T.C.
REPUBLIC OF TURKEY
HACETTEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

FACTORS AFFECTING THE DIAGNOSTIC PERFORMANCE OF TIME-DEPENDENT ROC CURVES FOR LONGITUDINAL DATA

Naime Meriç KONAR

Programme of Biostatistics

DOCTOR OF PHILOSOPHY THESIS

ANKARA

2018

T.C.
REPUBLIC OF TURKEY
HACETTEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

FACTORS AFFECTING THE DIAGNOSTIC PERFORMANCE OF TIME-DEPENDENT ROC CURVES FOR LONGITUDINAL DATA

Naime Meriç KONAR

Programme of Biostatistics

DOCTOR OF PHILOSOPHY THESIS

ADVISOR OF THE THESIS

Prof. Dr. Ahmet Ergun KARAAĞAOĞLU

ANKARA

2018

Factors Affecting the Diagnostic Performance of Time-Dependent ROC Curves for Longitudinal Data

Naime Meriç Konar

Supervisor: Prof.Dr. Ahmet Ergun Karaağaoğlu

This thesis study has been approved and accepted as a Combined Master and PhD dissertation in "Biostatistics Program " by the assesment committee, whose members are listed below, on 20/06/2018:

Chairman of the Committee :	Prof.Dr. Celal Reha ALPAR Hacettepe University
Member :	Prof.Dr.Atilla Halil ELHAN Ankara University
Member :	Prof.Dr.Erdem KARABULUT Hacettepe University
Member :	Prof.Dr.Mehtap AKÇİL OK Baskent University
Member :	Assoc.Prof.Jale KARAKAYA Hacettepe University

This dissertation has been approved by the above committee in conformity to the related issues of Hacettepe University Graduate Education and Examination Regulation.

06 Temmuz 2018

Prof. Diclehan ORHAN, MD, PhD
Institute Manager

YAYIMLAMA VE FİKRİ MÜLKİYET HAKLARI BEYANI

Enstitü tarafından onaylanan lisansüstü tezimin/raporumun tamamını veya herhangi bir kısmını, basılı (kağıt) ve elektronik formatta arşivleme ve aşağıda verilen koşullarla kullanıma açma iznini Hacettepe Üniversitesine verdiğimi bildiririm. Bu izinle Üniversiteye verilen kullanım hakları dışındaki tüm fikri mülkiyet haklarım bende kalacak, tezimin tamamının ya da bir bölümünün gelecekteki çalışmalarda (makale, kitap, lisans ve patent vb.) kullanım hakları bana ait olacaktır.

Tezin kendi orijinal çalışmam olduğunu, başkalarının haklarını ihlal etmediğimi ve tezimin tek yetkili sahibi olduğumu beyan ve taahhüt ederim. Tezimde yer alan telif hakkı bulunan ve sahiplerinden yazılı izin alınarak kullanılması zorunlu metinlerin yazılı izin alınarak kullandığımı ve istenildiğinde suretlerini
Üniversiteye teslim etmeyi taahhüt ederim.

o **Tezimin/Raporumun tamamı dünya çapında erişime açılabilir ve bir kısmı veya tamamının fotokopisi alınabilir.**
(Bu seçenekle teziniz arama motorlarında indekslenebilecek, daha sonra tezinizin erişim statüsünün değiştirilmesini talep etseniz ve kütüphane bu talebinizi yerine getirse bile, teziniz arama motorlarının önbelleklerinde kalmaya devam edebilecektir)

X **Tezimin/Raporumun 20/06/2020 tarihine kadar erişime açılmasını ve fotokopi alınmasını (İç kapak, Özet, İçindekiler ve Kaynakça hariç) istemiyorum.**
(Bu sürenin sonunda uzatma için başvuruda bulunmadığım takdirde, tezimin/raporumun tamamı her yerden erişime açılabilir, kaynak gösterilmek şartıyla bir kısmı veya tamamının fotokopisi alınabilir)

o **Tezimin/Raporumun……..tarihine kadar erişime açılmasını istemiyorum ancak kaynak gösterilmek şartıyla bir kısmı veya tamamının fotokopisinin alınmasını onaylıyorum.**

o **Serbest Seçenek/Yazarın Seçimi**

11 /07/2018

Naime Meriç KONAR

ETHICAL DECLARATION

In this thesis study, I declare that all the information and documents have been obtained in the base of the academic rules and all audio-visual and written information and results have been presented according to the rules of scientific ethics. I did not do any distortion in data set. In case of using other works, related studies have been fully cited in accordance with the scientific standards. I also declare that my thesis study is original except cited references. It was produced by myself in consultation with supervisor Prof. Ahmet Ergun KARAAĞAOĞLU and written according to the rules of thesis writing of Hacettepe University Institute of Health Sciences.

Naime Meriç KONAR

TEŞEKKÜR

Yazar, bu tez çalışmasının gerçekleşmesine olan katkılarından dolayı, aşağıda adı geçen kişi ve kuruluşlara teşekkür eder:

Tez danışmanım Sayın Prof. Dr. A. Ergun Karaağaoğlu, tezin planlanması, geliştirilmesi ve yürütülmesinde çok önemli katkılarda bulunmuştur.

Sayın Prof. Dr. Osman Saraçbaşı, gerek tez izleme komitesinde, gerek doktora eğitimim boyunca bilimsel birikimiyle akademik yaşantıma büyük katkı sağlamıştır.

Sayın Prof. Dr. Mehtap Akçil Ok, Sayın Prof .Dr. Erdem Karabulut ve Sayın Dr. Anıl Dolgun tez izleme komitesinde yer alarak tez çalışmasına değerli katkılarda bulunmuşlardır.

Sayın Prof. Dr. Zeliha Günnur Dikmen, Sayın Doç. Dr. Aslı Pınar ve Sayın Doç. Dr. Oytun Portakal, tezin uygulama kısmında bulunan gerçek verinin sağlanmasında ve bulguların klinik açıdan yorumlanmasında yardımcı olmuşlardır.

Sayın Dr. Eda Karaismailoğlu doktora eğitimim boyunca her konuda bana çok destek olmuştur.

Tez çalışmam boyunca Hacettepe Üniversitesi Biyoistatistik Anabilim Dalı'nın değerleri hocaları desteklerini esirgememişlerdir.

Doktora eğitimim ve tez çalışmam boyunca annem, babam ve arkadaşlarım sabır ve anlayışla bana destek olmuşlardır.

ABSTRACT

Konar, N.M. Factors Affecting the Performance of Time-Dependent ROC Curves for Longitudinal Data. Hacettepe University Institute of Health Sciences, Combined Masters and Ph.D. Thesis in Biostatistics, Ankara, 2018. In medicine, ROC Curve Analysis is frequently used to determine the diagnostic performances of biomarkers. However, time-dependent ROC Curve is utilized in assessing the diagnostic accuracies of longitudinal biomarkers. One of the objectives of this thesis is to evaluate and to compare the diagnostic values of serial biomarker measurements taken from adults in predicting death in Intensive Care Units (ICU) at the end of follow-up period. Time-dependent Area Under Curve (AUC) values, which are calculated by performing joint modeling approach are used for this aim. The other objective is to compare the diagnostic performances of single measurement taken at baseline (t=0) and serial biomarker measurements taken within the follow-up period to determine whether a single value is sufficient to predict the event of interest. Furthermore, time-dependent diagnostic accuracies of these biomarkers are evaluated throughout the follow-up to identify which biomarker should be used at which time-point. Moreover, for each biomarker, cut-off values are determined with the help of Monte-Carlo simulation procedure. Also time-dependent cut-off values are obtained for discriminating subjects at risk and without risk of death on the first three days after the last biomarker measurement for each gender group. Besides, different joint model combinations are constructed for each biomarker to find out the best combination that provides the optimal diagnostic accuracy. In application part, diagnostic performances of serial C-Reactive Protein (CRP) and serial Procalcitonin (PCT) values in predicting death at ICU are investigated and determined that serial CRP values have higher diagnostic accuracy than serial PCT values in predicting death at the end of follow-up. Furthermore, the highest diagnostic accuracy is observed when single measurement of PCT is taken. PCT values are found to have higher diagnostic accuracy than CRP at especially later time-points within the follow-up period. Cut-off value of CRP is proposed to distinguish the groups since it has smaller Coefficient of Quartile Variation and smaller Robust Coefficient of Variation values compared to PCT. The first three days after the last biomarker measurement, cut-off values for PCT are found to be in decreasing trend for men and women, while constant cut-off values in the first two days; then decreasing trend for CRP are observed for both genders. Standard joint model gives the optimal diagnostic accuracy for both CRP and PCT. In conclusion, a comprehensive study has been carried out to assess the factors affecting the diagnostic performance of longitudinal biomarkers via a real-life data application. Coefficient of Quartile Variation measure and Robust Coefficient of Variation are suggested in the decision of choosing the relevant cut-off value. Taking serial biomarker values are suggested to better evaluate the longitudinal profiles of the subjects when needed.

Keywords: time-dependent AUC, longitudinal data, survival data, joint model, cut-off.

ÖZET

Konar, N.M. Uzunlamasına Verilerde Zamana Bağlı ROC Eğrilerinin Tanısal Performansını Etkileyen Faktörler, Hacettepe Üniversitesi Sağlık Bilimleri Enstitüsü Biyoistatistik Programı Bütünleşik Doktora Tezi, Ankara, 2018. Tıpta, belirteçlerin tanısal performanslarının belirlenmesinde ROC Eğrisi sıklıkla kullanılmaktadır. İzlem süresi içinde tekrarlı ölçümleri alınan belirteçlerin tanısal doğruluğunun belirlenmesinde ise zamana bağlı ROC Eğrisi'nden yararlanılmaktadır. Bu tez çalışmasının amaçlarından ilki, Erişkin Yoğun Bakım'da yatan hastalara ait tekrarlı ölçümleri alınan belirteçlerin izlem süresi sonundaki tanısal performansını değerlendirmektir. Bu amaç için birleşik modelleme yaklaşımı yardımı ile elde edilebilen Zamana Bağlı Eğri Altında Kalan Alan (EAA) değerlerinden yararlanılmıştır. Bir diğer amaç, izlemin başında (t=0) alınan belirteç değeri ile izlem süresince alınan tekrarlı belirteç ölçümlerinin tanısal doğruluklarını karşılaştırmaktır. Bununla birlikte, tekrarlı ölçümleri alınan belirteçlerin zamana bağlı tanısal performansları, izlem süresi boyunca değerlendirilmiş ve yoğun bakımda ölümü kestirmede hangi zaman noktalarında hangi belirtecin kullanılması gerektiği belirlenmiştir. Her bir belirteç için izlem sonunda yoğun bakımda ölecek ve sağkalacak bireyleri ayrımsamada kullanılacak kesim noktaları, Monte-Carlo simülasyonu ile elde edilmiştir. Farklı birleşik modeller kurularak belirteçler için en yüksek tanısal doğruluğu veren kombinasyon saptanmıştır. Her bir belirteç için alınan son ölçümden sonraki ilk üç gün boyunca cinsiyet gruplarına göre zamana-bağlı kesim noktaları belirlenmiştir. Uygulamada, erişkin yoğun bakımda yatan hastalardan elde edilen C-Reaktif Protein (CRP) ve Prokalsitonin (PCT) belirteçlerinin yoğun bakımda ölümü kestirmedeki tanısal performansları değerlendirilmiş, izlem süresi sonunda ölümü kestirmede CRP'nin tanısal performansının, PCT'den daha yüksek olduğu belirlenmiştir. Bununla birlikte en yüksek tanısal doğruluğun, izlem başında alınan tek bir PCT ölçümü ile elde edildiği saptanmıştır. İzlem süresi içinde özellikle izlem sonuna yakın zaman noktalarında PCT'nin tanısal doğruluğunun, CRP'ye göre daha yüksek olduğu belirlenmiştir. Çeyrekler (Kartil) Değişim Katsayısı ile Dayanıklı Değişim Katsayısının daha küçük bulunmasından dolayı, CRP'ye ait kesim noktasının kullanılması önerilmiştir. Her bir belirteç için, son ölçümden sonra, hem erkek hem de kadınlarda PCT'nin kesim noktalarının giderek düştüğü, CRP için her iki cinsiyet grubunda da kesim noktalarının izlem sonundaki ilk iki gün sabit kalıp üçüncü günde düştüğü gözlenmiştir. Optimum tanısal doğruluğun elde edilmesinde, her iki belirteç için de standart birleşik modelin kullanılması gerektiği belirlenmiştir. Sonuç olarak, tekrarlı belirteç ölçümlerinin tanısal performansının belirlenebilmesi amacıyla gerçek veri seti üzerinde kapsamlı bir çalışma gerçekleştirilmiştir. Uygun kesim noktasının seçiminde çeyrekler (kartil) değişim katsayısı ile dayanıklı değişim katsayısının kullanılması ve bireylerin uzunlamasına profillerinin daha iyi incelenebilmesi için gerektiğinde belirteçlerden tekrarlı ölçümler alınması önerilmiştir.

Anahtar Kelimeler: zamana bağlı EAA, uzunlamasına veri, sağkalım verisi, birleşik model, kesim noktası.

