a dependency between variables GX_{wsmt} and G_{wsmt}, stipulating that if GX_{wsmt} is zero, then G_{wsmt} must be zero.

$$G_{wsmt} \leq GX_{wsmt} \quad \forall f \in F, w \in W, m \in M, t \in T \quad (20)$$

Constraints (21) to (23) specify the nature and bounds of the decision variables, imposing non-negativity and integrality requirements.

$$CT_{wmt}, CA_{ft} \geq 0 \quad (21)$$

$$Q_{hfvt}, E_{fwmt}, G_{wsmt}, R_f, L_s \in \{0,1\} \quad (22)$$

$$Y_{ht}, X_{hfvt}, GX_{wsmt}, Z_{fwmt} \in Integer \quad (23)$$

3.2) Solution Methodology

Given the complexity of the developed mathematical model for a sustainable CAR-T cell therapy supply chain under relapse conditions, the use of a powerful, adaptable, and multi-objective optimization algorithm is essential (Nazemi et al., 2022). The model simultaneously aims to minimize costs, reduce environmental impact, and maximize social satisfaction. Classic metaheuristic algorithms individually face challenges in simultaneously ensuring diversity, convergence, and precision within the Pareto front (Sajjadi et al., 2022). Therefore, this research presents a novel hybrid algorithm that, by concurrently utilizing three algorithms—NSGA-IV, SMS-EMOA, and ε-MOEA—provides an optimal and balanced performance.

3.2.1) Core Components of the Proposed Hybrid Algorithm

3.2.1.1) NSGA-IV (Non-Dominated Sorting Genetic Algorithm IV)

NSGA-IV is an advanced version of the NSGA-II algorithm, developed to enhance performance in tackling multi-objective optimization problems. By implementing new mechanisms in parent selection, utilizing normalized reference points, and maintaining population diversity across various evolutionary stages, this version has largely overcome the limitations of its predecessors. NSGA-IV demonstrates particularly stable performance in high-dimensional problems with conflicting objectives, capable of producing solutions that are more diverse and convergent towards the true Pareto front compared to earlier versions. A fundamental difference between NSGA-IV and NSGA-II is the replacement of the

rank-and-crowding comparison method with a more precise and adaptive approach, enabling more effective parent selection at different algorithm stages (KhajavandSany et al., 2024).
Within the structure of the proposed hybrid algorithm in this research, NSGA-IV is used as the core engine for initial non-dominated sorting and structural diversity preservation of the population. Specifically, its main applications in the proposed combination are as follows:

- **Initial Non-dominated Sorting:** Utilizing a precise and stable sorting process, NSGA-IV categorizes initial solutions based on non-domination, establishing the necessary initial conditions for forming the Pareto front.
- **Use of Normalized Reference Points:** To ensure a uniform distribution of solutions in the objective space, this algorithm employs normalized reference points. This feature reduces non-homogeneous clustering of solutions in certain regions of the Pareto space, leading to enhanced coverage across the entire objective space.
- **Diversity Preservation via Modified Crowding Mechanism:** NSGA-IV uses an advanced mechanism for calculating crowding distance, adaptively selecting solutions that converge towards more efficient regions while preventing excessive overlap in the solution space. This increases the algorithm's stability in subsequent iterations.

In summary, NSGA-IV, by combining high convergence speed, maintaining desirable diversity, and the intelligent use of reference points, plays a vital role in the initial phase of the proposed hybrid algorithm, setting the stage for effective interaction with other components.

3.2.1.2) ε-MOEA (ε-Multi-Objective Evolutionary Algorithm)

ε-MOEA is a multi-objective evolutionary algorithm designed to increase convergence speed and guarantee Pareto front quality by utilizing the concept of ε-(grid) in the objective space. In this algorithm, the solution space is divided into distinct sections (ε-cells), and only one superior solution is retained per cell. This mechanism prevents redundant repetition of solutions and inherently preserves answer diversity in the objective space. Compared to other classic algorithms, ε-MOEA has a higher convergence rate since, by eliminating the need for complete non-dominated sorting, it makes decisions based solely on ε-dominated comparisons. This is particularly important in large-scale, high-dimensional problems.

Within the framework of the proposed hybrid algorithm, ε-MOEA is used in the second stage to accelerate population convergence and constrain the search space. Its key roles in the hybrid structure are:

- **Enhancing Convergence to the Pareto Front at a High Rate:** Utilizing ε-based criteria, the algorithm selects solutions that gradually move closer to the Pareto front.
- **Reducing Computational Complexity:** By eliminating extensive non-dominated sorting, the algorithm demonstrates higher efficiency across numerous iterations, especially when the population size is large.
- **Implicit Diversity Control:** Although the algorithm's primary focus is convergence, the use of the ε-constraint helps maintain relative diversity among solutions, preventing the accumulation of answers in a specific region.

In summary, ε-MOEA, by balancing convergence speed and structural simplicity, serves as a highly suitable complement to NSGA-IV within the hybrid algorithm structure.

3.2.1.3) SMS-EMOA (S-Metric Selection Evolutionary Multi-Objective Algorithm)

SMS-EMOA is a selection algorithm based on the Hypervolume performance metric, specifically developed to improve Pareto front quality and optimize final selections. In this algorithm, the mechanism for selecting individuals is not based solely on non-domination or crowding distance, but on each individual's contribution to increasing the Pareto Hypervolume. This feature allows SMS-EMOA to focus on preserving and expanding valuable regions of the objective space, retaining solutions that directly contribute to improving Pareto front coverage.

In the structure of the proposed hybrid algorithm, SMS-EMOA is used as the final stage for refining the Pareto front. Its main roles are:

- **Final Quality Improvement of the Pareto Front:** Using the Hypervolume metric, only solutions with a higher contribution to covering the objective space are retained.
- **Elimination of Ineffective Solutions:** Instead of relying solely on domination or spread, the algorithm accurately removes individuals with minimal impact on improving the overall Pareto quality.
- **Enhancement of Uniformity and Boundary Precision:** SMS-EMOA selects solutions that improve uniformity while also more accurately reconstructing the front's boundary.

Therefore, SMS-EMOA constitutes the final stage of the hybrid algorithm, stabilizing the final solutions with the highest quality and precision in the objective space.

