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A Joint Model for a Longitudinal Pulse Rate and Respiratory Rate of Congestive Heart Failure Patients: In Ayder Referral Hospital of Mekelle University, Tigray, Ethiopia.

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A Joint Model for a Longitudinal Pulse Rate and Respiratory Rate of Congestive Heart Failure Patients: In Ayder Referral Hospital of Mekelle University

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As thesis research advisors, we herby certify that we have read the thesis prepared by **Yemane Hailu** under our guidance, which is entitled "**A Joint Model for a Longitudinal Pulse Rate and Respiratory Rate of Congestive Heart Failure Patients: In Ayder Referral Hospital of Mekelle University"**, in its final form and have found that (1) its format, citations, and bibliographical style are consistent and acceptable and fulfill university and department style requirements; (2) its illustrative materials including tables and figures are in place; and (3) the final manuscript is satisfactory to the graduate committee and is ready for submission to the university library.

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Dedication:

This Thesis paper is dedicated, praying for their eternal life, to my beloved father, the late Hailu Fissuh, and to my cousin and my friend, the late Gaim Massa. My father was God fearing, loving, hard working and outstanding in his concern for the common good. He is my inspiration, aspiration and the reason I am the man I am today. Daddy, I thank you and I love you. You are my hero, my teacher and my companion in spirit. Gaim was a brave young man, full of life and with great sense of humor. He was friendly, kind and magnanimous. Dear Gaim, I am sorry for your untimely death, but I remember and cherish all the good times with you.

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LIST OF ACRONYMS

Abbreviations	Extended items
ACF	Acute coronary failure
ADHD	Attention-Deficit Hyperactivity Disorder
AF	Acute failure
AIC	Akaki's Information Criteria
AICC	Akaki's Information Criteria Correction
ANOVA	Analysis of variance
AOE	Association of the Evolutions
BIC	Bayesian Information Criteria
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BS	Between Subjects
CHD	Coronary Heart Disease
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DBP	Diastolic blood pleasure
EOA	Evolution of Association
GLM	Generalized linear model
HF	Heart failure
HR	Heart Rate
LMM	Linear mixed model
LVEF	Left Ventricle Ejection Fraction
ML	Maximum Likelihood
MRN	Medical registration number
NYHA	New York Heart Association
QOL	Quality Of Life
REML	Restricted Maximum Likelihood
RSA	Respiratory Sinus Arrhythmia
SBP	Systolic blood pleasure
SNRI	Serotonergic And Noradrenergic Working Antidepressants
TCA	Tricyclic Antidepressants
WS	Within Subjects

Abstract

Background: Pulse rate and respiratory rates are main symptoms of congestive heart rate and the abnormal pulse rate and respiratory rate are broad indicators of major physiological instabilities. The lower pulse rate and respiratory rates are associated with a strong and healthier heart. CHF, also known simply as HF, is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

Objective: The main objective of this study is, therefore to investigate the joint evolution of pulse rate and respiratory rate of cognitive heart failure patients and identify the potential risk factors affecting the two end points in Ayder referral Hospital of Mekelle University.

Methods: The latest data from 2004 E.C. up to 2005 E.C. have been taken from medical charts of 264 adult CHF patients in Ayder Referral Hospital of Mekelle University. Linear mixed effects model was fitted for the pulse rate and respiratory rate outcomes. Furthermore, a joint mixed effects model was fitted for the two end points, and the potential risk factors affecting their joint evolution are identified.

Results: The baseline mean and standard deviation of both PR & RR were 126.11 &18.98bpm and 31.64 &10.99 brpm respectively. The association of the evolution for PR & RR was estimated to be ($\rho = 0.7054$) which is statistically significant at 1% level of significance with 95% CI of (0.642, 0.769).

Conclusions: The data analysis showed that pulse rate and respiratory rate showed a decreasing pattern over time based on the joint as well as the separate models. Furthermore, a positive and significant association was observed between the two end points and the covariates such as: sex, weight, New York Heart Association classes, age and interaction of time with weight and Left ventricle ejection fraction. While, negative and significant association was observed between two endpoints and the covariates such as: LVEF and time. Finally, to identify associated effect fitting joint model for paired endpoints is recommended.

Key words: Pulse Rate, Respiratory rate, CHF, joint mixed effect models

CHAPTER ONE

1. Introduction

1.1. Background of the study

Abnormal respiratory rates and changes in respiratory rate are broad indicators of major physiological instability, and in many cases RR is one of the earliest indicators of this instability. Therefore, it is critical to monitor RR as an indicator of patient status. RR performs at least as accurately in identifying patients at risk of these adverse events as pulse rate and the systolic blood pressure. A RR of greater than 24 breaths per minute is able to identify approximately 50% of patients at risk of serious adverse events with 95% specificity (American Heart Association, 2002). Although the main function of the respiratory system is gas exchange, a broad range of factors can affect ventilation. RR can be used to detect exacerbations and/or changes in the severity of chronic illnesses, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF). In patients with CHF, an increase in RR can warn of impending pulmonary edema, or fluid in the lungs, which is a common debilitating symptom of CHF (American Heart Association, 2002).

Heart rate is among the many vital signs (respiration rate, blood oxygen saturation, arterial blood pressure, etc.), one of the most commonly measured and monitored. Whatever will be the sensing principle or the monitoring method used, data referred to the heart rate can be considered the primary vital sign information which is needed on a patient approach in both emergency and clinical situations. Heart rate data are used to measure anomalous rate or irregular pulse rate (arrhythmias) or heart block (Gorgas, 2004). The heart (pulse) rate represents the number of times the heart beats in a certain period of time. It is usually measured in minutes, and normal resting HR is approximately 60 to 80 beats per minute. It can go as high as 100 in a healthy adult and as low as 40 in athletes (American Heart Association, 2002 and Gorgas, 2004). The HR can be measured in various areas of the body, but the two most common sites are the wrist and neck. A lower HR is associated with a stronger and healthier heart. A lower HR means the heart is not pumping or working hard to deliver blood and oxygen to the body. The pulse can be lowered through regular exercise, and there are also breathing exercises to lower the heart. Take slow

deep breaths to lower the pulse. This can help because breathing can be voluntarily controlled to alter the activity of the nervous system.

Heart failure is a condition in which one or both ventricles cannot pump sufficient blood to meet the metabolic needs of the body (Dennison, 2000). Heart failure, also known as congestive heart failure, is a chronic condition that develops over time. It is not only a personal tragedy for patients and their families but a serious public health burden for society. As it progresses, the heart's pumping action grows weaker. In some cases, the heart can't fill with enough blood; in other cases, the heart can't pump blood to the rest of the body with enough force. Patients with CHF have a poorer quality of life and shorter life expectancy compared with those of the same age in the general population. The condition can affect the right side of the heart only, or most commonly it can affect both sides of the heart (Dennison, 2000). Congestive heart failure is a chronic, debilitating illness, with ever-increasing prevalence in the aged peoples. It is one of the most familiar causes for hospital admission, and associated treatment costs are estimated at $20.2 billion (Susan, *et al.,* 2001).

Congestive heart failure (CHF) is a major chronic disease in the United States, with a massive impact on health care costs. It is estimated that more than 4 million persons in the United States have CHF, and it is present in almost 10% of persons older than 70 years. It is the only cardiovascular disease that is increasing in incidence and prevalence (Packer *et al.,* 1999; Schocken *et al.,* 1992). Heart failure is the most common diagnosis in hospitalized patients older than 65 years. One third of the patients hospitalized for CHF were readmitted within 90 days of discharge.' Prognosis with CHF is poor, with 1 in 5 patients dying within 1 year of diagnosis and half within 5 years (Packer *et al.,* 1999 and Ho *et al.,* 1993).

Approximately 30% to 50% of patients with heart failure have major intra-ventricular conduction delay, which is associated with higher risk for adverse events (MacIntyre *et al.,* 2000; Lloyd-Jones *et al.,* 2002). Biventricular pacemakers resynchronize the ventricular contraction to improve ejection fraction and relaxation of the left ventricle (Jong *et al.,* 2002) However, not all therapies that improve functional outcomes in patients with heart failure reduce mortality (Poole-Wilson *et al.,* 2003**)**. HF is the fastest-growing cardiovascular diagnosis in North America, and

the lifetime risk is now estimated at nearly 20% (American Heart Association, 2002; Jones *et al.,* 2002).

Despite many diagnostic and pharmaco-therapeutic advances over the past 2 decades, symptomatic heart failure still carries a poor prognosis.(MacIntyre *et al.,* 2000; American Heart Association, 2002) Thus, novel therapies for heart failure are still needed. To improve survival, these therapies must reduce either sudden cardiac death (the most common cause of death in patients with NYHA class I or II symptoms) or progressive heart failure (the predominant cause of death in those with NYHA class III or IV symptoms) (Jong *et al.,* 2002; Poole-Wilson *et al.,* 2003).

The study of the pattern of medical mortalities in a specialist hospital in north-central Nigeria which was carried out from 2008-2010 also indicated that, there were seventy-six deaths (11.1%) during the period in question with HIV and related complications accounting for most recorded mortality (32.9%) closely followed by 28.9%non-communicable cardiovascular conditions (hypertension, heart failure and CVD) (Joseph and Afolabi, 2010). They reported non-communicable conditions like hypertension, congestive heart failure, cerebrovascular accident and acute coronary syndrome contributed a very significant part of the total mortality in their study.

Hailu *et al* (2013) investigated the prevalence of depression and determinants among adult patients admitted in governmental hospitals, Mekelle, Tigray, Ethiopia. Thereafter they reported that the prevalence of depression and anxiety was high in both chronic obstructive pulmonary disease (8–80% depression; 6–74% anxiety) and chronic heart failure (10–60% depression; 11–45% anxiety). Similarly, the physical, psychological and social consequences of depression negatively impacted on CHF and CHF symptoms generate depression, especially in those with risk factors (Yohannes, 2010).

In 2008, an un-published annual summary report from Ayder referral hospital, the biggest tertiary care center in the Tigray region with more than 450 hospital beds for in-patient care showed prevalence of cardiovascular diseases among admitted patients to be around 15 % (Fikru, 2008). Moreover, an un-published annual summary report from Ayder referral hospital in 2012/2013, on cardiac syndromes 10% of the patients was with congestive heart failure.

Moreover, in 1988, Hodes reported that out of 385 cardiac patients seen at Black lion hospital in Addis Ababa 152 of them had Rheumatic heart diseases, 47 were Hypertensive, 39 had Cardiomyopathy and 36 had congenital heart diseases.

A preliminary report from Ayder referral hospital in 2012 also showed prevalence of Rheumatic heart disease is close to 40% of the cardiac patients presenting for Echocardiographic evaluation, which was consistent with a 2010 report from Jimma of a similar study over five years period (2003-2008) showing Rheumatic heart diseases to be the commonest accounting for 33% of cases (*Habte, et al.,* 2010). Cardiovascular care in Ethiopia can be labeled as rudimentary, as only basic therapies are delivered, and most patients do not even get the opportunity to get the available service for the scarcity in manpower and facility resources.

Furthermore, the study on outcome of children with acute post streptococcal glomerulonephritis in Tikur Anbessa Specialized Teaching Hospital Addis Ababa, Ethiopia indicated that, out of five patients who were admitted with severe manifestations such as seizure and/or encephalopathy for which phenytoin was prescribed apart from antibiotics and anti hypertensive three (60%) patients were diagnosed to have congestive heart failure at admission. Severe hypertension, encephalopathy and congestive heart failure are common complications despite benign feature of acute post streptococcal glomerulonephritis *(*Mossie and Shimelis, 2012).

1.1.1. A joint mixed effect model

Repeated observation of multiple outcomes is common in biomedical and public health research. Such experiments result in multivariate longitudinal data, which are unique in the sense that they allow the researcher to study the joint evolution of these outcomes over time. In many circumstances, more than one response variable is followed longitudinally, and analyzing all jointly may be beneficial (Laird and Ware, 1982). Until recently, methods for multiple longitudinal outcomes have largely been based on simple approaches where each outcome is analyzed separately, or by reducing the dimension of the multiple outcomes through a factor analysis or principal components type of approach. The former approach is reasonably easy to implement, with the approaches already discussed, but ignores both the correlation between longitudinal outcomes and/or other features such as measurement error likely to exist in one or more of the outcomes (Molenberghs and Verbeke, 2005).

Reducing the dimension of the multiple outcomes is also easy to implement, and can quite often capture much of the correlation between outcomes. Another frequently used method is to introduce random effects, but instead of sharing the random effect across the longitudinal responses, use separate, but correlated random effects in the longitudinal responses (Gueorguieva and Agresti, 2001). Such joint models are potentially advantageous in several statistical and practical aspects. Intrinsically multivariate questions concerning relationships between outcomes and the joint influence of covariates on them may be easily answered by fully exploiting the multivariate nature of the data through joint models. Generally, there exist many different approaches to the modeling of longitudinal data.

1.2. Statement of the problem

Even though the abnormal statuses of PR &RR are crucial problems on life quality & HF, there is no more intention on it in many societies especially in developing countries. That's why CHF becomes one of top diseases in death of peoples with a poorer quality of life and shorter life expectancy. The investigator was initiated to study on this study title due to the questions that arise in his mind about a joint model for a longitudinal process on PR & RR of CHF patients.

Most models for longitudinal analysis focus on a single outcome variable. However, it is important to investigate the associated or shared effect of more than one outcome of congestive heart failure patients. Many well established and standardized investigations always deal with only one repeatedly measured outcome for individual patients or subject i.e. separately analyzing longitudinal outcomes. Nevertheless, it is crucial to be familiar with analysis of joint random effect model which might be raised from unobserved variables.

Moreover, so far in earlier time, even though joint mixed effect model for the multivariate longitudinal outcomes was great role to capture the random effect of unobservable variable, Because of unavailability of well established statistical methods as well as shortage of software packages it was not well employed before decades. However, now a day there exist well established statistical methods accompanied by excellent software packages for joint mixed effect model. So, the investigator intended to capture the random effect of correlated outcomes of repeatedly measured symptoms of congestive heart failure patients i.e. PR and RR. The typical way of approaching this problem is by applying a joint mixed effects model for the two longitudinal outcomes. Generally, when several markers are measured repeatedly, longitudinal multivariate models could be used, like in econometrics. However, this extension of univariate models is rarely used in biomedicine although it could be useful to study the joint evolution of biomarkers. Finally, this study is going to answer the following basic questions.

- ✓ How is the evolution of pulse rate related to the evolution of respiratory rate?
- ✓ How is the association between pulse rate and respiratory rate evolved over time?

1.3. Significances of the study

The results of this study will be useful in the development of an effective CHF care and patient monitoring system. Specifically, this study will be helpful in:

- This study will enhance the attitude of societies towards effective treatment and sustained following up of clinical diagnosis to control the abnormality of pulse rate and respiratory rate of CHF patients.
- It will enable to identify the association of irregular pulse and respiratory rates with risk of CHF patients.
- To understand the importance of attending clinic/ hospital in early stage of CHF consistently and sustain follow up of taking repeated treatment with preferable drugs with respect to severity level in order to control the abnormality of the symptoms like PR and RR.
- It will enable to identify the risk factors those worsening abnormality of pulse rate and respiratory rate separately and jointly. This will in turn inform the respective policy makers of the health sector in the effort to propose an appropriate control and management plan.
- Finally, this study will give some guidance to the investigators on the area of joint mixed effect model for two continuous longitudinal outcomes to investigate joint and separate evolutions of the outcomes simultaneously.

