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Effects of Maintenance Treatment Duration on Relapse in ANCA-Associated Vasculitis

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Supervisor: James Ng

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This study analsyes the effects of maintenance treatment duration on relapse rates in patients with ANCA-associated vasculitis (AAV) by estimating Individual Treatment Effects (ITE) using advanced causal inference techniques. Real-world data from the PARADISE project, which contains comprehensive patient records, were used to assess the effectiveness of three distinct maintenance treatment durations 16, 20, and 24 months on patient outcomess. The analysis reveals a clear trend where longer maintenance treatments shows reduced relapse rates, with ITE estimates becoming increasingly positive as the treatment duration increases. Specifically, at 16 months, the average ITE was negative, indicating a higher risk of relapse, while at 24 months, the ITE turned positive, suggesting a protective effect against relapse. The study highlights significant variability in patient responses, emphasizing the critical need for personalized treatment strategies that are tailored to individual patient profiles. These findings offer valuable insights that can guide clinical decisions, particularly in optimizing the duration of maintenance treatment to improve patient outcomes in AAV management. Furthermore, this research underscores the importance of personalised approaches in managing AAV, providing a potential pathway to improve maintenance care. By using causal inference methods and real-world data, this study contributes to a more thorough understanding of treatment effectiveness, ultimately supporting the development of more effective, patient-centered care strategies in the management of AAV.

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Chapter 1

INTRODUCTION

1.1 Overview

AAV, or ANCA-associated vasculitis, is a group of rare autoimmune disease caused by inflammation of the small blood vessels. These diseases can cause organ failure and, in extreme cases, even possibly can cause death. Treatments such as cyclophosphamide and corticosteroids have been known since the 1950s, and this has greatly improved the short-term survival rates for patients with AAV. Despite these developments, the high relapse risk and continuous treatment need of AAV make management challenging. While the uses of modern therapeutic approaches has improved patient outcomes, it is still unclear how long maintenance therapy should last in order to efficiently reduce disease activity and avoid relapse.

This study focusses on the estimation of Individual Treatment Effects (ITE) and attempts to close this gap by using causal inference techniques. By using this approach, relapse may be thoroughly assessed and the effects of varying maintenance therapy durations can be thoroughly examined, perhaps leading to treatment modifications that better suit the needs of individual patients. The study aims to improve clinical standards and the quality of life for patients with this challenging illness with the aid of this comprehensive study. It also emphasises the necessity of precise ITE computation to direct more customised and for accurate ITE calculation in order to guide more personalised and successful treatment plans.

1.2 Paradise Project

The PARADISE project is a major European initiative focused on improving the treatment and management of autoimmune diseases, specifically ANCA-associated vasculitis (AAV). Supported by the European Union, the project collaborates with various research institutions, including the ADAPT Centre. Its primary objective is to develop AI-driven tools to refine treatment approaches for autoimmune diseases, enhancing patient care for those affected by vasculitis.

A critical element of the project is its innovative integration of diverse data sources to power the algorithms for its predictive tools. These sources include biomarkers, clinical records, and wellness data collected via smartphones. By combining this

data comprehensively, the project aims to accurately predict disease relapse, enabling more cautious adjustments to medication dosages or discontinuations as needed.

1.3 Motivation

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) presents an important medical issue due to its chronic relapsing nature and the potential for serious organ damage. Despite improvements in methods of treatment, such as the use of cyclophosphamide and corticosteroids since the middle of the 20th century, managing AAV is still difficult. Relapse rates are often high for patients, which has a substantial impact on their quality of life and long-term health consequences. There are important dangers related to current treatment methods, which mostly rely on long-term immunosuppressive medication use to maintain rlapse. These risks include major infections and other unfavorable outcomes.

The optimal duration of maintenance therapy in AAV remains a pressing, however not resolved issue within the field of rheumatology. The limitations of short-term randomized controlled trials (RCTs), that provide some insights but are unable to properly capture the long-term results or the likelihood of relapse over an extended amount of time, are the main cause of this knowledge gap.

This project is driven by the need to address these significant gaps by applying advanced causal inference techniques to robust, real-world datasets. This study aims to provide more precise analysis of the effects of different treatment durations on relapse rates by focusing on a thorough counterfactual analysis of maintenance treatment durations and using data from the PARADISE project. By focussing on the analysis of Individual Treatment Effects (ITE), it is possible to gain a more detailed understanding that can be personalised to each patient's unique profile. This could result in more effective and personalised treatment approaches that have the potential to drastically change the way AAV is managed.

1.4 Background

Causal Inference

Causal inference is a fundamental process in statistics that involves understanding how one variable impacts another. In the context of medical research, it is especially important for determine how different treatments impact patient outcomes, particularly in diseases with high variability in treatment responses, which tells why personalized treatment plans are important.

For example, imagine that Y represents patient recovery, X could include variables such as the patient's age and health status, T might represent the type of treatment administered, and could account for unknown factors like the patient's stress levels or genetic predispositions. The relationship between these variables can be mathematically represented as:

$$Y = f(X, T, \epsilon)$$

Where:

• Y: Outcome (e.g., recovery rate, symptom improvement)

• X: Covariates (patient characteristics like age, health status, genetic factors)

• T: Treatment variable (e.g., medication dosage)

• : Unobserved factors influencing the outcome

Medical research needs an understanding of causal relationships for a number of reasons. It first helps medical professionals and researchers to determine which medicines or treatment work most effectively for an individual. It also helps in the development of safe and effective interventions. Third, by offering data on the overall impact of treatments across a range of people, causal inference assists in the development of clinical guidelines and healthcare policies.

The main problem with causal inference, however, is that one cannot observe every possible result for a single person at the same time. This presents an obstacle to causal inference. For example, if a patient receives a low dose of medication (denoted as Y(0)), one cannot directly observe what the outcome would have been if they had received a high dose (Y(1)). This issue is addressed through the concept of the Average Treatment Effect (ATE), which represents the expected difference in outcomes between two treatment scenarios across the entire population:

$$\text{ATE} = \mathbb{E}[Y(1) - Y(0)]$$

The ATE is necessary because it gives a concise evaluation of a treatment's effect on a population, helping in making the decision of whether a treatment should be widely recommended or customized for certain populations.

Key Assumptions for Reliable Causal Inference: For causal inference to be reliable, especially in observational studies, it relies on severals critical assumptions:

1. Stable Unit Treatment Value Assumption (SUTVA): According to this assumption, how a particular individual is treated has little impact on how another individual turns out. For instance, it would be challenging to determine the actual impact of a treatment on each individual if it were given to Patient A and potentially affect Patient B's recovery. SUTVA is important since it guarantees that interactions between individuals have no impact on the treatment effect being examined.

2. Consistency: The assumption states that the results under specific treatments that are observed match the results that could have been obtained if that treatment had been given. When providing a certain medication to a patient, for instance, the observed result should coincide with the outcome predicted by the model for that particular treatment scenario. Ensuring consistency is crucial to guarantee that the model accurately captures the actual effects of treatment.

3. Ignorability (or Conditional Independence): This assumption states that the treatment assignment is independent of the potential results given a set of visible covariates. Essentially, the assignment of treatment can be viewed as random once these factors are taken into account. Because of this assumption, researchers can even estimate causal effects in non-randomized experiments by controlling for confounding variables that could otherwise alter the results.

In the absence of randomized controlled trials (RCTs), these assumptions form the basis of causal inference and allow researchers to make meaningful conclusions with regard to the causal effects of treatments.

While causal inference offer a structure for understanding the effects of a treatment, it inevitably faces limitations by its inability to see all potential outcomes for one individual. Here, counterfactual analysis comes into play. Counterfactual analysis estimates what might have occurred under other treatment situations that were not directly seen, so assisting with fixing the core issue of causal inference.

Counterfactual Analysis

Counterfactual analysis is a developed statistical approach that plays a important role in causal inference. By estimating the outcomes that might have happened in various treatment situations, it helps to gain insight into the possible effects of interventions that were not really applied. This kind of study is especially helpful in domains where knowing the entire range of potential treatment outcomes is necessary to make accurate decisions, such as the health care sector.

At the core of counterfactual analysis is the concept of potential outcomes:

- Y(1): The potential outcome if an individual receives the treatment
- Y(0): The potential outcome if an individual does not receive the treatment

A major challenge in causal inference is that one can only observe one of these outcomes for each individual, depending on their actual treatment status. This challenge is the essence of the fundamental problem of causal inference. To model the observed outcome Y, the equation used is:

$$Y = T \cdot Y(1) + (1 - T) \cdot Y(0)$$

Here, T is a binary indicator of treatment administration (1 if treated, 0 if not). The goal is often to estimate the Average Treatment Effect (ATE) across a population:

$$\text{ATE} = \mathbb{E}[Y(1) - Y(0)]$$

For accurate estimation, the assumption of conditional independence (or ignorability) is crucial. This assumption ensures that treatment assignment is independent of potential outcomes, given the observed covariates:

$$(Y(0), Y(1)) \perp T \mid X$$

This assumption allows to control for confounding variables and draw valid conclusions about causal effects from observational data.

Causal Forests: The Causal Forest algorithm is a comprehensive counterfactual analysis technique. Using a wide range of covariates, this method assesses treatment effects at the person level, building upon the basic counterfactual framework:

$$\tau(x) = \mathbb{E}[Y(1) - Y(0) \mid X = x]$$

In this context, (x) represents the treatment effect for an individual with specific characteristics x. Causal forests are especially useful in situations where treatment effects are expected to vary across individuals. By analyzing the covariates, the model can identify subgroups of individuals who may benefit more or less from a treatment, leading to more personalized treatment recommendations.

For example, consider a study comparing two groups of patients prescribed different intensities of cholesterol-lowering medication. The patients have various

treatment levels despite being similar in terms of age, lifestyle, and health status. Researchers may determine the treatment effect within each group using causal trees and counterfactual analysis, which sheds light on how various patient factors affect the effectiveness of treatment. This method helps with the development of more customized and successful treatment programs by evaluating the advantages and possible drawbacks of stronger cholesterol management techniques.

Individual Treatment Estimate

A important aspect of personalized medicine is individual treatment effect (ITE) estimation, in which each patient's medical care is personalised to meet their particular requirements. The ITE focuses on the distinctive effects of a treatment on an individual, in contrast to the ATE, that provides an average effect across a community. This makes it particularly helpful in various patient groups where treatment responses may differ significantly.

The ITE is formally defined as:

$$\tau(x) = \mathbb{E}[Y(1) - Y(0) \mid X = x]$$

Where:

• Y(1): Potential outcome if the individual receives the treatment

• Y(0): Potential outcome if the individual does not receive the treatment

• X: Vector of individual covariates (e.g., age, health status, genetic markers)

• T(x): The ITE, indicating the treatment effect for an individual with covariates x

The primary challenge in estimating ITEs arises from the fundamental problem of causal inference is the impossibiliity of observing both potential outcomes for the same individual simultaneously. To address this, several statistical methods have been developed:

1. Regression-based Approaches: Regression models are used in these approaches to evaluate the treatment effect for every individual. The general form of a regression model for ITE estimation is:

$$Y = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 TX + \epsilon$$

Where T is the treatment indicator, and TX represents the interaction between treatment and covariates. The ITE for an individual is calculated as:

$$\tau(x) = \beta_1 + \beta_3 x$$

2. Matching Methods: A different approach for estimating ITEs is by pairing together treated and untreated people with similar variables. Using this technique, pairs of people are created who are identical except for the treatment they received. Next, the results inside these matched pairs are compared to estimate the ITE:

$$\tau(x_i) = Y_i - Y_j$$

Where Yi is the outcome for the treated individual, and Yj is the outcome for the matched untreated individual. This method helps control for confounding factors by ensuring that comparisons are made between similar individuals.

