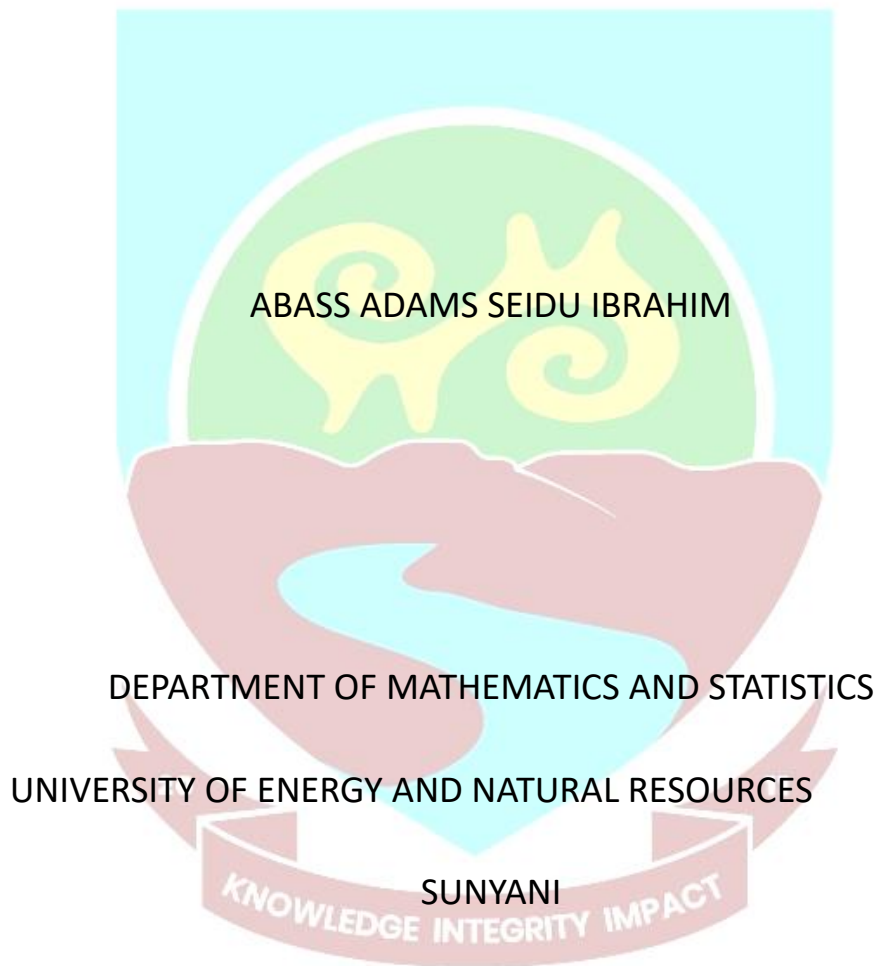
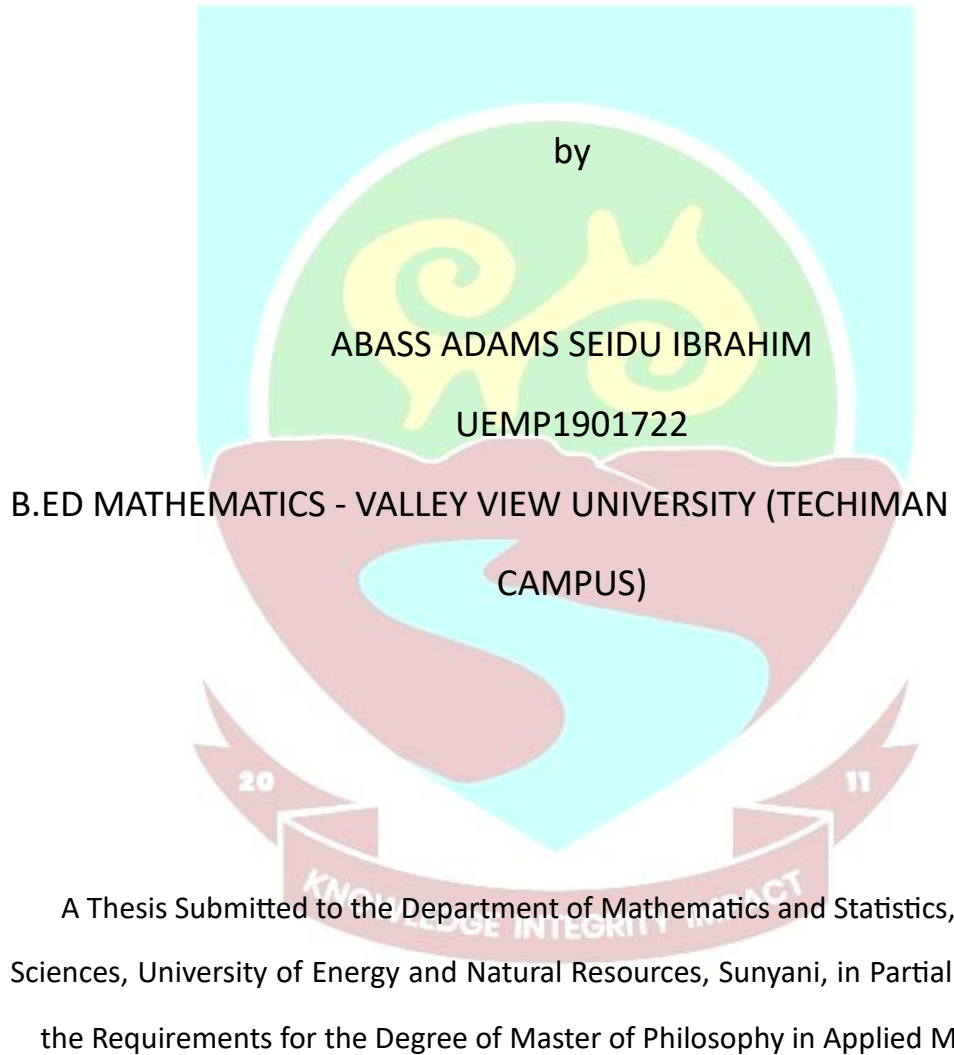


JOINT MODEL FOR CD4 COUNT MEASUREMENTS AND
TIME-TO-FIRST OCCURRENCE OF HOSPITALIZATION AND
DEATH AMONG HIV AND TUBERCULOSIS PERICARDITIS
PATIENTS



2025

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September, 2025

Declaration

I, ABASS ADAMS, Seidu Ibrahim (UEMP1901722), hereby declare that the study was conducted and written by me, and all sources of information are acknowledged and that I am solely responsible for any actions that may violate the research ethics policies of the university.

.....
Candidate's Signature
Supervisor's Certification
Date

This study was conducted under the guidance of Dr. Abdul-Karim Iddrisu and Prof. Dominic Otoo in accordance with the supervision of the Graduate Program guidelines.

Main Supervisor: Abdul-Karim Iddrisu (PhD)

Signature: Date

Co-Supervisor: Prof. Dominic Otoo

Signature: Date:

Head of Department: Prof. Elvis Kwabena Donkor

Signature: Date:

Abstract

This study investigated the effects of Mycobacterium immunotherapy (M.w) and timevarying CD4 counts on survival outcomes, specifically the time to first hospitalization and death, in patients with HIV and tuberculosis (TB) pericarditis. Joint modeling techniques were used to integrate longitudinal CD4 measurements and survival data, adjusting for factors like age, gender, and antiretroviral therapy (ART) status. The analysis was conducted using linear mixed effects models and the Cox proportional hazards model, and the best model was selected based on performance criteria. The results showed that M.w treatment did not significantly impact the risk of death with a hazard ratio (HR = 0.404) or hospitalization (HR = 0.014) compared to placebo. However, a one-unit increase in CD4 count was associated with a 2% reduction in the risk of death and hospitalization.

Older patients (46+ years) had a higher risk of death (HR = 7.510), while ART use with (HR = 0.169) and heart rates above 100 beats per minute (HR = 0.064) were associated with reduced mortality risk. In conclusion, M.w treatment had no significant effect on survival outcomes, but higher CD4 counts, ART use, and heart rate were key predictors of reduced death risk.

Keywords: Joint modeling, CD4 count, HIV, Tuberculosis pericarditis, Survival analysis, Mycobacterium indicus pranii

Key implications for stakeholders: Results suggest integrating serial immunological markers (CD4 trends) into patient risk stratification and highlight the need for cautious evaluation of adjunctive immunotherapy (M.w).

Dedication

I dedicate this research to my supervisor, Dr. Abdul-Karim Iddrisu, my late father, Alhaji Seidu Basawti (Ouattara Chamogo), my mother, Meri, my wife and siblings for their support and wishes for my success in this university. I also dedicated it to all those who contributed equally to the success of this thesis.



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My first and foremost expression of gratitude and appreciation is directed towards the Almighty Allah, whose infinite strength, profound wisdom, extensive knowledge, and deep understanding have been generously bestowed upon me, enabling me to successfully develop and articulate this thesis, as well as providing me with the necessary support to navigate and complete the rigorous demands of this two-year academic program.

I would like to express my sincere gratitude to my respected lecturer and supervisor, Abdul-Karim Iddrisu (PhD), whose invaluable suggestions, unwavering encouragement, and insightful discussions during the meticulous preparation of this thesis have been instrumental in transforming this endeavor into a successful academic contribution; may the Almighty Allah bestow His abundant blessings upon you for your profound impact on my scholarly journey.

Furthermore, I feel compelled to acknowledge the Head of the Department, Elvis Kwabena Donkor (Prof.), along with all the dedicated lecturers.

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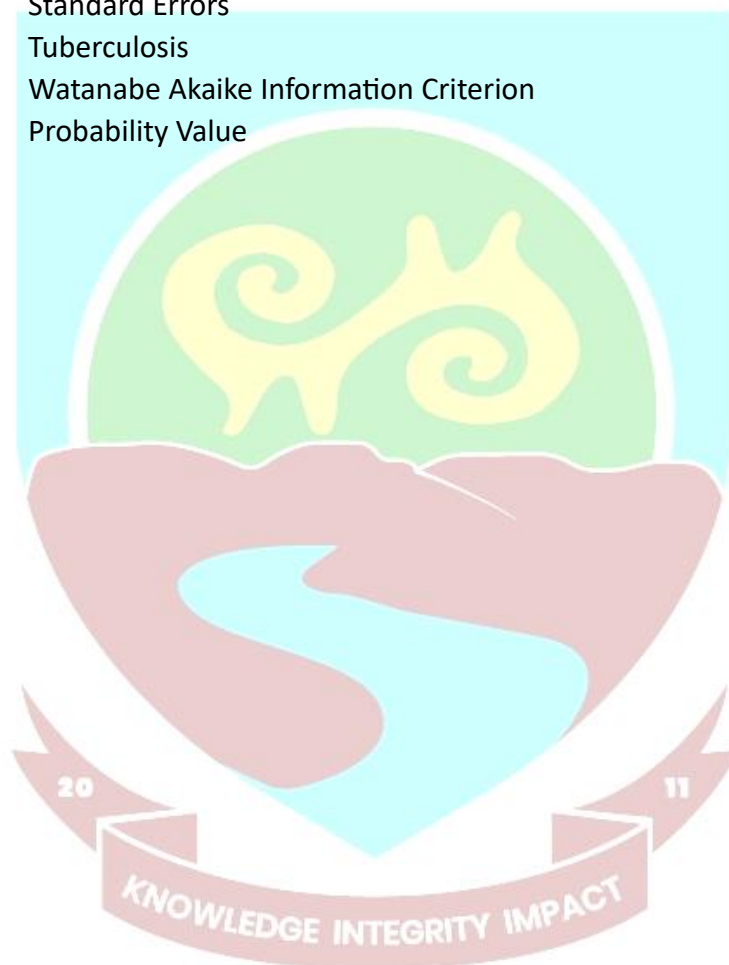
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List of Acronyms And Abbreviations

AFT	Accelerated Failure Time
ART	Antiretroviral Therapy
AR	Acute Rejection
C.L	Confidence Intervals
Cox-PH	Cox Proportional Hazard
DIC	Deviance Information Criterion
Est.	Estimate
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IMPI	Investigation of the Management of Pericarditis
JM	Joint Model
MAR	Missing At Random

MIP	Mycobacterium Induced Protein/Macrophage Inflammatory Protein
M.w	Mycobacterium indicus pranii
PCa	Prostate Cancer
PH	Proportional Hazard
PSA	Prostate-Specific Antigen
RDW	Red blood cell Distribution Width
S.E	Standard Errors
TB	Tuberculosis
WAIC	Watanabe Akaike Information Criterion
P-Value	Probability Value



Chapter 1 Introduction

1.1 Background of the Study

In various empirical research methodologies, it is of paramount importance to meticulously observe the study participants within a distinctly defined temporal framework, as this practice is essential for effectively identifying and understanding the patterns and transformations associated with the specific outcome of interest, which facilitates a comprehensive understanding of its progression over time. Such elaborate study designs are particularly prevalent in academic disciplines such as biostatistics and medical research, where they are specifically categorized as longitudinal study designs (Abdul-Karim & Gumedze; 2019a, 2019b, 2019c; Carpenter et al., 2013; Abdul-Karim et al., 2024; Iddrisu, 2019). Within the structured framework of longitudinal study designs, which are routinely applied in contexts characterized by repeated measures, data pertaining to a specific response variable is systematically collected at predetermined intervals during designated visits, thereby ensuring the development of a robust longitudinal dataset that can be leveraged for analytical endeavors.

In addition to the parameters established by these longitudinal assessments, it is also critically important within the majority of medical research contexts to meticulously document pertinent information concerning the time-to-first occurrence of significant events of interest, which may encompass a wide array of intervals, including time until death, duration until recovery from a specific illness, or the timeline for the progression to a more severe disease state, alongside other relevant metrics that may be of interest. The designation “survival data” is frequently utilized to encapsulate the overarching concept of time-to-event information (Collett, 1994, 2015a).

Indeed, the analysis of both longitudinal and survival data can be conducted independently of one another, and a considerable body of existing literature provides numerous well-established methodologies for executing such analyses with the utmost rigor and precision. Specifically, mixed effects models, Laird & Ware (1982) are employed to meticulously scrutinize the longitudinal characteristics inherent in the collected data (Abdul-Karim & Gumedze, 2019a, 2019b, 2019c; Carpenter et al., 2013; Abdul-Karim et al., 2024; Iddrisu 2019). In contrast, survival outcome are predominantly performed using Cox proportional hazards models (David et al., 1972).

However, it is essential to recognize that the trajectories or observable patterns discernible within the recurrent measurements of the response variable for individual subjects are likely to be influenced by the occurrences of the significant events under investigation, which renders these measurements endogenous in nature (Cekic et al., 2021). This particular observation posits that the measurement value recorded at a specific temporal point harbors critical information regarding the potential incidence or non-incidence of the event under scrutiny, further complicating the analytical landscape (Cekic et al., 2021).

Moreover, it is crucial to underscore that the response profile demonstrated by subjects is highly contingent upon the occurrence of the event in question; thus, the relationship between the two cannot be easily disentangled. Consequently, conducting separate analyses on longitudinal and survival data would effectively overlook the intricate and often complex relationship that exists between these two outcomes and would ultimately fail to yield meaningful insights regarding the extent and degree of association that may exist between them, thereby limiting the overall understanding of the phenomena being studied.