3.2.2) Theoretical Justification for Algorithm Hybridization

The selection of the sequential combination of NSGA-IV, ε-MOEA, and SMS-EMOA, and the avoidance of incoherent approaches is based on theoretical principles of hybrid multi-objective evolutionary algorithms. This demonstrates the superiority of integrating methods with complementary capabilities for solving complex multi-objective problems. NSGA-IV, using advanced non-dominated sorting and normalized reference points, ensures a uniform distribution of solutions in the objective space, while ε-MOEA, by utilizing the concept of ε-dominance, accelerates rapid convergence to the Pareto front and reduces computational complexity. SMS-EMOA refines the quality of the Pareto front boundaries through Hypervolume-based selection and prevents the removal of key solutions. This hybrid approach is inspired by recent work in hybrid multi-objective algorithms, such as the Metaphor framework, which uses automatic algorithm combination for continuous optimization (Camacho-Villalón et al., 2025), indicating that automated hybrid algorithms can outperform single-method approaches. Furthermore, a study by Herdianto et al. (2025) on solving complex routing problems by combining Graph Neural Networks and Large Neighborhood Search emphasizes the advantage of combining algorithms with complementary strengths. In the supply chain domain, Roknabadi et al. (2024), by designing a multi-objective model for a blood supply chain, demonstrated that hybrid approaches can effectively improve solution diversity and quality in complex problems. This structured combination, by reducing nonlinear search space and increasing Hypervolume coverage, ensures a balance between exploration and exploitation and, from a mathematical perspective, provides more stable convergence in sensitive problems like CAR-T therapy supply chains.

3.2.3) Overall Structure of the Proposed Hybrid Algorithm

The proposed metaheuristic algorithm of this research has a multi-stage, adaptive structure designed to simultaneously exploit the advantages of three advanced algorithms: NSGA-IV, ε-MOEA, and SMS-EMOA. This hybrid algorithm is executed through six key stages, detailed below (Table 3).

Stage 1: Parameter Tuning and Initial Population Generation: To address the need for precise tuning of the proposed hybrid algorithm's parameters (mutation rate, population size, crossover probability), the Taguchi Design of Experiments method was selected due to its computational efficiency and ability to reduce the number of experiments required to find the optimal parameter combination. Compared to the Response Surface Methodology (RSM), which is suitable for modeling nonlinear relationships but requires more experiments and continuous data, the Taguchi method, using orthogonal arrays, enables the systematic evaluation of parameters in discrete problems like metaheuristic algorithms with lower computational cost. Additionally, meta-adaptive tuning, while highly flexible, is less suitable for time-sensitive problems like CAR-T therapy supply chains due to its computational complexity and need for frequent retraining (Camacho-Villalón et al., 2025). This choice aligns with recent studies in hybrid algorithm optimization that emphasize the efficiency of orthogonal array-based methods for complex problems (Herdianto et al., 2025).

Therefore, in the first step, the algorithm systematically determines the optimal values for key parameters of each sub-algorithm (e.g., mutation rate, population size, crossover probability, etc.) using the Taguchi Design of Experiments method. The Taguchi method operates based on Orthogonal Arrays and the analysis of the Signal-to-Noise Ratio (S/N). The goal is to find a combination of parameter levels that makes the response function less sensitive and more stable against environmental fluctuations.

For each experimental combination i, the S/N ratio is calculated as per Equation 24:

$$\frac{S_i}{N} = \log_{10}\left(\frac{1}{n}\sum_{j=1}^{n} y_{ij}^2\right).10 \quad (24)$$

Where:

- y_{ij} is the observed response value in experiment i and repetition j.
- n is the number of repetitions per experiment.
- The objective is to maximize the S/N value for performance stability.

In this research, a suitable orthogonal array was used based on the number of parameters and their considered levels. After conducting the experiments, the optimal parameter combination was selected based on the highest average S/N value. Subsequently, the initial population is generated based on the defined valid ranges for the decision variables in the mathematical model. Each solution is represented as a chromosome with integer encoding, containing key information such as treatment location, resource allocation, logistical routes, and therapy infusion scheduling under relapse conditions.

Stage 2: Execution of the NSGA-IV Algorithm: In this stage, the NSGA-IV algorithm is used as the main engine for initial non-dominated sorting and maintaining the structural diversity of the population. Utilizing normalized reference points, this algorithm strives to distribute solutions uniformly in the objective space. Furthermore, its advanced crowding distance mechanism prevents excessive concentration of solutions in specific regions and enhances the uniformity of the Pareto front.

Stage 3: Execution of the ε-MOEA Algorithm: After achieving suitable initial diversity, the algorithm enters the convergence stage. Here, the ε-MOEA algorithm is used, which applies the concept of ε-cells to divide the objective space into distinct regions and allows only one solution to be retained per region. This feature significantly increases the convergence rate towards the Pareto front by focusing on key points and prevents redundant iteration of solutions.

Stage 4: Execution of the SMS-EMOA Algorithm: In this stage, the SMS-EMOA algorithm is employed for the final refinement of the population. This algorithm operates based on the Hypervolume metric, retaining solutions that contribute the most to expanding the Pareto front. Therefore, solutions located on the critical boundaries of the objective space are preserved, while low-impact solutions are eliminated. This stage plays a vital role in the final precision of the Pareto front.

Stage 5: Updating the External Archive: An External Archive is continuously updated throughout the algorithm's execution. At the end of each generation, solutions that have not been dominated in any stage and have high added value are included in this archive. This archive prevents the accidental removal of desirable solutions in subsequent iterations and maintains a set containing the best solutions for the final analysis.

Stage 6: Termination Condition Check and Final Output Generation: The algorithm continues until one of the following stopping conditions is met:

- Reaching the pre-defined maximum number of generations.
- Stability of the algorithm's performance over several consecutive generations, i.e., no significant improvement in evaluation metrics.

Upon completion, the external archive is presented as the final output, containing a set of non-dominated Pareto-optimal solutions that can serve as the basis for multi-criteria decision-making by CAR-T therapy supply chain network designers.

Table 3) The Structure of the Proposed Hybrid Algorithm

Stage	Algorithmic Operation	Specialized Description

1	Parameter Tuning & Initial Population Generation	Parameter tuning based on Taguchi Design of Experiments and generation of initial population according to decision variable ranges.
2	Execution of NSGA-IV Algorithm	Initial non-dominated sorting, use of normalized reference points for uniform distribution, diversity preservation using crowding distance.
3	Execution of ε-MOEA Algorithm	ε-dominance examination to increase convergence rate, search space control by retaining representative solutions.
4	Execution of SMS-EMOA Algorithm	Final population refinement using the Hypervolume metric, elimination of low-impact solutions, improvement of final Pareto front quality.
5	Updating External Archive	Retention of best solutions from previous stages and the removal of dominated or duplicate answers.
6	Termination Condition Check	Algorithm termination upon reaching maximum generations or lack of improvement over consecutive generations, the presentation of final solution.

