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JOINT MODEL ON LONGITUDINAL PULSE RATE AND RESPIRATORY RATE OF CONGESTIVE HEART FAILURE PATIENTS: THE CASE OF FELEGE- HIWOT REFERRAL HOSPITAL BAHIR DAR, ETHIOPIA

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DEPARTMENT OF STATISTICS

BAHIR DAR UNIVERSTY

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THESIS SUBMITTED TO THE DEPARTMENT OF STATISTICS, BAHIRDAR UNIVERSITY,IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTERS OF SCIENCE IN STATISTICS (BIOSTATISTCS)

BY

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Declaration

This is to certify that the thesis entitled “Joint model on Longitudinal pulse Rate and Respiratory Rate of Congestive Heart Failure Patients: the Case of Felege - Hiwot Referral Hospital Bahir Dar, Ethiopia’’ .submitted in partial fulfillment of the Degree of Masters of science in Statistics (Biostatistics) of Department of Statistics ,Bahr Dar University , and is a record of original work carried out by me and has never been submitted to this or any other institution to get any of Degree.

The assurance and help I received during the course of this investigation have been received during the course of this investigation have been duly acknowledged.

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Internal Examiner Date signature

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Abbreviations

RR Respiratory Rate

PR Pulse Rate

ACF Acute Coronary Failure

AIC Akaki's Information Criteria

ANOVA Analysis of Variance

BMI Body Mass Index

CHD Coronary Heart Disease

CHF Congestive Heart Failure

GLM Generalized Linear Model

HF Heart Failure

HR Heart Rate

LMM Linear Mixed Model

LVEF Left Ventricle Ejection Fraction

ML Maximum Likelihood

NYHA New York Heart Association

REML Restricted Maximum Likelihood

SBP Systolic Blood Pressure

SSA Sub Saharan Africa

WHO World Health Organization

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Abstract

Background: Pulse Rate and Respiratory Rate are main symptom of congestive heart failure patients and the abnormal PR and RR are broad indicators of major physiological instability. Congestive Heart Failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of ventricle to fill out or eject blood. The main objective of this study is to identify the factor that affects Pulse Rate and Respiratory Rate for CHF patients using joint random effect model.

Methods: Hospital based retrospective studies were conducted among adult congestive heart failure patients. Separate and Joint random effect model were used to infer the effect of bivariate longitudinal outcomes of Pulse Rate and Respiratory Rate for CHF patients. Data management was done by SPSS 23 and SAS 9.2.

Results: A total of 153 CHF patients were enrolled for this study. Of which, 67(43.79%) were biventricular heart failure type, 46(30.07%) were faced left sided heart failure and 40(26.14%) faced right sided heart failure. We compared the separate and joint model by considering their estimates and corresponding significant values and then we found that joint model having the most significant and precise estimates. Left Ventricle Ejection Fraction ($\hat{\beta} = 0.1221$, p=<0.0001), diagnostic history Coronary Heart Disease($\hat{\beta} = 6.59$, p=0.0241), age with month interaction ($\hat{\beta} = 0.004894$, p=0.0097), diagnostic history with month interaction for Coronary Heart Disease($\hat{\beta} = 0.0075$, $p = 0.0359$) , New York Heart Association class I with month interaction ($\hat{\beta} = 0.2838, p = 0.0024$) and New York Heart Association class II with month interaction $(\hat{\beta} = 0.3216,\ p =< 0.0001)$were positively associated with Pulse Rate. Age ($\hat{\beta} = -0.1995, p = 0.0013$) New York Heart Association class I ($\hat{\beta} = -17.57,\ p =< 0.0001$), New York Heart Association class II ($\hat{\beta} = -15.6475$, $p =< 0.0001$), New York Heart Association class III ($\hat{\beta} = -5.7491,\ p = 0.0290$) and Left Ventricle Ejection Fraction with month interaction ($\hat{\beta} = -0.00635, p = 0.0162$) were negatively associated with Pulse Rate. Left Ventricle Ejection Fraction ($\hat{\beta} = 0.1221, p =< 0.0001$), diagnostic history of others with month interaction($\hat{\beta} = 0.08018,\ p = 0.0203$) and Congestive Heart Failure type of left sided failure with month interaction $(\hat{\beta} = 0.057,\ p = 0.0148)$was positively associated with Respiratory Rate. While, month ($\hat{\beta} = -0.2009\ p = 0.0244$), Congestive Heart Failure type of Biventricular$(\widehat{\beta} = -1.1839\ p =< 0.0242)$, New York Heart Association class I ($\hat{\beta} = -2.09, p =< 0.0001$), New York Heart Association class II ($\hat{\beta} = -1.44\ p =< 0.0001$), New York Heart Association class III ($\hat{\beta} = -0.98\ p = 0.0007$) and Left Ventricle Ejection Fraction with month interaction ($\widehat{\beta} = -0.0032,\ p =< 0.0001$) was negatively associated with Respiratory Rate.

Conclusions: Age, Left Ventricle Ejection Fraction, New York Heart Association class ,diagnosis history of Coronary Heart Disease,age with month interaction , month with New York Heart Association class month with diagnostic history, month with Left Ventricle Ejection Fraction were the predicting factors for the longitudinal change of Pulse Rate. Left Ventricle Ejection Fraction,monthchftype Biventricular, New York Heart Association class,month with diagnostic history,month with chftype and month with Left Ventricle Ejection Fraction were the predicting factors for the longitudinal change of Respiratory Rate.

Keywords:-**Pulse Rate;Respiratory Rate;Congestive Heart Failure;joint mixed effect model;**

Chapter One

1. Introduction

1.1 Background of the Study

Abnormal respiratory rates (RR) 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. RR performs at least as accurately in identifying patients at risk of these adverse events as PR and the SBP. 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. Although the main function of the respiratory system is gas exchange, a broad range of factors can affect ventilation. In patients with CHF, an increase in RR can warn of impending fluid in the lungs, which is a common debilitating symptom of CHF as it was stated in American Heart Association*(Thom et al., 2006)*

Heart rate (HR) among the many vital signs (respiration rate, blood oxygen saturation, arterial blood pressure, etc.), of the most commonly measured and monitored. HR data are used to measure anomalous rate or irregular PR or heart block. The HR or PR 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 also go as high as 100 in a healthy adult and as low as 40 in athletes as it is described in American Heart Association and Gorgas. 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 means the heart is not pumping or working hard to deliver blood and oxygen to the body *(Gorgas, 2004)*.

Heart failure (HF) is a major public health issue with a current prevalence of over 5.8 million in the USA and over 23 million worldwide. Every year in the USA, more than 550,000 individuals are diagnosed with HF for the first time, and there is a lifetime risk of one in five of developing this syndrome. A diagnosis of HF carries substantial risk of morbidity and mortality, despite advances in management. Over 2.4 million patients who are hospitalized have HF as a primary or secondary diagnosis, and nearly 300,000 deaths annually are directly attributable to HF Congestive heart failure affects people of all ages, from children and young adults to the middle-aged and the elderly. Almost 1.4 million persons with CHF are under 60 years of age. CHF is present in 2 percent of persons age 40 to 59.More than 5 percent of persons age 60 to 69 have CHF.CHF annual incidence approaches 10 per 1,000

population after 65 years of age. The incidence of CHF is equally frequent in men and women, and African-Americans are 1.5 times more likely to develop heart failure than Caucasians. Heart failure is responsible for 11 million physician visits each year, and more hospitalizations than all forms of cancer combined. CHF is the first-listed diagnosis in 875,000 hospitalizations, and the most common diagnosis in hospital patients age 65 years and older. In that age group, one-fifth of all hospitalizations have a primary or secondary diagnosis of heart failure. More than half of those who develop CHF die within 5 years of diagnosis. Heart failure contributes to approximately 287,000 deaths a year. Sudden death is common in patients with CHF, occurring at a rate of six to nine times that of the general population. Deaths from heart failure have decreased on average by 12 percent per decade for women and men over the past fifty years *(Bui et al., 2011)*.

Based on ageing of the population and adoption of Western lifestyles, the African Union estimates that 10-

20 million people in SSA may currently be affected by CHF -"the greatest health challenge after AIDS"*(Bloomfield et al., 2013*).

Approximately 9% of all deaths in Ethiopia in 2012 were caused by CHF according to World Health Organization WHO (2014). Small scale local studies also reported an increasing burden from CHF and its risk factors, especially in urban settings in Ethiopia. In a systematic review of studies conducted in Ethiopia between 1960 and 2011, CHF was reported to be among the prevalent causes of morbidity (range 4–24 %); the main causes of hospital admission, especially among those older than 60 years, the leading causes of medical intensive care unit admission (ranges 8.9–9.8 %); and among the major causes of mortality range (6.5–24 %). In Addis Ababa, the capital Ethiopia, an estimated 25 % of all household deaths between 2006 and 2009 and 11 % of all hospital deaths between 2002 and 2010 were attributed to CHF, Myocardial infarction, stroke and hypertensive heart disease accounted for about 75 % of CHF deaths modifiable risk factors like smoking, high cholesterol and high blood pressure explain the major share of the CHF burden. The prevalence of hypertension in Ethiopia is estimated to range from 16 to 30 % *(WHO, 2014)*.

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. Heart failure (HF) is a condition in which one or both ventricles cannot pump sufficient blood to meet the metabolic needs of the body. HF, also known as CHF, is a chronic condition that develops over time. 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. CHF is a chronic, debilitating illness, with ever-increasing prevalence in the aged peoples*(Dennison, 2012)* .

Congestive heart failure (CHF) is a common clinical disorder that results in pulmonary vascular congestion and reduced cardiac output. However, awareness about treatment and control of CHF is extremely low among developing nations including Ethiopia. Little is known about the CHF control and the progression of PR and RR CHF patients in Ethiopia. In addition, the relationship between the effects of different variables on CHF control and longitudinal PR and RR changes has not been clarified in Ethiopia. Thus, this study aimed to determine the predictor factors that may affect the longitudinal change of PR and RR of CHF patients in FelegHiwot referral Hospital.

1.2 Statement of the Problem

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 overtime. Laird and Ware (1982) Stated that, in many circumstances, more than one response variable followed longitudinally, and analyzing all jointly may be beneficial.

Williamson (2006)also stated that, 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. 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 stated by Gueorguieva and Agresti (2001) 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. In tyrannically 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.

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 longitudinal change of these correlations with a certain treatment throughout the follow up time.

1.3. Research Questions

Having this statement of the problem and using model, the following research question will be answered.

- What is the Rate of change (pattern) of PR and RR for CHF patients over time separately?
- How do PR and RR Jointly change overtime?
- What are the potential risk factors that affect the rate of change PR and RR of CHF patients?
- Is a joint model good fit for PR and RR of CHF Patients
- Is joint or separate model good fit for the data?

1.4 Objective of the Study

1.4.1 General Objective

The main objective of this study was to identify the potential risk factors affecting the longitudinal change of PR and RR of CHF patients in Felege Hiwot referral Hospital.

1.4.2 Specific Objectives

The specific objectives of the study were:

- To explore the evolution of PR and RR of CHF patients over time separately
- To fit a mixed effect model for the PR and RR of CHF patients,
- To identify the potential risk factors that affect PR and RR of CHF patients

- To fit joint model for PR and RR of CHF patients
- To compare separate and joint models to fit the data

1.5. Significance of the study

The results of this study help to explore the evolution of PR and RR of CHF as well as know factors that are contributing to CHF. In addition to the result, it will help to propose the appropriate model for CHF cases. Thus, the results of this study could provide information to government and other concerned organizations in setting policies, strategies and further investigation for understanding factors that affecting CHF. The results will also help to understand risk factors that are related in CHF and take interventions to reduce CHF problems. On top of this, the result of the study may enable clinicians to enhance the awareness of the society about factors which increase the probability of death by heart failure. The result of this study will also be used as a source of information to other researchers in the future.

1.6 Dissemination of the results

The final report will be disseminated to the Department of Statistics, Bihar Dar University. Also the study findings will be disseminated to the, regional health bureau, respective health facility. An attempt will be made to publish the findings in scientific journal.

1.7 Limitation of the study

As this study is conducted based on secondary data and some socio demographic variables from direct patients during their follow up , data on some potentially important predictors is not available on patients chart .another limitation of this study was patients dalliance time from their follow up. Some patients came after 10 days after their appointed date.

Chapter Two

2. Literature Review

2.1 Introduction

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 PR and the SBP. 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. Although the main function of the respiratory system is gas exchange, a broad range of factors can affect ventilation. In patients with CHF, an increase in RR can warn of impending fluid in the lungs, which is a common debilitating symptom of CHF as it was stated in American Heart Association *(Thom et al., 2006).*

2.2 Common Demographic Variables in the Literature

Age:-Heart failure is especially common in the older age segments and the prevalence rate is 10-20% among those 80 years of age and over. The association between severe left ventricular dysfunction and systolic hypotension leading to cerebral hypo perfusion in patients with CHF has revived the old idea of "cardiogenic dementia." This is in line with the evidence that links CHF*(Hjelm et al., 2014)* .

Smoking:-Cigarette smoking directly increases the risk of CHF in addition to its effect on increasing the risk of CHD, a major cause of CHF. study also suggest that cigarette smoking might cause about 17% of the incident CHF cases in the US general population *(He et al., 2001).*

Hypertension:-Hypertension was the most common risk factor for CHF, and it contributed a large proportion of heart failure cases in this population-based sample. Preventive strategies directed toward earlier and more aggressive blood pressure control are likely to offer the greatest promise for reducing the incidence of CHF and its associated mortality. Hypertension (blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or current use of medications for treatment of high blood pressure) is the major CHF risk factors were assessed at periodic clinic examinations*(Levy et al., 1996).*

Diabetes:-Patients with diabetes were much more likely to develop CHF than patients without diabetes (incidence rate 30.9 vs. 12.4 cases per 1,000 person-years, rate ratio 2.5, 95% CI 2.3–2.7).. The difference in CHF development rates between persons with and without diabetes was much greater in younger age-groups *(Nichols et al., 2004)*

Obesity:-overweight/obesity predispose or is associated with numerous cardiac complications such as coronary heart disease, heart failure, and sudden death through its impact on the cardiovascular system*(Poirier et al., 2006*).

Alcohol:-Heavy consumption of alcohol is associated with subclinical impairment of left ventricular function and occasionally results in overt cardiomyopathy. This may be a consequence of direct toxic effects of alcohol or its metabolites this results developing CHF*(Walsh et al., 2002)*.

Cholesterol level:-Cholesterol and other types of fatty substances can block the coronary arteries, which are the small arteries that supply blood to the heart. This causes the arteries to become narrow. Narrower coronary arteries restrict your blood flow and can lead to CHF. The plasma levels of total cholesterol and low-density lipoprotein (LDL) cholesterol are important risk factors for congestive heart failure*(Sacks et al., 1996)*.

Exercise:-Regular physical exercise improves both basal endothelial nitric oxide (NO) formation and agonist-mediated endothelium-dependent vasodilation of the skeletal muscle vasculature in patients with CHF. The correction of endothelium dysfunction is associated with a significant increase in exercise capacity*(Hambrecht et al., 1998)*.

2.3 Joint Model for Longitudinal Data

Researchers investigated the bivariate random effects model between the evolution of CD4 and HIV RNA and reported that the bivariate random effects model was significantly better than two separate univariate random effects models *(Thiébaut et al., 2002)*.

In addition, the joint mixed effect model on evolution of occurrence and prevalence of antimicrobial resistant zoonotic agents were executed by. Ferrari (2004) They used beta-regression to illustrate the joint evolution on both outcome variables and they showing that there was a strong positive significant correlation between percentage resistant and prevalence and that both were increased with time. That correlation however ignores the effect of time.

Furthermore, Lambert (2002) studied that, the hemodynamic effect on diastolic blood pressure (DBP), systolic blood pressure (SBP) and HR. 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 HR, in beats/min, (DBP) and 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 and sex was additional covariate. First, the evolution of DBP, SBP and HR were separately analyzed. And time did not appear explicitly associated with regression parameters. Indeed, time was only used to describe serial dependence between the repeated measurements and serial dependence was only found necessary to model HR 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 HR and the covariates considered were location drug concentration and sex.

Lambert (2002)reported that, the marginal mean HR was significantly smaller for men than for women but not significantly related to the drug concentration and 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 Lambert and Vandenhende (2002). Two Joint models of HR with SBP and with DBP were modeled. Thus, they reported that there was no significant association between HR and SBP 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 and DBPTorbicki et al. (2008). 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. Then in line to this the joint mixed effect model of two PR and RR is modeled.

Njagi (2013)analyzed joint modeling on the risk of re-hospitalization and the mean number of times a patient's HR measurements which was classified as “abnormal", with LVEF as a baseline covariate for chronic HF data. He analyzed jointly model the recurrent time-to-re-hospitalization and a count version of the dichotomized longitudinal HR by understanding re-hospitalization is important in HF management. HR 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 HR 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, they considered the baseline LVEF.

Njagi (2013)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 HR measurements was borderline significant under the extended model; however, the case was quite different under the conventional model. There was also are mark able difference in the scale factor; it was highly significant under the conventional model, 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=0.1650; 0.1648) for the extended and the conventional model respectively.

Congestive heart failure (CHF) is a common clinical disorder that results in pulmonary vascular congestion and reduced cardiac output. CHF should be considered in the differential diagnosis of any adult patient who presents with dyspnea and/or respiratory failure. The diagnosis of heart failure is often determined by a careful history and physical examination and characteristic chest-radiograph findings. Measurements of serum brain natriuretic peptide and echocardiography have substantially improved the accuracy of diagnosis. Therapy for CHF is directed at restoring normal cardiopulmonary physiology and reducing the hyper adrenergic state. The cornerstone of treatment is a combination of an angiotens in-converting-enzyme inhibitor and slow titration of a blocker. Patients with CHF are prone to pulmonary complications, including obstructive sleep apnea, pulmonary edema, and pleural effusions.

Continuous positive airway pressure and non in-vasive positive-pressure ventilation benefit patients in CHF exacerbations*(Michael, 2006)*.

The overall 10-year risk of CHF in our sample population was 14.6% (95% confidence interval, 14.3%–14.9%). Of the 4,740 patients in our study, 26.7% were at high risk, 29.8% were at moderate risk, and 43.5% were at low risk for CHF over 10 years. The proportion of patients at high risk for CHF was significantly higher in the communities of low socioeconomic status. (Nasser Bagheri 2015) Individuals with CHF had a significantly higher prevalence of vascular (Carina Hjelm. et al., 2014)dementia, 16% vs. 6% (P<0.001), and of all types of dementia, 40% vs. 30% (P<0.01), than those not diagnosed with CHF. The GEE models showed that depression, hypertension, and/or increased levels of homo cysteine were all associated with a higher risk of dementia in individuals with CHF. Diabetes was specifically associated with an increased risk of vascular dementia.(*Carina Hjelm. et al., 2014*)

Chapter Three

3. Methodology

3.1 Study Area and Design

The Amhara Regional state is located in the Northwestern and North Central parts of Ethiopia and lie within 9^0 and $23^045'$N and 36^0 and $40^030'$E.It has a total area of 170,000km^2, which is divided in to 11 administrative Zones and 105 Weredas . Rugged mountains, plateau, valleys and Gorges characterize its physical landscape. Elevation ranges from 700m in the Eastern parts to over 4620m in the Northwest. Areas lying below 1500m are commonly classified as low lands and those with elevation of greater than or equal to 1500m are classified as highlands(Briggs, 1995) .A hospital based retrospective and prospective study will be conducted at the CHF patient Clinic. In Amhara region there are 5 Referral Hospital, 3 Zonal Hospital and 11 District Hospitals. A retrospective and prospective CHF patients at FelegeHiwot Referral hospital was be considered since September 2015 up to January 2017. FelegeHiwot is a tertiary health care label hospital serving the population of Bahir Dar town and remote areas of northwest Ethiopia. The total population served by the hospital is approximately 12 million.

3.2 Data Source

The data was obtained from Amhara region at FelegeHiwot Referral Hospitals of CHF patient Clinic. The longitudinal data was 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 and socio demographic variables asked patients when they came for follow-up. All of these data was collected by laboratory technicians and nurses after training. In this study, there are 13 covariates (five continues and 8 categorical) and two dependent variables (PR and RR) were encompassed.

3.4 Sample Size Determination

Determining the appropriate sample size required is basically dependent on available resources and level of precision required. Our sample size (number of CHF patients) is calculated using the following sample size calculation formula adopted for two groups (PR and RR):

$n = \frac{\left(Z_{\alpha/2}+Z_{\beta}\right)^2 (S_1+S_2)^2}{d^2(\mu_1-\mu_2)^2}$, where S_1=18.98 and μ_1=126.12 are the standard deviation and mean for PR as well as S_2=10.99 and μ_2=31.64 are the standard deviation and mean for RR taken from (Fissuh and Muleta, 2015). Thus, using 95% confidence level, 90% power of test and 0.075 margin of error the sample size in the study will be n =146. Finally 5 percent of the sample will be added to determine sample size to compensate for none response rate and the total sample size become 153 (=146+7). Further discussions on sampling are available at(Cochran W.G., 1977).

3.4 Study Variables

Response variables: Pulse rate (PR) - number of heart beat per minutes and Respiratory rate (RR) - number of breaths per minutes are our response variables.

Covariates: The following are some continuous and categorical covariates that were used for both separate and joint analysis.