TABLE OF CONTENTS

LIST OF ABBREVATIONS

AARD	Above Average Risk Difference
AD	Alzheimer's Disease
ADAS	Alzheimer's Disease Assessment Scale
ADAS-Cog 11	Alzheimer's Disease Assessment Scale-cognitive subscale 11 Score
ADAS-Cog 13	Alzheimer's Disease Assessment Scale-cognitive subscale 13 Score
AIDS	Acquired Immune Deficiency Syndrome
AKI	Acute Kidney Injure
AR	Acute Rejection
AUC	Area Under Curve
CD4	Cluster of Differentation 4
CDR-SB	Clinical Dementia Rating Sum of Boxes
CI	Confidence Interval
CQV	Coefficient of Quartile Variation
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DCS	Diabetes Care System
DDI	Dynamic Discrimination Index
DIVAT	Données Informatisées et VAlidées en Transplantation
EM	Expectation - Maximization
EPOCE	Expected Prognostic Observed Cross-Entropy
FAQ	Functional Assessment Questionare
FEV1	Forced Expiratory Volume in the first second
FPR	False Positive Rate
HbA1c	Hemoglobin A1c
HIV	Human Immmunodeficiency Virus
ICU	Intensive Care Unit
IST	Isaacs Set Test
JM	Joint Model
LR	Likelihood Ratio
LVEF	Left Ventricular Ejection Fraction
MACS	Multicenter AIDS Cohort Study
MLE	Maximum Likelihood Estimation
MMSE	Mini Mental Score Examination
MAR	Missing at Random
MCAR	Missing Completely at Random
MNAR	Missing Not At Random
MPA	Mycophenolic Acid
MRD	Difference in Mean Risk
NTproBNP	N-terminal prohormone of brain natriuretic peptide
PCT	Procalcitonin

PSA	Prostate Specific Antigen
QOL	Quality of Life
rAUC	Relative Aurea Under Curve
RCV	Robust Coefficient of Variation
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SE	Standard Error
SBP	Systolic Blood Pressure
SOFA	Sepsis-related Organ Failure Assessment
STR	Sight Threatening Retinopathy
td-AUC	Time-Dependent AUC
td-Cut-Off	Time-Dependent Cut-Off Value
td-ROC	Time-Dependent ROC Curve
td-Sens	Time-Dependent Sensitivity
td-Spec	Time-Dependent Specificity

LIST OF FIGURES

Figure **Page**

LIST OF TABLES

Table **Page**

1. INTRODUCTION

In medicine, gold standard tests are generally expensive, risky or might be impossible to apply for specific diseases. In such situations, diagnostic tests, which are non-risky and cost-effective, are utilized. Since the results of these diagnostic tests are not as accurate as gold standard tests, their diagnostic performances are obtained by means of several measures such as sensitivity, specificity, Youden Index etc. The most frequently used metric for evaluating the diagnostic accuracy of these tests is Area Under Curve (AUC) value obtained by Receiver Operating Characteristic (ROC) Curve (1). It is used for diagnostic tests and/or biomarkers whose results are continuous or ordinal. With the help of the ROC Curves,

- Evaluating the diagnostic performance of a diagnostic test,
- Comparing diagnostic performances of several diagnostic tests,
- Calculating cut-off values for discriminating diseased and non-diseased subjects could be possible.

In classical ROC curve analysis, the status of the subject is assumed to be stable over time. In other words, the measurement time and the event time is the same. However, when the time dimension is incorporated into the study, it's expected to change the status of the subject during the follow-up. In such situations, during the follow-up period some subjects develop disease while some of them do not. The subject who does not develop disease throughout the follow-up is named as censored subject. When there are censored subjects in data set, time-dependent ROC curves are used to evaluate the diagnostic performances of the diagnostic tests and/or biomarkers in predicting the event of interest (2). With the help of time-dependent ROC curves, given that the follow-up time is t_e, the diagnostic accuracy of a biomarker between time interval $[0, t_e]$ can be established. However, serial measurements of biomarkers can be taken during the follow-up period. Assessing the diagnostic performance of the biomarker in predicting the event of interest within the follow-up period by means of the repeated measurements of the biomarkers that were

taken during follow-up is determined by time-dependent ROC curves for longitudinal data (3). For that purpose, mostly time-dependent AUC value, which is obtained by time-dependent ROC Curves to indicate the discriminative ability of the biomarker, is used.

Even though there are numerous studies about time-dependent ROC Curve analysis in literature, most of them had analyzed the diagnostic accuracy of single biomarker measurement, a few studies have focused on evaluating the diagnostic accuracy of serial biomarker values taken within the follow-up period. Rizopoulos has two R packages, JM (4) and JMBayes (5) that have functions to calculate time-dependent diagnostic accuracy metrics, namely time-dependent AUC and Dynamic Discrimination Index (DDI), for serial biomarker measurements. In these packages diagnostic accuracy of longitudinal data has been evaluated by both Frequentist (JM package) and Bayesian (JMBayes package) approaches. On the other hand, Proust-Lima has an R package called lcmm (6), which enables to assess diagnostic accuracies of serial biomarker values via information-theory-based EPOCE metric.

The hypotheses of this thesis are listed below:

- Diagnostic accuracies of serial biomarker values may change in terms of pre-specified cut-off points within the follow-up period.

- Rather than taking a measurement at a single time-point, with the repeated measurements, the predictive ability of the biomarker at the end of the follow-up can be increased.

- Cut-off values that are used to distinguish subjects at risk and subjects that free of risk groups may change over time in terms of genders.

- Diagnostic performance of serial biomarker values may differ in terms of several factors.

For these hypotheses;

- Introducing time-dependent ROC Curves for repeated measurements that were taken during follow-up period,

- Introducing joint modeling approach, which is frequently used to model longitudinal and survival parts of the data simultaneously,

- Evaluating and comparing the diagnostic accuracies of serial biomarker values in predicting the event of interest at the end of follow-up period,

- Comparing diagnostic performances of single measurement taken at baseline (t=0) and serial biomarker measurements taken within the follow-up period in predicting occurrence of event at the end of follow-up,

- Obtaining the cut-off values for both of the biomarkers and choosing the most appropriate threshold value to distinguish the groups,

- Investigating factors affecting the diagnostic performance of serial biomarker measurements to find the optimal model combination,

- Assessing the time-dependent cut-off values during the period for discriminating subjects with and without risk of death after the last biomarker measurement are aimed.

2. GENERAL INFORMATION

2.1. Classical ROC Curve Method

Gold standard tests are described as the most accurate tests in diagnosing diseases in medicine. Even though these tests are the most accurate ones, they can be expensive in practice and risky for the subjects. In such situations, diagnostic tests, which are cost-effective and non-risky, are utilized. Since these tests are not as accurate as gold standard tests, their diagnostic performances are investigated with the help of several metrics. Sensitivity, Specificity, Youden Index, Brier Score, Odds Ratio are a few examples of diagnostic performance measures for diagnostic tests with binary results. On the other hand, if the test has continuous result, ROC Curve Analysis is the most common method for evaluating its performance. ROC Curve Analysis was first developed in 1940s and has been used commonly in different areas such as medicine, psychology, sociology etc.

ROC Curve is constructed with the help of Sensitivity and 1-Specificity metrics. When higher diagnostic test results indicate the disease, the probability of the test result of a diseased subject being higher than a pre-specified cut-off value, c, is defined as sensitivity. On the other hand, the probability of the test result of a non-diseased subject being equal or smaller than a pre-specified cut-off value, c, is defined as specificity.

Mathematical notations of these metrics are given below:

$$\text{Sensitivity}(c) = P(X > c | D = 1) \tag{2.1}$$

$$\text{Specificity}(c) = P(X \leq c | D = 0) \tag{2.2}$$

where D is the indicator of the disease status, 0 refers to non-diseased and 1 refers to diseased group, while X is the result of the diagnostic test.

ROC Curve Analysis is used in following situations:

- Evaluating diagnostic performance of diagnostic tests with continuous or ordinal result,
- Comparing the diagnostic performances of several tests utilized for specific disease,
- Calculating the cut-off value for distinguishing diseased and non-diseased subjects.

Both of the sensitivity and specificity metrics are true classification rates. However, a true classification rate, sensitivity, and a false classification rate, 1-specificity, are used for constructing the ROC Curve. False Positive Rate (FPR) is the probability of test result of a healthy subject being higher than a prespecified cut-off value, c. Mathematical notation of FPR is given below:

$$FPR = P(X > c|D = 0) \tag{2.3}$$

In theory, Area Under Curve (AUC) Value obtained from ROC Curve takes values between 0 and 1. For a diagnostic test with good discriminating capability of diseased and non-diseased subjects, its AUC value is close to 1; while for a diagnostic test with a poor discriminating capability, AUC is close to 0.5.

There are two main approaches to obtain AUC, namely parametric and nonparametric approaches. In parametric approach, AUC calculation is based on the assumption that biomarker values of either diseased or non-diseased groups should follow normal distribution. AUC can be calculated by taking the integral of ROC function. However as the name suggest, nonparametric approach does not require any distributional assumption about biomarker values. Rank-based Mann-Whitney U statistic or Wilcoxon statistic are used in AUC calculation (7).

AUC value obtained by ROC Curve Analysis has several advantages. Prevalance of the disease does not affect the AUC. Moreover, it is not affected by transformations such as logarithmic or square root. Furthermore, ROC Curve is unitless metric, therefore it is used to compare several diagnostic tests which have

different units. All these properities make AUC statistic a commonly-used measure in analyzing the discriminative ability of a diagnostic test or biomarker.

An example of ROC Curve for biomarkers is given below:

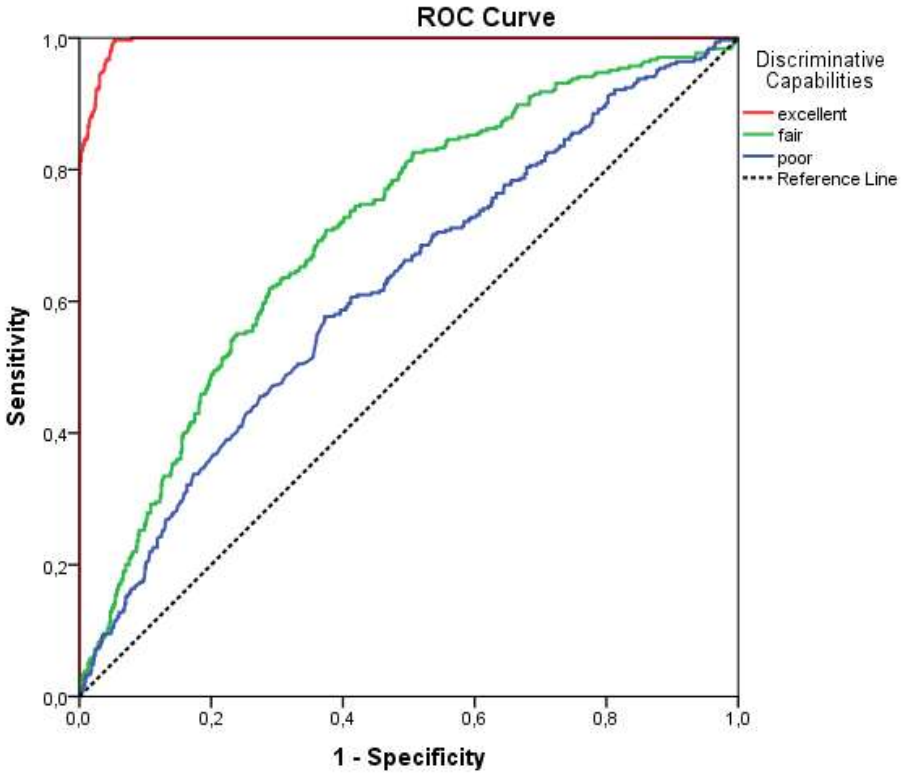

Figure 2.1. Different ROC Curves for 3 different biomarkers which have discriminative capabilities as fair, poor and excellent

In ROC Curve Analysis, closer line to upper-left side indicates that the true classification rate value increases and false classification rate decreases. Therefore, a biomarker that has closer line to upper-left corner has higher diagnostic accuracy; while a biomarker that has closer line to diagonal line has poor discriminating capability.

2.2. Time-Dependent ROC Curve

In classical ROC curves, the status of subject is assumed to be constant over time. Namely, the time that measurement was taken from the biomarker and the time of the occurrence of the event is the same. However, in many situations of clinical

studies, there has been a time interval between the measurement that was taken during follow-up and the event. Within the follow-up, some subjects develop disease, while some of them do not. A subject who does not develop disease during the follow-up is named as censored subject. When there are censored subjects in data set, time-dependent ROC curves are used to evaluate their diagnostic performances. By means of these time-dependent ROC curves, the predictive performances of biomarkers in discriminating events and non-events within the follow-up can be identified. In time-dependent ROC curves, given that the follow-up time is t_e and t is any time-point within the follow-up period, it could be possible to determine the diagnostic accuracy of a test at the end of follow-up (t_e), or any time-point during the follow-up period (t) with the help of a single value taken at baseline (t=0).

Etzioni et al. discussed incorporating the time dimension to the classical ROC Curve Analysis (8). Heagerty et al. published an article to explain the time-dependent ROC Curve in detail (2).

Since the time dimension is incorporated to classical ROC Curve, provided that t is any time-point within the follow-up period, AUC(t) value can be calculated using Sensitivity(t) and 1-Specificity(t) values calculated at time t. Mathematical notations of time-dependent sensitivity and time-dependent specificity are given below:

$$\text{Sensitivity}\ (c, t) = P(X > c | D(t) = 1) \tag{2.4}$$

$$\text{1-Specificity}\ (c, t) = P(X > c | D(t) = 0) \tag{2.5}$$

ROC Curve at time t, ROC(t), is drawn with the help of Sensitivity(t) and 1-Specificity(t) metrics. When higher diagnostic test results indicate the disease, the probability of the test result of a diseased subject being higher than a pre-specified cut-off value(c) at time t is defined as Sensitivity(t), while the probability of the test result of a non-diseased subject being higher than a pre-specified cut-off value(c) at time t is defined as 1-Specificity(t).

An example of time-dependent ROC Curve is depicted in Figure 2.2. Unlike classical ROC curve, time dimension is in the x-axis and time-dependent AUC values are in y-axis in time-dependent ROC curves. Therefore it could be possible to assess the time-dependent accuracy values of a biomarker throughout the period. It is also possible to detect in which time-points the biomarkers have the highest discriminative ability throughout the period by these curves. Another property of the curves is the ability of comparison of several biomarkers for a specific disease under one plot.

