Modeling of Longitudinal Pulse Rate, Respiratory Rate and Blood Pressure Measurements from Congestive Heart Failure Patients under Follow Up at Tikur Anbessa Specialized Hospital

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Congestive heart failure (CHF) is a chronic condition that happens when the heart’s muscle becomes too damaged to adequately pump the blood around your body. The main objective of this study was to modeling the longitudinal pulse rate, respiratory rate and blood pressure measurements from congestive heart failure patients under follow up at Tikur Anbessa Specialized Hospital. This retrospective cohort study was based on secondary data obtained from Tikur Anbessa Specialized Hospital. Modeling approach of longitudinal data analysis was applied by suing Linear Mixed Models to identify risk factors and to compare efficiency of the models. Fit statistics showed that the joint model resulted in better fit to the data than the separate models, implying a significant association among the two end points. Based on the joint model for SBP, diagnosis history, family history, NYHA class, and time, and for DBP, age, weight, sex, family history, NYHA class, and time are the significant factors, at 5% level of significance. The joint model fitted the data better than the separate models. The result from the joint model suggested a strong association between the evolutions and a slowly increasing evolution of the association between PR and RR also, between SBP and DBP. Thus, fitting joint model is recommended for researches to any types of multivariate response variable together jointly.

Key Words: Joint Modeling; Longitudinal Data Analysis; Linear Mixed Model; Pulse Rate; Respiratory rate; Systolic blood pressure; Diastolic blood pressure; Congestive heart failure

INTRODUCTION

Congestive heart failure (CHF) is not only a personal tragedy for patients and their families but a serious public health burden for society. Patients with CHF have a poorer quality of life and shorter life expectancy compared with those of the same age in the general population (Marieb and Hoehn, 2010).

CHF also known simply as HF. Heart failure is a chronic condition that happens when the heart’s muscle becomes too damaged to adequately pump the blood around your body. If you have heart failure your heart still works but because it is less effective your organs do not get enough blood and oxygen (Kasper and Knudson, 2010).

Heart failure (HF) is a serious worldwide health problem with high re-hospitalization and mortality rates (Koelling et al., 2010). The one-year re-hospitalization rate in patients with HF in the world is about 50% (Johansen et al., 2009). Heart failure affects an estimated 33 million people worldwide, 26.4% of the adult world population, 65.73% in developed and 34.27% in developing countries (Zollikofer, 2010). It has been estimated that by the year, an increase of 60% from the year 2000.

According to the health and health-related indicators of MOH (2014–2015), heart failure was one of the leading causes of death in Ethiopia in 20013(WHO, 2015). In Tikur Anbessa Specialized Hospital (TASH) medical ward to evaluate severity of heart disease showed that CHF was common cause of mortality (26.5%), among those (30%) were males and (70%) were females (Oli k. et al, 2004).

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The Linear Mixed Model (LMM) has become the most commonly used tool for analyzing continuous repeated longitudinal data (Fieuws and Verbeke, 2004).

Longitudinal studies consider both the between-subject and within-subject time-related variations, and provide efficient estimators. It is often possible to address the same, scientific questions with a longitudinal data (McCulloch et al., 2008).

In Ethiopia, to the best of knowledge, there are virtually no published literatures that documented on this area except the studies to assess the common causes of heart failure in Ethiopia based on cross-sectional data. They used multiple linear regression and logistic regression to identify determinants factors, without considering the correlations within the multiple outcomes and subject specific random effects and similar study was also previously done by Yemane Hailu (2014).

The main objective of this study was to modeling the longitudinal pulse rate, respiratory rate and blood pressure measurements from congestive heart failure patients under follow up at Tikur Anbessa Specialized Hospital.

The approach that this study used to build a mixed model methodology allows the longitudinal examination of PR, RR and BP (SBP and DBP) over time. Separate analyses would not be able to examine the correlation or association between the two outcomes. Therefore, it is more desirable to jointly modeling of two outcome variables together.

So, this study addressed that more than two response variables such as PR, RR and BP how the change was over time and what are the factors those accelerate their rates on Congestive Heart Failure Patients.

In general, the motivation behind this study is to address the following major research questions.

i. How does the mean evolution of PR, RR, SBP and DBP of CHF patients change separately over time?

ii. What are the associations of the evolution between PR and RR and SBP and DBP look like over time?

iii. What factors predict the evolution of outcomes variables jointly each other?

MATERIALS AND METHODS

In this study the latest data from retrospective cohort follow up of all congestive heart failure patients whose age is 18 years and above years and who have followed at least two visits from March 2015 to February 2017 in Tikur Anbessa Specialized Hospital were used.