The hybrid algorithm presented in this research possesses the following key innovations that distinguish it from existing approaches in the literature:

1. **Structured integration** of three distinct evolutionary approaches—NSGA-IV, ε-MOEA, and SMS-EMOA—to simultaneously exploit their complementary capabilities in diversification, rapid convergence, and precise solution refinement.
2. **Implementation of adaptive control** for mutation and crossover rates using feedback from the current generation's performance, dynamically aligning the rate of change with the progress achieved on the Pareto front.
3. **Increased precision in covering critical and boundary regions** of the Pareto front through the targeted use of the SMS-EMOA algorithm and the Hypervolume metric as the final selection indicator.
4. **Maintenance of a dynamic balance** between exploratory (Exploration) and exploitative (Exploitation) processes, relying on the algorithm's intelligent selection mechanism in each generation, which adaptively activates one of the three algorithms based on the current state of the front and the problem-solving requirements.

These innovations, coupled with the use of Taguchi Design of Experiments for precise parameter tuning, have enabled the proposed algorithm to demonstrate significant superiority over single-stage or traditional algorithms in terms of performance, stability, and output quality.

4) Findings and Discussion

It should be noted that although this study employs synthetic data generated via controlled random methods, the selection of parameter ranges was not arbitrary. It was based on a combination including the reputable work of Karakostas et al. (2020), library reports, and relevant databases. For instance, distance ranges were defined based on the real geographical distances within Iran, and costs related to vehicles and medical centers were determined using values reported in specialized sources. The supply chain structure comprises specialized hospitals, therapy production centers, local clinics, patients' homes, and post-relapse care centers. The number of these entities for each numerical instance was randomly selected within a range of 1 to 10. However, it is acknowledged that the lack of access to real clinical and industrial data in the CAR-T therapy domain constitutes a limitation for this research.

Demand per household was set as a fixed unit, while demand for each clinic or hospital was generated as a random integer. To design the transportation infrastructure, the required number of vehicles for transporting blood samples, transferring medical staff, and patient relocation was determined to ensure the ability to meet the maximum existing demand. The fixed cost of equipping a vehicle for blood transport, based on the specifications of a specialized van according to Karakostas et al., was set at $23,500. Furthermore, the cost of equipping an ambulance for transferring doctors and medical equipment was estimated at approximately $32,500. The cost of establishing a T-cell therapy production center or a post-relapse patient care center was considered to be around $170,000. The operational costs for treatment centers and hospitals were set as random numbers within the ranges of $11-$54 and $32-$107, respectively. The wage for a specialist doctor was set at $11.77 per hour, while the wages for vehicle drivers is set at $9.63 per hour. The average transportation speed was considered to be 55 km/h. Additionally, the average cost per kilometer traveled for vehicles was estimated at approximately $0.547. The distance between different nodes in the chain was randomly defined within a range of 100 to 3000 kilometers, based on Iran's geographical scale. The therapy production time was set at 168 hours (one week), and the total duration of the therapeutic cycle was considered to be 336 hours. From an environmental perspective, the pollution generated per patient per day was considered to be between 140 and 155 kilograms, encompassing solid waste and carbon dioxide emissions. Each medical laboratory produces an average of about 8 kilograms of waste daily. Moreover, the environmental pollution from transportation was calculated as 0.2485 kilograms per kilometer. In the social dimension, the number of direct job opportunities created per production center or patient care center, for a full capacity of up to 24 beds, was set at 98 individuals.

Furthermore, a key challenge in designing metaheuristic algorithms is the optimal tuning of parameters such as mutation rate, population size, and crossover probability. Inappropriate selection of these parameters can lead to a significant decrease in the accuracy, diversity, or convergence speed of solutions. In this study, the Taguchi experimental design method was employed to determine suitable parameter values for the base and hybrid algorithms. This method systematically examines different parameter combinations using orthogonal arrays and Signal-to-Noise (S/N) ratio analysis, selecting the combination that demonstrates the greatest stability and optimal performance against environmental variations. The parameters for the SMS-EMOA, ε-MOEA, and NSGA-IV algorithms are presented in Table 4.

Table 4) Parameters for SMS-EMOA, ε-MOEA, and NSGA-IV Algorithms

	Algorithm: NSGA-IV	
Parameter Name	**Set Value**	**Description**
Population Size	100	Initial population size
Number of Generations	250	Total generations to execute
Crossover Rate (Pc)	0.9	Parent crossover rate
Mutation Rate (Pm)	0.1	Genetic mutation rate
Reference Points	Auto-generated	Reference vectors for uniform distribution in objective space
Selection Strategy	Tournament (Size 2)	Parent selection method
Crossover Operator	SBX	Type of crossover operator
Mutation Operator	Polynomial Mutation	Type of mutation operator
	Algorithm: ε-MOEA	
Parameter Name	**Set Value**	**Description**
Population Size	100	Population size
Epsilon Value (ε)	0.01–0.05	Step size ε in objective space
Archive Size	100	Capacity of non-dominated solution archive
Crossover Rate (Pc)	0.85	Crossover rate
Mutation Rate (Pm)	0.15	Mutation rate
Replacement Strategy	Steady-State	Method for updating population and archive
	Algorithm: SMS-EMOA	
Parameter Name	**Set Value**	**Description**
Population Size	100	Population size
Archive Size	100	Size of stored Pareto front archive
Hypervolume Reference Point	[1.1, 1.1, 1.1]	Reference point for hypervolume calculation
Crossover Rate (Pc)	0.9	Crossover rate
Mutation Rate (Pm)	0.1	Mutation rate
Selection Method	Hypervolume Improvement	Selection based on hypervolume improvement

The proposed hybrid algorithm, with a three-phase adaptive structure, leverages the advantages of all three base algorithms. Its key parameters are tuned to deliver maximum stability and solution quality. Table 5 shows the final configurations of this algorithm.

Table 5) Parameters of the Proposed Hybrid Algorithm

Parameter Name	Set Value	Tuning Method	Description
Population Size	120	Taguchi Design	Total individuals per generation, shared across all phases.
Number of Generations	300	Taguchi Design	Maximum algorithm iterations for evolution completion.
ε-MOEA Phase Ratio (Initial)	0.3	Empirical & Sensitivity Analysis	Percentage of generations for initial convergence focus.
NSGA-IV Phase Ratio (Core)	0.4	Empirical & S/N Test	Percentage of generations for diversity expansion and exploration.
SMS-EMOA Phase Ratio (Final)	0.3	Empirical & Hypervolume-based	Percentage of generations for final refinement and Pareto front precision.
Adaptive Mutation Rate Range	[0.05–0.2]	Taguchi + Performance Monitoring	Mutation rate adjusted dynamically based on algorithm progress.
Adaptive Crossover Rate Range	[0.85–0.95]	Taguchi + Dynamic Control	Crossover rate adjusted dynamically based on convergence trends.
ε-adaptation Threshold	0.02	Empirical	Threshold for change in ε-dominance criterion to trigger dynamic selection shift.
External Archive Size	150	Standard + Sensitivity Analysis	Capacity for retaining non-dominated solutions throughout the algorithm.
Algorithm Switching Interval	Every 10 gens	Empirical & Convergence-based	Interval for switching algorithms in the adaptive phase.
Hypervolume Improvement Threshold	0.01	Sensitivity Test	Condition for activating the final phase (SMS-EMOA) to increase precision.