3. Causal Forests: Causal forests, as previously mentioned, are a way for evaluating different treatment effects by modifying the random forest approach. This approach makes it possible to estimate ITEs by identifying areas in the covariate space where treatment effects are consistent:

$$\tau(x) = \mathbb{E}[Y \mid X = x, T = 1] - \mathbb{E}[Y \mid X = x, T = 0]$$

Causal forests are very useful for customized medicine since they may be used to detect how treatment effects differ across subgroups. Causal forests give professionals an effective grasp of how individual factors influence treatment outcomes, enabling them to customize treatments to meet the particular requirements of each patient.

In cancer treatment, ITE estimation is especially crucial for selecting the most effective therapies. Oncologists are able to assess the likely effectiveness of different treatment choices, such as chemotherapy, immunotherapy, or targeted therapies, for a given patient by looking at the patient's genetic profile, tumor features, and other relevant criteria. This method helps prevent unnecessary toxicity from failed medications in addition to improving treatment outcomes.

For example, the ITE can be used in precision oncology to identify individuals whose tumors have genetic alterations that may make them more responsive to certain types of immunotherapy. Clinicians may reduce side effects while improving the likelihood of effective outcomes by customizing methods of treatment to each patient's profile.
This background establishes the theoretical framework for applying causal inference to estimate the effectiveness of maintenance treatment durations in ANCA-associated vasculitis using advanced statistical models.

1.5 Aims and objectives

The primary aim of this study is to analyse and estimate the individual treatment effects (ITE) of maintenance treatment duration on relapse rates in patients with ANCA-associated vasculitis (AAV).

1.6 Research Questions

To guide the project into the effects of maintenance treatment duration on relapse in ANCA-associated vasculitis,following research questions are formulated:

- 1. How can we effectively estimate the Individual Treatment Effect (ITE) of maintenance treatment duration on relapse rates in patients with ANCA-associated vasculitis (AAV)?

  This primary question addresses the core focus of the study, emphasizing the development and application of ITE estimation techniques in the context of AAV treatment.

- 2. How can an ITE-based statistical model for predicting relapse risk be effectively interpreted into a clinical decision for optimizing maintenance treatment duration in AAV patients?
  This question bridges the gap between statistical analysis and practical clinical application, addressing the ultimate goal of improving patient care.

1.7 Thesis Structure

The layout of this thesis is designed to give a thorough analysis of the impact of maintenance treatments on relapse in ANCA-associated vasculitis. After this introduction, Chapter 2 provides a comprehensive literature review of ANCA-associated vasculitis (AAV), including an understanding of the disease, its diagnosis, initial treatment, and relapse, as well as contemporary techniques in causal inference and counterfactual analysis. Chapter 3 focuses on the dataset used in this work, detailing the data description and preprocessing steps essential for the analysis. Chapter 4 delves into the methodology and implementation, covering the counterfactual analysis methods employed and the real-world data analysis. Chapter 5 presents a simulation study, discussing the purpose of the simulations, the synthetic data generation process, and the results obtained from the simulations. Chapter 6 provides the results and findings of the study, focusing on the estimated treatment effects across different timeframes, trends in relapse rates, and the clinical interpretation of individual treatment effects. Chapter 7 evaluates the different methods used, including

an analysis of real-world data, visualization of parameters, hyperparameter tuning, and key observations from the tuning results. Chapter 8 discusses the clinical impact of the findings, summarizing key results, exploring their clinical implications, and addressing the ethical considerations related to the study. Finally, Chapter 9 summarizes the findings and discusses the challenges encountered, offering thoughts on the future of personalized maintenance treatment in ANCA-associated vasculitis and providing recommendations for future research.

Chapter 2

LITERATURE REVIEW

2.1 Introduction

The identification of maintenance treatments in ANCA-associated vasculitis (AAV) is crucial in order to enhance the quality of life of patients affected by the disease since it tends to be recurrent. AAV that refer to the group of autoimmune diseases that affect small blood vessels, and which are known to cause severe organ damage and raised mortality rate (Berti and Specks, 2019). This remains true, even today, because the induction therapies have been improved but a relapse is still a problem, underlining the importance of a correct maintenance therapy to avoid the relapses and control the long-term course of the disease (Raffray Guillevin, 2020).

This review of the literature will be centered on the current understanding of AAV, as well as on the interventions that address various types of maintenance treatments with the purpose of lowering the rates of relapse. In this chapter to it is to write of what exists in literature and existing therapeutic approaches, methodologies of causal inference and machine learning interventions for personalised treatment are described. Special regard is given to the use of biomarkers as well as precision medicine for the adaption of the treatment to the patient's profile and enhance the success of maintenance therapies and duration. The information that will be obtained from this review is going to lay the foundation of the following research and analysis of the impact of the maintenance treatment duration on the relapse rates in the AAV patients.

2.2 Understanding ANCA-associated Vasculitis (AAV)

AAV is a group of systemic granulomatous vasculitis with anti-neutrophil cytoplasmic antibodies, which is a very rare set of diseases, whose common feature is the inflammation and destruction of the small vessels that can result in the damage of the target organs and death. AAV encompasses three main clinical entities: Reflected in three forms, of which are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). These are conditions that are featured by the presence of ANCA that have a pathogenetic role in the development of the disease (Berti Specks, 2019).

The etiology of AAV is hereditary, environmental and immunological dysfunctions. ANCA react with some proteins in neutrophils, mainly proteinase 3 (PR3) and myeloperoxidase (MPO) and in so doing the neutrophils get activated. The activated neutrophils adhere to the lining of the small blood vessels, release substances that damages the cells in the vessels' lining leading to inflammation and necrosis of the affected tissue (D. A., 2020). This leads to a generalised infection of the body with the kidney, lungs, and upper respiratory system being most commonly involved. The clinical features of AAV may present from relatively mild illnesses that include sinusitis and arthralgia to severe complications including rapidly progressive glomerulonephritis and pulmonary haemorrhage (Cooke et al., 2023).

The diagnosis of AAV is made clinically, serologically. Also, the finding of ANCA with immunofluorescence or enzyme-linked immunosorbent assay (ELISA) is typical of the disease. However, a certain group of patients may be serologically ANCA-negative, which raises a diagnostic problem (Cooke et al., 2023). Light microscopy of the affected tissues and organs usually shows necrotizing vasculitis with few, if any, immune deposits, which is a feature that differentiates AAV from other types of vasculitis. BVAS is the most commonly used marker for disease activity and management of patient treatment plans.

Management of AAV involves two main phases: induction treatment to achieve remission and maintenance treatment to prevent relapse. Induction typically involves high-dose glucocorticoids, often combined with immunosuppressive drugs like cyclophosphamide or rituximab (Jayne, 2020). Once disease activity is controlled, patients are transitioned to maintenance treatment to prevent flare-ups. Common maintenance strategies include the use of reduced glucocorticoids, azathioprine, methotrexate, mycophenolate mofetil, or rituximab (Woerner and P., 2021). Despite these strategies, relapse remains a significant concern, with about half of patients experiencing relapse within five years of remission thus underlining the need to find the right and, importantly, the most suitable maintenance strategies(Raffray and Guillevin, 2020).

The management of maintenance treatment can be influenced by several factors; such as the type of disease, the general health of the patient, and the earlier response to the treatment regimes. However, there is no general agreement on the most suitable approach to maintenance treatment and the management of the condition often depends on the clinician's experience and the patient's preference (Esposito et al., 2023).

This section tells about the complex nature of AAV and the critical need for effective maintenance treatments, reinforcing the importance of personalized approaches and the study's focus on ITE estimation to optimize treatment strategies.

2.3 Diagnosis, Initial Treatment, and Relapse in ANCA-associated Vasculitis (AAV)

Diagnosis of AAV entails clinical evaluation, biochemical tests of serum and occasionally tissue biopsy. Consequently, patients may present with non-specific signs and symptoms such as fever, fatigue and weight loss as well as manifestations affecting particular organs such as sinusitis, pulmonary infiltrates, haematuria and proteinuria (Berti and Specks, 2019). Thus, there is an obligatory understanding of a clinical suspicion in the initial diagnosis, particularly in patients with the aggressive glomerulonephritis or patients suspected of having pulmonary-renal syndrome. Antibody usage is rather very important in a diagnosis of AAV. Staining of anti-neutrophil cytoplasmic antibodies (ANCA) is one of the characteristic findings of the disease. These antibodies act on proteins in neutrophils and primarily on proteinase 3 (PR3) and myeloperoxidase (MPO). The administration of ANCA testing involves the indirect immunofluorescence and enzyme linked immunosorbent assay (ELISA) methods. Among these, PR3-ANCA is more frequently related to GPA while MPO-ANCA is more often seen in MPA and EgPA (Cooke et al., 2023). However, there is a group of patients who will be ANCA negative and such patients' diagnosis becomes a dilemma and the physician has to rely on the clinical presentation and/or histopathological examination. Pathological findings on the biopsy of the affected organs usually show necrotizing vasculitis without much immune complex deposition. Renal biopsies are particularly useful in the diagnosis and staging of the extent of glomerular lesions. BVAS is widely applied in the evaluation of disease activity and treatment strategies. The main objectives of induction treatment in AAV are to attain a prompt control of disease activity, and to prevent the occurrence of end-organ damage. Glucocorticoids are the most widely used agents in the induction setting primarily because of their high anti-inflammatory and immunosuppressive properties. Besides glucocorticoids, other drugs like cyclophosphamide or rituximab are also inducted to the therapeutic regimen. Cyclophosphamide is a cytotoxic agent of the alkylating type, which for many years has been used for severe cases and can be taken orally or by injection. However, because of the probable long-term risks on the body, the use of rituximab, a monoclonal antibody that has B cell CD20 positive cells targeted, has been on the rise. Rituximab is at least as

effective as cyclophosphamide for induction treatment, and is associated with fewer adverse effects (Raffray; Guillevin, 2020).

Relapse in AAV

The study also established that relapse remains a significant concern in AAV's management because half of the patients are prone to have a relapse within the first five years of attaining remission (D. A., 2020). The relapses may range from having little disease activity to as bad as having fatal involvement of organs. Therefore, preventive approaches, early diagnosis and individualized management for maintenance are crucial, to prevent a relapse and maintain complete sustained remission. The maintenance treatment regimens are also diverse and may be chosen depending on the type of the disease, the response to the treatment earlier, and presence of other diseases. The more frequent used maintenance agents include: azathioprine, methotrexate, mycophenolate mofetil and a low-dose of rituximab. However, there is no normative practice concerning the choice of the preferred maintenance strategy and the treatment plans are usually individualised depending on the patients' choice (Esposito et al., 2023). There is therefore hope that the recently developed advancements in the field of precision medicine may aid in developing better preventive interventions. The use of digital biomarkers and genomic assessments is being used to determine the potential of predicting the likelihood of relapse and consequently modify the strategy for maintenance treatment (Capobianco and Luigi, 2021). Furthermore, the causal inference and counterfactual analysis have remained strong methods of analysing the efficiency of various maintenance therapies and their influence on the relapse rates (Kuang et al., 2020).

Causal Inference in Medical Research

Causal inference in medical research is one of the most significant and commonly used methods of analysing the connection between treatments, interventions, and health outcomes. While the association aims at creating cause-and-effect relationships, causal inferences must develop cause-related treatment and procedure to establish the fact that such impacts affect the patient's outcome. In this section, efforts will be made to clarify the thread of causal inference and the principal techniques of the analysis in the exploration of AAV and precision medicine.

This field requires that one establishes cause and effect in order to be able to apply information in the management and treatment of patients with confidence in achieving the outcome expected. This makes causal inference instrumental in

allowing a researcher to separate between a treatment that improves patient's health and circumstances where a treatment seems beneficial when in reality there were other non-treatment factors at work. This differentiation is fairly subtle but very significant for the development of suitable therapies, for the direction of the clinic and for the planning of the health care strategies (Yao et al., 2021). In AAV, precise causal analysis may help to estimate the effectiveness of the treatment, prevent relapses, and predict individual patient's response to treatment.

