To mum, my brothers and Stephen
To the memory of my late dad

Declaration

This is to certify that this report was written by Stellah Mutua under our supervision.

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Acknowledgment

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Secondly would like to thank my supervisor Dr. Edmund Njeru Njagi, and my co-supervisors: Prof. Dr. Geert Molenberghs, Prof. Dr. Dimitris Rizopoulus and Prof. Dr. Paul Dendale for their insightful guidance, postive criticism and motivation during the course of this project. Dr. Njagi, I appreciate the various meetings we had and your invaluable guidance throughout .

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Stellah Mutua
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Abstract

Telemonitoring involves wireless technology for remote follow-up, where daily patient's measurements of biomarkers such as weight, heart rate, and blood pressure, are transimitted wirelessly to a server where they can be stored, reviewed, and analyzed by the clinicians. To manage heart failure , clinicians use these measurements to predict rehospitalization, so that intervention decisions can be made. This is important for clinical practice due to high rehospitalization rate in heart failure patients. In this project, we explore the relationship between the risk of rehospitalization and different features of the biomarkers. These features are expressed through different parameterizations. Such an exploration is important in the sense that more appropriate parameterizations will "more readily" reveal the true predictive ability of the biomarker. In Chronic Heart Failure data, the best parameterization was time dependent slopes for both weight and systolic blood pressure whereas the cumulative effect parameterization produced the best fit for diastolic blood pressure. For heart rate, the current value parameterization had the best fit.

1. Introduction

In clinical studies, patients are followed over a period of time and biomarkers are repeatedly collected at multiple time points. Besides the data can include the time when an event of particular interest occurred, eg., relapse of a disease, rehospitalization or death. The reasearch question in such studies often require separate analyis of recorded outcomes, but in many occassions interest may lie in studying the association of the biomarker and time-to-event [10]. When the interest is on the latter case, then joint modelling of the longitudinal and time-to-event framework is adopted. For example, the CD4+ lymphocyte count or the viral RNA (viral load) and AIDS or death in HIV studies, cognitive performance and survival in geriatric studies, systolic blood pressure and a coronary event, prostate-specific antigen biomarker and prostate cancer recurrence, and hemoglobin level and survival in type 2 diabetes [1]–[5].

The joint modelling field has evolved in the recent past, with one of the interests being dynamic predictions for either the survival or the longitudinal outcome. The quality of this prediction typically depends on two factors; first, on the capability of the longitudinal marker itself in predicting future events i.e the biological mechanism that the marker attempts to describe, and how strongly this mechanism is related to the event of outcome. Secondly, the correct formulation of the joint model to reveal the true predictive performance of the marker [10]. The second factor calls for different parameterizations which entail different assumptions about the dependence of the risk on different features of the biomarker. For example, the risk could depend on current/ previous, slope or the entire summary history of the biomarker. Besides the risk could be different in different patient subgroups due to the fact that the biomarker is different in those subgroups. Therefore it is important to find out the best formulation of the biomarker that determines the risk and fits the data well.

Heart failure (HF) develops when the pumping or the relaxing action of the heart is inadequate, typically because the heart muscle is weak, stiff, or both. As a result, blood may not flow out in adequate amounts [15] to cater for body needs. In response, the body initiates a mechanism to compensate for heart failure. The mechanism may help the body adjust to the effects of heart failure in the short term. But over time, for instance the kidneys may respond by causing the body to retain fluid (water) and salt. This may lead to recurrent hospitalization of the patient due to fluid overload and/or worsening of renal function [6]. The fluid accumulation may lead to weight gain and if proper treatment is given it may lead to loss of weight. Therefore it is important for HF patients to monitor their weight on daily basis[16]. The heart compensates for its pumping power by beating faster (tachycardia) in order to keep the same flow of blood around the body. This increased heart rate sometimes is irregular and therefore it's important to monitor

the heart rate daily [16]. Besides weight and heart rate, it's advisable for clinician to monitor systolic and diastolic blood pressure of HF patient for hypertension (abnormally high blood pressure) or hypotension (abnormally low blood pressure). Systolic blood pressure is the maximum arterial pressure during contraction of the left ventricle of the heart, while diastolic blood pressure can be defined as the minimum arterial pressure during relaxation and dilation of the ventricles of the heart when the ventricles fill with blood.

According to American Heart Association (AHA), HF is the primary diagnosis in more than one million hospitalizations annually. Patients hospitalized for HF are at high risk for rehospitalization, with a one month readmission rate of 25%. In 2013, physician office visitis for HF cost $1.8 billion. The total cost of HF care in the United States exceeds $30 billion annually, with over half of these costs spent on hospitalization [16].

Telemonitoring has been found to improve the care for HF patients [6]. It involves wireless technology for remote follow-up, where daily patient's measurements of biomarkers such as weight, heart rate, and blood pressure, are transimitted wirelessly (via a telephone line, a mobile phone, or a computer) to a server where they can be stored, reviewed, and analyzed by the research team.

The aim of this paper is to explore the relationship between risk of first rehospitalization and different features of biomarkers in Chronic Heart Failure (CHF) patients. These features are expressed through different parameterization. Such an exploration is important in the sense that more appropriate parameterizations will "more readily" reveal the true predictive ability of the biomarker. The choice of a time-dependent covariate involves the choice of a functional form for the time-dependence of the covariate. This choice is usually not self-evident but may be suggested by biological understanding or biological hypothesis [11]. For instance, considering only the current value of a time-varying covariate to be associated with the risk of rehospitalization may miss more complex forms of association between the longitudinal marker and the survial outcome leading to incorrect conclusion [10].

1.1 Data

The data originated from a study conducted in Belgium from the year 2008 to 2010, to determine whether follow-up of CHF patients by means of a telemonitoring programme reduced mortality and rehospitalization rates. 80 patients discharged from the hospital with a sufficient cognitive function to understand the aims of the study were followed for

six months. These patients were given monitoring devices upon discharge, to remotely transmit their daily measurements of systolic blood pressure (sbp), heart rate (hr), weight and diastolic blood pressure (dbp) to a central computer where they could be stored, reviewed and analysed by clinicians. The measurements were recorded every day at a fixed hour in the morning for a period of 6 months. Sixteen patients got rehospitalized at least once during the study period.

Before discharge from hospital, patient's baseline characteristics where recorded. This included: gender (sex), age, heart rhythm, cardiac muscle fibre stretch measured through NTproBNP, patients fitness indicator (given using the New York Heart Association (NYHA) score indicator) and the left ventrical ejection fraction (LVEF), which is a measure of heart performance .

2. Methodology

2.1 Exploratory Data Analysis

The CHF data consisted of two outcomes types: multivariate longitudinal (weight, heart rate, systolic and diastolic blood pressure) and time-to-rehospitalization. The subject-specific profiles, mean and variance structures were explored in the same way for all the biomaker. For the weight variable, the mean structure was explored by plotting lowess smoothed averaged observed weight for all patients and sub-populations (baseline patient characteristics) in CHF data. Average squared residuals over time were used to explore variance structure. Random samples of lowess smoothed individual profiles were plotted to explore the variability between and within individual patients. The average evolution describes how the profiles evolve over time and it is useful in order to select a fixed-effects structure for the linear mixed model of patients trajectories. In addition to the average evolution, the evolution of the variances is important to build an appropriate longitudinal model[17].

In order to gain insights of time to first rehospitalization, Kaplan-Meier curves were plotted for the baseline covariates (heart rhythm, NYHA, gender, LVEF and age). The distribution of the number of events each month was also explored. This was important in gaining insights of how risk varied over time and also in determing breakpoints of piecewise constant model baseline hazard. This baseline hazard allows risk to be constant at a given time interval [18].

2.2 The Joint Model

Joint modelling is used to estimate the association between survival and endogenous time-dependent covariate. It is important to differentiate between two time-dependent covariates (exogenous and endogenous). Exogenous covariates are predictable, their complete path can be determined before the study begins and are external to the subject under study. Examples may include seasonal patterns and air pollution. The longitudinal outcomes (biomarkers) are also referred as endogenous time-dependent covariates in survival modelling framework. Important features of these covariates are: (1) they require survival of the patient for them to exist, (2) they are measured with error and (3) their complete path up to any time t is not fully observed i.e the marker of the patient is only known at days when the patients provides the measurements [10]. The joint modelling of longitudinal and time-to-event data therefore takes into account these special features of the endogenous covariates and consists of survival and longitudinal submodels.

For the i^{th} patient, let T_i be the observed event time, T_i=min(T_i^*, C_i), with T_i^* the true event time, and C_i the censoring time. The survival submodel is written as follows:

$$h_i(t|\mathcal{M}_i(t), \mathbf{w_i}) = h_0(t) \exp\{\boldsymbol{\gamma}^T \mathbf{w_i} + \alpha m_i(t)\} \tag{2.2.1}$$

Where $\mathcal{M}_i = m_i(s), 0 \leq s < t$ is the history of the true unobserved longitudinal process up to time point t, $h_0(.)$ is the baseline risk function and α is the parameter representing the longitudinal effect on hazard. Similary, $\mathbf{w_i}$ is a vector of baseline covariates associated with parameter vector $\boldsymbol{\gamma}$. The risk for an event at time t therefore depends on the baseline hazard, baseline covariates and the true value of the longitudinal covariate at that time. The risk ratio associated with unit changes of baseline covariates is given by $\exp(\boldsymbol{\gamma})$ and the relative change in the risk for a unit change in the true value of the longitudinal covariate (biomarker) is $\exp(\alpha)$ [9].
The survival function is given by:

$$\mathcal{S}i(t|\mathcal{M}_i(t), \mathbf{w_i}) = exp\,(-\int_0^t h_0(s) \exp\{\boldsymbol{\gamma}^T \mathbf{w_i} + \alpha m_i(s)\} ds\,) \tag{2.2.2}$$

which implies that the function depends on the whole covariate history $\mathcal{M}_i(t)$. However, the biomarker measurements are collected intermittently and with error at time points t_{ij}, $j = 1, ..., ni$, for patient i.

The baseline hazard $h_0(.)$ in standard survival model is sometimes left unspecified to avoid incorrect specification of the distribution of survival times. However, if the same is done in joint modelling may lead to an underestimation of parameter estimates' standard errors [10]. Therefore, $h_0(.)$ was assumed to follow Weibull distribution or piecewise-constant (PC) model. One of the key issue with the PC model is determining the appropriate

number of time intervals to be used. Although any number of time periods can be chosen, it is important to strike a balance between flexibility and parsimony. A key requirement when choosing the number of time periods is that there should be units that experience the event within each of the different time intervals. If this is not the case, it is difficult to obtain reliable parameter estimates [18] [19]. The Weibull hazard is given by:

$$h_0(t) = \rho t^{\rho-1} \exp\{\gamma_0\}$$

Where ρ is the shape parameter and $\exp(\gamma_0)$ is the scale parameter. Note that if $\rho < 1$, the hazard is decreasing and if $\rho > 1$ the hazard is increasing in t. When $\rho = 1$, the hazard is a constant resulting to an exponential distributed survival time.
The piecewise-constant hazard on the other hand is given by

$$h_0(t) = \sum_{q=1}^{Q} a_q I(v_{q-1} < t \leq v_q)$$

where $0 = v_0 < v_1 < ... < v_Q$ denotes a split of the time scale, with v_Q being the largest observed time. a_q denotes the hazard in the interval $(v_{q-1}, v_q]$ and should be estimated from the data. The advantage of piecewise constant model compared to Weibull parametric is that; standard errors can be estimated directly from asymptotic maximum likelihood and is more flexible in describing changes in the shape hazard function rather assuming a monotonic shape hazard [10] [21].