Table 1:- **List of Covariates and their representing symbols and category levels**

No	Variables	Description	Value or code
1	sex	sex of patients	female =0 , male=1
2	Type of CHF	type of chf of chf patients	left=1 right=2,biventricular=3
3	Diaghistory	Diagnostic history of chf patients	severe anemia=1,CDH=2,ACF=3,others=4
4	NYHA	New York Heart Association of chf patients	class I=1,classII=2,classIII=3,classIV=4
5	LVEF	left ventricle ejection fraction	in%
6	Time	Time follow up in months	monthly follow up
7	Residence	residence of CHF patients	rural=1,urban=2
8	Marstatus	marital status of CHF patients	married=1,single=2,others=3
9	Edulevel	educational level of CHF patients	illiterate=1,informal education=2,primary=3 secondary=4,tertiary=5
10	Occupation	occupation of CHF patients	farmer=1,gov't employee=2,merchant=3,others=4
12	Age	age of CHF patients	conti….
13	Weight	weight of CHF patients	conti….
14	BMI	Body mass index of CHF patients	conti….
15	Pulse Rate	Pulse rate of CHF patients (heart beats per minute)	Conti(dependent variable)
16	Respiratory Rate	Respiratory Rate of CHF patients(breaths per minute)	Conti(dependent variable)

3.5 Statistical Analysis Technique

Different statistical analysis including both descriptive and inferential statistics, such as: summary statistics, data exploring and model comparison was used in this study. Separate and Joint random effects with LMM were modeled to infer the effect of bivariate longitudinal outcomes of PR and RR of CHF patients. Data management was done by SPSS 23 and SAS 9.2.

3.5.1 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 were considered.

3.5.2 Separate 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 the flexibility of modeling not only the means of your data but also their variances and covariance. The Linear Mixed Model is also an extension of the Linear Model that allows for incorporation of random effects and is represented in its most general fashions by (Verbeke and Molenberghs, 2009).

$$\boldsymbol{Y_i(t) = \beta X_i(t) + \gamma_i Z_i(t) + \varepsilon_i(t)}$$

where,

$\mathbf{Y}_i(t)$ is measurement of univariate response in i^{th} patient at time t,

$\mathbf{X}_i(t)$ is vector of fixed covariate for i^{th} subject at time t (of dimension k),

$\mathbf{Z}_i(t)$ is vector of random covariate for i^{th} subject at time t (of dimension q),

$\boldsymbol{\beta}$ is vector of unknown parameters associated with fixed covariate (of dimension k),

γ_i is vector of unknown parameters associated with random covariate for i^{th} subject (of dimension q) and $\gamma_i \sim$ MVN(0,**G**) and $\varepsilon_i(t)$: Random error component.

Further, $\mathbf{Z}_i(t)$ is subset of $\mathbf{X}_i(t)$ and $\boldsymbol{\varepsilon i} = [\varepsilon_i(t1), \varepsilon_i(t2), \ldots \varepsilon_i(tni)]^T \sim$ MVN (0,**R**); $\boldsymbol{\beta}$ represents parameters that are the same for all subjects and $\boldsymbol{\gamma}_i$represents parameters that are allowed to vary over subjects.

Terminology:

Fixed effects: $\boldsymbol{\beta}_i$,

Random effects: $\boldsymbol{\gamma}_i$

Variance components: elements in **G** and **R**.

Assumptions of the model are $E\begin{bmatrix}\gamma_i\\ \varepsilon_i\end{bmatrix}=\begin{bmatrix}0\\0\end{bmatrix}$, $var\begin{bmatrix}\gamma_i\\ \varepsilon_i\end{bmatrix}=\begin{bmatrix}\boldsymbol{G} & 0\\ 0 & \boldsymbol{R}\end{bmatrix}$ and Y $\sim$N (**Xβ**, **V**) where $\mathbf{V}=\mathbf{Z_i G_i Z_i^{'}}+\mathbf{R}$

3.5.3 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 will be presented. Longitudinal data are often collected in epidemiological studies, especially to study the evolution of biomedical markers. Thus, linear mixed models were stated by Laird and Ware (1982) which recently available in standard statistical packages Littell RC. et al. (1996) are used to take into account all available information and deal with the intra-subject correlation). Therefore, in this study bivariate set-up for two symptoms of CHF (PR and RR) as outcome variables will be observed in each occasion. The two end points will longitudinally measured as a vector of responses, $\mathbf{Y}_i(t)$, at each occasion with this model:

$$\boldsymbol{Y_i}(\boldsymbol{t})=\boldsymbol{\beta X_i}(\boldsymbol{t})+\boldsymbol{b_i Z_i}(\boldsymbol{t})+\boldsymbol{\varepsilon_i}(\boldsymbol{t})$$

Where $\boldsymbol{\varepsilon}_i=[\varepsilon_i(t1),\varepsilon_i(t2),\dots\varepsilon_i(tni)]^T$ ~ MVN (0, $\mathbf{R}_i$), b_i ~MVN(0, **G**), cov ($\mathbf{b}_i$, $\boldsymbol{\varepsilon}_i$) = 0 and $\mathbf{R}_i = I_{ni}\otimes\Sigma_{2x2}$, where, Σ_{2x2} is the variance-covariance matrix of 2 symptoms conditional on $\mathbf{b}_i$.

Let $\mathbf{Y}_i=\begin{bmatrix}Y_{1i}\\ Y_{2i}\end{bmatrix}$, the response vector for the subject i, with Y_{ki} the n_{ki}vector of the end points k (k=1, 2) with $n1_i = n2_i = n_i$. 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:

$\begin{bmatrix} a_{1i} \\ a_{2i} \\ b_{1i} \\ b_{2i} \end{bmatrix} \sim$ N(0, **G**), where, **G** is the covariance matrix of the random effects, has the structure of:

$$\mathbf{G}=\begin{bmatrix} \sigma_{a_1}^2 & \sigma_{a_1 b_1} & \sigma_{a_1 a_2} & \sigma_{a_1 b_2} \\ & \sigma_{b_1}^2 & \sigma_{b_1 a_2} & \sigma_{b_1 b_2} \\ & & \sigma_{a_2}^2 & \sigma_{a_2 b_2} \\ & & & \sigma_{b_2}^2 \end{bmatrix}$$

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

$$\begin{bmatrix} \varepsilon_{1i} \\ \varepsilon_{2i} \end{bmatrix} \sim \mathrm{N}\left[\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ & \sigma_2^2 \end{bmatrix}\right]$$

Clearly, the correlation between the evolution of Y_1 (PR) and Y_2(RR) is given by:

$r_E = \frac{Cov(b_1,b_2)}{\sqrt{Var(b_1)*Var(b_2)}} = \frac{\sigma_{b_1 b_2}}{\sqrt{\sigma_{b_1}^2 * \sigma_{b_2}^2}}$ and

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

$$r_m(t) = \frac{\sigma_{a_1 a_2} + t(\sigma_{a_1 b_2} + \sigma_{b_1 a_2}) + t^2 \sigma_{b_1 b_2} + \sigma_{12}}{\sqrt{\left(\sigma_{a_1}^2 + 2t\sigma_{a_1 b_1} + t^2\sigma_{b_1}^2 + \sigma_1^2\right) * (\sigma_{a_2}^2 + 2t\sigma_{a_2 b_2} + t^2\sigma_{b_2}^2 + \sigma_2^2)}}$$

3.5.4 Estimating both Fixed and Random Effects (Parameters) in LMM

Estimation of the parameters in LMM was usually based on maximum likelihood or restricted maximum likelihood (REML) for the marginal distribution. The maximum likelihood estimation includes both regression coefficient and the variance components ,that is ,both fixed-effects and random effects terms in the likelihood function and it treats β as fixed but unknown quantities when the variance component is estimated, but does not take in to account the degree of freedom lost by estimating the fixed effects .

This causes ML estimates to be biased with smaller variances. On the other hand the REML estimation includes only the variance component, that is the parameters that parameterize the random-effect terms in the linear mixed effects model which account for the degree of

freedom lost by estimating the fixed effects, and makes a less biased estimation of random effect variance. The estimates of **R** and **G** are invariant to the value of β and less sensitive to outliers in the data compared to ML estimates. However , if we use REML to estimate the parameters , we can only compare two models that have the identical fixed effects design matrices and are nested in their random effects term(McCulloch and Neuhaus, 2001).

The likelihood function of the covariance matrix of **R** and **G** in the case of ML and REML are given as follows.

$$ML: l(G,R) = -\frac{1}{2}\log|V| - \frac{1}{2}r'V^{-1}r - \frac{n}{2}\log 2\pi$$

$$REML: l(G,R) = -\frac{1}{2}\log|V| - \frac{1}{2}\log|X'V^{-1}X| - \frac{1}{2}r'V^{-1}r - \frac{n-p}{2}\log 2\pi$$

Where $r = y - X(X'V^{-1}X)^{-1}X'V^{-1}y$ and p is the rank of X

Minimize -2 times these functions by using a ridge-stabilized Newton-Raphson algorithm.

Once the V is estimated

The BLUE of β is $\hat{\beta} = (\mathbf{X'V^{-1}X})^{-1}\mathbf{X'V^{-1}y}$

A **b**est **l**inear **u**nbiased **p**redictor (BLUP) of γ is$\tilde{\gamma}$= $\mathbf{GZ'V^{-1}(y-X\beta)}$.

But the above estimation is not so simple, because of the difficulty in the estimation of **G** .since the matrix G is a non –full rank and hence the estimates of the fixed effect model are based on the Newton Raphson iteration method.

3.5.5 Model Selection and Comparison Methods

In order to select the best and final model which appropriately fits the given longitudinal data, it is necessary to compare different models by using different techniques. Hence, models are compared with Akaki Information Criteria (AIC), AIC judges the model by how close its fitted value tends to be to the true mean value .the criteria the selection the model that summarizes:

AIC= -2(maximum log likelihood - number of parameters in the model).Thus,a model with the smallest AIC value was taken as a best among the candidate models .AIC penalizes for a model having many parameters

The Second alternative criteria that penalizes more severely for the number of parameters in the model is Bayesian Information Criteria replaces 2 by log(n) as a multiple of the number of parameters The third Alternative criteria is Likelihood ratio test methods for nested will be used at 5% level of significance (Torbicki et al., 2008).

Measurements made on the same subject are likely to be more similar than measurements made on different individuals. That is, repeated measurements are correlated. For analysis to be valid, the covariance among repeated measures must be modeled properly. We need to select an appropriate covariance or correlation structure for the model to account for the correlation among measurements. In thinking of the response variables marginal covariance structure, therefore all structure $\sum_i$ is the sum of the random effects portion $Z_i\sum d_i$and the residual error portion $\sum e_i$. In case when the variability in the measurements cannot be completely modeled by the random effects, we use both random effects and residual errors to describe the covariance structure .However ,in practice it is often efficient to use one of the two common ways to model the covariance or correlation structure.

Commonly used covariance structures through the random effects include compound symmetry (CS) for constant correlation between any pair of repeated measurements , first–order autoregressive (AR(1) for stronger correlation among adjacent measurements with constant interval of measurement time , general unstructured (Yun) covariance model for non specific correlation among measurements and Toeplitz (TOEP) This structure similar to AR(1) in that all correlations at the same distance have the same correlation .but no assumption of exponential decay .the AR(1) model can be estimated with a single parameter (what is exponent of the distance);the Toeplitz model has as many parameters as there are distances. If there were 3 measures then there would be two distances one unit distant, two unit distant and hence two parameters would be estimated(Thompson et al., 1995).

The choice of the better covariance model is too difficult in a variety ways .Although we favor including more rather fewer fixed and random effects , it should be noted that over fitted models may result in divergence of the maximization procedure. The problem could be due to any combination of an insufficiently complex and untested covariance structure ,insufficient data for the specific goal, an inadequate model selection for fitting ,inadequate knowledge about the covariance structure when using mixed model software ,and computationally fragile(damaged) software .Therefore ,we have to care of in the selection

procedure of the working correlation for the model. Like the model selection criteria the better working correlation structure is also chosen on the value of the AIC and BIC in which the smallest the value is the better the covariance structure to fit the data in linear mixed model.

3.5.6 Model Building Strategies

In modeling with many independent variables, one is usually concerned with the goal of selecting those variables that result in the “best” model within the scientific context of the problem. Having a basic plan to follow in selecting the variables for the model and assessing the adequacy of the model both in terms of the individual variables and from the point of view of the overall fit of the model is required for achieving this “best” model. It is also highlighted in (that successful modeling of a complex data set is part science, part statistical methods, and part experience and common sense (HosmerJr and Lemeshow, 1999).

In this study, model building starts from single covariate analysis approach of first doing a single covariate analysis to “screen" out potentially significant variables for consideration in the multi covariate model in order to identify the importance of each predictor. All variables that were significant at 25% level, the modest level of significance from one explanatory single covariate regression model were taken into multi covariate model.The purely statistical method used an automatic process (‘stepwise’ regression), which could be ‘forward’: the variables are added successively (the most significant at each step) until no variable adds significant information. Finally, the importance of each variable included in the multi covariate model should be verified by different model assessment techniques.

3.5.7 Model Adequacy Checking

The residual analyses both classical and formal test will be used for model adequacy checking.

3.5.8 Model Diagnostics

The basic result that is used for making inference about the mixed model depends on whether the data met the required assumptions or not. Many diagnostics have been extended from the classical regression model to hierarchical regression models. In this study some graphical techniques will be used to assess peculiarities or the distinctive features of the model with regards to the data .for detecting outliers, histograms and scatter plots of empirical bayes(EB)

estimates are will be used. The EB residuals are defined as the conditional mean of the vector of random effects given the data and the estimated parameter values . Patients who seems to evolve differently from the other patients in the data set will be pinpointed from the scatter plot of empirical bayes estimates. a procedure to obtain the empirical bayes is presented in (Molenberghs and Verbeke, 2005) .In assessing the effect of measurements of PR and RR on the CHF patients in conclusion influential observations will be deleted.

3.5.9 Goodness of Fit test for the Model

Once a model has been developed through different techniques in estimating the model parameters, there were several mechanisms involved in assessing the appropriateness ,adequacy and usefulness of the model. first we had test the overall goodness of fit of the model and then after we test the importance of each of the explanatory variables and would be assessed by carrying out statistical tests of the significance of the coefficients (Agresti, 1999). The goodness of fit measures how the model describes the response variable and it also investigating how close were predicted by the model with the observed value(Andersen, 1973).

3.5.10 Likelihood – Ratio Test

The most widely used approach to test the significance of many explanatory variables in the likelihood ratio test. This is appropriate for a variety of types of statistical model .(Crainiceanu and Ruppert, 2004) argues that the likelihood ratio test is better ,particularly if the sample size is small or the parameter are large. The likelihood ratio test uses the ratio of the maximized value of the likelihood function for the full model(L_1) over the maximum value of the likelihood for the reduced model(L_0).for each of the variable removed from the full model one at a time, MLE_s are computed and likelihood function $L_0$is calculated. The likelihood –ratio test statistic is

$$G^2 = -2\{ln\, L_0 - lnL_1\}$$

Where L_0 is the likelihood function of the reduced model and L_1 is the likelihood function of the full model evaluated at the MLE_s

This natural log of the likelihood function G^2 yields an asymptotically chi-square distribution with degree of freedom equal to the difference between the number of parameters estimated in the two models. and use to test the null hypothesis that all fixed parameters are not significance to the model.

3.5.11 The Wald Test

The Wald test is an alternative test , which is commonly used to test the significance of individual model parameters for each independent variable. The Wald test , described by (Tu and Zhou, 1999) ,is used to test whether the parameter associated with the fixed effects explanatory variables is zero or not. for a particular explanatory variables or groups of explanatory variables ,if the wald test is significance for a particular predictor variables , then the parameter associated with these variable are not zero, and we have to include the variable in the model.

$z = \frac{\widehat{\beta i}}{se\,(\beta i}$ i=1, 2, 3,……p the square of the z statistic is the same as the chi-square distribution with one degree of freedom which is wad test.

$w = square\left[\frac{\beta i}{se\,(\beta i}\right] \sim X^2(1)$ i=1,2,3…….p

Under the null hypothesis $H_{0=}\hat{\beta}_I = 0$ for all i=1,2,3…..p the statistic w is approximately distributed as chi –square with one degree of freedom

Chapter Four

4. Result and Discussion

In this section, missing data treatment, the statistical analysis and the corresponding results and discussion are presented.

4.1. Missing Data Treatment

When exploring missing data, it is important to come to a conclusion about the mechanism of amusingness that is, the hypothesized reason for why data are missing. This can range from arbitrary or random influences to purposeful patterns of nonresponsive There are various methods of dealing with missing data, that range from simple classical methods to model based methods. These methods must be fully understood theoretically before they can be used practically. Furthermore each method is based upon a specific missing data mechanism but one needs to realize that at the heart of the missing value problem it is impossible in practice to identify the amusingness mechanisms. In a longitudinal setting, each unit is measured on several occasions and hence it is not unusual in practice for some sequences of measurements to terminate early for reasons outside of the control of the experimenter or investigator, and any unit so affected is called a dropout If a person drops out of a study before it ends, then his or her last observed score on the dependent variable is used for all subsequent (i.e., missing) observation points. Last Observation Carried Out Forward (LOCF) is used to maintain and to reduce the bias caused by the attrition of participants in a study (Diggle, 2002) .

Thus, In this study the missing data for both PR and RR were replaced by Last Observation Carried Out Forward (LOCF). As Verbeke and Molenberghs (2009) stated that the full likelihood analysis constitutes a very promising alternative to complete cases(CC) and LOCF for continuous outcome under the MAR(Missing At Random) assumption ,but Complete Cases(CC) gives an upward biased estimate(McCulloch and Neuhaus, 2001).

4.2 Data Descriptions and Descriptive Statistics

In this cohort study socio-demographic and clinical data of 153 patients whose age above 17 years and receiving preferable drugs to improve the symptom of CHF from September 2015 GC to January 2017 GC FelegeHiwot referral hospital were considered. The two symptoms of CHF, PR and RR have been used for the response variable. These longitudinal response

variables were measured for 8 visits among 153 CHF patients and constitutes 2448 visits. The time interval for all patients was 4 months equally observed. There was a sharply increase degree of missing data over time due to dropouts, missing clinical visits and transferring to the other hospital and also there is admitting and readmitting of the patients.

The baseline characteristics of patients are displayed in Table 2. Among 153 patients, 78 (50.58%) of them were females and the rest 75(49.02%) were males. Those of the CHF patients 67(43.79%) had had biventricular heart failure, 46(30.07%) had faced left sided heart failure and the rest 40(26.14%) had faced right sided heart failure .When we saw diagnostic history of CHF patients 94(61.44) of them were Acute coronary failure (ACF), 21 (13.73%) coronary heart disease (CHD), 25(16.34%) severe anemia and 13(8.50%) were other type of diagnostic history. When we observed the New York heart association class of CHF patients 28(18.30%) of them were NYHA class I, 48(31.37%) were class II, 35(22.88%) were class III and the rest 42 (27.45%) were class IV.

Residence area of CHF patients 92(60.13%) of them were rural and 61(39.87%) were urban resident. marital status 95(62.09%) were married, 48(31.37%) were single and 18(6.94%) were others. When we consider educational status of CHF patients, 66(43%) of them were illiterate, 23(15.03%) were informal education, 23(15.03%) were primary, 25(16.34%) were secondary and 16(10.46%) were tertiary. Furthermore, among 153 CHF patients in the study, 74 (48.37%) of them were farmer, 15 (9.8%) were government employee, 28 (18.30%) were merchant and 36(23.53%) were other types. Table 2 reveals in detail.

Table 2 :- Baseline Demographic and clinical characteristics of the CHF patients at FHRH

Characteristics		frequency(n)	Percent (%)
Sex	Male	75	49.02
	Female	78	50.58
CHF type	biventricular failure	67	43.79
	lift sided failure	46	30.07
	right sided failure	40	26.14
Diagnostic history	ACF	94	61.44
	CHD	21	13.73
	Severe anemia	25	16.34
	Others	13	8.50
NYHA	Class I	28	18.30
	Class II	48	31.37
	Class III	35	22.88
	Class IV	42	27.45
Residence area	Rural	92	60.13
	Urban	61	39.87
Marital status	Married	95	62.09
	Single	48	31.37
	Others	10	6.54
Education level	Illiterate	66	43.00
	informal education	23	15.03
	Primary	23	15.03
	Secondary	25	16.34
	Tertiary	16	10.46
Occupation	Farmer	74	48.37
	gov't employee	15	9.80
	Merchant	28	18.30
	Others	36	23.53

The mean and standard deviation of continues covariates are presented in Table 3. As can be seen from this Table, the mean and standard deviation of baseline PR were 85.37 and 13.86 beats per minute and while for RR were 23.16 and 3.74 breaths per minute. The mean and standard deviation of baseline age were 46.47 and 19.45 respectively. The mean and standard deviation of weight of CHF patients were 53.68 and 8.12 at baseline respectively. Similarly, the mean and standard deviation of LVEF were 51.69 and 11.17 respectively at baseline. Furthermore, the mean and standard deviation of BMI of CHF patients were 21.22 and 3.25 respectively at baseline. (Table 3)

Table 3:- Mean and standard deviation of continuous covariates and two outcomes

Variables	At baseline			
	Mean	StD	Max	Min
Pulse Rate	85.37	13.86	54	136
Respiratory Rate	23.16	3.74	16	36
Age	46.47	19.45	17	92
LVEF (%)	51.69	11.16	18	79
Weight	53.68	8.12	35	74
BMI	21.22	3.25	18	18

The mean and standard deviation of PR and RR of CHF patients for each categorical covariate at baseline are presented in Table 4. As can be seen from this Table, the mean and standard deviation of the PR and RR for male were 84.08(13.70) and 22.97 (3.63) while for females were 86.13(14.56) and 23.36(4.42). The mean and standard deviation of the PR and RR of CHF type biventricular were 83.86(13.63) and 22.7(3.71), left sided failure were 86.98(13.29) and 23.49(4.66), right sided failure were 84.43(13.64) and 23.3(3.8) respectively. Similarly, the mean and standard deviation of PR and RR with diagnostic history ACF were 84.06(13.09) and 22.79(4.03), for CHD were 90.20(19.47) and 27.76(4.79) and severe anemia were 84.86 (14.10) and 23.13(3.73). The mean and standard deviation of PR and RR with NYHA class were I 77.12(11.14) and 21.66(2.94) ,class II were 82.2(9.58) and 22.55(2.75), class III were 87.38(13.18) and 23.01(3.70) , and class IV were 91.43 (17.53) and 24.74(5.46).The mean and standard deviation of PR and RR of a patients whose

rural residence were85.1(14.35) and 23.13(4.28) while urban residence were 84.71(13.91) and 23.04(3.69). (Table 4)

Table 4:-The baseline mean and standard deviation of PR and RR at each characteristics

Charactersics		Pulse Rate		Respiratory Rate	
		Mean	StdDev	Mean	StdDev
Sex	Male	84.39	13.54	23.05	3.62
	Female	86.13	14.56	23.36	4.42
CHF type	biventricular failure	83.86	13.63	22.7	3.71
	left sided failure	86.98	13.29	23.49	4.66
	right sided failure	84.43	13.64	23.3	3.8
Diagnostic history	ACF	84.06	13.09	22.79	4.03
	CHD	90.2	19.47	27.76	4.79
	Severe anemia	84.86	14.10	23.13	3.73
	Others	83.53	9.70	22.51	2.75
NYHA	Class I	77.12	11.14	21.66	2.94
	Class II	82.2	9.58	22.55	2.75
	Class III	87.38	13.18	23.01	3.7
	Class IV	91.43	17.53	24.74	5.46
Residence area	Rural	85.1	14.35	23.13	4.28
	Urban	84.71	13.91	23.04	3.69
Marital status	Married	87.44	15.14	23.44	4.06
	single	81.36	12.17	22.45	3.29
	Others	79.16	6.80	22.91	6.35
Education level	Illiterate	85.49	14.85	23.47	4.5
	informal education	85.73	15.17	23.39	4.56
	Primary	87.03	13.13	23.83	3.63
	Secondary	83.68	11.93	22.23	2.91
	Tertiary	80.96	13.98	22.84	3.57
Occupation	farmer	87.74	14.74	23.23	4.42
	gov'nt employee	79.92	13.73	22.69	3.74
	Merchant	85.51	15.31	23.91	4.19
	Others	82.04	10.70	22.35	3.02

4.3 Exploratory Data Analysis

4.3.1. Profile Analysis

The individual profile analyses of the PR data result are presented in Figure 1. This Figure revealed that the Pulse Rate of CHF patients were decreases with increasing time. Pulse Rate (PR) was highest at the first visit of month and then tends to down throughout the follow up time. That means the variability of the measurements at the beginning (baseline) of the follow up was highly decreased relative to the end of the follow up. The decrement of PR through the follow up time indicates risk minimization of CHF. Low Pulse Rate means healthier heart.