CHAPTER TWO

2. Literature review

2.1. Introduction

2.1.1. Congestive heart failure (Heart Failure)

Congestive heart failure is a clinical condition encountered in the emergency and pre-hospital settings. The condition affects more than 400,000 Canadians, with over 50,000 new cases occurring annually (Kostuk, 2001). For example, in Montreal, Canada, a city with a current population of 3.6 million (Eckstein and Suyehara, 2002) the rates of hospital admission increased over the 1990-1997 period, while the length of stay decreased, and rates of re-admission were found to have increased (Feldman et al., 2001). CHF may be commonly confused with chronic obstructive pulmonary disease (COPD), pneumonia and other respiratory conditions, each with different treatment strategies

2.1.2. Risk Factors for Heart Failure

About 5.7 million people in the United States had heart failure, and it results in about 300,000 deaths each year. The number of people who have heart failure is steadily growing (American Heart Association, 2010).

Age: Heart failure is more common in people aged 65 or older, as aging can weaken the heart muscle.

Gender: Men had a higher rate of heart failure than women.

Race: African Americans were more likely than people of other races to have heart failure. They're also more likely to have symptoms at a younger age, have more hospital visits due to heart failure, and die from heart failure.

Weight: Excess weight puts strain on the heart. Being overweight also increases the risk of heart disease and type 2 diabetes. Not only those things but smoking, hypertension, obesity, valvular heart disease, and CHD are important risk factors for CHF (American Heart Association, 2010).

Left ventricular ejection fraction (LVEF): refers to the fraction of blood pumped out of the left ventricle with each heart beat. A distinction is often drawn between patients with preserved ejection fraction (usually defined as greater than 40 to 50%) and those with left ventricular systolic dysfunction (characterized by reduced LVEF) (Jessup *et al.,* 2009).

2.1.3. Statistical analysis of risk factors on congestive heart failure

Even if various disorders of the pericardium, myocardium, and endo-cardium can lead to congestive heart failure, 80% of CHF was due to left ventricular systolic dysfunction. The relation of daily activity levels in patients with CHF and long-term prognosis was analyzed in 84 patients with class II to III heart failure, all with ejection fraction (EF) less than 35% (Schocken *et al.,* 1992). The six months post discharge readmission rates for CHF were as high as 44% (Krumholz *et al.,* 1997) with exacerbation of CHF accounting for 18%. More than 65% of patients admitted for heart failure exacerbation were due to lack of compliance with either drugs or dietary indiscretions, or both (Ghali *et al.,* 1988). Other factors contributing to readmission of older heart failure patients include age, gender, early discharge, failing or nonexistent support system, and polypharmacy (Jaarsma *et al.,* 1996). Even though 66% of patients enrolled at baseline were either New York Heart Association (NYHA) class II or III at 6 months follow up, 76% of patients were listed as NYHA class I or II. This indicated the reduction of risk (severity) of CHF as written in (Shah *et al.,* 1990).

2.2. Longitudinal analysis on heart rat variability

Carmilla *et al* (2010) have studied longitudinal evidence for unfavorable effects of antidepressants on heart rat variability. Thereafter, at baseline and 2-year follow up on heart (pulse) rate and cardiac vagal control as indexed by respiratory sinus arrhythmia (RSA) were measured in 2114 subjects (mean age=42.0 years; more than half 66.2% females), who either used antidepressants at one or two time points (n=603) or did not use antidepressants at any time points (1511). At follow up, there were less healthy controls and fewer subjects had psychopathology than at baseline. RSA slightly decreased, whereas heart rate and respiration rate increased over the two year follow up period. Age was associated with RSA($r=-0.53$, P-value<0.001), and heart rate ($r=0.14$, P-value<0.001). Women had 8.1ms times higher RSA and 2.5bpm times higher HR than men (Carmilla *et al,* 2010).

The result of the fully adjusted mixed model analyses on HR and RSA in the different antidepressant groups, showed that the overall group by time interaction was significant for HR (F=9.274, df=11, p-value<0.001) and RSA (F=7.461, df=11, p-value<0.001), which indicated that changes in HR and RSA over time were significantly different across antidepressant groups taking into account all covariates such as sex, age, BMI and educational level. Both HR and RSA had no significant difference with those covariates (Carmilla *et al*, 2010).

Ferrari (2010) investigated the mixed model on heart rate in Alpine marmots, Orvielles Gran Paradiso National Park, Italy. Marmot id was nested within family group as random terms. Body mass, sex, social status, age c1ass and the interaction between body mass and age c1ass were included as fixed effects. The final model on heart rate included dominance status, age, body mass and age-body mass interaction as significant fixed effects. Heart rate decreased with age, pups having higher heart rates with mean value and standard deviation (71.25 ± 10.92) than sub-adult with mean value and standard deviation (64.26 ± 12.96) and adult individuals with mean value and standard deviation (53.56 ± 12.52).

Ferrari (2010) also analyzed the likelihood ratio test for the best random structure in models with body temperature, breathing or heart rate as response variable. All models were run using the Restricted Maximum Likelihood (REML) procedure and included the same fixed effects: age, dominance status, sex, body mass at the day of capture and the interaction between age and body mass. Rates were square-root transformed prior to analyses. Raw measures of heart rate, breathing rate and body temperature were all positively and significantly correlated with each other (breathing rate and heart rate (r_s =0.29; P-value < 0.0001); heart rate and temperature (r_s = 0.17; P-value = 0.05); breathing rate and temperature (r_s= 0.48; P-value < 0.0001).

2.3. Joint model for longitudinal data

Very few tools exist in the literature to model such data. Zeger and Liang (1991) considered, at each time point t, a model for the mean of each outcome conditional on its history and on the values of the other outcomes at time t. the conditional variance of each outcome are assumed proportional to a fixed function of the conditional mean. A joint model for mixed continuous and categorical data was proposed by Olkin and Tate (1961). It was extended to deal with missing values in Little and Schluchter (1985). Conditionally, on the categorical responses

combination (with a marginal multinomial distribution), they assume that the continuous variables were multivariate normal. Many models for mixed type data can be found in literature devoted to the analysis of toxicity studies. These usually involved clustered responses of mixed type (Ryan, 2000).

A joint multivariate normal distribution was considered for the corresponding latent variables and each outcome was analyzed with a marginal dose-response model. The covariance matrix takes into account the correlation between outcomes and the correlation due to clustering. That was an important improvement of (Catalano and Ryan, 1992; Fitzmaurice and Laird, 1995) as model estimates of the correlation between outcomes and evolution of these correlations with dose were available. Hence, in relation to those literatures, the joint model for two symptoms of CHF i.e. PR and RR was considered to assess and identify both estimate of the correlation between two outcomes and the evolution of these correlations with a certain treatment throughout the time.

For instance, Thiébauta *et al* (2007) investigated the bivariate random effects model between the evolution of CD4 and HIV RNA and he reported the bivariate random effects model was significantly better than two separate univariate random effects models with (p-value<0.0001). He found the highest correlations between the slopes of the two markers at the same period: (before 4 months and after 4 months).

In addition, the joint mixed effect model on evolution of occurrence and prevalence of antimicrobial resistant zoonotic agents were executed by Ferrari and Cribari-Neto (2004). They used beta-regression to illustrate the joint evolution on both outcome variables and they reported that, the correlation was estimated to be 0.95, with 95% confidence interval [0.414, 0.997] showing that the correlation was positively significant. Thus, there was a strong correlation between percentage resistant and prevalence and that both were increased with time. That correlation however ignores the effect of time.

Furthermore, the hemodynamic effect on diastolic blood pressure, systolic blood pressure and heart rate was studied by Lambert and Vandenhende (2001). These three responses were measured repeatedly over time on 10 healthy volunteers during the dose escalation. The available covariates included in the study were sex and the concentration of drug in the plasma at time of

measurement. The analysis was focused on the safety data, more safety data and more precisely on assessment of drug heart rate (HR, in beats/min), diastolic (DBP) and systolic blood pressures (SBP) (in mmHg) for the ten subjects in the treatment arm. These measurements were taken before the first dose on day 1 and 4 hours after the morning dose on days 6-8, 12-14, 18-22.

Thus, twelve repeated measurements were recorded per subject for each of the three outcome variables. In addition, the drug concentration (in ng/ml) was measure in plasma at the same times. An additional covariate was sex. First, the evolution of diastolic BP, systolic BP and heart rate were separately analyzed. And time did not appear explicitly associated with regression parameters (Lambert and Vandenhende, 2001). Indeed, time was only used to describe serial dependence between the repeated measurements as was explained by Lambert and Vandenhende (2001) and serial dependence was only found necessary to model heart rate profiles. In this dose escalation study, drug concentration tends to increase with time. For this reason, the effect of time appeared indirectly in the model as it was associated with the variation of the drug concentration in plasma. Gamma distribution was selected to fit the evolution of heart rate and the covariates considered were location drug concentration and sex.

Lambert and Vandenhende (2001) reported that, the marginal mean heart rate was significantly smaller for men than for women but not significantly related to the drug concentration. They suggested that, the choice to the normal copula as the dependence structure could easily be specified through the variance-covariance matrix. The dependence between any two of the three outcomes measured by a parameter ρ with $\rho \leq |1|$ was again related to Kendall's tau (Lambert and Vandenhende, 2001). Two Joint models of heart rate with Systolic BP and with Diastolic BP were modeled. Thus, Lambert and Vandenhende (2001) reported that there was no significant association between heart rate and systolic BP but there was significant positive association between HR and DBP with a fitted Kendall's tau equal to 0.53 before treatment and 0.07 when there was drug in the plasma. There was no significant effect of sex on HR (PR) and DBP. In addition, joint model for SBP and DBP was fitted and there was a significant positive association between two variables with a fitted Kendall's tau equal to 0 and 0.42 for females before and after drug administration respectively and 0.22 for males no significant treatment effect on the association parameter was detected (Lambert and Vandenhende, 2001). Then in line to this the

joint mixed effect model of two symptoms (endpoints) of CHF i.e. PR and RR are modeled in this study.

Njagi *et al* (2013) analyzed joint modeling on the risk of re-hospitalization and the mean number of times a patient's heart rate measurements which was classified as “abnormal", with LVEF as a baseline covariate for chronic heart failure data. Notice that the survival outcome is repeated (recurrent). He analyzed jointly model the recurrent time-to-re-hospitalization and a count version of the dichotomized longitudinal heart rate by understanding re-hospitalization is important in heart failure management. Heart rate was first dichotomized into “normal" (50-90; coded 0) and “abnormal" (values higher than 90; coded 1). Values less than 50 were not considered for that analysis.

During each period in which a patient was not under hospitalization, the number of times that the patient's heart rate measurements were classified as “abnormal" was enumerated, generating a count response. Notice that patients who were re-hospitalized and discharged at least once in the course of the study had at least 2 periods in which they were not under hospitalization, separated by a period of hospitalization. As a covariate, Njagi *et al* (2013) considered the baseline left ventricular ejection fraction, LVEF. LVEF indicates the fraction of blood being pumped out of the ventricle with each contraction. He also considered two categories for this covariate; (>45%; coded 0, and (<= 45%; coded 1), forthwith referred to as “preserved ejection," and “reduced ejection," respectively (Dendale *et al*., 2011). Njagi *et al* (2013) first looked at the results from the extended model.

The test for a joint effect of ejection status on both processes was not statistically significant ($p = 0.1650$), and therefore they concluded that there is no statistically significant evidence of a joint effect of ejection status on both the mean number of abnormal heart rate measurements and the risk of re-hospitalization. Based on exponentiation of the relevant parameter estimate, the mean number of abnormal heart rate measurements in patients with reduced ejection was found to be 3.3531 times that of patients with preserved ejection. That effect was at borderline statistical significant ($p = 0.0594$). The risk of re-hospitalization for patients with reduced ejection was obtained, by also exponentiating the corresponding parameter estimate, as 5.5168 times that of

patients with preserved ejection; however, that effect was clearly not statistically significant (p-value = 0.6498).

Njagi *et al* (2013) then compared the results from the extended and the conventional model. Based on an AIC-based comparison, they observed that their extended model provided improvement to model fit, without compromising parsimony. There was impact on both the point estimates and standard errors. As they noted, the effect of ejection status on the mean number of abnormal heart rate measurements was border-line significant under the extended model; however, the case was quite different under the conventional model (p-value = 0.0901). There was also a remarkable difference in the scale factor; it was highly significant under the conventional model (p-value = 0.0022), while that was clearly not the case under the extended model, as they mentioned. However, in terms of the hypothesis of a joint effect of ejection status on both processes, the two models had provided close results; (p-value = 0.1650; 0.1648) for the extended and the conventional model respectively. It was important to recall that in univariate generalized linear models for non-Gaussian outcomes overly restrictive variance functions pose the risk of incorrect standard errors (Agresti, 2002). Though the joint modeling case was different since more outcomes were involved, it would be expected that too parsimonious variance structures may pose similar problems.

CHAPTER THREE

3. Objective

3.1. General objective

The main objective of this study is to investigate the joint evolution of pulse rate and respiratory rate of congestive heart failure patients and identify the potential risk factors affecting the two end points in Ayder referral Hospital of Mekelle University.

3.2. Specific objectives

The specific objectives of the study are:

- To explore the evolution of pulse rate of CHF patients over time.
- To explore the evolution of respiratory rate of CHF patients over time.
- To fit a mixed effect model for the pulse rate and identify the associated factors.
- To fit a mixed effect model for the respiratory rate and identify the associated factors.
- To fit a joint model for pulse rate and respiratory rate of CHF patients and to compare with separated models.

CHAPTER FOUR

4. Methodology of the study

4.1. Data source

The data were obtained from Ayder Referral Hospital of Mekelle University of CHF patient Clinic, north of Ethiopia in Tigray region. Mekelle University is one of the higher learning institutions found in Tigray National Regional State, North Ethiopia. The longitudinal data are extracted from patients' chart which contains epidemiological, laboratory and clinical information of all CHF patients under different drug levels follow-up including a detailed heart failure history.

4.2. Study design

The study was structured as a prospective cohort study of longitudinal process research design. For the purpose of fitting separate and joint model for two outcomes with prospective treatment of CHF patients, one full day training for two workers and six days for supervisions has been provided on data extraction and organization in order to have relevant data. Eight days has been taken in data extraction and cleaning; data was extracted from CHF patients' card by identifying the patient cards according to respective MRN from medical center and then the extraction of the data was processed in card room as per agreement of researcher. After data extraction, data entry, data editing, data coding and organization was conducted.

4.3. Study population

The study used data taken from medical charts of adult CHF patients' weekly follow up which were taken from September 2004 E.C. up to August 2005 E.C. in Ayder Referral Hospital of Mekelle University. The follow up is not exactly started at the same time for all patients and also not equally repeated. This study is based on 264 CHF patients with total repetitions of 6494 weeks with minimum repetitions of 4 weeks and maximum repetition of 46 weeks and on average repetition of $16.103 \approx 17$ per individual subjects. All the patients of congestive heart failure were including.

4.4. Study variables

- Response variables
    - Pulse rate
    - Reparatory rate
- Covariates(independent variables)

Eight covariates are used for both separate & joint analyses. Four of these covariates are continuous while four of them are categorical covariates.

Table 3.1 Lists of covariates and their representing symbols and category levels

NO.	Variable	Description	Value/codes
1	Sex	Sex of the CHF patients	Male=0,Female=1
2	Age	Age of the CHF patients	In Year
3	Weight	Weight of the CHF patients	In Kilograms
4	NYHA	NYHA of the CHF patients	class I=1,class II=2,class III=3, class
5	Time	Time Follow up in Weeks	Weekly Follow up
6	Diagnosis	Diagnosis History of the CHF patients	others=0,Sever Anemia=1,CHD=2, ACF=3
7	Residence	Place of residences of the patients	0=Urban, 1= Rural
8	LVEF	Left ventricle ejection fraction	In Percentage (%)

4.5. Statistical Analysis technique

Different statistical analysis including both descriptive and inferential statistics, such as: summary statistics, data exploring and model comparison have been used in this study. Joint random effects with LMM have been modeled to infer the joint effect of bivariate longitudinal outcomes of CHF patients. Finally, Data were analyzed using SAS and R.