A highly feasible and effective approach to addressing the complex challenge posed by the integration of longitudinal and survival data is to incorporate estimated parameters that have been derived from the mixed effects model into the survival model as covariates, allowing for a more nuanced analysis of the data. However, it has been extensively and empirically established through rigorous research that this particular methodology may inadvertently result in invalid statistical inferences, predominantly due to the compounding bias that can arise in the estimation of parameters, leading to a significant loss of efficiency in the overall analysis process (Prentice, 1982; Rizopoulos, 2012a).

To adeptly navigate and mitigate this intricate issue, researchers have increasingly adopted a joint modeling approach, which enables the simultaneous analysis of results drawn from both longitudinal data and survival data, thereby enhancing the robustness of the findings (Rizopoulos; 2008, 2012a, 2014; Rizopoulos et al., 2008; Rizopoulos & Takkenberg, 2014a).

The joint modeling framework involves a sophisticated and complex evaluation process that concurrently assesses longitudinal components alongside survival components, which, as previous studies have indicated, significantly enhance performance in methodological evaluations, primarily due to its distinctive capability to assess the relative risk associated with survival outcomes while simultaneously accounting for longitudinal results (Henderson et al., 2000; Lawrence Gould et al., 2015; Papageorgio et al., 2019; Song et al., 2002; Tsiatized & David et al., 2004). This advanced modeling technique is characterized by the integration of two distinct submodels: one that is specifically designed for the longitudinal outcome and another that is tailored for the survival outcome, both of which are intricately intertwined through a complex association structure that facilitates the analysis (Alsefri et al., 2020).

A commonly utilized framework within the realm of joint modeling is the shared parameter modeling framework, which postulates that the two submodels are interconnected through common random effects, thereby establishing a link between them (Abdul-Karim & Gumedze, 2019c; Follmann & Wu, 1995; Rizopoulos et al., 2008; Terrera et al., 2011). These random effects are instrumental in elucidating subtle and intricate relationships that exist between the two submodels, as well as in uncovering correlations that manifest among repeated measurements taken over time. Within the specific context of the IMPI study, the influence of CD4 count measurements on the associated risks of death and hospitalization has been investigated using a joint model that captures both the temporal changes in CD4 count and the time to the first occurrence of death and hospitalization, a critical aspect that has not been previously explored in this research endeavor.

In the present research initiative, we have strategically implemented the joint modeling framework (Rizopoulos, 2010a, 2010b, 2016a, 2008; Rizopoulos & Takkenberg, 2014a) in order to concurrently model the continuous longitudinal measurements of CD4 count while simultaneously examining the time-to-first occurrence of death and hospitalization among patients who were randomized to receive either the mycobacterium indicus pranii (M.w) treatment or the corresponding placebo control. This particular investigation is centered on individuals who are suffering from the dual afflictions of tuberculosis pericarditis and HIV, and who were systematically randomized into distinct treatment groups to receive either the M.w intervention or its equivalent placebo treatment (Mayosi et al., 2006, 2013; Thabane et al., 2014).

1.2 Problem Statement

In the intricate sphere of academic exploration centered around the nuanced and complex interactions that exist between the Human Immunodeficiency Virus (HIV) and tuberculosis (TB) pericarditis, it becomes exceedingly vital to undertake a comprehensive examination of the diverse and multifaceted effects that both the functionality of the immune system, measured quantitatively through the assessment of CD4 counts (Laird & Ware, 1982; Rizopoulos, 2010), and the critical outcomes relating to survival, characterized by the duration until death or the necessity for hospitalization, are variably shaped by an array of therapeutic interventions and distinct patient characteristics (Bellera et al., 2010).

Traditional methodologies employed in analytical research often tend to analyze longitudinal data, with a particular focus on CD4 counts, in conjunction with survival data that specifically pertains to time-to-event outcomes, treating them as separate and isolated entities; however, this methodological stance is fraught with inefficiencies and potential biases, primarily because it inadequately captures the dynamic and interdependent relationship that inherently exists between a patient's immune response and their corresponding trajectory towards survival (Gupta et al., 2012; Tsiatis & Davidian, 2014).

For individuals who are suffering from the dual challenges posed by HIV and TB pericarditis, the quantification of CD4 counts serves not only as essential and indicative markers reflecting the overall health and functionality of the immune system but also as pivotal indicators of survival outcomes, which are principally represented by occurrences of hospitalization and death (Abdul-Karim & Gumedzi, 2019a; Celac et al., 2021).

The effectiveness of a variety of therapeutic interventions, including the administration of *Mycobacterium indicus pranii* (M.w) in conjunction with antiretroviral therapy (ART), aimed at enhancing these specific health outcomes, has not been thoroughly scrutinized within the framework of joint modeling methodologies, which are purposefully designed to amalgamate both longitudinal data and survival metrics into a cohesive analytical format (Rizopoulos, 2010; Carpenter et al., 2013).

By employing joint modeling techniques, researchers can engage in a simultaneous analytical approach that elucidates the intricate and often convoluted relationship between the time-dependent characteristics of CD4 counts and the related survival outcomes, thereby yielding estimations that are not only markedly more precise but also significantly more efficient in accurately capturing the underlying realities of the data (Thabane et al., 2014).

This particular scholarly pursuit endeavors to address a notable void that currently exists within the extant literature by utilizing advanced joint modeling strategies to analyze data obtained from the IMPI trial, a meticulously conducted study that focuses on individuals diagnosed with both HIV and tuberculous pericarditis (Iddrisu, 2019).

The overarching objective of this investigative effort is to scrutinize the impact of M.w treatment, ART, and a variety of additional confounding variables, including but not limited to demographic factors such as age and gender, on fluctuations in CD4 counts alongside the concomitant risk of death or the need for hospitalization. Through the application of joint models, this research aims to surpass the inherent limitations associated with traditional single analyzes and provide a more accurate and holistic understanding of how the trajectories of CD4 counts significantly influence the survival prospects of patients contending with these interrelated and complex diseases (Rizopoulos, 2010; Abdul-Karim & Gumedzi, 2019b).

1.3 Objectives of the Study

1.3.1 General Objective

The main objective of this study is to build an extended, multifaceted prediction model that aims to elucidate the survival outcomes experienced by patients suffering from HIV/Tuberculosis pericarditis, who have been systematically randomized into Mycobacterium Placebo treatment arms, with a keen emphasis on time-to-first occurrence of hospitalization and death.

1.3.2 Specific Objectives

The specific objectives that this paper seeks to achieve are stated as follows:

1. Determine the best joint model to fit the observed CD4 count measurements combined with the time-to the first occurrence of hospitalization and death, classified as the survival outcomes of interest in this study.
2. Investigate the effect of time-varying measures of CD4 count on the hazard ratio associated with survival outcomes in HIV-infected patients with tuberculous pericarditis randomized to mycobacterial therapy or placebo.
3. Conduct a comprehensive investigation of the influence exerted by the interaction between M.w and antiretroviral therapy (ART) on the hazard ratios corresponding to the identified survival outcomes.
4. identify the predictors that significantly contribute to the hazard ratios related to the survival outcomes, specifically focusing on hospitalization and death.

1.4 Research questions and hypotheses

For each specific objective, the following research questions and hypotheses are formulated.

Objective 1

RQ1: Which joint model specification (shared random-effects, current value, or slope parameterization) best fits the IMPI CD4 and survival data?

(No statistical hypothesis; model comparison via information criteria and predictive checks.)

Objective 2

RQ2: Is the current value (or slope) of CD4 trajectory associated with the hazard for death and hospitalization?

H0: There is no association between time-varying CD4 measurements and the hazard of the event.

H1: Higher CD4 values (or increasing CD4 slope) are associated with reduced hazard of the event.

Objective 3

RQ3: Does M.w treatment interact with ART to modify CD4 trajectory or hazards?

H0: No interaction exists between M.w and ART on CD4 trajectories or survival hazards.

H1: A significant interaction exists between M.w and ART influencing CD4 trajectories and/or hazards.

Objective 4

RQ4: What baseline or time-updated covariates predict hazard for hospitalization and death? (e.g., age group, gender, heart rate, ART status).

H0: Covariates listed do not predict hazard.

H1: One or more covariates significantly predict hazard.

It is paramount to underscore that the premise regarding the absence of CD4 count measurements is that, such data is considered to be missing at random (MAR) (Rubin, 1976, 1996). This position is corroborated by the investigations conducted by AbdulKarim & Gumedze (2019a, 2019b, 2019c), Iddrisu (2019) who illustrated through an array of sensitivity analysis methodologies that the missing CD4 count data emerges randomly.

1.5 Significance of the Study

The expected repercussions and conclusions that can be inferred from the present research are meticulously outlined as follows:

1. *Contribute crucial knowledge to the established body of literature within the academic community;*

This particular research endeavor aspires to significantly augment the existing scholarly literature regarding HIV-TB pericarditis by introducing groundbreaking data that elucidate the intricate and multifaceted relationship between various CD4 count measurements, the timing of patients' initial hospitalization, and subsequent mortality rates. The deductions made from this comprehensive analysis possess considerable potential to address and rectify the current inadequacies prevalent in the contemporary understanding of this specialized area

of study, either by challenging existing theories or by reinforcing established hypotheses. The ramifications of this investigation may profoundly affect the future trajectory of subsequent research endeavors and inquiries, thereby playing a pivotal role in the continuous advancement and refinement of this particular field of medical science.

2. *Guide healthcare practitioners and researchers towards more accurate and effective strategies aimed at the management of HIV-TB pericarditis;*

The outcomes and conclusions derived from this comprehensive study are poised to significantly contribute to the formulation of evidence-based clinical guidelines that will direct the management strategies for HIV-TB pericarditis, thereby equipping healthcare practitioners with the essential knowledge required to make judicious and informed decisions regarding patient care. Furthermore, investigators may leverage these insights to design and implement more effective intervention strategies that specifically target high-risk patient populations' while concurrently integrating personalized therapeutic approaches that cater to the unique needs of individual patients. The knowledge gained from this in-depth study is anticipated to facilitate more strategic resource allocation, enhance overall patient outcomes, and elevate the quality of care provided across various healthcare settings.

3. *Influence the development of tailored therapeutic approaches that consider both immunological parameters, such as CD4 count, and advanced immunotherapy techniques like MIP, in the comprehensive management of pericarditis among patients suffering from concurrent HIV and tuberculosis infections; This research underscores the paramount importance of integrating immunological*

parameters, particularly CD4 count measurements, with cutting-edge immunotherapeutic modalities, such as MIP, into the therapeutic frameworks established for managing pericarditis in patients who are co-infected with both HIV and TB. The insights and knowledge derived from this study can serve as a pivotal foundation for the creation of personalized treatment regimens that seamlessly incorporate both traditional therapeutic methods and innovative interventions, thereby ensuring a holistic and comprehensive approach to patient management in this complex clinical scenario.

1.6 Organization of the Study

This academic manuscript has been meticulously crafted and organized into a coherent structure that encompasses five interrelated chapters, each of which has been specifically devised with a targeted academic objective aimed at advancing knowledge within the field. In Chapter 1, readers are presented with a foundational introduction to the dissertation, which outlines the essential exploration and subsequent analytical pursuits that will be undertaken throughout the entirety of the research endeavor, thereby setting the stage for the comprehensive inquiry that follows. Chapter 2 provides an extensive and detailed review of the existing literature that pertains to joint modeling techniques specifically tailored for the intricate analysis of survival data in conjunction with longitudinal data, while simultaneously delivering a thorough examination of the contextual landscape surrounding tuberculosis-associated pericarditis, a condition of considerable clinical significance. The primary objective of this chapter is to elucidate the myriad challenges and complex issues to which the joint modeling framework can be aptly applied, along with offering in-depth insights into the nature of tuberculous

pericarditis and the pharmacological interventions relevant to its treatment, while also presenting a comprehensive overview of the contemporary circumstances and the multifaceted obstacles faced by patients afflicted with this debilitating condition. In Chapter 3, the discourse expands to elaborate on various mathematical formulations of the Cox proportional hazards (PH) model as they relate to the nuanced analysis of survival outcomes, in addition to the linear mixed-effects models that have been devised for the thorough evaluation of longitudinal outcomes, ultimately culminating in a comprehensive integrated model that synthesizes both survival and longitudinal outcomes within a unified and cohesive analytical framework. Special emphasis throughout this chapter is placed on the investigation of alternative parameterizations of the association structure that effectively connect and unify the survival and longitudinal components, thereby significantly enhancing the analytical rigor and depth of the study. These sophisticated formulations are intended to serve as robust methodological instruments that empower researchers to achieve a nuanced and precise interpretation of the results derived from the implementation of such advanced models. Chapter 4 meticulously presents the empirical outcomes that have been derived from the application of these methodological strategies to data obtained from the IMPI study, with a concentrated focus on patients who have been diagnosed with both HIV and TB-associated pericarditis, thereby highlighting the intersection of these critical health issues. Subsequently, Chapter 5 offers a comprehensive and exhaustive discussion of the findings derived from the research, culminating in a well-articulated summary that encapsulates the implications of the research conducted, thus providing valuable insights for future inquiries in this vital area of study. Each chapter within this manuscript serves to enrich the academic discourse and to contribute significantly to the ongoing

dialogue surrounding joint modeling techniques, survival analysis, and the complex interplay of health conditions such as tuberculosis and its associated complications.



Chapter 2

Review of Related Literature

2.1 Introduction

In this specific segment of our discourse, we undertake a comprehensive and meticulous examination of the existing scholarly literature that pertains to the foundational principles underlying the complex processes involved in joint modeling, while simultaneously engaging in a focused and in-depth inquiry into the specific medical condition known as tuberculosis pericarditis; this dual exploration aims to elucidate the significant advancements and notable findings that have been realized within these respective fields of study.

2.2 Joint modeling on longitudinal and survival data

The field of joint modeling has experienced a remarkable surge in scholarly interest and academic recognition, particularly within the specialized disciplines of biostatistics and medical research, as evidenced by the substantial contributions made by a diverse array of researchers who have dedicated their efforts to this area of inquiry (Abdi et al., 2013; Buta et al., 2015; Erango et al., 2017; He & Luo, 2016; Núñez et al., 2014; Rizopoulos & Takkenberg, 2014a; Serrat et al., 2015; Taylor et al., 2013). For example, a notable study undertaken by Abdi et al. (2013) meticulously examined the complex association between the protracted exposure to mycophenolic acid (MPA) and the ensuing hazard of experiencing acute rejection (AR) during the critical initial year following kidney

transplantation, making use of a sophisticated joint modeling framework to facilitate their analysis.

In the course of their rigorously designed research, they took into consideration a multitude of relevant factors, such as the specific surveillance strategy employed in the study (which included distinctions between a fixed-dose methodology and a controlled concentration approach), as well as the age of the recipients at the time of transplantation, thereby ensuring a comprehensive understanding of the variables at play.

In addition to previous findings, an independent investigation carried out by Núñez et al. (2014) introduced an innovative joint modeling approach that effectively integrates multiple Markov processes, which serves to facilitate a comprehensive examination of the relationship between the width of red blood cells, commonly referred to as red cell distribution width (RDW), and its significant role as an independent variable intricately linked to adverse health outcomes, including all-cause mortality and the prevalence of anemia among patients diagnosed with heart failure (HF).