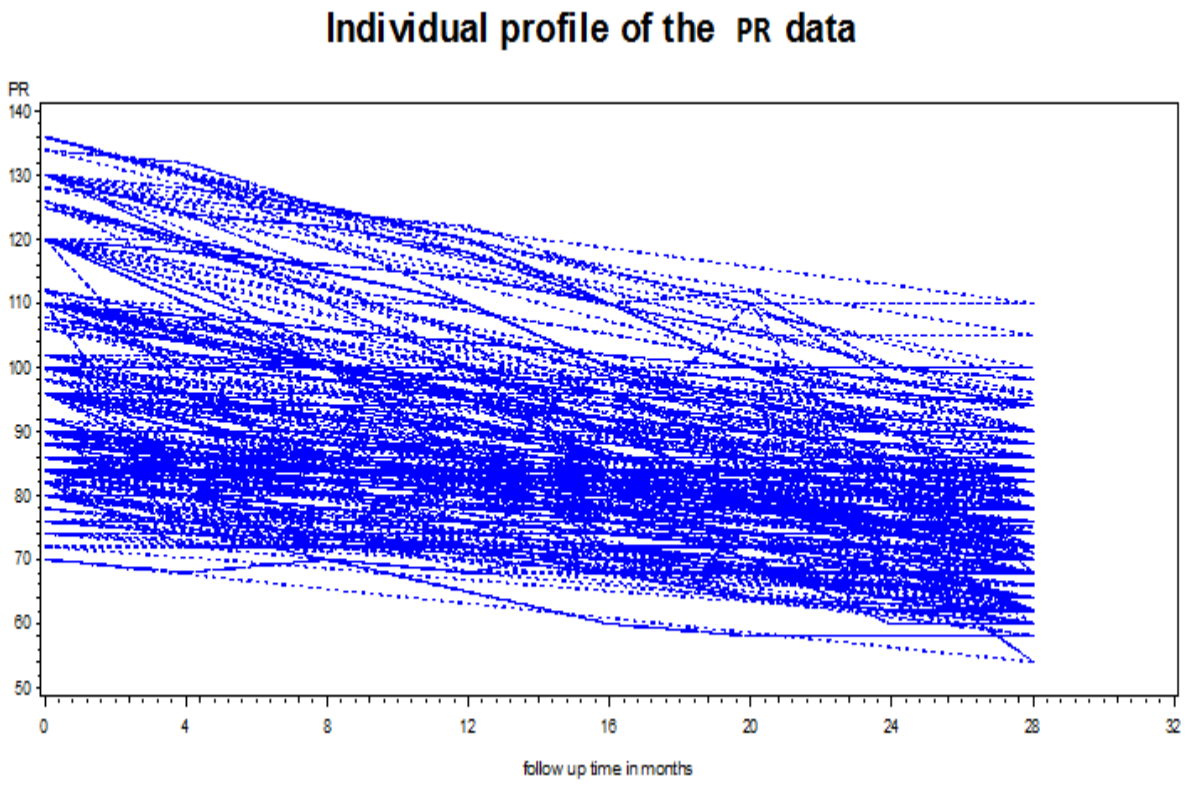


Figure 1:-Individual profile plot of Pulse Rate (PR) of CHF patients through the follow up time

The individual profile analyses of the RR data result are presented in Figure 2. This Figure revealed that the Respiratory Rate of CHF patients were decreases through the follow up time. Respiratory Rate (RR) was highest at the first visit of month and then tends to down throughout the follow up time. That means the variability of the measurements at the beginning (baseline) of the follow up was highly decreased relative to the end of the follow

up. The decrement of RR through the follow up time indicates risk minimization of CHF. Low Respiratory Rate means healthier heart.

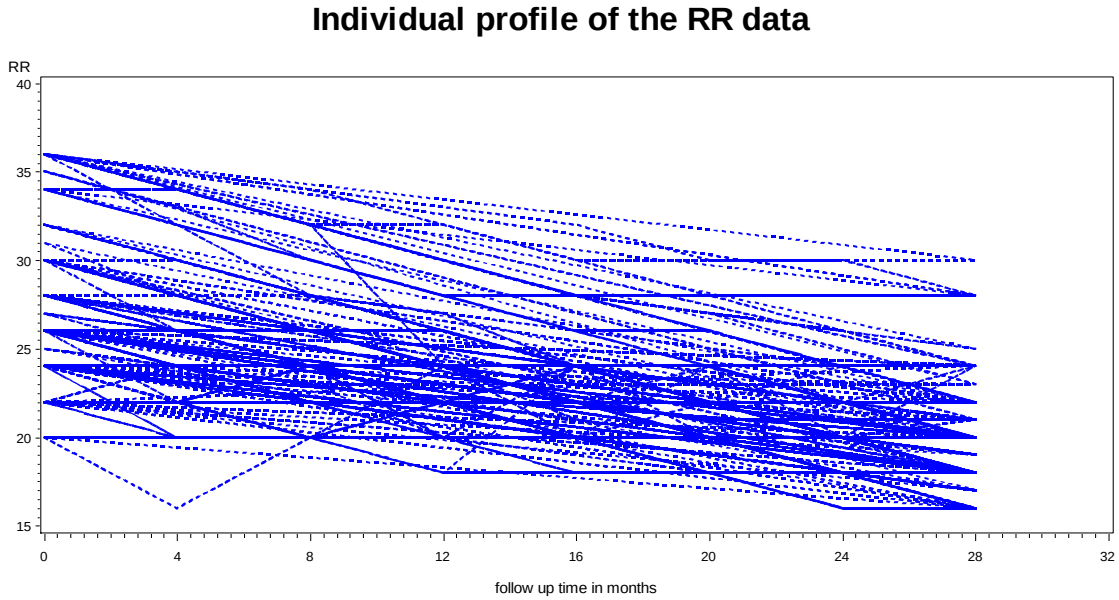


Figure 2:-Individual profile plot of Respiratory Rate (RR) of CHF patients through the follow up time

4.3.2. Mean Plot of PR and RR for each categorical covariates

As can be observed in Figure 1A, the mean (PR) for male and female of CHF patients decreases with increasing time. Specifically, the mean PR for male CHF patients was slightly less than for those female patients. Similarly, the mean Pulse Rate (PR) for patients who have different CHF type decreases with increasing of time. This indicates that the patient starts follow up; the treatments improve their pulse rate. (Figure 1B)

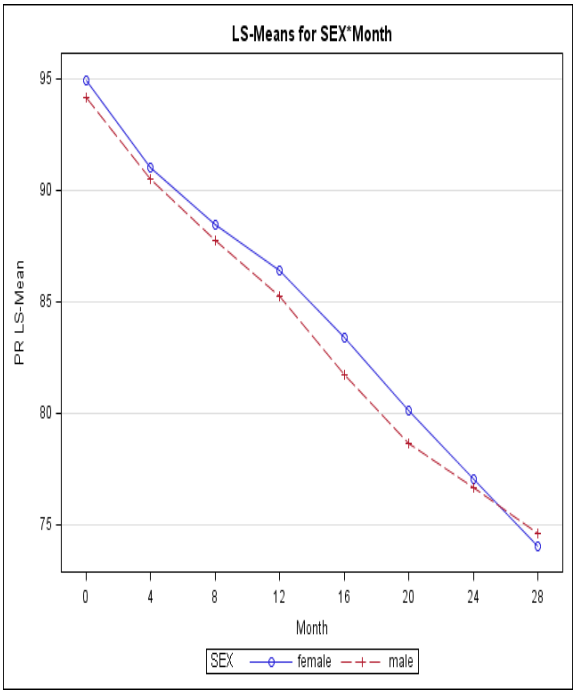
The mean plot of PR with different types New York Heart Association classes are presented in Figure 1C. This Figure showed initially NYHA class IV were high RR while NYHA class I were low PR. through follow up time increases four type of NYAC decreased. AS NYHA class increases PR increased and NYHA class decreases PR also decreases.

The mean plot of PR with different Diagnostic history of CHF patients are presented in Figure 1D. As can be observed in this figure 1D, at the initial follow up time CHD had high PR and other were small PR. As follow up time increased all different types of diagnostic history CHF patients PR decreased .this is the effect of proper follow up with and treatment though time.

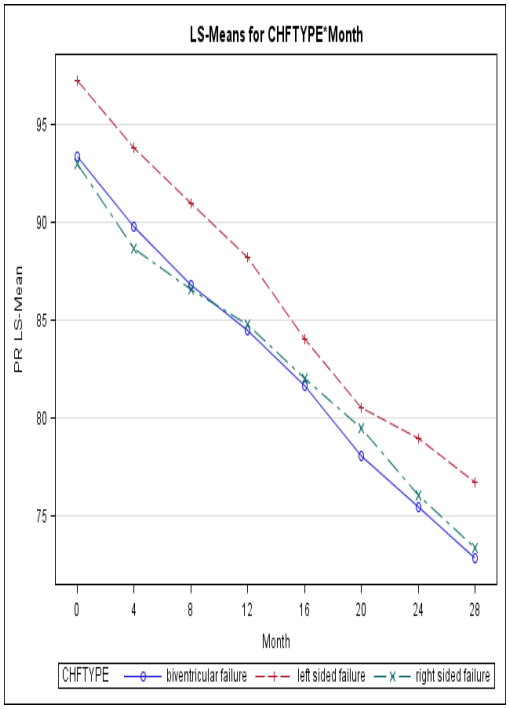
The mean plot of PR with residence area of CHF patients are presented in Figure 1E. As can be observed in figure 1(E), the variability of patients who comes from rural area is higher that of the urban area, at initial time rural individuals has lower values of PR values than the urban or simply there was mean difference in PR value between urban and rural at the starting time As the follow up time increases PR of both rural and urban CHF patients decreased. The mean plot of PR with marital status of CHF patients are presented in Figure 1F. As can be observed in figure 1(F) the plot initially, others marital statuses were high PR while married were low PR. As the follow up time increases all type of marital status decreased the follow up and treatments improve their pulse rate.

As can be observed in figure 1(G), the mean plots of PR with different types of occupations of CHF patient were decrease with increasing time. Specifically, the initial PR of merchant were high while the farmer was low .as the follow up time increases all type of occupation of CHF patients PR decreased the follow up and treatments improve their pulse rate. The mean plot of PR with different level education of CHF patients are presented in Figure 1H. the figure shows that at the initial illiterate were high PR while secondary were low PR. though follow up time PR of all types of education level decreased. this was the effect of proper follow up and treatment.

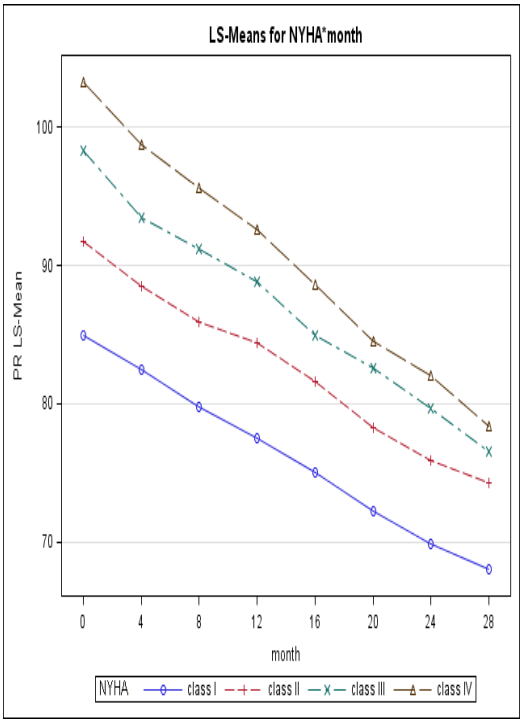
A


LS-Means for SEX*Month
PR LS-Mean
95
90
85
80
75
0
4
8
12
16
20
24
28
Month
SEX
female
male

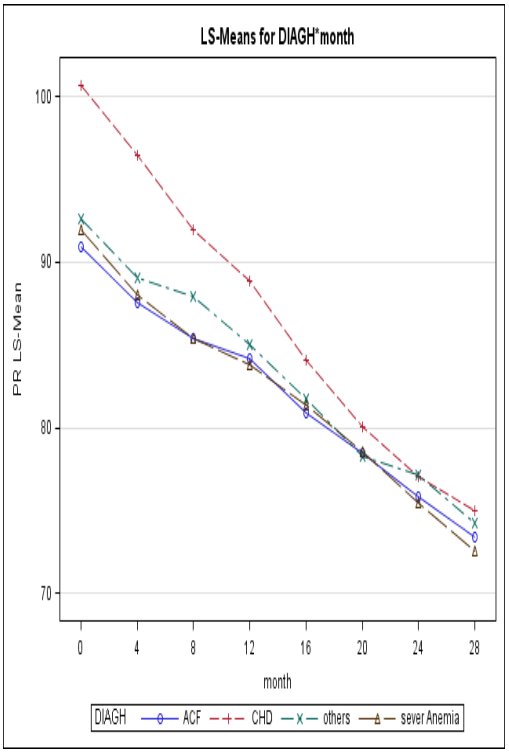
B


LS-Means for CHFTYPE*Month
PR LS-Mean
95
90
85
80
75
0
4
8
12
16
20
24
28
Month
CHFTYPE
biventricular failure
left sided failure
right sided failure

C


LS-Means for NYHA*month
PR LS-Mean
100
90
80
70
0
4
8
12
16
20
24
28
month
NYHA
class I
class II
class III
class IV

D


LS-Means for DIAGH*month
PR LS-Mean
100
90
80
70
0
4
8
12
16
20
24
28
month
DIAGH
ACF
CHD
others
sever Anemia

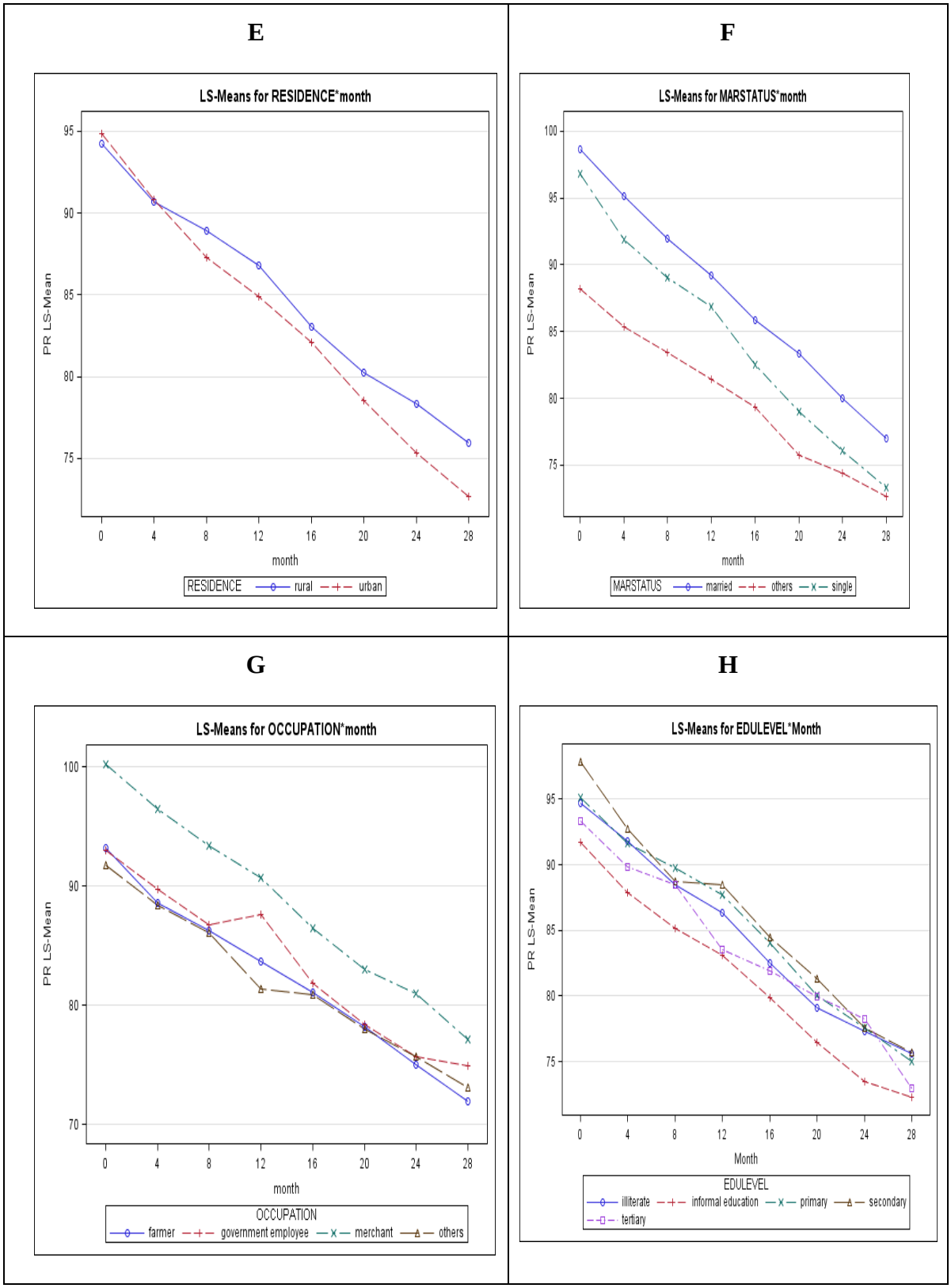


Figure 3:- Mean plot of PR by the variable A) Sex, B) CHF type, C) type of NYHA class D) Diagnostic history E) Residence Area F) Marital Status G) Occupation H) Educational Label

As can be observed in Figure 2A, the mean (RR) for male and female of CHF patients decreases with increasing time. Specifically, the mean RR for male CHF patients was slightly less than for those female patients. Similarly, the mean Respiratory Rate (RR) for patients who have different CHF type decreases with increasing of time. This indicates that the patient starts follow up; the treatments improve their pulse rate. (Figure 2B)

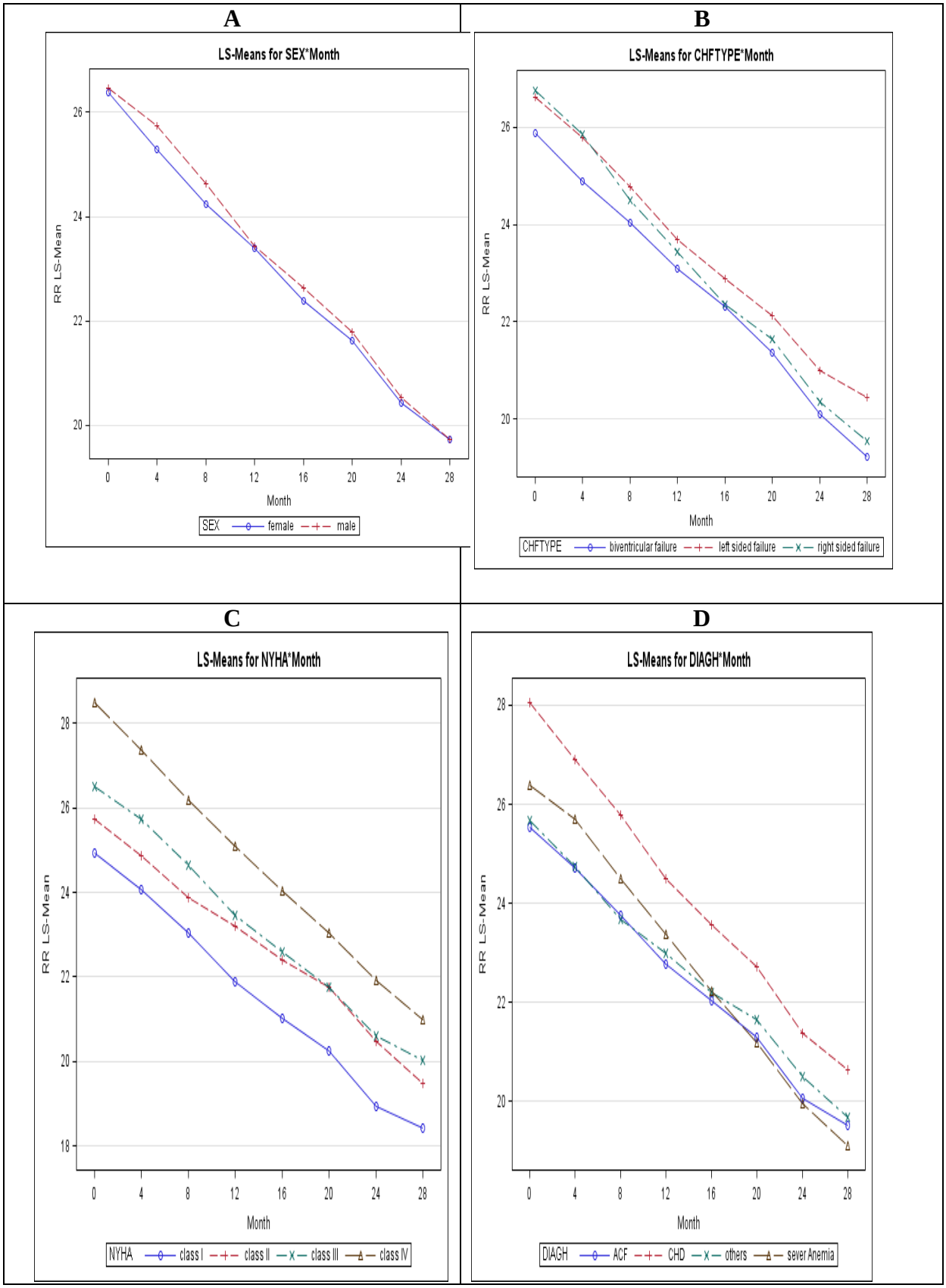
The mean plot of RR with different types New York Heart Association classes are presented in Figure 2C. This Figure showed initially NYHA class IV were high RR while NYHA class I were low RR. Through follow up time increases four type of NYAC decreased. AS NYHA class increases RR increased and NYHA class decreases RR also decreases.