4.5.1. Descriptive statistics and Data exploring

Data exploration is a very helpful tool in the selection of appropriate models. Thus, individual profiles plot, the mean profile plot and exploring the random effects and other data exploratory analysis for the data sets have been considered.

4.6. Statistical Model

A joint linear mixed effects model is considered to study the joint evolution and association of PR and RR end points. Furthermore, the two outcomes are analyzed separately for comparison purpose. Mixed effects models contain both fixed and random effects:

Fixed Effects: - factors for which the only levels under consideration are contained in the coding of those effects for instance, sex: where both male and female genders are included in the factor, it is fixed effect.

Random Effects: - factors for which the levels contained in the coding of those factors are a random sample of the total number of levels in the population for that factor. A Subject (in this case MRN) which is a random sample of the target population can be considered as random. Through random effects models, the researcher can make inferences over a wider population in LMM than possible with GLM.

The first step in the model building process for a linear mixed-effects model, after the functional form of the model has been decided, is choosing which parameters in the model, if any, should have a random-effect component included to account for between-group variation.

4.6.1. Separated Linear Mixed effect Model

A mixed linear model is a generalization of the standard linear model used in the GLM procedure, the generalization being that the data are permitted to exhibit correlation and non-constant variability. The mixed linear model, therefore, provides you with the flexibility of modeling not only the means of your data (as in the standard linear model) but also their variances and covariance. The Linear Mixed Model (LMM) is also a generalization (extension) of the Linear Model (LM) that allows for incorporation of random effects and is represented in its most general fashions (Molenberghs and Verbeke, 2000):

$Y_i(t) = X_i(t)^T\beta + Z_i(t)^T\gamma_i + \varepsilon_i(t)$ Where,

$Y_i(t)$: Measurement of univariate response in i^{th} patient at time t

$X_i(t)$: Vector of fixed covariate for i^{th} subject at time t (of dimension k)

$Z_i(t)$: Vector of random covariate for i^{th} subject at time t (of dimension q)

β: Vector of unknown parameters associated with fixed covariate (of dimension k)

γ_i: Vector of unknown parameters associated with random covariate for i^{th} subject (of dimension q), $\gamma_i \sim MVN(0, D)$

ε_i: Random error component

Further, $Z_i(t)$ is subset of $X_i(t)$ and $\varepsilon_i = [\varepsilon_i(t_1), \varepsilon_i(t_2), \dots, \varepsilon_i(t_{ni})]^T \sim MVN(0, R)$

$\varepsilon_i$is independent of γ_i

Where, X_i and Z_i are the fixed and random design of covariates, respectively, β is a vector of unknown fixed effects, γ_i is a vector of unknown random effects and ε_i is the unknown random error. β represents parameters that are the same for all subjects; γ_i represents parameters that are allowed to vary over subjects.

Terminology:

Fixed effects: β_i

Random effects: γ_i

Variance components: elements in D and R

Assumptions:

$$\mathbf{E}\begin{bmatrix}\gamma_i \\ \varepsilon_i\end{bmatrix} = \begin{bmatrix}\mathbf{0} \\ \mathbf{0}\end{bmatrix} \quad \text{and} \quad \mathbf{Var}\begin{bmatrix}\gamma_i \\ \varepsilon_i\end{bmatrix} = \begin{bmatrix}\mathbf{D} & \mathbf{0} \\ \mathbf{0} & \mathbf{R}\end{bmatrix}$$

Assumptions: $Y \sim N(X\beta, V)$ where, $V = Z_i D Z_i^{'} + R$

4.7. Model-Building Strategies

A primary goal of model selection is to choose the simplest model that provides the best fit to the observed data. There may be several choices concerning which fixed and random effects should be included in an LMM. There are also many possible choices of covariance structures for the D and R_i matrices. All these considerations have an impact on both the estimated marginal mean (X_i) and the estimated marginal variance-covariance matrix V_i ($= Z_i D Z_i^{'} + R$) for the observed responses in Y_i based on the specified model. The process of building an LMM for a given set of longitudinal or clustered data is an iterative one that requires a series of model-fitting steps and investigations, and selection of appropriate mean and covariance structures for the observed data. Model building typically involves a balance of statistical and subject matter considerations; there is no single strategy that applies to every application.

4.7.1. Variable selection for fixed and random effects

The Top-Down Strategy: - The following broadly defined steps are suggested by Verbeke and Molenberghs (2000) for building an LMM for a given data set, a top-down strategy for model building is used because it involves starting with a model that includes the maximum number of fixed effects that we wish to consider in a model.

Start with a well-specified mean structure for the model: This step typically involves adding the fixed effects of as many covariates (and interactions between the covariates) as possible to the model to make sure that the systematic variation in the responses is well explained before investigating various covariance structures to describe random variation in the data.

Select a structure for the random effects in the model: This step involves the selection of a set of random effects to include in the model. The need for including the selected random effects can be tested by performing REML/ML-based likelihood ratio tests for the associated covariance parameters.

Select a covariance structure for the residuals in the model: Once fixed effects and random effects have been added to the model, the remaining variation in the observed responses is due to residual error, and an appropriate covariance structure for the residuals should be investigated.

Reduce the model: This step involves using appropriate statistical tests to determine whether certain fixed-effect parameters are needed in the model.

4.7.2. Different covariance structure

Variance components (VC):- The VC structure is the standard variance components and is default structure.

$$\begin{bmatrix} \sigma_1^2 & 0 & 0 & 0 \\ 0 & \sigma_2^2 & 0 & 0 \\ 0 & 0 & \sigma_3^2 & 0 \\ 0 & 0 & 0 & \sigma_4^2 \end{bmatrix}$$

Autoregressive (1):- The AR (1) structure has homogeneous variances and correlations that decline exponentially with distance. It also means that two measurements that are right to next to

each other in time are going to be pretty correlated (depending on the value of ρ), but that as measurements get farther and farther apart they are less correlated.

$$\sigma^2\begin{bmatrix}1 & \rho & \rho^2 & \rho^3\\ \rho & 1 & \rho & \rho^2\\ \rho^2 & \rho & 1 & \rho\\ \rho^3 & \rho^2 & \rho & 1\end{bmatrix}$$

Compound symmetry (CS):- The CS structure is well-known compound symmetry structure required for split plot designs "in the old days". In CS structure the variances are homogeneous. There is a correlation between two separate measurements, but it is assumed that the correlation is constant regardless of how far apart the measurements are.

$$\begin{bmatrix}\sigma^2+\sigma_1^2 & \sigma_1^2 & \sigma_1^2 & \sigma_1^2\\ \sigma_1^2 & \sigma^2+\sigma_1^2 & \sigma_1^2 & \sigma_1^2\\ \sigma_1^2 & \sigma_1^2 & \sigma^2+\sigma_1^2 & \sigma_1^2\\ \sigma_1^2 & \sigma_1^2 & \sigma_1^2 & \sigma^2+\sigma_1^2\end{bmatrix}$$

Unstructured (UN):- The UN structured is the most "liberal" of all allowing every term to be different. It requires fitting the most parameters of any structure, t (t+1)/2.

$$\begin{bmatrix}\sigma_1^2 & \sigma_{12}^2 & \sigma_{13}^2 & \sigma_{14}^2\\ \sigma_{12}^2 & \sigma_2^2 & \sigma_{23}^2 & \sigma_{24}^2\\ \sigma_{13}^2 & \sigma_{23}^2 & \sigma_3^2 & \sigma_{34}^2\\ \sigma_{14}^2 & \sigma_{24}^2 & \sigma_{34}^2 & \sigma_4^2\end{bmatrix}$$

TOEPLITZ:-The TOEP structure is similar to the AR(1) in that all measurements next to each other have the same correlation, measurements two apart have the same correlation different from the first, measurements three apart have the same correlation different from the first two, etc. However, the correlations do not necessarily have the same pattern as in the AR (1). Technically, the AR (1) is special case of the Toepliz.

$$\begin{bmatrix}\sigma^2 & \sigma_1^2 & \sigma_2^2 & \sigma_3^2\\ \sigma_1^2 & \sigma^2 & \sigma_1^2 & \sigma_2^2\\ \sigma_2^2 & \sigma_1^2 & \sigma^2 & \sigma_1^2\\ \sigma_3^2 & \sigma_2^2 & \sigma_1^2 & \sigma^2\end{bmatrix}$$

Heterogeneous versions of the above are a simple extension. That is the variances, along the diagonal of the matrix, do not have to be the same. Note that this adds more parameters to be estimated, one for every measurement.

4.8. Checking Model Assumptions for independent mixed models

After fitting an LMM, it is important to carry out model diagnostics to check whether distributional assumptions for the residuals are satisfied and whether the fit of the model is sensitive to unusual observations. The process of carrying out model diagnostics involves several informal and formal techniques. Diagnostic methods for standard linear models are well established in the statistics literature. In contrast, diagnostics for LMMs are more difficult to perform and interpret, because the model itself is more complex due to the presence of random effects and different covariance structures. In this section, we focus on the definitions of a selected set of terms related to residual and influence diagnostics in LMMs (Schabenberger, 2004). In general, model diagnostics should be part of the model-building process throughout the analysis of a clustered or longitudinal data set. In this case diagnostics only for the final model fitted has been considered.

Residual Diagnostics: - Informal techniques are commonly used to check residual diagnostics; these techniques rely on the human mind and eye, and are used to decide whether or not a specific pattern exists in the residuals. In the context of the standard linear model, the simplest example is to decide whether a given set of residuals plotted against predicted values represents a random pattern or not. These residual vs. fitted plots are used to verify model assumptions and to detect outliers and potentially influential observations. In general, residuals should be assessed for normality, constant variance, and outliers. In the context of LMMs, we consider conditional residuals and their "studentized" versions.

Diagnostics for Random Effects: - The natural choice to diagnose random effects is to consider the empirical Bayes (EB) predictors. EB predictors are also referred to as random-effects predictors or, due to their properties, empirical best linear unbiased predictors (EBLUPs). Brady *et al.* (2008) recommend using standard diagnostic plots (e.g., histograms, Q–Q plots, and scatter plots) to investigate EBLUPs for potential outliers that may warrant further investigation. In general, checking EBLUPs for normality is of limited value, because their distribution does not necessarily reflect the true distribution of the random effects.

4.9. Joint model for bivariate continuous longitudinal data

In many circumstances, more than one response variable is followed longitudinally, and analyzing both jointly may be beneficial. Until recently, methods for multiple longitudinal outcomes have largely been based on simple approaches where each outcome is analyzed separately, or by reducing the dimension of the multiple outcomes through a factor analysis or principal components type of approach. Bivariate linear mixed models are useful when analyzing longitudinal data of two associated markers. In this paper, a bivariate linear mixed model including random effects and independent measurement error for both PR and RR was presented. Longitudinal data are often collected in epidemiological studies, especially to study the evolution of biomedical markers. Thus, linear mixed models (Laird and Ware, 1982) recently available in standard statistical packages (Seattle, 1991; Littell *et al.*, 1996) are increasingly used to take into account all available information and deal with the intra-subject correlation.

Extension to bivariate Case: Now under bivariate set-up two endpoints or symptoms of CHF (PR and RR) as outcome variables are observed in each occasion. The two end points were longitudinally measured as a vector of responses, $Y_i(\mathrm{t})$, at each occasion and thus the following model was used:

$$Y_i(\mathrm{t}) = \mathrm{X_i}(\mathrm{t})^{\mathrm{T}}\beta + Z_i(t)^{T} b_i + \varepsilon_i(t),$$

Where, $\varepsilon_i = \left[\varepsilon_i(t_1), \varepsilon_i(t_2), \ldots, \varepsilon_i(t_{ni})\right]^{\mathrm{T}} \sim \mathrm{MVN}(0, R_i)$

$b_i \sim \mathrm{MVN}(0,\ \mathrm{D})$ $\qquad\qquad$ $\mathrm{cov}(b_i, \varepsilon_i) = 0$

$R_i = I_{n_i} \otimes \sum_{2x2}$, where, $\sum_{2x2}$ is the variance covariance matrix of 2 endpoints (symptoms) conditional on $\mathrm{b_i}$.

Let $\mathrm{Y_i} = \begin{bmatrix} \mathrm{Y_{1i}} \\ \mathrm{Y_{2i}} \end{bmatrix}$, the response vector for the subject i, with $\mathrm{Y_{Ki}}$ the $\mathrm{n_{ki}}$ vector of the end points k (k=1, 2) with $\mathrm{n_{1i}} = \mathrm{n_{2i}} = \mathrm{n_i}$ so model for bivariate longitudinal Gaussian data is:

$$\begin{cases} Y_{1i}(t) = \mu_1(t) + a_{1i} + b_{1i}t + \varepsilon_{1i}(t) \\ Y_{2i}(t) = \mu_2(t) + a_{2i} + b_{2i}t + \varepsilon_{2i}(t) \end{cases}$$

where $\mu_1(t)$ and $\mu_2(t)$ refer to the population means at time t. We assume that random effects are jointly distributed as follows: $\begin{bmatrix} a_{1i} \\ a_{2i} \\ b_{1i} \\ b_{2i} \end{bmatrix} \sim N(0, D)$

where, D, the covariance matrix of the random effects, has the following structure:

$$\begin{bmatrix} \sigma^2_{a_1} & \sigma_{a_1}\sigma_{a_2} & \sigma_{a_1}\sigma_{b_1} & \sigma_{a_2}\sigma_{b_2} \\ & \sigma^2_{a_2} & \sigma_{a_2}\sigma_{b_1} & \sigma_{a_2}\sigma_{b_2} \\ & & \sigma^2_{b_1} & \sigma_{b_1}\sigma_{b_2} \\ & & & \sigma^2_{b_2} \end{bmatrix}$$

The error components are uncorrelated and not associated with the random effects

$$\begin{bmatrix} \varepsilon_{1i} \\ \varepsilon_{2i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2_1 & \sigma_{12} \\ & \sigma^2_2 \end{bmatrix} \right)$$

Clearly, the correlation between the evolution of Y_1 and Y_2 is given by:

$$r_E = \frac{\text{cov}(b_1, b_2)}{\sqrt{\text{var}(b_1) \times \text{var}(b_2)}} = \frac{\sigma_{b_1 b_2}}{\sqrt{\sigma^2_{b_1} \times \sigma^2_{b_2}}}$$

And the marginal correlation between Y_1 and Y_2 at time t is given by:

$$r_M(t) = \frac{\text{cov}(Y_{1i}(t), Y_{2i}(t))}{\sqrt{\text{var}(Y_{1i}(t)) \times \text{var}(Y_{2i}(t))}} = \frac{\sigma_{a_1 a_2} + t\sigma_{a_1 b_2} + t\sigma_{a_2 b_1} + t^2\sigma_{b_1 b_2} + \sigma_{12}}{\sqrt{\left(\sigma^2_{a_1} + 2t\sigma_{a_1 b_1} + t^2\sigma^2_{b_1} + \sigma^2_1\right) \times \left(\sigma^2_{a_2} + 2t\sigma_{a_2 b_2} + t^2\sigma^2_{b_2} + \sigma^2_2\right)}}$$

It is not difficult to comprehend that as the number of response variables (or the dimension of multivariate response) increases, the number of covariance parameters increase exponentially and the problem of estimation of covariance parameters becomes more and more difficult.

If we have m response variables and 2 random effects (random slope and intercept) for each response variables, then we have 2m random effects. If we assume that random effects follow $\text{MVN}(0, D)$ then D will have $\binom{2m}{2} + 2m$ covariance parameters and R will contain $\binom{m}{2} + m$ unknown parameters. Therefore, together D and R will have $\binom{2m}{2} + \binom{m}{2} + 3m$ covariance parameters. For instance in this case, when m=2, this quantity will be 6+1+6=13.