2.4 Key Methodologies in Causal Inference

Several strategies are used in causal inference and each has its peculiar characteristics. RCTs are viewed as the most appropriate means of determining cause-and-effect relationships due to their design. Through the process of randomly assigning participants to treatment or control groups, RCTs prevent undesirable influences such as confounding factors, enabling the identification of the intervention's effects on the outcomes. However, RCTs are costly, and often, take a long time to complete; besides, there are instances when they are unethical or impossible to conduct. Cohort and case-control studies that are observational are used when RCTs are not suitable. Such studies need to control for confounding and other sources of bias and these are best done using statistical methods. The most frequently used approach to estimate causal effects in the absence of randomisation is Propensity score matching, instrumental variable analysis and Regression Discontinuity Designs. For example, in propensity score matching, it is possible to form two groups with similar characteristics regarding the covariates to mimic the randomized assignment (Mwangi et al., 2021). Counterfactual analysis is another important technique in causal inference that allows comparing the actual outcomes with the hypothetical ones, where the treatment was not applied. This approach enables the researchers to remove the impact of other variables to some extent. Counterfactual predictions are being improved by machine learning techniques especially for big data sets and other applications where counterfactual predictions are useful (Wang et al., 2022).

2.5 Counterfactual Analysis and Individual Treatment Effects (ITE)

Counterfactual thinking and estimation of ITE are actually significant methods in precision medicine and clinical investigation. These techniques allow the researches to analyze how patients will response to upcoming treatment in other to make the medical treatment effective as possible. This section explains: what counterfactual analysis is; how ITEs are calculated; and how ITEs are applied in medical research

with specific reference to AAV. The technique of counterfactual analysis involves a comparison between the actual outcome of an intervention and the outcome that would have been obtained if the intervention had not taken place. It is also valuable when other factors might confound the results of the intervention and could have affected the results. Its main idea is as follows: one should create an 'as-treated' design similar to the real world in terms of all aspects except the treatment; that will allow for seeing causality (Yao et al., 2021).

Estimating Individual Treatment Effects (ITE)

Estimating ITEs required assessing how various patients would be affected by a treatment compared to if they had not been treated at all. This estimation is important in precision medicine where the aim is to provide treatment based on individual patient's characteristics. There are several methods which have been developed to carry out the estimation of ITEs and each of them has its own merits and demerits.

1. Randomized Controlled Trials (RCTs) RCTs are the most effective methodology to estimate treatment effects because they reduce confounding to the level of individual patients through randomisation. However, while RCTs can give the treatment effects for an average subject in a population, they are often insufficient to estimate ITEs. More complex methods of data analysis including subgroup analysis and stratification together with regression analysis can be used to obtain ITEs from RCT data by comparing treatment efficacy in certain patient subgroups (Raffray and Guillevin 2020).

2. Observational Studies and Propensity Score Matching In the observational studies where randomization is not possible, propensity score matching is one of the most used techniques to estimate ITEs. The PSM requires that the analyst makes pairs of treated and control subjects who are similar in terms of their likelihood of receiving the treatment given their observed characteristics. This matching assists in reducing the confounding factors' imbalance between the treatment and control groups, which makes the study resemble a randomized trial (Mwangi et al., 2021).

3. Machine Learning Approaches Techniques like causal forests and neural networks have been proposed in the literature and are considered efficient in estimating ITEs. It is also useful in dealing with intricate and large datasets and learns the non-linear interaction between covariates and treatment effects. For example, causal forests are an extension of random forests for the causal setting; it builds a forest of decision trees that estimate treatment effects at the individual level (Wang et al., 2022).

Applications in Medical Research

- **Treatment Heterogeneity in ANCA-Associated Vasculitis (AAV)**: As it has been observed, AAV is an extremely diverse condition, which may be manifested and responded to treatment in numerous ways. Counter factual analysis can be of help while trying to find patients who are most likely to benefit from some treatments for example cyclophosphamide or rituximab. For instance, Kuang et al. have recently reported a study that used counterfactual models for the late prognosis assessment of patients exposed to distinct induction therapies in order to identify the patient-specific responses and tailor the treatment strategies.

- **Personalized Medicine**: Personalized medicine aims at individual approach to the chosen therapy depending on the patient's gene, protein, and phenotype profiles, as well as medical history. The two concepts useful to this approach are counter factual analysis and ITE estimation, for they assist in identifying the likely treatment outcome of a patient in question. Miyagawa et al. (2020) outlined how ITE estimation can be used for the improvement of the treatment regimens used in autoimmune diseases in an effort to improve therapeutic efficacy and to lessen side effects.

- **Real-World Evidence and Electronic Health Records (EHRs)**: Real-world data such as EHR and other RWD contribute to treatment effect in multiple setting in real-world and thus serves to bridge the gap created by RCT. Indeed, counterfactual analysis is very useful in making causal inferences from these data because it enables one to control for confounding and other sources of bias that are inevitable in observational studies. In another study by Evans (2019) highlighted the aspect of using RWE applied in the practice and the formation of policies; the above findings justified the need to ensure that techniques required for the confirmation of the result are followed.

Chapter 3

DATASET

3.1 Data Description

The dataset used in this analysis was obtained from the PARADISE project, containing medical records of 591 patients diagnosed with ANCA-associated vasculitis (AAV). Key variables include demographic factors (e.g. age, gender, ethnicity), clinical features (e.g. affected organs, disease severity), treatment details (e.g. drug regimens, dosage), and outcomes such as relapse status. All the patients included in the study went through 12 months of maintenance treatment after initial induction treatment. This was the inclusion criteria for the analysis. Following this, three datasets were created, one each for 16 months, 20 months, and 24 months of maintenance treatment.

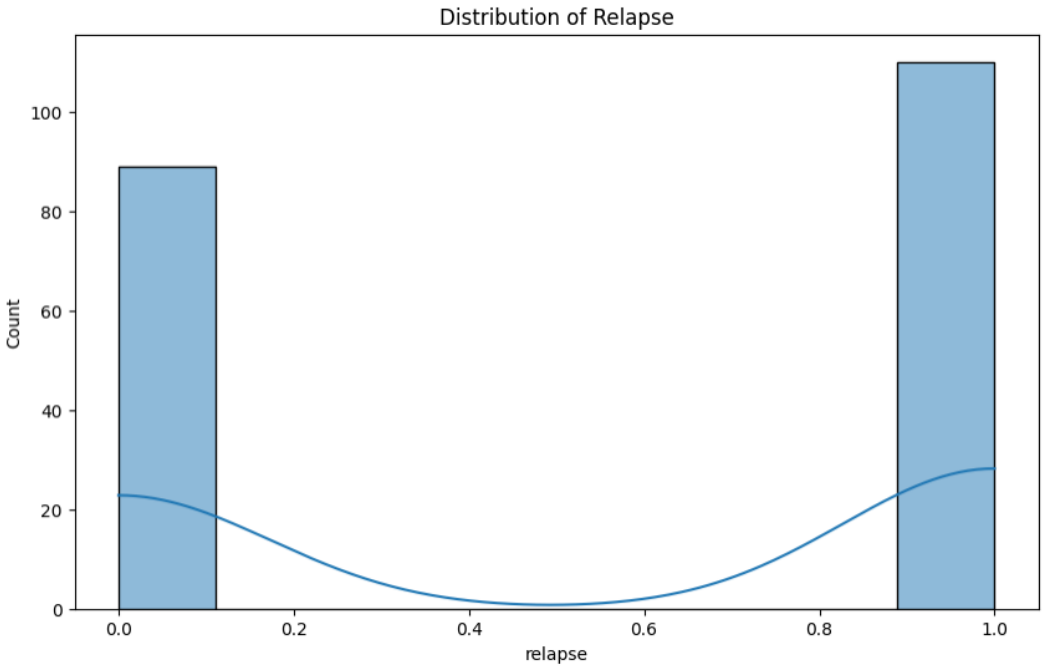

Figure 3.1: Distribution of Relapse

3.2 Data Preprocessing

The data preprocessing phase is a important step in preparing the raw dataset for analysis, ensuring that the data is clean, consistent, and suitable for statis-

tical modeling and analysis. This section details the preprocessing methodology, the rationale behind each step, and the transformations applied to create a final, robust dataset ready for analysis.

Initial Data Cleaning

The preprocessing pipeline began by loading the necessary datasets, including the primary dataset (*data.xlsx*), a metadata file specifying columns to exclude (*delete_details.csv*), and additional date-related information (*dateInfo.xlsx*). The first task was to clean the data by removing unnecessary columns that were irrelevant to the analysis or contained excessive missing values. This was achieved using the `delete_data()` function, which cross-referenced the columns in the dataset with those listed in the *delete_details.csv* file. Columns identified for exclusion were removed, and additional filtering was applied to remove any columns with more than 40% missing values.

Data Type Conversion and Further Cleaning

With the cleaned dataset in place, the next step addressed any remaining missing values. The `fill_missing()` function was designed to fill these gaps in the data. For categorical columns, missing values were imputed using the mode, which is the most frequently occurring value in the column. This approach helps maintain the integrity of categorical variables by preserving the distribution of the data. For numerical columns, missing values were filled with the mean of the column, ensuring that the central tendency of the data is maintained.

Handling Missing Values

The next step involved reframing the dataset, performed by the `reframe_data()` function. The original dataset contained multiple records per patient, each representing different visits or time periods. To transform the data into a format more suitable for analysis and model fitting, these records were combined into a single row per patient, summarizing their treatment history and outcomes over time. This process involved calculating key variables, such as `relapse` and `treatment_on_n_plus` where n is duration, based on the patient's treatment timeline and outcomes.

Reframing the Data

The next step involved reframing the dataset, performed by the `reframe_data()` function. The original dataset contained multiple records per patient, each representing different visits or time periods. To transform the data into a

format more suitable for analysis and model fitting, these records were combined into a single row per patient, summarizing their treatment history and outcomes over time. This process included calculating key variables, such as `relapse` and `treatment_on_n_plus` where n is duration, based on the patient's treatment timeline and outcomes. By combining the data into one row per patient, this step significantly streamlined the dataset, making it more suitable for statistical modeling.

Correlation and Association Filtering

The final step in the preprocessing workflow was to refine the dataset by retaining only the most relevant variables those strongly associated with the target outcome, `relapse`. This was accomplished through the `cc_calculation()` function, which evaluated the correlation between numerical variables and `relapse` and assessed the association between categorical variables and `relapse` using Cramér's V statistic. Columns that exhibited weak correlations or associations with the target variable were removed from the dataset. This filtering process ensured that the final dataset contained 199 patient data and only the variables that were most predictive of the outcome.

Data Privacy

When working with medical research data, especially for rare diseases like Rare Kidney Disease (RKD), protecting patient privacy is crucial. Even though patient information is made anonymous, certain details like symptoms or visit dates might still identify someone. To keep patient data safe, followed strict rules: all RKD data is stored on encrypted and password-protected devices; it's not sent through email or stored online without strong encryption; and it's not shared or discussed outside the research team. Also made sure that any information shared in reports or at public events does not reveal individual patient details. These steps are vital for maintaining patient confidentiality in our research.

Chapter 4

METHODOLOGY AND IMPLEMENTATION

4.1 Overview

This chapter presents a methodology for analysing the effects of maintenance treatment duration on relapse rates in ANCA-associated vasculitis (AAV) patients. The approach uses advanced causal inference techniques with machine learning methods to estimate both average and individual treatment effects. The methodology is designed to address the complex nature of AAV treatment outcomes and the heterogeneity in patient responses.

Using strategy that combines counterfactual analysis and individual treatment effect (ITE) estimation. This approach allows to not only understand the overall impact of different maintenance treatment duration but also to predict personalized treatment effects for individual patients.

4.2 Counterfactual Analysis Methods

This section explores the methodologies used for counterfactual analysis in estimating individual treatment effects (ITEs) for ANCA-associated vasculitis (AAV) maintenance treatment which are Virtual Twins, Counterfactual Random Forests, and Synthetic Counterfactual Forests. Each method uses a different set of techniques to estimate ITEs, providing detailed information on how effectively a treatment is working for indivduals.