The mean plot of RR with different Diagnostic history of CHF patients are presented in Figure 2D. As can be observed in this figure 2D, at the initial follow up time CHD had high RR and other were small RR. As follow up time increased all different types of diagnostic history CHF patients RR decreased .this is the effect of proper follow up with and treatment though time.

The mean plot of RR with residence area of CHF patients are presented in Figure 2E. As can be observed in figure 2(E), the variability of patients who comes from rural area is higher that of the urban area, at initial time rural individuals has lower values of RR values than the urban or simply there was mean difference in RR value between urban and rural at the starting time As the follow up time increases RR of both rural and urban CHF patients decreased. The mean plot of RR with marital status of CHF patients are presented in Figure 2F. As can be observed in figure 2(F) the plot initially, others marital statuses were high RR while married were low RR. As the follow up time increases all type of marital status decreased the follow up and treatments improve their pulse rate.

As can be observed in figure 2(G), the mean plots of RR with different types of occupations of CHF patient were decrease with increasing time. Specifically, the initial RR of merchant were high while the farmer was low .as the follow up time increases all type of occupation of CHF patients RR decreased the follow up and treatments improve their pulse rate. The mean plot of RR with different level education of CHF patients are presented in Figure 2H. the figure shows that at the initial illiterate were high RR while secondary were low RR. though

follow up time RR of all types of education level decreased. this was the effect of proper follow up and treatment.



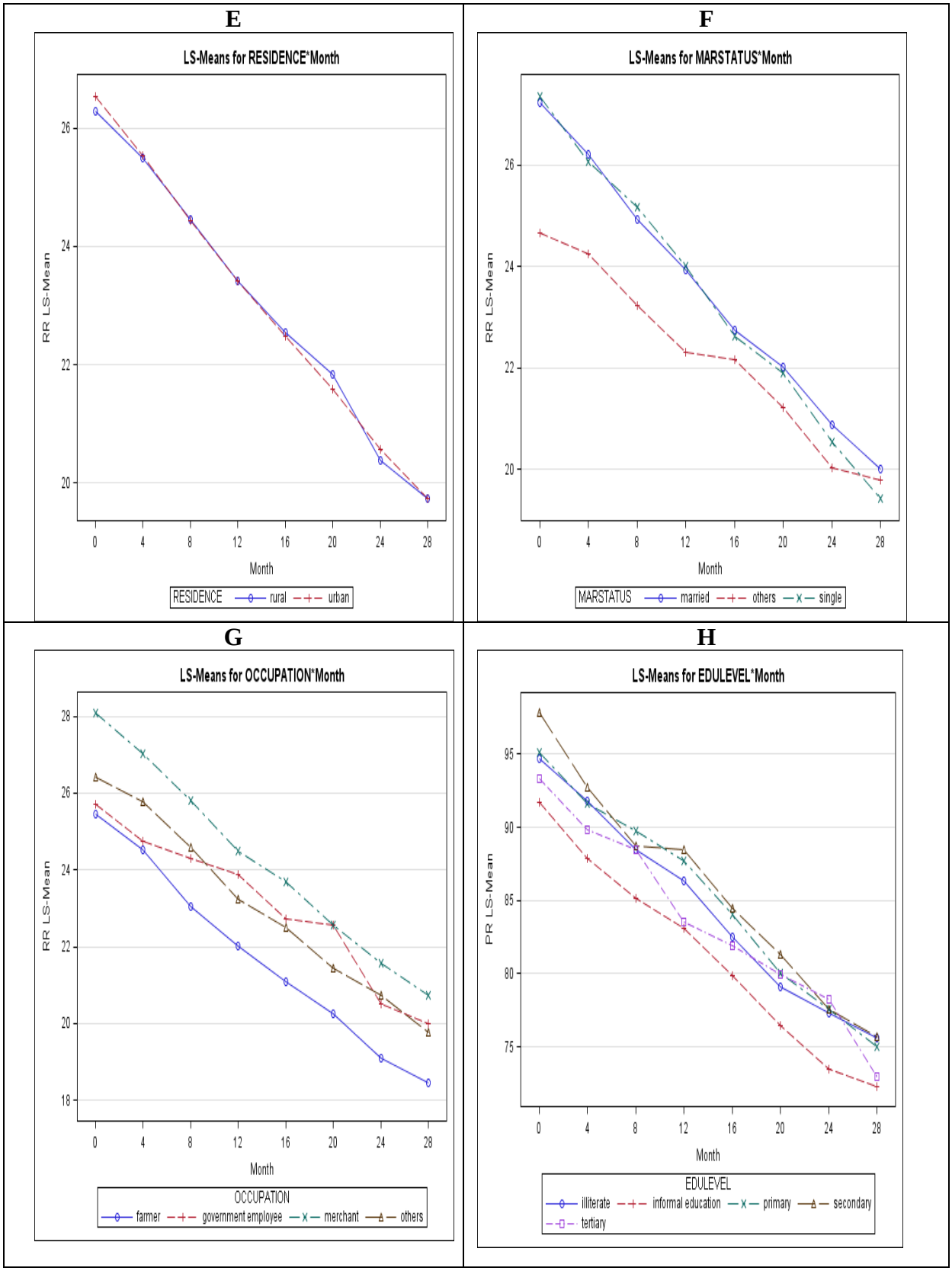


Figure 4:- Mean plot of RR by the variable A) Sex, B) CHF type, C) type of NYHA class D) Diagnostic history E) Residence Area F) Marital Status G) Occupation H) Educational Label

4.3.3. Joint Plot of PR and RR through Follow up time on the same plane (with their CHF status)

The joint plots of PR and RR on the same plane CHF with time are presented in Figure 5. As can be seen from this Figure the two outcomes (responses) jointly decreased as follow up time increases.

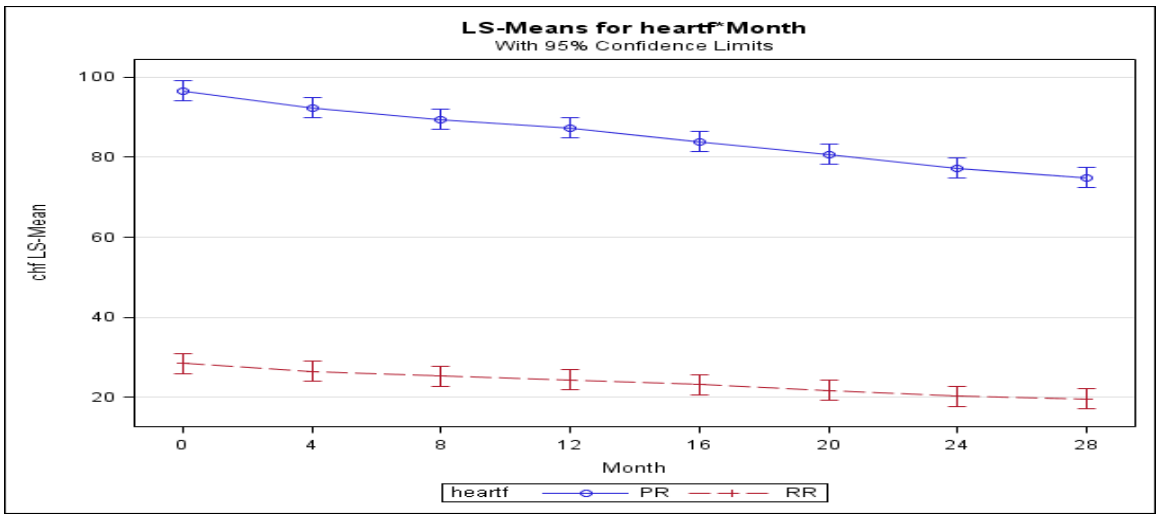


Figure 5:-Joint plots of PR and RR with their CHF status through follow up time .

4.4. Model Selection

Primary goal of model selection is to choose the simplest model that provides the best fit to the observed data. There are several choices concerning which fixed and random effects should be included in a linear mixed model (LMM) .There are also many possible choices of covariance structure for the G and R_i matrices.

4.4.1 Model fitting for fixed and random effects

In this study, model building starts from single covariate analysis approach of first doing a single covariate analysis to “screen" out potentially significant variables for consideration in the multi covariate model in order to identify the importance of each predictor. All variables that are significant at 25% level, the modest level of significance from one explanatory single covariate regression model are taken into multi covariate model. The purely statistical method is to use an automatic process (‘stepwise’ regression), which can be ‘forward’: the

variables are added successively (the most significant at each step) until no variable adds significant information. To select statistically significance covariates for the two independent mixed effect models with outcome variables PR and RR stepwise method was implemented. 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.

4.4.2 Model selection with covariance structure best model for Pulse Rate

Comparing different covariance structure for the best model for Pulse Rate (PR): The following table shows the value of fit statistics for different types of covariance structure to select best model for pulse rate.

Table 5:-selections of covariance structure for Pulse Rate Models.

Covariance structure	Fit Statistics			
	-2LL	AIC	AIC	BIC
UN	10834	11024	11032	11310
CS	13659	13841	13848	14115
AR(1)	13659	13841	13848	14115
TEOP	13051	13227	13245	13517

According to the Above table the final model with unstructured covariance structure was preferred Pulse rate model with respective small values of -2LL AIC AICC and BIC of 10834, 11024 11032 and 11310 respectively.

Table 6:- The proc mixed type three fixed effect results for both PR and RR

Type 3 Tests of Fixed Effects					
Effect	**Num DF**	**Den DF**	**F Value**	**P-value**	**Sig status**
Heartf	1	173	94.77	<.0001	***
Month	1	179	11.33	0.0009	***
AGE	1	176	9.91	0.0019	***
SEX	1	182	0.84	0.3620	
NYHA	3	180	23.15	<.0001	***
LVEF	1	184	40.94	<.0001	***
RESIDENCE	1	165	0.28	0.5973	
MARSTATUS	2	167	2.53	0.0831	
EDULEVEL	4	167	0.20	0.9397	
CHFTYPE	2	200	2.83	0.0615	
DIAGH	3	185	5.08	0.0021	***
OCCUPATION	3	166	1.20	0.3133	
month*heartf	1	179	8.73	0.0036	**

Type 3 Tests of Fixed Effects					
Effect	**Num DF**	**Den DF**	**F Value**	**P-value**	**Sig status**
AGE*heartf	1	176	10.87	0.0012	**
heartf*SEX	1	182	3.65	0.0576	
heartf*NYHA	3	180	16.46	<.0001	***
LVEF*heartf	1	184	12.69	0.0005	***
heartf*RESIDENCE	1	165	0.15	0.6988	
heartf*MARSTATUS	2	167	1.39	0.2524	
heartf*EDULEVEL	4	167	0.13	0.9707	
heartf*CHFTYPE	2	200	2.95	0.0548	
heartf*DIAGH	3	185	2.18	0.0923	
heartf*OCCUPATION	3	166	0.58	0.6267	
month*AGE*heartf	2	161	3.90	0.0222	*
month*heartf*SEX	2	167	1.99	0.1403	
month*heartf*NYHA	6	167	4.04	0.0008	***
month*LVEF*heartf	2	165	12.31	<.0001	***
month*heartf*RESIDEN	2	144	1.77	0.1745	
month*heartf*MARSTAT	4	147	1.60	0.1779	
month*heartf*EDULEVE	8	146	1.87	0.0682	
month*heartf*CHFTYPE	4	178	2.24	0.0665	
month*heartf*DIAGH	6	171	3.55	0.0025	**
month*heartf*OCCUPAT	6	145	0.47	0.8280	

Note :- * means significance ** high significance *** highly significance

The Pulse Rate (PR) was modeled with sets of covariates and the result was described in the following table .the final model was somewhat complex and include 13 fixed effect parameters for Pulse rate including intercept and random slops were fitted to account for with in subject correlation.

Table 7:- Results of Separate Model for Pulse Rate (PR)

Effect		Separate Model(PR)		
		Estimate(SE)	P-value	95 % CI
Intercept		82.9042(10.1191)	<0.0001	(62.9092,102.90)
Age		-0.2079(0.06306)	0.0012	(-0.3323,-0.08341)
LVEF		0.3098(0.08698)	0.0183	(-0.01143,-0.00107)
NYHA	class I	-15.8007(3.1403)	<0.0001	(-21.9994,-9.6021)
	class II	-14.7203(2.2861)	<0.0001	(-19.2280,-10.2125)
	class III	-4.9951(2.7006)	0.0661	(-10.3255,0.3354)
	Class IV	1[a]	1[a]	1[a]
age*month1[b]		0.00500(0.001876)	0.0085	(0.001295,0.008705)
LVEF*month1[b]		0.00625(0.002621)	0.0183	(-0.01143,-0.00107)
Diagnostic history*month1[b]	ACF*month	0.02966(0.6930)	0.6691	(-0.1070,0.1663)
	CHD*month	-0.3023(0.9657)	0.0020	(-0.4927,-0.1120)
	Others*month	0.03958(0.1178)	0.7372	(-0.7372,0.2721)
	Severe anemia	1[a]	1[a]	1[a]
NYHA*month1[b]	class I*month	0.2893(0.09219)	0.0020	(0.1072,0.4741)
	class II*month	0.3300(0.07230)	<0.0001	(0.1874,0.04726)
	class III*month	0.1347(0.07980)	0.0933	(-0.02287,0.2924)
	Class IV *month	1[a]	1[a]	1[a]
Sigma1 (σ_1)		8.1690(0.02892)	<0.0001	(7.46,8.9723)
$\sigma^2 b10$		130.60(15.6418)	<0.0001	(104.65,167.63)
$\sigma b10$b11		-2.7907(0.4128)	<0.0001	(-3.52,-1.90)
$\sigma^2 b11$		0.1058(0.01396)	<0.0001	(0.08304,0.1396)

Note:- 1) 1[a]reference category 2) 1[b] follow up time with 4 month interval

Final model for Pulse Rate as follows

$$\boldsymbol{Y_{i1}(PR) = 82.9042 - 0.2079age + 0.3098LVEF - 15.8007NYHAclassI - 14.7203NIYHAclassII - 4.9951NYHAclassIII + 0.005age * month + 0.00625LVEF * month + 0.02966ACF * month - 0.3023CHD * month + 0.03958others * month + 0.2893NYHAclassI * month + 0.3300NYHAclassII * month + 0.1347NYHAclassIII * month} \quad \boldsymbol{(1)}$$

Note:-LVEF=Left Ventricle Ejection Fraction, ACF=Acute Coronary failure CHD=coronary heart disease others=other than (ACF, CHD, severe anemia, NYHA =New York Heart Association month=visiting time (month).

According to the above model the fixed effect intercept coefficient $\hat{\beta}$=82.9042 (se=10.1191) represents an estimate of the Average PR at month=0 and excluding all covariates in the model. Among all covariates age, NYHA class, and CHD*month were negatively associated with Pulse Rate (PR) that means the repeatedly follow up made a particular decrease on Pulse Rate of CHF patients with small p values. In other ways, LVEF (p=<0.0001),age with month interaction (p=0.00500),Left Ventricle Ejection Fraction with month interaction (0.00625),NYHA class I with month interaction (p=<0.0001)and NYHA class II with month interaction (p=<0.0001) were positively associated with Pulse Rate (PR). NYHA class was significantly associated with PR with small p-value.

Patients under NYHA class I had 15.80 points lower evolutions PR (p=<0.0001) as compared with patients categorized under NYHA class IV of CHF patients. Patients categorized under NYHA class II had 14.72 points lower evolutions of PR (p=<0.0001) when compared with patients under NYHA class IV.

Interaction of Month with NYHA class I and Class II had positively associated with PR. Patients under categorized month*with NYHA class I had 0.2893 times higher evolutions of PR when compared with patients under categorized NYHA class IV with month interaction. Patients under categorized month*with NYHA class II had 0.33 times higher evolutions of PR when compared with patients under categorized NYHA class IV with month interaction. Diagnostic history of CHF patients with month interaction had positively associated with PR. Patients whose diagnostic history CHD with visiting time interaction had 0.30 times lower evolution PR when compared with patients categorized under diagnostic history of severe anemia with visiting time interaction.

Generally, as indicated in the above model and Table PR have decreasing pattern though out the follow up with respective clinical treatment .this concept indirectly indicated the improvement of the risk of Congestive Heart Failure. Because the lower value of PR is directly related with a stronger and healthier heart.

4.4.3 Variability of Error and Random in Pulse Rate model.

From the above table the subject specific random intercept variance is estimated to be 130.60 (s.e=15.64) with 95 % confident interval (104.65, 167.23) Pulse Rate of CHF patients. The subject specific random slope variance is estimated to be 0.1058(se=0.01396) with 95 % confident interval (0.08304, 0.1396) and estimated variance of the random error is $\delta 2e = 8.1690$ (se=0.3819) with 95 % confident interval (7.46, 8.9723).

4.4.4 Model fitting for fixed and random effects for Respiratory Rate (RR)

Comparing different covariance structure for the best model for Respiratory Rate (PR): the following table shows the value of fit statistics for different types of covariance structure to select best model for Respiratory Rate.

Table 8:-selections of covariance structure for Respiratory Rate Models.

	Fit Statistics			
Covariance structure	-2LL	AIC	AICC	BIC
UN	10834	11024	11032	11310
CS	13659	13841	13848	14115
AR(1)	13659	13841	13848	14115
TEOP	13051	13227	13245	13517

According to the Above table the final model with unstructured covariance structure was preferred for Respiratory Rate model with respective small values of -2LL AIC AICC and BIC of 10834, 11024 11032 and 11310 respectively

Table 9:- type thee result of fixed effects for Respiratory Rate (RR)

Type 3 Tests of Fixed Effects					
Effect	**Num DF**	**Den DF**	**F Value**	**P_value**	**Sig status**
Heartf	1	173	94.77	<.0001	***
Month	1	179	11.33	0.0009	***
AGE	1	176	9.91	0.0019	***
SEX	1	182	0.84	0.3620	
NYHA	3	180	23.15	<.0001	***
LVEF	1	184	40.94	<.0001	***
RESIDENCE	1	165	0.28	0.5973	
MARSTATUS	2	167	2.53	0.0831	
EDULEVEL	4	167	0.20	0.9397	
CHFTYPE	2	200	2.83	0.0615	

Type 3 Tests of Fixed Effects					
Effect	**Num DF**	**Den DF**	**F Value**	**P_value**	**Sig status**
DIAGH	3	185	5.08	0.0021	***
OCCUPATION	3	166	1.20	0.3133	
month*heartf	1	179	8.73	0.0036	**
AGE*heartf	1	176	10.87	0.0012	**
heartf*SEX	1	182	3.65	0.0576	
heartf*NYHA	3	180	16.46	<.0001	***
LVEF*heartf	1	184	12.69	0.0005	***
heartf*RESIDENCE	1	165	0.15	0.6988	
heartf*MARSTATUS	2	167	1.39	0.2524	
heartf*EDULEVEL	4	167	0.13	0.9707	
heartf*CHFTYPE	2	200	2.95	0.0548	
heartf*DIAGH	3	185	2.18	0.0923	
heartf*OCCUPATION	3	166	0.58	0.6267	
month*AGE*heartf	2	161	3.90	0.0222	*
month*heartf*SEX	2	167	1.99	0.1403	
month*heartf*NYHA	6	167	4.04	0.0008	***
month*LVEF*heartf	2	165	12.31	<.0001	***
month*heartf*RESIDEN	2	144	1.77	0.1745	
month*heartf*MARSTAT	4	147	1.60	0.1779	
month*heartf*EDULEVE	8	146	1.87	0.0682	
month*heartf*CHFTYPE	4	178	2.24	0.0665	
month*heartf*DIAGH	6	171	3.55	0.0025	**
month*heartf *OCCUPAT	6	145	0.47	0.8280	

Note :- * means significance ** high significance *** highly significance

The Respiratory Rate (RR) was modeled with sets of covariates and the result was described in the following table .the final model was somewhat complex and include 10 fixed effect parameters for Pulse rate including intercept and sex LVEF month and with interaction of month LVEF, congestive heart failure type and educational level and random slops were fitted to account for with in subject correlation. The following table shows the significance factors that affect Respiratory Rate of CHF patients at $\alpha = 0.05$ level of significance.