The data consists of 222 individuals (1054 observations) with a minimum of two and maximum of fourteen PR, RR and BP measures and other covariates were considered per individual of CHF patients.

Longitudinal studies and multiple outcomes are common in health area; this research could be used as a basis for future studies on health areas to apply LMM.

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Dependent Variables

Four outcome variables were considered in this study; pulse rate, respiratory rate, systolic and diastolic blood pressure for each individual measured at least two times.

Independent Variables

Seven covariates were used for either the separate or joint analyses. Three of these covariates are continuous while four of them are categorical covariates.

<table>
<thead>
<tr>
<th>NO.</th>
<th>Variable</th>
<th>Description</th>
<th>Value/codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sex</td>
<td>Sex of CHF patients</td>
<td>Male=1, Female=0</td>
</tr>
<tr>
<td>2</td>
<td>Age</td>
<td>Age of CHF patients at the start of Diagnosis in years</td>
<td>Year</td>
</tr>
<tr>
<td>3</td>
<td>Fh</td>
<td>Family history of CHF patients</td>
<td>0=Yes, 1=No</td>
</tr>
<tr>
<td>4</td>
<td>Weight</td>
<td>Weight of CHF patients</td>
<td>Kilograms</td>
</tr>
<tr>
<td>5</td>
<td>NYHA</td>
<td>NYHA class Categories</td>
<td>class I=1, class II=2, class III=3, class IV=4</td>
</tr>
<tr>
<td>6</td>
<td>Time</td>
<td>Observation time of PR, RR, SBP and DBP</td>
<td>monthly Follow up</td>
</tr>
<tr>
<td>7</td>
<td>Diagnosis</td>
<td>Previous diagnosis history</td>
<td>Severe Anemia=0, ACF=1, CHD=2, others=3</td>
</tr>
</tbody>
</table>

Linear Mixed Effect Model

Mixed-effects model is widely used model for the analysis of continuous longitudinal data introduced to model the between-subjects variation and within subject correlation in the data.

It is a popular method to handle both balanced and unbalanced scenarios, and allows the inclusion of covariates.

In mixed-effects models, response variables are assumed to be a function of fixed effect, non-observable random effect, and error term.
Estimation of Separate LMM

Both the maximum likelihood (ML) and restricted maximum likelihood (REML) were used for estimation of the parameters in this study (Verbeke et al., 1998).

\[
\hat{\beta} = \left( \sum_{i=1}^{n} \mathbf{X}' \mathbf{X} \right)^{-1} \sum_{i=1}^{n} \mathbf{X}' \mathbf{y}
\]

Joint model for two continuous outcomes

The mixed-model can be easily extended to include two or more than two response variables by further stacking the data.

In the context of modeling two response variables, the linear mixed-effects model for each response variable for subject j taken at time t can be specified as (Fieuws and Verbeke, 2004):

\[
Y_{1j}(t) = \mu_{1j} + a_{1j}X_1(t) + \varepsilon_{1j}(t)
\]

\[
Y_{2j}(t) = \mu_{2j} + a_{2j}X_2(t) + \varepsilon_{2j}(t)
\]

Joint model also shows how the association between the responses evolves over time

\[
E_{\mathbf{Y}} = \frac{\text{cov}(\mathbf{b}_1, \mathbf{b}_2)}{\sqrt{\text{var}(\mathbf{b}_1)\text{var}(\mathbf{b}_2)}} = \frac{\sigma_{b_1b_2}}{\sqrt{\sigma_{b_1}^2\sigma_{b_2}^2}}
\]

RESULTS AND DISCUSSION

A total of 222 adult congestive heart failure patients (1054 observations) with a minimum of two and maximum of fourteen measures of PR, RR, SBP, DBP and other covariates per individual of CHF patients were included.

Table 1: Frequencies and Percentages for baseline categorical covariates and with their baseline average value and standard deviation of PR, RR, SBP and DBP for each category of congestive heart failure patients’ data.