Virtual Twins Method

Assuming two hypothetical scenarios—one in which the patient receives the treatment and another in which they do not—the Virtual Twins (VT) approach is a complex causal inference technique used to estimate ITEs. This technique allows for the accurate estimate of treatment effects at the individual level by simulating outcomes under both treated and untreated conditions. The VT technique is especially helpful in personalized medicine, because it's critical to understand how different treatments affect different people.

The VT methodology, introduced by Foster et al. (2011), leverages a predictive model to simulate outcomes for both treated and untreated scenarios. The mathematical formulation for estimating ITE for an individual with covariates

X is as follows:

$$\tau(x) = \mathbb{E}[Y \mid X = x, T = 1] - \mathbb{E}[Y \mid X = x, T = 0]$$

Where Y represents the outcome, T is the treatment indicator (1 for treated, 0 for untreated), and X is the covariate matrix. The core of the VT method involves training a random forest model, denoted as f(X,T), to predict outcomes based on covariates, treatment status, and their interactions. The estimated ITE is computed as:

$$\tau(x) = f(x, 1) - f(x, 0)$$

In this study, the VT model is implemented using a Random Forest Regressor as the base learner. The implementation involves several key steps, which are detailed below:

Data Preparation: To create a larger feature set, the input features (covariates X) are combined with the treatment the purpose T and their interaction terms X×T. When trying to estimate the effects of varied treatments, it is important that the model be able to capture the interaction effects between variables and treatment. The addition of interaction factors in the model enables the accounting for possible differences in treatment effects among distinct subgroups within the population.

Model Training: A Random Forest Regressor with the outcome variable Y as its objective is trained using the enlarged feature set. Because of its ability to adapt while handling high-dimensional data and its ability to represent complex, non-linear relationships, the Random Forest algorithm was chosen. The ensemble nature of the technique, which combines the predictions of multiple decision trees, aids in decreasing variance and increasing prediction accuracy.

ITE Estimation: To estimate the ITE for an individual, the model makes two predictions:

- f(x,1): The predicted outcome assuming the individual receives the treatment more then certain duration.
- f(x,0): The predicted outcome assuming the individual does not receive the treatment less than duration .

The estimated ITE (x) can be calculated by taking the difference between these two forecasts. With this method, the predicted treatment impact is customized to the unique variables of each individual.

Hyperparameter Tuning Process: To optimize the VT model's performance, a grid search is conducted over a predefined hyperparameter space. The parameters that are tuned include:

- `n_estimators`: The number of trees in the forest (options: 100, 500, 1000). A higher number of trees generally improves the model's robustness, but it also increases computational complexity.
- `max_features`: The number of features considered when looking for the best split (options: 2, 5, 7). This parameter controls the diversity of the trees in the forest, which is crucial for the model's generalization capability.
- `min_samples_leaf`: The minimum number of samples required at a leaf node (options: 1, 3, 5). This parameter helps prevent the model from overfitting by ensuring that leaf nodes are not too small.

To identify the ideal set of hyperparameters that minimizes prediction error, the grid search uses 5-fold cross-validation with negative mean squared error (MSE) as the scoring metric. By doing this, the model's ability to generalize effectively to new data is guaranteed, providing ITE estimates that are accurate and dependable.

Counterfactual Random Forests

Utilizing different models for treated and untreated groups, Counterfactual Random Forests (CF) offer a further and very successful method for ITE estimate. The idea behind this methodology, which was initially laid out by Wager and Athey (2018), is that there may be variations in these groups' relationships between variables and outcomes. The CF technique captures treatment effect heterogeneity more effectively by modeling the relationships separately, which is especially helpful when there are important individual differences in the treatment impact.
Mathematically, the ITE for an individual with covariates X is defined as:

$$\tau(x) = \mathbb{E}[Y(1) \mid X = x] - \mathbb{E}[Y(0) \mid X = x]$$

where $Y(1)$ and $Y(0)$ are the potential outcomes under treatment and control, respectively.

In this study, the CF model is implemented using two separate Random Forest Regressors. The process involves the following steps:
Data Splitting: The dataset is divided into two subsets:

- Treated subset (T=1): Contains individuals who received the treatment for more than certain duration.
- Untreated subset (T=0): Contains individuals who did not receive the treatment for less than certain duration.

This division enhances the accuracy of treatment effect estimates by enabling each model to concentrate on identifying the particular relationships among variables and outcomes within its own subgroup.
Model Training: Two Random Forest Regressors are trained:

- One on the treated subset, predicting outcomes for treated individuals for more than certain duration.
- One on the untreated subset, predicting outcomes for untreated individuals for less than certain duration.

Since each model is trained independently, it can capture the possible differences in covariate-outcome associations between the groups that get treatment versus those that do not.

ITE Estimation: To estimate the ITE for an individual:

- The treated model predicts the outcome assuming the individual was treated more than certain duration E[Y(1)X=x].
- The untreated model predicts the outcome assuming the individual was not treated less than certain duration E[Y(0)X=x].

The difference between these two predictions yields the estimated ITE (X). This approach enables the model to account for heterogeneity in treatment effects across different individuals.
Hyperparameter Tuning Process: Similar to the VT model, a grid search is conducted separately for the treated and untreated models. The hyperparameters tuned include:

- `n_estimators`: The number of trees in the forest (options: 100, 500, 1000).
- `max_features`: The number of features considered when looking for the best split (options: 2, 5, 7).
- `min_samples_leaf`: The minimum number of samples required at a leaf node (options: 1, 3, 5).

5-fold cross-validation is used in the grid search, and the scoring measure is negative MSE. Since this procedure is carried out individually for the two models, several ideal hyperparameters may be chosen in each scenario. By taking into account possible variations in the complexity of the outcome-covariate relationships between the groups that received treatment and those that did not, this method ensures that every model is most appropriate for the particular task at hand.

Synthetic Counterfactual Forests

An advanced framework for causal inference, Synthetic Counterfactual Forests (SynCF) combines components of random forests and synthetic controls. SynCF's main concept is to create synthetic features through the creation of predictions from a series of base learners, or random forests, and then train a final model using these synthetic features in addition to the original variables. By combining the benefits of synthetic control methods and ensemble approaches, this strategy seeks to produce estimates of ITEs that may be more reliable and accurate.

Mathematically, let $\{f_k(X)\}$ be a set of K base learners. For each individual in the dataset, synthetic features $S = \{s_k\}$ are generated where:

$$s_k = f_k(X)$$

The individual treatment effect (ITE) $\tau(x)$ is then estimated using a random forest g trained on $[X, S]$:

$$\tau(x) = g([x, s], 1) - g([x, s], 0)$$

Implementation Details: The SynCF method in this study is implemented through the following steps:

1. Base Learner Training: Multiple Random Forest models (base learners) are trained on different subsets of the data or with different hyperparameter settings. By capturing different facets of the covariate-outcome correlations, these base learners help boost the final model's robustness. The final model's estimation power is increased because the variety of base learners ensures that the synthetic features capture a wide range of data patterns.

2. Synthetic Feature Generation: All base learners are used to make predictions for each individual in the dataset. The synthetic features, which reflect various aspects of the underlying data structure, are formed by these predictions. The synthetic features act as a compressed representation of the information captured by the base learners, providing the final model with additional, potentially more informative inputs.

3. Feature Combination: The original covariates X are combined with the synthetic features S to create an expanded feature set. It is expected that this expanded feature set will provide a more comprehensive depiction of the data, enhancing the estimation abilities of the model. The model makes use of both the raw input data and the derived patterns found by the base learners thanks to the combination of synthetic and original characteristics.

4. Final Model Training: A Random Forest Regressor is trained on the expanded feature set with the outcome Y as the target variable. The final model estimates ITEs more precisely by utilizing both the synthetic and original properties. Because it can handle high-dimensional data and is resistant to overfitting, the Random Forest algorithm is especially well-suited for this kind of work.

ITE Estimation:

Similar to the VT and CF models, the ITE for each individual is estimated by making two predictions:

- g([x,s],1): The predicted outcome assuming the individual was treated for more than certain duration.
- g([x,s],0): The predicted outcome assuming the individual was not treated for less than certain duration.

The estimated ITE (X) is determined by the difference between these estimates. This approach improves the model's capacity to represent intricate treatment

effects by utilizing the synthetic features, which makes it an effective tool for counterfactual analysis.

Performance metrics

To evaluate the performance of the causal inference models, two primary metrics is used: bias estimation and Root Mean Square Error (RMSE).

Bias estimation

Bias in the context of causal inference refers to the systematic deviation of estimated treatment effects from the true treatment effects. In this study, estimation of bias is done using the difference between the predicted Individual Treatment Effect (ITE) and the true treatment effect.

For each model, the average bias across all samples is calculated in the test set as:

$$\text{Bias} = \frac{1}{n}\sum_{i=1}^{n}(\tau_{\text{pred}}(x_i) - \tau_{\text{true}}(x_i))$$

where:

- n is the number of samples in the test set
- $\tau_{\text{pred}}(x_i)$ is the predicted ITE for sample i
- $\tau_{\text{true}}(x_i)$ is the true ITE for sample i (known in simulation studies, estimated in real-world data)

Root Mean Square Error (RMSE) provides a measure of the average magnitude of estimation errors. It is calculated as the square root of the average of squared differences between predicted and true ITEs:

$$\text{RMSE} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(\tau_{\text{pred}}(x_i) - \tau_{\text{true}}(x_i))^2}$$

RMSE is particularly useful as it penalizes larger errors more heavily, giving us a good indication of the model's overall accuracy in estimating ITEs.

Analysis Across Timeframes:

This analysis is conducted using data from three timeframes: 16, 20, and 24 months.

The data is prepared using the preprocessing steps mentioned in chapter 3. The prepared data is split into training and testing sets using the `train_test_split`

function from scikit-learn. This function randomly assigns 80 percent of the data to the training set and 20 percent to the testing set.

Chapter 5

SIMULATION STUDY

The simulations conducted in this study is important for checking the performance of Individual Treatment Effect (ITE) estimation methods—Virtual Twins (VT), Counterfactual Random Forests (CF), and Synthetic Counterfactual Forests (SynCF)—in the context of ANCA-associated vasculitis (AAV). The primary goal is to understand how these methods behave under conditions that mimic the complex; real-world data characteristics typical of medical data. Given that AAV is a rare and complex disease with heterogeneous treatment responses, these simulations provide a controlled environment to evaluate the robustness of each method in capturing treatment effects that could vary significantly across patients.

5.1 Purpose of the Simulations:

- To systematically compare the performance of VT, CF, and SynCF methods in estimating ITEs under various synthetic conditions that resemble the real-world challenges encountered in AAV patient data.
- To identify the best method for application to actual AAV data, ensuring that the chosen method can robustly handle the complexities of the disease and provide accurate treatment effect estimates.

  The simulation parameters in this study were carefully chosen to show the complex relationships found in ANCA-associated vasculitis (AAV) treatment scenarios. The focus was on creating synthetic data that could effectively test the robustness of different Individual Treatment Effect (ITE) estimation methods under conditions that mimic real-world clinical data. The three models linear, non-linear, and complex were designed to assess how these methods perform as the complexity of the underlying data increases.

5.2 Synthetic Data Generation Process

To evaluate the causal inference methods, simulation study was conducted, creating synthetic data that simulates the complexities typically seen in real-

world medical patient data. The design of the synthetic data generation aims to closely mimic the attributes of clinical data, thus providing a robust foundation for validating the effectiveness of causal inference methodologies under controlled yet complex conditions. Generate Covariates X:

Generated 20 distinct covariates. This included 11 continuous variables (X1 to X11), drawn from a standard normal distribution N (0,1). This selection is based on the premise that many clinical measurements typically follow a normal distribution. Additionally, 9 binary variables (X12 to X20) are generated using a Bernoulli distribution with a probability p=0.5. These binary variables are intended to represent binary clinical decisions or patient characteristics, such as the presence or absence of specific symptoms, providing a diverse nature reflective of certain clinical data types.