For the longitudinal outcome, the unobserved true value of the i^{th} patient is assumed to be related with the observed value $y_i(t)$ through the following submodel:

$$y_i(t) = m_i(t) + \varepsilon_i(t) = \mathbf{X_i}^T(t)\boldsymbol{\beta} + \mathbf{Z_i}(t)\mathbf{b_i} + \varepsilon_i(t), \tag{2.2.3}$$

where $\varepsilon_i(t) \sim N(0, \sigma^2)$ and $\mathbf{b_i} \sim N(0, D)$. $\mathbf{X_i}$ and $\mathbf{Z_i}$ are design matrices for the fixed effects $\boldsymbol{\beta}$ and random effects $\mathbf{b_i}$ vectors respectively. The measurement error $\varepsilon_i(t)$ is assumed to be independent of the random effects $\mathbf{Z_i}$. The equation is a linear mixed model which accounts for measurement error problem by postulating that the observed level of longitudinal outcome $y_i(t)$ comprises of true value $m_i(t)$ contaminated by a random error term $\varepsilon_i(t)$. If observations are taken on daily basis, it is difficult to disregard autocorrelation. However, it is difficult to impliment a model with both random-effects and autocorrelation term [13] therefore random-effects model was preferred due to its computational ease in implementation. By fitting the linear mixed submodel the true biomarker value is estimated and the complete patient's longitudinal history $\mathcal{M}_i(t)$ is reconstructed [10].

The likelihood method is a widely used approach for the parameter estimation in the joint model [10] [13]. In defining the joint distribution, we assume the vector of time-dependent random effects $\mathbf{b_i}$ is shared by both the longitudinal and survival process i.e the random effects account for both the association between the longitudinal and event outcomes, and the correlation between the repeated measurements in the longitudinal process [10]. Assumming that the censoring, timing, and measurement processes depend only on the observed history and latent random effects and not on the future event time itself [13], the likelihood contribution of the i^{th} patient is:

$$f(T_i, \delta_i, \mathbf{y_i}; \boldsymbol{\theta}) = \int (T_i, \delta_i | \mathbf{b_i}; \boldsymbol{\theta}) \Big[\prod_j f\{\mathbf{y_i}(\mathbf{t_{ij}}) | \mathbf{b_i}; \boldsymbol{\theta}\} \Big] f(\mathbf{b_i}; \boldsymbol{\theta}) d\mathbf{b_i},$$

where $\boldsymbol{\theta}$ is the parameter vector, $\mathbf{y_i}$ is a $(n_i \times 1)$ vector of longitudinal response for the i^{th} patient, $\delta_i = I(T_i^* \leq C_i)$ is the event indicator. The likelihood funcion is given by

$$f(T_i, \delta_i | \mathbf{b_i}; \boldsymbol{\theta}) = \big[h_0(T) \exp\{\boldsymbol{\gamma}^T \mathbf{w_i} + \alpha m_i(T)\} \big]^{\delta_i} exp\Big(- \int_0^t h_0(t) \exp\{\boldsymbol{\gamma}^T \mathbf{w_i} + \alpha m_i(t)\} dt \Big)$$

2.3 Different Parameterizations

Assuming the association between risk of an event to be dependent only on the current value of a time-varying covariate may miss some complex forms of the association [10] and lead to incorrect conclusions. The choice of a time-dependent covariate involves the choice of a functional form for the time-dependence of the covariate. This choice is usually not obvious but can be found by understanding the biological mechanism of the biomarker [11]. The different parameterization are special cases of the general formulation of the following survival submodel .

$$h_i(t) = h_0(t) \exp\big[\gamma^T \mathbf{w_{i1}} + f\{m_i(t-c), b_i, \mathbf{w_{i2}}; \alpha\} \big] \tag{2.3.1}$$

Where f(.) is a function of the true marker value $m_i(.)$ depended on the random effects b_i and extra covariates $\mathbf{w_{i2}}$.

2.3.1 Interaction Effects Parameterization

We assume the longitudinal marker behaves differently in patients subgroups. To achieve this parameterization an interaction term between the marker and a categorical baseline covariate is included. The resulting model was:

$$h_i(t | \mathcal{M}_i(t), \mathbf{w_i}) = h_0(t) \exp\big[\boldsymbol{\gamma}^T \mathbf{w_i} + \boldsymbol{\alpha}^T \{k_i \times m_i(t)\} \big] \tag{2.3.2}$$

Where k_i is categorical baseline covariate that expand the association of $m_i(t)$ in the different subgroup, everything else defined as in 2.2.1.

2.3.2 Lagged Effects Parameterization

This parameterization assumes that, the risk at time t depends on the true longitudinal marker at time t-c. The model is given by

$$h_i(t|\mathcal{M}_i(t), \mathbf{w_i}) = h_0(t) \exp\left[\boldsymbol{\gamma}^T \mathbf{w_i} + \alpha m_i\{max(t-c, 0)\}\right] \tag{2.3.3}$$

where c is the time lag of interest.

2.3.3 Time-Dependent Slopes Effects Parameterization

The parameterization assumes that, the risk of rehospitalization depends on both the current true value of the trajectory and the slope of the true trajectory at time t [10] . The relative risk survival submodel is given by:

$$h_i(t) = h_0(t) \exp\left\{\boldsymbol{\gamma}^T \mathbf{w_i} + \alpha_1 m_i(t) + \alpha_2 m_i{}'(t)\right\} \tag{2.3.4}$$

$$m_i{}'(t) = \frac{d}{dt} m_i(t) = \frac{d}{dt}\{\mathbf{X_i}^T(t)\boldsymbol{\beta} + \mathbf{Z_i}(t)\mathbf{b_i}\}$$

where parameter α_1 is interpreted as in equation 2.2.1 while α_2 parameter measures the association of true longitudinal trajectory slope at time t and risk of the event, provided $m_i(t)$ is constant. This parameterization is useful when two patients show similar true marker levels, but differ in the rate of change of the marker [10].

2.3.4 Cumulative Effect Parameterization

Here, the whole history of the marker is assumed to be associated with the risk of an event. The survival submodel written as:

$$h_i(t) = h_0(t) \exp\left\{\boldsymbol{\gamma}^T \mathbf{w_i} + \alpha \int_0^t m_i(s) ds\right\} \tag{2.3.5}$$

Where α measures the association between the the risk of an event at time t, with the area under the longitudinal trajectory which is regarded as the whole trajectory [10].

2.4 Software

Exploratory data analysis was done using SAS version 9.3 and R while while statistical modelling was done using JM package [12] in R version 3.0.2.

3. Results

3.1 Exploratory Data Analysis

In total there were 80 patients as shown in Table 1. 30 (37.50%) were females and 7 of them were rehospitalized. 36 (45%) patients had normal heart rhythm and 7 of them were rehospitalized. In total 16(20%) patients were rehospitalized. The mean age at baseline was about 76 years (sd=9.7). The dbp and sbp range was 31-123 and 74-205 respectively. The heart rate ranged between 40 and 134 while weight (measured in $Kg \times 10$) ranged from 350.5 to 1478. The baseline cardiac muscle fibre stretch was highly variable with a mean of 70.787 and a sd of 588.265 as shown on Table 1. The NYHA score at baseline was also explored, 5 (6.25%) patients were classified to score 2 , 14 (17.5%) to score 2.5, 34 (42%) to score 3, 21 (26.25%) to score 3.5 and 6 (7.5%) score 4.

Table 1: *CHF data. Varible distribution, heart rhythm of 0=normal, 1=not normal and status; 0= not rehospitalized and 1= rehospitalized*

	continuous variable					Discrete varible		Status	
variable	Mean	Std Dev	Min	max	variable	group	No. of Patient (%)	1	0
Diastolic blood pressure			31	125	Sex	female	30 (37%)	6	24
Systolic blood pressure			74	205		Male	50(62.50%)	10	40
Heart Rate			40	134	Heart rhythm	0	44(44%)	7	37
NTproBNP	4993.22	6835.61	16	37690		1	36(45%)	9	27
LVEF	35.575	15.452	12.5	80	NYHA score	2	5 (6.25%)		
Age	75.875	9.679	46	95		2.5	14 (17.5%)		
Weight			350.5	1478		3	34 (42%)		
						3.5	21 (26.25%)		
						4	6 (7.5%)		

The distribution of number of rehospitalization cases over time (months) was as follows: 6 (37.5%) in the first, 5(31.25%) in the second, 2(12.5%) in the third and sixth month,1 (6.25%) in the fourth and 0 in the fifth month. This indicates a decreasing risk over time though modelling is needed to confirm this trend. From this observation, piecewise constant hazard model with breakpoints at day 30, 60, 90 and 120 could be a plausible starting points.

To investigate survival probabilities by different baseline covariates, Kaplan-Meier curves were plotted. Figure 1 shows a Kaplan-Meier survival estimate, with the 95% confidence interval, for the time to first rehospitalization. The risk of rehospitalization seem to be high before day 100 but decreases afterwards.

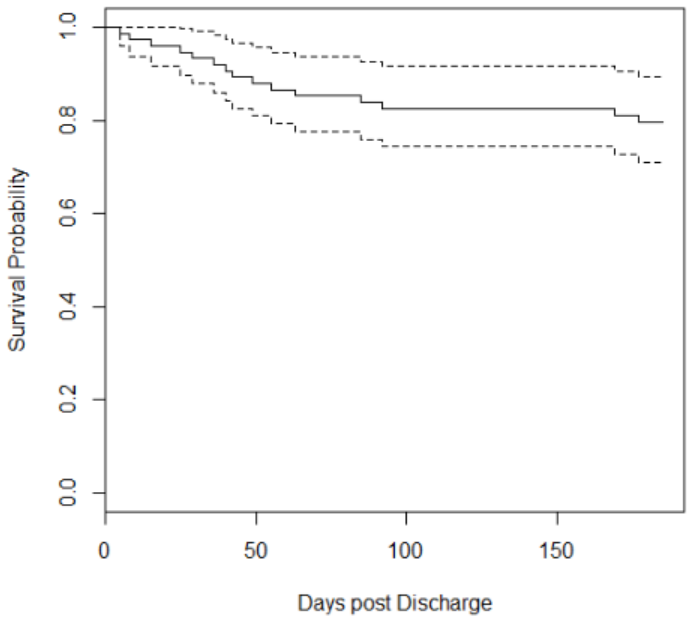

Figure 1: *CHF data, Kaplan-Meier survival estimate for time to first rehospitalization*

To explore the continous baseline variable such as age and LVEF we had to figure out a way of dichotomising them. According to Yancy et al. (2013), HF Patients aged 65 years and above are at higher risk of rehospitalization than younger patients. On the other hand, LVEF can be classified as either preserved or reduced ejection fraction. Therefore, age was dichotomised as follows: age $\geq$ 65 years was classified as old and younger otherwise. Similary, LVEF was dichotomised as follows; patients with LVEF $\geq$ 45 were classified to have preserved ejection fraction and reduced ejection fraction if their LVEF was otherwise.