Furthermore, within the context of an advanced Bayesian modeling framework, both individual and joint models were meticulously crafted to rigorously investigate the longitudinal health implications and survival outcomes associated with individuals living with HIV/AIDS. In this regard, the linear mixed-effects model (Laird & Ware, 1982), was utilized to model CD4 counts, accounting for both homoscedasticity and heteroscedasticity, while the Weibull survival model characterized the temporal aspect of mortality (Dessiso & Goshu, 2017). Within this methodological framework, adjustments for random effects were systematically implemented to establish a robust

association between longitudinal data and survival outcomes, all under the overarching paradigm of common parameter modeling.

In a noteworthy contribution, Serrat et al. (2015) outlined both Bayesian and frequentist approaches, focusing particularly on longitudinal measurement of prostate specific antigen (PSA) levels in relation to prostate cancer (PCa) risk. Their findings revealed a statistically significant correlation between PSA levels and prostate cancer risk, thereby shedding light on the age-related influences of PSA levels on the probability of developing this malignancy. They also found that both frequentist and Bayesian methodologies yielded similar parameter estimates, alongside consistent 95% confidence intervals.

Additionally, Long & Mills (2018) applied multivariate combined models to longitudinal observational studies of Huntington's disease, carefully assessing external validity through individual predictions aimed at characterizing disease progression.

Joint models, which represent an advanced statistical framework, can be utilized across disciplines beyond biostatistics, demonstrating versatility and relevance in modern research. For instance, many scholars have harnessed joint models in behavioral sciences to analyze the interconnections between longitudinal datasets and survival outcomes (Ghisletta, 2008; Ghisletta et al., 2006; Muniz-Terrera et al., 2019; Terrera et al., 2011). Ghisletta (2008), for example, established a multilevel longitudinal model with a Weibull survival model, providing insights into prognostic factors influencing survival.

My own meticulous examination has delved into functioning, with emphasis on detrimental factors such as recurrent influences, age, gender, general health status, socioeconomic determinants, and sensory abilities. In a related context, Ghisletta et al. (2006) introduced complex methodologies combining longitudinal and survival components to evaluate recognitions of aging and change. Their work emphasized the

elderly, addressing a crucial demographic in aging studies. Their models effectively simulated trajectories of visual-spatial reasoning (via the Kohs design test), while addressing hypotheses concerning missing data and its relationship with mortality risk.

Muniz-Terrera et al.(2019) integrated longitudinal measures with pre-event data, enabling a nuanced understanding of cognitive trajectories. They conducted sensitivity analyses to scrutinize assumptions about missing data (Little et al., 2012; Little & Rubin, 1987; Rubin, 1976).

In another investigation, Terrera et al.(2011) employed prose recall scores from the OCTO-Twin study in Sweden to design a joint model for longitudinal and survival analysis. Their aim was to investigate mortality risk and aging. Mixed-effects models (Laird & Ware, 1982), predicted accelerated decline trajectories in memory performance, while Weibull survival models analyzed time-to-event data.

Finally (Cekic et al., 2021), highlighted challenges faced by non-expert users in applying collaborative models due to limited guidance. They provided accessible instructions tailored for readers with basic knowledge of mixed-effects and survival models, and further applied the methodology to their own dataset, thereby demonstrating its practical utility.

2.3 Literature on TB pericarditis

Tuberculosis pericarditis is an intricate clinical manifestation that arises as a consequence of tuberculosis (TB), primarily affecting the pericardial sac that envelops the human heart, thereby leading to significant pathophysiological implications. Extensive academic inquiry has shed light on the fact that the incidence of this particular

ailment is significantly elevated in regions such as sub-Saharan Africa and certain areas in Asia, where it often serves as a precursor to a multitude of severe complications, which include but are not limited to pericardial effusion, cardiac tamponade, and constrictive pericarditis (Cherian, 2004; Mayosi et al., 2006; Mutyaba et al., 2014).

It is of paramount importance to emphasize that individuals who receive a diagnosis of tuberculosis pericarditis frequently present with a co-infection involving the human immunodeficiency virus (HIV), which considerably complicates the clinical management and therapeutic strategies employed in these cases.

Disturbingly, it has been reported that nearly 50 percent of patients diagnosed with tuberculosis pericarditis face a substantial risk of either mortality or enduring long-term disability, even with the administration of antituberculosis chemotherapy (Mayosi et al., 2005). Upon completion of a careful six-month observational period, the mortality rate associated with this debilitating condition may rise alarmingly to 26%, a statistic that warrants serious concern among healthcare professionals. Furthermore, this figure becomes even more alarming for those patients diagnosed with Acquired Immune Deficiency Syndrome (AIDS), as the mortality rate for this vulnerable population approaches an alarming 40% (Mayosi et al., 2008).

In order to enhance the clinical outcomes for patients suffering from the severe ramifications of tuberculosis pericarditis, it may be imperative to implement targeted interventions that are specifically designed to reduce the inflammatory response, which is a significant contributor to the development of both cardiac tamponade and pericardial constriction (Evans, 2008). Nevertheless, it is essential to recognize that there currently exists a notable lack of consensus within the medical community concerning the safety and therapeutic efficacy associated with the application of

immunomodulatory strategies, such as corticosteroids and *Mycobacterium indicus pranii* (M.w) immunotherapy, particularly in relation to alleviating the mortality and morbidity associated with this complex infection (European Society of Cardiology Working Group on the Diagnosis and Management of Pericardial Disease, 2004; Mayosi et al., 2000; Ntsekhe et al., 2000).

The presence of conflicting evidence pertaining to this combined therapeutic approach has resulted in a diverse array of recommendations being put forth within the medical community (Mayosi et al., 2012), which underscores the need for further research to arrive at a more unified clinical protocol.

The administration of corticosteroids, for example, has been systematically shown through various studies to significantly reduce the risk of infections among individuals who are co-infected with the HIV virus (Mayosi et al., 2014). However, it is vitally important to acknowledge that while the integration of adjunctive steroid therapy into treatment regimens has exhibited several potential benefits, the body of research regarding its overall efficacy and effectiveness remains decidedly inconclusive and ambiguous (Ntsekhe et al., 2014).

Conversely, preliminary findings from initial research studies imply that the repetitive administration of M.w could potentially lead to a decrease in the inflammation associated with extrapulmonary tuberculosis (TB) while simultaneously increasing CD4 cell counts in individuals living with HIV (Mayosi et al., 2013). Nonetheless, it is of utmost importance to recognize and emphasize that these initial observations require further detailed investigation through a large-scale randomized controlled trial that prioritizes mortality as the principal outcome measure (Ntsekhe et al., 2014).

Furthermore, a comprehensive meta-analysis that evaluated randomized controlled trials focusing on corticosteroid therapy for tuberculosis pericarditis indicated a

noticeable reduction in mortality rates; however, it should be noted that these results did not reach statistical significance, highlighting a critical gap in the findings (Mayosi et al., 2000; Mayosi et al., 2014; Ntsekhe et al., 2003). Inherent limitations associated with this particular study included the relatively small number of documented adverse events, as well as the limited cohort of patients included in the overall analysis, which may affect the generalizability of the results (Mayosi et al., 2000; Mayosi et al., 2014; Ntsekhe et al., 2003). In contrast, a different meta-analysis that meticulously evaluated all clinical trials assessing the effects of adjunctive glucocorticoid therapy across a variety of tuberculosis manifestations also indicated a potential for decreased mortality rates, suggesting a need for further investigation (Critchley et al., 2013).

Moreover, there is a notable divergence in the recommendations articulated within international guidelines regarding the management of pericardial diseases, as thoroughly documented in the comprehensive report entitled Guidelines on the Diagnosis and Management of Pericardial Diseases Executive Summary: The Task Force on Diagnosis and Treatment of Pericardial Disease, European Society of Cardiology (2004, 2010), which specifically tackles the contentious and complex issue surrounding the application of adjunctive glucocorticoid therapy in patients diagnosed with tuberculosis pericarditis. This complicated situation arises from a multitude of factors that significantly convolute the clinical decision-making process for healthcare providers.

Although extensive research and clinical trials have provided substantial evidence supporting the potential efficacy of glucocorticoids in markedly reducing mortality rates among patients suffering from tuberculosis, there persists considerable concern regarding the elevated risk of cancer, particularly among individuals who are exposed to HIV and are subsequently treated with glucocorticoids, as documented in the

aforementioned studies. Additionally, the current body of evidence concerning the ramifications of glucocorticoid treatment within the context of tuberculosis management specifically for HIV-infected individuals remains exceedingly limited, thereby exacerbating the uncertainty surrounding the therapeutic role of glucocorticoids in the effective treatment of tuberculosis.

In an earnest attempt to shed light on and possibly address the persistent and intricate discourse surrounding this matter, a dedicated research team, spearheaded by Mayosi in collaboration with his colleagues, endeavored to launch the Investigative Management of Pericarditis, or IMPI study (Mayosi et al., 2012; Thabane et al., 2014). The foundational hypothesis that the researchers meticulously crafted for the purpose of this thorough investigation was fundamentally based on the premise that the incorporation of prednisolone as an adjunctive therapeutic intervention would ultimately provide a range of multifaceted and comprehensive benefits for individuals suffering from this particular health condition (Thabane et al., 2014).

Initial findings emanating from this in-depth investigation appear to indicate that the administration of several doses of heat-killed intradermal *Mycobacterium indicus pranii*, previously denoted as *Mycobacterium w*, as a form of immunotherapy, possesses considerable potential in terms of its ability to mitigate inflammation that is typically associated with tuberculosis, while also promoting a notable increase in CD4+ T-cell counts among patients diagnosed with HIV infection (Gupta et al., 2012; Mathur, 2006; Saini et al., 2009). *Mycobacterium indicus pranii*, which is classified as a nonpathogenic, saprophytic, and rapidly replicating atypical mycobacterial species, has revealed significant clinical benefits when administered in a heat-killed intradermal formulation to patients afflicted with leprosy, and it is plausible that similar therapeutic results could

be achieved for individuals experiencing pulmonary tuberculosis and HIV infection (Gupta et al., 2008; Mathur, 2006; Nath, 1998; Sharma et al., 2005; Talwar, 1999).

In consideration of these preliminary findings, Mayosi et al. (2012) posited the hypothesis that the intradermal delivery of Mycobacterium M.w could proficiently reduce inflammation and its associated adverse impacts in patients diagnosed with tuberculosis pericarditis. To rigorously evaluate this hypothesis and its implications, the Investigative Management of Pericarditis (IMPI) study was meticulously conceptualized and executed with the aim of examining the efficacy and safety of the combined administration of prednisolone and Mycobacterium M.w within a specific cohort of African patients diagnosed with tuberculosis pericarditis.

The primary objective of the IMPI study was to systematically evaluate the efficacy and safety of adjuvant treatments involving prednisolone and Mycobacterium M.w in terms of their effectiveness in reducing the overall incidence of mortality, constricted pericarditis, or cardiac tamponade, which may necessitate invasive pericardial procedures within the thoracic cavity. A thoughtfully chosen cohort, comprising a total of 1,400 patients suffering from pericardial effusion linked to tuberculosis, was enlisted for this significant study (Mayosi et al., 2013; Ntsekhe, 2014). Thabane et al. (2014) undertook a comprehensive evaluation of the study data, ultimately concluding that there was no observable interaction between the administration of prednisolone and the variable known as M.w; as a result, detailed assessments were conducted for the group receiving prednisolone versus placebo, as well as for the M.w group versus its respective placebo.

The results derived from the comprehensive IMPI study unequivocally revealed compelling evidence indicating that the primary outcomes showed no statistically significant differences when comparing the placebo cohort to those receiving

Prednisolone (Thabane et al., 2014). Despite this observation, it was discerned that therapy involving prednisolone led to a decrease in the frequency of associated complications. Additionally, it was noted that prednisolone and M.w correlated with a significant increase in cancer incidence compared to the placebo control group, a phenomenon primarily attributed to malignancies associated with HIV (Thabane et al., 2014).

Furthermore, the influence of the drugs used in the IMPI study and their potential interactions with antiretroviral therapy (ART) on the observed variations in CD4 counts remains subject to considerable uncertainty and debate. The identification of substantial interaction effects on CD4 count changes could provide invaluable insights into the wider ramifications of the pharmacological interventions employed in the IMPI trial, warranting further exploration. To propel this investigation forward, Abdul-Karim & Gumedze (2019a, 2019b, 2019c) and Iddrisu (2019) embarked on a study that explicitly concentrated on elucidating the effects of prednisolone, the interplay between prednisolone and ART, as well as other determinants influencing CD4 count variations over time (Thabane et al., 2014).

To ensure the comprehensiveness and validity of the statistical inferences, and considering the complexities associated with missing CD4 values, these researchers implemented several extended sensitivity analysis techniques to address the challenges posed by missing data (Abdul-Karim & Gumedze, 2019; Mayosi et al., 2014). They further elucidated that the interventions employed necessitate careful consideration of the assertion that participants were formally diagnosed with tuberculosis pericarditis, highlighting the complexities involved in clinical assessments. Nevertheless, their findings indicate that even among patients with confirmed or likely tuberculosis, prednisolone administration confers a protective effect against adverse outcomes,

including cardiac tamponade and constrictive pericarditis, thereby potentially providing significant therapeutic benefits.

2.4 Summary of Reviewed Literature

The extensive body of literature that has undergone rigorous review has yielded a plethora of substantial insights concerning the multifaceted applications of joint modeling methodologies, as well as the intricate clinical complexities surrounding tuberculosis pericarditis, especially when considered within the particular context of co-infection with the Human Immune deficiency Virus (HIV). In the specialized field of joint modeling, numerous prior studies have consistently elucidated the remarkable capacity of these sophisticated statistical frameworks to seamlessly integrate both longitudinal data and survival data, which in turn facilitates the generation of estimations that are not only more accurate but also significantly more efficient when juxtaposed with traditional statistical methods (Abdi et al., 2013; Serrat et al., 2015; Rizopoulos & Takkenberg, 2014a). Such scholarly contributions serve to underscore the inherent robustness and versatility of joint modeling techniques across a diverse array of disciplines, which encompass, but are not limited to, transplantation medicine, behavioral sciences, and the management of chronic diseases.

In relation to the specific condition of tuberculosis pericarditis, the existing literature emphatically highlights the substantial burden it imposes in regions such as sub-Saharan Africa and Asia, where it is frequently observed to co-occur with HIV infection and where it is associated with alarmingly high levels of morbidity and mortality, despite the administration of standard antituberculosis chemotherapy regimens (Cherian, 2004; Mayosi et al., 2005, 2008). A variety of therapeutic interventions, including corticosteroid therapy and the use of *Mycobacterium indicus pranii* (M.w)

immunotherapy, have been the subject of investigation; however, the findings that have emerged from these studies remain largely inconclusive at times, they present contradictory outcomes (Mayosi et al., 2012; Ntsekhe et al., 2014). Analysis conducted within this research domain reported potential reductions in mortality rates associated with these interventions, and the statistical significance of these findings is often lacking. There remain persistent concerns regarding adverse effects, particularly within populations that are HIV-positive (Critchley et al., 2013; Mayosi et al., 2014).

Despite the extensive contributions to the scholarly discourse, several notable gaps in the existing literature are evident. First and foremost, while joint modeling has been extensively applied in numerous other medical domains, its application in the analysis of tuberculosis pericarditis within the context of HIV co-infection is still markedly scarce, with a limited number of studies that successfully integrate both CD4 count trajectories and survival outcomes. Secondly, a significant portion of the empirical evidence pertaining to the efficacy of corticosteroid and M.w therapies is either outdated, inconsistent in its findings, or derived from studies that are based on limited sample sizes, which inherently constrain the generalizability of these results. Thirdly, very few studies have explicitly investigated the intricate interactions between antiretroviral therapy (ART) and adjunctive therapies, particularly in terms of how these interactions influence CD4 count dynamics and corresponding survival outcomes. Lastly, there is a conspicuous paucity of large-scale and robust applications of joint modeling techniques to datasets concerning tuberculosis pericarditis, particularly those that adequately address issues such as missing values, random effects, and the complexities inherent in interaction structures.