Generate treatment assignment T: Treatment assignment is crucial and is modelled through a logistic regression framework, defined by the formula:

Logistic Model:

$$F_X = -2+0.028X_1-0.374X_2-0.03X_3+0.118X_4-0.394X_{11}+0.875X_{12}+0.9X_{13}$$

The probability of a patient receiving treatment, $P(T = 1 \mid X)$, is calculated using the logistic function:

$$P(T = 1 \mid X) = \frac{1}{1 + \exp(-F_X)}$$

This setup allows to simulate the clinical decision-making process, where treatment likelihood is influenced by a combination of multiple covariates, reflecting real-world complexities.

Generate outcomes Y: designed three distinct outcome models to test the resilience of the causal inference methods against different data behaviors.

The coefficients in the simulation models were selected to capture a range of interactions between covariates and treatment effects, reflecting real-world clinical scenarios. For instance, the linear terms in the models (e.g., $0.4 \times X[:$

, 0], $0.154 \times X[:, 1]$) are meant to simulate straightforward relationships where patient characteristics like age and gender have a direct, linear effect on treatment outcomes.The inclusion of interaction terms (e.g., $-0.4 \times X[:, 1]^2$) and sinusoidal transformations (e.g.,$\sin(0.4 \times X[:, 0] + 0.154 \times X[:, 1])$) were introduced to reflect more complex, non-linear interactions that could occur in real-world treatment scenarios, particularly in a heterogeneous condition like AAV.

Model 1 (Linear):

$$Y = 2.455 - (1-T) \cdot (0.4X_1 + 0.154X_2 - 0.152X_{11} - 0.126X_{12}) - T \cdot (0.254X_2 - 0.152X_{11} - 0.4X_2^2 - 0.126X$$

This model assumes that treatment effects are linear combinations of the covariates, making it the simplest scenario. It is designed to test the basic performance of the ITE estimation methods when the data structure is relatively straightforward.

Model 2 (Non-linear):

$$Y = 2.455 - (1-T) \cdot \sin(0.4X_1 + 0.154X_2 - 0.152X_{11} - 0.126X_{12}) - T \cdot (0.254X_2 - 0.152X_{11} - 0.4X_2^2 - 0.12$$

This model introduces non-linearity through a sinusoidal function, simulating more complex relationships between covariates and outcomes. This complexity tests how well the methods can capture non-linear treatment effects.

Model 3 (Complex):

$$Y = 2.455 - (1-T) \cdot \sin(0.4X_1 + 0.154X_2 - 0.152X_{11} - 0.126X_{12}) - T \cdot (0.254X_2 - 0.152X_{11} - 0.126X_3 - 0.$$

The most complex model includes both non-linear interactions and additional interaction terms between multiple covariates. This model is intended to challenge the methods with the kind of intricate relationships that might be present in real-world AAV patient data, particularly when multiple patient characteristics interact to influence treatment outcomes.

Noise Addition: A small amount of Gaussian noise (with a standard deviation of 0.1) was added to the outcome variable YYY to mimic the variability seen in real-world clinical data. This noise represents unmeasured factors and random variation in patient responses, telling that in practice, patient outcomes are

influenced by many factors beyond those captured by the covariates in the model. By designing the simulation parameters in this manner, the study aims to evaluate the ability of the ITE estimation methods to handle a range of complexity levels, from simple linear relationships to highly complex, non-linear interactions. This approach ensures that the methods are tested under conditions that are representative of the challenges posed by real-world AAV data and guiding the selection of the most robust method for clinical application.

5.3 Simulation Study Results

The simulation studies were conducted to evaluate the performance of the Virtual Twins (VT), Counterfactual Random Forests (CF), and Synthetic Counterfactual Forests (SyncF) methods on controlled synthetic datasets. Data was simulated to mimic complex real-world relationships. and models were tasked with estimating individual treatment effects (ITEs) under various scenarios. The graph below shows results.

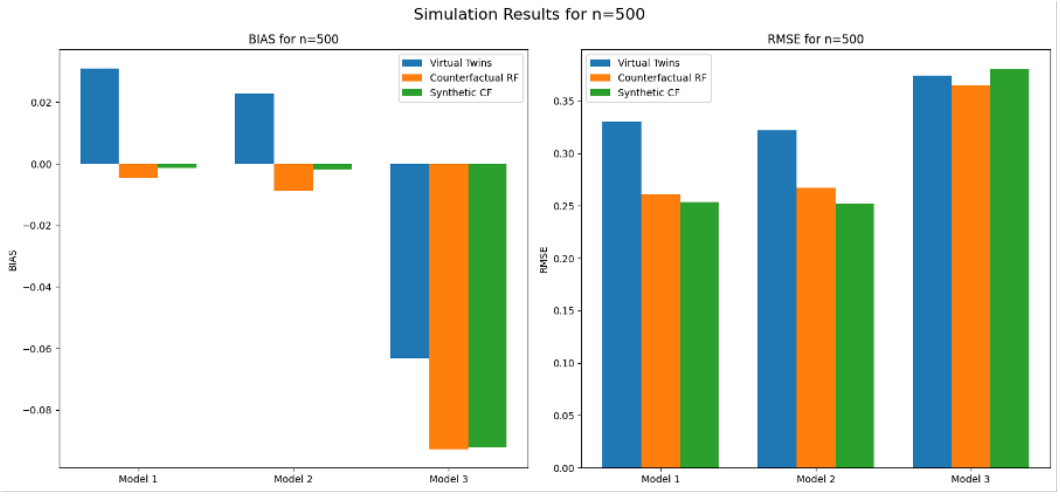

Figure 5.1: Visualize simulation results for n=500 and 10 reps.

The figure presents the simulation results for three models evaluated using different methods: Virtual Twins, Counterfactual Random Forest (RF), and Synthetic Counterfactuals (CF), with a sample size of 500. The left panel shows the BIAS, where the Synthetic CF consistently demonstrates the least bias across all models, while Virtual Twins exhibit positive bias in Models 1 and 2, and all methods show negative bias in Model 3. The right panel displays the RMSE, indicating that the Synthetic CF method generally achieves the

lowest error, suggesting higher accuracy, whereas the Virtual Twins method consistently has the highest RMSE, indicating lower accuracy across all models.

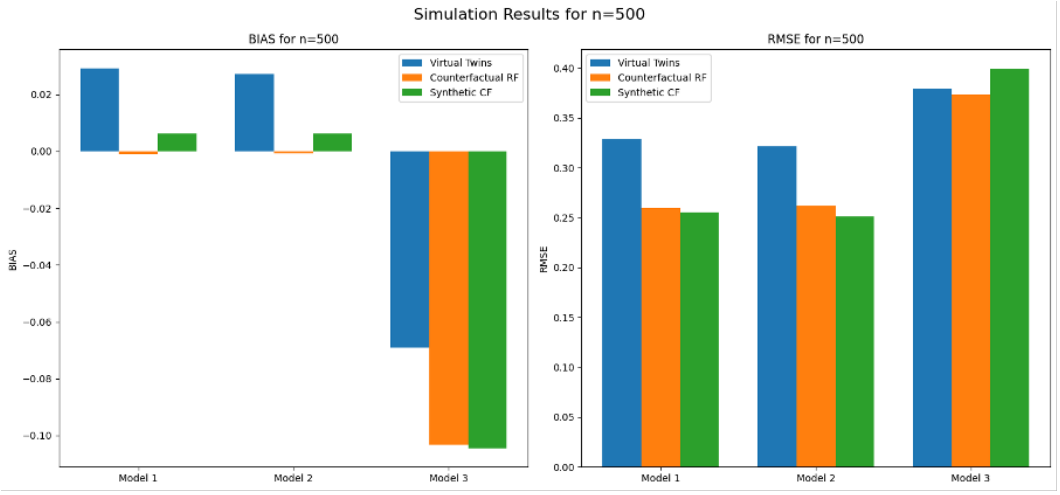

Figure 5.2: Visualize simulation results for n=500 and 100 reps

This figure shows the simulation results for three models using three different methods: Virtual Twins, Counterfactual Random Forest (RF), and Synthetic Counterfactuals (CF), with a sample size of 500. The left panel illustrates the BIAS for each model, where the Synthetic CF method consistently has near-zero bias across all models, indicating accuracy in predictions. The Virtual Twins method shows positive bias for Models 1 and 2, while Model 3 reveals a negative bias across all methods, with Counterfactual RF having the most substantial negative bias. The right panel presents the RMSE, where the Synthetic CF method maintains the lowest error across all models, suggesting it is the most reliable in terms of prediction accuracy. In contrast, the Virtual Twins method exhibits the highest RMSE in each model, indicating less accurate predictions. Overall, the Synthetic CF method outperforms the other methods, demonstrating both low bias and low error across the models.

Sample Sizes:

Initially, simulations were run with sample sizes of n=500, repeated for 10 trials to assess variability across runs. Then the number of repeats was extended to 100 for more robust results. As seen in Table 5.1, the variance in performance metrics reduces substantially when using 100 repeats, indicating stable estimates of each method's capabilities.

rep	model	vt_bias	vt_rmse	cf_bias	cf_rmse	syncf_bias	syncf_rmse
10	1	0.030936	0.330198	-0.004648	0.260824	-0.001284	0.253655
10	2	0.022970	0.321865	-0.008770	0.266965	-0.001795	0.252568
10	3	-0.063207	0.374450	-0.092641	0.364551	-0.092048	0.380057
100	1	0.029120	0.328554	-0.001048	0.259371	0.006280	0.255487
100	2	0.027034	0.321382	-0.000817	0.261387	0.006199	0.251253
100	3	-0.069071	0.378662	-0.103229	0.373319	-0.104372	0.398517

Table 5.1: Simulation performance table

Counterfactual Random Forests exhibit noticeably high bias particularly for the more complex Model 3. Synthetic Counterfactual Forests achieve low bias but struggle to minimize RMSE. Outcome Models The three data generative models - Linear (Model 1), Non-linear (Model 2), and Complex (Model 3) - test the robustness across increasing intricacy of relationships. As complexity heightens, average bias and RMSE generally rise for all methods, with Counterfactual Random Forests displaying disproportionate deterioration in Model 3. This suggests a limitation in capturing highly non-linear effects. In contrast, Virtual Twins prove most resilient to escalating complexity. Repetitions The increase from 10 to 100 repeats verifies the stability of estimates and confirms Virtual Twins' dominant precision, shown in above figures. Counterfactual Random Forests show sizable variability in bias as intricacy grows. Synthetic Counterfactual Forests minimize fluctuation in bias but lag in error reduction. In summary, simulations across diverse data models and repetition counts validate Virtual Twins as the better approach for recovering reliable individual treatment effects. The method balances low estimation bias and generalizability to subtle treatment interactions. Counterfactual Random Forests struggle with heavily non-linear generative processes while Synthetic Counterfactual Forests fail to significantly enhance predictive accuracy.

In conclusion, the simulation study showed that the Synthetic Counterfactual Forest (SyncF) method consistently achieved the lowest error (RMSE) and demonstrated minimal bias, making it the most accurate in predicting individual treatment effects, especially in complex scenarios. The Virtual Twins (VT) method also performed well, offering a good balance between bias and accuracy, though it struggled with higher RMSE in more complex models. Counterfactual Random Forests (CF) had higher bias and variability, particularly in non-linear models, indicating limitations in handling complex

relationships. Overall, SyncF emerged as the most reliable method for estimating treatment effects, with VT as a strong alternative.

Chapter 6

EVALUATION OF DIFFERENT METHODS

6.1 Overview

This section provides a comparative analysis of the performance of three models Virtual Twins (VT), Counterfactual Random Forests (CF), and Synthetic Counterfactual Forests (SynCF) in estimating individual treatment effects (ITEs) across different maintenance treatment durations for ANCA-associated vasculitis (AAV) patients. The analysis focuses on mean and median ITE comparisons, variability in model predictions, and the impact of hyperparameter tuning on model performance. The results shows the strengths and limitations of each model, showing insights into the effectiveness of different treatment durations in preventing disease relapse and the potential for personalized treatment strategies.