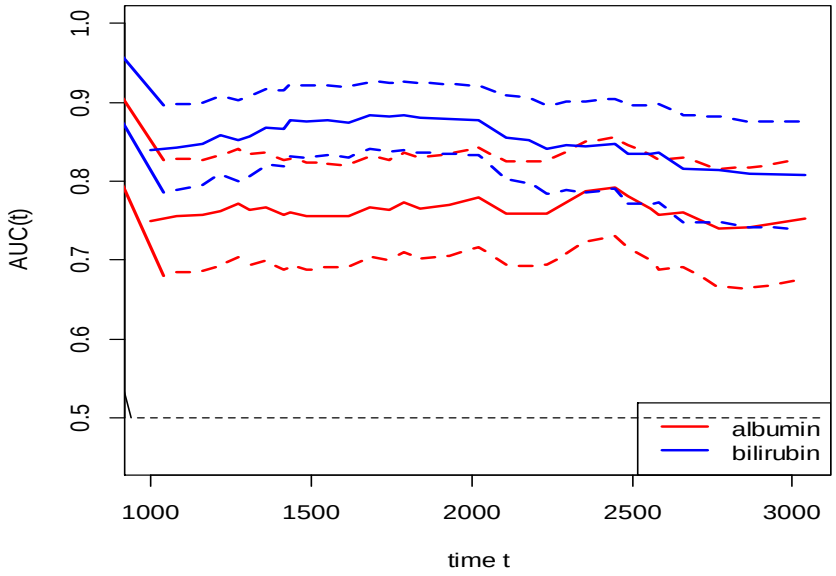

Figure 2.2. Time-dependent ROC curves to compare the diagnostic accuracies of Albumin and Bilirubin biomarkers (solid lines represent time-dependent AUC values over time and dashed lines represent their 95% confidence intervals) (9)

2.3. Time-Dependent ROC Curves for Longitudinal Data

Given that t_e is the follow-up time, it is possible with time-dependent ROC Curve to determine the diagnostic accuracy of a test at the end of follow-up (t_e) or any time-point during the follow-up period (t) with the help of a single value taken at baseline (t=0). However in many situations in clinics, a single measaurement might be insufficient to indicate whether the event will occur in future time points. Therefore taking serial biomarker measurements rather than a single biomarker value

to predict the event of interest is preferred. Given that the follow-up period is t_e, the diagnostic accuracy of serial biomarker values within the period, [0, t_e] is evaluated by time-dependent ROC Curves for longitudinal data.

Time-dependent ROC curves are useful tools for identifying the diagnostic performance of serial biomarker values. Likewise time-dependent ROC Curves obtained from a single biomarker value, time-dependent ROC Curves for longitudinal data assesses predictive ability of biomarkers in predicting the risk of the event of interest for future time points. Therefore measures than can be obtained in longitudinal setting to evaluate diagnostic accuracy, such as time-dependent AUC, obtained from time-dependent ROC Curve, time-dependent sensitivity, time-dependent specificity etc. are also defined as prospective accuracy measures. To evaluate the diagnostic accuracy for the time point t+Δt, (Δt refers to time-interval for the prediction of the event of interest) serial biomarker values which were measured up to t are used. Prior to obtaining AUC (t, Δt) and in constructing ROC(t, Δt); two basic diagnostic accuracy metrics, namely sensitivity(t, Δt) and specificity(t, Δt), are calculated.

Instead of using raw serial biomarker measurements, survival probabilities are used in calculating the diagnostic accuracy metrics for repeated biomarker measurements. Provided that π is the survival probability of a subject who had lived up to time t, $\pi \leq c$ (c is a specified cut-off value in [0, 1] interval) is the probability of "developing the event" within the time interval t+Δt; whereas $\pi > c$ is defined as "censored subject". Under these information, ttime-dependent sensitivity (td-Sens(c, t)) and time-dependent specificity (td-Spec(c,t)) are calculated for varying c ($c \in [0,1]$) with the formulas given below:

$$\textbf{td-Sens(c,t)} = \Pr\left\{\pi_j(t+\Delta t|t) \leq c \middle| T_j^* \epsilon (t, t+\Delta t]\right\} \quad (2.6)$$

$$\textbf{td-Spec(c,t)} = \Pr\left\{\pi_j(t+\Delta t|t) > c \middle| T_j^* > t+\Delta t\right\} \quad (2.7)$$

By means of these values, it could be possible to obtain the time-dependent AUC value, which indicates the discrimination ability of the biomarker within the time interval t+Δt using longitudinal information which were measured until time t. The formula of time-dependent AUC is given below:

$$AUC(t, \Delta t) = \Pr\left[\pi_i(t + \Delta t|t) < \pi_j(t + \Delta t|t) \middle| \{T_i^* \epsilon (t, t + \Delta t]\} \cap \{T_j^* > t + \Delta t\}\right] \quad (2.8)$$

where, i and j refer to comparable subjects, while T_i^* and T_j^* indicates the survival times and π_i and π_j refer to survival probabilities of i^{th} and j^{th} subjects, respectively. The time-dependent AUC value is calculated as in the same logic as classical AUC value. That is, for a specific time point t, under the assumption of having longitudinal information of two subjects, one of whom has the event at time interval t+Δt, and the other one survives, then the survival probability of a subject that has the event of interest should be lower.

The visual representation of a time-dependent ROC Curve for longitudinal data is demonstrated in Figure 2.3. The appearance is similar to classical ROC Curve, that is, sensitivity and 1-specificity values are located on the y and x axes, respectively. Three different curves for each of the future time-point are drawn in one plot (Figure 2.3.)

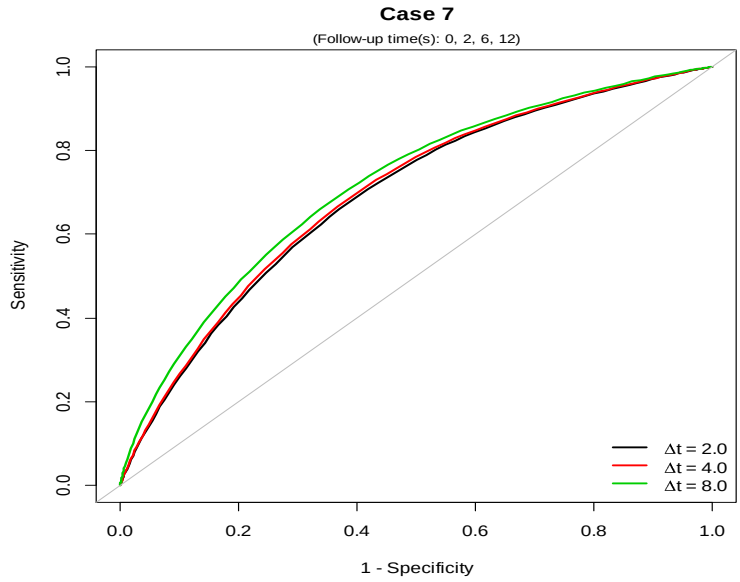

Figure 2.3. Time-dependent ROC Curve for longitudinal data for 7th subject of dataset (black, red and green lines represent prospective diagnostic accuracies of serial CD4 measurements after 2, 4 and 8 months after the last CD4 measurement taken within the follow-up period, respectively.) (4)

2.4. Literature Review for Diagnostic Performance of Longitudinal Data

Even though there are several studies involving different predictive accuracy measures in literature (6, 10-12), diagnostic performance of serial biomarker values is observed to be determined mostly by time-dependent ROC Curves.

The first study about time-dependent ROC curves for a single-biomarker value is based on an article that was published in 2000, by Heagerty et al. (2). In this article, diagnostic performances of biomarkers in discriminating the events and non-events within the period are determined by time-dependent ROC curves. Two different methods, namely Kaplan-Meier Estimator and Nearest Neighbor Estimator are proposed to estimate these time-dependent ROC Curves. In the application part, ROC(t) estimations obtained by these two methods are used to determine the diagnostic accuracies of the standard and a modified flow cytometry measurement for predicting the death caused by breast cancer. At the end of the analyses, at earlier time-points of the follow-up, modified flow cytometry measurement is found to have higher diagnostic value in both estimators, while at later time-points two biomarkers have similar predictive accuracy.

Heagerty and Zheng extended the semiparametric estimation method based on regression quantile approach for time-dependent ROC curves for longitudinal data. The authors focused on asymmetric distribution theory for the estimators of ROC Curve. In their study, the distributional shape of the marker depends on covariates. In application part they have evaluated diagnostic value of serial Forced Expiratory Volume (FEV1) measurements in predicting the risk of death from cystic fibrosis in case-control setting. At the end of the analysis it is demonstrated that measurements which are close to death have higher diagnostic accuracy than measurements that are away from the event (13).

Heagerty and Zheng proposed flexible semiparametric model based on partly conditional joint distribution of longitudinal biomarker values and event times to evaluate diagnostic performance of repeated measurements. In the application part, the AIDS data obtained from MACS (Multicenter AIDS Cohort Study) is used to analyze the association between longitudinal marker CD4 cell counts and status variable is defined as time-to-AIDS or death. Time-dependent ROC curves are obtained to assess the diagnostic accuracy of serial CD4 values. Also, a composite marker, which can be obtained by considering both CD4 and its slope at time s, is defined by the authors to determine whether there is an improvement in discriminative capacity of serial CD4 values. Results revealed that, CD4 values, whose measurement time is away from the time of seroconversion are found as more predictive of the event of interest for both single marker and composite marker cases (14).

Rizopoulos proposed time-dependent diagnostic accuracy metrics and dynamic discrimination index (DDI) to measure the predictive ability of a longitudinal biomarker with the help of joint modeling approach. For this objective, firstly serial longitudinal marker values and time-to-event data have been modeled with joint model, then survival probabilities of the subjects are obtained by performing either Bayesian Approach or Monte Carlo simulation schemes. With the help of these survival probabilities, diagnostic accuracy measures, namely time-dependent sensitivity, time-dependent specificity and time-dependent AUC values

are calculated under the Monte Carlo Approach. Moreover, Dynamic Discrimination Index, which is the average of time-dependent AUC values over the follow-up period, is also proposed. In the application part of the study, the relationship between serial CD4 values and risk of death from AIDS are investigated and diagnostic accuracy of repeated CD4 values are determined by means of time-dependent AUC and Dynamic Discrimination Index (DDI) metrics for the 2, 4 and 8 months after the last CD4 measurements taken from the subjects. Furthermore, two different joint models are constructed, namely the one with focusing on the last CD4 measurement and the other one that focuses on last two CD4 measurements (composite rule) to investigate whether composite rule increases the predictive ability. Moreover, within the context of the study, joint model with current CD4 value (standard joint model parameterization) and joint model with current CD4 value and its slope at time t (joint model with slope parameterization) are compared in terms of predictive accuracies. At the end of the analysis, serial CD4 counts are found to have moderate discriminative capability for almost each comparison (3).

Njagi et al. have investigated the discriminative ability of serial measurements of systolic, diastolic blood pressure, heart rate and weight in telemonitored chronic hearth failure subjects with the help of joint modeling approach. The event is described as rehospitalization of the subjects. Also risk factors such as age, sex, LVEF, NTproBNP and heart rhythm are included in the joint model to investigate their effects on predictive ability of each serial biomarker values. At the end of the analysis, serial diastolic blood pressure values are found to have poor diagnostic accuracy whereas repeated systolic blood pressure have moderate predictive ability. Diagnostic performance of serial heart rate values are classified as good; while weight has the lowest predictive ability over the follow-up period (15).

Abdi et al. performed joint modeling to investigate the relationship between serial mycophenolic acid (MPA) values and acute rejection (AR). They have obtained time-dependent threshold values for serial MPA values based on fitted joint models. Time-dependent ROC Curves have been drawn to obtain time-dependent

threshold values for MPA. Moreover, 95% confidence intervals obtained by nonparametric bootstrap method were also given along with these time-varying cut-off values within the context of the study (16).

Blanche et al. proposed time-dependent AUC and Brier Score in dynamic setting for evaluating the diagnostic accuracy in competing risks data. They proposed nonparametric inverse probability of censoring weighting to estimate dynamic AUC and Brier Score metrics. They used Paquid Cohort Data as training set for constructing two different joint models by using serial Mini Mental Score Examination (MMSE) and Isaacs Set Test (IST) in predicting dementia. French Three-City Cohort Data is used as validation set for obtaining predictive accuracies of these repeated test values for the next 5 years. The time-dependent AUC values of both IST and MMSE are found as high, ranging from 0.79 to 0.90, suggesting good discrimination capability for the next 5 years. Moreover, repeated IST values are found to have higher predictive ability than MMSE, since serial IST either have higher time-dependent AUC values and lower Brier Score compared to those of MMSE (17).

Yang et al. used joint modeling approach to model multiple longitudinal outcomes and a time-to-event outcome by performing Expectation-Maximization (EM) algorithm. They have utilized two recently proposed measures to evaluate the diagnostic values of the longitudinal biomarkers, namely Above Average Risk Difference (AARD) and Difference in Mean Risk (MRD), which are considered to be useful tools when comparing joint models with different predictors. Moreover, the authors calculated two metrics with the help of time-dependent AUC values, namely true percentage gain and estimated percentage gain, whose calculations are based on time-dependent AUC values obtained by two different joint models, which are constructed within the context of the study. Two different joint models are performed, JM1 including only serial diastolic blood pressures (DBP); and the other JM1 including only serial systolic blood pressure (SBP) measurements along with other covariates such as age, sex, race etc; on the other hand JM2 is formed as including both of the serial SBP and DBP values with the covariates and the survival

outcome is defined as time to cardiovascular disease (CVD) for all of the joint models. Predictive performances of these models are assessed via time-dependent AUC values along with AARD and MRD metrics. JM2 has been reported to have better predictive accuracy than both of the JM1 models in terms of all of the diagnostic accuracy values, namely time-dependent AUC, AARD, MRD, true percentage gain and estimated percentage gain. Therefore, modeling two biomarkers under one joint model has been mentioned to enhance the predictive performance (18).