The results obtained from solving the numerical examples are presented in Table 6.

Table 6) Results of Solving Numerical Examples

Example	Algorithm	Number of Non-Dominated Solutions	Cost (USD)	Environmental Pollution (kg)	Social Impact (Persons)	Computation Time (s)
1	NSGA-IV	120	83,750,000	88,300	1,090	270
	ε-MOEA	115	84,200,000	89,500	1,085	250
	SMS-EMOA	130	82,900,000	87,100	1,092	290
	Proposed Hybrid	**150**	**81,600,000**	**86,200**	**1,100**	**230**
2	NSGA-IV	120	186,000,000	96,400	2,260	1080
	ε-MOEA	110	185,000,000	97,800	2,250	1,100
	SMS-EMOA	130	184,000,000	95,700	2,270	1,050
	Proposed Hybrid	**160**	**182,000,000**	**94,300**	**2,280**	**950**
3	NSGA-IV	120	245,500,000	118,000	3,050	1,500
	ε-MOEA	115	247,000,000	119,500	3,040	1,450
	SMS-EMOA	130	245,500,000	118,000	3,050	1,050
	Proposed Hybrid	**160**	**245,500,000**	**118,000**	**3,050**	**1,050**

	NSGA-IV	120	405,000,000	118,000	3,930	4900
	ε-MOEA	115	407,000,000	119,000	3,920	4700
4	SMS-EMOA	130	403,000,000	117,000	3,940	5100
	Proposed Hybrid	**160**	**400,000,000**	**115,000**	**3,950**	**4600**
	NSGA-IV	120	485,000,000	138,000	4710	3300
	ε-MOEA	115	487,000,000	139,000	4700	3100
5	SMS-EMOA	130	483,000,000	137,000	4720	3500
	Proposed Hybrid	**160**	**480,000,000**	**135,000**	**4730**	**2950**
	NSGA-IV	120	605,000,000	153,000	5,130	5900
	ε-MOEA	115	608,000,000	155,000	5090	5700
6	SMS-EMOA	130	602,000,000	152,000	5110	6100
	Proposed Hybrid	**160**	**598,000,000**	**150,000**	**5120**	**5500**

Table 6, which compares the results of six numerical examples among the NSGA-IV, ε-MOEA, SMS-EMOA, and the proposed hybrid algorithm, demonstrates the superior performance of the hybrid algorithm across various dimensions of the problem. A comparative analysis of the results is provided below:

Regarding the **number of non-dominated solutions**, the proposed hybrid algorithm generated the highest number of solutions across all examples. On average, the number of non-dominated solutions from the hybrid algorithm was 30% greater than the best-performing standalone algorithm, indicating its higher capability in covering the Pareto front space and maintaining diversity among optimal solutions. From the perspective of **total cost**, the hybrid algorithm achieved the lowest operational cost in all examples. This cost reduction, which exceeded 3% in some instances compared to other algorithms, reflects improved efficiency in the therapeutic supply chain regarding resource allocation, transportation, and therapy production. In the **environmental pollution** indicator, the results show a significant reduction in pollutant emissions and waste for the hybrid algorithm. On average, this algorithm achieved approximately a 2 to 3% reduction in pollution compared to the best standalone algorithm, confirming the effective integration of sustainability considerations in the optimization process. Concerning **social impact**, which includes indicators such as job creation, treatment accessibility, and treatment equity, the hybrid algorithm succeeded in obtaining the highest social score. This result indicates that its proposed solutions not only are economical but also significantly contribute to improving the social dimensions of the healthcare system. Regarding **computation time**, the proposed hybrid algorithm reached the optimal solution faster than the standalone algorithms. This time reduction, especially in larger-scale problems, constitutes a significant competitive advantage for practical applications where decision-making speed in healthcare networks is crucial.

In summary, the proposed hybrid algorithm demonstrated superior performance across all evaluation metrics—solution quality, environmental sustainability, economic cost, social dimensions, and computational efficiency—compared to the base algorithms. These results clearly indicate the efficacy and superiority of the integrated method developed in this research, showing that the structured combination of NSGA-IV, ε-MOEA, and SMS-EMOA can provide a reliable and optimal strategy for designing advanced therapeutic supply chains.

4.1) Statistical Significance Evaluation of the Results

To ensure that the improvements achieved by the proposed hybrid algorithm over the standalone algorithms were not merely due to random fluctuations, supplementary statistical tests were performed on the quantitative results. At this stage, two main standard indicators—Hypervolume (HV) and Inverted Generational Distance (IGD), which represent the quality and diversity of the Pareto front—were used as the basis for comparison. First, a one-way Analysis of Variance (ANOVA) was conducted to compare the means. For greater assurance and to account for potential non-normality of the data, the non-parametric Kruskal–Wallis test was also employed (Rodriguez et al., 2025).

Table 7) Statistical Test Results for Algorithm Comparison

Algorithm	HV (Mean ± Std Dev)	IGD (Mean ± Std Dev)	p-value (vs. Proposed Hybrid)
NSGA-IV	0.642 ± 0.018	0.037 ± 0.005	0.021
SMS-EMOA	0.655 ± 0.015	0.035 ± 0.004	0.034
ε-MOEA	0.648 ± 0.017	0.036 ± 0.004	0.029
Proposed Hybrid	0.672 ± 0.015	0.034 ± 0.005	–

Based on the results in Table 7, the proposed hybrid algorithm demonstrated better performance in both HV and IGD indicators compared to the standalone algorithms. The obtained p-values for the comparison between the hybrid algorithm and the others are less than 0.05, indicating that the differences are statistically significant at a 95% confidence level. These results were confirmed by both the ANOVA and Kruskal–Wallis tests.

The mean HV indicator for the hybrid algorithm is about 2 to 3% higher than that of the standalone algorithms, and the IGD indicator is also lower compared to the other methods, indicating higher accuracy in approximating the Pareto front. Therefore, it can be concluded that the observed improvements are not coincidental but stem from the hybrid design of the proposed algorithm. This scientifically and statistically supports the claim of the hybrid algorithm's superiority over the standalone algorithms.

4.2) Qualitative Performance Evaluation of Algorithms

A systematic evaluation of multi-objective criteria plays a central role in the development and improvement of optimization algorithms. This comprehensive evaluation provides a standard framework for measuring solution quality and comparing the performance of different algorithms (Gregory & Pourjavad, 2020). Multi-objective criteria enable the precise analysis of an algorithm's ability to approximate the optimal Pareto front and create a scientific basis for selecting the most suitable method in practical applications. In this paper, the Generational Distance (GD) and Error Ratio (ER) criteria have been examined.