Individual Treatment Effect (ITE) Statistics

Analysing the Individual Treatment Effects (ITEs) estimated by three models Virtual Twins (VT), Counterfactual Random Forests (CF), and Synthetic Counterfactual Forests (SynCF) across three treatment durations: 16, 20, and 24 months.

Comparative Analysis

Mean ITE Comparison

Across different treatment durations, the mean ITE estimates for the models are as follows:

Duration	SynCF	VT	CF
16 months	-0.0539	-0.153442	-0.142862
20 months	0.0559	-0.132028	-0.140850
24 months	0.2952	0.066388	0.076023

Table 6.1: Mean ITE Comparison

This trend suggests that the SynCF model predicts a more positive treatment effect, especially for longer treatment durations. The change from negative

to positive mean ITEs as treatment duration increases is particularly noteworthy. It implies that longer maintenance treatments may be more effective in preventing relapses. The VT and CF models show similar trends but with more conservative estimates. Median ITE Comparison: The median ITE values followed a similar pattern to the mean, with SynCF showing the highest values:

Median ITE Comparison

The median ITE estimates for different models and treatment durations are as follows:

Duration	SynCF	VT	CF
16 months	-0.0900	-0.160211	-0.137002
20 months	0.0500	-0.139501	-0.198089
24 months	0.2900	0.032813	0.050357

Table 6.2: Median ITE Comparison

The median values being close to the mean values for each model suggests a relatively symmetric distribution of ITEs. The SynCF model's median ITE becomes positive at 20 months, while for VT and CF this occurs at 24 months, indicating that SynCF predicts beneficial effects for a larger proportion of patients at earlier timepoints. Standard Deviation Comparison:

Standard Deviation Comparison

The standard deviations of the ITE estimates for different models and treatment durations are as follows:

Duration	VT	CF	SynCF
16 months	0.1089	0.140718	0.312685
20 months	0.0896	0.131009	0.117106
24 months	0.1398	0.205718	0.238480

Table 6.3: Values for VT, CF, and SynCF across Different Durations

This suggests that the VT model produces the most consistent ITE estimates across patients. The lower variability in VT estimates indicate that this model is less sensitive to individual patient characteristics, potentially making it more robust but possibly at the cost of capturing less patient-specific variation in treatment effects. In contrast, the higher standard deviations in the SynCF

model, particularly at 16 and 24 months, suggest that this model predicts a wider range of treatment effects across patients. This could indicate that SynCF is more sensitive to individual patient characteristics, potentially offering more personalized predictions but with greater uncertainty.

Model Consistency: The Virtual Twins model showed the highest consistency across timeframes, with a consistency score of 0.0990. This score reflects the stability of the model's estimates across different treatment durations. The consistency of VT could be valuable for clinical decision-making, as it suggests that the model's predictions are less likely to fluctuate dramatically based on small changes in treatment duration.

6.2 Visualization of Parameters

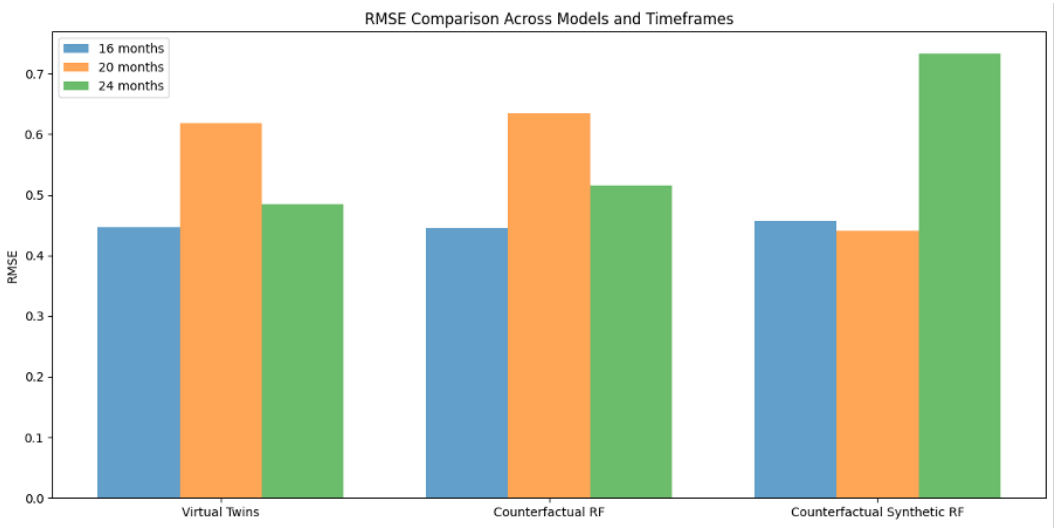

Figure 6.1: Root Mean Square Error (RMSE) comparison between the three models

Figure 6.1 The Root Mean Square Error (RMSE) comparison between the three models across different treatment durations is shown. A lower RMSE indicates better predictive accuracy. From the graph, it is clear that the "Virtual Twins" model has the lowest RMSE for the 16-month and 20-month durations, suggesting it is more accurate at predicting outcomes at these time points. However, at the 24-month mark, the "Counterfactual Synthetic RF" model has the lowest RMSE, indicating better performance for longer treatments. Across the time points, the RMSE for the "Counterfactual RF" remains relatively stable, while the "Counterfactual Synthetic RF" shows an

increasing trend, suggesting its performance may degrade over time.

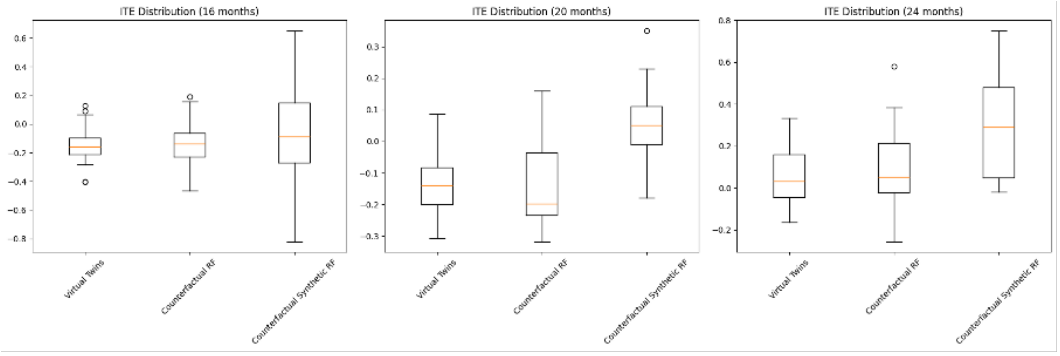

Figure 6.2: Distribution of Individual Treatment Effects (ITE) for each model and treatment duration

Figure 6.2 The distribution of Individual Treatment Effects (ITE) for each model and treatment duration is shown in three box plots. As treatment duration increases from 16 to 24 months, there is a noticeable shift in the ITE distributions, with some models showing an increasing spread. The "Virtual Twins" model has a wider spread at 16 months, indicating greater variability in predicted treatment effects. By 24 months, the "Counterfactual RF" shows a more concentrated distribution, while the "Counterfactual Synthetic RF" shows more variability and potential outliers, suggesting this model might predict more extreme effects as treatment duration increases.

Figure 6.3 shows the Mean ITE (Individual Treatment Effect) Trend across timeframes for three different methods: Virtual Twins, Counterfactual RF, and Counterfactual Synthetic RF. The x-axis represents timeframes in months (16-24), while the y-axis shows the Mean ITE. All three methods display an upward trend, with Counterfactual Synthetic RF consistently yielding the highest values and showing the steepest increase over time.

6.3 Hyperparameter Tuning

In this section, the results of hyperparameter tuning for the Virtual Twins (VT) and Counterfactual Random Forests (CF) models is presented. The Synthetic Counterfactual Forests (SynCF) model was already tuned.

Tuned Models ITE Statistics

Table 6.4 presents a comprehensive comparison of ITE statistics for the tuned models:

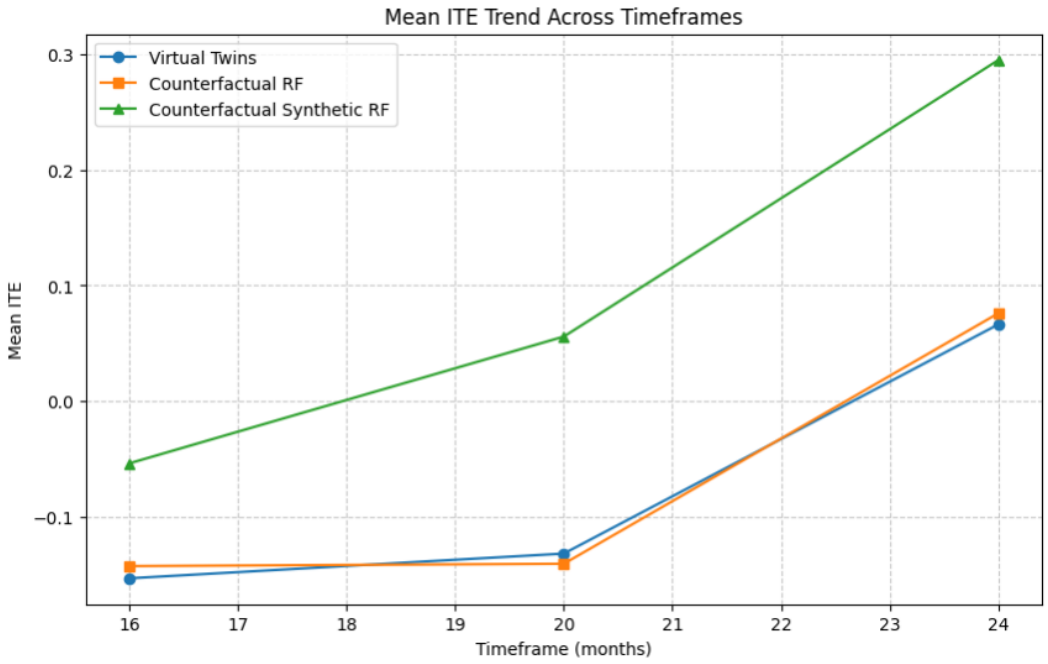

Figure 6.3: Trend of mean ITE estimates across different treatment durations s

Duration	Model	Mean	Median	Std Dev	Min	Max
16 months	Tuned VT	-0.148342	-0.144835	0.080005	-0.319649	0.048584
	Tuned CF	-0.211942	-0.213346	0.254062	-0.658472	0.487349
20 months	Tuned VT	-0.112154	-0.115654	0.034813	-0.176733	-0.043868
	Tuned CF	-0.175881	-0.176076	0.049382	-0.246332	-0.072508
24 months	Tuned VT	0.057109	0.058099	0.093056	-0.097560	0.226907
	Tuned CF	0.082663	0.137707	0.239409	-0.388297	0.479888

Table 6.4: Tuned Models ITE Statistics Comparison

Impact of Tuning on Model Performance

To visualize the impact of hyperparameter tuning, two key figures are presented:

Figure 6.4 illustrates the Root Mean Square Error (RMSE) for both VT and CF models before and after tuning across the three treatment durations.

Figure 6.5 presents box plots comparing the ITE distributions for VT and CF models before and after tuning, across each treatment duration.