It is precisely in response to these identified gaps in the literature that the present research endeavors to make a meaningful contribution. By employing advanced joint

modeling methodologies to meticulously analyze the data derived from the IMPI trial, this study aspires to provide a more comprehensive and nuanced understanding of the ways in which CD4 count trajectories interact with survival outcomes in patients who have been diagnosed with the dual challenges of both HIV and tuberculosis pericarditis. In undertaking this investigation, it aims to offer evidence-based insights into the effectiveness of various adjunctive therapies, the nature of their interactions with ART, and the broader implications these findings may hold for clinical management practices as well as public health policy formulation.



Chapter 3

Methodology

3.1 Introduction

In this section of our comprehensive research, we provide an in-depth analysis and discussion of the Cox proportional hazards (Cox-PH) model, which serves as a fundamental tool for analyzing survival data (Baek et al., 2021; Bradburn et al., 2003; Collett, 2015a; Cox, 1992). Furthermore, we explicitly develop and define different forms and structures of joint models relevant to both survival outcomes and CD4 count measurements that are essential to our study.

3.2 Statistical Methods

3.2.1 Cox proportional hazards model (Cox-PH)

The Cox proportional hazards model (Cox, 1992), constitutes a highly sophisticated statistical method that employed with the objective of determining the effects of a variety of covariates on the potential risk associated with the occurrence of a specific event. It is critical to recognize that a multitude of models has been developed for the assessment and evaluation of time-to-event data (Meier, 2013). However, the semi-parametric CoxPH model (Cox, 1992), is particularly noteworthy as it stands out as the model most prevalently utilized within this specialized field of research.

Within the confines of the Cox proportional hazards model, the fundamental hazard function is amenable to non-parametric estimation, which consequently facilitates significant versatility in the modeling procedure. In scenarios where it is considered requisite for the fundamental hazard function to adhere to a particular parametric form, such as the Weibull, Gamma, or Exponential distributions, investigators maintain the capacity to delineate a parametric model; nevertheless, it is often noted that the exact articulation of the hazard function is frequently neglected by academics within the scholarly community (Cekic et al., 2021). A pivotal study conducted by Fox & Weisberg (2023), demonstrated that the Cox-PH model effectively provides a reliable approximation of unknown parametric hazard functions (Cekic et al., 2021).

Considering p risk factors or explanatory variables, denoted as $x_1, x_2, \dots, x_p$, alongside $\beta_0, \dots, \beta_p$, which signify the regression coefficients that encapsulate the influence of the covariates on the likelihood of the event transpiring, it is imperative to acknowledge that h_0 represents the fundamental hazard function for individuals whose explanatory variables are entirely zero. The structural formulation of the Cox proportional hazards model is articulated in a manner that encapsulates the aforementioned variables and their interrelationships, thereby providing a comprehensive understanding of the model's operational dynamics.

$$h_i(j) = h_0(j) \exp(\beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_p x_{ip}), \quad (3.1)$$

where $\eta_i = \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_p x_{ip}$ constitutes the linear aspect of the model and is referred to as the "risk score" or "prognostic index." This model can alternatively be represented as:

$$\log \frac{h_i(j)}{h_0(j)} = \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_p x_{ip} \dots \quad (3.2)$$

This discernment suggests that the Cox-Proportional Hazards (Cox-PH) framework may be construed as a linear model that is predicated upon the logarithmic transformation of the hazard ratio, which constitutes a fundamental component of survival analysis. It is important to emphasize that we do not impose any specific assumptions regarding the true functional form of the underlying risk function, denoted by $h_0(j)$, which constitutes the basic component of the model. In fact, the coefficient β can be estimated independently of the shape and actual properties of the function $h_0(j)$. However, there are some scenarios in which it is necessary to estimate the underlying hazard function $h_0(j)$ to fully understand the dynamics of the model.

In the same way as generalized linear models, covariates included in the linear part of the proportional hazard model can take many forms. These can cover continuous variables such as age, blood pressure, weight, hemoglobin levels, and height, along with binary variables such as sex (classified as male or female), infection status, or categorical variables that have two levels or more, such as various treatment groups that may be of interest for analysis. The categorical variables that are the factors can be easily integrated into the linear component of the model using linear combinations of binary fictitious variables, which is a method similar to the approaches used in linear regression and logistic regression.

In order to effectively comply with the Cox-PH model, the dataset available for the analysis. It is important to assess the two main components that are integral to the model:

(1) the vector of unknown coefficients that exists in the linear component model and (2) the function of the basic hazard, which plays an important role in the general interpretation of the model outputs. These two main components of the Cox-PH model can be evaluated separately and independently, and the coefficients are generally evaluated primarily in terms of practical application and methodological convenience. The preliminary estimates derived from the coefficient estimation process serve as a cornerstone for subsequently obtaining an estimate of the underlying hazard function, which facilitates a deeper understanding of the relationships within the data. This methodological framework allows for robust inferences to be drawn regarding the influence of the explanatory variable p on the relative risk associated with the event being studied.

It is particularly critical to note that an estimate of the underlying hazard function is not a prerequisite for conducting this inference process, which adds a level of flexibility and practicality to the Cox proportional hazards model. Coefficients associated with the Cox-PH model can be determined using maximum likelihood estimation methods, which are well-established and conventional approaches employed in the realm of statistical modeling. The process of achieving the maximum attainable value of the log-likelihood function is efficiently carried out through the application of the iterative Newton-Raphson algorithm, which is widely recognized for its effectiveness in converging to the optimal estimate in a reliable manner, thereby supporting the robustness of the analysis conducted using the Cox-PH model.

3.2.2 Assessment of Cox-PH Assumptions

In this particular segment of our study, we engage in a thorough and meticulous assessment, as well as a comprehensive investigation into the essential and foundational

premises that serve as the backbone for the Cox proportional hazards model, which is frequently referred to in the literature as the Cox-PH model. The key principle that governs the critical proportional hazards assumption posits that the hazard functions, often referred to in statistical terminology as hazard ratios, for different distinct groups must maintain a consistent and proportional relationship throughout the entire duration of the study being conducted. This particular requirement necessitates that the influence exerted by various covariates, which can change over time, must remain stable and unaltered across different temporal intervals, thereby ensuring a level of consistency that is vital for the integrity of the analysis.

Consequently, this leads us to infer that the hazard ratio, which is a pivotal component of the model, should exhibit both consistency and uniformity throughout the complete observation period, which is essential for deriving meaningful conclusions from the data. It is of utmost importance to diligently and rigorously verify these critical assumptions prior to proceeding with the implementation of regression analysis concerning the proportional hazards associated with Cox, as such verification plays a crucial role in ensuring the validity and reliability of the results produced by the model. A multitude of statistical methodologies' readily available and can be employed to scrutinize these foundational assumptions effectively (Dessai et al., 2019).

Among these evaluative techniques are: (1) the analysis of Kaplan-Meier survivorship curves, where the convergence of Kaplan-Meier curves for diverse groups suggests an increased likelihood of violating the proportional hazards assumption; conversely, a situation in which the Kaplan-Meier curve for one group exhibits a decline while the curve for another group remains relatively unchanged also indicates a potential breach of this crucial assumption. (2) The evaluation of scaled Schoenfeld residuals comprises a

combination of both statistical examinations and graphical representations designed to assess the integrity of the proportional hazards assumption thoroughly. In the event that covariates are identified as transgressing the premise of constant covariate effects, it becomes an imperative necessity to adopt an extension or a time-dependent variant of the Cox proportional hazards model (Bellera et al., 2010).

3.2.3 Kaplan-Meier estimator

The Kaplan–Meier (KM) methodology, which is widely recognized in the field of survival analysis, was meticulously employed to derive an estimation of the survival function pertaining to the participants involved in the study, thereby providing a robust framework for understanding survival probabilities. This particular non-parametric estimator is adept at calculating the likelihood of individuals surviving beyond designated time intervals, all the while meticulously considering the nuances of censored data, which may include instances of patients who were lost to follow-up or those who had not yet encountered the event of interest by the conclusion of the study period. The mathematical representation of the KM survival function can be succinctly articulated as follows:

$$S(t) = \prod_{t_i \leq t} \left(1 - \frac{d_i}{n_i}\right) \quad (3.3)$$

where the notation t_i signifies the sequence of ordered event times, d_i denotes the count of events occurring at each specific time t_i , and n_i indicates the total number of individuals who remain at risk immediately prior to the time t_i .

The Kaplan–Meier survival curves were meticulously generated in order to facilitate a comprehensive comparison of the probability of survival among the various study groups, which included, but were not limited to, the treatment group and the placebo group. Additionally, median survival times were calculated, and survival probabilities were ascertained at specific, predetermined time points to provide a more nuanced understanding of the survival outcomes associated with each intervention. This rigorous analysis allows for a deeper examination of the effectiveness of the treatment relative to the control, thereby contributing valuable insights into the potential benefits and limitations of the therapeutic strategies being evaluated in the context of this research.

3.2.4 Log-rank test

To statistically assess whether differences in survival distributions between the study groups were significant, the log-rank test was applied. This non-parametric test compares the observed and expected number of events in each group under the null hypothesis that the survival curves are equal.

The log-rank test statistic is expressed as:

$$\chi^2 = \frac{\sum [(O_i - E_i)]^2}{\sum V_i} \quad (3.4)$$

where O_i is the observed number of events in group i , E_i is the expected number under the null hypothesis, and V_i is the variance of the difference.

A p-value less than 0.05 was considered evidence of a statistically significant difference between the groups. The log-rank test assumes proportional hazards between groups, and the results were interpreted under this assumption.

3.2.5 Joint model

In the subsequent section of our academic inquiry, we provide an exhaustive and methodical exploration of joint statistical models that have been meticulously crafted to analyze and interpret CD4 count data in conjunction with various survival outcomes, thus enabling a comprehensive understanding of the relationships between these variables. In addition to this rigorous examination, we also presented R software code that has been specifically designed to facilitate and optimize the fitting process of these complex joint models, which will serve as a foundational element underpinning the scholarly discourse and analysis that follows.

To formalize our approach, we denote the time of the observed event for the i -th participant within the study as T_i , which represents a crucial component of our analysis. Furthermore, we define C_i as the censoring time, which is mathematically characterized as the minimum value between the actual event time T_i and the censoring time C_i itself; thus, we express this relationship as:

$$T_i = \min(T_i, C_i)$$

In addition to these definitions, we have also established an event indicator δ_i , which serves as a binary marker, assuming the value of 1 when the condition $T_i \leq C_i$ is satisfied, and taking the value of 0 otherwise. Utilizing these fundamental definitions, we constructed the observed dataset pertinent to time-to-event outcomes, which is composed of pairs in the form of (T_i, δ_i) .

Within the realm of longitudinal responses, we denote the longitudinal measures collected for each individual subject as $y_i(j)$, where j corresponds to the time points $t =$

1,2,...,n, thereby encapsulating the repeated measures aspect of our data. The main objective of this analytical framework is to establish a reliable and statistically significant relationship between the true unobserved value Y_i^* of a longitudinal outcome at a specific time j and the corresponding event outcome T_i , which is of primary importance in our study.

It is essential to highlight the critical difference between Y_i^* and $y_i(j)$, since the latter is a longitudinally observed outcome at time j and is subject to measurement error, potentially complicating the analysis. Within this comprehensive analytical framework, the model describing the longitudinal measurement articulates in a structured manner, as delineated in the works of Rizopoulos et al. (2010a, 2010b, 2012a, 2016a, 2008) and Rizopoulos & Takkenberg (2014a), which provide a solid theoretical grounding for our subsequent discussions and analysis. $y_i(j) = m_i(j) + \varepsilon_i(j)$

$$= x_i^T(j)\beta + z_i^T(j)b_i + \varepsilon_i(j), \quad \varepsilon_i(j) \sim N(0, \sigma^2) \quad (3.5)$$

In the mathematical formulation presented herein, the notation $m_i(j) = \{m_i(\mu) \mid 0 \leq \mu < j\}$ serves to elucidate the historical development and trajectory of the unobserved true longitudinal process that precedes the designated time point j . Simultaneously, the variable ω_i is defined as a vector that encapsulates essential covariates, complemented by a corresponding vector of regression coefficients denoted as γ , which are integral to the survival model being employed in this analysis.

Furthermore, the expression $y_i(j) = x_i(j)\beta + z_i(j)b_i$ delineates the specific model (3.5) that is utilized for articulating the longitudinal component of our study, with α_1 acting as a crucial connector between both models, thereby signifying the risk ratio that is

associated with the occurrence of the event in question for each incremental unit increase observed in the current value of $\mu_i(j)$ (Cekic et al., 2019, 2021; Rizopoulos & Takkenberg, 2014a).

Additionally, it is imperative to consider the exploration of a sophisticated joint model, which fundamentally operates under the premise that the risk function that pertains to the emergence of a particular event at a specific time is intricately interconnected with the instantaneous rate of change, commonly identified as the slope measured at that identical moment in time. This analytical framework enables the mathematical characterization of the aforementioned relationship to be articulated in a manner that encapsulates the complexity and interdependencies inherent in the data being examined, thus providing deeper insights into the underlying mechanisms at play. The implications of this model are profound, as they allow researchers to draw significant conclusions regarding the interplay between longitudinal factors and event occurrence, thereby enhancing the robustness of the findings. Ultimately, through such comprehensive modeling approaches, we can achieve a more nuanced understanding of the dynamics governing survival outcomes in the context of longitudinal data analysis.

$$h_i(j | m_i(j), \omega_i) = h_0(j) \exp \{ \gamma^\top \omega_i + \alpha_i \mu_i(j) \} \quad (3.6)$$

Where $m_i(j) = \{m_i(\mu) | 0 \leq \mu < j\}$ represents the historical trajectory of the real longitudinal process not observed leading to the time point j , and ω_i is a vector including basic covariates with an associated vector of regression coefficients γ for these basic covariates used in the survival model. The term $y_i(j) = x_i(j)\beta + z_i(j)b_i$ represents the model (3.5) for the longitudinal component, and α_1 is used to link the two models and indicates

the risk ratio associated with the event for each increase in a unit of the current value of $\mu_i(j)$ (Cekic et al., 2019, 2021; Rizopoulos & Takkenberg, 2014a).

We can also explore the potential of a complete joint model, which operates by assuming that the risk function associated with the occurrence of a specific event at a given time is complexly linked to the instantaneous change rate, commonly called the slope, observed at that same time, allows the mathematical representation of this relationship to be expressed as follows:

$$h_i(j | m_i(j), \omega_i) = h_0(j) \exp \left\{ \gamma^\top \omega_i + \alpha_2 \mu'_i(j) \right\}, \quad (3.7)$$

Alternatively, it is quite possible that the hazard function, essentially defined as the probability or likelihood of a particular event occurring at a particular time, denoted (j), is not simply related to the underlying true baseline $\mu_i(j)$ of the longitudinal , which is a process at a given time (j), but also depends critically on the contemporaneous rate of change of this same process, represented by $\mu'_i(j)$ (commonly understood as the slope) at the same time (j). Consequently, within the context of this analytical framework, one can delineate the specification of model (3.6) with greater clarity, articulated in the following manner:

$$h_i(j | m_i(j), \omega_i) = h_0(j) \exp \left\{ \gamma^\top \omega_i + \alpha_1 \mu_i(j) + \alpha_2 \mu'_i(j) \right\}, \quad (3.8)$$

where the parameter α_2 denotes the relevant coefficient relative to the current rate of change of the longitudinal process under study. However, it is essential to note that the assumption that the risk associated with an event occurring at an arbitrary time (j) is intrinsically related to both the current value of $\mu_i(j)$ and the instantaneous slope of $\mu'_i(j)$ at that same time junction may not necessarily be true, since these analytical models

μ_i

often neglect the longitudinal history of CD4 counts, which could provide vital contextual information.