Li et al. investigated the relationship between 33 longitudinal biomarkers, including ADAS-Cog 13, ADAS-Cog 11, CDR-SB, AV45-PET… and conversion to Alzheimer's Disease (AD) utilizing joint modeling approach. They also evaluated diagnostic performances of these biomarkers by means of time-dependent AUC values and Dynamic Discrimination Index (DDI). They have reported functional and cognitive biomarkers such as ADAS, FAQ, MMSE have higher diagnostic accuracy than imaging biomarkers in predicting conversion to Alzheimer's Disease (19).

Mauff et al. extended cumulative effects parameterization type of joint model with a weight function that gives importance to most recent measurements. They performed normal and skewed normal probability density functions as weight function and adopted this extended version to the calculation of diagnostic performance and proposed relative Area Under Curve (rAUC) metric using Bayesian approach. In application part they utilized Hoorn Diabetes Care System (DCS) Cohort to investigate the relationship between HbA1c and developing sight threatening retinopathy (STR). Diagnostic performance of serial HbA1c measurements in predicting the occurrence of STR is determined for different time-intervals over the follow-up by means of rAUC values, which were calculated for both normal and skewed normal density weight functions. Results suggest that measurements which were taken at earlier time-points are found to have better predictive ability in skewed-normal case (20).

Rizopoulos et al. constructed various joint models with different parameterizations and compared these models in terms of diagnostic performances, calibration values and survival probabilities. Time-dependent AUC values are given for comparison process of discrimination part of the study. They have used aortic valve dataset to evaluate the diagnostic accuracy of serial aortic gradient measurement in predicting the composite event, which was described as reoperation or death. At the end of the analysis, standart joint model and joint model with slope parameterization are found to have higher predictive ability than joint model with cumulative effects parameterization (21).

Musoro et al. evaluated diagnostic performances of serial Sepsis-related Organ Failure Assessment (SOFA) scores throughout the follow-up period in competing risk-setting by using joint modeling. They have obtained time-dependent AUC values and Brier Score as diagnostic performance metrics with the help of joint modeling. The authors have investigated the behaviours of time-dependent AUC values and Brier Score over the follow-up period to predict the risk of death in hospital. Results revelaed that either time-dependent AUC or Brier Score metrics gave similar results (22).

2.5. Model Types

In health studies, usually serial biomarker measurements are taken from subjects and with the help of these measures, whether a subject will develop a disease or condition could be determined. Serial CD4 values in HIV studies, serial PSA measurements in prostate cancer studies, cardiac panel measurements for cardiovascular diseases are a few examples in areas where the serial measurements are taken. If the data has two different data structures, including serial biomarker values and survival times, there are several modeling options in literature. The most commonly used methods are listed below:

- Two-stage modeling approach
- Time-dependent Cox regression analysis
- Joint modeling approach

In this thesis, because of several advantages, joint modeling approach will be used for modeling longitudinal and survival data simultaneously. Also this approach will be utilized in obtaining the diagnostic performance metrics of serial biomarker measurements. Therefore the alternatives of Joint Modeling Approach will be explained in brief:

2.5.1. Two-Stage Modeling

In this approach serial biomarker values are modeled with linear mixed effects model (LME) in the first stage and they enter as a time-dependent covariate into the Cox Model in the second stage. The most important disadvantage of this modeling type is that the parameter estimates are underestimated, also the association between repeated measurements and survival times is not taken into account when two stage modeling approach is performed (23).

2.5.2. Time-Dependent Cox Regression Analysis

Raw biomarker values are taken directly into Time-Dependent Cox Regression Analysis as a time-dependent covariate in this approach. Likewise two-stage modeling, this approach also underestimates the model parameters (24). However, there are other disadvantages for using time-dependent Cox model. They are listed below:

- Serial biomarker measurements are endogenous type, which are considered to come from the subjects of the study and have effects on the event of interest. For example, when a study includes the event as risk of death from cardiovascular diseases (CVD), serial cardiac panel biomarkers could be considered as endogenous (internal) biomarkers since either they are measured from the subjects or they affect the risk of death. However, time-dependent Cox Regression can only model exogenous (external) type of measurements, which do not have effect on the event of the study. In other words exogeneous type can be defined as variables which endure independent of the event of interest. For example, levels of humidity in the air and also the

air temperature values can be considered as the external risk factors in a study whose event of interest is defined as “having flu”. Moreover, the time variable itself or seasons of the year (winter, summer etc.) can also be listed as another examples of exogeneous (external) variable type.

- Time-dependent Cox Model assumes that the measurements are obtained without error, however in clinics, biomarker values are measured with biological error of subjects (25).

2.5.3. Joint Modeling Approach

In this approach serial biomarker values are modeled with LME Model and Cox regression model is used to model survival times. The relationship between these two different data structures can be explained by random effects (25).

Joint modeling approach is used to model serial biomarker values (longitudinal data) and survival data in this study. Model parameters are estimated by Maximum Likelihood Estimation Method (MLE). In following parts, LME model for longitudinal data and Cox Regression for survival times are introduced briefly.

2.6. Linear Mixed Effects Model

As mentioned before, serial biomarker values are often taken within the follow-up period in clinics. Positive correlation structure between these serial measurements in clinics is assumed between these repeated measurements. This situation makes it impossible to analyze the data at hand with classical modeling options such as t-test, linear regression etc (25). In such situations, different modeling strategies are used to model correlated data structures. LME model is used for modeling serial biomarker values taken within the follow-up period. This modeling option assumes that each subject has his or her own longitudinal trajectory. This approach does not only allows investigating the longitudinal profile of each subject, but also makes it possible to evaluate the changes of the subjects in the whole sample (25).

In follow-up studies it is very usual to have drop-outs or withdrawals caused by the long follow-up periods. The most important property of LME models is that this approach takes these missing data structures into account while modeling repeated biomarker values. Also this approach takes into account the correlation structure between repeated biomarker measurements and random visit times. These are also important properities for performing LME models for longitudinal data.

2.6.1. Parameter Estimation in Linear Mixed Effects Model

Parameter estimates of the model are obtained by Maximum Likelihood Estimation (MLE) Method. It's assumed that the random effects are normally distributed with 0 mean and variance covariance matrix, D. Error terms of the model are also assumed to follow normal distribution with 0 mean and σ^2 variance. It is also assumed that variance-covariance matrix of random effects are independent of the error terms (25).

The formula for LME model is given below:

$$Y_i = X_i\beta + Z_i b_i + \varepsilon_i \tag{2.9}$$

$$b_i \sim N(0, D) \tag{2.10}$$

$$\varepsilon_i \sim N(0, \sigma^2) \tag{2.11}$$

$$Y_i \sim N(X_i\beta, V_i) \tag{2.12}$$

where,

Y_i : repeated biomarker measurements taken at time t from i^{th} subject

X_i : fixed-effects matrix

Z_i : random-effects matrix

β : fixed-effects regression coefficients

b_i : random-effects regression coefficients

ε_i : error term for i^{th} subject

D : variance-covariance matrix for random-effects

σ^2: variance of error terms

V_i: variance-covariance matrix for Y_i, with V_i=$Z_i D Z_i^T + \Omega_i$

The formula given above can be reformulated by omitting index i. Reformulated equation is given below:

$$Y = X\beta + Zb + \varepsilon \tag{2.13}$$

where X and Z are block diagonal matrices with blocks X_i and Z_i, respectively. Y, b and ε are the vectors which include information from all the subjects in the study. On the other hand, the variance-covariance matrix of Y can be reformulated as $V = ZDZ^T + \Omega$, with D and Ω representing the block diagonal matrices with blocks D and Ω_i, respectively (26).

Under the information of θ is a vector of unknown parameters D and Ω_i, with the notation of $\theta = (D, \Omega_i)$, parameter estimates of LME model are obtained by maximizing the estimation of θ, namely $\hat{\theta}_M$ (26).

$$l(\theta) = -\frac{1}{2} log|V| - \frac{1}{2} r^T V^{-1} r - \frac{N}{2} \log(2\pi) \tag{2.14}$$

where,

$$r = Y - X(X^T V^{-1} X)^{X^T V^{-1} Y}$$

Maximizing the above log-likelihood equation provides the estimates of θ, D and Ω. Then fixed-effects and random-effects coefficients are calculated by solving the below linear equations (26).

$$\begin{bmatrix} X^T \hat{\Omega}^{-1} X & X^T \hat{\Omega}^{-1} Z \\ Z^T \hat{\Omega}^{-1} X & \hat{D}^{-1} + Z^T \hat{\Omega}^{-1} Z \end{bmatrix} \begin{bmatrix} \beta \\ b \end{bmatrix} = \begin{bmatrix} X^T \hat{\Omega}^{-1} Y \\ Z^T \hat{\Omega}^{-1} Y \end{bmatrix} \tag{2.15}$$

The formulas for the fixed-effects and random-effects coefficients are as follows (26):

$$\hat{\beta} = (X^T \hat{V}^{-1} X)^{X^T \hat{V}^{-1} Y} \tag{2.16}$$

$$\hat{b} = \hat{D} Z^T \hat{V}^{-1} (Y - X\hat{\beta}) \tag{2.17}$$

Fixed-effects and random effects describe the population-average and subject-specific effects, respectively. An example figure showing these effects are given below (Figure 2.4.).

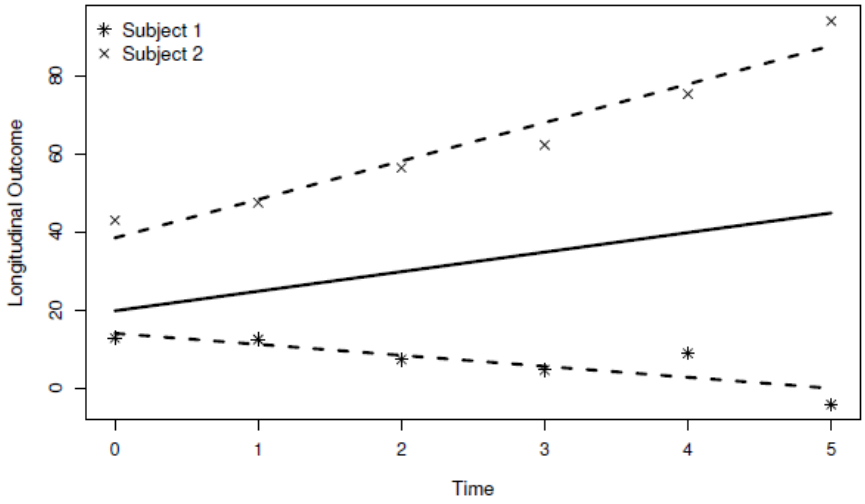

Figure 2.4. Illustiration of average and subjects-specific trajectories in LME model. Points demonstrate hypothetical longitudinal responses of two subjects. (25)

2.7. Cox Proportional Hazard Regression Model

Cox Proportional Hazard Regression Model is used to analyze the time until an event occurs (27). This event could be death, remission, relapse or the diagnosis of any disease. The most important property of Cox Proportional Hazard Regression Model is the presence of censored subjects. The exact survival times are unknown for these subjects. Therefore statistical analyses such as t-test, linear regression analysis can not be used to analyze survival times and simple descriptive statistics

such as aritmetic mean, standard deviation can not be utilized to describe survival times. The reason for that is for such statistical analyses and such descriptive statistics, all subjects in the dataset are needed (25).

T_i^* is assumed to denote the true event time and C_i represent the censoring time for subject i in the sample. The observed event time for the ith subject is described as T_i, which is equivalent to minimum of the true event time and censoring time. It is notated as $\delta_i = I(T_i^* \leq C_i)$. It should also be noted that δ_i is event indicator which takes values 0 or 1.

Under these information, censoring mechanism could be defined as follows:

$\delta_i = 1$ if $T_i^* \leq C_i$ and in this case ith subject has the event,

$\delta_i = 0$ if $T_i^* > C_i$ in that case ith subject is censored

2.7.1. Parameter Estimation in Cox Proportional Hazard Regression Model

Cox proportional regression analysis, which was proposed by Cox in 1972, is frequently used to determine the factors affecting survival times (27). Parameters of this model is estimated by maximum likelihood estimation (MLE) method. Survival times of the subjects are modeled via baseline hazard function. However, the distribution of survival times are unknown. Therefore Cox proportional regression model is a semi-parametric modeling approach. The most important assumption of the model is proportional hazard assumption, which assumes that changes in covariates in the model are constant over time. Hazard ratio is calculated as a risk measure in this model. Given survival up to time point t, it describes the instantaneous risk of the event in the time interval [t, t+Δt) . Formula for hazard ratio is given below (25).

$$h_i(t) = \lim_{dt \to 0} \frac{\Pr(t \leq T^* < t + dt | T^* \geq t)}{dt} = h_0(t) exp(\gamma^T w_i), \quad t > 0 \qquad (2.18)$$

where,

$h_i(t)$: hazard risk for subject i at time t

$h_0(t)$: baseline hazard function

γ : Cox regression coefficients vector

w_i : covariate vector for subject i

To obtain the parameters of interest, Cox (1972) proposed partial log-likelihood function (27).

$$p\ell(\gamma) = \sum_{i=1}^{n} \delta_i \left[\gamma^T w_i - log \left\{ \sum_{T_j \geq T_i} exp(\gamma^T w_j) \right\} \right] \tag{2.19}$$

Maximum Partial Likelihood estimators of parameters are found below (27).

$$\frac{\partial pl(\gamma)}{\partial \gamma^T} = \sum_{i=1}^{n} \delta_i \left\{ w_i - \frac{\sum_{T_j \geq T_i} w_j exp(\gamma^T w_j)}{\sum_{T_j \geq T_i} exp(\gamma^T w_j)} \right\} = 0 \tag{2.20}$$

2.8. Joint Modeling Approach

This approach was first proposed by Schluchter in 1992 to model longitudinal and survival data simultaneously (28). Starting from 2000s, it has become more popular in different areas of health studies ranging from CVD research to cancer studies (29-34). The most important advantage in utilizing this approach is that it allows to model the two different data structures simultaneously while taking the association between them into account. MLE method is used to obtain the parameter estimates in this approach.