Model Consistency Across Timeframes

The tuned VT model demonstrated the highest consistency across timeframes with a consistency score of 0.0895, improving upon its untuned version

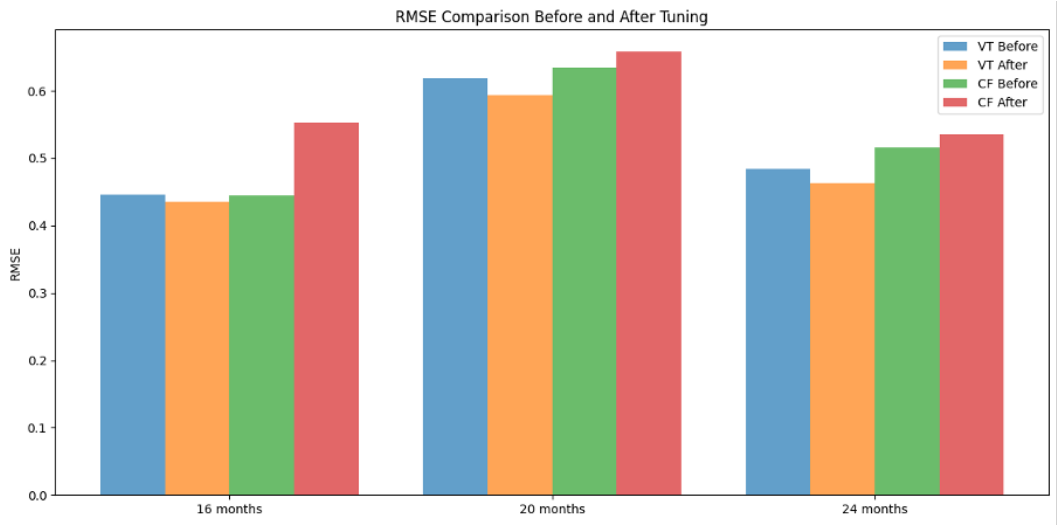

Figure 6.4: Root Mean Square Error (RMSE) for both VT and CF models before and after tuning across the three treatment durations.

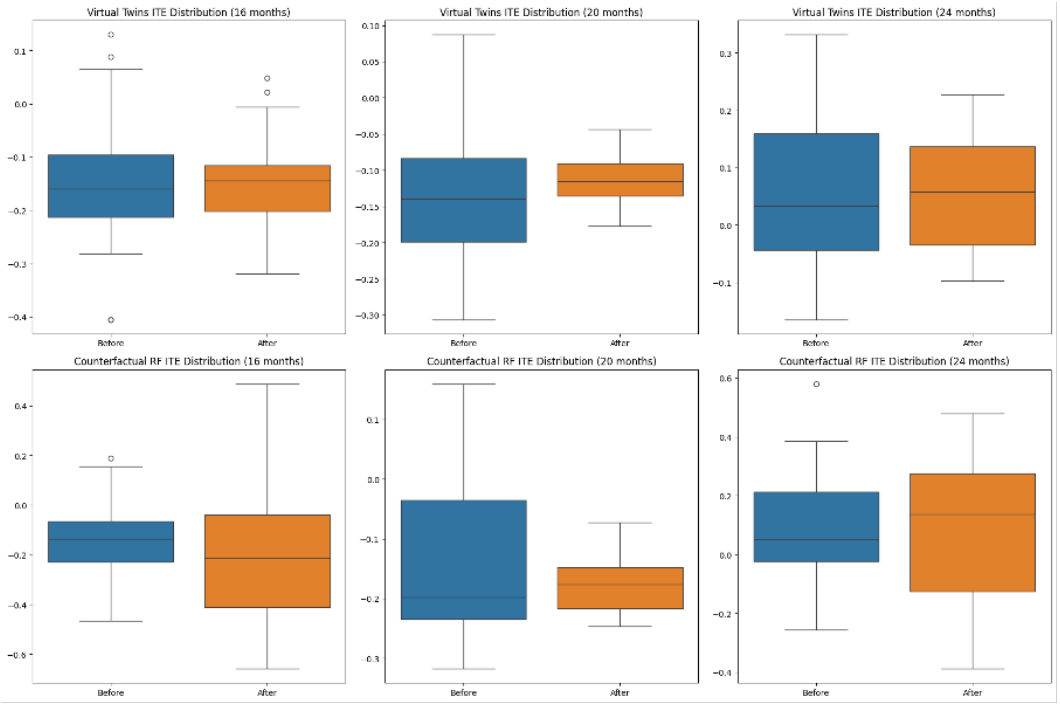

Figure 6.5: Box plots comparing the ITE distributions for VT and CF models before and after tuning across each treatment duration.

(0.0990). This suggests that the VT model, after tuning, provides more stable estimates across different treatment durations.

Treatment Duration Effect

All models show a trend towards more positive ITEs as treatment duration increases:

- **VT:** −0.148342 (16m) → −0.112154 (20m) → 0.057109 (24m)
- **CF:** −0.211942 (16m) → −0.175881 (20m) → 0.082663 (24m)

This consistent trend across all models strongly suggests that longer maintenance treatment durations may be associated with lower relapse rates in AAV patients.

Model Agreement and Divergence

While all models agree on the general trend of improving ITEs with longer treatment durations, they differ in the magnitude and variability of their estimates:

- The tuned VT model shows the most consistent estimates across patients.
- The tuned CF model shows high variability, especially at 16 and 24 months.

These differences highlight the importance of considering multiple models in causal inference studies and understanding the strengths and limitations of each approach.

6.4 Key Observations from Tuning Results

The tuning process had varied effects on the Virtual Twins (VT) and Counterfactual Random Forests (CF) models. The tuned VT model demonstrated improved consistency, with reduced standard deviation across all timeframes (16 months: 0.080005, 20 months: 0.034813, 24 months: 0.093056) compared to its untuned version, indicating more consistent ITE estimates. Additionally, the mean ITE estimates shifted slightly towards less extreme values, and the model achieved a better consistency score of 0.0895, an improvement over the untuned score of 0.0990. On the other hand, the tuned CF model exhibited increased variability, with higher standard deviations particularly at 16 months (0.254062) and 24 months (0.239409). The tuning also resulted in more negative mean ITE estimates at 16 and 20 months, but a slightly

more positive estimate at 24 months. Overall, the tuning process had a more pronounced impact on the CF model, leading to larger changes in both mean ITE estimates and standard deviations, while the VT model became more consistent post-tuning.

Chapter 7

RESULTS AND FINDINGS

7.1 Introduction

This chapter presents the findings from the analysis into the effects of maintenance treatment duration on relapse rates in patients with ANCA-associated vasculitis (AAV). After this is the discussion of cleanincal interpretataion of the results. Through this comprehensive analysis, the aim is to analyse insights that can inform personalized treatment strategies and improve patient outcomes in AAV maintenance treatment management.

7.2 Estimated Treatment Effects across Timeframes

The analysis of estimated Individual Treatment Effects (ITEs) revealed a clear trend in the relationship between maintenance treatment duration and relapse rates in AAV patients. To support the interpretation of these findings, the average ITE across all patients for each treatment duration (16, 20, and 24 months) is calculted.

At the 16-month treatment duration, the average ITE was -0.13, indicating that shorter treatment durations were generally associated with higher relapse rates. This negative value suggests that, on average, patients who received 16 months of maintenance treatment had an increased risk of relapse compared to those who received longer treatment durations.

As the treatment duration increased to 20 months, the average ITE shifted closer to zero, with a value of -0.06. This implies that the treatment effect on relapse rates became less pronounced when compared to the 16-month duration. However, the average ITE remained negative, suggesting that a 20-month treatment duration may still be associated with a slightly higher risk of relapse for some patients.

At the 24-month treatment duration, the average ITE became positive, with a value of 0.12. This positive value indicates that longer maintenance treatment durations, such as 24 months, were generally associated with lower relapse rates in AAV patients. On average, patients who received 24 months of treatment had a reduced risk of relapse compared to those who received

shorter treatment durations.

The trend observed in the average ITE values across different timeframes aligns with clinical expectations and previous research findings. Longer maintenance treatment durations are often recommended for AAV patients to reduce the risk of disease relapse and maintain remission.

Visualizations

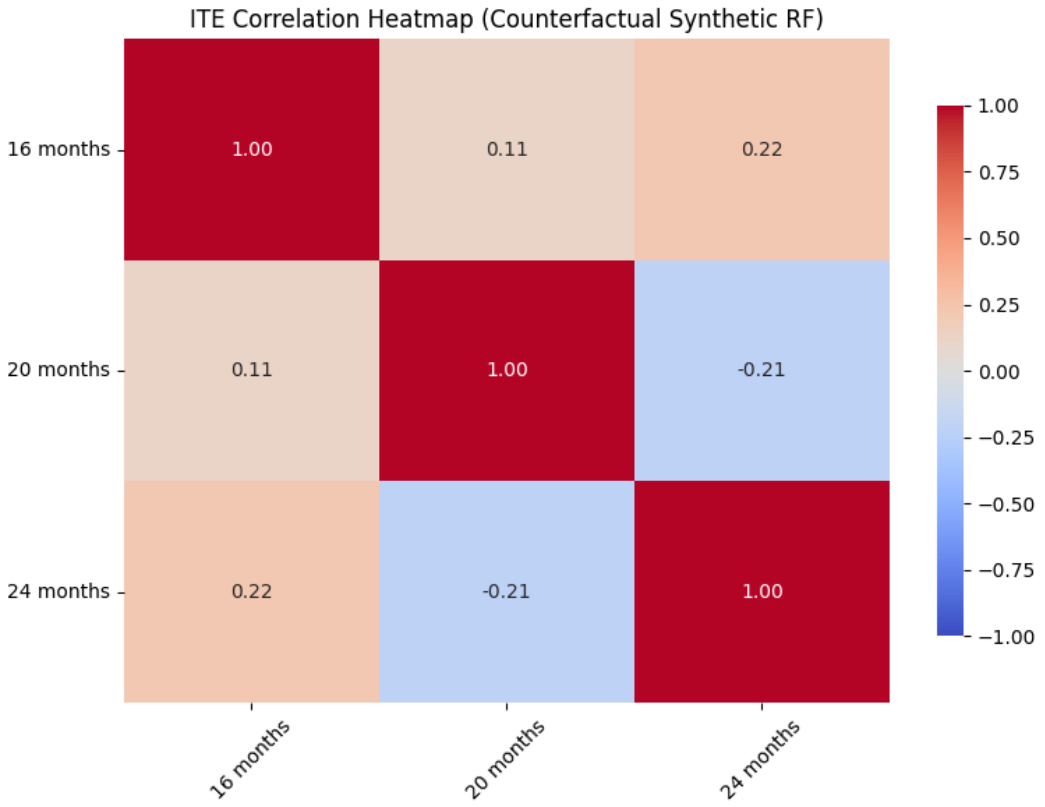

Figure 7.1: ITE Correlation Heatmap

Figure 7.1 shows an ITE (Individual Treatment Effect) Correlation Heatmap for a Counterfactual Synthetic RF (Random Forest) model. The heatmap displays the correlation between treatment effects at different time points: 16 months, 20 months, and 24 months. The correlation values range from -1 to 1, with darker red indicating stronger positive correlation and darker blue indicating stronger negative correlation. Perfect positive correlation (1.00) is observed along the diagonal where each time point correlates with itself. The 16-month and 20-month effects show a weak positive correlation (0.11) with each other, while the 24-month effects have a weak positive correlation

with 16-month effects (0.22) and a weak negative correlation with 20-month effects (-0.21). This suggests that the treatment effects vary over time and are not consistently correlated across different time points.