From Figure A1 patients aged less than 65 years seemed to have better survival than older patients. Patients with normal heart rhythm seem to have better survival than patients with abnormal one as shown in Figure A2. Similarly patients with preserved ejection fraction had better survival than their counterparts with reduced ejection fraction as shown in Figure A3. By looking at NYHA scores, Patients with lower score seemed to have better survival than those with higher scores Figure A5. Females seemed to have better survival than males A4. However, to determine if the observed differences are significant modelling is required.

The time-varying biomarkers were explored by plotting the average profiles, average squared residuals over time and subject-specific evolution profiles.

3.1.1 Weight

Mean structure
Exploration of the mean structure was done using average profile plots. An overall as well as a different average profile for each of the different levels of the baseline covariates were plotted. From the overall average profile plot in Figure 2 (left), a linear time trend was observed. It was observed that males had on average had high weight than females Figure A10. This was expected because naturally males weigh more than females. From Figure A7 Patients in NYHA class 2 had higher and less fluctuating weight compared to patients in higher classes.

Patients aged 65 years and above had on average higher, increasing and slightly fluctuating weight compared to younger patients who seemed to exhibit lower and stable weight as shown in Figure A6 . This could be because chronic heart failure gets severe at age 65 and leads to fluid accumulation which leads to weight gain by the patient as suggested by Yancy et al. (2013). On the other hand, there was no observable weight differences between patients with normal and abnormal heart rhythm Figure A9 .

Patients with preserved ejection fraction had consistently higher weight than their counterparts with reduced Figure A8. From Figure A12 individual patients seem to exhibit linear evolution with less within variability. Patients getting rehospitalized seemed to have lower and highly fluctuating weight compared to those who didn't experience the event as shown in Figure A11.

From the overall impression from the overall average profile plot Figure 2 (left) a linear time evolution would be a plausible starting point in modelling the evolution of weight over time.

Variance Structure
The average evolution of variance as function of time is shown in Figure 2 (right). The general evolution of the variance function is not constant. This suggests that a constant variance structure is not plausible.

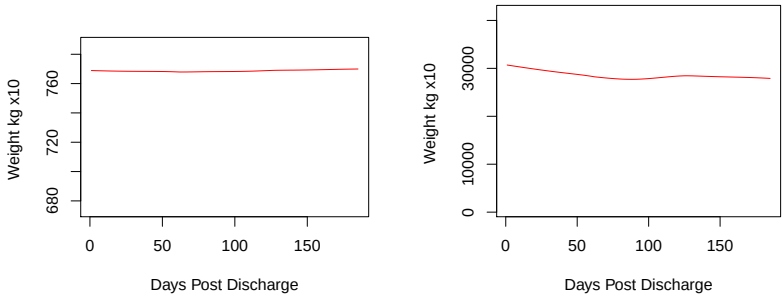

Figure 2: *Weight variable: Mean Structure (left) and Variance Structure (right)*

3.1.2 Heart Rate

Mean Structure
From the overall average profile plot in Figure 3 (left), a linear decreasing trend before day 100 and a constant time trend afterwards was observed. It was observed that there was no observable differences of heart rate in patients with different ages, and NYHA scores Figures A13 and A14 respectively, although modelling is needed to conclude this observation. From Figure A15 patients with preserved ejection fraction had consistently lower heart rate than patients with reduced ejection fraction. From Figure A17 females seemed on average to have slightly higher heart rate than males. Patients with abnormal heart rhythm had higher heart rate than their counterparts with normal heart rhythm Figure A16.

From Figure A19 the individual profile show linear time evolution for heart rate with some patients having very few observations due to missing data. There seem to be alot of between and less within variability. Patients rehospitalized seemed to exhibit highly fluctuating and decreasing average evolution as shown in Figure A18. Patients who don't get rehospitalised seem to exhibit on average, a linear and less fluctuating evolution .

From overall impression from the average profile plot Figure 3 (left) modeling the heart rate over time, a linear time evolution could be a plausible starting point.

Variance Structure
The average evolution of variance as function of time is shown in 3 (right). The general evolution of the variance function is not constant. This suggests a random intercept model is not a good choice.

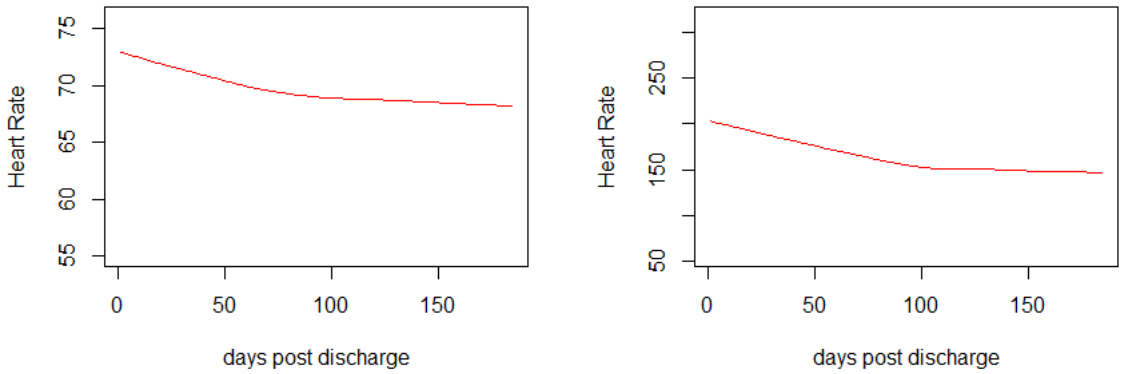

Figure 3: *Heart Rate: Mean Structure (left) Variance Structure (right)*

3.1.3 Diastolic Blood Pressure(dbp)

Mean Structure
From the overall average profile plot in Figure 4 (left), a general linear trend was observed. There was no observable difference in dbp in patients with different gender and heart rhythm Figures A24 and A23 respectively. Young patients had on average higher dbp compared to older patients Figure A20. Patients with NYHA score of 4 had lower and highly fluctuating dbp than patients with lower scores. Similary from Figure A22 patients with reduced ejection fraction had lower dbp than those with preserved ejection fraction.

From overall impression from the average profile plot Figure 4 (left) modelling the evolution of diastolic blood pressure over time, a linear time evolution could be a plausible starting point.

Variance Structure
The average evolution of variance as function of time is shown in 4 (right). The general evolution of the variance function is not constant. This suggests a random intercept model is not a good choice.

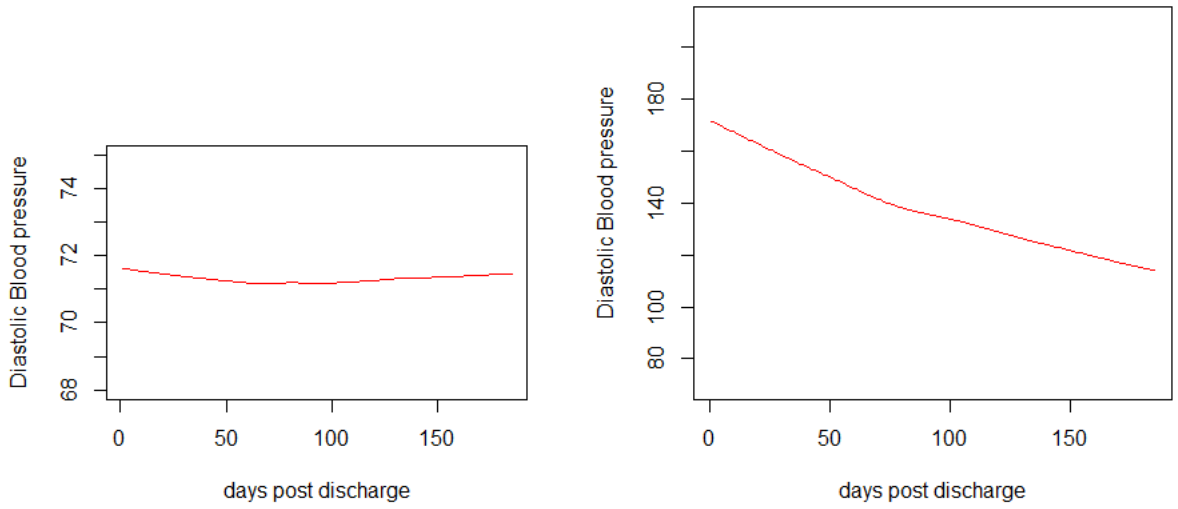

Figure 4: *Diastolic Blood Pressure: Mean Structure (left) and Variance Structure (right)*

3.1.4 Systolic Blood Pressure (sbp)

Mean Structure
From the overall average profile plot in Figure 5 (left), a general increasing linear trend with some fluctuations was observed. There was no observable difference of sbp in patients with different ages, NYHA scores and heart rhythm Figures A27 , A28 and A30 respectively. Patients with preserved ejection fraction had consistently higher sbp than those with reduced ejection fraction as shown in Figure A29. Females exhibited higher sbp than males Figure A31. From Figure A33 the individual patient profiles show linear time evolution for sbp. There seem to be alot of between and less within variability. Patients rehospitalized seemed to exhibit a low and highly fluctuating averange evolution as shown in Figure A32.

Just like in dbp, a linear time evolution could be a plausible starting point in modelling the evolution of sbp .

Variance Structure
From the mean variance structure in Figure 5 suggests than a random intercept model is not a plausible choice.

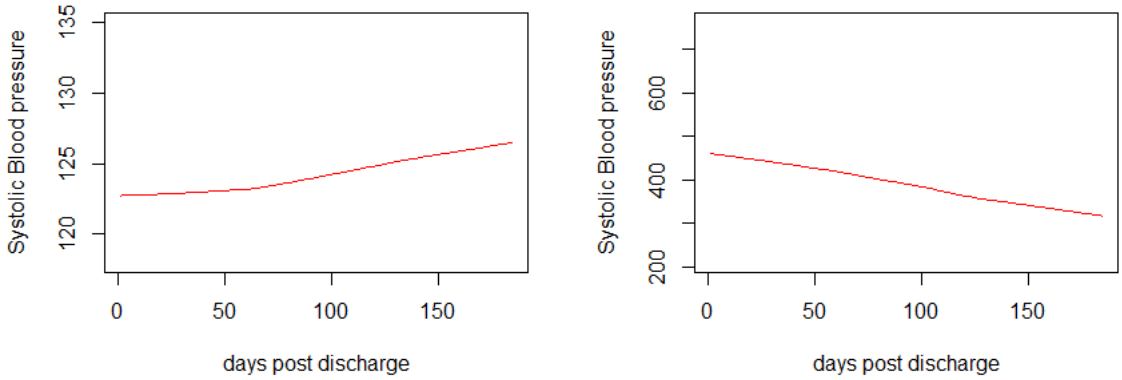

Figure 5: *Systolic Blood Pressure:Variance structure*

All the four longitudinal biomarkers had some missing values. Moreover, one patient didn't have any post discharge measurement for all biomarkers and another patient lacked post discharge measurements for weight. Besides, other four patients had missing baseline cardiac muscle fibre stretch (NTproBNP). These patients were excluded from the analysis and thus the analysis was done on 74 patients.