Table 10:- Results of Separate Model for Respiratory Rate (RR)

Effect		Separate model(RR)		
		estimate(SE)	P-value	95%CI
Intercept		23.7916(2.5338)	<0.0001	(18.7847,28.7985)
Month 1[b]		0.4061(0.3160)	0.2004	(-0.2176,1.0299)
Age		0.2079(0.06306)	0.0012	(0.08341,0.3323)
Sex	Female	-3.6752(1.9231)	0.0500	(-7.4696,-0.1192)
	Male	1[a]	1[a]	1[a]
LVEF		-0.3098(0.08698)	0.0005	(-0.4814,-0.1382)
NYHA	class I	-2.49(0.7582)	<0.0001	(-3.5894,-0.5938)
	class II	-1.36(0.5569)	<0.0001	(-2.5442,-0.3467)
	class III	-.87(0.6524)	0.0661	(-2.2695,0.3078)
	Class IV	1[a]	1[a]	1[a]
LVEF*month 1[b]		-0.00335(0.000769)	<0.0001	(-0.00487,-0.00183)
Chftype*month1[b]	biventricular*month	0.03029(0.02027)	0.1367	(-0.00968 , 0.07026)
	Left sided *month	0.06006(0.02333)	0.0110	(0.01397,0.1061)
	Right sided*month	1[a]	1[a]	1[a]
Sigma 2(σ_2)		0.6197(0.02892)	<0.0001	(0.5667,0.6805)
$\sigma^2 b20$		8.1235(0.9829)	<0.0001	(6.4952,10.4548)
$(\sigma) b20$.b21		-0.2030(0.03031)	<0.0001	(-0.2601,-0.1416)
$\sigma^2 b22$		0.009234	<0.0001	(0.007273,0.01211)

Note:-1) 1[a]reference category 2) 1[b] follow up time with 4 month interval

Final model for respiratory Rate as follows

$$\boldsymbol{Y_{i2}(RR) = 23.7916 - 0.2079age - 3.6752female - 0.3098LVEF - 2.149NYHA\ classI - 1.36NYHA\ classII - 0.87NYHA\ classIII - 0.00335LVEF * month + 0.03029chftype\ of Biventricular * month + 0.06006chftype\ of left\ sided * month} \quad ------(2)$$

Note:-LVEF=Left Ventricle Ejection Fraction, New York Heart Association (class I, class II, class III class IV) chftype= types of congestive heart failure patients (biventricular, left sided and right sided) month=visiting time.

According to the above model and Table $intercept = 23.7916$ represents an estimate of the average Respiratory Rate (RR) at time month=0 and excluding all the covariates in the model. NYHA(p=0.0005), LVEF(p=0.0005) and LVEF with month interaction (p=<0.0001) was negatively associated with RR that means repeatedly follow up made a particular decrease on respiratory Rate of CHF patients. A decrease in RR means minimize the risk of CHF. In addition age, congestive heart failure type left, sided failure with month interaction was positively associated with RR. Sex was significantly associated with Respiratory Rate of CHF patients.

Female patients had almost 3.67 points lower evolution of RR (p=0.05) when compared with males. NYHA class was significantly associated with RR with small p-value, for instance patients under NYHA class I had 3.6752 points lower evolutions RR (p=<0.0001) when compared with NYHA class IV. NYHA class II had 1.34 points lower evolutions of RR (p=<0.0001) when compared with patients under NYHA class IV. congestive heart failure type with month (visiting time interaction) had significantly associated with RR. congestive heart failure type left sided with visiting time (month) interaction had 0.06 times over evolution RR when compared CHF patients under congestive heart failure type right sided(p=0.0110).

Generally, as indicated in the above model and Table RR have decreasing pattern though out the follow up with respective clinical treatment .this concept indirectly indicated the improvement of the risk of Congestive Heart Failure. Because the lower value of RR is directly related with a stronger and healthier heart.

4.4.5 Variability of Error and Random in Respiratory Rate model.

From the above table the subject specific random intercept variance is estimated to be 8.1235(s.e= 0.9829) with 95 % confident interval (6.4952, 10.4548) of Respiratory Rate of CHF patients. The subject specific random slope variance is estimated to be 0.009234(se=0.001197) with 95 % confident interval (0.007273,0.01211) and estimated variance of the random error is $\delta^2 e = 0.6197$ (se=0.02892) with 95 % confident interval(0.5667, 0.6805).

4.4.6 Results of joint effect model

A joint fixed effect model for the two symptoms of CHF syndrome PR and RR was fitted with an unstructured variance covariance structure with the following fit statistics and as we

saw from the table fit statistics the an unstructured covariance structure had small fit statistics of -2LL AIC AICC and BIC 10812 ,11012,11021 and14313 respectively. Because of this UN was preferred to fit the joint model of PR and RR on CHF patients

Table 11:- Covariance structure comparison of joint mixed effect model

Covariance structure	Fit Statistics			
	-2LL	AIC	AICC	BIC
UN	10812	11012	11021	14313
CS	13852	14036	14043	14313
AR(1)	13876	14068	14067	14337
TEOP	Not converge	Not converge	Not converge	Not converge

The model is almost the same as the separate model except some covariates included in PR model but exclude from RR model and vice versa and sets of random intercept slopes of 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 intercept and random slope were fitted to account for within subject correlations.

4.4.7 Joint fixed effect model for PR

Table 12:-Estimate values of pulse Rate in joint case

Effect		Joint case for model(PR)		
		estimate(SE)	P-value	95 % CI
Intercept		82.9594(10.0766)	<0.0001	(62.6218,102.44)
Age		-0.1995(0.06090)	0.0013	(-0.3198,-0.07921)
Month1[b]		-0.5908(0.3024)	0.0500	(-1.1885,0.006791)
LVEF		0.1221(0.02108)	<0.0001	(0.2727,0.6043)
Diagnostic history	ACF	-2.5177(2.1015)	0.2325	(-6.6643,1.6289)
	CHD	6.5916(2.8978)	0.0241	(0.8746,12.3085)
	Others	-4.4996(33.7863)	0.2396	(-11.9469,3.0077)
	Severe anemia	1[a]	1[a]	1[a]
NYHA	class I	-17.5782(3.0331)	<0.0001	(-23.5626,-11.5781)
	class II	-15.6475(2.2065)	<0.0001	(-20.0017,-11.2932)
	class III	-5.7491(2.6084)	0.0290	(-10.9020,-0.5962)
	Class IV	1[a]	1[a]	1[a]
age*month		0.004894(0.001871)	0.0097	(0.001199,0.008590)
LVEF*month		-0.00635(0.002614)	0.0162	(-0.01151,-0.00119)
Diagnostic history*month	ACF*month	0.03591(0.02006)	0.7000	(-0.1096,0.1630)
	CHD*month	0.007532(0.02794)	0.0019	(-0.4926,-0.1128)
	Others*month	0.08018(0.03421)	0.7407	(-0.1930,0.2708)
	Severe anemia	1[a]	1[a]	1[a]
NYHA*month	class I*month	.2838(0.09194)	0.0024	(0.1021,0.4654)
	class II*month	0.3216(0.07212)	<0.0001	(0.1794,0.4638)
	class III*month	0.1313(0.07959)	0.1010	(-0.02590,0.2855)
	Class IV *month	1[a]	1[a]	1[a]
Sigma1 (σ_1)		8.1827(0.3831)	<0.0001	(7.4809,8.9886)
$\sigma^2 b10$		129.47(15.4979)	<0.0001	(103.76,166.15)
$\sigma b10$b11		-2.7631(0.4091)	<0.0001	(-3.5647,-1.9612)
$\sigma^2 b11$		0.1052(0.01386)	<0.0001	(0.08254,0.1387)

Note:-1) 1[a] reference category 2) 1[b] follow up time with 4 month interval

Final model in joint case for Pulse Rate (PR) is as follows

$Y_{i1}(PR) = 82.9594 - 0.1995age - 0.5908month + 0.1221LVEF - 2.5177ACF + 6.5916CHD - 4.4996others - 17.5782NYHA\ class\ I - 15.6475NYHA\ class\ II - 5.7491NYHA\ classIII$+0.004894age*month+0.03591LVEF*month+0.03591ACF*month+0.007532CHD*month+0.08018others*month+.2838NYHAclassI*month0.3216NYHA ClassII*month+0.1313NYHA class III*month----------(3)

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According to equation (3) and the above table the fixed effect intercept coefficient =82.9594 (se=10.0766) represents an estimate of the average PR at visiting month=0 and excluding all covariates in the model. Age, month, diagnostic history of ACF, diagnostic history of others and NYHA (class I class II class III) negatively associated with Pulse Rate (PR) that means the repeatedly follow up made a particular decrease on pulse rate while the rest were positively associated with PR.

Month (visiting time) were negatively associated with PR (p=0.05) as visiting time (month) were increase Pulse Rate decrease. LVEF were positively associated with PR (p=<0.0001). Patients classified under diagnostic history CHD had 6.59 points higher over evolution of PR (p=0.0241) when compared with patients classified under diagnostic history severe anemia. NYHA class was significantly associated with PR with small p-value, for instance patients under NYHA class I had 17.57 points lower 15.64 points lower evolutions of PR (p=<0.0001) when compared with patients under NYHA class IV. NYHA class III had 5.74 points lower evolutions of PR (p=<0.0001) when compared with patients under NYHA class IV.

Age with month interaction is positively associated with PR. The same was the interaction of LVEF with month. Diagnostic history of CHD with month interaction had a significance effect on PR (p=0.0019). Patients classified under diagnostic history of CHD with month interaction had 0.0075 times higher evolution PR when compared with patients classified under Diagnostic history severe anemia with visiting time interaction. NYHA class with month interaction had positively associated with PR (p=<0.0001).

4.4.7 Variability of Error and Random effect in joint model PR

Alike parameter estimation and testing, variability analysis of both fixed and random effect are also another important aspect. High variability is the indicator of less accuracy or high

error in prediction of the association of outcome evolution with respective risk factor. As indicated in the above table the subject specific random intercept variance is estimated to be 129.47(s.e =15.4979) (p=<0.0001) with 95% CL (103.76,166.15) .In addition to that the subject specific random slope variance is estimated to be 0.1052(se=0.01386)(p=<0.0001) and 95% CI (0.08254,0.1387)the estimated variance of the random error is 8.1827(se=0.3831)p=(<0.0001) and with 95%CI (7.4809,8.9886) thus the variability due to subject specific random intercept is higher than that of random slope for PR model.

4.4.8 Joint mixed effect model for RR in joint case;

Table 13:-Estimate values of respiratory Rate joint case

Effect		Join case for model(RR)		
		estimate(SE)	P-value	95%CI
Intercept		23.9594(2.5153)	<0.0001	18.9892,28.9296
Month1[b]		-0.2005(0.08820)	0.0244	-0.3748,-0.02628
LVEF		0.1221(0.02108)	<0.0001	0.08050,0.1637
Chftype	Biventricular	-1.1839(0.5414)	0.0242	-2.2118,-0.1560
	Left sided	-1.022(0.6534)	0.1271	-2.2931,0.2886
	Right sided	1[a]	1[a]	1[a]
NYHA	class I	-2.0916(0.7582)	<0.0001	-4.4196,-1.9780
	class II	-1.4454(0.5569)	<0.0001	-3.8342,-1.8602
	class III	-0.9808(0.6524)	0.0007	-2.9333,-0.7897
	Class IV	1[a]	1[a]	1[a]
LVEF*month		-0.00328(0.000594)	<0.0001	-0.00478,-0.00177
Diagnostic history*month	ACF*month	0.03591(0.02006)	0.0749	-0.00364,0.07545
	CHD*month	0.007532(0.02794)	0.7877	-0.04753,0.06260
	Others*month	0.08018(0.03421)	0.0203	0.01264,0.0.1477
	Severe anemia*month	1[a]	1[a]	1[a]
Chftype*month	Biventricular*month	0.02949(0.02004)	0.1427	-0.01003,0.06901
	Left sided*month	0.05700(0.02313)	0.0148	0.01132,0.1027
	Right sided*month	1[a]	1[a]	1[a]
Sigma 2(σ_2)		0.6218(0.02909)	<0.0001	(0.5685,0.6830)
$\sigma^2 b20$		8.0023(0.9664)	<0.0001	(6.4,10.29)
$(\sigma) b20$b21		-0.1994(0.08350)	<0.0001	(-0.3631,-0.03574)
$\sigma^2 b22$		0.009068(0.001170)	<0.0001	(0.007150,0.01188)

Note:-1) 1[a] reference category2) 1[b]follow up time with 4 month interval

Final model in joint case for Respiratory Rate (RR) is as follows

$$Yi2(RR) = 23.9594 - 0.2005month + 0.1221LVEF - 1.1839chftype\ bivertricular - 1.022chftype\ left\ sided - 2.0916NYHA\ class\ I - 1.4454NYHA\ class\ II - 0.9808NYHA\ class\ III - 0.00328LVEF * month + 0.03591diah\ ACF * month + 0.007532diagh\ CHD * month + 0.08018diagh\ others * month +$$

$0.02949 chftype\ biventricular * month + 0.05700 chftype\ left\ sided * month -$
$- -$ (4)

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According to the equation (4) and the above table the fixed effect intercept coefficient =23.9594 represents an estimate of the average RR at visiting time =0 (month) when all covariates excluded from the model. All parameters in the model were statistically significance except congestive heart failure type of left sided failure, diagnostic history with month interaction of CHD and congestive heart failure type biventricular with month interaction.

Month (visiting time) was negatively associated with RR (p=0.0244) as visiting time (month) increase RR decrease and vice versa. LVEF was positively associated with RR (p=<0.0001). congestive heart failure type biventricular was negatively associated with RR that is patients classified under congestive heart failure type Biventricular were 1.18 lower evolution RR when compared with patients classified under congestive heart failure type right sided. NYHA class was significantly associated with RR with small p-value , for instance patients under NYHA class I had 2.09 points lower evolution RR (p=<0.0001) when compared with patientsclassified under NYHA class IV. Patients classified under NYHA class II had 1.44 points lower evolutions of RR (p=<0.0001) when compared with patients under NYHA class IV. Patients classified under NYHA class III had 0.98 points lower evolutions of RR (p=<0.0001) when compared with patients under NYHA class IV.

Month with LVEF had negatively associated with RR with (p=<0.0001). diagnostic history of others with visiting time(month) interaction had a significance effect on RR that is diagnostic history of others had 0.08 times over evolution RR when compared with patients classified as diagnostic history of severe anemia. congestive heart failure type were significance with time interaction on RR (p=0.0148) patients classified under congestive heart failure type left sided failure with month interaction had 0.057 times higher evolution RR than patients classified under congestive heart failure type right sided failure.

4.4.9 Variability of error and random effect in joint model RR

Alike parameter estimation and testing, variability analysis of both fixed and random effect are also another important aspect. High variability is the indicator of less accuracy or high error in prediction of the association of outcome evolution with respective risk factor. As

indicated in the above table the subject specific random intercept variance is estimated to be 8.0023(s. e =0.9664) (p=<0.0001) with 95% CL (6.4,10.29) .In addition to that the subject specific random slope variance is estimated to be 0.009068(se=0.08350)(p=<0.0001) and 95% CI (0.007150,0.01188) the estimated variance of the random error is 0.6218 (se=0.02909)p=(<0.0001) and with 95%CI (0.5685,0.6830)

Generally in joint case when we observed the variability between PR and RR variability due to subject specific random intercept is higher than that of random slope for both models model. The random effect variability is greater in PR than RR.

4.4.10 Association (common) effect parameters

Table 14:- common parameters for PR and RR injoint case

Common parameters	Estimate (SE)	P –value	95% CI
σ_{b10b20}	**-0.1984(0.02965)**	**<0.0001**	**(-0.2565,-0.1403)**
σ_{b10b21}	**-0.1994(0.08350)**	**<0.0001**	**(-0.3631,-0.03574)**
σ_{b20b11}	**-0.3477(0.09973)**	**<0.0001**	**(-0.5432,-0.1522)**
σ_{b11b21}	**-2.7630(0.4091)**	**<0.0001**	**(-3.5647,-1.9612)**
Rho(ρ)	**0.6707(0.030)**	**<0.0001**	**(0.6102,0.732)**

By referring table 14 based on 2448 pair symptoms of CHF assessment from 153 subjects a substantial correlation ($\rho = 0.6707$ $se = 0.030$) with 95 % CI (0.6102,0.732) between the PR and RR with in the same subject is noted. From the random effect it may be seen that variability is relatively higher for PR than RR. The covariance for subject specific random intercept of PR and RR with σ_{b10b20} =-0.1984(0.02965) with 95 % CI (-0.2565,-0.1403) and the covariance for subject specific random slope of PR and RR σ_{b11b21}=2.7630(0.4091) with 95 % CI (-3.5647, -1.9612).

It is possible to investigate how the evolution of PR associated with RR. Hence, the association of evolution (AOE) is to be estimated 0.6707(se=0.030) with 95 % CI (0.6102, 0.732) (p=0.0001). It is also possible to determine how the association the two symptom of CHF (PR and RR) evolves over time. For instance at a baseline evolution of the association was 0.351409 and at first second third….month follow up it increase in to 0.361077, 0.367800, 0.38777 …respectively indicating the evolution of association between PR and RR over time .i.e there is a positive evolutions of association between two outcomes PR and RR.

Thus, the association positively evolved over time .generally there is evidence that visiting time (month) has reasonable effect on association of evolutions of both outcomes.

4.4.11 Comparison of separate and joint effect model

Table 15:-Joint model (PR&RR jointly) Fit Statistics

Fit Statistics	
-2 Log Likelihood	10812.8
AIC (smaller is better)	11012.8
AICC (smaller is better)	11021.4
BIC (smaller is better)	11313.9

Table 16:-Joint Null Model Likelihood Ratio Test

Null Model Likelihood Ratio Test		
DF	**Chi-Square**	**Pr > ChiSq**
11	5458.38	<.0001

Table 17:-Separate model (PR and RR independently) *Fit Statistics*

Fit Statistics	
-2 Log Likelihood	10834.9
AIC (smaller is better)	11024.9
AICC (smaller is better)	11032.6
BIC (smaller is better)	11310.9

Table 18:-Separate model Null Model Likelihood Ratio Test

Null Model Likelihood Ratio Test		
DF	**Chi-Square**	**Pr > ChiSq**
7	5436.34	<.0001

LRT = -2LL(PR&RR separate)-(-2LL(PR &RR joint) =10834.9-10812.8= 22.10----------(5)

Here, both separate and joint mixed effect models have been considered and parameter estimates for the separate and joint models are summarized on their respective table numbers. Technically the separate model was fitted for two outcomes together. But assuming that $\rho = 0$ which entirely equivalent to fit the two independent models separately as results were shown in their respective table number. It allows for a single likelihood for the model parameters enabling direct comparison with the corrected bivariate model fitted subsequently.

PR and RR show a strong positive relationship as evidenced by the correlation of random effects in joint mixed (models. In addition, likelihood comparison shows a convincing

improvement in a 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 a parameter of some covariates.

When comparing the results from the separate settings to the result from joint settings there are several points of interest. The -2LL value corresponding to the two separate models (i.e fitted as a joint model assuming $\rho = 0$)was equal 10834.90 and -2LL value for the joint model was 10812.80 .Hence, the joint random effect model of the two symptom of CHF ,PR and RR was significantly better than two separate random effect models for PR and RR.(-2LL:10834.90 vs 10812.80 LRT: DF =7 chi-square=5436.34 P-value<.0001 Vs DF=11 chi-square =5458.38 p-value <.0001) with regards to AIC joint model (AIC=11012.80) is also included as a better fit than the separate model (AIC=11024.90), Notice how the joint model of the two symptom of CHF i. e PR and RR seems to decrease the variability in the random effects ,this is shown on their respective tables. Taking in to account the standard error for the variance and covariance estimate, the joint model is general allowed for more accurate prediction (small error) of the variability in the random effects, though just slightly.

Comparing the fixed effects of the separate and joint mixed models, some important things may consider for the two symptoms of CHF patients. First, and foremost, there are the questions of whether the differences models reached the same bottom line conclusion .comparing the covariates between two types of models we yield further information of interest. Both separate and joint model found a significant relationship between NYHA and PR and RR. For example NYHA was negatively associated with both separate and joint mixed effect models. the estimate values are presented on the respective table number.

4.5 Model Diagnostic Checking

4.5.1 Diagnostic checking and residual plots for PR.

Different diagnostic checking plots for the Pulse Rate are presented in the following plots .as we observed from the below plots even if there are some outliers it was indicated that the variability of the error in Pulse Rate (PR) was almost constant. That means the error does not far deviate from each other .distance of individual residual were equally far from the horizontal line.