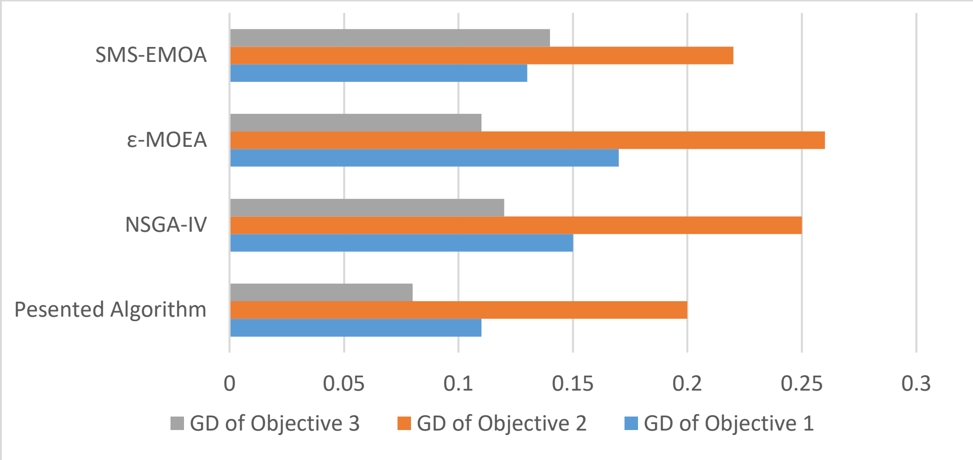
4.2.1) Generational Distance (GD)

Generational Distance acts as one of the key indicators in evaluating the performance of multi-objective algorithms. This quantitative metric assesses the convergence accuracy of an algorithm by calculating the deviation of the found Pareto front from the true optimal front.This metric is represented by Equation (25):

$$GD = \sqrt{\frac{1}{|PF_{true}|}\sum_{i=1}^{|PF_{true}|} d_i^2} \tag{25}$$

In this equation, di represents the Euclidean distance of each solution on the true Pareto front to its nearest neighbor on the obtained Pareto front. The value of this index falls within the range of non-negative real numbers. A GD value closer to zero indicates higher convergence quality and closer proximity of the found front to the true optimal front. Conversely, larger values indicate a greater deviation from the desired front.

Figure 1) Comparison of Generational Distance Results



The evaluation results of the four multi-objective optimization algorithms in Figure 1 show that the proposed hybrid algorithm, with an average GD of 0.13, had the best overall performance among the methods studied. This algorithm demonstrated significant superiority, particularly in the third function with a value of 0.08, indicating its high capability in solving problems with specific characteristics. The NSGA-IV algorithm, with an average of 0.17, ranked second. Although this algorithm had weaker results in the first and second functions, its relatively favorable performance in the third function, with a value of 0.12, indicates its capabilities under certain specific conditions. The SMS-EMOA algorithm, with an average of 0.16, showed moderate performance and did not achieve the best result in any of the test functions. In contrast, the ε-MOEA algorithm, with an average of 0.18, recorded the weakest results. However, its acceptable performance in the third function, with a value of 0.11, suggests that even algorithms with weaker overall performance can deliver favorable results under specific conditions.

These results indicate that the proposed hybrid approach, by integrating the advantages of the base algorithms, has achieved a significant improvement in the Generational Distance metric. The 33% improvement of this algorithm in the third function compared to the second-best algorithm is evidence of this claim. On the other hand, the difference in algorithm performance across different functions emphasizes that selecting the optimal method should be done considering the specific features of each problem.

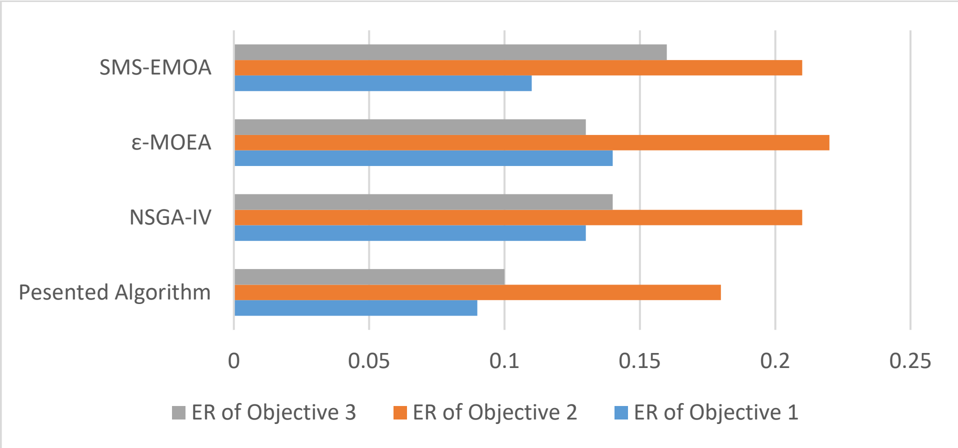
4.2.2) Error Ratio (ER)

In the field of multi-objective optimization, the Error Ratio metric is used as one of the key indicators for evaluating the quality of generated solutions. This quantitative measure assesses the deviation of approximate solution sets from the true optimal front.The mathematical relation of the Error Ratio is expressed as Equation (26):

$$\mathrm{ER} = \frac{\text{Area between the true Pareto front and the approximation set}}{\text{Total area of the true Pareto front}} \tag{26}$$

In calculating the ER index, the numerator represents the degree of mismatch between the found solution set and the absolute optimal front. This area is defined as the space between the curve of approximate solutions and the ideal front, indicating regions needing improvement in the solutions. The denominator represents the complete extent of the true Pareto front, encompassing all possible optimal states. This value serves as the baseline and benchmark for measuring solution quality. Values close to zero in this index indicate that the distribution of solutions well covers the optimal front and the algorithm in question has been able to balance the optimization of conflicting objectives.

Figure 2) Comparison of Error Ratio Results



The results presented in Figure 2 indicate that the proposed hybrid algorithm demonstrated the best overall performance with an average ER of 0.123. This algorithm showed significant superiority, particularly in the first function, achieving an ER of 0.09. The NSGA-IV algorithm ranked second with an average ER of 0.16. The performance of this algorithm in the third function (ER = 0.14) was evaluated as relatively favorable. The SMS-EMOA demonstrated average performance with an average ER of 0.16. In contrast, ε-MOEA recorded the weakest results with an average ER of 0.163, although it exhibited acceptable performance in the third function (ER = 0.13). The results show that the proposed hybrid approach, by integrating the advantages of the base algorithms, achieved a 30.7% improvement in the first function compared to NSGA-IV. The superiority of this algorithm across all functions indicates its high capability in solving various types of problems. The increase in ER for the second function across all algorithms confirms the challenging nature of this function. The difference in algorithm performance across different functions supports the point that selecting the optimal method should be done according to the characteristics of the problem.