3.2 Joint Modelling With Different Parameterizations Results.

For the time to first rehospitalization and for each of the longitudinal marker separately, the joint model was used. The basic model (assuming risk is dependent on the current value of the marker) was built in two stages. In stage one, the linear predictor of the of the survival submodel only contained the effect of the biomarker. The submodel was fitted with both Weibull baseline hazard and Piecewise constant model with four breakpoints at days 30, 60, 90 and 120. The fixed effects structure of the longitudinal submodel only included the time evolution while the random structure had random slope and intercept. In the stage two the baseline covariates were added one by one in both the longitudinal and survival submodels. The likelihood ratio test was used to test if the covariate was important or not at 5% significant level. Once the final basic model was found, different parametarizations were applied to check which parameterization produced the best fit. This was achieved by comparing them using Akaike's information criterion (AIC) calculated as:

$$AIC = 2 \times loglikelihood + 2k$$

Where k is the number of parameters in the fitted model. This criteria finds balance between accuracy and complexity of the fitted model. The model with smallest AIC is preferred. To compare different AIC values, information loss when fitted model is used rather than the best approximating model is calculated as follows $\Delta_i = AIC_i - AIC_{min}$. Where AIC_{min} is the minimum AIC. The following rule of thumb is then applied [22] :

- if $0 \leq \Delta_i \leq 2$ then the two models have equivalent support
- if $4 \leq \Delta_i \leq 7$ then the two models are clearly distinguishable
- $\Delta_i > 10$ then the two models are definitely different

For numerical stability, several covariates were transformed or rescaled. Time, weight, heart rate, systolic and diastolic blood pressure were rescaled to unit magnitude by dividing by the largest value. The cardiac muscle fibre stretch (NTproBNP) values were transformed by square root and age values were rescaled by dividing with the minimum value. Left ventricle ejection fraction (LVEF) was dichotomized as follows according to Yancy et al. (2013), LVEF ≥ 45 were considerd high (preserved ejection fraction) coded 1 and low (reduced ejection fraction) otherwise coded as 0.

3.2.1 Weight

From exploratory data analysis, weight seemed to exhibit a linear time trend evolution structure figure 2 left. To start with, the basic survival submodel only containing weight as a covariate as described above was fitted.

No baseline covariates were added to this model since likelihood ratio test showed there was no need of including them, a P-value > 0.05. Initially the numerical integration was done using adaptive Gauss-Hermite rule with 15 points and then the points were gradually increased. Convergence was concluded when the parameter estimates and the AIC values were no longer changing. It is worth noting that, analysis was conducted assuming both Piecewise constant hazard and Weibull baseline hazard for the survival submodel. The basic longitudinal submodel and survival submodel with weibull baseline hazard were written as follows respectively.

$$weight_{ij} = m_i(t) + \varepsilon_i t = \beta_0 + \beta_1 Time_{ij} + b_{0i} + b_{1i} Time_{ij} + \varepsilon_{ij}$$

$$h_i(t|\mathcal{M}_i(t)) = \rho t^{\rho-1} \exp\{\gamma_0 + \alpha m_i(t)\}$$

Different parameterizations were extended on these submodels. For interaction effect we looked at interaction between weight and and categorical baseline covariate (gender and heart rhythm). The survival submodel was written as follows:

$$h_i(t|\mathcal{M}_i(t)) = \rho t^{\rho-1} \exp\left[\gamma_0 + \alpha_1 m_i(t) + \alpha_2\{sex_i \times m_i(t)\}\right]$$

For the lagged effect parameterization the model was written as follows:

$$h_i(t|\mathcal{M}_i(t)) = \rho t^{\rho-1} \exp\left[\gamma_0 + \alpha m_i(max(t-c,0))\right]$$

For c=1,2.

The time dependent slope parameterization model was formulated as follows;

$$h_i(t|\mathcal{M}_i(t)) = \rho t^{\rho-1} \exp\{\gamma_0 + \alpha_1 m_i(t) + \alpha_2 m_i\prime(t)\}$$

where $m_i\prime(t)$ is the derivative of $m_i(t)$ with respect to t.

$$m_i\prime(t) = \beta_1 + b_{1i}$$

Finally the cumulative effect parameterization model was written as follows;

$$h_i(t|\mathcal{M}_i(t)) = \rho t^{\rho-1} \exp\{\gamma_0 + \alpha \int_0^t m_i(s)ds\}$$

Where the integral has a closed form solution:

$$\int_0^t m_i(s)ds = \beta_0 Time + \beta_1 \frac{Time^2}{2} + b_{0i} Time + b_{1i} \frac{Time^2}{2}$$

The results for the different parameterizations assuming weibull and PC baseline hazard are presented in Tables 2 and A1 respectively. From Table 2 survival submodel with weibull baseline hazard has smaller AIC than PC. The current value and lagged effect parameterization produced the poorest fit to the data and the association parameters were not statistically significant. The interaction effect by sex and heart rhythm have the same AIC value, this is because both had similar distribution in terms of events as shown in Table 1. A unit decrease of weight for female patient/ a patient with abnormal heart rhythm increases the risk of rehospitalization by 0.00037. Similarly, a unit increase in weight for a male/a patient with normal heart rhythm is associated with 36.62 increase in the risk of rehospitalization. The time depended slopes parameterization has the best fit to the data with the smallest AIC value of -51619.02 and -51615.95 for Weibull

and PC baseline hazards respectively. A unit decrease in the current value of weight is associated with 0.17 increase in the risk of rehospitalization. For patients having the same weight, the log hazard ratio for a unit decrease in the current slope of weight trajectory is -29.245(sd=9) with a Pvalue=0.0012. This finding confirms the observation in Figure A11, where patients getting rehospitalized seemed to have on average low and highly fluctuating weight evolution. From Table 2 the the Weibull shape parameter in all parameterazation except in cumulative effect is less than one implying a decreasing hazard of rehospitalization with time. According to Yancy et al.(2013) weight loss in CHF patients could be due to increase of dose or frequency of diuretic administration which is intended to eliminate clinical evidence of fluid retention.

From the piecewise constant hazard model table A1, the hazard increased from first to second month and afterwards it decreased with increasing time, implying that once a patient is discharded, he/she is more likely to be rehospitalized during early months.

Table 2: *CHF data. Parameter estimates and standard error (SE) in brackets of different parameterization for weight varible: Current value, Lagged effect,Time dependent slopes,cumulative and Interaction Effect . sex/H.Rhythm represents main effects for sex(males) or Heart rhythm(normal), assoct is the association parameter , assoct.s is slope association parameter and interaction is the interaction between true weight with sex or Heart rhythm.** implies a pvalue of 0.0012 and *implies a pvalue=0.0346.* Δ_i *was computed for Weibull baseline hazard survival submodel*

	Current Value	Lagged Effect		Time Dependent Slopes	Cumulative Effect	Interaction Effect	
		Lag1	Lag 2			by sex	by H.Rhythm
Effect	Estimate(SE)	Estimate(SE)	Estimate(SE)	Estimate(SE)	Estimate(SE)	Effect(SE)	Estimate(SE)
Intercept(γ_0)	-1.276 (1.223)	-1.490 (1.206)	-1.490 (1.206)	-0.797 (1.201)	-0.603 (0.792)	2.115 (2.271)	2.115 (2.271)
sex/H.Rhythm						-5.113 (2.659)	-5.113 (2.659)
Assoct	-0.319 (2.310)	0.095 (2.269)	0.095 (2.269)	-1.772 (2.378)	-3.879 (3.307)	-7.902 (4.869)	-7.902 (4.869)
assoct .s				-29.245 (9.009)**			
Interaction						11.502(5.443)*	11.502(5.443)*
log(shape)	-0.369 (0.270)	-0.370 (0.270)	-0.370 (0.270)	-0.136 (0.265)	0.053 (0.364)	-0.319 (0.261)	-0.319 (0.261)
Shape	0.692	0.691	0.691	0.873	1.054	0.727	0.727
Weibull AIC	-51612.82	-51612.81	-51612.81	-51619.02	-51614.27	-51614.21	-51614.21
Piecewise AIC	-51610.76	-51610.76	-51610.76	-51615.95	-51611.13	-51612.12	-51612.12
Δ_i	6.2	6.21	6.21	0	4.75	4.81	4.81

3.2.2 Systolic blood pressure(sbp)

A similar procedure as described for weight was repeated for systolic blood pressure. From exploratory data analysis Figure 5 left, it seemed sensible to begin from linear time evolution of sbp for the longitudinal submodel, with random intercept and linear slope. We first built the basic model (assuming risk to be depended on the current marker value). LVEF was included in both the longitudinal and survival submodels as a baseline covariate. Although it was not important in the survival process it was found

to influence the longitudinal process. Initially the numerical integration was done using adaptive Gauss-Hermite rule with 15 points and then the points were gradually increased. Convergence was concluded when the parameter estimates and the AIC values were no longer changing. For interaction effect parameterization we considered interaction between sbp with categorical baseline covariates (heart ryhthm and sex). The survival submodel had Weibull and PC baseline hazard model. The longitudinal and basic survival with Weibull baseline hazard submodels were respectively written as follows.

$$Sbp_{ij} = m_i(t) + \varepsilon_i t = \beta_0 + \beta_1 LVEF_i + \beta_2(LVEF_i \times Time) + \beta_3 Time_{ij} + b_{0i} + b_{1i} Time_{ij} + \varepsilon_{ij}$$

$$h_i(t|\mathcal{M}_i(t)) = \rho t^{\rho-1} \exp\{\gamma_0 + \gamma_1 LVEF_i + \alpha m_i(t)\}$$

Different parameterizations were extended on these submodels as described in weight.

The results for different parameterization with Weibull and PC baseline hazard are presented on Tables 3 and A2 respectively. From Table 3 there was no difference between lag1 and lag2 parameterizations. The interaction effect by sex and heart rhythm have the same AIC value, this is because both had similar distribution in terms of events as shown Table 1. The time dependent slopes parameterization produced the best fit to the data with AIC value of -30147.71 and -30142.75 for Weibull and PC baseline hazard models respectively. This implies that, a unit decrease in current value of systolic blood pressure is associated with 0.0009 increase in the risk of rehospitalization though not statistically significant. Similary, for patients with the same sbp, a unit decrease in the current slope of sbp trajectory is associated with 0.0004 increase in the risk of rehospitalization. Therefore the risk of rehospitalization depends on both the current value and slope of the sbp.

Although, the time dependent slopes parametarization gave the best fit to the data, the fit was not different from that of current value and cumulative effect parameterization. A unit decrease in current value of sbp, is associated with 0.007 increase in the risk of rehospitalization though not statistically significant. For the cumulative effect parameterization, a unit decrease in the area under sbp longitudinal profile corresponds to 0.0036 increase in the risk of rehospitalization though not statistically significant. These results are similar to what was observed in exploratory data analysis in Figure A32, where patients getting rehospitalized had decreasing and highly fluctuating sbp compared to those who did not.