Serial biomarker measurements are modeled via LME model, while survival times are modeled with Cox proportional hazard regression model. The relationship

between the longitudinal and survival data is explained by random effects. The effect of serial biomarker measurements taken within the follow-up period on the event of interest is described by α parameter. Under the assumption of modeling serial measurements with LME Model and Cox Regression Model for survival times, standard joint model can be formulated as follows (25).

$$h_i(t) = h_0(t)exp\left[\gamma^T w_i + \alpha\left\{\underbrace{x_i^T(t)\beta + z_i^T(t)b_i}_{m_i(t)}\right\}\right] \quad (2.21)$$

$m_i(t)$: repeated biomarker measurements taken at time t from i[th] subject without measurement error

$x_i(t)$: fixed-effects matrix

$z_i(t)$: random-effects matrix

β: fixed-effects regression coefficients

b_i: random-effects regression coefficients

α: association structure indicating the effect of repeated biomarker measurement taken at time t

$h_i(t)$: hazard risk at time t for i[th] subject

$h_0(t)$: baseline hazard function

γ : Cox regression coefficients

w_i : covariate vector for i[th] subject

2.8.1. Assumptions of Joint Modelling Approach

1. The underlying structure is random effects. Random effects explain both the relationship between survival and longitudinal data and the correlation structure between the measurements taken from the same subject.

2. Given random effects, the two different data structures are independent.

3. Random effects explain all dependence structures in the model.

4. The association structure can be explained by alpha (α) parameter. This parameter is considered as coefficient of joint model that depicts the effect of serial biomarker value on risk at time t.

Other than these assumptions, joint models have assumptions of LME Models, namely normality of response variable, normality of errors, independence of residuals, independence of random effects and errors, and also assuptions of Cox Regression Model, Proportional Hazards Assumption for time-dependent variables, non-informative censoring etc.

2.8.2. Estimation Methods in Joint Modeling Approach

There are two main methods for parameter estimation, namely two-stage method and MLE method. In this thesis, parameter estimates are obtained by MLE method. Therefore this estimation method is explained in brief.

2.8.2.1. Maximum Likelihood Estimation Method

This is the main estimation method to obtain parameters of joint models. This estimation method is based on joint distribution of event time (T_i), longitudinal marker values (y_i) and censoring mechanism (δ_i). To define this joint distribution it is assumed that the vector of random effects underlie both the longitudinal and survival processes. This means that given random effects, survival longitudinal data structures are independent (conditional independence).

This conditional independence of these two data structues is formulated as follows:

$$p(T_i, \delta_i, y_i|b_i; \theta) = p(T_i, \delta_i|b_i; \theta)p(y_i|b_i; \theta) \tag{2.22}$$

$$p(y_i|b_i; \theta) = \prod_j p\{y_i(t_{ij})|b_i; \theta\} \tag{2.23}$$

Under these assumptions, likelihood function for the ith subject can be written below:

$$\log p(T_i, \delta_i, y_i; \theta) = log \int p\ (T_i, \delta_i, y_i, b_i; \theta) db_i \tag{2.24}$$

$$= log \int p(T_i, \delta_i | b_i; \theta_t, \beta) \left[\prod_j p\{y_i(t_{ij}) | b_i; \theta_y\} \right] p(b_i; \theta_b) db_i$$

where,

$$p(T_i, \delta_i | b_i; \theta_t, \beta) = [h_0(T_i) exp\{\gamma^T w_i + \alpha m_i(T_i)\}]^{\delta_i} *$$

$$exp\left(-\int_0^{T_i} h_0(s) exp\{\gamma^T w_i + \alpha m_i(s)\} d_s\right)$$

and

$$p(y_i | b_i; \theta) p(b_i; \theta) = \prod_j p\{y_i(t_{ij}) | b_i; \theta_y\} p(b_i; \theta_b)$$

$$= (2\pi\sigma^2)^{-n_i/2} exp\{-\|y_i - X_i\beta - Z_i b_i\|^2 / 2\sigma^2\} *$$

$$(2\pi)^{-q_i/2} det(D)^{-1/2} exp(-b_i^T D^{-1} b_i / 2)$$

q_b is the dimensionality of random-effects vector, $\|x\| = \{\sum_i x_i^2\}^{1/2}$ is the Euclidean vector form (25).

Calculation of the random-effects of the joint model requires to perform the Gauss-Hermite integration rule since they don't have closed-form solution (35). On the other hand, Gauss-Kronrod Method is utilized for the solution of the integral part of the survival function (4).

In order to calculate the parameter estimates, log-likelihood function, $l(\theta) = \sum_i log p(T_i, \delta_i, y_i; \theta)$, is needed to be maximized.

To maximize the likelihood-function given in the above, there are several maximization algorithms (25).

- Expectation-Maximization (EM)
- Newton-Raphson
- Hybrids

Among these options, EM Algorithm is frequently used compared to its alternatives since model parameters have closed-form in maximization part (25).

2.9. Missing Data Structures in Longitudinal Data

One of the most important property of longitudinal data is missing data, which occurs when some subjects miss their planned visits within the follow- up period. Linear Mixed Effects Models can be described as a useful modeling option since these models can handle this type of data.

Missing data structure can be defined as the probability model describing the relation between the missing and response data (25). There are three main missing data structures in literature, namely Missing At Random (MAR), Missing Completely in Random (MCAR) and Missing Not at Random (MNAR).

MAR structure occurs when missing data related to observed responses but unrelated to the values which should have been obtained (25). Example for this type of structure can be given as study plan which indicating patients with a high biomarker values are needed to be excluded from the study. Not all statistical modeling processes give valid inferences with this mechanism.

MCAR is the case when missingness is unrelated to both observed and unobserved response values. Quitting the study after planned number of measurements can be given as an example of MCAR. Any statistical modeling approach that requires complete data can be performed on datasets with MCAR mechanism.

MNAR occurs when missingness dependes on a part of responses that would have been observed (25). Quality-of-life (QOL) studies can be given as an example for this type of missing data mechanism, since in QOL studies subjects may leave the study at some situations where their QOL come to an agreement.

When missing data mechanism is MAR or MCAR, statistical inferences can be made by ignoring the missing data in the dataset. In such situations, likelihood-based inferences can be performed even after ignoring the missing data. Therefore MAR and MCAR are in the class of ignorable missing data. However, when missing data is decribed as MNAR, then missing values of the data are considered as informative and nonignorable. When missing data structure is MNAR, valid infererences can be obtained based on the joint distribution of measurement and missing processes (25), thus MNAR is considered to be the most appropriate missing data mechanism under joint modeling approach.

2.9.1. Modeling the Missing Data

In the literature, there are three main options to model missing data mechanism along with longitudinal measurements.

These options are listed below:

- Selection Models
- Pattern Mixture Models
- Shared Parameter Models

Selection Models and Pattern Mixture Models are used to model discrete missing data, while Shared Parameter Models are utilized to model continuous missing data structure. Within the context of this thesis, Shared Parameter Models are used to link two data structures and also to handle the missing data structure in longitudinal data analysis:

2.9.1.1. Shared Parameter Models

Shared Parameter Models allow missing data structure and longitudinal data to be modeled simultaneously based on their joint distributions (25). Random effects underlie both the longitudinal and survival processes. Dependence structure between these structures is explained by random effects.

2.9.1.1.1. Conditional Independence Assumption

$$\mathrm{P}(T_i|y_i^0, y_i^m) = \int p(T_i, b_i|y_i^0, y_i^m)\, db_i \qquad (2.25)$$

$$= \int p(T_i|b_i, y_i^0, y_i^m)p(b_i|y_i^0, y_i^m)db_i$$

$$= \int p(T_i|b_i)p(b_i|y_i^o, y_i^m)db_i$$

where y_i^o indicates the observed-data vector, whereas y_i^mrefers to missing-data vector. b_i indicates random-effects and T_i is event time.

According to the conditional independence assumption of joint models, it has been shown that the longitudinal and survival processes share the same random effects; therefore joint models are considered to belong to shared parameter models.

2.10. Parameterization Types in Joint Modeling Approach

Standard joint model assumes that the power of the relationship between biomarker measurement taken at time *t* and hazard at time *t* is explained by α parameter. In other words, the risk at time *t* is depend on the biomarker value measured at time *t* (current value parameterization). But over the years several authors indicated that this could be misleading and may cause information loss (36 - 38). Therefore, parameterization types that indicates the strength of the relationship in more detailed functional forms were developed.

These parameterization types can be listed below:

- Time-dependent slopes parameterization
- Current value and time-dependent slope parameterization
- Cumulative effects parameterization

2.10.1. Time-Dependent Slopes Parameterization

In this parameterization type, the risk at time *t* depends on the slope of the biomarker value measured at time *t* (4). The formula for this parameterization type is given below:

$$h_i(t) = h_0(t)\exp[\gamma^T w_i + \alpha_1 m_i'(t)] \tag{2.26}$$

where

$$m_i'(t) = \frac{d}{dt}\{x_i^T(t)\beta + z_i^T(t)b_i\}$$

$m_i'(t)$ value indicates the slope of value taken at time *t.*

2.10.2. Current Value and Time-Dependent Slope Parameterization

In this parameterization type, the risk at time *t* depends on biomarker value measured at time *t* and its slope at that time (4). The adopted formula for this type is given below:

$$h_i(t) = h_0(t)\exp[\gamma^T w_i + \alpha_1 m_i(t) + \alpha_2 m_i'(t)] \tag{2.27}$$

where

$$m_i'(t) = \frac{d}{dt}\{x_i^T(t)\beta + z_i^T(t)b_i\}$$

$m_i'(t)$ value demonstrates the slope of value taken at time *t*, and α_2 indicates the association between the slope value and the event of interest.

2.10.3. Cumulative Effects Parameterization

In this parameterization type the risk at time *t* depends on the serial biomarker measurements taken up to time *t* (25). Considerations of focusing only on the measurement taken at time *t* and ignoring the longitudinal information throughout the follow-up period led the development of this parameterization type (25, 37, 39, 40).

Formulation of joint model for this parameterization is as follows:

$$h_i(t) = h_0(t) \exp\left[\gamma^T w_i + \alpha \int_0^t m_i(s) ds\right] \quad (2.28)$$

where the integral $\int_0^t m_i(s) ds$ in the formula represents the longitudinal information taken up to time s (25).

2.11. Survival Distribution Types

In many studies, survival times are modeled without specifying the distribution. However, there are several studies in literature that utilize survival distributions such as Weibull, Gamma, Log-Normal, Gompertz, Piecewise-Constant (15, 41, 42). Within the context of this thesis, Piecewise-Constant Distribution is used in the survival part of the joint model in all analyzes. Hence, this distribution is explained briefly.

2.11.1. Piecewise Constant Distribution

In this study, Piecewise Constant Distribution is utilized in survival part because of its ease in practice and allowance to flexibility while modeling. In this distribution, survival times are separated into pieces. The basic assumption of this distribution is that the hazard ratio in each piece is constant but hazard ratios of inter-pieces are different. Quartiles of survival times are used in constructing the pieces. The baseline hazard function is formulated as follows when piecewise constant function is used for modeling survival times:

$$h_0(t) = \sum_{q=1}^{Q} \xi_q I(v_{q-1} < t \leq v_q) \quad (2.29)$$

In the formula, $v_1 < v_2 < \cdots < v_Q$ indicates the order of survival times of subjects from minimum to maximum; and v_Q, is the time period which is greater than the longest survival time. On the other hand, ξ_q indicates hazard in the interval of $(v_{q-1,}v_q]$. q refers to number of pieces (4).

In this thesis Piecewise-Constant Distribution is used as a survival distribution option for modeling process of both of the biomarkers.

2.12. Diagnostic Performance in Joint Modeling Approach

In longitudinal studies, the diagnostic performances of biomarkers are mostly determined by means of time-dependent AUC values. Moreover, time-dependent sensitivity and time-dependent specificity values are obtained as diagnostic accuracy measures in order to determine the specificities and sensitivities of the serial biomarker values over the follow-up period.

Rather than using raw serial biomarker measurements, survival probabilities are used in determining the diagnostic accuracy of repeated biomarker measurements. Provided that π is the survival probability of an subject who had longitudinal biomarker information until time *t*, $\pi \leq c$ (c is a specified cut-off value in [0,1] interval) is the probability of "developing the event" within the time interval $t+\Delta t$; and $\pi > c$ is described as "censored subject". Under these information, time-dependent specificity and time-dependent sensitivity for varying values of c are formulated as follows:

$$\textbf{td-Sens} = \Pr\{\pi_j(t + \Delta t|t) \leq c \,|\, T_j^* \epsilon(t, t + \Delta t]\} \quad (2.30)$$

$$\textbf{td-Spec} = \Pr\{\pi_j(t + \Delta t|t) > c \,|\, T_j^* > t + \Delta t\} \quad (2.31)$$

By means of these values, it could be possible to determine the time-dependent AUC value, which indicates the discrimination ability of the biomarker of the subjects at risk and subjects without the risk of the event within the time interval t+Δt using longitudinal information which were taken up to time *t*. The formula of time-dependent AUC is given below:

$$AUC(t,\Delta t) = \Pr\left[\pi_i(t+\Delta t|t) < \pi_j(t+\Delta t|t)\middle|\{T_i^* \epsilon (t, t+\Delta t]\} \cap \{T_j^* > t+\Delta t\}\right] \quad (2.32)$$

where, i and j refer to comparable subjects, while T_i^* and T_j^* indicates the true event times for i^{th} and j^{th} subject, respectively. The time-dependent AUC value is calculated as in the same logic as classical AUC value. That is, for a specific time point t in the follow-up period, under the information of having two subjects, one of whom has the event at time interval t+Δt, and the other one survives during this interval, then the survival probability of a subject that has the event should be lower (25).