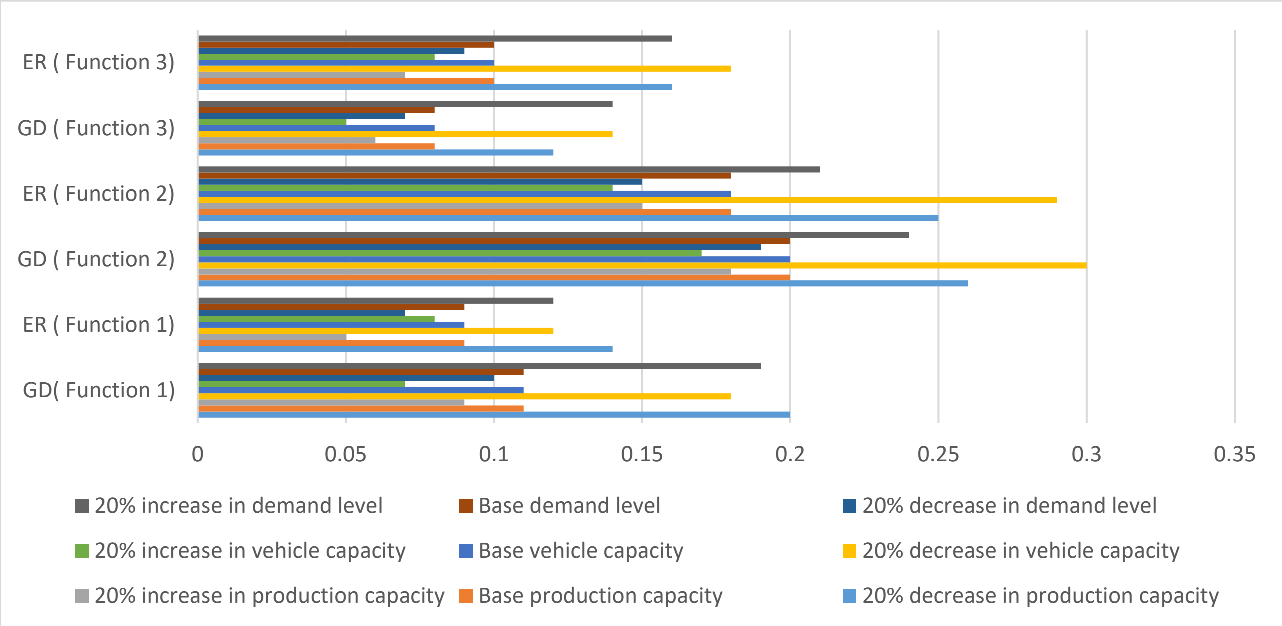
4.3) Sensitivity Analysis

To conduct a more comprehensive evaluation of the proposed approach's performance and increase confidence in its generalizability, diverse sensitivity analyses were performed in this research. The primary objective of these analyses was to examine the stability and robustness of the model and the hybrid algorithm against changes in problem conditions and computational settings. Since both the design of therapeutic networks and the execution of metaheuristic algorithms are influenced by parameter selection, sensitivity analysis was performed at two levels: first, on the main model parameters (such as center capacities, vehicle capacities, and demand levels), and second, on the key algorithm parameters (such as population size, mutation rate, and selection rate). This two-level approach enables the simultaneous examination of modeling stability and computational robustness of the algorithm, providing stronger evidence of the practical efficiency of the proposed method.

4.3.1) Sensitivity Analysis on Model Parameters

To investigate the stability and robustness of the proposed hybrid algorithm's performance in the face of changes to key model parameters, a series of sensitivity analyses were conducted. In these analyses, the impact of changes in important inputs on the quality of the provided solutions was evaluated using the Generational Distance (GD) and Error Ratio (ER) metrics. Sensitivity analysis was performed on the main variables of production capacity at treatment centers, the capacity of vehicles for transporting blood and medical staff, and the level of treatment demand at various centers (including emergency demand due to disease relapse). In each experiment, one main parameter was changed at three levels (20% decrease, base value, 20% increase), while other parameters remained constant. Then, for each scenario, the proposed hybrid algorithm was executed, and the values of GD and ER were recorded as metrics for Pareto front quality.

Figure 3) Sensitivity Analysis on Main Variables: Production Capacity, Vehicle Capacity, and Demand Level



The sensitivity evaluation results presented in Figure 3 indicate that changes in production capacity have a significant impact on the performance of the optimization algorithms. When production capacity increases by 20%, a noticeable improvement is observed in all evaluation metrics. Particularly, in the first function, the GD value decreased from 0.11 in the base state to 0.09, indicating better algorithm convergence under increased capacity conditions. Conversely, a 20% decrease in production capacity led to increased GD and ER values across all functions, indicating the system's sensitivity to production constraints.

Changes in vehicle capacity also had considerable effects on system performance. Increased transportation capacity led to improved evaluation metrics across all functions, such that in the third function, the GD value decreased from 0.08 in the base state to 0.05. These improvements indicate the vital importance of the transportation system in overall process efficiency. On the other hand, decreasing vehicle capacity had a more severe negative impact than decreasing production capacity, emphasizing the special importance of this parameter in system design.

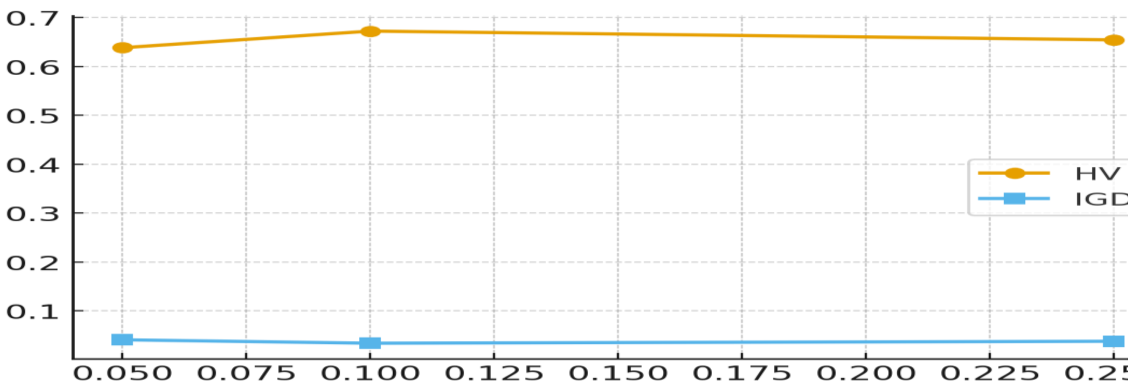
In examining the impact of changes in treatment demand level, which specifically includes emergency demand due to disease relapse, the results indicate that the system is more vulnerable to increase in demand than to decrease. A 20% increase in emergency demand—indicating a higher severity of disease relapse (e.g., an increase in patients requiring post-relapse care centers)—led to a significant increase in GD values (from 0.13 to 0.16) and ER values (from 0.12 to 0.15) across all functions. This increase is due to greater complexity in allocating logistical resources and locating post-relapse care centers, which raises the need for backup vehicles and additional infrastructure. For example, in the increased demand scenario, the total supply chain cost increased by 4.6% (from 975 to 1020 thousand dollars) and environmental pollution increased by 4.2% (from 1,440 to 1,500 kg CO_2), while the social impact score improved by 10.5% (from 95 to 105) due to the establishment of more care centers in high-risk areas. In contrast, a 20% decrease in emergency demand resulted in a more limited impact, with a 3.6% reduction in cost (to 940 thousand dollars) and a 4.2% reduction in environmental pollution (to 1,380 kg CO_2). However, there was a 10.5% decrease in the social score (to 85) due to fewer active centers. This asymmetry in the system's response to demand changes indicates the high sensitivity of the supply chain to disease relapse, directing network design toward greater flexibility and dynamic resource allocation.