The decrease in systolic blood pressure may lead to a condition known as hypotension, which occurs when sbp < 90 (mm Hg). In CHF patients, this condition could result due to use of inappropriately high doses of diuretics which lead to volume contraction causing an increased risk of hypotension and renal insufficiency [16]. From previous studies,

patients in need of high diuretic doses are the sickiest ones [23] hence more likely to be rehospitalized.

The interaction effect gave the poorest fit to the data and also the lagged effect parameterization. From the Piecewise constant hazard model Table A2, the hazard increased from first to second month and afterwards it decreased with increasing time, implying that once a patient is discharged, he/she is more likely to be rehospitalised during early months. This observation was also seen in weight biomarker.

Table 3: *CHF data. Parameter estimates and standard error (SE) in brackets of different parameterization for Systolic blood pressure (sbp) varible: current value, Lagged effect,Time dependent slopes,cumulative and Interaction Effect (by heart ryhtm and sex). sex/H.Rhythm represents main effects for sex(males) or Heart rhythm(normal), LVEF(=1),represents the main effects for LVEF, assoct is the association parameter , assoct.s is slope association parameter and interaction is the interaction between true sbp with sex or Heart rhythm.*

	Current Value	Lagged Effect		Time Dependent Slopes	Cumulative Effect	Interaction Effect	
Effect	Estimate(SE)	Lag1 Estimate(SE)	Lag 2 Estimate(SE)	Estimate(SE)	Estimate(SE)	by sex Effect(SE)	by H.Rhythm Estimate(SE)
Intercept(γ_0)	1.449 (2.059)	-0.297 (1.811)	-0.297 (1.811)	2.558 (2.073)	0.030 (0.993)	3.189 (3.135)	3.189 (3.135)
sex/H.Rhythm						-2.499 (3.955)	-2.499 (3.955)
LVEF(=1)	0.272 (0.658)	0.050 (0.651)	0.050 (0.651)	-0.012 (0.682)	0.021 (0.591)	0.258 (0.646)	0.258 (0.646)
Assoct	-5.030 (3.681)	-1.954 (3.185)	-1.954 (3.185)	-7.021 (3.804)	-5.626 (3.435)	-8.724 (5.693)	-8.724 (5.693)
assoct .s				-7.872 (5.377)			
Interaction						5.562 (6.928)	5.562 (6.928)
log(shape)	-0.333 (0.264)	-0.365 (0.269)	-0.365 (0.269)	-0.366 (0.269)	0.287 (0.357)	-0.323 (0.263)	-0.323 (0.263)
Shape	0.717	0.694	0.694	0.694	1.333	0.724	0.724
Weibull AIC	-30146.68	-30144.83	-30144.83	-30147.71	-30147.1	-30144.65	-30144.65
Piecewise AIC	-30144.43	-30142.75	-30142.75	-30145.75	-30142.42	-30142.37	-30142.37
Δ_i	1.03	2.88	2.88	0	0.61	3.06	3.06

3.2.3 Diastolic blood pressure(dbp)

To model the longitudinal evolution of dbp we started with assuming linear time evolution as suggested by Figure 4 (left) with random slope and intercept. Model building proceeded as described in section 4.2 and in weight subsection. No baseline covariate was added in both the longitudinal and survival submodels. The survival submodel was fitted with both Weibull and PC hazard baseline hazard. However, for lagged effect parameterization, the survival submodel with PC baseline hazard did not converge.

The final longitudinal and Weibull baseline hazard survival (assuming risk to depend on current marker value) submodels were written in that order as follows,

$$dbp_{ij} = m_i(t) + \varepsilon_i t = \beta_0 + \beta_1 Time_{ij} + b_{0i} + b_{1i} Time_{ij} + \varepsilon_{ij}$$

$$h_i(t|\mathcal{M}_i(t)) = \rho t^{\rho-1} \exp\{\gamma_0 + \alpha m_i(t)\}$$

Different parameterizations were extended on these submodels as described in weight subsections. The results for different parameterization with Weibull and PC baseline hazard are presented on Tables 4 and A3 respectively. From Tables 4 the cumulative effect parameterization gave the smallest AIC value of -27865.53 and -27862.18 for Weibull and PC baseline hazard models respectively. However, the model fit was not different from that of current value, lagged effect and time dependent slopes parameterizations. For cumulative effect, a unit decrease in the area under the longitudinal profile corresponds to 0.001 increase in the risk of rehospitalization though not statistically significant. A unit decrease in the current value of dbp is associated with 0.0368 increase in the risk of rehospitalization but not statistically significant. These findings are similar to what we saw in exploratory data analysis Figure A25, where patients getting rehospitalized had on average lower and slightly fluctuating dbp compared to those who did not.

Just like in systolic blood pressure, low dbp is a result of hypotension which occurs when dbp goes below 60 (mm Hg). In CHF patients, this condition could result due to use of inappropriately high doses of diuretics which lead to volume contraction causing an increased risk of hypotension and renal insufficiency [16]. From previous studies, patients in need of high diuretic doses are the sickiest one [23] hence more likely to be rehospitalized.

Table 4: *CHF data. Parameter estimates and standard error (SE) in brackets of different parameterization for diastolic blood pressure(dbp) varible: current value, Lagged effect,Time dependent slopes, cumulative and Interaction Effect (by heart ryhtm and sex). sex/H.Rhythm represents main effects for sex(males) or Heart rhythm(normal), assoct is the association parameter, assoct.s is slope association parameter and interaction is the interaction between true dbp with sex or Heart rhythm.*

	Current Value	Lagged Effect		Time dependent Slopes	Cumulative Effect	Interaction Effect	
Effect	Estimate(SE)	Lag1 Estimate(SE)	Lag 2 Estimate(SE)	Estimate(SE)	Estimate(SE)	by sex Effect(SE)	by H.Rhythm Estimate(SE)
Intercept(γ_0)	0.414 (2.050)	-0.303 (1.764)	-0.303 (1.764)	1.887 (2.154)	0.298 (1.109)	-1.897 (2.807)	-1.897 (2.807)
sex/H.Rhythm						4.894 (4.291)	4.895 (4.291)
Assoct	-3.303 (3.679)	-2.010 (3.123)	-2.010 (3.123)	-6.307 (4.077)			
assoct .s				-7.008 (4.486)	-6.897 (3.974)		
Interaction						-7.521 (7.674)	-7.521 (7.674)
log(shape)	-0.362 (0.268)	-0.362 (0.267)	-0.362 (0.269)	-0.384 (0.272)	0.355(0.368)	-0.361	-0.361
Shape	0.697	0.696	0.696	0.682	1.426	0.697	0.697
Weibull AIC	-27864.8	-27864.41	-27864.41	-27864.41	-27865.53	-27861.94	-27861.94
Piecewise AIC	-27862.72			-27862.48	-27862.18	-27860.01	-27860.01
Δ_i	0.73	1.12	1.12	1.12	0	3.59	3.59

3.2.4 Heart Rate (hr)

To model the longitudinal evolution of heart rate we started with assuming linear time evolution as suggested by Figure 3(left) with random slope and intercept. Model building proceeded as described in section 4.2 and has described in weight. No baseline covariate was added in both the longitudinal and survival submodels. The survival submodel was fit with both Weibull and PC hazard baseline hazard.

The final basic longitudinal and survival submodels were written in that order as follows,

$$hr_{ij} = m_i(t) + \varepsilon_i t = \beta_0 + \beta_1 Time_{ij} + b_{0i} + b_{1i} Time_{ij} + \varepsilon_{ij}$$

$$h_i(t|\mathcal{M}_i(t)) = \rho t^{\rho-1} \exp\{\gamma_0 + \alpha m_i(t)\}$$

Different parameterizations were extended on these submodels as described in weight. The results for the different parameterization assuming weibull and PC baseline hazard are presented in Tables 5 and A4 respectively. From Table 5 survival submodel with Weibull baseline hazard has smaller AIC than PC. The cumulative effect and lagged effect parameterizations produced the poorest fit to the data.

The interaction effect by sex and heart rhythm have the same AIC value, this is because both had similar distribution interms of events as shown in Table 1. The log hazard ratio for a unit increase of heart rate for female patient/ a patient with abnormal heart rhythm is 9.252 (Pvalue=0.0448). Similary the log hazard ratio for unit increase in heart rate for a male/a patient with normal heart rhythm is 12.6903 (Pvalue=0.0448) . The current value parameterization has the best fit to the data with the smallest AIC value of -29051.95 and -29049.25 for Weibull and PC baseline hazards respectively. However, the model fit was not different from that of time depended slopes parameterization. A unit increase in the current value of heart rate is associated with 76657.29 (pvalue=0.003) increase in the risk of rehospitalization.

For time dependent slopes parameterization, a unit increase in the current heart rate value is associated with 73570.54 (Pvalue=0.0002) increase in the risk of rehospitalization. For Patients having the same heart rate, a unit increase in the current slope of heart rate trajectory increases the risk of rehospitalization by 14.404 but not statistically significant. This finding confirms the observation in Figure A18, where patients getting rehospitalized seemed to have on average higher and decreasing heart rate evolution. From Table 5 the the Weibull shape parameter in all parameterazations except in cumulative effect is less than one implying a decreasing hazard of rehospitalization with time. The increase in heart rate could be due to the adverse effects of diuretics which oftenly causes arrhythmias

(irregular heart beat) [16].

Table 5: *CHF data. Parameter estimates and standard error (SE) in brackets of different parameterization for heart rate(hr) varible: current value, Lagged effect, Time dependent slopes, cumulative and Interaction Effect (by heart ryhthm and sex). A * implies a statistically significant estimate with p-value < 0.05. Sex/H.Rhythm represents main effects for sex(males) or Heart rhythm(normal), assoct is the association parameter , assoct.s is slope association parameter and interaction is the interaction between true heart rate with sex or Heart rhythm.** implies a Pvalue<0.005 * implies pvalue<0.0455*

	Current Value	Lagged Effect		Time dependent Slopes	Cumulative Effect	Interaction Effect	
Effect	Estimate(SE)	Lag1 Estimate(SE)	Lag 2 Estimate(SE)	Estimate(SE)	Estimate(SE)	by sex Effect(SE)	by H.Rhythm Estimate(SE)
Intercept (γ_0)	-7.780 (1.876)**	-4.427 (1.580)**	-4.427 (1.580)**	-7.775 (1.823)**	-0.513(0.873)	-6.838 (2.719)*	-6.838 (2.7188)*
sex						-1.637 (3.612)	-1.637 (3.612)
Assoct	11.247 (3.087)**	5.379(2.689)*	5.379(2.689)*	11.206 (2.984)**	-4.201 (3.570)	9.252 (4.612)*	9.252 (4.612)*
assoct .s				2.668 (1.837)			
Ass.Sex						3.438 (5.947)	3.438 (5.947)
log(shape)	-0.197 (0.239)	-0.340 (0.262)	-0.340 (0.262)	-0.293 (0.260)	0.080 (0.384)	-0.183 (0.234)	-0.183 (0.234)
Shape	0.821	0.712	0.712	0.746	1.083	0.833	1.833
Weibull AIC	-29051.95	-29042.28	-29042.28	-29051.8	-29039.18	-29049.21	-29049.21
Piecewise AIC	-29049.25	-29040.17	-29040.17	-29050.19	-29038.4	-29046.84	-29046.84
Δ_i	0	9.67	9.67	0.15	12.77	2.74	2.74

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4. Discussion and Conclusions

In total 80 patients were considered in this study, of whom 37.50% were females. 45% of the patients had normal heart rhythm while the rest had abnormal heart rhythm. In total 20% of the patients were rehospitalized. The mean age at baseline was about 76 years with a standard deviation of 9.7. The dbp and sbp ranged between 31 to 123 and 74 to 205 mmHg respectively. The heart rate ranged between 40 and 134 heart beats per minute while weight ranged from 35.05 to 147.8 Kg. The baseline cardiac muscle fibre stretch was highly variable with a mean of 70.787 and a standard deviation of 588.265. The NYHA score classification at baseline was as follows: 6.25% patients were classified to score 2, 17.5% to score 2.5, 42% to score 3, 26.25% to score 3.5 and 7.5% to score 4. Out of the 80 patients, the analysis was done on 74 patients due to missing baseline covariate in four patients and missing post discharge measurement in two patients. Of the 15 patients rehospitalized, six were females. Six out of the 15 patients had abnormal heart rhythm.