By undertaking a reparameterization of the joint model in order to incorporate more realistic structures reflective of the longitudinal process, researchers can attain a more accurate estimation of event hazards' (Sylvestre & Abrahamowicz, 2009). In this regard, model (3.6) can be reformulated and represented in the following manner (Brown, 2009; Rizopoulos, 2012a):

$$h_i(j | M_i(j)) = h_0(j) \exp \left\{ \gamma^\top \omega_i(j) + \alpha_3 \frac{\int_0^j \mu_i(u) du}{j} \right\}, \quad (3.9)$$

The mathematical formulation encapsulated in model (3.9) shows that at any time, denoted as j , the associated parameter α_3 helps to quantify the strength of the relationship that exists between the risk of an event occurring at a particular time (j) and the cumulative area of the longitudinal trajectory calculated up to the exact moment.

On the other hand, the joint model allows us to express the risk associated with an event at a particular time as a function of the longitudinal trajectory, j does not depend only on the current value of $\mu_i(j)$, but also on its instantaneous rate of change, with $\mu'_i(j)$ representing the slope at this specific moment in time j along with the cumulative area under the longitudinal trajectory calculated up until that very instant. In this scenario, the expression for model (3.6) can thus be articulated as follows:

$$h_i(j | M_i(j)) = h_0(j) \exp \left\{ \gamma^\top \omega_i(j) + \alpha_1 \mu_i(j) + \alpha_2 \mu'_i(j) + \alpha_3 \frac{\int_0^j \mu_i(u) du}{j} \right\}. \quad (3.10)$$

In order to facilitate effective discourse within the realm of academic communication, we adopt the designated notation JM1 to refer comprehensively to the ensemble of collaboration models, which encompasses models (3.6), (3.7), (3.8), (3.9), and (3.10), as well as JM2, JM3, JM4, and JM5, thereby providing a structured framework for future discussions and analyses.

A multitude of joint modeling packages can be found within the expansive and versatile open-source R programming environment, which has been meticulously designed with the intention of estimating parameters that emerge from the intricacies of a joint model framework (R Core Team, 2014, 2016; R Foundation for Statistical Computing, 2015). Among these, the JMbayes package, Rizopoulos (2014), Rizopoulos & Takkenberg (2014a) stands out as the most comprehensive, extensible, and adaptable option available for the successful implementation of joint modeling methodologies that are pertinent to our research endeavors.

In the context of the present investigation, we have made a conscious decision to employ the JMbayes2 package in tandem with the JM functions (Cekic et al., 2021; Rizopoulos, 2016; Rizopoulos & Takkenberg, 2014), specifically for the purpose of estimating parameters relevant to the joint model we are examining. More particularly the JMbayes2 package by Rizopoulos (2016) features the core function essential for model fitting, which is denoted as `jm(.)`. This function embodies a sophisticated construct of a mixed-effects framework developed (Cekic et al., 2021; Pinheiro et al., 2007; Pinheiro & Bates, 1995). This specific package provides researchers with the capability to fit joint models that incorporate both longitudinal data and survival outcomes within a robust Bayesian modeling framework that has been thoroughly vetted by the academic community (Rizopoulos, 2016). These intricate statistical models are meticulously calibrated to align with the data at hand, and a rigorous comparative

analysis is subsequently executed utilizing the `compare_jm()` function, which is a specialized tool that is conveniently available within the JMbayes2 package.

Through this detailed evaluation process, the model that exhibits the most superior fit characteristics for the outcomes related to mortality and hospitalization is judiciously selected, ensuring that our findings are grounded in robust statistical evidence. It is of paramount importance to emphasize that only the results obtained from this optimally fitted model will be disseminated and reported in the subsequent analyses, thereby maintaining the integrity of our research findings. The function `compare_jm()` operates by systematically juxtaposing fitted joint models alongside one another, employing advanced metrics that include the deviance information criterion (DIC) (Spiegelhalter et al., 2002) and the Watanabe-Akaike information criterion (WAIC) (Watanabe & Opper, 2010). It is worth noting that WAIC represents a generalized enhancement to the traditional Akaike information criterion (AIC), thereby facilitating a more nuanced and comprehensive understanding of the performance of the models being evaluated.

3.2.6 Statistical Estimation Techniques

The estimation of the parameters specified in Equations (3.5)–(3.10) requires the adoption of appropriate statistical estimation techniques. It is important to emphasize that while software packages such as JMbayes2 in R provide a computational environment, they are not estimation techniques in themselves. Rather, they serve as implementations of the underlying statistical methods.

In the context of this study, parameter estimation is primarily carried out within a Bayesian framework, which relies on *Markov Chain Monte Carlo* (MCMC) sampling algorithms (e.g., Gibbs sampling and Metropolis–Hastings) to generate approximate posterior distributions of the parameters (Rizopoulos, 2016). This approach offers

several advantages, including the ability to incorporate prior information and to account for model uncertainty.

Alternatively, Maximum Likelihood Estimation (MLE) remains a standard frequentist approach that employed to estimate both the longitudinal and survival components of joint models (Laird & Ware, 1982). For cases where missing data or latent variables are present, the Expectation–Maximization (EM) algorithm also adopted (Dempster, Laird, & Rubin, 1977). These methodologies ensure that the parameters of interest are consistently and efficiently estimated, thereby enhancing the robustness of the analytical results.

3.2.7 Explanation of Parameters in the Equations

To ensure clarity, the parameters and components specified in the equations (3.5)–(3.10) are explained with respect to the variables under consideration in this study:

- $y_i(j)$: the observed CD4 count for patient i at time point j .
- $m_i(j)$: the underlying true (latent) CD4 trajectory for patient i at time j .
- $\varepsilon_i(j)$: the measurement error in CD4 counts, assumed $\sim N(0, \sigma^2)$.
- $x_i(j)$: a vector of covariates (e.g., ART status, demographic factors) with fixed effects β .
- $z_i(j)$: the design matrix for random effects with subject-specific random effects b_i .
- ω_i : a vector of baseline covariates (e.g., age, sex, hospitalization timing).
- γ : regression coefficients associated with ω_i in the survival model.

- $h_0(j)$: the baseline hazard function at time j .
- $\alpha_1, \alpha_2, \alpha_3$: association parameters linking the longitudinal CD4 trajectory ($\mu_i(j)$), its slope ($\mu_i'(j)$), or its cumulative history to survival outcomes.
- T_i : observed time-to-event (mortality or censoring) for participant i .
- δ_i : event indicator, with value 1 if $T_i \leq C_i$ (death observed), and 0 otherwise.

These definitions highlight how the mathematical models map directly onto the clinical and demographic characteristics of patients in the present study.

3.2.8 Model Selection Criteria: BIC and WAIC

Model selection constitutes a critical step in the joint modeling process, as it ensures that the most appropriate model is retained for subsequent inference. In this study, two information criteria are employed: the Bayesian Information Criterion (BIC) and the Watanabe–Akaike Information Criterion (WAIC).

Bayesian Information Criterion (BIC). The BIC is formally defined as:

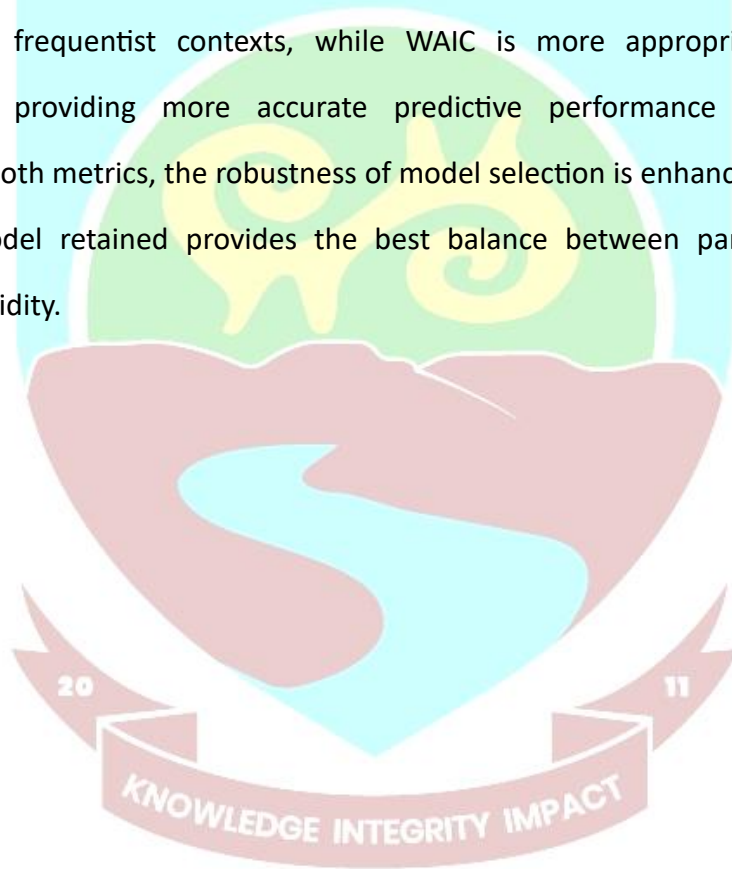
$$BIC = -2\ln(L) + k\ln(n),$$

where L denotes the maximized likelihood, k the number of model parameters, and n the sample size. The BIC penalizes model complexity more heavily than other criteria, thereby favoring parsimonious models, particularly when n is large (Schwarz, 1978).

Watanabe–Akaike Information Criterion (WAIC). The WAIC is a fully Bayesian criterion designed to assess model fit by averaging over the posterior distribution of the

parameters. It is computed based on the pointwise predictive density and provides an asymptotically unbiased estimate of out-of-sample prediction error (Watanabe, 2010). WAIC is particularly well-suited to hierarchical and joint modeling frameworks, as it accounts for model uncertainty in a principled manner.

Comparative Advantages. While both BIC and WAIC are employed in this study, their comparative strengths are noteworthy. BIC is more conservative and performs well in large-sample frequentist contexts, while WAIC is more appropriate in Bayesian frameworks, providing more accurate predictive performance assessment. By considering both metrics, the robustness of model selection is enhanced, ensuring that the final model retained provides the best balance between parsimony, fit, and predictive validity.



Chapter 4

Results and Discussion of Findings

4.1 Introduction

In this particular segment of our research work, we provide an extensive and detailed elucidation of the data that was meticulously acquired from the IMPI trial, wherein we place significant emphasis on the longitudinal assessments pertaining to CD4 counts and the correlated survival outcomes, which encompass a comprehensive analysis of both hospitalization and death rates within the studied population. Subsequently, we employed the Cox proportional hazards model in tandem with joint models that are characterized by a variety of reporting frameworks, thereby enabling us to rigorously scrutinize the survival outcomes while simultaneously adjusting for a multitude of confounding factors, which include the variable M.w, the individual's historical engagement with antiretroviral therapy (ART), the intricate interaction between M.w and ART, as well as essential demographic variables such as age and sex, in addition to the specific type of ART that was administered to the participants.

For the joint models employed in this analysis, we undertook a meticulous and rigorous comparison of their efficacy across several diverse association structures and ultimately made the decision to present the findings exclusively from those joint models that demonstrated the highest level of concordance with the observed survival outcomes, which importantly included both death rates and hospitalization statistics. Through this comprehensive approach, we aim to provide a robust interpretation of the intricate relationships between these variables, thereby contributing valuable insights

to the ongoing discourse surrounding the management and treatment of individuals affected by conditions related to HIV/AIDS.

4.1.1 IMPI Trial and Data Description

In the context of this comprehensive investigation, we engaged in the utilization of a dataset that was initially compiled during the IMPI study (Mayosi et al., 2013; Ntsekhe, 2014). The design of the IMPI study was meticulously structured as a multicenter, international, randomized, double-blind, placebo-controlled trial that employed a 2×2 factorial approach (Mayosi et al., 2013). The primary aim of the IMPI study was to critically evaluate the therapeutic efficacy associated with two distinct interventions aimed at combating tuberculosis (TB), specifically focusing on the administration of prednisolone in conjunction with the immunotherapeutic agent known scientifically as *Mycobacterium indicus pranii* (*M. indicus pranii*), with a particular emphasis on individuals who had been diagnosed with tuberculosis pericarditis (TBP) across diverse geographical locations throughout Africa.

Tuberculosis pericarditis represents a severe manifestation of tuberculosis that has significant implications for the heart's health and poses a unique diagnostic conundrum, often resulting in challenges that complicate timely and accurate diagnosis, leading to scenarios where diagnosis may be delayed or even entirely overlooked. Consequently, this oversight can precipitate a series of substantial late complications that are frequently associated with elevated rates of both incidence and mortality, necessitating urgent attention and intervention. Owing to the composite outcomes that include mortality, the development of cardiac tamponade, or late complications such as pericardial constriction, there is a pronounced increase in mortality rates (Lucero et al., 2022). Patients who meet the meticulously defined inclusion criteria are systematically

randomized into one of four distinct treatment groups, with each participant who has been randomized receiving a specific combination of either M.w or its corresponding placebo counterpart, along with either prednisolone or its respective placebo counterpart, where M.w and its placebo are designated as M^+ and M^- , respectively, while prednisolone and its placebo arm are similarly classified as P^+ and P^- .

The phenomenon of tuberculosis pericarditis is profoundly associated with significantly elevated rates of both morbidity and mortality, irrespective of the strict adherence exhibited by patients to the prescribed anti-tuberculosis treatment regimens that have been established (Mayosi et al., 2013; Ntsekhe et al., 2014). The potential for an enhancement in patients' quality of life, which could stem from the successful mitigation of the inflammatory response that is characteristically associated with tuberculosis pericarditis, as evidenced by the measurement of CD4 counts, could lead to a substantial reduction in the incidence of severe complications that include cardiac tamponade and pericardial constriction, as indicated by the findings presented in the studies (Mayosi et al., 2013; Ntsekhe et al., 2014).

Nevertheless, the questions surrounding the efficacy and safety of adjunctive immunomodulatory strategies that incorporate a combination of corticosteroids and *M. indicus pranii*, aimed at diminishing both mortality and morbidity, remain an area characterized by considerable uncertainty and is presently the subject of ongoing and rigorous investigation (Mayosi et al., 2012; Ntsekhe et al., 2014). In order to rigorously assess the potential impact that the introduction of corticosteroids and adjunctive immunomodulation with *M. indicus pranii* would have on the significant reduction of mortality and morbidity rates, (Mayosi et al., 2012; Ntsekhe et al., 2014) undertook the meticulous design of the IMPI trial, ensuring that all critical variables were accounted for in the study's framework.