Therefore, in this case D will have 10 covariance parameters and R will contain 3 covariance unknown parameters.

4.10. Estimation methods

Estimation for separate mixed effect model**:** - Estimation of the parameters in LMM is usually based on maximum likelihood (ML) or restricted maximum likelihood (REML) estimation for the marginal distribution of Y_i which can easily be seen to be $Y_i \sim N(X_i\beta, Z_iDZ_i^T + \Sigma_i)$. Note that model LMM implies a model with very specific mean and covariance structures, which may or may not be valid, and hence needs to be checked for every specific data set at hand. Note also that, when $\Sigma_i = \sigma^2 I_{ni}$, with I_{ni} equal to the identity matrix of dimension n_i, the observations of subject i are independent conditionally on the random effect bi. The model is therefore called the conditional independence model. Even in this simple case, the assumed random-effects structure still imposes a marginal correlation structure for the outcomes Y_{ij}. Indeed, even if all Σ_i equal $\sigma^2 I_{ni}$, the covariance matrix in $Y_i \sim N(X_i\beta, Z_iDZ_i^T + R$ is not a diagonal matrix, illustrating that, marginally, the repeated measurements Y_{ij} of subject i are not assumed to be uncorrelated. The marginal mean (expected value) and marginal variance-covariance matrix of the vector Y_i is equal to: $E(Y_i) = X\beta$ and $Var(Y_i) = V_i = Z_iDZ_i^T + R$

Maximum likelihood estimation:- Suppose a random sample of N observations is obtained from a linear mixed effect model as defined above, then the likelihood of the model parameters, given the vector of N observations, is defined as:

$$L = l(\beta, \theta, Y_i) = \prod \left\{ 2\pi^{\frac{-n_i}{2}} \det(V_i)^{\frac{-1}{2}} \exp\left(\frac{-1}{2}(Y_i - X_i\beta)^T V_i^{-1}(Y_i - X_i\beta)\right)\right\}$$

Then, the MLE of $\widehat{\beta}$ on combining all the information from all the N subjects equals.

$$\widehat{\beta} = \left(\sum X_i V_i^{-1} X_i\right)^{-1} \left(\sum X_i V_i^{-1} Y_i\right)$$

Where det refers to the determinant and the elements of the $\boldsymbol{V}_i$ matrix are functions of the covariance parameters in Θ. (Brady *et al.,* 2008)

Gaussian Quadrature: - The Gaussian Quadrature approximates the integral of a function, with respect to a given kernel, by a weighted sum over predefined abscissas for the random effects. Unlike other numerical integration techniques, the abscissas are spaced unevenly throughout the interval of integration. With a modest number of Quadrature points, along with appropriate

centering and scaling of the abscissas, the Gaussian Quadrature approximation can be highly effective (see Abramowitz and Stegun 1964 for details). In the particular context of random-effects models, so-called adaptive Quadrature rules can be used (Pinheiro and Bates, 2000), where the numerical integration is centered on the estimates of the random effects, and the number of Quadrature points is then selected in terms of the desired accuracy. To illustrate the main ideas, we consider Gaussian and adaptive Gaussian Quadrature, designed for the approximation of integrals of the form $\int f(z)\phi(z)dz$ for a known function f (z) and for $\phi(z)$ the density of the multivariate standard normal distribution. Therefore first standardize the random effects such that they get the identity covariance matrix. Then, the likelihood contribution for subject i equals

$$f_i\ (y_i\ |\beta, D, \phi) = \int \prod_{j=1}^{ni} f_{ij}(y_{ij}|b_i, \beta, \phi) f(b_i|D) db_i$$

Where: b_i is $q_{\times 1}$ dimensional vector of unknown random effects, $b_i \sim N(0, D)$

D is variance-covariance matrix f (z) and for $\phi(z)$ denotes the density of the multivariate standard normal distribution

4.11. Model Comparison Technique

In order to select the best and final model which is appropriately fits with the given longitudinal data, it is necessary to compare the different models by using different techniques and methods. Hence, models are compared with Akaki Information Criteria (AIC), the Bayesian Information Criteria (BIC), and the Likelihood ratio test methods for nested were used at 5% level of significance. AIC = -2log L + 2p BIC=-2log Likelihood + n Par log (N),

Where, -2 logL is twice the negative log-likelihood value for the model

P: - is the number of estimated parameters.

npar: -denotes the total number of parameters in the model

N: - is the total number of observations used to fit the model. Smaller values of AIC and BIC reflect an overall better fit.

4.12. Ethical consideration

Ethical consideration which has been provided previously by the Ethiopian Health and Nutrition Research Institute (EHNRI) Review Board, the National Research Ethics Review Committee (NRERC) at the Ministry of Science and Technology, the Institutional Review Board of ICF International, and the Center for Disease Control and Prevention (CDC) currently conferred to Jimma University. Accordingly, an ethical clearance for the study has been provided by the Research and Ethical Review Board of Jimma University. The data for analysis has been brought from Ayder Referral Hospital of Mekelle University and to do this, the official co-operation letter to the Ayder Referral Hospital of Mekelle University from where data was obtained. For this research all the data were obtained through the legal permission of medical director of the hosting university and other concerned body of the Ayder Referral Hospital of Mekelle University. Moreover, the researcher assured the university/patients that the confidentiality of all the information taken will be kept secured and will not be given to third party. The information has been extracted from medical registration number excluding the patients' name.

CHAPTER FIVE

5. Results and Discussions

5.1. Results

5.1.1. Data descriptions and Descriptive statistics

In this cohort study, socio-demographic and clinical data of 264 patients who were 15 years and above receiving preferable drugs to improve the symptoms of CHF from September 2004 to August 2005 in Ayder referral Hospital of Mekelle University at baseline were considered. The two symptoms of CHF such as: pulse and respiratory rates have been used. These longitudinal response variables were measured for at least 4 visits. There were a total of 6494 visits from 264 subjects in the CHF treatment, The number of visits per subject varied from 4 to 46 weeks with a mean follow-up time of 16.103 (SD=10.85), but the time interval for all patients is not equally observed i.e. visits were unequally spaced. The sample sizes at the six consecutive time points were 264, 232, 188, 206, 245 and 184. There is a sharply increasing degree of missing data over time due to deaths, dropouts, missed clinic visits and transferring to other hospital and also there is admitting and readmitting of the patients. Moreover, eight covariates which four continuous and four categorical such as: time, age, sex, weight LVEF, NYHA, place of residence and diagnostic history of the patients were encompassed in this study.

Table 4.1 Baseline demographic and clinical characteristics of CHF data

Characteristics		Frequency(n)	Percent (%)
Sex	Male	113	42.8
	Female	151	57.2
NYHA	Class I	59	22.35
	Class II	87	32.95
	Class III	64	24.24
	Class IV	54	20.46
Place Of residence	Rural	145	54.92
	Urban	119	54.08
Diagnosis History	Sever anemia	82	31.06
	ACF	56	21.21
	CHD	48	18.18
	Others	78	29.55

The baseline characteristics of patients are displayed in table 4.1. Among these patients, more than half 151 (57.2%) of them are females and 113 (42.8%) are males. About 59(22.35%) patients are NYHA class I, 87(32.95%) class II, 64(24.24%) class III and 54(20.46%) class IV. Similarly, 82 (31.06%) of patients had previous diagnosis of sever anemia, 56 (21.21%) had ACF, 48 (18.18%) had CHD and 78 (29.55%) patients who had other diagnosis. Likewise, 145(54.92%) were from rural area and 119(54.08%) were from urban area.

Table 4.2 Mean and Standard deviation of continuous covariates and two outcomes

Variable	At Baseline	
	Mean	Std Dev
Pulse Rate	126.12	18.98
Respiratory Rate	31.64	10.99
WEIGHT	75.47	8.37
AGE	45.74	18.42
LVEF	26.40	9.33

As indicated in table 4.2 above, the longitudinally measured symptoms of congestive heart failure PR (in beats/minutes) and RR (in breaths/minutes) were considered as bivariate responses. They were measured approximately every week at the study entry, and again a common measuring time is used for all patients. Hence, the baseline mean and standard deviation of PR were 126.11 &18.98bpm respectively and of the RR were 31.64 &10.99 brpm respectively.

Table 4.3 The baseline mean & standard Deviations of PR & RR at each characteristics

Characteristics		Pulse Rate		Respiratory Rate	
		At baseline		At baseline	
		Mean	Std Dev	Mean	Std Dev
Sex	Male	118.96	16.82	26.42	8.84
	Female	131.46	18.78	35.54	10.84
NYHA	Class I	112.47	10.46	21.61	2.17
	Class II	118.63	10.96	26.75	7.31
	Class III	129.95	14.28	36.28	9.31
	Class IV	148.5	20.07	44.98	6.76
Place Of residence	Urban	125.15	19.94	31.23	11.06
	Rural	126.9	18.17	31.98	10.95

According to the table 4.3 above, the baseline mean of PR were 131.46 (SD= 18.78 bpm) in female patients and 118.96 (SD=16.82 bpm) in male patients. Likewise, the baseline mean of RR was 35.54 (SD= 10.84 brpm) in female patients and 26.42 (SD=8.84 brpm) in male patients.

5.1.2. Exploratory Data analysis

Exploring individual profile and mean structure profile plot

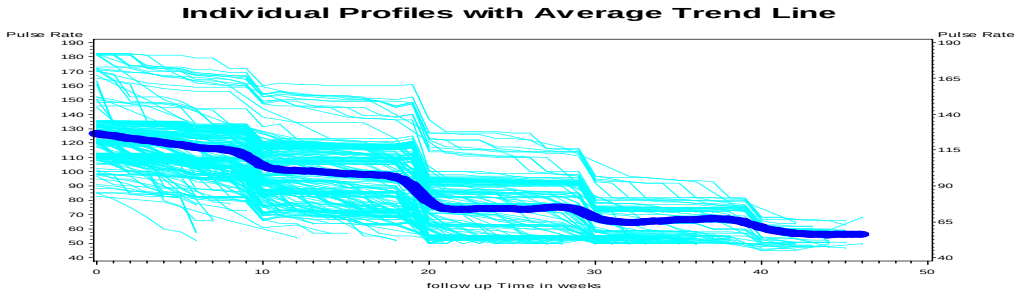

Figure 4.1 Individual Profile Plot with Average Trend Line for PR

Figure 4.1, indicated that there is decreasing trend on the PR of CHF patients throughout the follow up. The PR that was the heaviest at the beginning tends to be turn down throughout the follow up. That means, the variability of the measurements, at the beginning (baseline) of the follow up were highly decreased relative to the end of the follow up. Likewise, there is variation with in groups throughout the time by decreasing the PR from week to week. According to the average trend line that putted on the individual profile plot with blue color, the PR of the CHF patients was declined throughout the time. Hence, there is the negative evolution on the PR over the time. Furthermore, the average trend line is almost near to straight downward line indicating linear relationship with absence of quadratic effect on the negative evolution of PR of CHF patients.

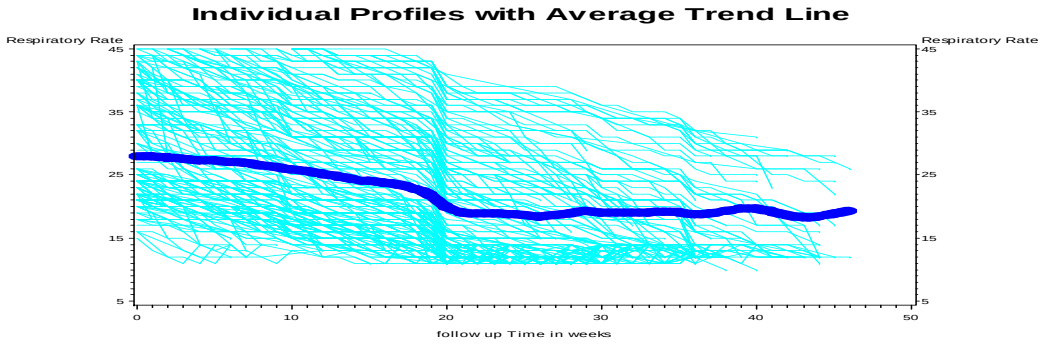

Figure 4.2 Individual Profile Plot with Average Trend Line for RR

Based on the figure 4.2, the individual profile plot indicated decreasing trend on the RR of CHF patients. The RR that was the heaviest at the beginning tends to be turn down throughout the follow up. That means, the variability of the measurements at the beginning (baseline) of the follow up were decreased relative to the end of the follow up. Likewise, there is variation with in groups throughout the time by decreasing the RR variation from week to week. According to the average trend line with blue color, the RR of the CHF patients has declined throughout the time. Hence, there is a negative evolution on the RR over the time. Furthermore, the average trend line is almost downward line indicating linear relationship with absence of quadratic effect on the negative evolution of RR of CHF patients,

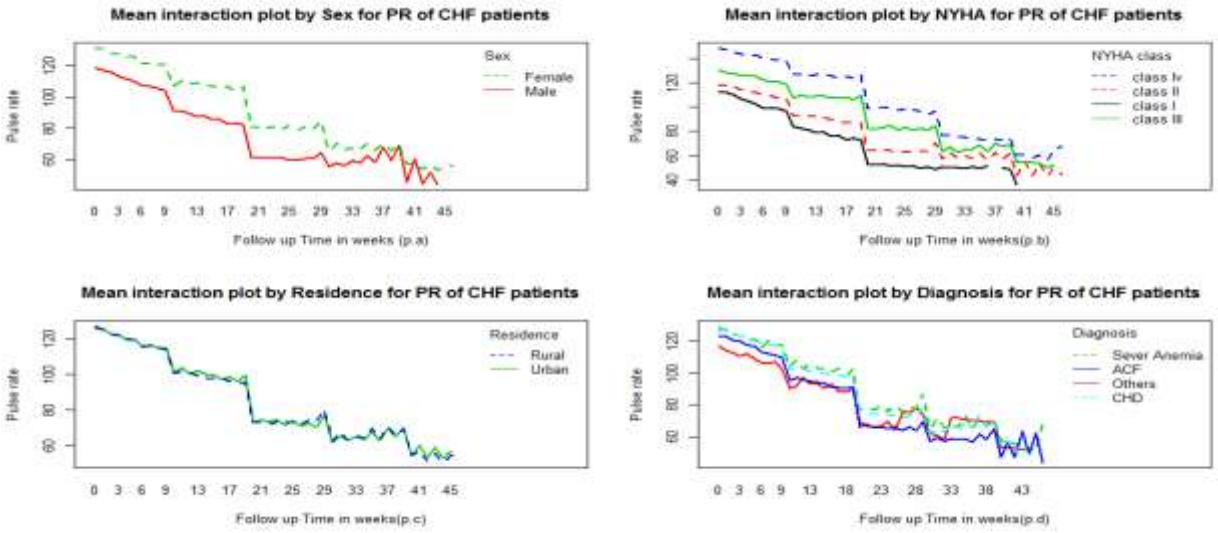

Figure 4.3 Mean Interaction Plot by demographic and clinical characteristics for PR of CHF Patients

Besides plotting the PR over follow up time in weeks, it is also useful to include different subgroups on the same graph to illustrate the relationship between the response variable PR and an explanatory variable sex over follow up in weeks as it was shown on figure 4.3 of (P.a). Thus the mean profile plot of PR by sex presented on figure 4.3 of (P.a) indicated that PR decreased for both men and women over the follow up. However, the slope for the women seems more visibly higher than the slope for the men from baseline up to end of follow up which did not indicated the interaction effect as did not crossed each other.

Similarly, it is also useful to illustrate the relationship between the response variable PR and an explanatory variable NYHA over follow up time in weeks as it was shown on figure 4.3 of (P.b).

Thus the mean profile plot of PR by NYHA presented on figure 4.3 of (P.b) indicated that all categories have decreasing trend on PR over follow up time in weeks. However, the slope for the NYHA class IV seems to be higher than the slope of the others from baseline up to end follow up which does not indicate the interaction effect as they did not crossed each others.