All longitudinal models had linear time evolution for fixed effects while random effects consisted of both intercept and slope. No baseline covariate was added in the final joint model except for systolic blood pressure model which had LVEF baseline covariate.

Considering weight, the time dependent slopes parameterization had the best fit to the data with the smallest AIC values of -51619.02 and -51615.95 for Weibull and PC baseline hazards respectively. Similarly, for systolic blood pressure the time dependent slopes parameterization produced the best fit to the data with AIC values of -30147.71 and -30142.75 for Weibull and PC baseline hazard models respectively. The fit to the data was not different from that of current value and cumulative effect parameterizations since they had equivalent support (Δ_i of 1.03 and 0.61 respectively). For diastolic blood pressure, the cumulative effect parameterization gave the smallest AIC value of -27865.53 and -27862.18 for Weibull and PC baseline hazard models respectively. However, the model fit was not different from that of current value, lagged effect and time dependent slopes parameterizations as they had equivalent support. The current value parameterization had the best fit to the data for the heart rate with the smallest AIC value of -29051.95 and -29049.25 for Weibull and PC baseline hazards respectively. However, the model fit was not different from that of time depended slopes parameterization.

In general, the risk of rehospitalization could be associated with increased use of diuretics. From the piecewise constant hazard models, the hazard increased from first to second month and afterwards it decreased with increasing time, implying that once a patient is discharded, he/she is more likely to be rehospitalized during early months.

A limitation of the study was that only 15 (20%) patients were rehospitalized leading to 80% censoring. In the cumulative effect parameterization, equal weights were placed in

all past values of the markers, which might not be reasonable. Maybe an integrand should be adjusted by multiplying the true marker ($m_i(t)$) with appropriate weight functions that places different weights at different time points [10]. Finally the biomarkers were analysed separately, it would be important to consider them jointly accounting for their association structure.

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Appendix

A. Appendices

A.1 Exploratory Data Analysis

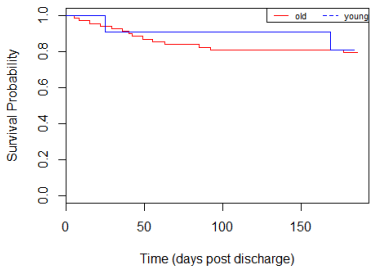

Figure A1: *KM curves by Age*

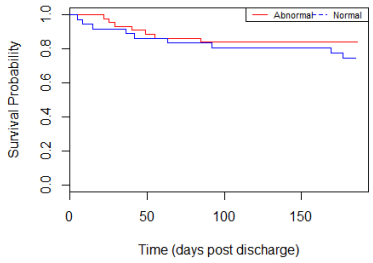

Figure A2: *KM curves by Heart rhythm*

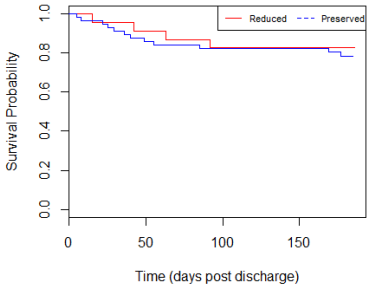

Figure A3: *KM curves by LVEF*

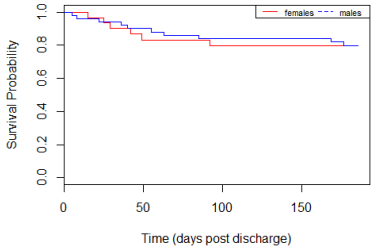

Figure A4: *KM curves by Sex*

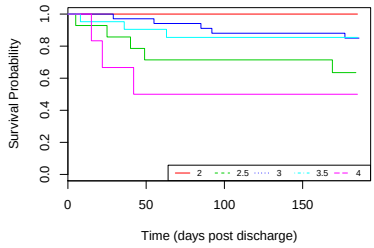

Figure A5: *KM curves by NYHA Class*

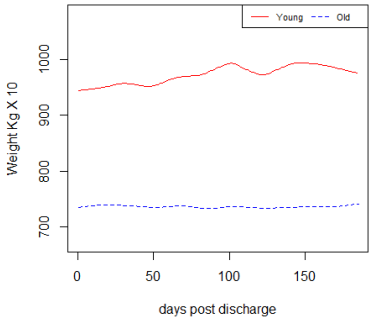

Figure A6: *Weight by age*

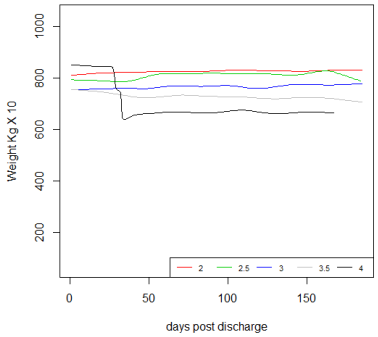

Figure A7: *Weight by NYHA score*

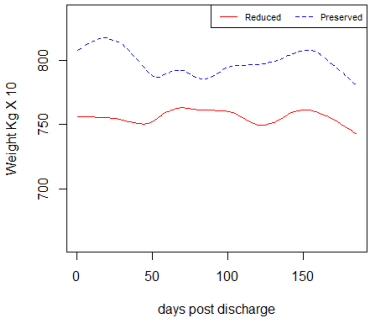

Figure A8: *Weight by LVEF*

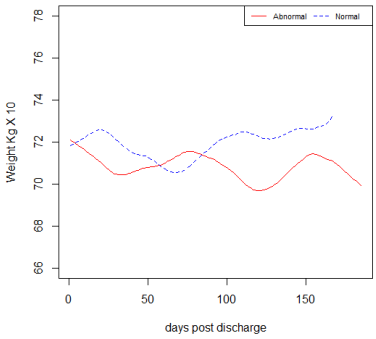

Figure A9: *Weight by heart rhythm*

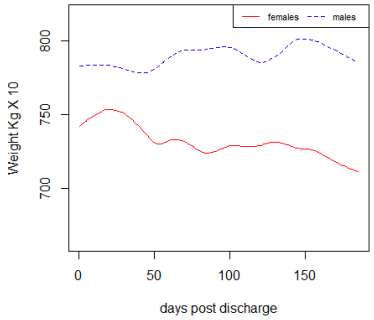

Figure A10: *Weight by sex*

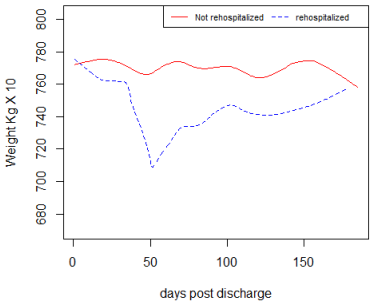

Figure A11: *Weight by status*

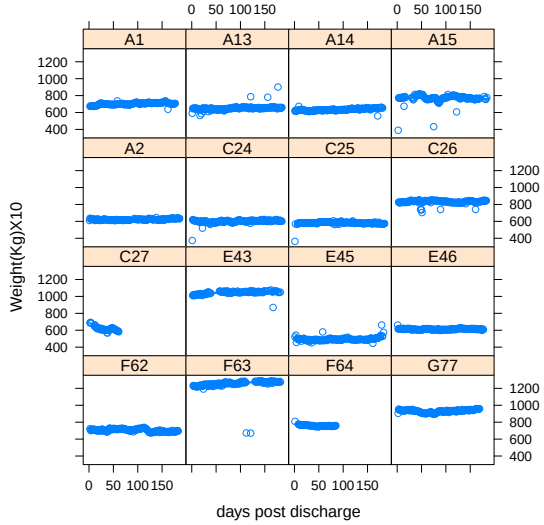

Figure A12: *Weight: Random sample of lowess smoothed longitudinal profiles of 16 patients*

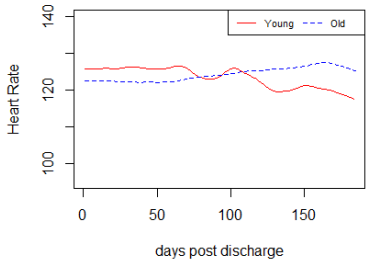

Figure A13: *Heart rate by age*

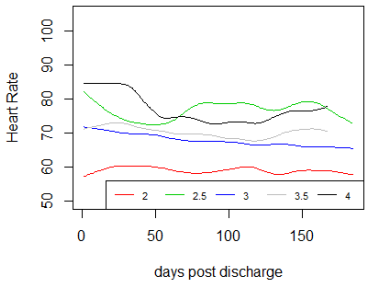

Figure A14: *Heart rate by NYHA score*

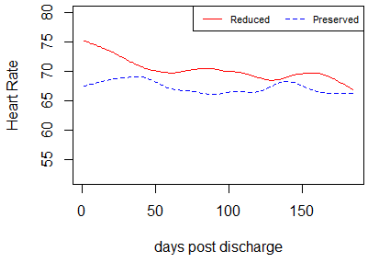

Figure A15: *Heart rate by LVEF*

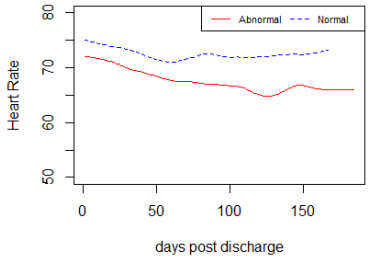

Figure A16: *Heart rate by heart rhythm*

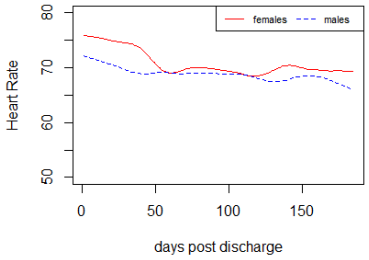

Figure A17: *Heart rate by sex*

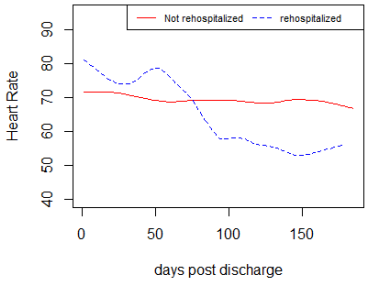

Figure A18: *Heart rate by status*

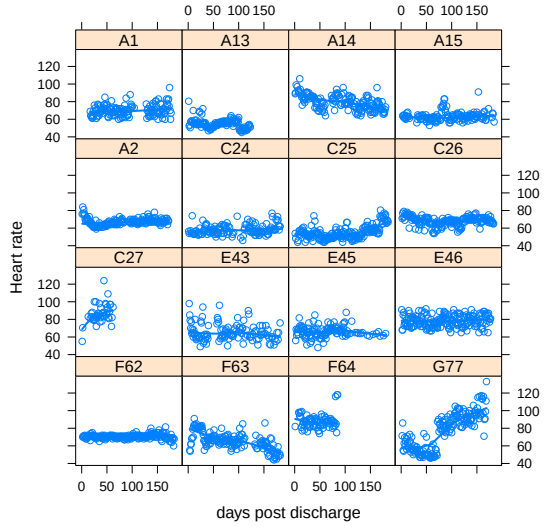

Figure A19: *Heart rate: Random sample of lowess smoothed longitudinal profiles of 16 patients*