Within the framework of the IMPI trial, an extensive and diverse cohort comprising a substantial total of 1,400 patients, who had either been definitively diagnosed or were strongly suspected to be suffering from tuberculosis pericardial effusion, was meticulously recruited from a wide array of 9 distinct African nations, and this recruitment spanned across 19 different medical facilities that were strategically selected for their relevance to the study, all conducted over the course of a comprehensive four-year investigative research initiative. The patients who met the rigorous and meticulously defined inclusion criteria were then subjected to a highly controlled randomization process, whereby they were assigned either to an intensive six-week therapeutic regimen that incorporated oral prednisolone in conjunction with the immunomodulatory agent *M. indicus pranii*, or alternatively, they received a placebo treatment that was administered over an extended period lasting three months. After undergoing the initial baseline randomization process at week 0, the patients were scheduled to participate in a series of thorough follow-up evaluations, which were meticulously planned to occur at weeks 2 and 4 during the intervention phase, and subsequently at three and six months following the conclusion of the intervention phase.

Adhering to this meticulously structured follow-up timetable, additional assessments for follow-up were executed every six months thereafter, with the maximum duration of follow-up being extended to an impressive total of four years, (Mayosi et al., 2012; Ntsekhe et al., 2014). Of particular note is the fact that the patients who participated in the *M. indicus pranii* arm of the study had their treatment regimen prematurely discontinued after three months due to the manifestation of intolerable side effects, which underscores the complexities involved in managing therapeutic interventions in this patient population (Mayosi et al., 2012; Ntsekhe et al., 2014).

The IMPI trial was conducted over an extensive and well-defined timeframe, commencing in January of 2009 and concluding in February of 2014, and it was executed with meticulous precision across a total of 19 strategically positioned hospitals located in eight different African nations (Mayosi et al., 2014). Within the overarching framework aimed at evaluating the comparative efficacy of the corticosteroid prednisolone versus a placebo treatment, a total of 706 patients were judiciously selected and allocated to the treatment cohort that received prednisolone, while concurrently, an additional group of 694 patients was designated to receive a placebo intervention. In the context of the comparative evaluation specifically targeting *M. indicus pranii* in contrast to a placebo, a total of 625 participants were systematically assigned to the treatment cohort that received *M. indicus pranii*, with an equivalent cohort of 625 patients allocated to the placebo group in a manner consistent with the study's design.

The study was methodologically constructed with sufficient statistical power to account for the anticipated levels of non-compliance that could potentially arise within the active treatment cohorts, an expectation which was corroborated by the documented noncompliance rates observed among the treatment group that received prednisolone. Conversely, the cohort that received *M. indicus pranii* experienced compliance deviations of a notably high magnitude, a situation that was primarily attributed to the adverse effects resulting from the injections administered as part of the therapeutic regimen (Mayosi et al., 2014).

Moreover, it is posited that a percentage of mortality cases observed within the study may be associated with a wide variety of etiological factors, which include but are not limited to complications arising from tuberculosis pericarditis, issues related to tuberculosis that are not restricted to pericardial involvement, complications linked to

HIV infection, incidents related to cardiovascular health, and fatalities that may occur due to tuberculosis pericarditis of an indeterminate origin (Abdul-Karim & Gumedze, 2019c, 2019a, 2019b; Iddrisu, 2019).

The overarching aim of the IMPI trial was to conduct a comprehensive and systematic investigation into the efficacy and safety profile associated with the administration of prednisolone and *M. indicus pranii* injections, specifically focusing on their ability to significantly reduce the duration until the first manifestation of critical clinical outcomes, which encompass mortality, pericardial constriction, and cardiac tamponade that would require pericardial drainage interventions in patients diagnosed with tuberculosis pericardial effusion (Mayosi et al., 2012; Ntsekhe et al. 2014). In their meticulous scholarly investigation regarding the evolution of CD4 counts among individuals infected with HIV who were randomized into either the prednisolone or placebo cohorts of the study, Abdul-Karim & Gumedze (2019a, 2019b, 2019c) posited that subsequent research initiatives should delve into the joint modeling of CD4 count trajectories alongside the temporal patterns of mortality that may arise within this patient population. This advanced methodological approach has the potential to provide a more intricate and profound understanding of the relationship between variations in CD4 counts and the primary survival outcomes that were presented in the IMPI trial, thereby enhancing the interpretative framework within which these findings can be contextualized.

The primary focus of this thesis has been to establish and employ a joint modeling framework that will facilitate a rigorous examination of both longitudinal CD4 count data and survival-related outcomes, with a particular focus on critical aspects such as death and the incidence of hospitalization. This in-depth analytical endeavor was intentionally designed to scrutinize the extent to which longitudinal measurements of CD4 counts

operate to modulate the associated risks linked to death and hospitalization, thereby contributing to the broader discourse on patient outcomes. Within the framework of this investigation, the designated intervals for the evaluation of CD4 counts encompassed an initial assessment conducted at baseline week 0, succeeded by systematic follow-up evaluations at week 2 (which corresponds to 0.5 months), one month, and 3 months thereafter.

4.1.2 Description of CD4 Count Measurements

In an extensive investigation involving a cohort of 584 individuals diagnosed with HIV (+), of which 126 were identified as HIV positive, the monotone data acquired comprised a subset of patients, wherein 55 were randomly allocated to receive a placebo treatment, while 71 were randomly designated to receive the M.w. intervention. Figure (1A) proficiently delineates the observed count profile plots corresponding to each individual patient, thereby offering a comprehensive visualization of the data distribution. It is noteworthy that participant attrition occurred during the one-month and three-month intervals, although a subset of subjects successfully completed the full study duration.

Figure (1B) illustrates profile plots of mean counts classified by distinct treatment groups, revealing significant elevations in CD4 count levels during scheduled measurement visits and indicating a discernible linear progression in CD4 count measurements for both the placebo and M.w. treatment cohorts. Furthermore, Figure 1B emphasizes a potential interaction effect between treatment assignment and temporal factors, necessitating the incorporation of an M.w-time interaction term in the specification of the fitted linear mixed model employed for data analysis. It was observed that mean CD4 counts, when averaged across the various measurement periods,

exhibited non-significantly elevated values, particularly within the M.w treatment group, in comparison to the mean CD4 counts documented in the placebo cohort.

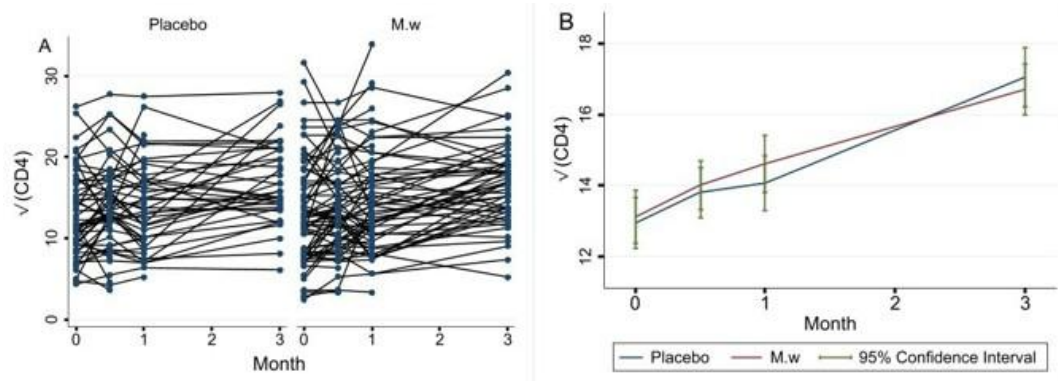


Figure 1. Individual data profile plots of $\sqrt{(\text{CD4})}$ CD4 counts.

The box-and-Whisker plots in Figure 2A show that the mean CD4 cell counts were essentially the same in both treatment groups, whereas Figure 2B shows that the mean CD4 cell counts increased in both treatment groups.

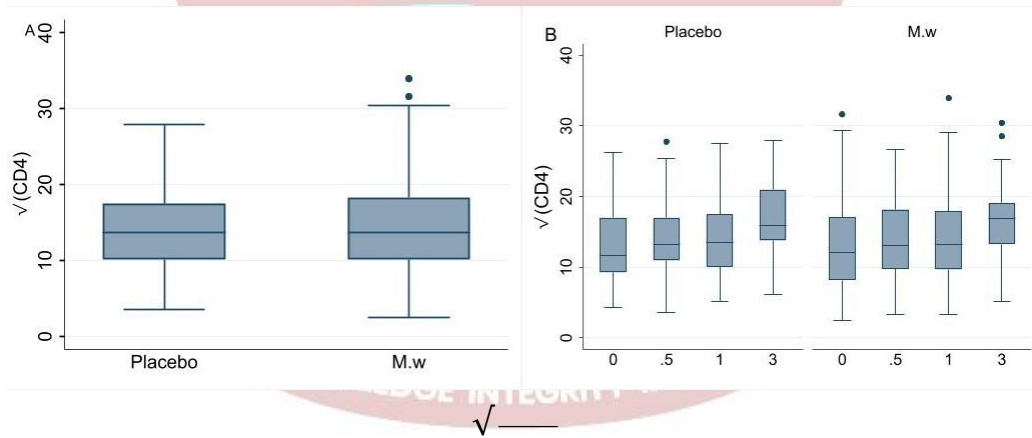


Figure 2. Box-and-Whisker plots of $\sqrt{(\text{CD4})}$ CD4 count measurements.

The number and percentage of patients retained at each visit are shown by treatment group in Table 4.1. The completion rate in the placebo group was 37 (67%) and in the M.w treatment group was 50 (70%).

Table 4.1: Proportion of patients remaining in the study at each visit.

	<i>M.w</i>	placebo
Month	<i>N</i> (%)	<i>N</i> (%)
0	71(100)	55(100)
0.5	71(100)	55(100)
1	63(89)	47(85)
3	50(70)	37(67)

Since these factors fluctuate temporarily, we have paid close attention to the data classified in accordance with a separate stall model, classified by therapeutic groups, a detailed outline that elucidates the results. This information is separated by the exposure described in Table 4.2. In this extended table, three identification abandoned models can be identified. Table 4.2 is important to emphasize that the average value corresponding to these models is clarified to each evaluation compiled by the treatment cohort. The attrition models denoted as 3, 2, and 1 represent participants who successfully completed the study, participants who withdrew from the study after 2 months, and participants who withdrew from the study after 1 month, respectively.

Furthermore, it is important to highlight that there were no statistically significant differences in the distributions associated with outlier trends between the two treatment cohorts, as determined by a chi-square test (statistic = 3.5, $p = 0.825$). Figure 4 provides a graphical representation of the profile plots showing the means of the three variance models for participants assigned to the placebo group shown in Figure 4 A in contrast to participants in the active treatment cohort shown in Figure 4 B. Figure 4 confirms the results displayed in the mean profile plots and is consistent with the observations shown in Figure 2 B, highlighting the larger increases in outcome measures

shown among participants receiving active treatment, whereas the placebo group showed smaller increases over a 3-week compared to 3-month period. This study used imputation methodologies to deal with missing data, then obtaining a complete dataset before performing model fitting and statistical inference techniques.

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Table 4.2: Mean CD4 count measurements at each visit by type of dropout and treatment group.

Dropout pattern	Dropout time (months)				N(%)
	0	0.5	1	3	
Placebo arm 3	14.014	15.284	14.625	17.045	37(67)
2	9.835	11.664	12.006	-	10(85)
1	11.971	9.662	-	-	8(1)
All patients mean (std)	12.957(5.237)	13.808(5.217)	14.068(5.355)	17.045(5.101)	55(100)
M.w arm					
3	13.238	14.171	14.292	16.696	50(70)
2	12.038	14.252	15.852	-	13(89)
1	9.04	12.546	-	-	8(16)

All patients	13.126(6.276)	14.003(5.785)	14.614(6.324)	16.696(5.072)	71(100)
mean (std)					

4.1.3 Description of Survival Outcomes

In this extensive investigation, we have explicitly delineated that the principal event of focus, which we designate as the time-to-event, is specifically related to the occurrences of death, referred to as (death), in conjunction with hospitalization events, abbreviated as (hosp). Moreover, we have meticulously characterized the key time-to-event outcomes that hold significant relevance within the framework of this research study as follows: the incidence of death (coded as 1 if it occurs and 0 if the individual is censored), while the occurrence of hospitalization is similarly represented (coded as 1 if it occurs and 0 if the individual is censored). In addition to these definitions, variables associated with the mycobacterium arm identified as M.w are also integrated (a value of 1 is attributed to individuals assigned to the treatment group M.w and a value of 0 for those in the placebo group).

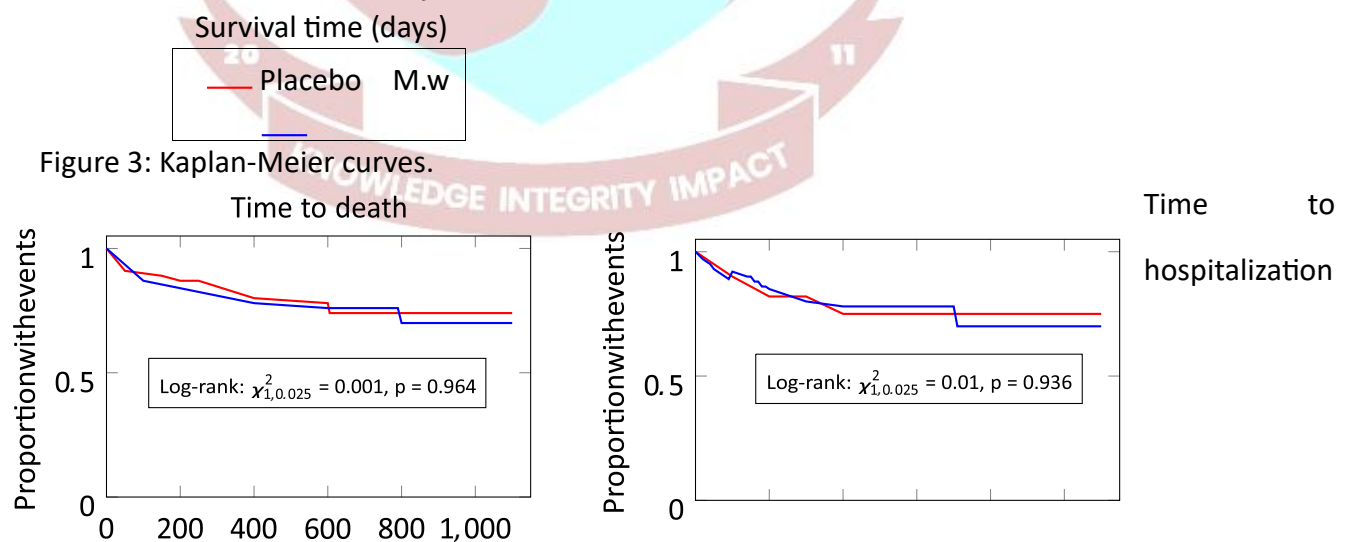
4.1.4 Covariates in the joint model

In addition to M.w, the joint model evaluated the following covariates: Sex (1 if the patient is male and 0 if female), ART (1 if the patient had ever utilized ART during the study period and 0 if the patient had never accessed ART), Age group (1 if age > 46 and 0 if age ≤ 46), HR (1 if heart rate > 100 and 0 if heart rate ≤ 100), Tamponade (1 if tamponade was present at the commencement of the study and 0 if no tamponade was observed at the outset of the study), Constriction (1 if constriction was observed at the initiation of the study and 0 if no constriction occurred), and chest X-ray pulmonary infiltrate, pulmfirate (assigned a value of 1 if present and 0 if absent).