Generally, lower NYHA class has lower PR whereas higher NYHA class has higher PR throughout the time. As it was shown on figure 4.3 at (P.c), the mean interaction plot of PR by residence for CHF patients indicated that, even if there is a down ward trend for both categories, almost both categories have the same effect on PR, since the plot for both rural and urban was almost overlapped and it seems like the absence of significant difference between rural and urban on the evolution of PR. According to figure 4.3 at (P.d), the mean interaction plot of PR by diagnosis for CHF patients indicated that, almost all categories have the same effect on PR, since the plot for all levels was overlapped. However, the PR of patients with previous diagnosis history of sever anemia and CHD were relatively higher than others and ACF. Generally, PR in all categories has declining trend as it was shown by figure 4.3 at (P.d).

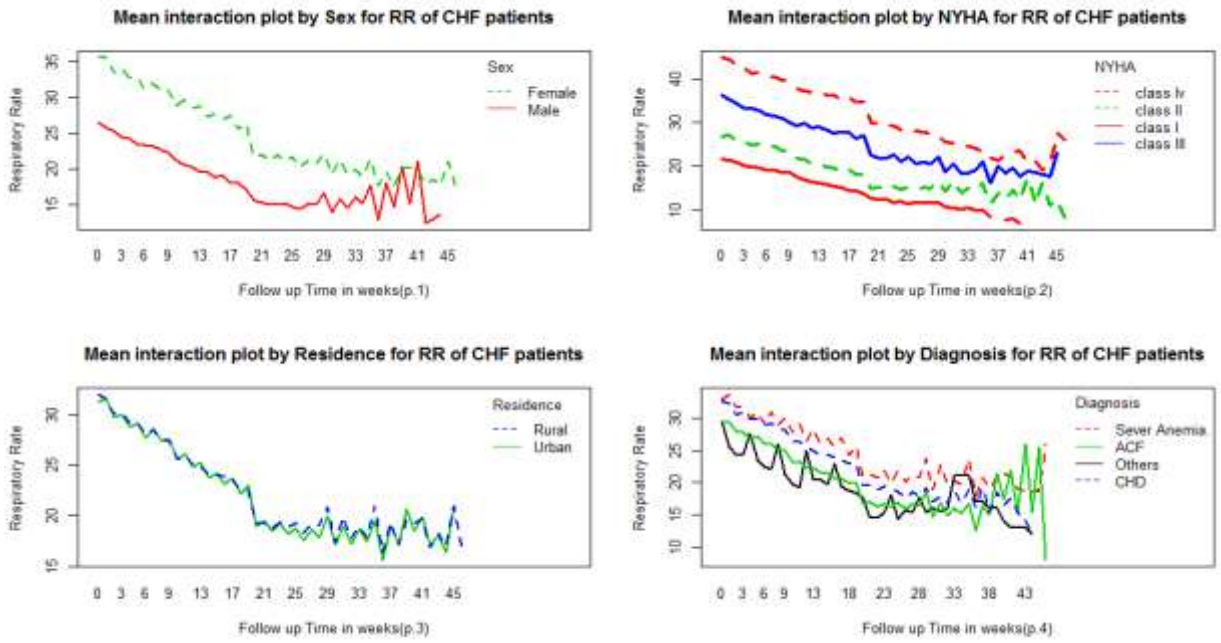

Figure 4.4 Mean Interaction Plot by demographic and clinical characteristics for RR of CHF Patients

Besides plotting the RR over follow up time in weeks, it is also useful to include different subgroups on the same graph to illustrate the relationship between the response variable RR and an explanatory variable sex over follow up time in weeks. Thus the mean profile plot of RR sex presented on figure 4.4 at (P.1) indicated that RR decreased for both men and women over the follow up. However, the slope for the women is above the slope for the men from baseline up to end of the follow up which did not reflect the interaction effect as plots did not crossed each other. Similarly, it is also useful to illustrate the relationship between the response variable RR and an explanatory variable NYHA over follow up time in weeks. Thus the mean profile plot of RR by NYHA presented figure 4.4 at (P.2) indicated that all categories have decreasing trend on RR over follow up time in weeks. However, the slope for the NYHA class IV seems to be higher than the slope of the others from baseline up to end of the follow up which did not indicate the interaction effect as they were not crossed each other.

Generally, lower NYHA classes have lower RR whereas higher NYHA classes have higher RR throughout the time. According to figure 4.4 at (P.3), mean interaction plot of RR by residence for CHF patients indicate that, even if there is a down ward trend for both categories, almost both categories have the same effect on RR, since the plot for both rural and urban was overlapped and it seems like the absence of significant difference between rural and urban on the evolution of RR. Similarly, as is was shown by figure 4.4 at (P.4), the mean interaction plot of RR by diagnosis for CHF patients indicated that, more or less all categories have the same effect on RR, since the plot for all levels was overlapped. However, the RR of patients with previous diagnosis history of Sever anemia and CHD were relatively higher than others and ACF. Generally, RR in all categories had declining trend.

Exploring the random effect

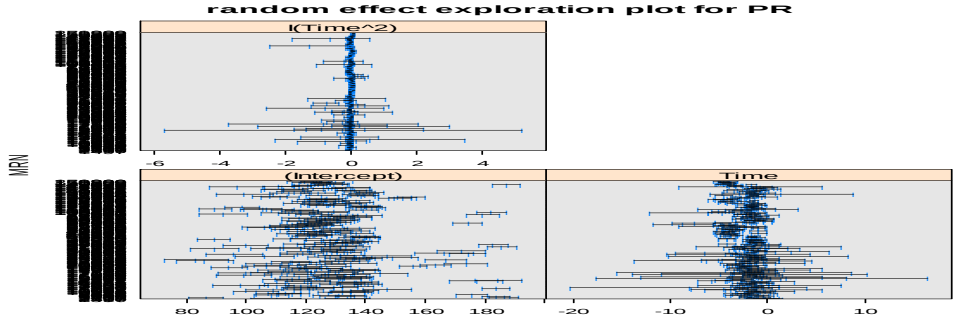

Figure 4.5 Interval Plots for Subject Specific Intercepts and Slope for RR

As it is indicated on figure 4.5, even though, most of points overlapped for both slope and quadratic slope plot, there is certain variability in the slope which mean that, considering slope random effect for this model is important. But as it is clearly depicted on the subject specific intercept plot, there is high variable in the intercept and it became crucial to add both intercept and slope in the random term.

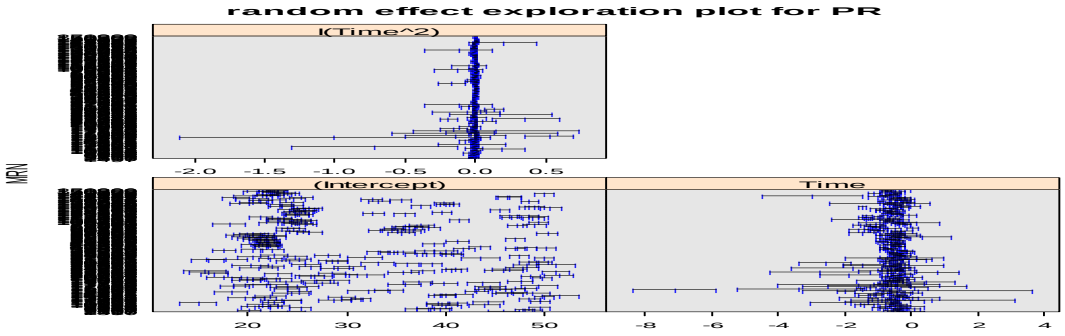

Figure 4.6 Interval Plots for Subject Specific Intercepts and Slope for RR

As it is indicated on figure 4.6, even though, most of points overlapped for both slope and quadratic slope plot, there is a certain variability in the slope which mean random slope could a preferred one for this model. But as it is clearly depicted on the subject specific intercept plot, there is high variable in the intercept and it became essential to add both intercept and slope in the random term.

5.2. Model Selection

A primary goal of model selection is to choose the simplest model that provides the best fit to the observed data. There may be several choices concerning which fixed and random effects should be included in an LMM. There are also many possible choices of covariance structures for the **D** and R_i matrices.

5.2.1. Model fitting for fixed and random effects

The top-down strategy was used to select statistically significant covariates for the two independent mixed effect models with outcome variables PR & RR. The models based on only fixed effects were selected with constant random effects at first and then after, the significance of random effects was also checked. Hence, passing through procedures, the model which included

the covariates time, age, sex, NYHA, LVEF, weight and interaction of time with LVEF and weight for fixed effect with subject specific random intercept and random slope for both models with outcome variables PR & RR were preferred regardless of relatively small values of AIC=42645.03, BIC=42746.71 and log-Likelihood ratio test with P-value of <0.0001 for model with outcome variable PR and AIC=24344.10, BIC=24445.78 and log-Likelihood ratio test with P-value of <0.0001 for model with outcome variable RR. The saturated model including the covariates diagnosis history and place of residence in addition to the covariates that were included in the reduced model were fitted and compared with reduced model. But saturated model did not improve the model. Thus, statistically insignificant covariates such as diagnosis history and place of residence were excluded from the final model. Finally, quadratic fixed effect and random effect did not improve the models and that's why it is also excluded in the model. In addition, the ML method with covariance structure of unstructured covariance structure with covariates time, age, sex, NYHA, LVEF, weight and interaction of time with LVEF and weight for fixed effect with subject specific random intercept and random slope were preferred as the best model.

5.2.2. Model selection with Covariance structure for the best model

a) Comparing different covariance structure for the best model with response variable Pulse Rate

Table 4.4. Selection of Covariance structure for PR and RR Models

covariance structure	**Fit statistics**					
	-2LL		AIC		BIC	
	For PR	For RR	For PR	For RR	For PR	For RR
Compound Symmetry (CS)	43924.2	25530.2	43930.2	25536.2	43940.9	25546.9
Unstructured(UN)	**42644.7**	**24321.3**	**42652.7**	**24329.3**	**42667.0**	**24343.6**
Autoregressive (AR(1))	43924.2	25530.2	43930.2	25536.2	43940.9	25546.9
Variance component(VC)	42685.3	24351.8	42691.3	24357.8	42702.1	24368.6
Toeplitz (TOEP)	43924.2	25530.2	43930.2	25536.2	43940.9	25546.9

As it is shown in table 4.4, among different covariance structure mentioned, the model with covariance structure of unstructured covariance structure was preferred for PR model with respective small values of -2LL, AIC, AICC and BIC of 42644.7, 42652.7, 42652.7 and 42667.0. Likewise, the model with covariance structure of unstructured covariance structure was preferred

with respective small values of 2LL, AIC, AICC and BIC of 24321.3, 24329.3, 24329.3 and 24343.6

5.3. Separate and joint Mixed effect Models

After passing a lot of procedures of model selection criteria's, along with Akaki's information criteria, Bayesian information criteria and likelihood ratio tests, the finally selected model for separate & joint mixed models were fitted with the same covariates and interaction of Time with continuous covariates such as Weight & LVEF. Thus, finally the following models are considered.

Note: The Notations used in the model represents: T=time, A=age, SF= sex (female), W= weight, L=LVEF, NCII = NYHA class II, NCIII= NYHA class III and NCIV= NYHA class IV

- **Final Model in Separated case:**

$$\begin{cases} \mathrm{PR}(Y_{i1}) = 107.04 - 3.145\mathrm{T} - 0.409\mathrm{A} + 4.804\mathrm{SF} + 2.743\mathrm{NCII} + 5.167\mathrm{NCIII} \\ \qquad +15.153\mathrm{NCIV} - 0.307\mathrm{L} + 0.009\mathrm{T} * \mathrm{L} + 0.538\mathrm{W} + 0.016\mathrm{T} * \mathrm{W} \\ \\ \mathrm{RR}(Y_{i2}) = 37.08 - 0.787\mathrm{T} - 0.258\mathrm{A} + 1.605\mathrm{SF} + 2.056\mathrm{NCII} + 4.022\mathrm{NCIII} \\ \qquad +8.937\mathrm{NCIV} - 0.075\mathrm{L} + 0.002\mathrm{T} * \mathrm{L} + 0.054\mathrm{W} + 0.003\mathrm{T} * \mathrm{W} \end{cases}$$

- **Final Model in Joint Case:**

$$\begin{cases} \mathrm{PR}(Y_{i1}) = 108.58 - 3.162\mathrm{T} - 0.427\mathrm{A} + 4.528\mathrm{SF} + 3.187\mathrm{NCII} + 5.896\mathrm{NCIII} \\ \qquad +16.055\mathrm{NCIV} - 0.295\mathrm{L} + 0.009\mathrm{T} * \mathrm{L} + 0.521\mathrm{W} + 0.016\mathrm{T} * \mathrm{W} \\ \\ \mathrm{RR}(Y_{i2}) = 36.57 - 0.779\mathrm{T} - 0.256\,\mathrm{A} + 1.734\mathrm{SF} + 1.99\mathrm{NCII} + 3.936\mathrm{NCIII} \\ \qquad +8.83\mathrm{NCIV} - 0.075\,\mathrm{L} + 0.002\,\mathrm{T} * \mathrm{L} + 0.059\,\mathrm{W} + 0.003\,\mathrm{T} * \mathrm{W} \end{cases}$$