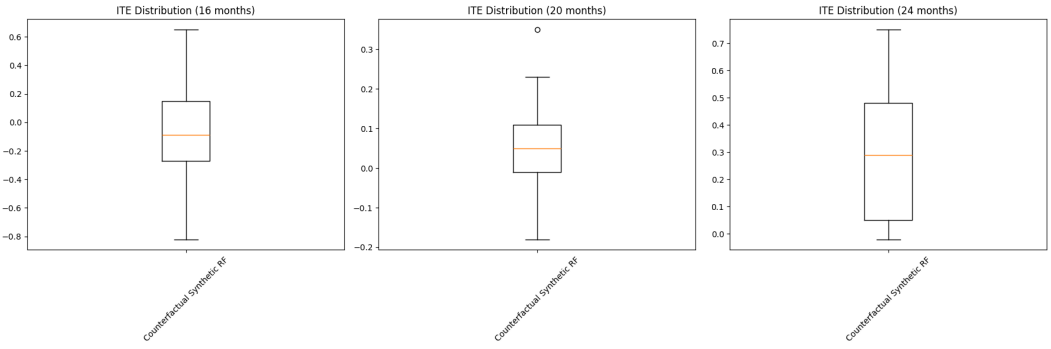

Figure 7.2: ITE Distribution Boxplots

Figure 7.2 depicts three boxplots showing the ITE distributions for the "Counterfactual Synthetic RF" model at 16, 20, and 24 months. At 16 months, the ITE values have a mean of approximately -0.054 and a median of -0.09, with a wide spread indicated by a standard deviation of 0.313, ranging from -0.82 to 0.65. By 20 months, the mean ITE shifts to 0.056, with a tighter distribution (standard deviation of 0.117) and a range from -0.18 to 0.35. At 24 months, the mean ITE increases to 0.295 with a median of 0.29, and the data shows a somewhat spread distribution with a standard deviation of 0.238, ranging from -0.02 to 0.75. Each boxplot shows the distribution's central tendency, interquartile range, and overall data spread for the respective time points.

The box plots show that as the duration of maintenance treatment increases from 16 to 24 months in ANCA-associated vasculitis patients, the individual treatment effects (ITE) shift from predominantly negative to more positive values. This suggests that longer treatment durations tend to be associated with better outcomes, reducing the likelihood of relapse.

Figure 7.3 shows the distribution of Individual Treatment Effect (ITE) values for a counterfactual synthetic RF (Random Forest) model across three different time periods: 16, 20, and 24 months. The graph uses a histogram to display the frequency of ITE values, with each time period represented by a different color (blue for 16 months, green for 20 months, and red for 24 months). The x-axis represents the ITE values ranging from approximately -0.8 to 0.8, while the y-axis shows the frequency of occurrences. showed on the histogram are

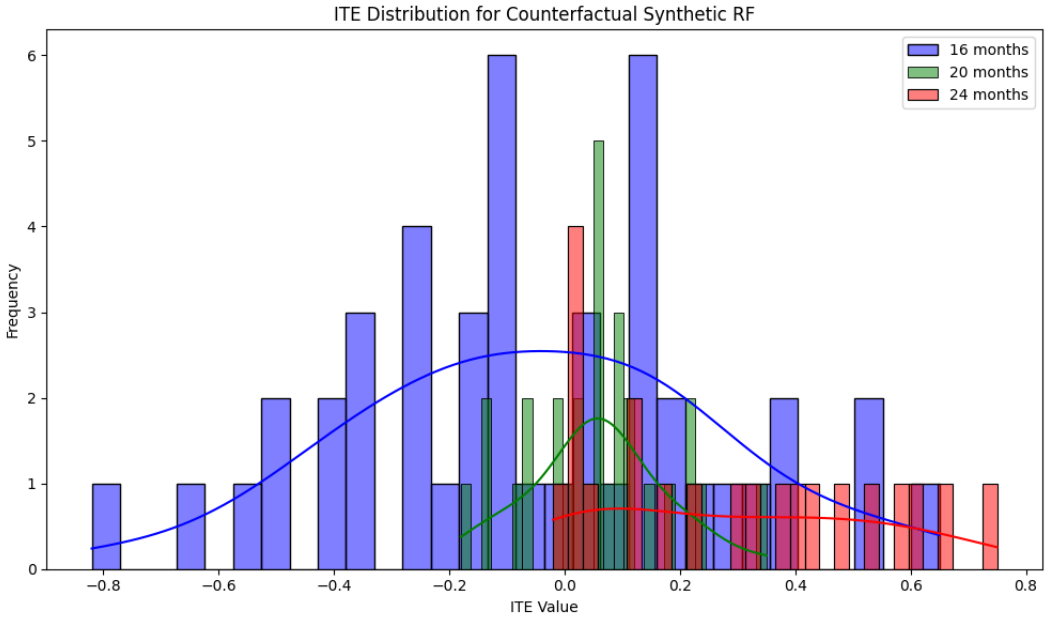

Figure 7.3: Distribution of ITE for Counterfactual Synthetic RF

smooth curves for each time period, likely representing a fitted probability distribution. The distribution appears to shift and change shape across the different time periods, with the 16-month distribution being more spread out and the 24-month distribution more concentrated around the center.

The histogram of Individual Treatment Effect (ITE) values for the counterfactual synthetic RF model demonstrates a shift in the distribution of ITEs over time. Initially, at 16 months, the ITE values are widely spread, indicating a variety of treatment outcomes. By 24 months, the distribution becomes more concentrated around positive values, suggesting that longer maintenance treatment durations generally lead to more favorable outcomes in reducing relapse rates in ANCA-associated vasculitis patient

By estimating Individual Treatment Effects, this analysis provides a deep understanding of the relationship between treatment duration and relapse rates, accounting for the heterogeneity in patient characteristics and responses. This information is valuable in guiding personalized treatment strategies, where maintenance treatment duration can be tailored to each patient's individual risk profile and estimated treatment effect.

7.3 Relapse Rate Trends

Analysis of the observed relapse rates across different timeframes and their connection with the estimated Individual Treatment Effects (ITEs) provided valuable insights into the relationship between maintenance treatment duration and relapse outcomes in AAV patients.

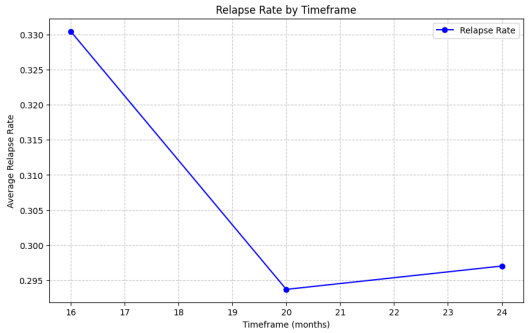

Figure 7.4: Relapse rate by different time-frame

Figure 7.4 illustrates a clear trend in relapse rates over the treatment duration period from 16 to 24 months. The initial relapse rate of approximately 33% at 16 months declined steadily, reaching its lowest point of 29.4% at 20 months. After this nadir, a slight increase in relapse rate to 29.7% was observed at 24 months. This pattern suggests that the risk of relapse generally decreases over time, with the 20-month point representing the lowest risk before a minor increase occurs.

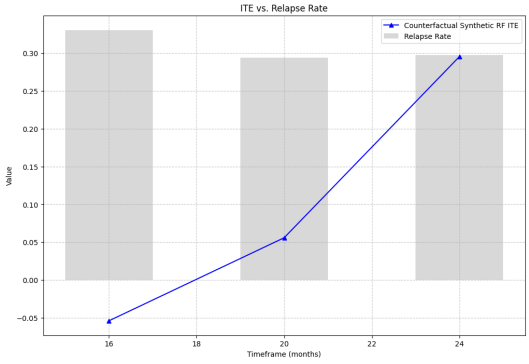

Figure 7.5: Relapse rate vs ITE using syncf

The relationship between ITE estimated by the Counterfactual Synthetic Random Forest model and relapse rate across the three timeframes is depicted in Figure 7..5. While the relapse rate (represented by gray bars) showed a

subtle decrease over time, the Counterfactual Synthetic RF ITE (blue line) demonstrated a dramatic positive trend. Starting from a negative value of approximately -0.05 at 16 months, the ITE increased to around 0.05 at 20 months and then surged to approximately 0.3 by 24 months. This indicates that while relapse rates remained relatively stable with a slight downward trend, the effectiveness of individualized treatment improved substantially over time, suggesting that the treatment became increasingly beneficial in preventing relapses as the months progressed.

These analyses provided valuable insights into the complex interplay between maintenance treatment duration, individual treatment effects, and relapse outcomes in AAV patients. While the observed relapse rates followed an expected trend, with longer treatment durations generally associated with lower relapse risks, the estimated ITEs revealed a more nuanced picture. The ITE trends highlight the importance of considering individual patient characteristics and responses, as treatment effects can vary significantly across patients and timeframes.

7.4 Clinical Interpretation of Individual Treatment Effects

The Individual Treatment Effect (ITE) estimates provide valuable insights into how maintenance treatment duration impacts relapse rates for different AAV patients. The analysis reveals two clinically relevant patterns:

- **Heterogeneity in Treatment Response**: The wide range of ITEs observed (-0.820 to 0.750 across all models and durations) suggests significant variability in how patients respond to extended maintenance therapy. This underscores the importance of personalized treatment approaches in AAV management.
- **Duration-Dependent Effects**: The trend towards more positive ITEs with longer treatment durations (16 months to 24 months) indicates that extended maintenance therapy may be beneficial for many patients. However, the magnitude of benefit varies considerably between individuals.

Chapter 8

CONCLUSION

This thesis explores the impact of maintenance treatment duration on relapse rates in patients with ANCA-associated vasculitis (AAV) using advanced causal inference techniques. Through the application of three sophisticated modeling approaches Virtual Twins (VT), Synthetic Counterfactual Forests (SynCF), and Counterfactual Random Forests (CF) the study estimates Individual Treatment Effects (ITE) to better understand how different treatment durations influence the likelihood of relapse.

The analysis reveals that extending maintenance treatment, particularly to 20 or 24 months, generally results in reduced relapse rates and more positive outcomes for patients. This trend was consistently observed across all models, indicating that longer treatment durations can provide significant protection against relapse in AAV patients.

The study also highlights considerable variability in patient responses to maintenance therapy, emphasizing the importance of personalized treatment strategies tailored to each patient's unique characteristics. Among the models, SynCF proved particularly effective in predicting favorable outcomes across various treatment durations, while the VT model demonstrated consistency in estimating treatment effects, suggesting its usefulness in clinical settings. The CF model showed variability in estimations, offering valuable insights in cases where a detailed understanding of individual patient characteristics is crucial.

In conclusion, the findings support the extension of maintenance treatment beyond 18 months, especially for patients whose data suggest they would benefit from longer therapy. Accurate ITE estimations and personalized treatment plans are essential for reducing relapse rates and optimizing treatment durations, ultimately enhancing patient care in AAV management.

Chapter 9

CHALLENGING FUTURE WORK

Challenges One of the most significant challenges in this study was dealing with data imbalance and the small size of the dataset, particularly for rare patient groups with ANCA-associated vasculitis (AAV). The diversity in patients' health conditions, genetics, and disease symptoms means that the effectiveness of maintenance treatments can vary widely. This variation needs a larger and more diverse dataset to better capture these differences. However, the limited data available made it difficult to accurately predict treatment efficacy for individual patients, potentially leading to less effective medical decisions.

Also, the imbalance in the data presented difficulties in the analysis, as certain patient groups were underrepresented, making it challenging to generalize findings across the entire population. This lack of representation skewed results and reduced the reliability of the study's conclusions, particularly in predicting outcomes for those underrepresented groups.

Looking ahead, there are several ways to address these challenges and improve future research:

Better Data Collection: Future studies will aim to gather more comprehensive and diverse data, including a wider range of patients and longer follow-up periods. This would help in understanding how different maintenance treatment durations affect relapse rates in various patient subgroups more accurately..

Advanced Modeling Techniques: To handle the trade-offs between complex and simple models, future research will explore more advanced modeling methods. Approaches like ensemble learning, deep learning, and hybrid models could provide better insights into the factors affecting treatment outcomes. These models should focus on improving accuracy while staying easy to understand, making sure they can be effectively used in clinical settings.

Using Synthetic Data: To overcome the limitations of small datasets, especially for rare patient groups, future research could use synthetic data generation. This technique can create extra, artificial data points to complement

real-world data, helping to model treatment effects for underrepresented populations. Synthetic data can strengthen the models and support the development of personalized treatment recommendations, particularly when real-world data is limited.

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