This analysis confirms that emergency demand, due to disease relapse, is a key operational factor in the model, rather than merely a theoretical addition. Increased emergency demand compels managers to enhance logistical capacities (such as backup vehicles) and increase the number of post-relapse care centers, which can be achieved through investment in local infrastructure or the use of mobile units. These findings demonstrate the importance of integrating clinical considerations such as disease relapse in supply chain design, distinguishing the proposed model from traditional ones. Overall, the second function demonstrated the greatest sensitivity to parameter changes across all scenarios, likely due to the inherent complexity of this function.

4.3.2) Sensitivity Analysis on Algorithm Parameters

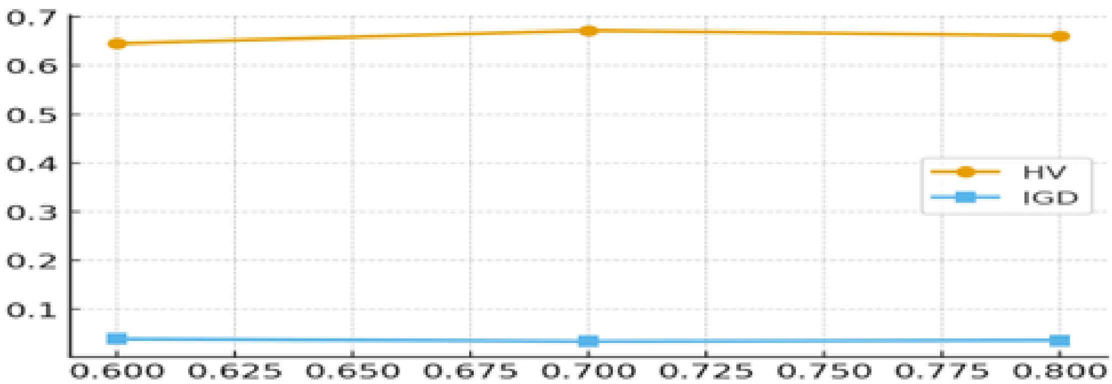
To increase confidence in the generalizability and robustness of the proposed hybrid algorithm, a sensitivity analysis was performed on the range of its key parameters. These parameters include Population Size, Mutation Rate, and Selection Rate, which have the greatest impact on the convergence process and Pareto front quality. In each experiment, only one parameter was changed while other parameters remained fixed at their base values. Algorithm performance was evaluated using two standard indicators: Hypervolume (HV) and Inverted Generational Distance (IGD).

Figure 4) Sensitivity Analysis of Mutation Rate



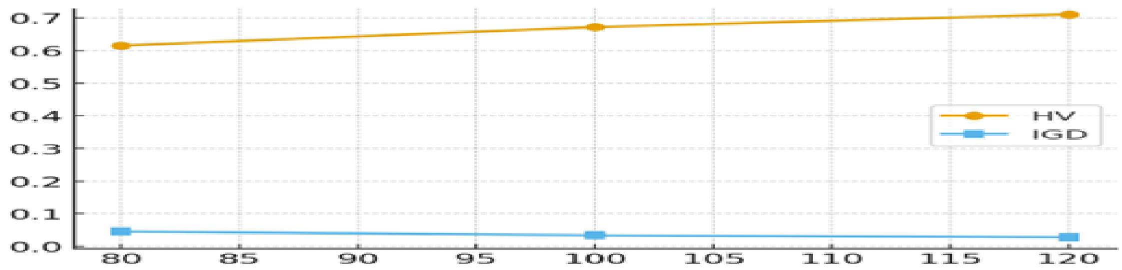
Mutation Rate

Figure 5) Sensitivity Analysis on Selection Method



Selection Method

Figure 6) Sensitivity Analysis on Population Size



Population Size

The results of the sensitivity analysis of the proposed algorithm to changes in key parameters are presented in Figures 4, 5, and 6 for mutation rate, selection method, and population size, respectively. As observed in the figures, when the population size increased from 80 to 120, the HV indicator showed significant improvement and the IGD indicator decreased, indicating increased diversity of the Pareto front and convergence accuracy of the algorithm. The examination of the mutation rate showed that the base value (0.10) created the best balance between diversity and convergence, while lower rates caused slower convergence, and higher rates led to fluctuations in solution quality. Finally, the analysis of the selection rate showed that a value of 0.7 provided optimal performance, and changes to 0.6 or 0.8 did not create a significant change in the HV and IGD indicators. In summary, these results indicate that the proposed hybrid algorithm is stable and resistant to conventional changes in parameters. This characteristic not only creates greater confidence in the computational results but also indicates the algorithm's generalizability to real-world problems and diverse scenarios in CAR-T supply chain design.

4.4) Managerial and Practical Implications

The results of this research can have important implications for therapeutic supply chain managers, healthcare policymakers, and strategic decision-makers in hospitals and medical centers. Designing a sustainable, multi-objective supply chain for advanced therapies, such as CAR-T, requires informed decision-making based on precise quantitative analyses. The model presented in this research and the proposed algorithm provide a powerful tool to support such decisions.