Table 4.5 Results for separate and joint or shared model

Effect		Separate model (PR&RR)			Joint model (PR&RR)		
		Estimate (SE)	P-value	(1-α)100% CI	Estimate (SE)	P-value	(1-α)100% CI
For PR							
Inter(β_{10})		107.04(4.415)	<.0001	(98.37,115.71)	108.58(4.384)	<.0001	(99.97,117.1)
Time(β_{11})		-3.15(0.123)	<.0001	(-3.39,-2.904)	-3.16(0.122)	<.0001	(-3.4,-2.923)
Age(β_{12})		-0.41(0.053)	<.0001	(-0.513,-0.304)	-0.43(0.053)	<.0001	(-0.53,-0.32)
Sex(β_{13})		4.804(1.422)	0.0008	(2.007,7.602)	4.528(1.335)	0.0008	(1.902,7.153)
NYHA	II(β_{14})	2.743(1.913)	0.1528	(-1.024,6.51)	3.187(1.908)	0.0961	(-0.57,6.944)
	III(β_{15})	5.167(2.423)	0.0339	(0.396,9.938)	5.896(2.415)	0.0153	(1.14,10.652)
	IV(β_{16})	15.153(2.801)	<.0001	(9.637,20.669)	16.055(2.794)	<.0001	(10.55,21.56)
L(β_{17})		-0.31(0.016)	<.0001	(-0.339,-0.275)	-0.30(0.016)	<.0001	(-0.33,-0.26)
T*L(β_{18})		0.009(0.0008)	<.0001	(0.0075,0.011)	0.009(0.0008)	<.0001	(0.007,0.01)
W(β_{19})		0.538(0.033)	<.0001	(0.474,0.603)	0.521(0.032)	<.0001	(0.458,0.584)
T*W(β_{110})		0.016(0.0014)	<.0001	(0.013, 0.019)	0.016(0.0014)	<.0001	(0.013,0.019)
Sigma1(σ_1)		31.53(0.58)	<.0001	(30.423,32.699)	31.579(0.582)	<.0001	(30.47,32.751)
$\sigma^2_{b_{10}}$		141.27(13.14)	<.0001	(118.68,171.03)	140.62(13.16)	<.0001	(118.02,170.44)
$\sigma_{b_{10},b_{11}}$		-2.207(0.395)	<.0001	(-2.982,-1.432)	-2.078(0.388)	<.0001	-2.84(-1.317)
$\sigma^2_{b_{11}}$		0.182(0.02)	<.0001	(0.148,0.229)	0.176(0.019)	<.0001	(0.143,0.221)
For RR							
Inter(β_{20})		37.08(1.785)	<.0001	(33.57,40.59)	36.57(1.78)	<.0001	(33.06,40.07)
Time(β_{21})		-0.787(0.034)	<.0001	(-0.853,-0.72)	-0.779(0.034)	<.0001	(-0.845,-0.713)
Age(β_{22})		-0.258(0.025)	<.0001	(-0.308,-0.209)	-0.256(0.025)	<.0001	(-0.305,-0.207)
Sex(β_{23})		1.605(0.578)	0.0057	(0.47,2.739)	1.734(0.569)	0.0024	(0.617,2.851)
NYHA	II(β_{24})	2.056 (0.898)	0.0227	(0.289,3.823)	1.99(0.895)	0.0270	(0.228,3.753)
	III(β_{25})	4.022 (1.136)	0.0005	(1.786,6.258)	3.936(1.133)	0.0006	(1.706,6.166)
	IV(β_{26})	8.937(1.314)	<.0001	(6.349,11.525)	8.83(1.311)	<.0001	(6.249,11.412)
L(β_{27})		-0.075(0.004)	<.0001	(-0.082,-0.067)	-0.075(0.004)	<.0001	(-0.082,-0.067)
T*L(β_{28})		0.002(0.0002)	<.0001	(0.0019,0.0026)	0.002(0.00019)	<.0001	(0.002,0.0026)
W (β_{29})		0.054 (0.0081)	<.0001	(0.038,0.07)	0.059 (0.008)	<.0001	(0.043,0.075)
T*W(β_{210})		0.003 (0.0004)	<.0001	(0.002,0.0034)	0.003(0.00035)	<.0001	(0.002,0.0033)
Sigma2(σ_2)		1.654 (0.031)	<.0001	(1.595,1.715)	1.657(0.031)	<.0001	(1.598,1.719)
$\sigma^2_{b_{20}}$		31.63 (2.915)	<.0001	(26.61,38.22)	31.696 (2.93)	<.0001	(26.658,38.319)
$\sigma_{b_{20},b_{21}}$		-0.604(0.112)	<.0001	(-0.82,-0.39)	-0.6 (0.11)	<.0001	(-0.82,-0.38)
$\sigma^2_{b_{20}}$		0.066 (0.007)	<.0001	(0.054,0.083)	0.064(0.0068)	<.0001	(0.052,0.079)
Common parameters	$\sigma_{b_{10},b_{20}}$			-	32.626(4.763)	<.0001	(23.292,41.96)
	$\sigma_{b_{10},b_{21}}$				0.23(0.22)	0.2939	(-0.2,0.66)
	$\sigma_{b_{20},b_{11}}$				-0.037(0.172)	0.8283	(-0.375,0.3)
	$\sigma_{b_{11},b_{21}}$				0.075(0.004)	<.0001	(0.012, 0.138)
	Rho (ρ)				0.7054(0.032)	<.0001	(0.642,0.769)

NB: T=Time, W=Weight, L= LVEF, inter=intercept

The PR and RR outcomes were modeled with the set of covariates, and the results were described in table 4.5. The final model was somewhat complex and included 11 fixed effect parameters for both outcome variables PR and RR including intercept and Time to Weight & LVEF interactions for both separate and joint mixed effect models.

5.3.1. Results of Joint mixed effect model

A joint mixed effect model for the two symptoms (endpoints) of CHF syndrome PR and RR was fitted with an unstructured variance-covariance structure. This model is the same as the separate model except the sets of random intercepts and slopes for each response are now correlated rather than independent. This model was fitted allowing for a linear time effect for each covariate that was selected as a fixed effect in the separate linear mixed model. The subject specific random intercepts and random slopes were fitted to account for within-subject correlations.

According to table 4.5, the fixed-effect intercept coefficient $\hat{\beta}_{10}$= 108.58 (S.E. =4.384) represents an estimate of the average pulse rate at time = 0 and excluding all covariates in the model. Likewise, the fixed-effect intercept coefficient $\hat{\beta}_{20}$= 36.57 (S.E. =1.78) represents an estimate of the average respiratory rate at time = 0 and excluding all covariates in the model. All parameters are statistically significant except there is no evidence of a significant relationship between NYHA class II and PR (p-value=0.0961) at 0.05 level of significance. Among all covariates, Time, Age, and LVEF were negatively associated with both outcomes that mean the repeatedly follow up made a particular decrease on both outcomes with (P-value<0.0001).

In addition, sex was significantly associated with both PR and RR outcomes; thus, female patients had 4.528 points higher over evolution of PR (P-value=0.0008) and 1.734 points higher over evolution of RR (P-value=0.0024) compared to males. Moreover, there was evidence of a statistically positive relationship between weight and both PR ($\hat{\beta} = 0.521(0.032)$; 95%CI= [0.458, 0.584]) and RR ($\hat{\beta}$= 0.059 (0.008); 95%CI= [0.043, 0.075]). Similarly, NYHA class was significantly associated with both PR and RR, for instance, patients under NYHA class IV had 16.055points higher over evolution of PR (P-value<0.0001) and 8.83 points higher over evolution of RR (P-value<0.0001) relative to class I. Time-LVEF has positive effect on the PR with ($\hat{\beta} = 0.009$); [S.E. =0.0008]; P-value=<.0001) and on the RR with ($\hat{\beta} = 0.002$); [S.E.

=0.00019]; P-value=<.0001). In similar way, time –weight interaction was also significantly and positively associated with PR($\hat{\beta}$= 0.016; P-value<0.0001) and significantly and positively associated with RR($\hat{\beta}$= 0.003; P-value<0.0001). Generally, as it is indicate in the results in table 4.5, both PR and RR have decreasing pattern throughout the follow up with respective clinical treatments. This concept indirectly indicated the improvement on risk of congestive heart failure because the lower value of both symptoms PR and RR is directly related with a stronger and healthier heart.

Variability of error and random effect in joint model

Alike parameter estimation and testing, variability analysis of both fixed and random effects are also another important aspects. High variability is the indicator of less accuracy or high error on prediction of the association of outcome evolutions with respective risk factors. Then as it is shown in table 4.5, the subject specific random intercept variance is estimated to be 140.62 (S.E. =13.157) with 95% CI of (30.47, 32.751) for PR and 31.696 (S.E. =2.928) with 95% CI of (26.658, 38.319) for RR. In addition to that, the subject specific random slope variance is estimated to be 0.176 (S.E. =0.019) with 95% CI of (0.143, 0.221) for PR and 0.064 (S.E. =0.0068) with 95% CI of (0.052, 0.079) for RR. The estimated variance of the random error is ($\hat{\sigma}^2_{\varepsilon_1} = 31.579(\text{S.E.} = 0.582)$; 95%CI= [30.47, 32.751]) for PR and ($\hat{\sigma}^2_{\varepsilon_2} = 1.657(\text{S.E.} = 0.031)$; 95%CI= [1.598, 1.719]) for RR. Thus, the variability due to subject specific random intercepts was higher than that of random slopes for both models. The random effect variability is greater on PR than RR.

5.3.2. Associated (common) effect parameters

By referring table 4.5, based on 6494 pair symptoms of CHF assessments from 264 subjects, a substantial correlation (ρ=0.7054, S.E. =0.032) with 95% CI: [0.642, 0.769] between the PR and RR within the same subjects is noted. From the random effects, it may be seen that variability is relatively higher for PR than RR. The same may be said of the covariance for subject specific random intercept of PR and RR with ($\sigma_{b_{10},b_{20}}$ =32.626 (S.E. = 4.763); 95%CI= [23.292, 41.96]) and the covariance for subject specific random slopes of PR and RR with ($\sigma_{b_{11},b_{21}}$ =0.075 (S.E. =0.004); 95%CI= [0.012, 0.138]). Also, the covariances for both PR and RR are positive, which

is indicative of positive correlation, as it is being shown in table 4.5. With the joint mixed effect model for the two symptoms of CHF, it is possible to investigate how the evolution of PR is associated with RR. Hence, the association of the evolution (AOE) is to be estimated 0.7054(S.E. =0.032, p-value<0.0001). Not only that but also it is possible to determine how the association between the two symptoms of CHF (PR and RR) evolves over time; thus, the evolution of the association (EOA). For instance, at baseline the evolution of the association was 0.45029 and at first, second and third weeks follow up it increased into 0.4505118, 0.4508186 and 0.4523747 respectively indicating the evolution of association between PR and RR over the time. In addition to that, the evolution of the association (EOA) throughout the time is well visualized as it is shown on the marginal association plot of figure 4.7; there is the positive evolution of the association between two outcomes PR and RR. Thus, the association positively evolved over the time. Generally, there is evidence that time has reasonable effect on association of evolution of both outcomes.

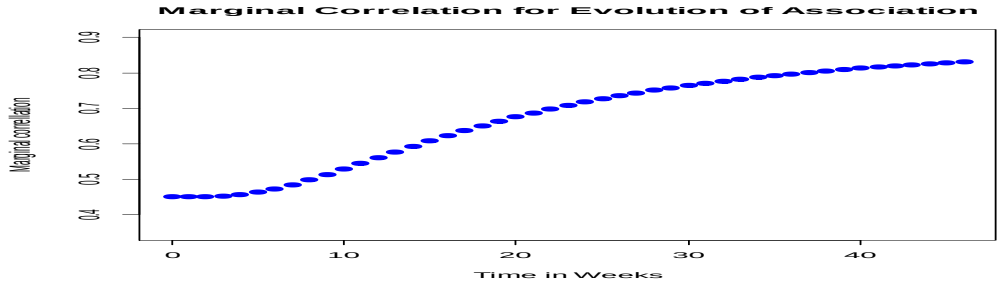

Figure 4.7 Marginal Correlations for EOA between Two Outcomes (PR and RR)

5.3.3. Results of separate mixed effect model

Technically, the separate models were fitted for the two outcomes, PR and RR together but assuming that ρ = 0, which is entirely equivalent to fitting the models separately or independently as their results were shown in table A.1 in appendix A. Hence, as interpretations for the models those modeled independently for PR & RR is entirely equivalent to that of separate models by assuming ρ = 0.

As shown in table 4.5, the fixed-effect intercept coefficient $\hat{\beta}_{10}$= 107.04(S.E. =4.415) represents an estimate of the average of pulse rate at time = 0 excluding all covariates in the model. Likewise, the fixed-effect intercept coefficient $\hat{\beta}_{20}$= 37.08(S.E. =1.785) represents an estimate of the average of respiratory rate at time = 0 and excluding all covariates in the model. Alike to

joint mixed model in separate mixed model all parameters are statistically significant except there is no evidence of a significant relationship between NYHA class II and PR (p-value=0.1528) at 0.05 level of significance. Among all covariates, time, age, and LVEF were negatively associated with both outcomes that mean the repeatedly follow up made a particular decrease on both outcomes with (P-value<0.0001). There was also evidence that age had a negative effect on evolution of PR ($\hat{\beta} = -0.409; S.E. = 0.053$) and on RR ($\hat{\beta} = -0.258; S.E. = 0.025$). Sex was significantly associated with both PR and RR outcomes; female patients had 4.804(s.e=1.422) points higher over evolution of PR (P-value=0.0008) and 1.605(s.e=0.578) points higher over evolution of RR (P-value=0.0057) compared to males. Similarly, NYHA class was significantly associated with both PR and RR, thus, patients under NYHA class IV had 15.153 points higher over evolution of PR (P-value<0.0001) and 8.937 points higher over evolution of RR (P-value<0.0001) relative to class I.

In the same way, Time-LVEF has positive effect on the PR with ($\hat{\beta} = 0.009$); [S.E. =0.0008]; P-value=<.0001) and on the RR with ($\hat{\beta} = 0.002$); [s.e=0.0002]; P-value=<.0001). Likewise, Time –weight interaction was also significantly and positively associated with PR($\hat{\beta}$= 0.016(0.0014); P-value<0.0001) and significantly and positively associated with RR($\hat{\beta}$= 0.003 (0.0004); P-value<0.0001). Generally, alike to joint mixed model there is also decreasing pattern of PR and RR over time with respect to associated risk factors on respective treatments in separate mixed model.

Variability of error and random effect in separate model

By referring table 4.5, even if there is slight difference variability's in joint mixed model results, there is almost similar results are computed for separate one. Thus, the subject specific random intercept variance is estimated to be 141.27(S.E. =13.14) with 95% CI of (118.68, 171.03) for PR and 31.63 (S.E. =2.915) with 95% CI of (26.612, 38.222) for RR. The subject specific random slope variance is estimated to be 0.182(S.E. =0.02) with 95% CI of (0.148, 0.229) for PR and 0.066 (S.E. =0.007) with 95% CI of (0.054, 0.083) for RR. The estimated variance of the random error is ($\hat{\sigma}^2_{\varepsilon_1} = 31.53(\mathrm{S.E.} = 0.58)$; 95%CI= [30.423, 32.699]) for PR and ($\hat{\sigma}^2_{\varepsilon_2} = 1.654\ (\mathrm{s,e} = 0.031)$; 95%CI= [1.595, 1.715]) for RR. Finally, similar to that of joint mixed

model results, the variability due to subject specific random intercepts was higher than that of random slopes for both models. The random effect variability is greater on PR than RR.

5.4. Comparison of separate and joint or shared mixed effect models

$$LRT = -2LL(PR\&RR) - (-2LL(PRRR) = 66929.1 - 66802.9 = 126.2$$

Now that both separate and joint mixed effect models have been considered and parameter estimates for the separate and joint models are summarized in table 4.4. Technically, the separate models were fitted for two outcomes together, but assuming that ρ=0, which entirely equivalent to fitting the two independent models separately as results were shown in appendix A [table A.1]. It also allows for a single likelihood for the model parameters enabling direct comparison with the correlated bivariate model fitted subsequently. Clearly, PR and RR show a strong positive relationship as evidenced by the correlation of the random effects in joint mixed models. In addition, likelihood comparison shows a convincing improvement in model fit, when random effects are allowed to correlate. Comparing the separate and joint models, although parameter estimates for both outcomes are nearly equivalent, small changes are observed in parameter of some covariate. When comparing the results from the separate settings to the results from joint settings, there are several points of interest. The -2log-likelihood value corresponding to the two separate models (i.e. fitted as a joint model but assuming ρ=0) was equal to 66929.1 and the -2loglikelihood value for the joint model was 66802.9. Hence, the joint random effect model of the two symptoms of CHF, PR and RR was significantly better than two separate random effect models of PR and RR (-2LL=66802.9 vs 66929.1; LRT=, 126.2 DF=4, P-value<0.0001). With regards to Akaki's information criteria (AIC), the joint model (AIC=66870.9) is also indicated as a better fit than the separate model (AIC=66989.1). Notice how the joint model two symptoms of CHF i.e. PR and RR seem to decrease the variability in the random effects, this may be seen in table 4.5. Taking into account the standard errors for the variance and covariance estimates, the joint model in general allowed for more accurate prediction (small errors) of the variability in the random effects, though just slightly.

Comparing the fixed effects for the separate and joint mixed models, some important things may be considered for the two symptoms of CHF patients. First, and foremost, there is the question of whether the different models reached the same bottom line conclusion. Comparing the covariates

between two types of models will yield further information of interest. Both separate and joint models found a significant relationship between weight and PR and RR. Weight was positively associated with PR ($\hat{\beta} = 0.538$ compared to 0.521), hence, the 95%CI (0.474, 0.603 vs 0.458, 0.584) was also tighter for joint model. Similarly, Weight was positively associated with RR ($\hat{\beta} = 0.054$ compared to 0.059), and the 95%CI (0.038, 0.07 vs 0.043, 0.075) was also equally tighter for both models. Sex (females) was positively associated with RR ($\hat{\beta} = 1.605$ compared to 1.734), hence, the 95%CI (0.47, 2.739 vs 0.617, 2.851) was also tighter for joint model. Similarly, sex (females) was positively associated with PR ($\hat{\beta} = 4.804$compared to 4.528), and the 95%CI (2.007, 7.602 vs 1.902, 7.153) was also tighter for joint model relative to males. Both models also concluded a nominal decrease with regards to LVEF for both PR ($\hat{\beta} = -0.307$ compared to -0.295), 95%CI ((-0.339,-0.275 vs -0.327,-0.263) and RR ($\hat{\beta} = -0.075$ compared to -0.075), 95%CI (-0.082,-0.067 vs -0.082,-0.067) has no difference in both models as it was shown in table 4.5. All parameters except NYHA class II on PR are statistically significant in both models. Finally, similar explanation could be given through the rest covariates displayed in table 4.5.