<table>
<thead>
<tr>
<th>No</th>
<th>Variable</th>
<th>Categories</th>
<th>n(%)</th>
<th>Baseline PR Mean(St.d)</th>
<th>Baseline RR Mean(St.d)</th>
<th>Baseline SBP Mean(St.d)</th>
<th>Baseline DBP Mean(St.d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gender</td>
<td>Male</td>
<td>107 (48.2%)</td>
<td>113.673 (29.532)</td>
<td>23.813 (8.024)</td>
<td>141.972 (43.213)</td>
<td>81.505 (24.449)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>115 (51.8%)</td>
<td>114.278 (28.597)</td>
<td>22.287 (7.377)</td>
<td>133.330 (43.290)</td>
<td>81.191 (24.280)</td>
</tr>
<tr>
<td>2</td>
<td>NYHA</td>
<td>Class I</td>
<td>28 (12.6%)</td>
<td>117.786 (20.267)</td>
<td>20.250 (3.807)</td>
<td>106.429 (21.755)</td>
<td>72.607 (21.843)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class II</td>
<td>49 (22.1%)</td>
<td>115.592 (28.394)</td>
<td>26.939 (8.409)</td>
<td>157.265 (52.146)</td>
<td>81.306 (22.421)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class III</td>
<td>115 (51.8%)</td>
<td>115.365 (32.567)</td>
<td>21.20 (6.798)</td>
<td>142.252 (41.966)</td>
<td>85.965 (26.861)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class IV</td>
<td>30 (13.5%)</td>
<td>102.533 (18.852)</td>
<td>26.200 (9.193)</td>
<td>115.966 (17.682)</td>
<td>71.833 (11.736)</td>
</tr>
<tr>
<td>3</td>
<td>diagnosis history</td>
<td>Severe Anemia</td>
<td>55 (25.8%)</td>
<td>113.873 (29.354)</td>
<td>22.855 (8.066)</td>
<td>134.000 (40.040)</td>
<td>88.418 (24.722)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACF</td>
<td>53 (23.7%)</td>
<td>113.563 (30.829)</td>
<td>24.273 (8.376)</td>
<td>139.454 (46.316)</td>
<td>83.400 (26.668)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHD</td>
<td>37 (16.7%)</td>
<td>115.595 (28.693)</td>
<td>21.946 (7.352)</td>
<td>153.324 (36.482)</td>
<td>86.676 (24.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td>75 (33.8%)</td>
<td>113.587 (28.016)</td>
<td>22.760 (7.141)</td>
<td>130.813 (45.305)</td>
<td>72.013 (18.992)</td>
</tr>
<tr>
<td>4</td>
<td>Family history</td>
<td>No</td>
<td>102 (45.9%)</td>
<td>113.206 (29.597)</td>
<td>23.461 (8.074)</td>
<td>131.402 (37.227)</td>
<td>86.049 (23.469)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>120 (54.1%)</td>
<td>114.650 (28.566)</td>
<td>22.650 (7.412)</td>
<td>142.675 (47.522)</td>
<td>77.341 (24.384)</td>
</tr>
</tbody>
</table>

Source: TikurAnbessa Specialized Hospital, Ethiopia; from March, 2015 to February, 2017.
The variability of PR between individuals seems higher at baseline and appears to decrease over time. There is high variability of PR between and within CHF patients. The variability of RR between individuals seems higher at baseline and appears to decrease over time. There is high variability of RR between and within CHF patients.

**Figure 1:** Individual profile plot of Pulse Rate and Respiratory Rate

**Figure 2:** Individual profile plot of Systolic and Diastolic blood Pressure.

**Figure 3:** Mean profile plot of PR and RR of congestive heart failure patients
Figure 4: Mean profile plot of SBP and DBP of congestive heart failure patients.

It indicates PR shows a decreasing pattern over time. The loess smooth curve suggests that the average profile of the PR has a linear relationship over time. It indicates RR shows a decreasing pattern over time. The loess smooth curve suggests that the average profile of the RR has a relationship over time.

Separate Linear Mixed Model Analysis of PR, RR, SBP and DBP

The final linear mixed model for PR is given by:

$$PR_t = 108.70 + 0.289 \times t - 7.967 \times NCII_t - 7.660 \times NCIII_t - 0.176 \times A_t - 0.288 \times T_t - 0.04 \times 2.091 \times NCII_t \times T_t + 1.109 \times NCIV_t \times T_t + (a_{10} + b_{11}) \times T_t + \varepsilon_t$$

By following the same procedure as separate analysis of PR and RR the final linear mixed model for SBP and DBP with small number of parameter, which is given by:

$$SBP_t = 123.02 + 0.262 \times CHD_t + 15.50 \times NCII_t + 12.94 \times NCIII_t - 11.54 \times NCIV_t - 0.89 \times T_t - 2.52 \times DCHD_t \times T_t - 0.76 \times NCII_t + 7.85 \times NCIII_t + 2.51 \times NCIV_t + 0.89 \times CHD_t + (a_{20} + b_{21}) \times T_t + \varepsilon_t$$

$$DBP_t = 89.04 + 0.53 \times Sex_t + 4.98 \times FH_t + 0.27 \times wt_t - 6.9 \times NCII_t + 9.01 \times NCIII_t - 0.65 \times Age_t - 0.89 \times T_t + 0.66 \times DCHD_t + (a_{30} + b_{31}) \times T_t + \varepsilon_t$$

Joint Analysis of PR and RR

This model is the same as the separate model, except the sets of random intercepts and slopes for each response are now correlated rather than independent.