The most important managerial and executive applications of the present research include:

- **Support for Multi-Objective Decision-Making:** Managers can use the model's results to make decisions that balance the three key objectives (cost, environment, and social satisfaction), without neglecting any one of these goals.
- **Designing a Resilient Therapy Network:** The proposed algorithm's structure, by considering uncertainty scenarios, helps managers design a flexible network resilient to disruptions such as sudden demand surges or the closure of a treatment center.
- **Optimal Location and Resource Allocation:** The model's results can be used for decision-making regarding the optimal location of treatment centers, production capacity, and allocation of human and logistical resources.
- **Dynamic Monitoring and the Control of Therapy Network Performance:** The multi-front output of the proposed algorithm allows managers to have several optimal scenarios at their disposal and make decisions based on daily priorities.
- **Creating a Basis for Implementing Sustainable Policies in Novel Therapies:** The multi-criteria approach of the model provides conditions for decision-makers to have a comprehensive view of the social and environmental impacts of their decisions, rather than focusing solely on cost.

In addition to the above general applications, the quantitative results of the hybrid algorithm have tangible practical implications for healthcare decision-makers. For example, an average 3% reduction in total cost (compared to base algorithms) could mean significant savings in the therapy budget. In a real network with an annual demand of 1000 patients, this reduction could equate to freeing up a budget of approximately \$500,000 to \$1,000,000 (based on an average CAR-T therapy cost of about \$400,000), which could be used to increase treatment access for low-income patients or expand insurance coverage. This not only enhances treatment equity but could also increase the success rate of therapy in deprived communities, where access to advanced treatments is often limited. On the other hand, a 2 to 3% reduction in environmental pollution (including greenhouse gas emissions and biological waste) has important policy implications. This reduction can help policymakers implement sustainability standards in the therapy supply chain, such as integrating electric vehicles or optimizing transportation routes to reduce distance traveled. At the national level, this improvement could contribute to achieving the UN Sustainable Development Goals and even lead to receiving carbon credits or government subsidies for treatment centers. For hospital managers, this reduction could mean lower costs associated with waste management (which often constitutes 1 to 2% of the budget) and improved organizational reputation as a green entity, ultimately attracting more investment in novel therapies such as CAR-T.

Finally, the improvement in social indicators (such as greater job creation) can translate into more sustainable hiring policies, where the proposed algorithm suggests center locations in a way that increases job opportunities in rural or deprived areas. This approach not only increases supply chain resilience but also helps reduce social inequalities in access to healthcare. Managers can use this model and algorithm to optimize other healthcare supply chains, such as vaccine or biologic drug supply chains, to enhance efficiency and sustainability in broader health domains. Managers can use these insights to negotiate with key stakeholders, such as governments or pharmaceutical companies, to gain more support for implementing these models.

5) Conclusion

This study presents a multi-objective mathematical model for designing a Chimeric Antigen Receptor T-cell (CAR-T) therapy supply chain, which not only incorporates cost considerations but also emphasizes environmental and social dimensions to establish a sustainable equilibrium among these three critical pillars. Given the problem's complexity and large scale, a novel hybrid metaheuristic algorithm was developed, adaptively integrating NSGA-IV, ε-MOEA, and SMS-EMOA. This adaptive approach led to significant improvements in convergence, diversity, and the quality of the Pareto front. Numerical results and statistical analyses confirmed the algorithm's superior performance over baseline algorithms in both quantitative metrics—achieving a 3% reduction in total cost, a 2 to 3% decrease in environmental pollution, and enhanced social impact—and qualitative metrics, such as generational distance and error ratio. Sensitivity analysis demonstrated the high robustness of the proposed algorithm against standard parameter variations, including emergency demand surges due to disease relapse; however, limited performance degradation was observed under extreme fluctuations in production capacity or demand. From a theoretical perspective, this research makes a substantial contribution to the multi-objective optimization literature. The proposed hybrid algorithm, by synergistically combining the strengths of NSGA-IV (for Pareto front diversity), ε-MOEA (for constraint handling), and SMS-EMOA (for convergence enhancement), introduces an innovative approach to metaheuristic design. This adaptive integration, reinforced by dynamic selection mechanisms and automatic parameter tuning, is applicable not only to CAR-T supply chain problems but also to other complex, large-scale multi-objective optimization problems with conflicting objectives. This advancement positions the proposed algorithm as a general-purpose tool for multi-objective optimization, extending beyond the specific application of this study. Its potential for extension to other healthcare supply chains and adaptation to uncertainty frameworks further amplifies its significance in broader domains. From a practical standpoint, these improvements have tangible implications for healthcare systems. For instance, the 3% cost savings could free up resources to improve access to expensive CAR-T therapies for low-income patients, while the 2-3% reduction in environmental pollution facilitates compliance with sustainability standards and potentially enables access to carbon credits. The sensitivity analysis on emergency demand due to relapse highlighted its role as a key driver pushing network design towards greater flexibility, underscoring its practical importance in CAR-T supply chains. By providing an innovative and applicable framework, this study offers an effective solution for designing and optimizing supply chains for advanced therapies within the complex and sensitive context of personalized healthcare. This framework aids managers and policymakers in moving towards a more sustainable and equitable health system.

5.1. Research Limitations

Despite its innovations, this study has limitations that may affect the generalizability of its results. First, the proposed model employs a deterministic approach, while inherent uncertainties in CAR-T therapy supply chains—such as sudden fluctuations in emergency demand due to disease relapse or logistical disruptions—are not explicitly modeled. This deterministic assumption may limit the model's ability to predict real-world scenarios under high uncertainty. Second, the assumption of linear environmental emissions (e.g., greenhouse gases and bio-waste) within the model may overlook real-world complexities, such as non-linear effects arising from economies of scale or specific operational conditions (e.g., variations in transportation routes). Third, due to the novelty of CAR-T therapy and limited access to real-world clinical and industrial data, synthetically generated data using controlled random methods was utilized. Although this data was calibrated based on reputable sources and realistic geographical intervals, the lack of real data may limit the generalizability of the results in certain practical scenarios. Fourth, the conducted sensitivity analysis was confined to key parameters such as production capacity, vehicle capacity, and emergency relapse demand, and did not investigate the impact of external factors such as regulatory policies or technological changes.

5.2. Future Research Directions

To address the aforementioned limitations, future research is recommended. Stochastic programming models should be developed to account for dynamic uncertainties, such as sudden changes in emergency relapse demand or logistical disruptions. For example, probabilistic models could represent emergency demand as probability distributions to provide greater flexibility against fluctuations. Furthermore, robust optimization techniques could be employed to design networks resilient to worst-case uncertainty scenarios, such as treatment center closures or vehicle shortages. Additionally, scenario-based validation using real-world data from treatment centers or pharmaceutical companies would enhance the model's generalizability, particularly for scenarios simulating emergency relapse demand. Integrating emerging technologies, such as AI for predicting emergency demand and Blockchain for enhancing transparency and traceability within the supply chain, could also improve model resilience. Finally, investigating the non-linear effects of environmental emissions, using dynamic or non-linear models, could increase the accuracy of environmental impact predictions and support sustainable policymaking. These suggestions can enrich the model's policy implications and assist decision-makers in the practical implementation of the proposed solutions.

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