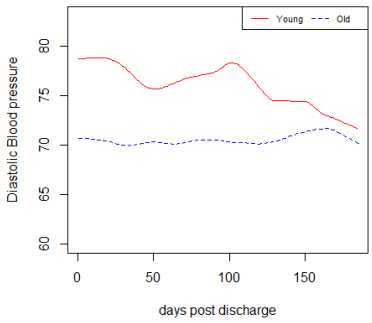

Figure A20: *dbp by age*

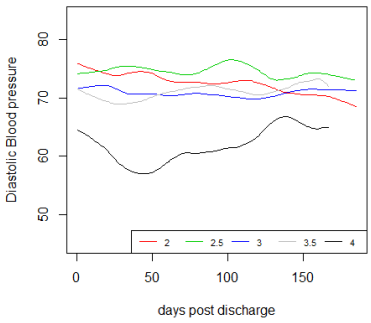

Figure A21: *dbp by NYHA score*

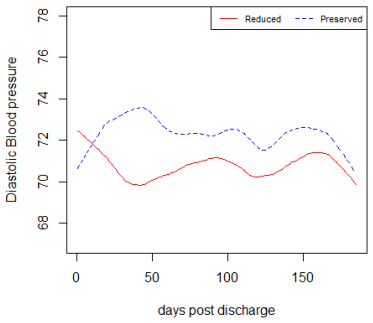

Figure A22: *dbp by LVEF*

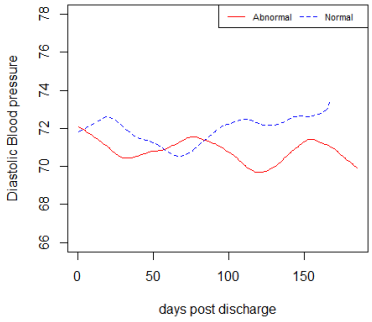

Figure A23: *dbp by heart rhythm*

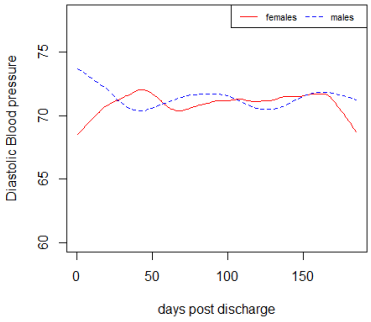

Figure A24: *dbp by sex*

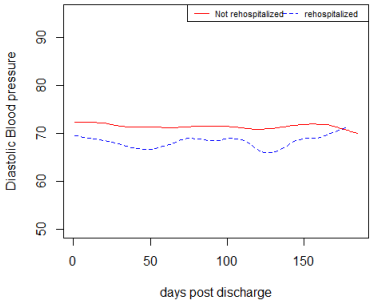

Figure A25: *dbp by status*

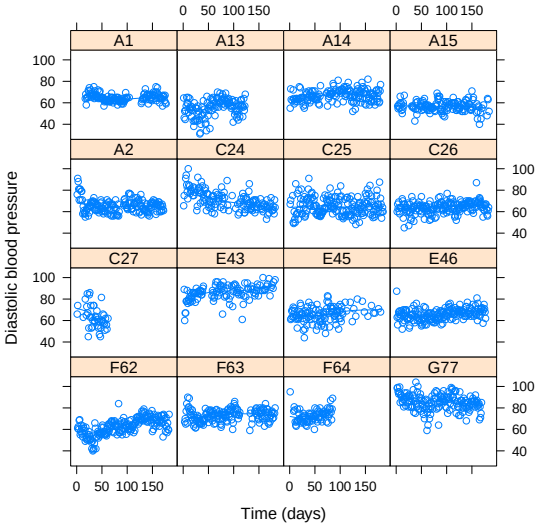

Figure A26: *dbp: Random sample of lowess smoothed longitudinal profiles of 16 patients*

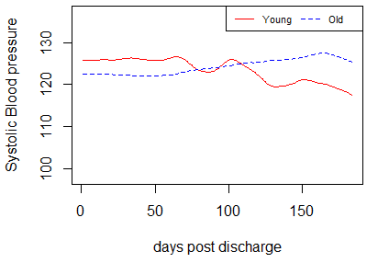

Figure A27: *sbp by age*

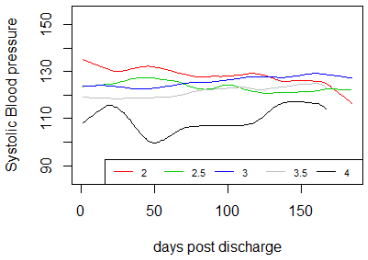

Figure A28: *sbp by NYHA score*

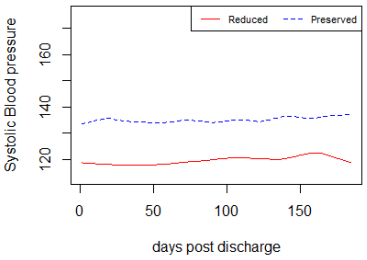

Figure A29: *sbp by LVEF*

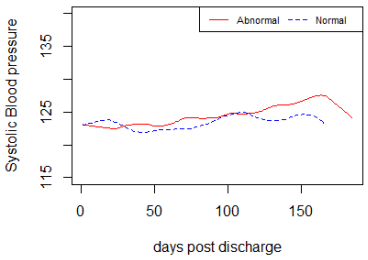

Figure A30: *sbp by heart rhythm*

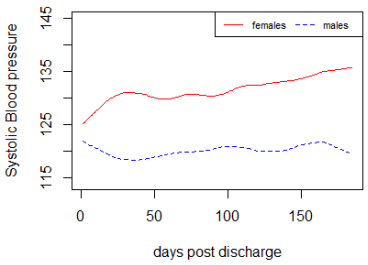

Figure A31: *sbp by sex*

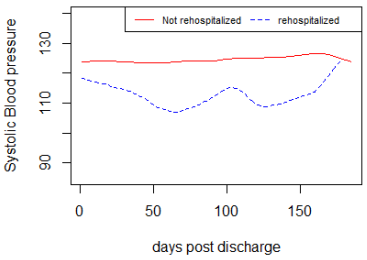

Figure A32: *sbp by status*

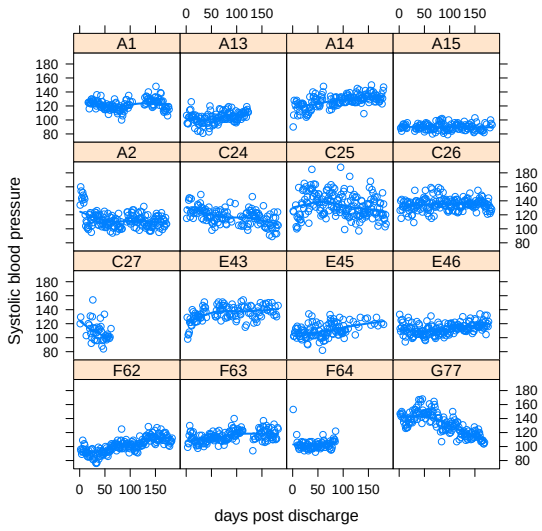

Figure A33: *Sbp: Random sample of lowess smoothed longitudinal profiles of 16 patients*

A.2 Joint modelling with different parameterization Results.

A.2.1 Weight

Table A1: *CHF data. Parameter estimates and standard error (SE) in brackets of different parameterization for weight varible with piecewise constant model: Lagged effect,Time dependent slopes,cumulative and Interaction Effect . sex/H.Rhythm represents main effects for sex(males) or Heart rhythm(normal), assoct is the association parameter , assoct.s is slope association parameter and interaction is the interaction between true weight with sex or Heart rhythm. **implies a pvalue=0.0022*

	Current Value	Lagged Effect		Time depended Slopes	Cumulative Effect	Interaction Effect	
Effect	Estimate(SE)	Lag1 Estimate(SE)	Lag 2 Estimate(SE)	Estimate(SE)	Estimate(SE)	by sex Effect(SE)	by H.Rhythm Estimate(SE)
sex/H.Rhythm						-4.3182 (2.6020)	-4.3182 (2.6020)
Assoct	-0.3391 (2.3128)	0.0854 (2.2647)	0.0854 (2.2647)	-1.4992 (2.2887)	2.3456 (4.4893)	-6.7003 (4.6644)	-6.7003 (4.6644)
Assoct .s				-25.6384 (8.3696)**			
Interaction						9.8812 (5.2552)	9.8812 (5.2552)
log(xi.1)	-0.6707 (1.2692)	-0.8839 (1.2565)	-0.8839 (1.2565)	-0.5329 (1.2423)	-0.9422(0.4872)	2.1055 (2.2347)	2.1055 (2.2347)
log(xi.2)	-0.5784 (1.2708)	-0.8049 (1.2550)	-0.8049 (1.2550)	-0.2312 (1.2101)	-1.0544 (0.7287)	2.2304 (2.2453)	2.2304 (2.2453)
log(xi.3)	-1.4322 (1.3894)	-1.6543 (1.3705)	-1.6543 (1.3705)	-0.8456 (1.3408)	-2.1014 (1.2007)	1.4140 (2.3172)	1.4140 (2.3172)
log(xi.4)	-2.0606 (1.5616)	-2.2834 (1.5441)	-2.2834 (1.5441)	-1.4523 (1.5209)	-2.9415 (1.7025)	0.7855 (2.4206)	0.7855 (2.4206)
log(xi.5)	-2.1136 (1.3970)	-2.3370 (1.3732)	-2.3370 (1.3732)	-1.5057 (1.3424)	-3.3093 (2.1680)	0.7431 (2.3215)	0.7431 (2.3215)

A.2.2 Systolic blood pressure(sbp)

Table A2: *CHF data. Parameter estimates and standard error (SE) in brackets of different parameterization with piecewise constant model for Systolic blood pressure (sbp) varible: Lagged effect,Time dependent slopes,cumulative and Interaction Effect (by heart ryhtm and sex). sex/H.Rhythm represents main effects for sex(males) or Heart rhythm(normal), LVEF(=1),represents the main effects for LVEF, assoct is the association parameter , assoct.s is slope association parameter and interaction is the interaction between true sbp with sex or Heart rhythm.*