4.1.5 Kaplan-Meier curves and log-rank tests

Our analytical approach uses the Kaplan-Meier method to estimate the proportion of survival outcomes covering both death and hospitalization in the two different treatment groups, M.w. and placebo, while rigorously assessing the statistics using the log-rank of the test. The significance of the differences identified in the incidence of these events between the two treatment cohorts, as previously described in the literature (Cleves et al., 2008; Collett, 2015b; Kaplan & Meier, 1958). The resulting Kaplan-Meier curves, combined with the results of the log-rank test, are systematically displayed in Figure 3 for further analysis. The results shown in the left panel of Figure 3 indicate that there is no statistically significant difference in the percentage of survivors when comparing

the M.w treatment group with the placebo group ($\chi^2_{1,0.025} = 0.001, p\text{-value} = 0.964$) as calculated by the accompanying p-value. Similarly, the results shown in the right panel of Figure 3 indicate that there is no statistically significant difference in the percentage of survivors when comparing the M.w treatment group with the placebo group ($\chi^2_{1,0.025} = 0.01, p\text{-value} = 0.936$) as calculated by the accompanying p-value.



0 200 400 600 800 1,000

Survival time (days)



4.2 Results: Joint model for longitudinal and survival outcomes.

In this particular section of the study, we undertake the fitting of joint models (JM), which serve as a sophisticated statistical framework for simultaneously analyzing both longitudinal and survival outcomes, specifically focusing on critical events such as death and hospitalization, all of which have been meticulously delineated in the preceding Sections 4.1.1 and 4.1.2.

The comprehensive description of the joint models utilized in this analysis can be found in Section 3.1.4, where we elucidate the underlying methodologies and theoretical foundations. These advanced models are specifically designed to investigate and quantify the influence of longitudinal outcomes, alongside various covariates, on the risk associated with the occurrence of death and hospitalization events in the studied population.

The initial joint model, denoted as JM1 and represented mathematically as model (2), operates under the fundamental assumption that the probability of an event transpiring at a designated time point j is intrinsically linked to the average value of the longitudinal measurements collected at that same time point j , denoted as $\mu_i(j)$, and can therefore be expressed through the following equation:

$$\begin{cases} y_i(j) = m_i(j) + \epsilon_i(j) \\ m_i(j) = \beta_0 + \beta_1 Mw_i + \beta_3 Mw_i \times t_{ij} + \beta_4 ART_{ij} + \beta_5 gender_i + \beta_8 constriction_i \end{cases}$$

$$\begin{aligned} \sqrt{CD4_{ij}} &= (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2 \text{Mwoart}_{ij} + \beta_6 \text{agegrp}_i + \beta_7 \text{tampon}_i + \beta_{10} \text{pulmfitrate}_i + \beta_{11} HR_i + \varepsilon_{ij}, (7) \\ h_i &= h_0(j) \exp \{ \beta_1 M_i + \beta_2 \text{Mwoart}_{ij} + \beta_3 \text{agegrp}_i + \beta_4 \text{tampon}_i + \beta_5 \text{constriction}_i + \beta_7 \text{tampon}_i \} \\ &\times \exp \{ \beta_{10} \text{pulmfitrate}_i + \beta_{11} HR_i + \alpha_1 \mu_i(j) \} \end{aligned}$$

The joint models JM2 (equation (3)), JM3 (equation (4)), JM4 (equation (5)), and JM5 (equation (6)) are detailed in equations (A.1), (A.2), (A.3), and (A.4) in Appendix A, respectively. The DIC and WAIC estimates for these models are presented in Table 4.3. Among the candidate models, JM4 (equation (5)) for time to death and JM3 (equation (4)) for hospitalization exhibit the lowest DIC and WAIC values. For illustration, we provide the convergence diagnostics for JM4 regarding death. The convergence diagnostics of the parameter estimates for JM4 (time to death) are shown in Figure 3, where the normally distributed density plots of the parameter estimates indicate that convergence has been achieved.

Parameter estimations (Est.), hazard ratios (HR), standard errors (s.e.), and 95% confidence intervals (95% CI) derived from the most optimal models, specifically JM4 pertaining to death and JM3 concerning hospitalization, are elucidated in Table 4.4 and Table 4.5, respectively.

Furthermore, each table encompasses findings from both the longitudinal and survival elements of the integrated model.

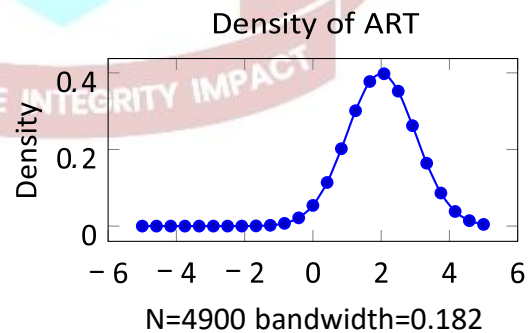
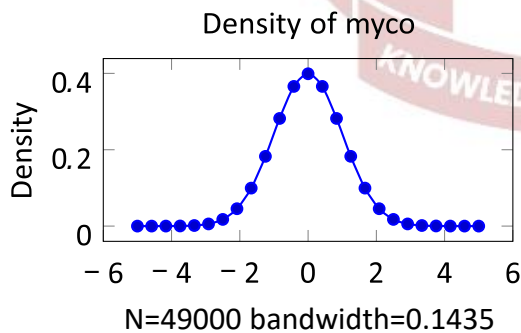
Table 4.3: Joint models compared, using DIC and WAIC to select the best fitting model.

Death

JM	Association Structure	DIC	WAIC
JM1	$\alpha_1 \mu_i(j)$	2.023547×10^8	7.127528×10^{18}
JM2	$\alpha_2 \mu_i'(j)$	1.247459×10^8	3.500067×10^{17}
JM3	$\alpha_1 \mu_i(j) + \alpha_2 \mu_i'(j)$	4.447078×10^{23}	1.309843×10^{50}
JM4	$\alpha_3 \frac{\int_0^j \mu_i(u) du}{j}$	1.447689×10^6	1.642286×10^{14}
JM5	$\frac{\alpha_1 \mu_i(j) + \alpha_2 \mu_i'(j) + \alpha_3 \frac{\int_0^j \mu_i(u) du}{j}}{\alpha_1 \mu_i + \alpha_2 \mu_i' + \alpha_3 \frac{\int_0^j \mu_i(u) du}{j}}$	4.458332×10^8	1.916545×10^{20}

Hospitalization

JM	Association Structure	DIC	WAIC
JM1	$\alpha_1 \mu_i(j)$	3.290481×10^4	1.447660×10^{11}
JM2	$\alpha_2 \mu_i'(j)$	1.690078×10^{12}	2.262674×10^{26}
JM3	$\alpha_1 \mu_i(j) + \alpha_2 \mu_i'(j)$	9.233797×10^3	2.613842×10^8
JM4	$\alpha_3 \frac{\int_0^j \mu_i(u) du}{j}$	1.416069×10^6	2.272569×10^{15}
JM5	$\frac{\alpha_1 \mu_i(j) + \alpha_2 \mu_i'(j) + \alpha_3 \frac{\int_0^j \mu_i(u) du}{j}}{\alpha_1 \mu_i + \alpha_2 \mu_i' + \alpha_3 \frac{\int_0^j \mu_i(u) du}{j}}$	6.992023×10^5	9.138542×10^{13}



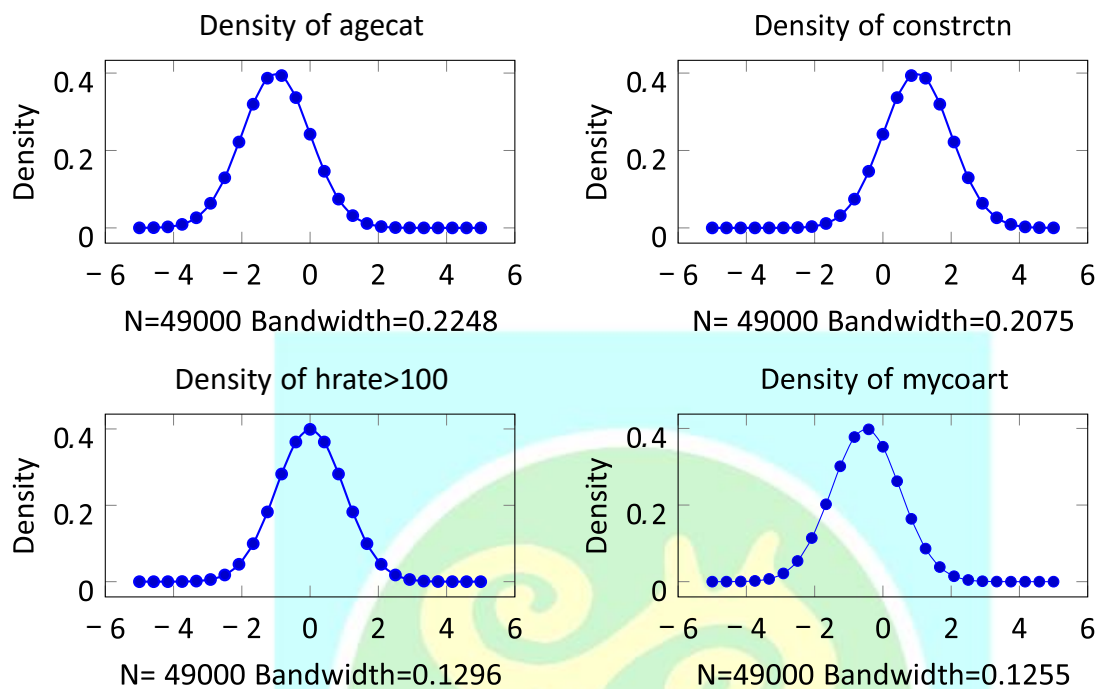


Figure 4. JM4 for time to death.

This illustrates the convergence diagnostics pertaining to the parameter estimates, namely Mw, ART, age group categorization, constriction, heart rate metrics, pulmonary infiltrate presence, and the variable of gender, which is often denoted as sex, in relation to the time until death occurs.

The empirical findings outlined in Table 4.4 clearly indicate that the association parameter interprets a statistically significant correlation between the hazard of death and the mean measurements of CD4 count, which manifests as an approximate increase of

2.7% in the hazard of death, specifically represented as 1.027 with a confidence interval of 1.021 to 1.031 (HR = 1.025, 95% CI: 1.021, 1.031, $p < 0.001$). Furthermore, it is important to note that the hazard of death, quantified as HR = 0.404 with a 95% confidence interval ranging from 0.053 to 2.319 and a p-value of 0.331, does not exhibit

a statistically significant difference when comparing patients who were administered the mycobacterium indicus pranii treatment arm in contrast to those who received a placebo treatment. Furthermore, there is a remarkable observation of a 7.5-fold increase in the risk of death, represented by a hazard ratio of $HR = 7.510$ with a confidence interval of 1.573 to 38.193 and a p-value of 0.016, in those aged 46 years and older; furthermore, men had a 44.6% reduction in the risk of death, as evidenced by a hazard ratio of $HR = 0.554$ with a confidence interval of 0.170 to 1.902 and a p-value of 0.314, compared to women. Patients receiving antiretroviral therapy (ART) at any time during the study experienced an exceptionally significant reduction in the risk of death of 83.1%, as demonstrated by a hazard ratio of $HR = 0.169$ with a 95% confidence interval of 0.040 to 0.640 and pvalue 0.013 compared with those who had never received ART. In addition, this study was released with a significant decrease of 93.6% in the hazard of death.

This is indicated by $HR = 0.064$, and the value of 0.001, which covers 0.010 to 0.288, is low in p-value = 0.001 among participants exhibiting a heart rate exceeding 100 beats per minute. Finally, it should be emphasized that the hazard of death did not demonstrate a statistically significant difference between participants who presented with constriction, tamponade, or pulmonary infiltrate at the time of enrollment and those who did not exhibit such conditions.

Table 4.4: Parameter estimates from JM4 for time to death.

JM4	Est.	s.e	95%CI	p-value
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Longitudinal part				
Myco	0.197	0.867	(-1.500, 1.900)	0.818
Time	1.906	0.340	(1.256, 2.589)	<0.001
agecat	-0.865	1.623	(-4.040, 2.311)	0.594
sex	-1.962	0.907	(-3.751, -0.208)	0.028
ART	0.479	0.740	(-1.088, 1.854)	0.477
hrate	0.727	0.852	(-0.933, 2.397)	0.397
constrctn	1.001	0.930	(-0.823, 2.822)	0.279
cartampon	0.470	0.900	(-1.290, 2.231)	0.605
pulmonary	0.568	0.940	(-1.257, 2.429)	0.550
Survival part	HR	s.e	95%CI	p-value
Myco	0.404	2.605	(0.053, 2.319)	0.331
agecat	7.510	0.787	(1.573, 38.193)	0.016**
sex	0.554	0.612	(0.170, 1.902)	0.314
ART	0.169	0.696	(0.040, 0.640)	0.013**
hrate	0.064	0.845	(0.010, 0.288)	<0.001**
constrctn	0.599	0.685	(0.1435, 2.247)	0.440
cartampon	0.802	0.665	(0.2195, 3.086)	0.710
pulmonary	0.671	0.778	(0.132, 2.896)	0.606

α_3	1.025	0.002	(1.021, 1.031)	<0.001**
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Table 4.5: Parameter estimates from JM3 for time to hospitalization

JM3	Est.	s.e	95%CI	p-value
Longitudinal part				
Myco	8.379	3.847	(1.343, 14.916)	0.007
Time	14.998	5.302	(4.234,21.479)	<0.001
agecat	-1.568	2.447	(-6.473, 3.203)	0.515
Sex	-2.929	1.402	(-5.846, -0.312)	0.028
ART	-10.661	4.027	(-17.645,-2.659)	0.005
hrate	1.599	1.303	(-0.897, 4.297)	0.202
constrctn	1.906	1.413	(-0.733, 4.858)	0.160
cartampon	0.013	1.346	(-2.701, 2.628)	0.978
pulmonary	-0.054	1.402	(-2.927, 2.650)	0.983
Survival part	HR	s.e	95%CI	p-value
Myco	0.014	2.158	(0.003,1.488)	0.072
agecat	10.577	2.102	(0.120,419.451)	0.260
Sex	1.007	1.169	(0.102, 9.301)	0.977
ART	0.309	1.637	(0.012,7.346)	0.467
hrate	0.361	1.108	(0.037, 3.097)	0.353
constrctn	15.482	1.367	(0.993,203.114)	0.051
cartampon	0.215	1.228	(0.016, 2.265)	0.199
pulmonary	3.416	1.225	(0.302,42.327)	0.301
α_1	1.008	0.001	(1.005, 1.011)	<0.001**

α_2	21.711	0.413	(11.994,58.058)	<0.001**
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It can be thoroughly ascertained from the comprehensive data presented in Table 4.5 that a 1-unit increase in the mean measurements of CD4 counts is associated with a consequential and approximately significant increase in the hazard of hospitalization, while simultaneously, a 1-unit increase unit in the mean change of CD4 counts is associated with a remarkable 22-fold significant increase in the risk of hospitalization. The analysis further reveals that the risk of hospitalization remains statistically indistinguishable between individuals who were administered the mycobacterium indicus pranii treatment and those who received a placebo intervention, indicating a lack of variance in outcomes related to this particular therapeutic approach.