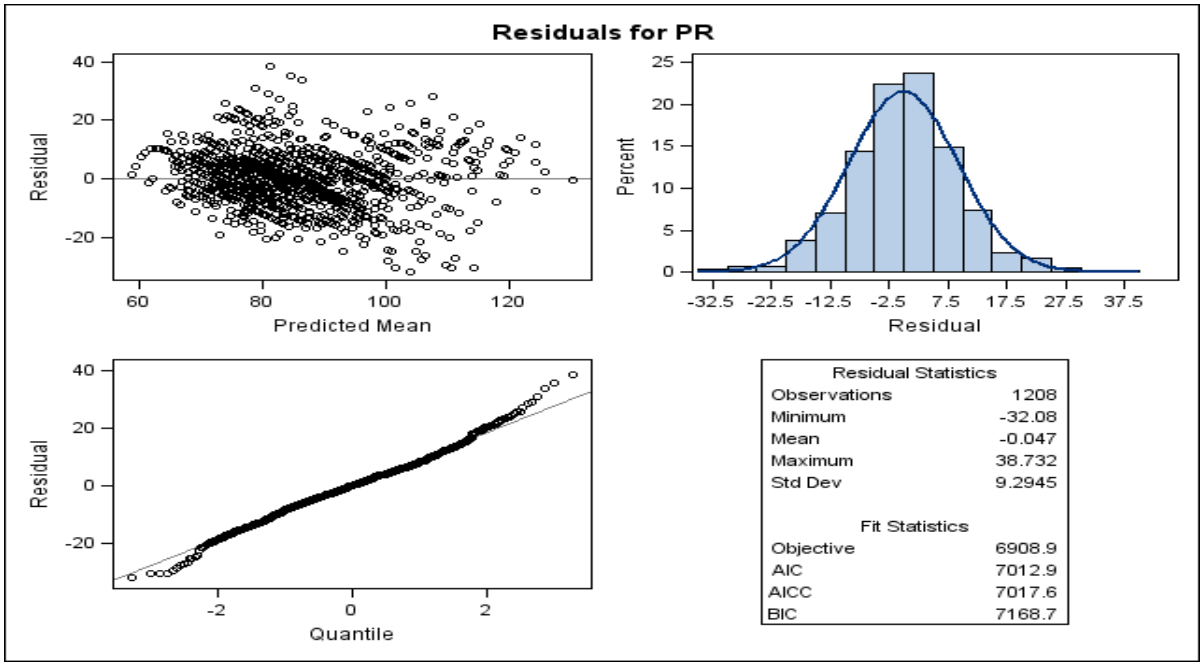

Figure 6:-Residual plots of Pulse Rate of CHF patients for checking diagnostics

Furthermore, according to the probability plots those were shown below. We observed that the normality assumption was supported through the upward nearly straight line of normal plots.

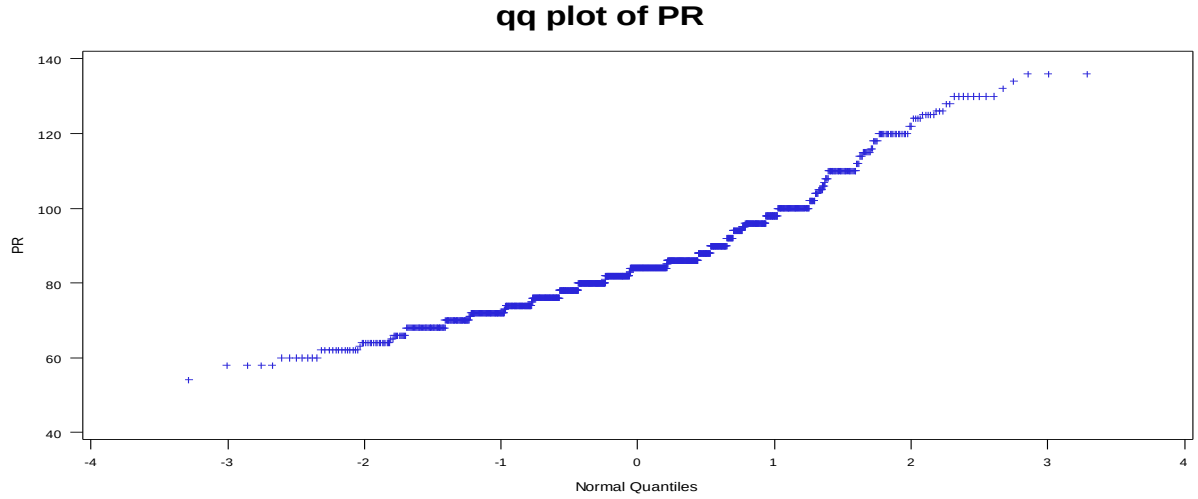

Figure 7:-QQ normal plot for Pulse Rate to check linearity

Based on the normal probability plots random effects with subject specification variable (id) specific randomintercepts and random slopes are shown below. Even if it seems slight deviation of normality at the bottom and top the normality assumption is fulfilled.

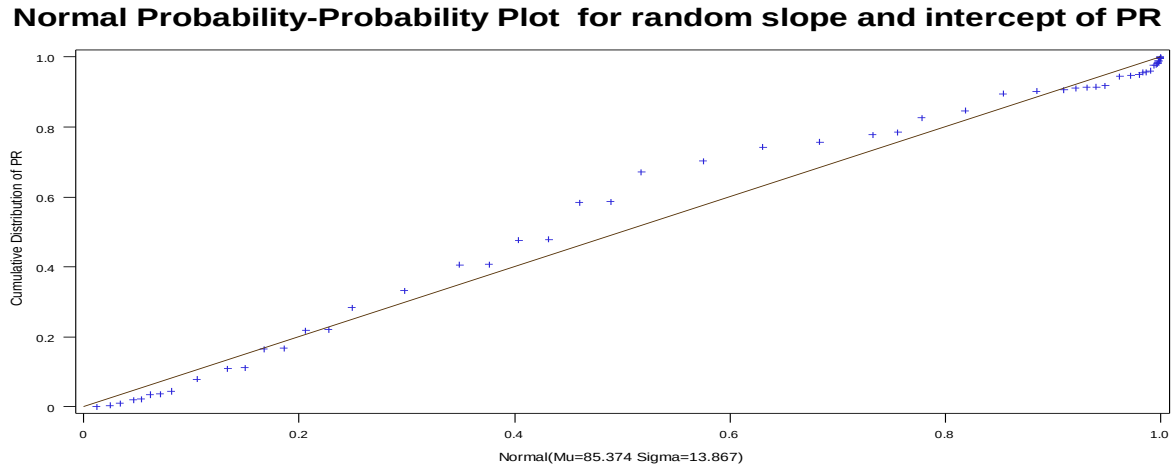

Figure 8:-Normal PP plot for Pulse Rate to check normality

4.5.2 Diagnostic checking and residual plots for RR.

Different diagnostic checking plots for the Respiratory Rate are presented in the following plots. As we observed from the plots below even if there are some outliers it was indicated that the variability of the error in respiratory rate (RR) was almost constant. That means the error does not far deviate from each other. Distances of individual residual were equally far from the horizontal line.

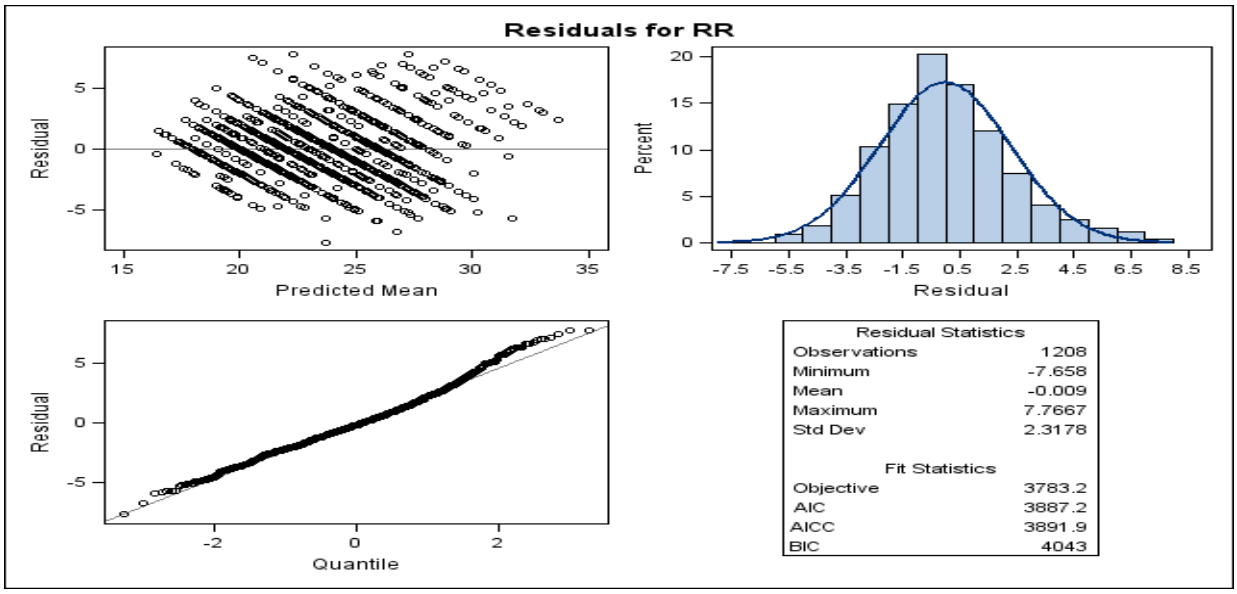

Figure 9:-Residual plots of Respiratory Rate of CHF patients for checking diagnostics

Furthermore, according to the probability plots those were shown below. We observed that the normality assumption was supported through the upward nearly straight line of normal plots.

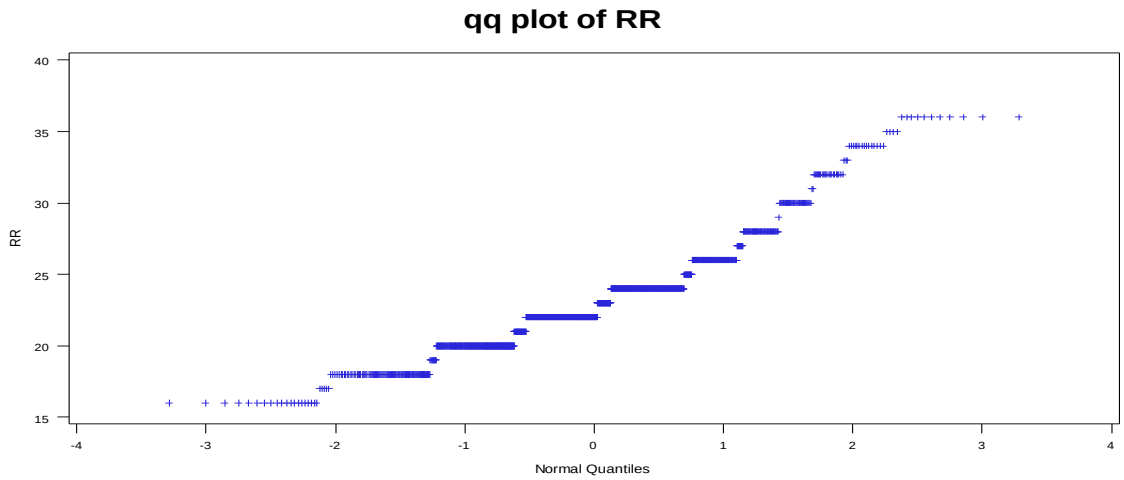

Figure 10:-QQ normal plot for Respiratory Rate to check linearity

Based on the normal probability plots random effects with subject specification variable (id) specific random intercepts and random slopes are shown below. Even if it seems slight deviation of normality at the bottom and top the normality assumption is fulfilled.

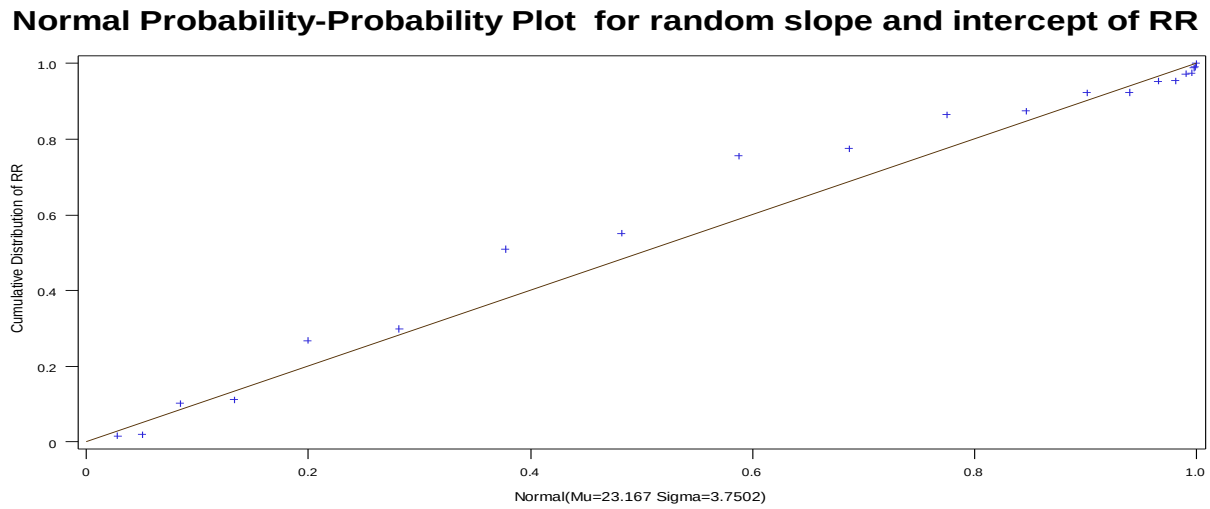

Figure 11:-Normal PP plot for Respiratory Rate to check normality

4.6. Discussions

The study was conducted on the tile of joint model for a longitudinal PR and RR of CHF patients in FelegeHiwotReferal hospital Amhara Regional State Bahir Dar Ethiopia. A joint mixed effect model for paired outcomes with the set of both continuous and categorical covariates and the interaction of time with those covariates is presented.the model extends Previous work by accommodating longitudinally measured two main symptoms of CHF as outcomes PR and RR is executed.since joint model building starts from separate model 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 effect to be included in the longitudinal model can be easilydetermined and thirdly initial value to be provided for the joint models can be obtained.

The finding provides direct evidence that decreasing in LVEF in(%) is the primary driver of the risk of CHF by causing reasonable increase RR and reverse with PR longitudinally through out the follow up time in months. The finding is consistent with the latest literature which suggested by Njagi (2013) based on exponentiation the relevant parameter estimate, the mean number of abnormal HR measurement in patients with reduced ejection was found to be 3.3531 times that of patients with equal 0.53 before treatment and 0.07 when there was during in the plasma. The finding is consistent with it because PR had significance positive association with PR while significantly negative association with RR. Furthermore ,there was a significance association between sex and RR in contrast to Lambert and Vandenhende (2002) and there is no significance association between sex and PR consistent with Lambert and Vandenhende (2002).

The finding provides direct evidence of strong correlation between two symptoms of CHF (PR and RR) estimated to be 0.67071 (67%) .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 Thiébaut et al. (2002) on bivariate mixed effect model or firs order authoregressive process and independent measurement error for both markers CD4 and HIVRNA in HIV patients. Similarly the finding is also consistent with a Previous literatures of Ferrari (2004) studied on application of joint model for resistance and prevalence a strong correlation between percentage resistant and prevalence and both increase with time.the correlation is estimated to be 0.95 with 95% CI (0.414,0.997) showing that the correlation is significant. That correlation however ignore the effect of time.finally ,joint mixed model was

preferred to find and identify joint evolution in this finding and this is consistent to (Njagi (2013)) who compare the results from the extended and the conventional model .based on an AIC based comparisons ,they observed that their extended model provided improvement to model fit,with out compromising parsimony .there was an impact on both the point estimate and standard error.

Chapter Five

5. Conclusions and Recommendations

5.1 Conclusions

The main goal of this thesis was to identify the potential risk factors affecting the two end points using joint model of CHF patients and comparisons of separate and joint linear mixed effect model for PR and RR. Towards this goal, the previously introduced joint model allows the joint modeling of mixed model for PR and RR with specification of subject specific random intercept and slope (time in month), by excluding quadratic random slopes in individual linear mixed models for PR and RR. An 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 association (EOA). Thus the questions of AOE and the EOA of the PR and RR were clearly addressed.

After passing many procedures among all covariates BMI, educational level, occupation, residence, marital status were excluded in the final models because of their insignificant effect on both outcomes. But the rest covariates such as visiting time(month), age, sex, LVEF, NYHA, diagnostic history of CHF, Congestive Heart Failure type of patients , and interaction of month (visiting time) with age, sex, LVEF, NYHA, diagnostic history of CHF,Congestive Heart Failure type were included in the final model.

Separate mixed effect model result: Out of thosecovariates age,NYHA(classI classII classIII),diagnostic history of CHD,were negatively associated with PR while LVEF,age with month interaction ,diagnostic history of ACF and other,month with NYHA (classI classII classIII) were positively associated with PR. Age,visiting time (month), Congestive Heart Failure type with month interaction were positively associated with RR while sex, LVEF, NYHA(classI classII classIII), and LVEF with month interaction were negatively associated with RR.

Joint mixed effect result: out of those covariates age,month,diagnostic history of ACF and others,NYHA (classI classII classIII) and LVEF with month interaction were negatively associated with PR while LVEF and diagnostic history CHD were positively associated with

PR. Visiting time (month), Congestive Heart Failure type Biventricular Congestive Heart Failure type left sided failure, NYHA (classI classII classIII) ,LVEF with month interaction were negatively associated with RR while LVEF ,month with diagnostic history of ACF,CHD and others ,month with Congestive Heart Failure type of Biventricular failure and left sided failure were positively associated with RR.

Moreover, among all the covariates included in the separate and joint mixed effect model NYHA class III, month with diagnostic history of ACF and others,month with NYHA classIII were statistically insignificant on the evolution of PR(in PR separate case), Inaddition NYHA class III and month with chftype of Biventricular were statistically insignificant on the evolution of RR(in RR separate case). Diagnostic history of ACF and others and month with Diagnostic history of ACF and others were statistically insignificant on the evolution of PR (in PR joint case). Congestive Heart Failure type of left sided failure ,month with diagnostic history of ACF and CHD and month with Congestive Heart Failure type biventricular were statistically insignificant on the evolution of RR(in RR joint case).

Non-zero covariance of random intercept and random slopes explained the statistical significance of association between two outcomes.Likewise, it can be generalized the two outcome have a strong positive correlation and the correlation were statistically significant. Thus ,the joint mixed effect model was preferred because the joint fixed effect 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, whileaccommodating 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 value of PR and RR has been shown .That decrease trend on PR and RR indirectly indicated the reduction of the risk of congestive heart failure .

Finally, it is conclude that, joint modeling of longitudinal bivariate response is necessary to explore the association between paired response variable 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 more than two responses variables over time. This issue typically can be 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 and the complexity is high.

5.2 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 variable could not assessed .Therefore, special attention should be given to the quality of the data.

A lot of investigators doing longitudinal research used to model repeated outcomes separately, to assess the evolution of the outcomes through time by ignoring the associated effect.But it is recommended to chick the association evolution in some cases of the outcome might have association of the evolutions .Even if almost equivalent questions through joint model and separate model ,joint model is able to 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 effect models,but in some cases it is crucial to consider correlated error in models because using un correlated error model may display less accurate results if there is suspension of correlated measurement error in the data.

Based on the finding of the study we recommend that:-

- Health professionals give attention to minimize the risk of CHF by reducing patients PR and RR and create awareness for patients about CHF and potential risk factors.
- Health professionals recommended to give more attention for CHF patients whose PR and RR is high.
- Health professionals,Governmental organizations and Non Governmental Organizations promote and allocate budget in adequate amount for treatment of CHF patients to minimize the risk level of CHF.
- Fitting joint model is recommended.