5.5. Model diagnostic checking

Diagnostic checking and Residual plot for fixed effects: - Different diagnostic checking plots for the final separate mixed linear models of pulse rate and respiratory rates are presented in appendix B. Thus; the result is explained as shown below. According to the figure B.1 and figure B.2, plot of fitted versus standardized residuals for PR & RR respectively, even if there are some outliers, it was indicated that the variability of the errors in both PR & RR were almost nearly constant. That means the errors did not far deviate from each other. Distances of individual residuals were equally far from the horizontal lines. Furthermore, according to the probability plots those were shown on figure B.3 and figure B.4, even if the points were compacted at the two end tails for both outcomes PR and RR, the normality assumption was supported through the upward nearly straight line of normal plots. Similarly, based on the normal probability plots of random effects with subject (MRN) specific random intercepts and random slopes those are shown on figure B.5 and figure B.6, even if it seems a slight deviation of normality at the bottom tail on the random slope (Time) for RR that is not that much worse deviation. Hence, there is no

problem with normality assumptions of both random intercepts and random slopes for both PR & RR models and the normality assumption are almost fulfilled.

5.6. Discussions

Based on different well organized literatures and analysis that were included in this thesis, some discussions and review of works is organized as following.

This study was conducted on the title of a joint model for a longitudinal pulse rate and respiratory rate of congestive heart failure patients in Ayder Referral Hospital of Mekelle University. In summary, a joint mixed effect model for paired outcomes with the sets of both continuous and categorical covariates such as: time, age, weight, sex, NYHA classes, LVEF and the interaction of time with weight and LVEF is presented in this study. This model extends previous work by accommodating longitudinally measured two main symptoms of CHF as outcome variables. According to some related works that were reviewed in this thesis, even if old age, sex, smoking, hypertension, diabetes, obesity, valvular heart disease, and CHD were considered as the important risk factors for CHF, as a result of the absence of those particular covariates, only some of those covariates were included in this thesis. For implementation a necessary computational procedure is developed. Using the proposed methods, the influence of different covariates which were listed earlier in this thesis is examined. Few studies have directly examined the relative contributions of such covariates, partly due to the lack of appropriate analytical tools to discern these simultaneous effects. With the proc mixed statistical methods, the influences of the covariates on longitudinally measured bivariate outcomes PR and RR (symptoms of CHF) is executed. Since joint model building usually starts from separate models for each component, initially each data are analyzed separately. Such separate analysis is preferred for several reasons. Firstly, it helps to specify the mean response of the model. Secondly, the random effects to be included in the longitudinal model can be easily determined, and thirdly initial values to be provided for the joint models can be obtained.

The finding provides direct evidence that weight (in Kg) increase as reflected in the analysis is the primarily driver of the risk of CHF by causing reasonable increase on both symptoms PR and RR. The finding is consistent with the latest (American Heart association,2010) literature on the connection between excess weight and risk of CHF that excess weight strain on heart, so being

overweight increase the risk of heart failure which is consistent with increasing the rate of both symptoms in CHF patients. Furthermore, as finding indicated decreasing in LVEF (in percent) is also the primarily driver of the risk of CHF by causing reasonable increase on both symptoms PR and RR longitudinally throughout the follow up. The finding is consistent with the latest literature which suggests low LVEF is most poor prognosis of in patients with CHF; lower LVEF is highly correlated with CHF(p-value<0.0001)(Asanin *et al*.,2005). The finding is also in line with Njagi *et al* (2013) Based on exponentiation of the relevant parameter estimate, the mean number of abnormal heart rate measurements in patients with reduced ejection was found to be 3.3531 times that of patients with preserved ejection. That effect was at borderline statistical significant (p = 0.0594). The test for a joint effect of ejection status on both processes was not statistically significant (p = 0.1650) but in contrast to that in this finding there is statistically negative significant association between the LVEF and both PR and RR. As they noted, the effect of ejection status on the mean number of abnormal heart rate measurements was border-line significant under the extended model; however, the case was quite different under the conventional model (p-value = 0.0901), this statement contrasts the finding of this study.

Carmilla *et al* (2011) stated that at follow up, there were less healthy controls and fewer subjects had psychopathology than at baseline. RSA slightly decreased, whereas heart rate and respiration rate increased over the two year follow up period and this inconsistent to findings in this study both PR and RR is decreased throughout the follow up. The finding realized that PR and RR are higher in female than males and is consistent with (Carmilla *et al,* 2010) in connection to women had 8.1ms times higher RSA and 2.5bpm times higher HR than men. The finding also indicated that PR and RR decrease with age and is consistent with Ferrari (2010); heart rate decreased with age, pups having higher heart rates with mean value and standard deviation (71.25 ± 10.92) than sub-adult with mean value and standard deviation (64.26 ± 12.96) and adult individuals with mean value and standard deviation (53.56 ± 12.52). Lambert and Vandenhende (2001) reported that there was no significant association between heart rate and systolic BP but there was significant positive association between HR and DBP with a fitted Kendall's tau equal to 0.53 before treatment and 0.07 when there was drug in the plasma. The finding is consistent with it because PR and RR have significant positive association. Furthermore, there was significant association between sex and both PR and RR in contrast to Lambert and Vandenhende (2001) that there was no significant effect of sex on HR (PR) and DBP.

According to American Heart Association (2010), men have higher rate of heart failure than women. Conversely the finding of this study indicated that it is not consistent with it as PR and RR are higher in female than males. However, is consistent with Lambert and Vandenhende (2001) who reported that the marginal mean heart rate was significantly smaller for men than for women but not significantly related to the drug concentration. To improve survival, CHF therapies must reduce either sudden cardiac death (the most common cause of death in patients with New York Heart Association [NYHA] class I or II symptoms) or progressive heart failure (the predominant cause of death in those with NYHA class III or IV symptoms) (Jong et al., 2002**;** Poole-Wilson *et al*., 2003). This finding is also consistent with the results of the study as NYHA class increase from I- IV the risk of raising PR and RR increase which is associated with leading the risk of CHF. Clinically, my finding highlights the importance of weight and LVEF management in CHF patients. The excessive weight gain could significantly increase the risk of CHF by causing reasonable increase on the PR and RR which are two main symptoms of CHF. Such an observation is consistent with the previously published data of (American Heart Association, 2010).

Turning to the separate analysis of the CHF longitudinal data, the variables included in the model are determined using automatic variable selection methods. Then, of the seven covariates considered two of them (place of residence and diagnosis History) were not found to be statistically significant. The finding provides direct evidence of strong correlation between two symptoms of CHF (PR and RR) estimated to be 0.7054(70.54%) with 95% CI of (0.642, 0.769). thus, the joint mixed effect model was better fit than two separate random effect models. This finding is consistent with the previous literatures that was studied by Thiébauta (2007) on bivariate mixed effect model or first-order autoregressive process and independent measurement error for both markers of CD4 and HIVRNA in HIV patients($\mathrm{p-valu} < 10^{-4}$). Similarly the finding is also consistent with the previous literatures of Ferrari and Cribari-Neto (2004) studied on application of joint models for resistance and prevalence a strong correlation between percentage resistant and prevalence and that both increase with time. The correlation is estimated to be 0.95, with 95% confidence interval [0.414, 0.997] showing that the correlation is significant. That correlation however ignores the effect of time. In contrast to this finding, statistically significant marginal correlations over time have increased throughout the time. The

finding indicated the positively significant association of evolution and is consistent with the study of Ferrari (2010) on raw measures of heart rate, breathing rate and body temperature which were all positively and significantly correlated with each other.

Finally, joint mixed model was preferred to find and identify joint evolutions in this finding and this is consistent to Njagi *et al* (2013) who compared the results from the extended and the conventional model. Based on an AIC-based comparison, they observed that their extended model provided improvement to model fit, without compromising parsimony. There was a impact on both the point estimates and standard errors.

CHAPTER SIX

6. Conclusions and Recommendations

6.1. Conclusions

The main aim of this thesis was to develop joint mixed effects model for paired symptoms of congestive heart failure (i.e. pulse rate measured in beats per minutes and respiratory rate measured in breaths per minute) as outcome variables. Toward this goal, the previously introduced joint model allows the joint modeling of mixed model for two symptoms of CHF (PR and RR) which are two continuous outcome variables with specification of subject specific random intercepts and slopes. Then it can be generalized the joint model to the longitudinal data, which necessitates the modeling of association between the continuous outcomes (PR and RR) considered very important. This is accomplished with incorporation of random effects (i.e. subject specific random intercepts and random slopes (time), by excluding quadratic random slopes) in individual linear mixed effect models for outcomes (PR and RR). The unstructured covariance structure was preferred to fit both separate and joint mixed effect model. Estimation of the fixed and random effects was described, along with formal definitions of the association in the evolution (AOE) of the two responses and the evolution in the associations (EOA). Thus, the question of AOE and the EOA of the PR and RR were clearly addressed.

After passing many procedures, among all covariates diagnosis history and place of residence were excluded in final models because of their insignificant effect on both outcomes but the rest covariates such as time, age, sex, weight LVEF, NYHA and interaction of time with weight and LVEF were included in final models. Out of those covariates three covariates time, age and LVEF were found to be negatively associated with both outcomes in both separate and joint mixed model. Moreover, among all the covariates included in separated and joint mixed models, only NYHA class II were statistically insignificant on the evolution of PR. Non-zero covariance of random intercepts and random slopes explained the statistical significance of association between two outcomes. Likewise, it can be generalized that, the two outcomes have a strong positive correlation and the correlation was statistically significant. Thus, the joint mixed effect model was preferred because the joint mixed effects model is more flexible in allowing separate

fixed and random effects for each response i.e. PR and RR through appropriate choice of potential risk factors (covariates) or fixed effect and random effects, while accommodating dependence in the longitudinal trajectories through dependence in the random effects. The baseline mean of the two symptoms PR and RR were out of the normal range for CHF patients but throughout the consecutive follow up of the clinical treatment, decreasing values of PR and RR has been shown. That decreasing trend on PR and RR indirectly indicated the reduction of the risk of congestive heart failure.

Finally, it is concluded that, joint modeling of longitudinal bivariate responses is necessary to explore the association between paired response variables like PR and RR. A usual problem with the joint modeling is failing to convergence because of large number of association parameter to estimate.

Gradually, for future work, one might want to look at modeling the joint mixed model with correlated measurement errors which may violate the result of mixed effect when uncorrelated error is considered. Moreover, some one also might want to look at modeling more than two response variables over time. This issue is typically can implemented using modern computing methods for a joint model in which there are more than two response variables. However, with increasing response variables, there is an exponential increase in the amount of computing power necessary to produce estimates and the complexity is high.

6.2. Recommendation

As the selection of an appropriate statistical model is directly related to the qualities and nature of the data, in the case of limited quality data, the associations of factors or covariates with outcome variables could not assessed. Regarding data collection, special efforts are needed to get data of better quality in order to study joint time trends in the evolution of PR and RR of CHF. Then the collection of paired data of two symptoms of CHF (PR and RR) at aggregation levels of at least the hierarchical level of cardiac syndromes is necessary and recommended.

A lot of investigators doing longitudinal research used to model repeated outcomes separately, to assess the evolutions of the outcomes through time by ignoring the associated effects. But it is recommended to check the associated evolutions in some case as the outcomes might have the association of the evolutions. Even if almost equivalent questions answered through joint model and separate model, joint model is able to address the same questions with better accuracy. And also address the additional and important concepts of AOE and the EOA of the outcomes. Thus, fitting joint model is recommended. In many cases including in this study, uncorrelated error is considered in modeling joint mixed models, but in some cases it is crucial to consider correlated error in models because using uncorrelated error model may display less accurate results if there is suspicion of correlated measurement errors in the data. So, considering heterogeneity of error term in some case is necessary and recommended.

6.3. Limitation of the study

The investigator intended to study in brief about the joint evolutions of PR & RR over time with associated covariates. However, there were a lot of constraints starting form extraction of data up to the end of the works. Some of them are listed as following:

- The first limitation was lack of enough literature and materials with regards to joint mixed effect model on PR & RR of CHF and also about CHF in Ethiopian experiences.
- The positive-definiteness constraint was a major obstacle in modeling covariance matrices due to model over-parameterization.
- Another some potential risk factors or covariates which may have high influence on evolution of PR and RR which were mentioned in some literatures may not measured in the data.

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Appendix A

Table A.1 Linear Mixed effect Model results for PR and RR Independently

Effect (Parameters)		For PR model		For RR model	
		Estimate (SE)	(1-α)100% CI	Estimate (SE)	(1-α)100% CI
Intercept($\boldsymbol{\beta_{i0}}$)		107.04(4.43)	(98.33,115.74)	37.083(1.794)	(33.555,40.611)
Time($\boldsymbol{\beta_{i1}}$)		-3.144(0.123)	(-3.385,-2.903)	-0.786 (0.034)	(-0.853,-0.72)
Age($\boldsymbol{\beta_{i2}}$)		-0.409(0.053)	(-0.513,-0.304)	-0.258 (0.0251)	-0.308(-0.209)
Sex($\boldsymbol{\beta_{i3}}$)		4.804(1.429)	(1.993,7.616)	1.605 (0.581)	0.463(2.746)
NYHA	II($\boldsymbol{\beta}_{i4}$)	2.743(1.922)	(-1.042,6.528)	2.0562 (0.9029)	(0.2785,3.8338)
	III($\boldsymbol{\beta}_{i5}$)	5.167 (2.434)	(0.3740,9.9606)	4.0221(1.1426)	(1.7725,6.2718)
	IV($\boldsymbol{\beta}_{i6}$)	15.153(2.814)	(9.611,20.694)	8.9368(1.3223)	(6.3333,11.5402)
LVEF($\boldsymbol{\beta_{i7}}$)		-0.3066(0.0164)	(-0.339,-0.275)	-0.0745(0.004)	(-0.0822,-0.0667)
Time*LVEF($\boldsymbol{\beta_{i8}}$)		0.0091(0.0008)	(0.008, 0.012)	0.0022 (0.0002)	(0.0019,0.0026)
Weight($\boldsymbol{\beta_{i9}}$)		0.5384(0.0329)	(0.4738,0.6029)	0.0535 (0.0082)	(0.0376,0.0695)
Time*Weight($\boldsymbol{\beta_{i10}}$)		0.0159(0.0014)	(0.0131,0.0187)	0.0027 (0.0004)	(0.002,0.0034)
Sigma($\boldsymbol{\sigma_i}$)		31.5302(0.5801)	(30.424,32.699)	1.6536 (0.0306)	(1.5952,1.7153)
$\boldsymbol{\sigma^2_{b_{ji}}}$		141.27 (13.141)	(118.68,171.03)	31.6299(2.9151)	(26.612,38.222)
$\boldsymbol{\sigma_{b_{ji},b_{2i}}}$		-2.2069(0.3952)	(-2.982,-1.432)	-0.6035 (0.1115)	(-0.8221,-0.3849)
$\boldsymbol{\sigma^2_{b_{ji}}}$		0.1817 (0.0202)	(0.148, 0.229)	0.0664 (0.0072)	(0.0543,0.083)

NB: $\mathbf{i = 1}$ index for PR parameters and $\mathbf{i = 2}$ index for RR parameters $\mathbf{j = 0, 1}$ indexes for intercept and slope at random effects.