Additionally, the findings reveal that there is no significant difference in the heightened risk of hospitalization when comparing male subjects to their female counterparts, and furthermore, the risk of hospitalization does not exhibit a statistically significant increase when examining individuals who are older than 46 years in contrast to those who are 46 years or younger.

Moreover, the data suggests that the risk of hospitalization does not significantly vary between participants who have ever been on antiretroviral therapy (ART) throughout the duration of the study and those who have never undergone such treatment during the same timeframe. Interestingly, patients who present with a heart rate exceeding 100 beats per minute demonstrate an insignificant reduction in the risk of hospitalization when compared to those whose heart rate is recorded at 100 beats per minute or lower. Furthermore, it is noteworthy that constriction at baseline is linked with a 15.4-fold increase in the risk of hospitalization; however, this particular increase fails to reach statistical significance, thus questioning the robustness of this association. In a similar

vein, the presence of tamponade at baseline is associated with an insignificant reduction in the risk of hospitalization, while the occurrence of pulmonary infiltrates results in a 3.4-fold increase in the risk of hospitalization that is also deemed insignificant from a statistical perspective.

Chapter 5

Summary, Conclusions and Recommendations

5.1 Introduction

This chapter presents a comprehensive overview of the study findings in direct relation to the research objectives outlined in Chapter One. It begins with a summary of results organized according to each of the stated objectives, highlighting the key insights derived from the analysis. This is followed by the main conclusions of the study and a discussion of the broader implications of the findings for policy, clinical practice, and future research.

The chapter concludes with specific recommendations drawn from the results.

5.2 Summary of Results

This scholarly research undertaking embarked upon an extensive investigation into the multifaceted ramifications that arise from the assessment of longitudinal CD4 counts, particularly as these assessments pertain to various survival metrics, which include, but are not limited to, rates of hospitalization and overall death. In conducting this analysis,

meticulous control was exercised over a range of potential confounding variables, which encompassed the baseline treatment with *Mycobacterium indicus pranii* (known to be utilized in tuberculosis therapy), the administration of antiretroviral therapy (ART), as well as demographic and clinical factors such as age, sex, constriction, tamponade, and the presence of pulmonary infiltrates that might influence the outcomes under investigation.

The comprehensive dataset that served as the foundation for this analytical endeavor was meticulously sourced from the IMPI trial (Abdul-Karim & Gumedze, 2019b, 2019a; Iddrisu, 2019; Iddrisu & Gumedze, 2020; Mayosi et al., 2013; Ntsekhe et al., 2014). In order to critically evaluate the impact that CD4 count assessments exert on survival outcomes, a sophisticated joint modeling framework was employed, which is specifically designed to facilitate the concurrent analysis of both longitudinal data and survival data, all while adequately accounting for additional risk factors that may significantly influence the overall risk associated with various survival outcomes.

Objective 1: Determine the best joint model to fit observed CD4 counts measurements combined with time-to-first occurrence of hospitalization and death, classified as the survival outcomes of interest in this study.

The complex models that were formulated to address both longitudinal and survival outcomes are intricately intertwined through a carefully constructed association structure. A series of distinct joint models, designated as JM1, JM2, JM3, JM4, and JM5, were fitted to each of the four identified survival outcomes. The culmination of these empirical investigations yielded unequivocal findings that clearly demonstrated JM4 to be the optimal joint model for death, whereas JM3 was distinguished as the most suitable model for the analysis of hospitalization events.

Objective 2: Investigate the effect of time-varying measures of CD4 count on the hazard ratio associated with survival outcomes in HIV-infected patients with tuberculous pericarditis randomized to mycobacterial therapy or placebo.

The findings revealed that the association parameter indicated a statistically significant correlation between the average measurements of CD4 counts and the hazard of death. Specifically, for each incremental unit increase in the average CD4 count, there was a corresponding elevation of 2.7% in the hazard of death. This unexpected revelation suggests that, in contrast to the traditional expectations that posit elevated CD4 counts as indicative of improved immune function, within this particular cohort higher CD4 counts were paradoxically associated with an increased death risk.

Objective 3: Conduct a comprehensive investigation of the influence exerted by the interaction between M.w and antiretroviral therapy (ART) on the hazard ratios corresponding to the identified survival outcomes.

For patients undergoing treatment with *Mycobacterium indicus pranii*, the analysis indicated that the hazard of death did not exhibit any statistically significant difference when compared with individuals receiving placebo, thereby implying that within the parameters of this study the treatment modality failed to exert any statistically significant impact on survival outcomes, which aligns seamlessly with the prior findings (Mayosi et al., 2014).

Objective 4: To identify the predictors that significantly contribute to the hazard ratios related to the survival outcomes, specifically focusing on the instances of hospitalization and death.

Age emerged as a critically significant risk factor, with individuals aged 46 years and older observed to experience a 7.5-fold increase in the risk of mortality. Gender also influenced mortality risk, as male subjects demonstrated a 44.6% reduced hazard of death compared to their female counterparts; however, this specific outcome did not achieve statistical significance.

Within the realm of antiretroviral therapy (ART), patients who received such treatment at any juncture during the study exhibited an 83.1% significant reduction in the hazard of mortality compared to individuals who had never received ART, underscoring its substantial protective effects. Additionally, a noteworthy 93.6% reduction in the hazard of mortality was found among participants whose heart rates exceeded 100 beats per minute, an observation that warrants further investigation. The analysis further indicated that constriction, tamponade, and pulmonary infiltrates did not significantly influence mortality outcomes within this study population.

5.3 Implications of the Results

The findings from this research carry profound implications for both clinical practice and policy formulation in the management of HIV-associated tuberculosis pericarditis.

5.3.1 Clinical Implications

The results highlight several important clinical considerations. First, the observation that higher average CD4 counts were paradoxically associated with an increased hazard of death suggests that clinicians should exercise caution when interpreting CD4 measurements in this specific patient population. This finding challenges the

conventional understanding that higher CD4 levels always reflect improved immune function and calls for further biological investigation.

Second, the absence of statistically significant survival benefits associated with *Mycobacterium indicus pranii* (M.w) treatment reinforces the need for clinicians to critically evaluate adjunctive therapies in tuberculosis pericarditis. This aligns with prior studies and underscores that reliance on M.w therapy may not yield tangible improvements in patient survival.

Third, the results confirm the substantial protective role of antiretroviral therapy (ART). Patients receiving ART demonstrated a remarkable reduction in mortality risk, thus reaffirming the necessity of integrating ART early and consistently in the treatment of HIV-positive patients with tuberculosis pericarditis.

Finally, demographic and clinical variables such as age and heart rate provide further clinical insights. Older individuals (46 years and above) exhibited markedly elevated mortality risk, which points to the need for heightened monitoring and tailored interventions for this vulnerable group. Similarly, the protective association with elevated heart rate, though unconventional, highlights areas that warrant further clinical inquiry.

5.3.2 Policy Implications

From a policy perspective, these findings carry significant weight. The demonstration that ART substantially reduces mortality risk provides compelling evidence to strengthen policies promoting universal and sustained access to ART for all HIV-positive patients with tuberculosis pericarditis. Policymakers should prioritize resource allocation toward

ensuring ART availability, adherence, and monitoring as part of national treatment protocols.

The absence of measurable benefit from M.w therapy also has policy relevance. Given its lack of significant impact on survival outcomes, health authorities should carefully evaluate the cost-effectiveness of including M.w as part of treatment regimens. Policies could instead direct resources toward proven interventions, such as ART, and toward research aimed at uncovering the mechanisms underlying the paradoxical CD4-mortality association.

Furthermore, the heightened vulnerability of older patients calls for age-sensitive health policies. Screening, follow-up, and supportive care for patients aged 46 years and above should be integrated into tuberculosis pericarditis management frameworks. Such targeted interventions could contribute to reducing the disproportionately high mortality burden in this group.

In summary, the results of this study not only advance scientific understanding but also provide actionable insights with direct relevance to clinical decision-making and health policy formulation.

5.3.3 Research Implications

Beyond clinical and policy relevance, the results of this study also hold significant implications for future research. The paradoxical finding that higher average CD4 counts are associated with increased mortality risk challenges existing theoretical assumptions within HIV and tuberculosis research. This unexpected association underscores the necessity for further scientific inquiry into the biological and immunological mechanisms

underlying this relationship. Future studies should explore whether this effect is cohort-specific, or whether it reflects broader immunopathological processes that have not yet been adequately characterized in the literature.

The inconclusive effect of *Mycobacterium indicus pranii* (M.w) therapy also highlights the pressing need for additional large-scale randomized controlled trials to rigorously evaluate the role of immunomodulatory therapies in tuberculosis pericarditis. Such studies should aim not only to clarify the survival implications of M.w but also to assess its potential immunological benefits in terms of reducing inflammation and improving immune recovery in HIV-positive patients.

Furthermore, the robust protective role of ART observed in this study emphasizes the value of conducting longitudinal investigations into ART adherence, timing of initiation, and drug regimen optimization, particularly within populations at risk of tuberculosis pericarditis. This line of research could provide further evidence for refining ART delivery strategies in clinical and public health settings.

Finally, the advanced joint modeling framework employed in this research contributes methodologically to the growing body of literature on longitudinal-survival data analysis. Future research could extend this modeling approach to incorporate additional time-varying covariates, explore potential non-linear associations, and address challenges related to missing data. In so doing, researchers may further enhance the precision and reliability of joint models, thereby enriching their applicability to diverse biomedical con-

texts.

In sum, the findings of this investigation open new avenues for scientific exploration, reinforcing the importance of continued interdisciplinary research at the intersection of biostatistics, immunology, and clinical medicine.

5.4 Conclusion

The results obtained from this comprehensive investigation serve to clarify a multitude of critical dimensions concerning the intricate relationship that exists between CD4 count and the likelihood of hospitalization within the demographic group that is being studied, where it has become evident that a statistically significant increase of 1% in the risk of hospitalization is observable with every incremental rise in the average CD4 count; this particular finding implies that increased levels of CD4, which are conventionally regarded as indicators of enhanced immune system performance, may, in a rather paradoxical manner, be associated with a heightened risk of hospitalization specifically within the confines of this context. In a related sphere of inquiry, the astonishing 22-fold increase in the risk of hospitalization that corresponds with variations in CD4 count underscores the pivotal importance of changes in immune status and their consequential effects on hospitalization risk, thus accentuating the critical need for maintaining a stable and healthy immune environment. It is generally expected that a rise in CD4 count levels would favorably correlate with improvements in a patient's overall health condition, thereby leading to a decrease in the likelihood of hospitalization; however, within the specific framework of the IMPI trial, it was noted that patients who were administered the M.w injection experienced a range of adverse effects linked to the treatment (Mayosi et al., 2014), which may have plausibly contributed to the increased likelihood of hospitalization that was correlated with

elevated CD4 count levels among the participants involved in this particular study. The absence of statistically significant differences in the risk of hospitalization when evaluated against parameters such as treatment with mycobacterium indicus pranii, gender, age, ART status, and heart rate indicates that these particular variables do not exert a statistically significant independent effect on hospitalization outcomes within this uniquely defined cohort of patients. However, the observation of a non-significant yet noteworthy increase in hospitalization risk associated with baseline conditions, such as constriction and pulmonary infiltrate, suggests potential avenues for more focused investigation, as these underlying conditions might still have a significant impact on patient outcomes in ways that are meaningful and consequential. In summary, the findings derived from this study shed light on the complex and multifaceted interactions that exist between immune function and the risk of hospitalization, while simultaneously indicating specific areas where further research endeavors could provide deeper insights and understanding into these intricate interrelationships.

5.5 Recommendation

While the present investigation has primarily focused its analytical lens on the JM1-JM5 parameterization framework specifically tailored for joint models, it is of paramount importance to recognize that a multitude of alternative parameterization strategies have been meticulously explored in previous scholarly literature (Rizopoulos, 2012b, 2014, 2016b, Rizopoulos et al., 2008). For example, one prominent methodology involves the intricate parameterization of a joint model by proposing the existence of shared random effects that simultaneously influence both the longitudinal data and the survival processes, thereby allowing for a deeper understanding of how these shared random

effects can significantly clarify the complex interplay between longitudinal measurements and the associated risk of events, in addition to elucidating the intricate relationships among the longitudinal measurements themselves.

In contrast, another methodological approach establishes a direct connection between the probability of an event transpiring at a specific time point, denoted as time j , and the observed level of the longitudinal outcome that was recorded at a preceding time point (Rizopoulos, 2012b, 2014, 2016b; Rizopoulos et al., 2008). Such alternative parameterization techniques are not merely theoretical constructs; rather, they may carry considerable implications for the dataset that has been employed in the current research endeavor, as well as for future studies that utilize similar data frameworks and methodologies in their analyses. The recognition of these diverse parameterization strategies underscores the complexity and richness of joint modeling approaches, highlighting the necessity for researchers to remain cognizant of the broader landscape of methodological advancements that could potentially enhance the interpretability and applicability of their findings.

Moreover, the consideration of these alternative frameworks may also foster a more nuanced understanding of the underlying mechanisms at play, thereby contributing to the ongoing discourse surrounding the optimization of joint modeling techniques within the relevant academic community. Ultimately, the integration of insights gleaned from these varied parameterization approaches could significantly bolster the robustness and generalizability of research outcomes within this domain.

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Appendix A

Specification of joint models: JM2, JM3, JM4 and JM5

$$\left[\begin{array}{l} y_i(j) = m_i(j) + \varepsilon_i(j) \\ \sqrt{CD4_{ij}} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2 M_{w_i} + \beta_3 M_{w_i} \times t_{ij} + \beta_4 ART_{ij} \\ + \beta_5 M_{wart_{ij}} + \beta_6 agegrp_i + \beta_7 gender_i + \beta_8 constriction_i + \beta_{10} + \beta_9 pulmfitrate_i + \beta_{11} HR_i + \varepsilon_{ij} \end{array} \right] \quad (A.1)$$

$$h_i(j) = h_0(j) \exp \{ \beta_1 M_{w_i} + \beta_2 ART_{ij} + \beta_3 M_{wart_{ij}} + \beta_4 agegrp_i \\ \times \exp \{ \beta_5 gender_i + \beta_6 constriction_i + \beta_7 tampon_i \} \\ \times \exp \{ \beta_8 pulmfitrate_i + \beta_9 HR_i + \alpha_2 \mu'_i(j) \}$$

$$\left[\begin{array}{l} y_i(j) = m_i(j) + \varepsilon_i(j) \\ \sqrt{CD4_{ij}} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2 M_{w_i} + \beta_3 M_{w_i} \times t_{ij} + \beta_4 ART_{ij} \\ + \beta_5 M_{wart_{ij}} + \beta_6 agegrp_i + \beta_7 gender_i + \beta_8 constriction_i + \beta_9 tampon_i + \beta_{10} pulmfitrate_i + \beta_{11} HR_i + \varepsilon_{ij} \end{array} \right] \quad (A.2)$$

$$(j) = h_0(j) \exp \{ \beta_1 M_{w_i} + \beta_2 ART_{ij} + \beta_3 M_{wart_{ij}} + \beta_4 agegrp_i \\ \times \exp \{ \beta_5 gender_i + \beta_6 constriction_i + \beta_7 tampon_i + \beta_8 pulmfitrate_i + \beta_9 HR_i + \alpha_1 \mu_i(j) + \alpha_2 \mu'_i(j) \}$$

$$\times \exp \{ \beta_8 pulmfitrate_i + \beta_9 HR_i + \alpha_1 \mu_i(j) + \alpha_2 \mu'_i(j) \}$$