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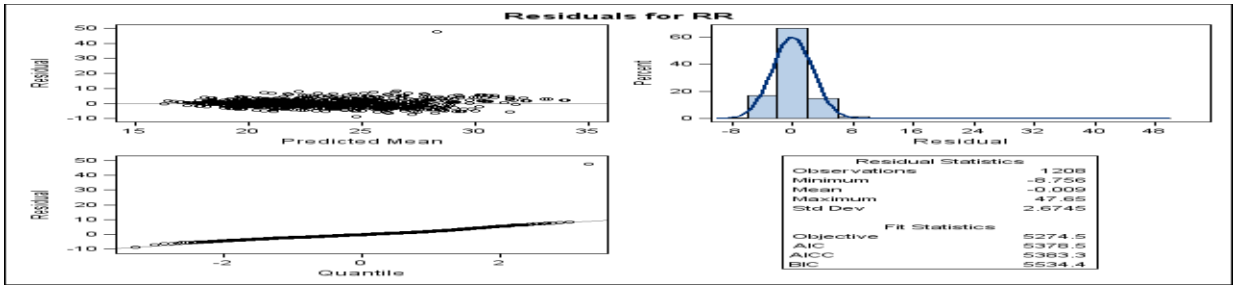
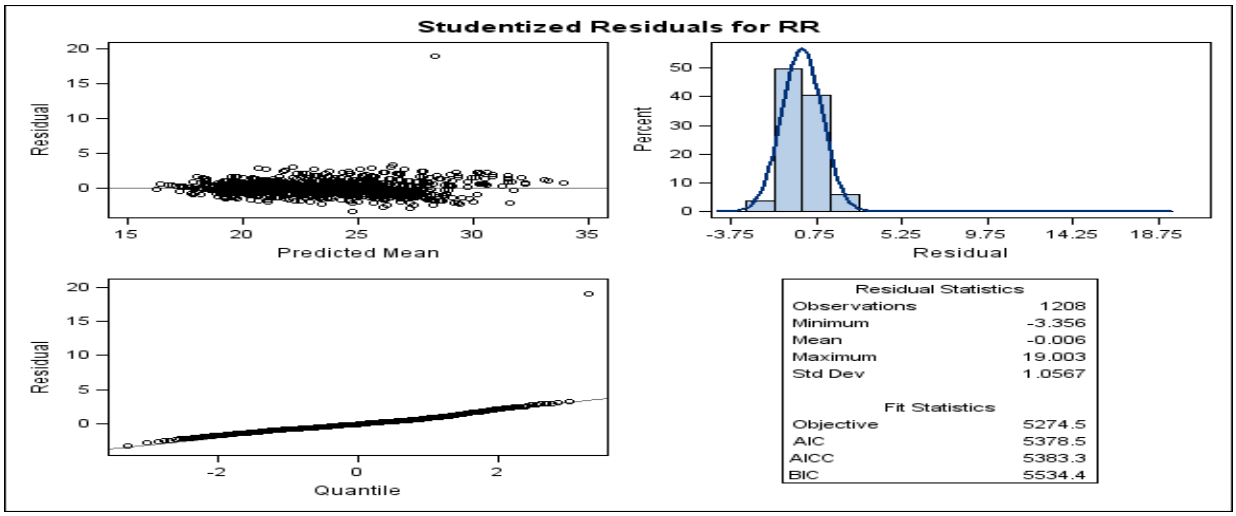
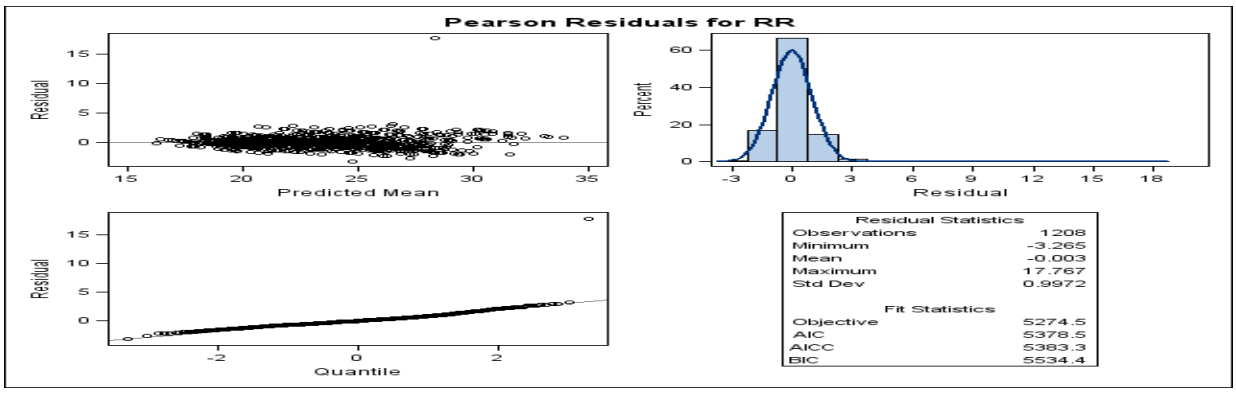
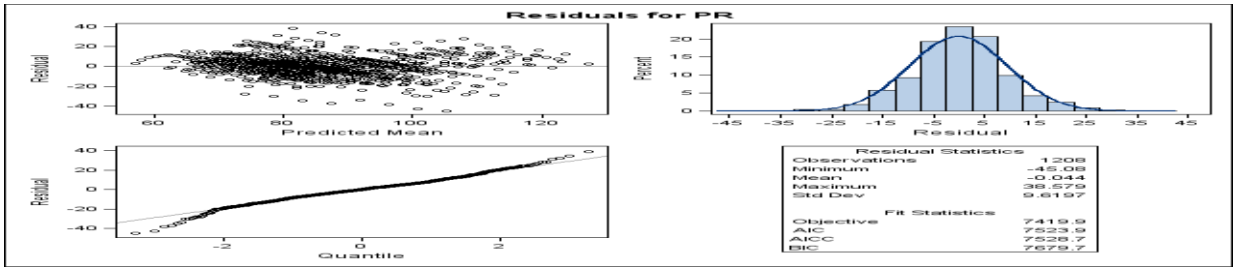
APPENDEX


Residuals for RR
Residual
Predicted Mean
Quantile
Percent
Residual
Residual Statistics
Observations 1208
Minimum -8.756
Mean -0.009
Maximum 47.65
Std Dev 2.6745
Fit Statistics
Objective 5274.5
AIC 5378.5
AICC 5383.3
BIC 5534.4


Studentized Residuals for RR
Residual
Predicted Mean
Quantile
Percent
Residual
Residual Statistics
Observations 1208
Minimum -3.356
Mean -0.006
Maximum 19.003
Std Dev 1.0567
Fit Statistics
Objective 5274.5
AIC 5378.5
AICC 5383.3
BIC 5534.4


Pearson Residuals for RR
Residual
Predicted Mean
Quantile
Percent
Residual
Residual Statistics
Observations 1208
Minimum -3.265
Mean -0.003
Maximum 17.767
Std Dev 0.9972
Fit Statistics
Objective 5274.5
AIC 5378.5
AICC 5383.3
BIC 5534.4


Residuals for PR
Residual
Predicted Mean
Quantile
Percent
Residual
Residual Statistics
Observations 1208
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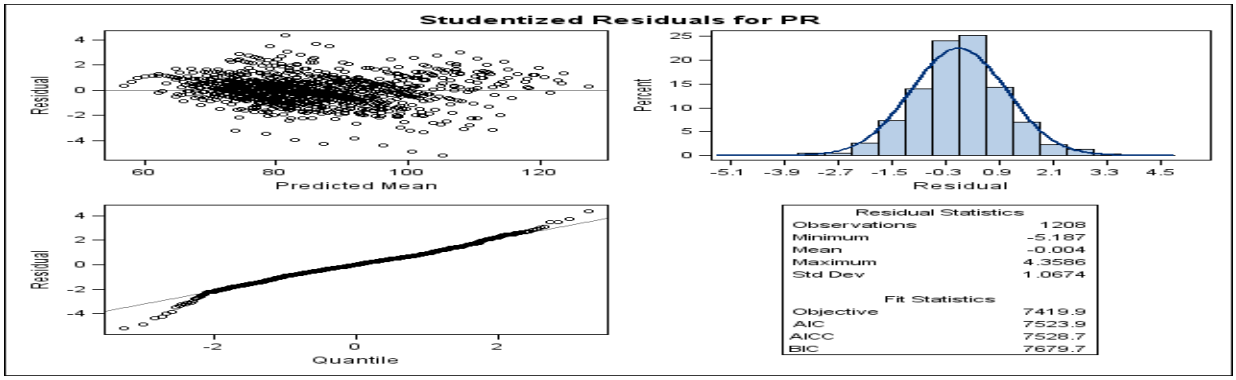
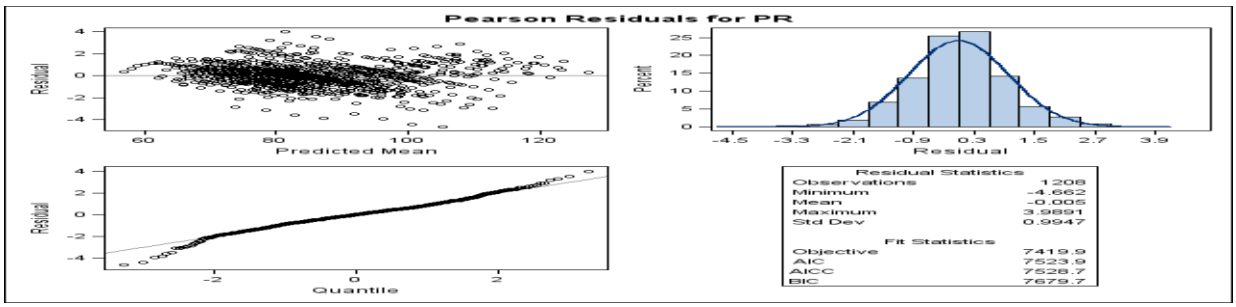
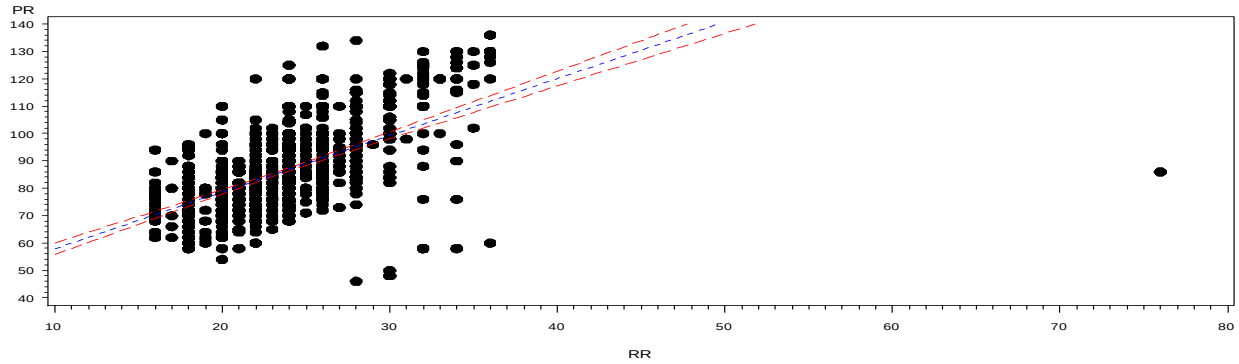
Mean -0.044
Maximum 38.579
Std Dev 9.6197
Fit Statistics
Objective 7419.9
AIC 7523.9
AICC 7528.7
BIC 7679.7

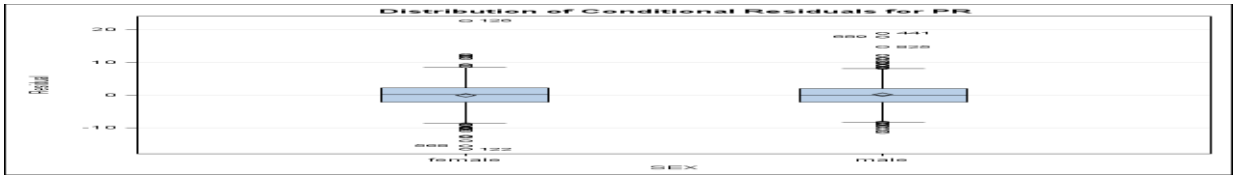


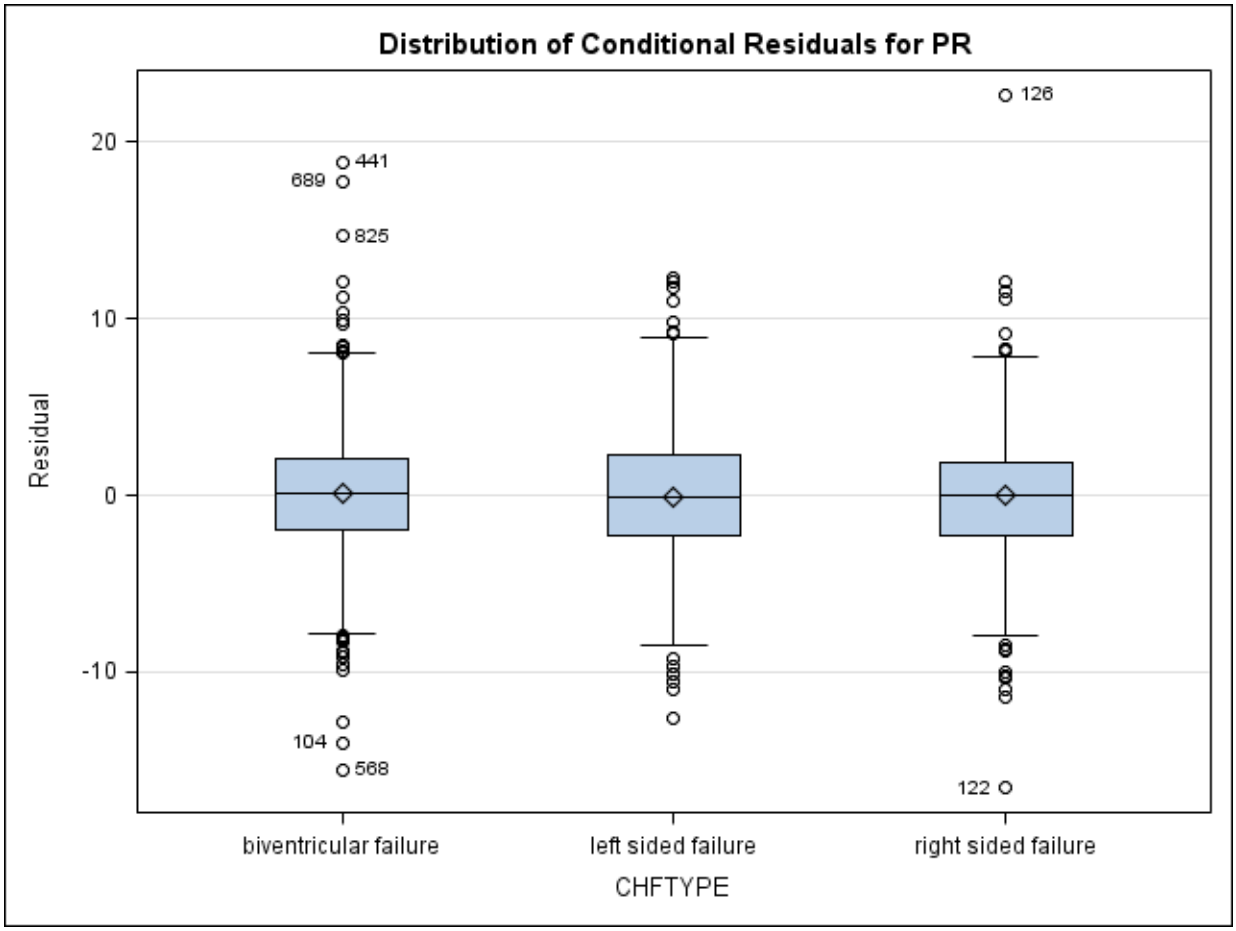


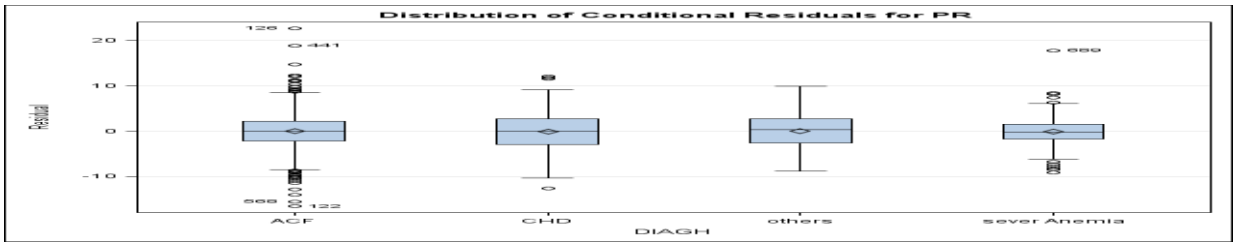
Fitting GLM model for Pulse Rate

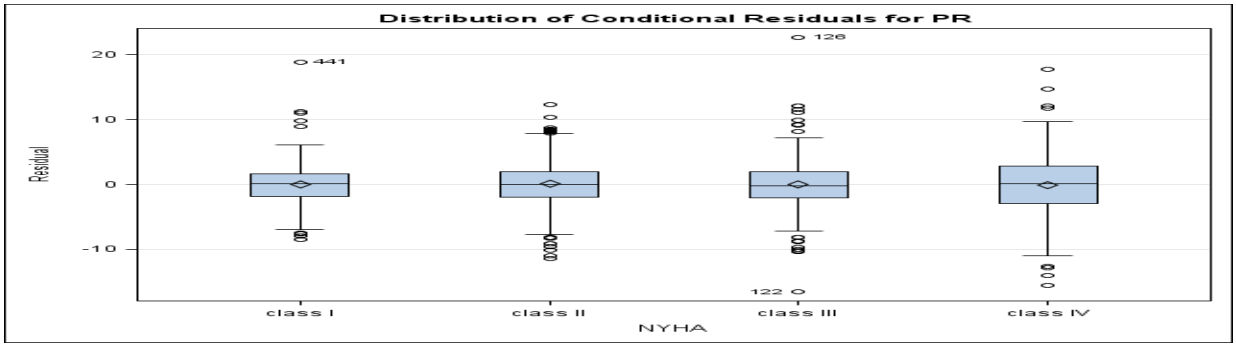


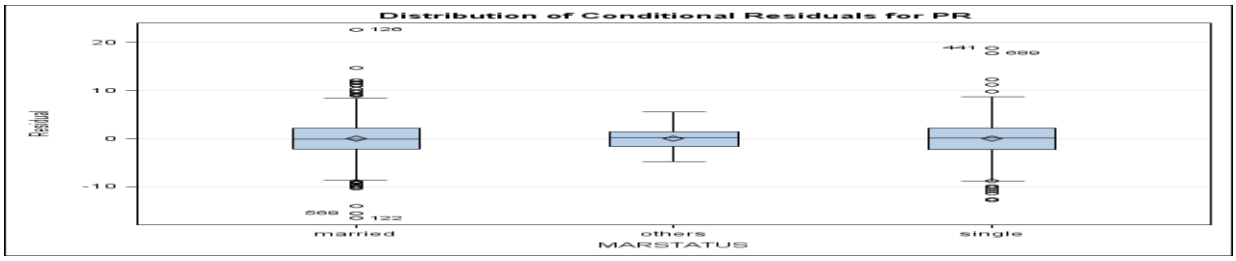
Regression Equation:
PR = 37.14573 + 2.072723*RR

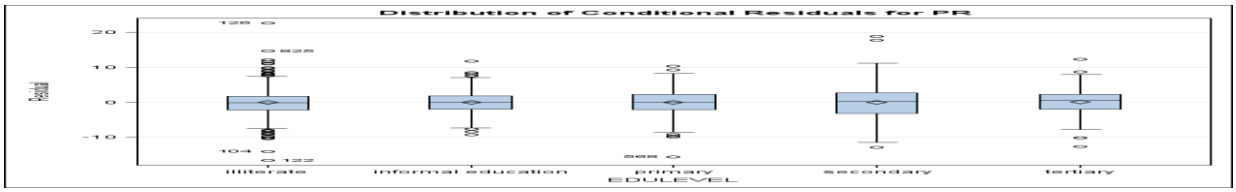


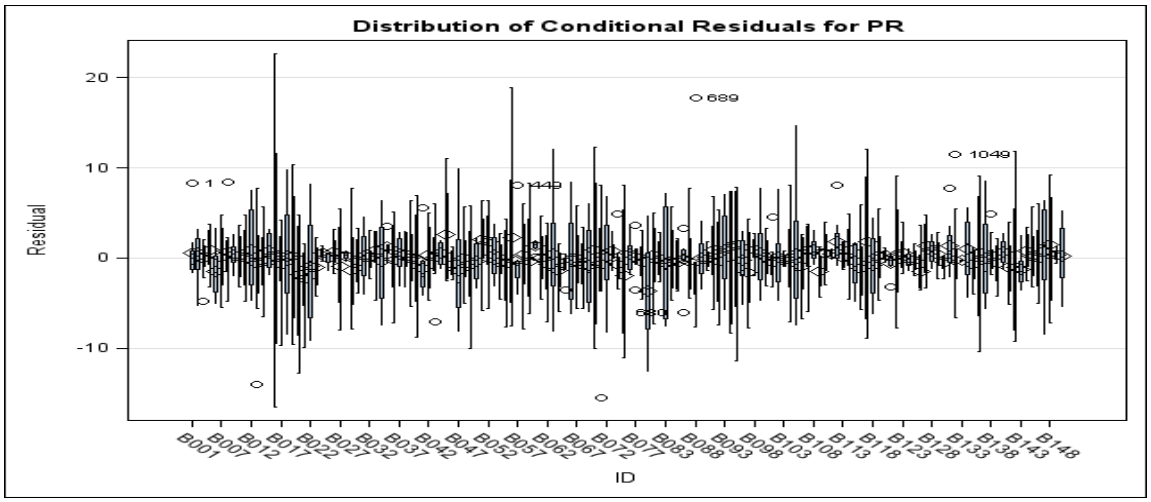

Distribution of Conditional Residuals for PR
Residual
20
10
0
-10
126
441
689
825
104
568
122
biventricular failure
left sided failure
right sided failure
CHFTYPE


Distribution of Conditional Residuals for PR
Residual
ACF
CHD
DIAGH
others
sever Anemia