The logic behind the calculation of time-dependent AUC values for longitudinal data is the same as the calculation of Harrell's C index for survival data (43). Given that $\pi_1, \pi_2, \ldots, \pi_n$ are the survival probabilities of the subjects and $T_1, T_2, \ldots, T_n$ are the survival times of these subjects, for a random pair, if the cases of $\pi_i < \pi_j$ and $T_i < Tj$ or $\pi_i > \pi_j$ and $T_i > T_j$ are met, then the the pair is named as concordant. On the other hand, if $\pi_i < \pi_j$ and $T_i > Tj$ or $\pi_i > \pi_j$ and $T_i < T_j$; then the pair is named as discordant. Under these information, discriminative accuracy of a biomarker at time t+Δt is obtained by using longitudinal information obtained up to time *t*, AUC (t, Δt), is the proportion of concordant pairs over all-possible pairs (concordant and discordant) at time *t*, in other words this measure can be described as sum of concordant subjects in both comparable and non-comparable subjects at time *t* :

$$\widehat{AUC}(t,\Delta t) = \widehat{AUC}_1(t,\Delta t) + \widehat{AUC}_2(t,\Delta t) \quad (2.33)$$

Formula for concordant pairs in comparable subjects at time t :

$$\widehat{AUC}_1(t,\Delta t) = \frac{\sum_{i=1}^{n}\sum_{j=1;j\neq i}^{n} I\{\hat{\pi}_i(t+\Delta t|t) < \hat{\pi}_j(t+\Delta t|t)\} * I\left\{\Omega_{ij}^{(1)}(t)\right\}}{\sum_{i=1}^{n}\sum_{j=1;j\neq i}^{n} I\left\{\Omega_{ij}^{(1)}(t)\right\}} \quad (2.34)$$

where,

$$\Omega_{ij}^{(1)}(t) = [\{T_i \in (t, t+\Delta t]\} \cap \{\delta_i = 1\}] \cap \{T_j > t + \Delta t\}$$

Formula for concordant pairs in non-comparable subjects at time *t* due to censoring is given below:

$$\widehat{AUC}_2(t, \Delta t) = \frac{\sum_{i=1}^{n} \sum_{j=1; j\neq i}^{n} I\{\hat{\pi}_i(t+\Delta t|t) < \hat{\pi}_j(t+\Delta t|t)\} * I\{\Omega_{ij}^{(2)}(t)\} * \hat{K}}{\sum_{i=1}^{n} \sum_{j=1; j\neq i}^{n} I\{\Omega_{ij}^{(2)}(t)\} * \hat{K}} \qquad (2.35)$$

where,

$$\Omega_{ij}^{(2)}(t) = [\{T_i \in (t, t+\Delta t]\} \cap \{\delta_i = 0\}] \cap \{T_j > t + \Delta t\}$$

$$\hat{K} = 1 - \hat{\pi}_i(t + \Delta t|T_i)$$

In the above formulas, $\Omega_{ij}^{(1)}(t)$ and $\Omega_{ij}^{(2)}(t)$ denote all the comparable and non-comparable subjects at time *t*, respectively, while $\hat{K}$ represents the probability of the pairs which can not be used in calculation of $\widehat{AUC}(t, \Delta t)$ due to lack of event in the pair (43).

As mentioned before, time-dependent sensitivity and time-dependent specificity for longitudinal data are calculated with the help of survival probabilities rather than raw biomarker values. However, these time-dependent diagnostic accuracy metrics can also be notated as a function of longitudinal information. These formulas are given below:

"Success" or "Event" can be defined as:

$$S_i(t, k, c) = \{y_i(s) \geq c_s; k \leq s \leq t\} \qquad (2.36)$$

"Censored subject" can be specified as:

$$F_i(t, k, c) = \{y_i(s) < c_s; k \leq s \leq t\} \qquad (2.37)$$

$y_i(s)$: the value of the biomarker taken at time s for subject i

c_s : vector of threshold values

k : past biomarker values

Under these information, time-dependent sensitivity and time-dependent specificity can be defined as follows:

Time – Dependent Sensitivity :

$$TP_t^{\Delta t} = Pr\{S_i(t,k,c)|T_i^* > t, T_i^* \in (t, t+\Delta t]\}$$
$$= \frac{Pr\{S_i(t,k,c), T_i^* \in (t, t+\Delta t]|T_i^* > t\}}{1 - Pr(T_i^* > t + \Delta t \big| T_i^* > t)} \quad (2.38)$$

Time – Dependent Specificity :

$$1 - FP_t^{\Delta t} = Pr\{F_i(t,k,c)|T_i^* > t, T_i^* > t + \Delta t\}$$
$$= \frac{Pr\{F_i(t,k,c), T_i^* > t + \Delta t|T_i^* > t\}}{Pr(T_i^* > t + \Delta t \big| T_i^* > t)} \quad (2.39)$$

Under the assumption of joint models, which states random effects b_i underlie both the longitudinal and survival processes, numerators and denominators of these time-dependent diagnostic accuracy metrics are reformulated and they can be estimated with the help of Monte-Carlo simulation schemes.

After the estimation of time-dependent sensitivity and time-dependent specificity, and under the information that c is the vector of as all possible thresholds in the study, time-dependent ROC Curve for longitudinal data can be formulated as follows:

$$ROC_t^{\Delta t}(p) = TP_t^{\Delta t}\left\{\left[FP_t^{\Delta t}\right]^{-1}(p)\right\} \quad (2.40)$$

In this formula p takes values between 0 and 1 and $\left[FP_t^{\Delta t}\right]^{-1}(p)$ can be defined as the infimum value which mets the $\left[FP_t^{\Delta t}\right]^{-1}(p) = inf_c\{c: FP_t^{\Delta t}(c) \leq p\}$ criteria (25).

3. MATERIAL AND METHOD

Patients who were admitted to Hacettepe University Adult Intensive Care Units between January 2015 to March 2017 were included in the study. Data set was obtained by files of the subjects by using the database of Hacettepe University Hospital Informatıon System. (NUCLEUS).

Patients' age, gender and intensive care unit where they stay (emergency ICU, brain surgery ICU, general surgery ICU, internal diseases ICU, cardiology ICU, neurology ICU) along with C-reactive Protein (CRP) and Procalcitonin (PCT) biomarkers are recorded. Inclusion criteria are defined as age 18 or older, length of stay in any intensive care unit is at least 24 hours or longer; exclusion criteria is defined as having any additional disease (orthopedics, oncology, psychiatry etc.)

One of the recorded biomarkers, CRP, is a protein, produced by liver and lipid cells. When there is an inflammation in the body, CRP value increases. Also this biomarker takes higher values in case of stress, trauma and infection (44-46). On the other hand, there are studies in literature indicating that this biomarker is a risk factor for cardiovascular diseases (47-48), while some studies describe CRP as an important marker for sepsis (49-50).

The other biomarker Procalcitonin is synthezied in tiroid and known as pro-hormone of calcitonin. It is un-measurable in healthy subjects, its values increase in case of infection in the body (51-52). Likewise CRP, this biomarker is also defined as the most promising marker for sepsis (53-54). This biomarker also has been reported to be mostly used to demonstrate the difference between viral and bacterial infections (55).

To evaluate acute inflammatory response clinically, follow-up period is determined as 30 days in this thesis.

The event of interest is determined as death in intensive care units, in other words the event is defined as ICU mortality. No specific cause of death was

determined for the event. That is, the death could be from CVD or infectional diseases could cause the death. Therefore, the event is defined as death from any cause in Adult Intensive Care Units (in hospital).

This study was approved by the Hacettepe University non-interventional Clinical Studies Ethical Committee (Approval date: 14.03.2017, Number: GO:17/233)

The descriptive statistics, univariate analysis and graphics were obtained using IBM SPSS Statistics version 22.0 from Hacettepe University and R Statistical Programming Language 3.4.3. Chi-Square Test is used for categorical variables, while Mann-Whitney U Test is used to compare the numerical and non-normal distributed variables between two groups. Kolmogorov-Smirnov Normality Test is used to determine whether the CRP and PCT measurements are normally distributed. Median values and minimum-maximum values along with mean and standard deviations for biomarkers are given as basic descriptive statistics. Since both of these biomarkers do not follow normal distribution ($p<0.05$), logarithmic transformation was applied. Kolmogorov-Smirnov normality test results revealed that even log-transformed CRP and PCT values are not normally distributed ($p<0.05$). Therefore nonparametric hypothesis test is performed for the comparison of log-transformed CRP and PCT values in the analyses.

CRP and PCT biomarkers are used in this thesis and their diagnostic values are evaluated throughout the follow-up period by means of Time-Dependent AUC (td-AUC) values obtained by joint models. Time-dependent ROC Curves are constructed for each biomarker to visualize the results. The dataset is formed by using Hacettepe University Hospital Information System (NUCLEUS), retrospectively. Age and gender information are recorded as basic demographic characteristics with serial CRP and PCT values. Two different datasets for each biomarker are created and two different joint models are used to obtain diagnostic accuracies. Each dataset has one longitudinal biomarker (CRP or PCT) and a survival outcome, which is ICU mortality. Part of these datasets are given for each

biomarker in Appendix-II and Appendix-III. Shared parameter models are utilized to link the two different data structures. Parameter estimates are obtained by MLE method. JM R package is used for constructing joint models, obtaining td-AUC values, td-Cut-Off values and drawing td-ROC curves (4). SurvivalROC R package is utilized for calculating td-AUC value for a single biomarker value taken at baseline (t=0) (56). Boot R package is used in obtaining confidence intervals of td-AUC values by performing nonparametric percentile bootstrap method (57, 58). Boot package is also used to obtain standard errors for td-AUC values, Coefficient of Quartile Variation (CQV) (59) and Robust Coefficient of Variation (RCV) statistics are proposed for deciding the relevant cut-off value to discriminate subjects at risk and without risk of event of interest. Both of the CQV and RCV statistics are used to compare the variability of non-normal distributed samples.

The formula of Coefficient of Quartile Variation is given below:

$$CQV = \frac{Q_3 - Q_1}{Q_3 + Q_1} \tag{3.1}$$

where Q_3 and Q_1 refers to the third and first quartiles in the population, respectively.

When Q_1 and Q_3 are not known, their estimates are used in calculation of Coefficient of Quartile Variation. Given that q_1 and q_3 are estimates of Q_1 and Q_3, respectively, estimation of Coefficient of Quartile Variation is formulated below:

$$cqv = \frac{q_3 - q_1}{q_3 + q_1} \tag{3.2}$$

Moreover, semi-interquartile range to median ratio statistic, which can be considered as the robust alternative of Coefficient of Variation is also calculated along with CQV value in order to determine the most relevant cut-off point.

Formula for semi- interquartile range to median ratio (Robust Coefficient of Variation (RCV)) is as follows:

$$RCV = \frac{\frac{Q_3 - Q_1}{2}}{M} \tag{3.3}$$

where $(Q_3 - Q_1)/2$ refers to semi-interquartile range and M is median of the sample.

rcv can be describes as estimator of RCV, and used when Q_1, $Q_3$and M are unknown. Its formula is given below:

$$rcv = \frac{\frac{q_3 - q_1}{2}}{m} \tag{3.4}$$

where q_1 , q_3 and m are estimators of Q_1, $Q_3$and M, respectively.

4. RESULTS

Serial measurements of CRP of 457 subjects and serial values of PCT of 534 subjects are analyzed. Basic descriptive statistics for recorded variables are given in Table 4.1a and Table 4.1b:

Table 4.1a. Descriptive Statistics for C-reactive Protein (CRP) and Procalcitonin (PCT) Datasets in terms of status and gender

Variable	CRP	n (%)	Variable	PCT	n (%)
Status	**Censored**	322 (70.5)	**Status**	**Censored**	384 (71.9)
	Event	135 (29.5)		**Event**	150 (28.1)
Gender	**Female**	223 (48.8)	**Gender**	**Female**	251 (47)
	Male	234 (51.2)		**Male**	283 (53)

Table 4.1b. Descriptive Statistics for baseline measurements of C-reactive Protein (CRP) and Procalcitonin (PCT) measurements, age and survival times in both datasets

Biomarker	Variable	Median [Min, Max]	Mean ± SD
CRP	**CRP (Untransformed)**	8.850 [0.138, 57.500]	11.059 ± 9.759
	CRP (Transformed)	0.947 [-0.860, 1.760]	0.838 ± 0.487
	Age	69 [18, 96]	65.94 ± 17.524
	Survival Time	18 [2, 30]	21.42 ± 8.854
PCT	**PCT (Untransformed)**	0.318 [0.001, 289.7]	5.168 ± 26.234
	PCT (Transformed)	-0.498 [-3, 2.462]	-0.305 ± 0.821
	Age	68 [18, 95]	65.34 ±17.812
	Survival Time	17 [1, 30]	20.88 ± 8.98

Descriptive statistics for dead and censored subjects for each biomarker are given in Table 4.2a and Table 4.2b:

Table 4.2a. Results of univariate analysis of categorical variables for CRP and PCT datasets

		Status		p -value
CRP	**Gender**	**Censored**	**Dead**	
	Female	154 (47.8)	69 (51.1)	
	Male	168 (52.2)	66 (48.9)	0.547
		Status		**p -value**
PCT	**Gender**	**Censored**	**Dead**	
	Female	179 (46.6)	73 (48.7)	
	Male	205 (53.4)	77 (51.3)	0.700

Table 4.2b. Results of univariate analysis of numerical variables for CRP and PCT datasets

Biomarker	Variable	Median [Min, Max]		p-value
		Censored	Dead	
CRP	Age	68.5 [18, 95]	69 [18, 96]	0.180
	CRP (Untransformed)	7.985 [0.148, 57.500]	11 [0.138, 47.700]	0.001
	CRP (Transformed)	0.902 [-0.830, 1.760]	1.041 [-0.860, 1.679]	0.001
	Survival Time	18 [2, 30]	18 [2, 30]	0.436
PCT	Age	67 [18, 95]	71 [18, 95]	0.008
	PCT (Untransformed)	0.230 [0.001, 289.7]	0.676 [0.055, 253.9]	<0.001
	PCT (Transformed)	-0.638 [-3, 2.462]	-0.170 [-1.260, 2.405]	<0.001
	Survival Time	18 [1, 30]	15 [2, 30]	0.038

In the survival part, univariate Cox regression analysis is applied for each biomarker and variables with $p<0.20$ are aimed to include in the final Cox Model as potential factors. The univariate analysis results are given in the following table (Table 4.3.)**.**

Table 4.3. Results for univariate Cox Regression Analysis

Biomarker	Variable	β	SE (β)	Hazard Ratio (Exp(β))	95% CI of Exp(β)	p-value
CRP	Age	0.001	0.005	1.001	0.992 - 1.010	0.854
	Gender	-0.051	0.172	0.951	0.678 - 1.332	0.768
PCT	Age	0.005	0.005	1.005	0.995 - 1.014	0.346
	Gender	-0.024	0.163	0.976	0.709 - 1.344	0.882

Results of the univariate Cox Regression suggest that there is not any factor that could affect the survival times of CRP and PCT biomarkers($p>0.05$). Therefore, survival part is modeled without any factor, only using baseline hazards for both CRP and PCT.