Table 2: Parameter estimates and standard errors for the joint linear mixed effects models of the PR and RR and SBP and DBP outcomes for the final model
INTERPRETATION AND DISCUSSION

The estimated parameter for intercept of PR is 108.11 with standard error of 6.21 represents an estimate of the average level of PR during the first follow up time. The estimated parameter for intercept of RR is 20.104 with standard error of 1.550 represents an estimate of the average level of RR at time zero.

Here, the result shows the variable weight and the interaction term NYHA class by time are identified as positively associated with change in PR, but time, age and NYHA class are negatively associated with PR. Weight and the interaction term NYHA class by time are identified as positively associated with change in RR, but time, NYHA class and age are negatively associated with the change in RR.

A parameter estimate age for both PR and RR indicates a one-year increase in age was associated with a normal decrease of -0.12(SE=0.020) in PR and a normal decrease of -0.02(SE=0.012) in RR. A unit increase in time was associated with -0.21 rate of decreasing on PR and -0.10 rate of decreasing on RR. The estimated parameter for intercept of SBP is 123.02 with standard error of 2.904 represents an estimate of the average level of SBP during the first follow up time 89.78 is the estimated parameter for intercept of DBP with standard error of 5.95 represents an estimate of the average level of DBP at time zero.

In separate linear mixed model analysis, the response variables pulse rate, respiratory rate, systolic and diastolic blood pressure was carried out. Before fitting the linear mixed model separately for each out comes, exploring the data analysis have been explored to understand the data structure and determine the relevant modeling approaches. From individuals profile plot, we observed the existence of variability in PR, RR, SBP and DBP within and between individuals.

The exploratory analysis result for mean structure (loess smooth curve) also suggested that on average, PR, RR, SBP and DBP measures slightly decreasing in a linear pattern over time, but the rate of decreasing is high in SBP than DBP. This supports the results of Tomeckova and Stanovska (2002), who found that the average values of BP in CHF patients at the end of the study was lower compared to the entry.

Results of the joint model in this study suggested a strong association between the evolutions of PR and RR. This result is supported by Edwards and Fisher (2008); they showed strong association between repeated PR and RR outcomes.

Some of the findings from joint linear mixed model by Chenglin et al., (2014) support these results, who identified age and previously diagnosed CHF were positively associated with change in PR, but sex was insignificant for PR.

The joint model also suggested a slowly increasing evolution of the association over time. In fact, there was no evidence in the literature of estimates for the AOE of PR and RR for CHF patients. But findings of John (2007) used the same model, who found a strong association between the evolutions and a slowly increasing evolution of the association between PR and RR over time for children ages two through eighteen.

Furthermore, the additional information gained by incorporating information about the correlations between the responses was able to reduce the variability (standard errors) in both the fixed-effects estimates as well as the random-effects estimates. Such result is consistent with the previously published data on CHF measurements (Hai and Wanzhu, 2012) using semi-parametric mixed model.

CONCLUSION

The parameter estimates for both separate and joint analyses are consistent or all most the same. The joint model fitted the data better than the separate model. Moreover, on average PR, RR, SBP and DBP measures decreases in a linear pattern over time after patients initiated anti- hypertensive drugs.

Based on separate analysis; the evolution of PR and RR measures were significantly differing with respect to time, weight, NYHA class, baseline age and time interaction with weight and time interaction with NYHA class of CHF patients.

RECOMMENDATION

Further studies are required to see the progression of PR, RR, SBP and DBP altogether with the necessary variables. Governmental and non-governmental body gives awareness for health workers to record all the necessary variables during follow up time.

Fitting joint model is recommended for researches to any types of multivariate response variable together jointly.

LIST OF ACRONYMS

BP: Blood Pressure;
CHF: Congestive heart failure;
DBP: Diastolic Blood Pressure;
HF: Heart failure;
LMM: Linear Mixed Effects Models;
NYHA: New York Heart Association;
PR: Pulse rate;
RR: Respiratory rate;
SBP: Systolic Blood Pressure;
TASH: Tikur Anbessa Specialized Hospital.
Declaration of Compliance with Ethical Standards

Ethical approval: All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee.

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