Appendix B

Diagnostic Checking

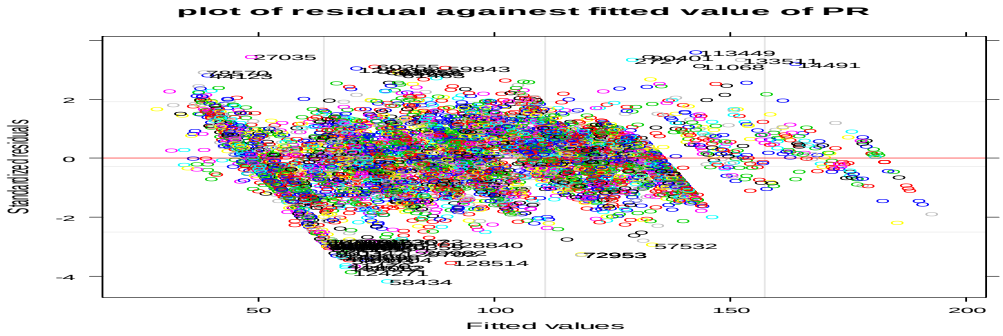

Figure B.1 Plot of Residuals versus Fitted Value for PR

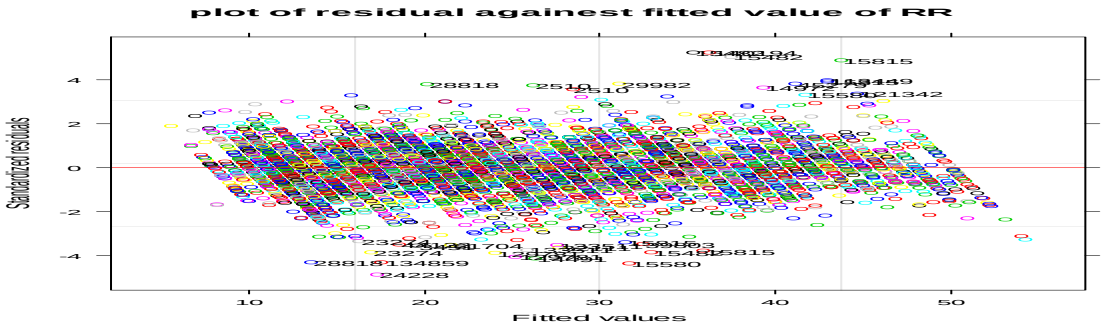

Figure B.2 Plot of Residual versus Fitted Values for RR

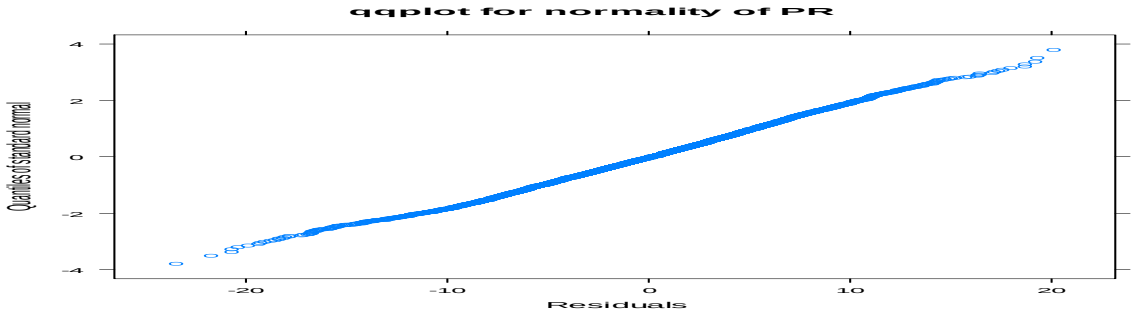

Figure B.3 QQ-Plot for Normality of PR

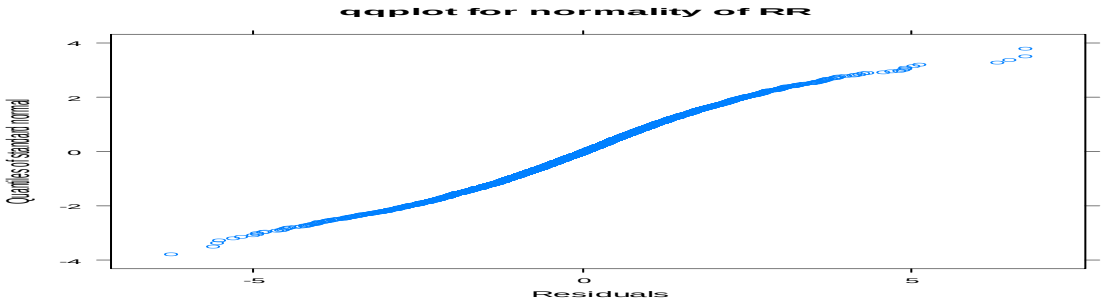

Figure B.4 QQ-Plot for Normality of RR

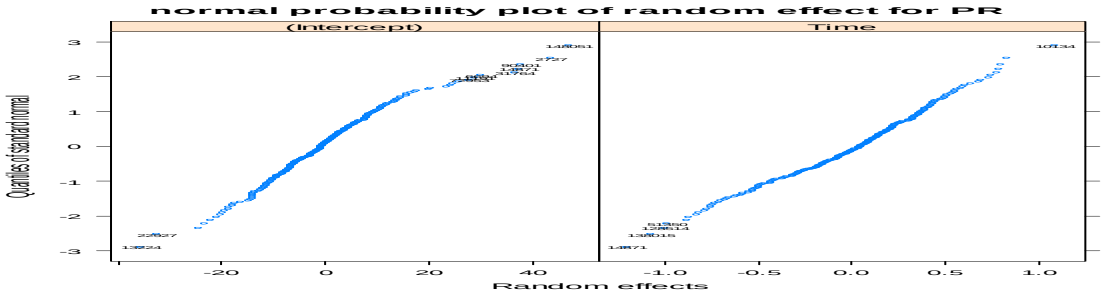

Figure B.5 Normal Probability Plot of Random Effect for PR

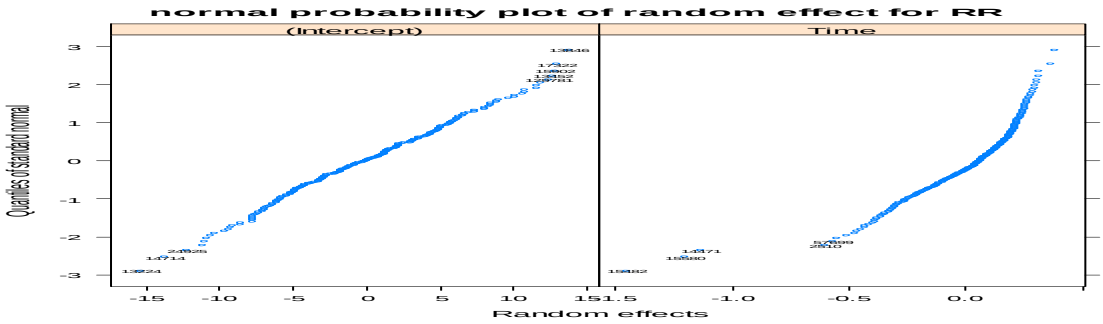

Figure B.6 Normal Probability Plot of Random Effect for RR

Appendix C

SAS codes and R-codes

```
*/ reading data/*
ROC IMPORT OUT= WORK.CHFdata
            DATAFILE= "C:\yema\Mura.sav"
            DBMS=SAV REPLACE;
RUN;
*/summary statistics/*
proc means data=CHFdata n min max mean median std;
var PR RR;
class Time;
title 'Descriptive Statistics for PR Data';
run;
*/plotting individual profile plot with average trends/*
proc gplot data=CHFdata;
plot PR*Time=MRN
/ haxis=0 TO 50 by 5
vaxis=50 TO 190 by 20;
symbol v=none repeat=264 i=join color=blue;
label time='weeks';
title 'Individual Profiles of the PR Data';
run;
*/ proc mixed model for PR/*
proc mixed data =CHFdata order=FREQ method=ML covtest cl;
class MRN Sex  NYHA;
model PR=Time Age Sex NYHA LVEF Time*LVEF Weight Time*Weight/solution ddfm=kr;
random int Time/sub=MRN type=un;
run;
*/proc mixed model for RR/*
proc mixed data =CHFdata order=FREQ method=ml cl covtest;
class MRN Sex  NYHA;
model RR = Time  Age Time*Age Sex NYHA LVEF Time*LVEF  weight Time*Weight/ solution
ddfm=kr;
 random int Time/sub=MRN type=un;
run;
/*reading data for joint mixed model/*
PROC IMPORT OUT= WORK.HH
            DATAFILE= "C:\yema\MuraJ..sav"
```

```
            DBMS=SAV REPLACE;
RUN;
*/ Separate mixed model using proc mixed /*
proc mixed data=HH method=ml order=freq covtest cl;
class MRN Name Sex NYHA;
model PRRR = Name Time Name*Time Name*Age Age Name*Sex Sex Name*NYHA NYHA
Name*LVEF LVEF Name*Time*LVEF Time*LVEF Name*Weight Weight Name*Time*Weight
Time*Weight / noint solution ddfm=satterthwaite cl;
random intercept Time/ subject=MRN type=UN group=Name g gcorr v vcorr;
Repeated /group=Name Sub=MRN Type=vc r rcorr;
run;
*/ joint mixed model using proc mixed/*
proc mixed data=HH method=ml order=freq covtest cl;
class MRN Name Sex NYHA;
model PRRR = Name Name*Time Name*Age Name*Sex Name*NYHA Name*LVEF Name*Time*LVEF
Name*Weight Name*Time*Weight/noint solution ddfm=satterthwaite cl;
random  Name Name*Time/ subject=MRN type=un ;
Repeated /group=Name Sub=MRN Type=vc;
run;*/uncorrelated error/*
/*R-code/*
rm(list=ls())
library(lattice)
library(foreign)
library(nlme)
CHF<-read.spss("Mura.sav")
HF=as.data.frame(CHF)
attach(HF)
## Individual profile plot for Respiratory Rate##
xyplot(RR~Time,data=HF,groups=MRN,type="l",ylim=c(5,50),xlim=c(0,46),xlab="Follow  up
Time in weeks",ylab="Respiratory Rate",main=" Individual profile plot for Respiratory
Rate of CHF patients")
lines(loess.smooth(Time,RR),col=28,lwd=12,labels=c("Mean of RR"),pos=4,cex=0.8))
## Mean profile plot for Pulse Rate##
mean2<-tapply(PR,Time, mean,data=HF)
Time2=as.numeric(unique(sort(Time)))
plot(Time2,mean2,type="l",ylim=c(min(mean2),max(mean2)),xlim=c(0,46),lwd=4,xlab="Foll
ow up Time in weeks",ylab="Pulse Rate",main="Mean Profile plot for Pulse rate of CHF
patients")
lines(loess.smooth(Time,PR),col=4,lwd="4",pos=4,cex=0.8)
###exploring random effect for pulse rate ##
PRRE=lmList(PR~Time+I(Time^2)|MRN,HF)
summary(PRRE)
pairs(PRRE,MRN=0.01,adj=-0.05,is.na.na=T)
intervals(PRRE)
plot(intervals(PRRE),main="random effect exploration plot for PR")
## Model selection without considering quadratic and interaction term in the model
with response variable Pulse rate##
Model1<-lme(fixed=PR~Time+Age+factor(Sex)+factor(NYHA)+LVEF+Weight+factor(Residence)+
factor(Diagnosis),method="ML",data=HF,random=~Time+I(Time^2)|MRN)
Model2<-lme(fixed=PR~Time+Age+factor(Sex)+factor(NYHA)+LVEF+Weight+factor(Residence),
method="ML",data=HF,random=~Time+I(Time^2)|MRN)
Model3<-lme(fixed=PR~Time+Age+factor(Sex)+factor(NYHA)+LVEF+Weight,
method="ML",data=HF,random=~Time+I(Time^2)|MRN)
 anova(model1,model2,model3)
```

```
## adding interaction and quadratic term in the best modelwith response variable
Pulse rate##
Model3<-lme(fixed=PR~Time+Age+factor(Sex)+factor(NYHA)+LVEF+Weight,
method="ML",data=HF,random=~Time+I(Time^2)|MRN)
Model4<-lme(fixed=PR~Time+I(Time^2)+Age+factor(Sex)+factor(NYHA)+LVEF+Weight,
method="ML",data=HF,random=~Time+I(Time^2)|MRN)
anova(model3,model4)
## Adding some interaction terms ##
Model3<-lme(fixed=PR~Time+Age+factor(Sex)+factor(NYHA)+LVEF+Weight,
method="ML",data=HF,random=~Time+I(Time^2)|MRN)
model11<-lme(fixed=PR~Time+Age+factor(Sex)+as.factor(NYHA)+Time*LVEF+Weight,
method="ML",data=HF,random=~Time+I(Time^2)|MRN)
model12<-lme(fixed=PR~Time+Age+factor(Sex)+as.factor(NYHA)+Time*LVEF+Time*Weight,
method="ML",data=HF,random=~Time+I(Time^2)|MRN)
model13<-lme(fixed=PR~Time+Time*Age+factor(Sex)+factor(NYHA)+Time*LVEF+Time*Weight,
method="ML",data=HF,random=~Time+I(Time^2)|MRN)
model14<-lme(fixed=PR~Time+Time*Age+Time*factor(Sex)+factor(NYHA)+
Time*LVEF+Time*Weight, method="ML",data=HF,random=~Time+I(Time^2)|MRN)
model15<-lme(fixed=PR~Time+Time*Age+Time*factor(Sex)+Time*factor(NYHA)+
Time*LVEF+Time*Weight, method="ML",data=HF,random=~Time+I(Time^2)|MRN)
model16<-lme(fixed=PR~Time+Time*Age+Time*factor(Sex)+Time*factor(NYHA)+
Time*LVEF+Time*Weight, method="ML",data=HF,random=~Time+I(Time^2)|MRN)
anova(model3,model11,model12,model13,model14,model15,model16)
## Model selection for random effect with response variable Pulse rate ##
model12<-lme(fixed=PR~Time+Age+factor(Sex)+factor(NYHA)+Time*LVEF+Time*Weight,
method="ML",data=HF,random=~Time+I(Time^2)|MRN)
model17<-lme(fixed=PR~Time+Age+factor(Sex)+factor(NYHA)+Time*LVEF+Time*Weight,
method="ML",data=HF,random=~Time|MRN)
model18<-lme(fixed=PR~Time+Age+factor(Sex)+factor(NYHA)+Time*LVEF+Time*Weight,
method="ML",data=HF,random=~1|MRN)
anova(model18,model17,model12)
## comparing ML and REML methods of the selected model##
model21<-lme(fixed=PR~Time+I(Time^2)+Age+factor(Sex)+factor(NYHA)+Time:LVEF+
Time*Weight, method="REML",data=HF,random=~Time+I(Time^2)|MRN)
## Diagnostic checking##
## Residual Plots ##
plot(model17,resid(.,type="p")~fitted(.),id=0.005,adj=-
0.03,abline=0,col=2:12,main="plot of residual against fitted value of PR")
plot(model017,resid(.,type="p")~fitted(.)|NYHA, id=0.04, adj=0.3, abline=0, col=2:16,
main="plot of residual against fitted value for RR ")
##QQ_Plot##
qqnorm(model17,~resid(.),main="qqplot for normality of PR")
## random effect normality ##
qqnorm(model17,~ranef(.),id=0.03,cex=0.5,main="normal probability plot of random
effect")
```