Subject-specific longitudinal profiles for randomly selected 16 subjects for both of the samples of CRP and PCT PCT to help modeling the random effects of linear mixed-effects model for serial biomarker values.

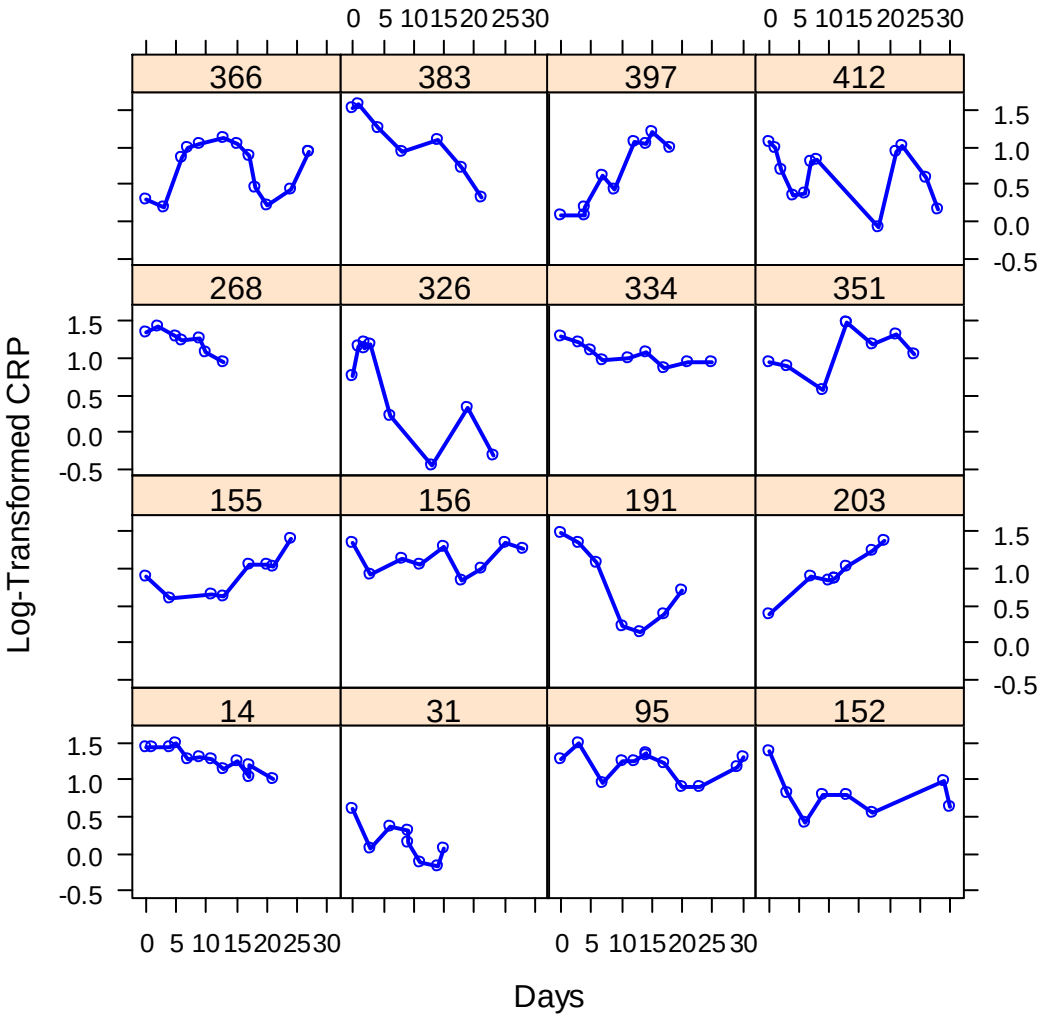

Figure 4.1a. Subject-specific longitudinal profiles of serial log-transformed CRP measurements for randomly selected 16 patients.

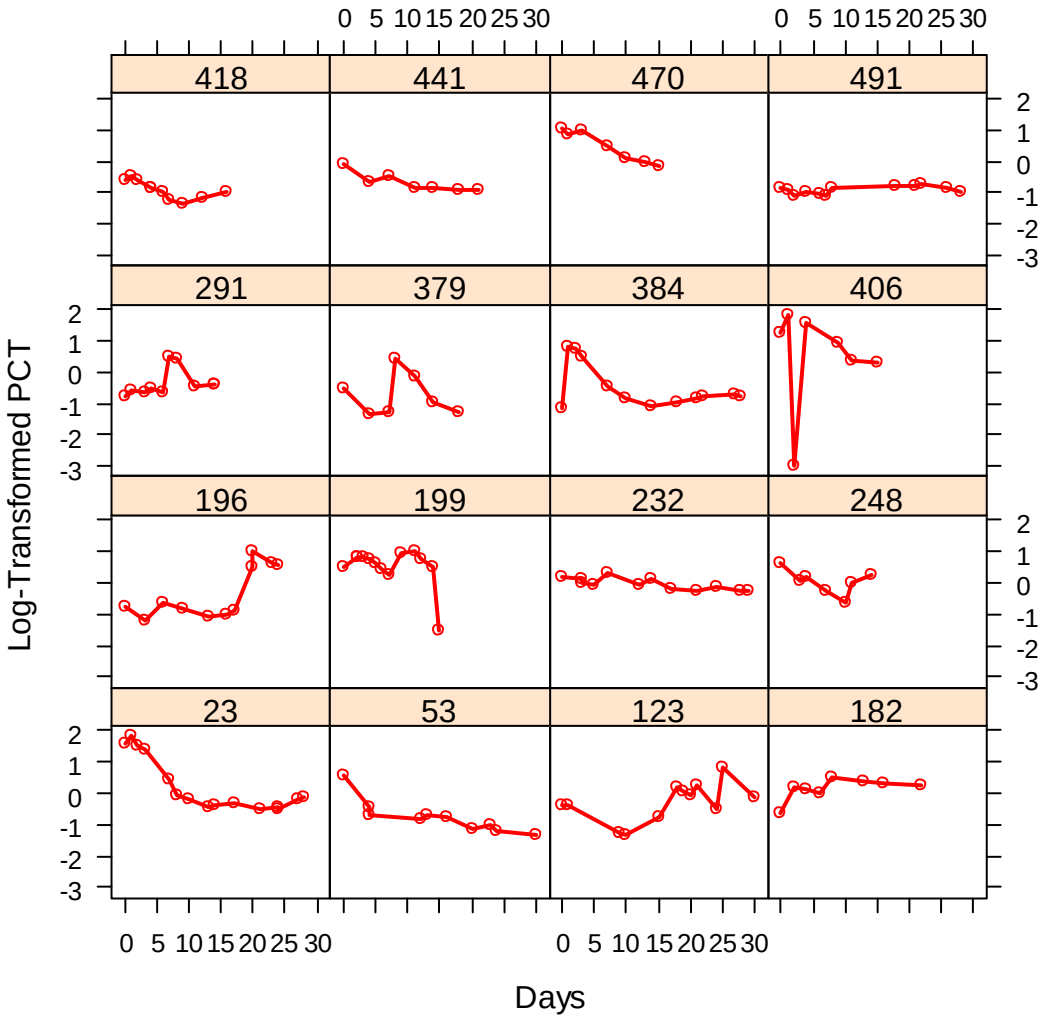

Figure 4.1b. Subject-specific longitudinal profiles of serial log-transformed PCT measurements for randomly selected 16 patients.

In both of the figures, numbers on the top of each figure depict ID numbers for each subject.Figure 4.1a and Figure 4.1b. show that subjects-specfic profiles of either CRP or PCT have almost nonlinear trajectory over the follow-up period. Visually, quadratic function of time in random-effects part of the linear mixed effects model for both of the biomarkers is considered to be a plausible option. Moreover, random intercept+random slope models are also constructed for each biomarker to take the change in each subject within the period into account. Random intercept+random slope models are also considered as an alternative option for the comparison of these models.

In the modeling of longitudinal CRP and PCT biomarkers, several modeling options are applied to data at hand for both fixed and random effects to find out the optimum model for both biomarkers. Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) metrics and p-values are utilized for this purpose.

For the random-effects part, two different modeling options, namely Random Intercept-Random Slope and Quadratic Random Effects, are applied. The random intercept-Random Slope model was constructed with the main effect of time both in fixed and random-effects part of the linear mixed-effects model. On the other hand quadratic random effects model was constructed bu using qjuadratic form as a function of time-points in random-effects part. Results are given below (Table 4.4.)

Table 4.4. Results of Comparison of Two Different Models Applied to Random-Effects Part of Longitudinal Sub-Model

Biomarker	Model	AIC	BIC	LR	Comparison of LR	p-value
CRP	Random Intercept+Random Slope	2125.921	2160.690	-1056.960		
	Quadratic Random Effects	2021.285	2073.439	-1001.643	110.6355	<0.0001
PCT	Random Intercept+Random Slope	5349.765	5385.508	-2668.882		
	Quadratic Random Effects	5177.135	5230.75	-2579.567	178.6299	<0.0001

Quadratic random effects models are chosen for both CRP and PCT biomarkers since these models have smaller AIC and BIC values, which means quadratic random effects model option fits both of the CRP and PCT datasets better than the random intercept-random slope model alternatives.

AIC, BIC and Likelihood Ratio (LR) values are given for both fixed and random effects of the longitudinal model in the following table (Table 4.5):

Table 4.5. Model Selection Measures for Each Model Applied to Fixed-Effects Part of Longitudinal Sub-Model

Biomarker	Model	Model Selection Measures		
		AIC	BIC	LR
CRP	**time**	2021.285	2073.439	-1001.643
	time+age	2032.347	2090.291	-1006.174
	time+gender	2026.823	2084.767	-1003.412
	time*age	**2045.454**	**2109.188**	**-1011.727**
	time*gender	2037.419	2101.153	-1007.709
	time*(age+gender)	2061.668	2136.979	-1017.834
PCT	**time**	5177.135	5230.75	-2579.567
	time+age	5189.647	5249.215	-2584.823
	time+gender	5182.364	5241.932	-2581.182
	time*age	**5199.653**	**5265.175**	**-2588.827**
	time*gender	5190.543	5256.065	-2584.272
	time*(age+gender)	5213.405	5290.830	-2593.703

Other than model selection criteria, p-values are also utilized to help select the best model that fits the data most in the fixed-effects part. Following table indicates all the models applied for fixed-effects part and p-values of the variables in these models.

Table 4.6. Coefficients and p-values for each model applied to Fixed-Effects Part of Longitudinal Sub-Model

Biomarker	Model	Variables	β	SE(β)	p-value
CRP	time	time	-0.0030	0.0016	0.0374
	time+age	time	-0.003	0.0016	0.0342
		age	0.002	0.001	0.093
	time+gender	time	-0.003	0.0016	0.0371
		gender	0.041	0.039	0.2923
	time*age	time	**-0.0180**	**0.0064**	**0.0042**
		age	**0.0003**	**0.0012**	**0.7887**
		time:age	**0.0002**	**0.00009**	**0.0163**
	time*gender	time	-0.002	0.002	0.4525
		gender	0.0642	0.045	0.1559
		time:gender	-0.003	0.003	0.3068
	time* (age+gender)	time	-0.017	0.0067	0.0133
		age	0.0004	0.00125	0.7236
		gender	0.0650	0.045	0.1503
		time:age	0.0002	0.00009	0.0194
		time:gender	-0.003	0.0032	0.4147
PCT	time	time	-0.0078	0.0366	0.003
	time+age	time	-0.0078	0.00262	0.0027
		age	0.0011	0.0016	0.4653
	time+gender	time	-0.0077	0.0026	0.0031
		gender	0.0463	0.0579	0.4233
	time*age	time	**-0.0352**	**0.01**	**0.0005**
		age	**-0.0022**	**0.002**	**0.2639**
		time:age	**0.0004**	**0.0001**	**0.0048**
	time*gender	time	-0.0035	0.003	0.3522
		gender	0.1168	0.0733	0.1114
		time:gender	-0.0083	0.0052	0.1133
	time* (age+gender)	time	-0.0310	0.143	0.1504
		age	-0.0020	0.002	0.2964
		gender	0.1140	0.073	0.1204
		time:age	0.0004	0.0001	0.006
		time:gender	-0.0075	0.0051	0.145

Results revealed that, both of the biomarkers should be modeled with the main-effects of time and age and their interaction term time*age since main effecs of time and time*age interaction term are statistically significant in both CRP and PCT samples ($p<0.05$). Variance-covariance matrix of random-effects and standard error

of the linear mixed-effects models are also given for linear mixed-effects models for both CRP and PCT samples (Table 4.7).