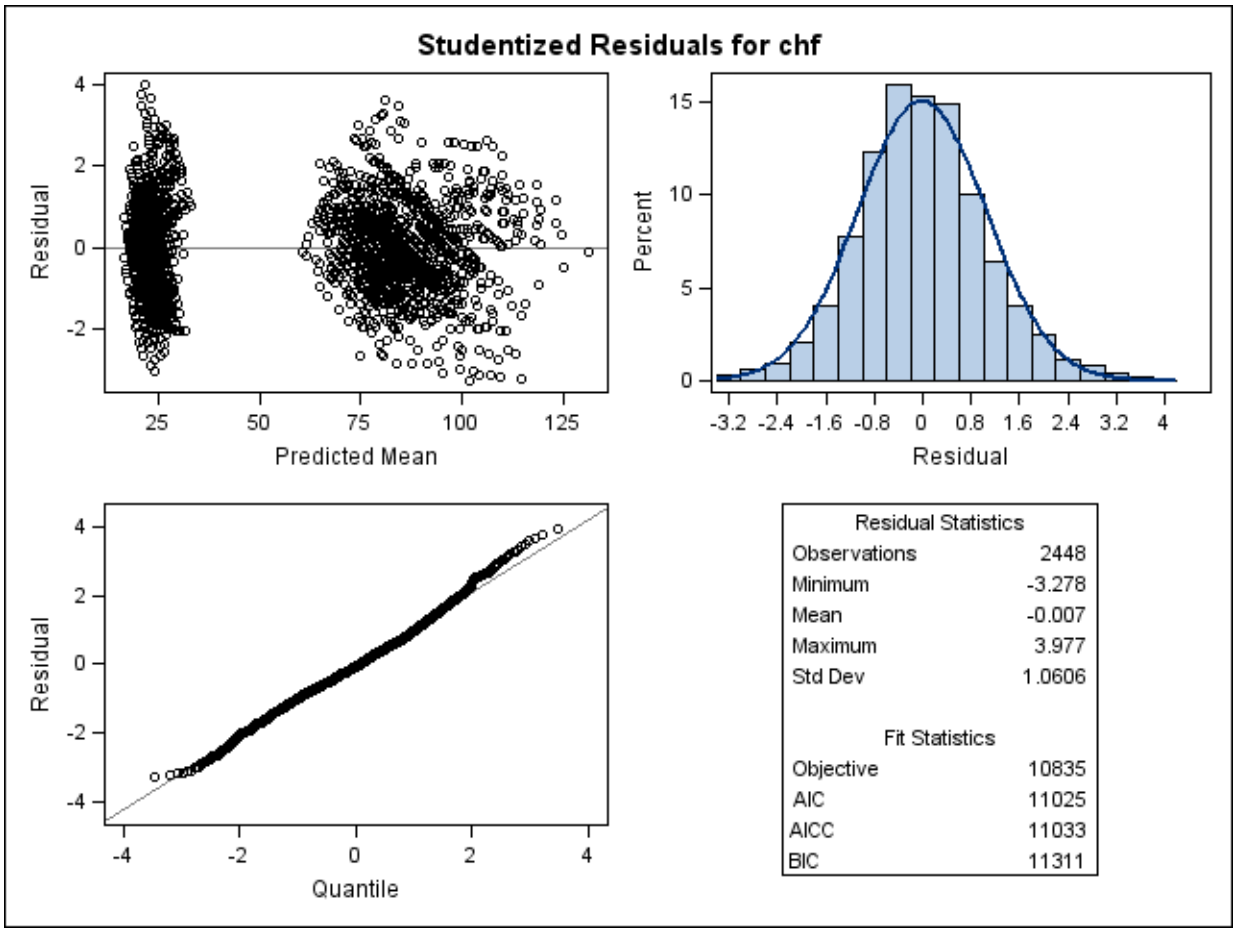

Distribution of Conditional Residuals for PR
Residual
20
10
0
-10
441
126
122
class I
class II
class III
class IV
NYHA


Distribution of Conditional Residuals for PR
Residual
married
others
single
MARSTATUS


Distribution of Conditional Residuals for PR
Residual
illiterate
informal education
primary
secondary
tertiary
EDULEVEL


Distribution of Conditional Residuals for PR
Residual
689
1049
ID


Distribution of Conditional Residuals for PR
Residual
farmer
government employee
merchant
others
OCCUPATION


Studentized Residuals for chf
Residual
Predicted Mean
Percent
Residual
Residual
Quantile
Residual Statistics
Observations 2448
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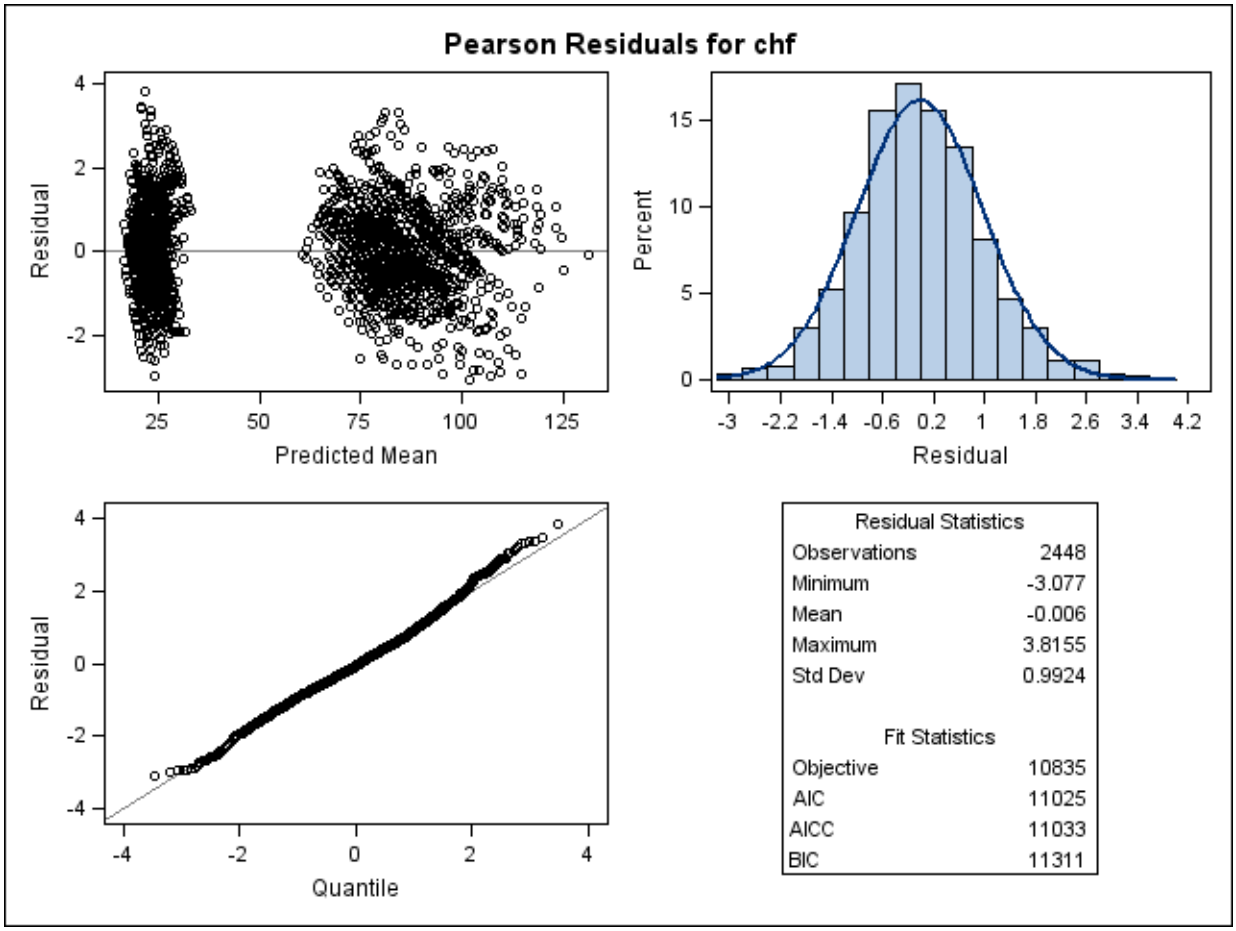
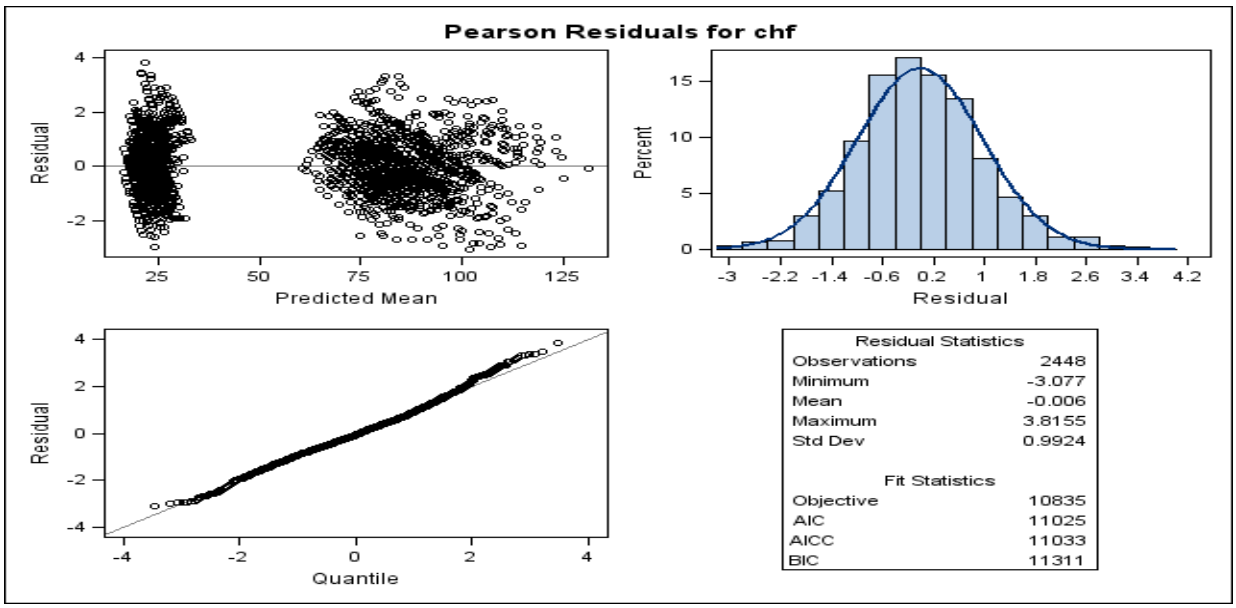
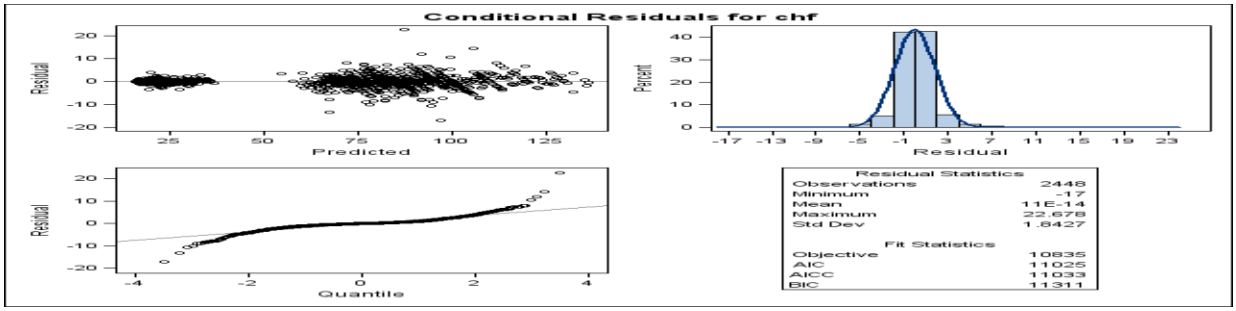
Mean -0.007
Maximum 3.977
Std Dev 1.0606
Fit Statistics
Objective 10835
AIC 11025
AICC 11033
BIC 11311


Pearson Residuals for chf
Residual
Predicted Mean
Percent
Residual
Residual
Quantile
Residual Statistics
Observations 2448
Minimum -3.077
Mean -0.006
Maximum 3.8155
Std Dev 0.9924
Fit Statistics
Objective 10835
AIC 11025
AICC 11033
BIC 11311


Pearson Residuals for chf
Residual
Predicted Mean
Percent
Residual
Residual
Quantile
Residual Statistics
Observations 2448
Minimum -3.077
Mean -0.006
Maximum 3.8155
Std Dev 0.9924
Fit Statistics
Objective 10835
AIC 11025
AICC 11033
BIC 11311


Conditional Residuals for chf
Residual
Predicted
Percent
Residual
Quantile
Residual Statistics
Observations 2448
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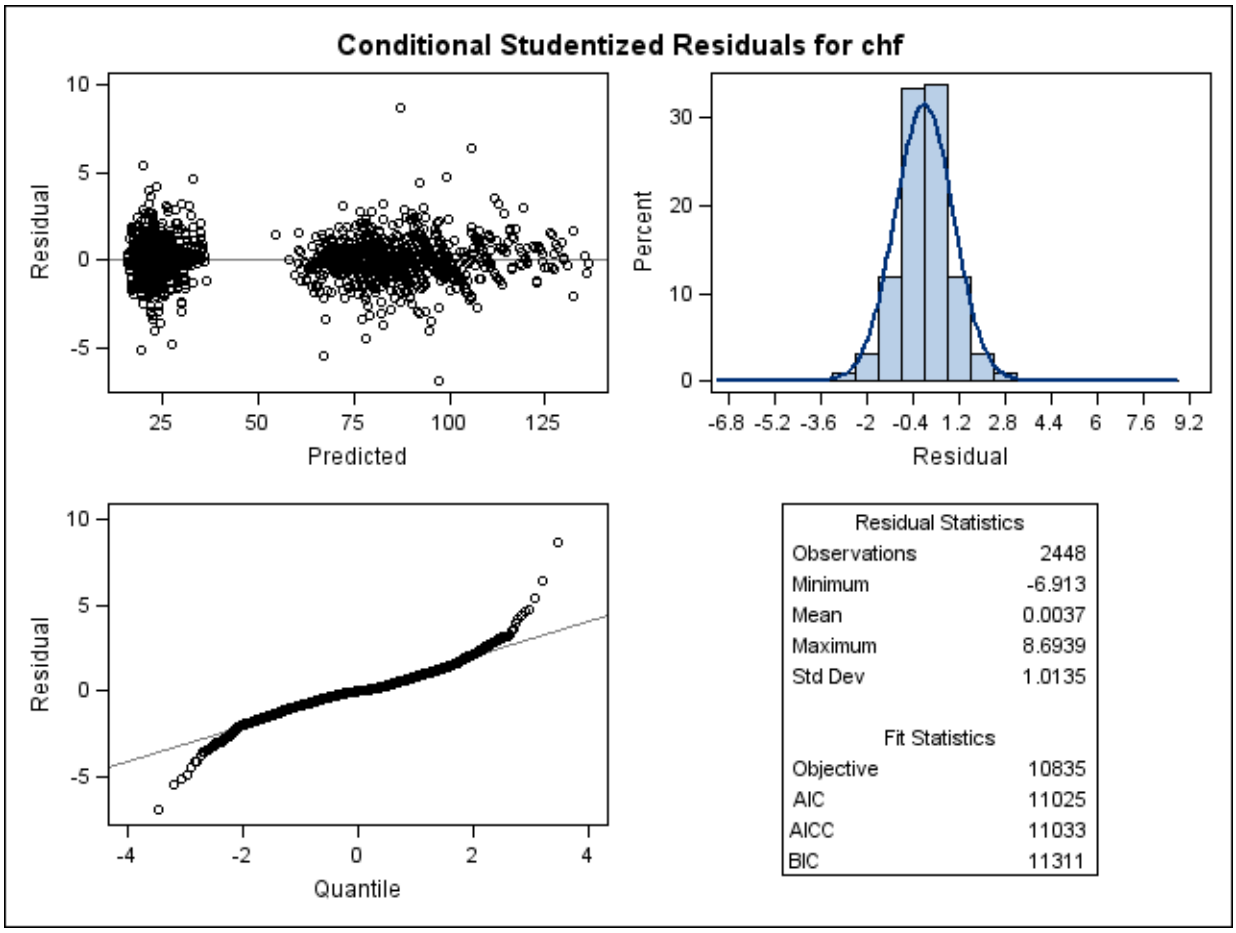
Mean 11E-14
Maximum 22.678
Std Dev 1.8427
Fit Statistics
Objective 10835
AIC 11025
AICC 11033
BIC 11311


Conditional Studentized Residuals for chf
Residual
Predicted
Percent
Residual
Quantile
Residual Statistics
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Std Dev 1.0135
Fit Statistics
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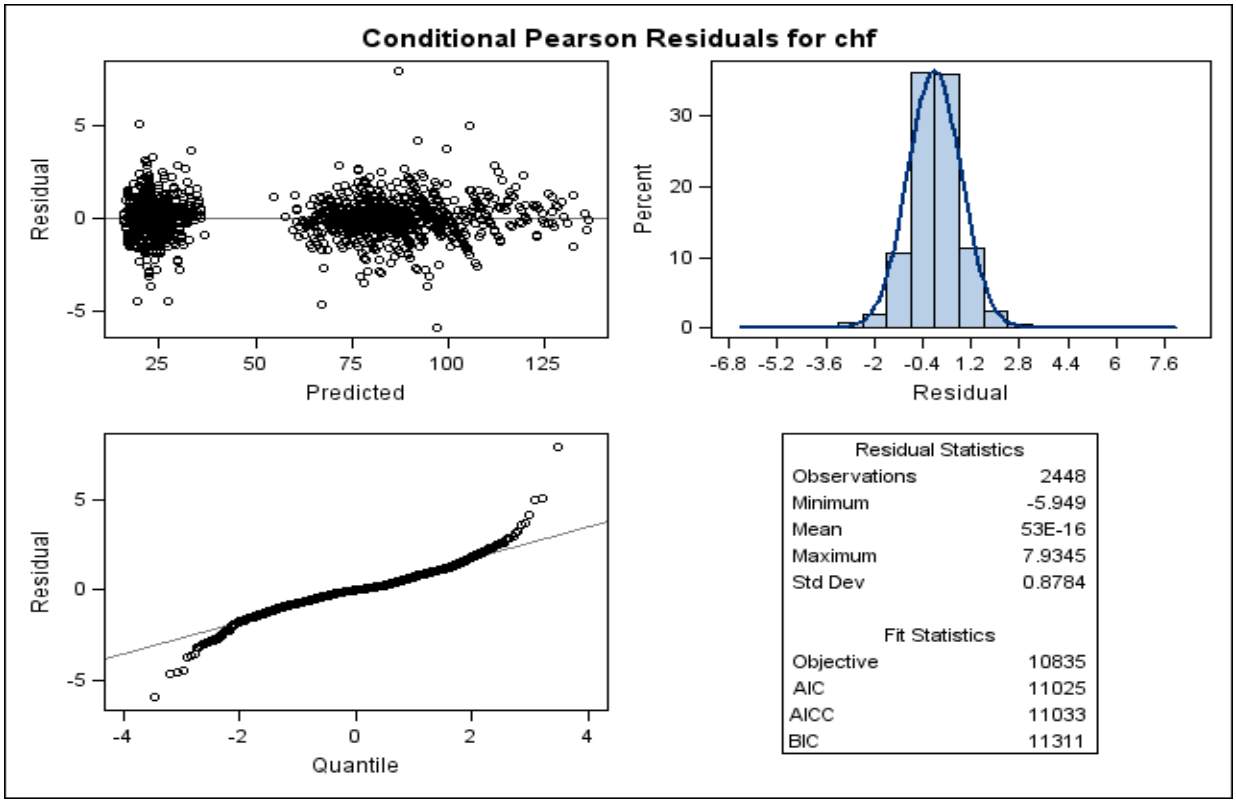
AIC 11025
AICC 11033
BIC 11311


Conditional Pearson Residuals for chf
Residual
Predicted
Percent
Residual
Residual
Quantile
Residual Statistics
Observations 2448
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Fit Statistics
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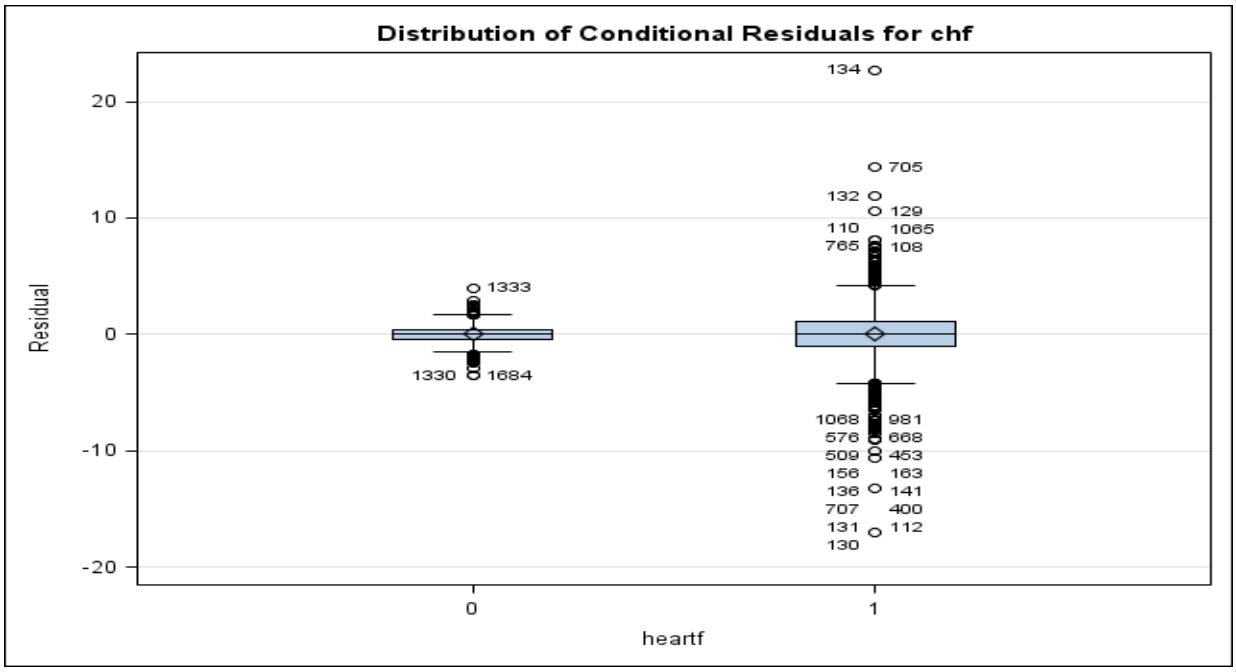
AIC 11025
AICC 11033
BIC 11311


Distribution of Conditional Residuals for chf
Residual
heartf
1333
1330
1684
134
705
132
129
110
1065
765
108
1068
981
576
668
509
453
156
163
136
141
707
400
131
112
130