	Current Value	Lagged Effect		Time depended Slopes	Cumulative Effect	Interaction Effect	
Effect	Estimate(SE)	Lag1 Estimate(SE)	Lag 2 Estimate(SE)	Estimate(SE)	Estimate(SE)	by sex Effect(SE)	by H.Rhythm Estimate(SE)
LVEF_cat1	0.2827 (0.6618)	0.0581 (0.6520)	0.0578 (0.6518)	-0.0551 (0.6901)	-0.1502 (0.5991)	0.2110 (0.6491)	0.2110 (0.6491)
sex/H.Rhythm						-2.0634 (3.9453)	-2.0634 (3.9453)
Assoct	-5.0201 (3.6964)	-2.0496 (3.2033)	-2.0429 (3.2021)	-7.2970 (3.8138)	1.1360 (5.5464)	-7.6971 (5.5929)	-7.6971 (5.5929)
Assoct .s				-8.6959 (5.3379)			
Interaction						4.7931 (6.8831)	4.7931 (6.8831)
log(xi.1)	2.0002(2.0659)	0.3495 (1.8490)	0.3459(1.8485)	3.2808 (2.0924)	-0.8584 (0.5277)	3.1714 (3.0875)	3.1714 (3.0875)
log(xi.2)	2.1063(2.0873)	0.4352(1.8522)	0.4319 (1.8517)	3.3709 (2.1029)	-0.8836 (0.9082)	3.2760 (3.1086)	3.2760 (3.1086)
log(xi.3)	1.2781 (2.1774)	-0.4125 (1.9330)	-0.4161 (1.9326)	2.5768 (2.2063)	-1.8463 (1.5109)	2.4509 (3.1747)	2.4509 (3.1747)
log(xi.4)	0.6678 (2.3057)	-1.0382 (2.0664)	-1.0420 (2.0660)	1.9239 (2.3103)	-2.5921 (2.1396)	1.8492(3.2750)	1.8492(3.2750)
log(xi.5)	0.6258(2.1937)	-1.0900 (1.9408)	-1.0936 (1.9403)	1.8070(2.1462)	-2.8201(2.8607)	1.8135 (3.1998)	1.8135 (3.1998)

A.2.3 Diastolic blood pressure(sbp)

Table A3: *CHF data. Parameter estimates and standard error (SE) in brackets of different parameterization with piecewise constant model for diastolic blood pressure(dbp) varible: Lagged effect,Time dependent slopes and cumulative . sex/H.Rhythm represents main effects for sex(males) or Heart rhythm(normal), assoct is the association parameter , assoct.s is slope association parameter . Interaction effect parameterization model did not converge.*

	Current Value	Lagged Effect		Time depended Slopes	Cumulative Effect	Interaction Effect	
Effect	Estimate(SE)	Lag1 Estimate(SE)	Lag 2 Estimate(SE)	Estimate(SE)	Estimate(SE)	by sex Effect(SE)	by H.Rhythm Estimate(SE)
sex/H.Rhythm						4.5751 (4.2657)	4.5751 (4.2657)
Assoct	-3.2041 (3.6577)			-6.1074 (4.1783)	2.6381 (5.6107)	-0.1312 (4.8409)	-0.1312 (4.8409)
Interaction				-6.4464 (4.5566)			
Asso.Sex						-6.9235 (7.6321)	-6.9235 (7.6321)
log(xi.1)	0.9464 (2.0583)			2.4117 (2.2510)	-0.9668 (0.5213)	-1.1481 (2.8000)	-1.1481 (2.8000)
log(xi.2)	1.0405 (2.0729)			2.4947 (2.2476)	-1.1273 (0.9111)	-1.0342 (2.8043)	-1.0342 (2.8043)
log(xi.3)	0.1968 (2.1540)			1.6917 (2.3387)	-2.2345 (1.5084)	-1.8860 (2.8598)	-1.8860 (2.8598)
log(xi.4)	-0.4357 (2.2702)			1.0265 (2.4243)	-3.1123 (2.1228)	-2.5196 (2.9468)	-2.5196 (2.9468)
log(xi.5)	-0.4907 (2.1496)			0.8996 (2.2504)	-3.5679 (2.8362)	-2.5746 (2.8566)	-2.5746 (2.8566)

A.2.4 Heart rate (hr)

Table A4: *CHF data. Parameter estimates and standard error (SE) in brackets of different parameterization with piecewise constant model for heart rate varible:Current value, Lagged effect,Time dependent slopes and cumulative . sex/H.Rhythm represents main effects for sex(males) or Heart rhythm(normal), assoct is the association parameter , assoct.s is slope association parameter . Interaction effect parameterization model did not converge. Where ** implies Pvalue=0.0002,* implies a pvalue =0.0471*

	Lagged Effect		Time depended Slopes	cumulative Effect	Interaction Effect by		
Effect	Lag1 Estimate(SE)	Lag 0 Estimate(SE)	Estimate(SE)	Estimate(SE)	by sex Estimate(SE)	by H.Rhythm Estimate(SE)	
sex/H.Rhythm						-1.7139 (3.7206)	-1.7139 (3.7206)
Assoct	11.0657 (3.1329)	5.4173 (2.7344)*0.0467	5.4173 (2.7344)*	11.7471 (3.1368)**	7.9122 (5.6715)	9.2264(4.6462)*	9.2264(4.6462)*
Assoct .s				3.5775 (1.9290)			
Interaction						3.6258(6.1034)	3.6258(6.1034)
log(xi.1)	-7.2680 (2.0186)	-3.8766 (1.6578)	-3.8766 (1.6578)	-7.5557 (1.9838)	-1.2055(0.5248)	-6.4519 (2.8234)	-6.4519 (2.8234)
log(xi.2)	-7.0439 (1.9413)	-3.7743 (1.6470)	-3.7743 (1.6470)	-7.4233 (1.9372)	-1.8123(0.8983)	-6.1991 (2.7934)	-6.1991 (2.7934)
log(xi.3)	-7.7995 (1.9850)	-4.6153 (1.7347)	-4.6153 (1.7347)	-8.2031 (1.9914)	-3.3563 (1.4742)	-6.9533 (2.8266)	-6.9533 (2.8266)
log(xi.4)	-8.3235(2.0768)	-5.2279 (1.8667)	-5.2279 (1.8667)	-8.8204 (2.1160)	-4.6709 (2.0642)	-7.4957 (2.8879)	-7.4957 (2.8879)
log(xi.5)	-8.3768 (1.9825)	-5.2783 (1.7282)	-5.2783 (1.7282)	-9.1309 (2.1665)	-5.8793(2.8270)	-7.5893(2.7969)	-7.5893(2.7969)

A.3 Codes

```
############################
##Diastolic blood pressure##
############################
#1.Current value parameterization#

#longitudinal submodel#
LMeFIT.Diast=lme(dbpt~T,
                    random = ~1+T| ptID,
               na.action = na.omit, data = CHF_Long)

summary(LMeFIT.Diast)

##survial submodel#
coxFit.CHF= coxph(Surv(CHF_surv$T, CHF_surv$status) ~1,
                  data= CHF_surv, x = TRUE)
summary(coxFit.CHF)

####JOINT model###


##Weibull baseline##
jointFit.diast= jointModel(LMeFIT.Diast, coxFit.CHF,
    timeVar = "T" , method = "weibull-PH-aGH",GHk=15,verbose=TRUE)

summary(jointFit.diast)
AIC(jointFit.diast)

###piecewise##
jointFit.diast.P= jointModel(LMeFIT.Diast,coxFit.CHF,
    timeVar = "T" , method = "piecewise-PH-aGH",
 knots=c(30/185,60/185,90/185,120/185),GHk=20 )

 AIC(jointFit.diast.P)
summary(jointFit.diast.P)

 #2.Lagged Effect parameterization#
 #weibull#
lag1_jointFit.diast=update(jointFit.diast,lag=1)
```

```
summary(lag1_jointFit.diast)
AIC(lag1_jointFit.diast)#--18366.7

lag2_jointFit.diast=update(jointFit.diast,lag=2)
summary(lag2_jointFit.diast)
AIC(lag2_jointFit.diast)#-18366.7

##piecewise##
lag1_jointFit.diast.P=update(jointFit.diast.P,lag=1)
summary(lag1_jointFit.diast.P)
AIC(lag1_jointFit.diast.P)-18364.65

lag2_jointFit.diast.P=update(jointFit.diast.P,lag=2)
summary(lag2_jointFit.diast.P)
AIC(lag2_jointFit.diast.P)-18364.65

#################################
#3.Time depeended slopes#########
#################################
dform.diasto=list(fixed=~1,indFixed=2,random=~1,
 indRandom=2)

#weibul#

Slope_jointFit.diast=update(jointFit.diast,parameterization="both",
                derivForm=dform.diasto)
summary(Slope_jointFit.diast)
AIC(Slope_jointFit.diast)

#Piecewise##

Slope_jointFit.diast.P=update(jointFit.diast.P,parameterization="both",
                derivForm=dform.diasto)
summary(Slope_jointFit.diast.P)
AIC(Slope_jointFit.diast.P)

#################################
###4.Cumulative effect parameterization###
#################################
```

```
iform.diasto=list(fixed=~-1+T+I(T^2/2),indFixed=1:2,
             random=~-1 +T +I(T^2/2),indRandom=1:2)
##weibull#

cum_jointFit.diast=update(jointFit.diast,
parameterization="slope",derivForm=iform.diasto)
summary(cum_jointFit.diast)
AIC(cum_jointFit.diast)
plot(cum_jointFit.diast)

#Piecewise#

cum_jointFit.diast.P=update(jointFit.diast.P,
parameterization="slope",derivForm=iform.diasto)
summary(cum_jointFit.diast.P)
AIC(cum_jointFit.diast.P)
plot(cum_jointFit.diast.P)

############################
#5.Interaction Effect#####
############################
##by sex#
##longitudinal submodel##
LMeFIT.Diast.I=lme(dbpt~T,
                     random = ~1+T| ptID,
           na.action = na.omit, data = Long_data)

summary(LMeFIT.Diast.I)

##survial submodel#
coxFit.CHF.I= coxph(Surv(surv_data$T, surv_data$status) ~sex,
                  data= surv_data, x = TRUE)
summary(coxFit.CHF.I)

##JOINT model##

##weibul#
jointFit.diast.I= jointModel(LMeFIT.Diast.I,coxFit.CHF.I,
    timeVar = "T" , method = "weibull-PH-aGH",GHk=15,
     interFact=list(value=~sex,data=surv_data))
```

```
summary(jointFit.diast.I)
AIC(jointFit.diast.I)

####piecewise#
jointFit.diast.P.I= jointModel(LMeFIT.Diast.I,coxFit.CHF.I,
    timeVar = "T" , method = "piecewise-PH-aGH",GHk=15,
 knots=c(30/185,60/185,90/185,120/185),
 interFact=list(value=~sex,data=surv_data))
summary(jointFit.diast.P.I)
AIC(jointFit.diast.P.I)
```

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Modelling Rehospitalization in Telemonitored Chronic Heart Failure Patients: Joint Survival-Longitudinal Approaches with Different Parameterizations

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Datum: **10/09/2014**