Table 4.7. Variance-covariance matrix of random-effects in linear mixed-effects models for CRP and PCT

		Intercept	**time**	**time^2**
CRP	**Intercept**	0.241	-0.017	0.000434
	time	-0.017	0.0036	-0.0001
	time^2	0.000434	-0.0001	0.00000343
		σ = 0.2520431		
		Intercept	**time**	**time^2**
PCT	**Intercept**	0.681	-0.0442	0.000859
	time	-0.0442	0.00977	-0.0003
	time^2	0.000859	-0.0003	0.0000124
		σ = 0.4096713		

After the modeling processes of survival and longitudinal data final joint models are formulated as follows for both of the biomarkers:

$$h_i(t) = h_0(t)[\alpha\{\beta_0 + \beta_1 * \text{time} + \beta_2 * \text{age} + \beta_3 \text{time} * \text{age} + b_0 + b_1 * \text{time} + b_2 * (time)^2\}] \quad (4.1)$$

Results of joint models are given in following table for both of the biomarkers (Table 4.8a and Table 4.8b).

Table 4.8a. Coefficients, standard errors, p-values and goodness of fit statistics of joint models for both CRP and PCT

Biomarker	Process	Variable	β	SE (β)	p-value
CRP	Longitudinal	**Intercept**	**0.8082**	**0,0845**	**<0.0001**
		time	**-0.0181**	**0.0065**	**0.0049**
		age	0.0003	0.0012	0.8025
		time*age	**0.0002**	**0.0001**	**0.0171**
	Survival	**α**	**0.0338**	**0.0156**	**0.0296**
		log (xi.1)	-5.0018	0.2186	
		log (xi.2)	-4.1232	0.236	
		log (xi.3)	-4.3704	0.2298	
		log (xi.4)	-3.9563	0.1937	
		log (xi.5)	-3.772	0.2113	
		log (xi.6)	-3.7413	0.3365	
		log (xi.7)	11.9553	0.2401	
		σ = 0.2521199			
		AIC = 2822.321, **BIC** = 2900.69			
PCT	Longitudinal	**Intercept**	-0.1301	0.1353	0.3363
		time	**-0.0358**	**0.0100**	**0.0003**
		age	-0.0024	0.0020	0.2394
		time*age	**0.0004**	**0.0001**	**0.0034**
	Survival	**α**	**0.0247**	**0.0109**	**0.0235**
		log (xi.1)	-5.0257	0.2236	
		log (xi.2)	-4.0087	0.1826	
		log (xi.3)	-4.1978	0.2238	
		log (xi.4)	-3.8772	0.1927	
		log (xi.5)	-3.9117	0.1895	
		log (xi.6)	-3.4461	0.2782	
		log (xi.7)	11.5741	0.2899	
		σ = 0.4094836			
		AIC = 6327.039, **BIC** = 26408.367			

Table 4.8b. Variance-covariance matrix of random-effects in joint models for CRP and PCT

		Intercept	time	time^2
CRP	**Intercept**	0.238	-0.0168	0.000423
	time	-0.0168	0.0036	-0.0001
	time^2	0.00042	-0.0001	0.0000034
		Intercept	**time**	**time^2**
PCT	**Intercept**	0.669	-0.043	0.000833
	time	-0.043	0.0098	-0.0003
	time^2	0.000833	-0.0003	0.0000125

Both of the models have statistically significant time main-effect and time*age interaction terms in fixed-effects models. Moreover, either serial CRP values or repeated PCT measurements are shown to have an effect on ICU mortality. Their effects are found as statistically significant ($p<0.05$).

4.1.Evaluating Diagnostic Performances of Serial CRP and PCT Values

Time-dependent AUC values are used as diagnostic performance measures of CRP and PCT biomarkers to be able to distinguish subjects with and without risk of death at Intensive Care Units at the end of the follow-up period, 30 days.

To assess the diagnostic values of repeated measurements of these biomarkers, several cut-off points are defined. The objective is to be able to evaluate the change in time-dependent diagnostic accuracy values under these different cut-off points. Utilizing serial biomarker values taken up to these cut-off points, determining the discriminative ability of the CRP and PCT biomarkers at the end of follow-up period is aimed. The first cut-off point option is considering the median of time points that the serial biomarker values are taken within the period. It's observed that about half of the measurements are taken at around 7th and 6th day for CRP and PCT biomarkers, respectively. Until 7th day, mean of 2.932 and median of 3 CRP measurements per subject are taken, while until 6th day, mean of 2.702 and median of 3 measurements of PCT are taken from per subject. Time-dependent diagnostic accuracy metrics are calculated using measurements up to 7th day for CRP, and while measurements taken up to 6th day for PCT are used to predict ICU mortality at 30th

day. Another cut-off point consideration would be taking into median of survival times of the subjects into account. For CRP, approximately half of the subjects are observed to survive 18 days and for PCT, about half of the subjects are observed to survive 17 days. Until 18^{th} day, median of 3 and mean of 3.735 CRP measurements are taken from per subject. On the other hand for PCT, median of 3 and mean of 3.808 measurements are taken per subject until 17^{th} day. Utilizing measurements taken until 18^{th} day and 17^{th} day for CRP and PCT biomarkers, their predictive abilities at the end of follow-up period are also determined. Moreover, 95% confidence intervals, which are obtained by performing nonparametric percentile bootstrap approach along with time-dependent AUC values are given to indicate whether observed accuracies are statistically significant.

In this part, only two cut-off options are specified and their results are interpreted. However, taking more threshold alternatives into account and comparing the variation of these points would also be possible.

All these descriptive statistics of the measurements and time-dependent AUC values with corresponding 95% confidence intervals are summarized in Table 4.9.

4.2. Comparison of Single vs. Serial Biomarker Measurements in Predicting Time-to-Event Outcome

In health studies, usually a single biomarker measurement is taken from subjects and this single value is used in making diagnosis. However, in many situations in clinics, the single measurement may not be sufficient to diagnose. Having longitudinal biomarker information of the subjects and being able to screen the variability of these values over the follow-up period are considered to be more effective way for making more reliable diagnoses. In such situations, rather than taking a single measurement, taking serial measurements of the biomarkers to determine the optimum treatment for subjects or to make a diagnosis are much more preferred due to these aforementioned advantages.

Within the context of the study, comparing the diagnostic values of the single measurement taken at the baseline (t=0) and serial biomarker measurements taken

within the follow-up period are intended to determine the efficiacy of a single biomarker value in diagnosis process. Joint Modeling Approach with cumulative effects parameterization is used for modeling serial biomarker values, while Cox Regression Model is performed for modeling single biomarker values taken at baseline (t=0). Single and serial biomarker values are compared by means of time-dependent AUC values. p-values are calculated as a comparison criteria for these AUC values in this study, results obtained from 1000 bootstrap samples are given. Confidence intervals are also constructed in order to indicate whether the time-dependent AUC values are statistically significant. To calculate the p-values, firstly z-statistic is calculated. Then p-value is obtained with the help of z-statistic. The formula for calculation of z-statistic is given below:

$$z = \frac{\theta_1 - \theta_2}{\sqrt{var(\theta_1^*) + var(\theta_2^*) - 2 * cov(\theta_1^*, \theta_2^*)}} \tag{4.2}$$

where θ_1 is the point-estimate of td-AUC value for CRP, and θ_2 is the point-estimate for PCT. $var(\theta_1^*)$ and $var(\theta_2^*)$ values are variances of td-AUC values obtained from 1000 bootstrap sample for CRP and PCT, respectively. Formula (4.2) is also used in comparison of single and serial biomarkers values. In that case θ_1 is the point-estimate of td-AUC obtained from single biomarker value, and θ_2 is the point-estimate for td-AUC of the serial biomarker measurements. $cov(\theta_1^*, \theta_2^*)$ term indicates the covariance between these td-AUC values. Even though there are serial CRP values of 457 subjects and serial PCT measurements of 534 subjects in the study, there are 264 subjects that have serial CRP and PCT measurements taken at the same time-points. For the CRP-PCT biomarker comparison, measurements of these 264 subjects are considered to create the dependency. Even in the comparison of td-AUC values obtained from the same biomarker, dependence structure is considered to be observable since same measurements will be used in the calculation of td-AUC statistic. For example, for the CRP biomarker, obtaining of td-AUC value using measurements up to 18th day (cut-off point is median of survival times) will include all the time points up to day 18. For instance measurements up to 7th day will be included in that calculation, therefore, td-AUC values obtained from

measurements up to 7th days and up to 18th day are expected to have dependencies since same measurements will be using in calculation.

However, $cov(\theta_1^*, \theta_2^*)$ value is assumed to be 0 and all comparisons in this thesis are made by ignoring the covariance term in formula (4.2).

The results are given below:

Table 4.9. Cut-Off Points, basic descriptive statistics for number of measurements, diagnostic performances of serial CRP and PCT values, their standard errors and 95% confidence intervals

Biomarker	Cut-off point(t)	Mean	Median	td-AUC ± SE	95% CI of td-AUC
CRP	7	2.702	3	0.489 ± 0.026	0.427 - 0.531
CRP	18	3.735	3	0.570 ± 0.034	0.476 - 0.615
PCT	6	2.932	3	0.456 ± 0.022	0.422 - 0.512
PCT	**17**	**3.808**	**3**	**0.547 ±0.032**	**0.509 - 0.632**

Table 4.10. Basic descriptive statistics for number of measurements and diagnostic performances of single CRP and PCT values taken at baseline(t=0), their standard errors and 95% confidence intervals

Biomarker	Baseline Measurement (t=0)	Mean	Median	td-AUC ± SE	95% CI of td-AUC
CRP	0	1	1	0.547 ± 0.034	0.478 - 0.618
PCT	**0**	**1**	**1**	**0.645 ± 0.027**	**0.589 - 0.695**

Table 4.9 is created as minimum to maximum value of cut-off points to be able to interprete the results more readily. Statistically significant time-dependent diagnostic accuracy values are also highlighted to indicate their significance.

It is observed that for both cut-off points options, both of diagnostic performances of serial CRP and PCT values are found as moderate for ICU patients in predicting death at the end of follow-up period. Even though there are diagnostic performance values below 0.5 for both biomarkers, they are obtained in earlier time-points of the follow-up period, therefore these low diagnostic values can be attributed to lack of longitudinal information of either CRP or PCT (Table 4.9.). On the other hand, diagnostic accuracies are found to be higher in case of taking

medians of survival times of the biomarkers as cut-off point for both CRP and PCT compared to consideration of taking the medians of the time-points as the cut-off option. At the end of day 30, diagnostic accuracies are found to be 0.547 and 0.570 for PCT and CRP, respectively for survival-time cut-off, whereas they are 0.489 and 0.456 for CRP and PCT, respectively for time-points cut-off. For biomarker comparison, serial CRP values are observed to have slightly higher diagnostic performance than those of PCT in both of the cut-off options. Confidence intervals for survival-time cut-off shows that time-dependent AUC of CRP is not statistically significant since its confidence interval includes 0.5, while discriminative ability of PCT is statistically significant since its confidence interval does not include 0.5. On the other hand in case of using time-points as cut-off option, diagnostic accuracies of serial CRP and serial PCT values are not statistically significant since their intervals include 0.5.

Diagnostic performances of single biomarker value taken at baseline (t=0) indicates that PCT has better discrimination ability compared to CRP (td-$AUC_{baseline}$=0.645 for PCT and td-$AUC_{baseline}$=0.547 for CRP). Baseline measurements of PCT values can be considered as measurements taken before anthibiotic or drug treatment. Hence, the reason for this relatively higher diagnostic performance of PCT can be consequence of this situation. For the confidence interval perspective, it's observed that confidence interval of CRP includes 0.5, meaning that this value is not statistically significant, while time-dependent diagnostic accuracy for PCT is statistically significant since its confidence interval does not include 0.5 (Table 4.10.).

For the interval width comparison, CRP has the tighter confidence interval than PCT in single and serial measurements case and for both survival time cut-off and time-points cut-off options (Table 4.9. and Table 4.10.).

Furthermore, within the context of the study, diagnostic values of serial and baseline biomarker values are compared to determine whether a single biomarker value is effective in predicting the event of interest at the end of follow-up period.

For this purpose, p-values are given as a comparison criteria. Results are shown in the following tables:

Table 4.11a. Comparison of time-dependent AUC of single and serial values of CRP and PCT Biomarkers

Biomarker	Time-Dependent AUC		p-value
	Baseline	Serial (cut-off is survival time)	
CRP	0.547	0.570	0.628
PCT	**0.645**	**0.547**	**0.018**
Biomarker	**Time-Dependent AUC**		**p-value**
	Baseline	**Serial (cut-off is time-points)**	
CRP	0.547	0.489	0.180
PCT	**0.645**	**0.456**	**<0.001**
Biomarker	**Time-Dependent AUC**		**p-value**
	Serial (cut-off is survival time)	**Serial (cut-off is time-points)**	
CRP	0.570	0.489	0.064
PCT	**0.547**	**0.456**	**0.020**

Table 4.11b. Comparison of time-dependent AUC values of CRP and PCT Biomarkers

Measurement	Time-Dependent AUC		p-value
	CRP	PCT	
Baseline	**0.547**	**0.645**	**0.022**
Serial (cut-off is survival time)	0.570	0.547	0.619
Serial (cut-off is time-points)	0.489	0.456	0.352

In case of median of survival time of the biomarkers is utilized as cut-off point, there is not a statistically significant difference between single and serial measurements for CRP ($p=0.628$); whereas there found to be a statistically significant difference between single and serial measurements for PCT ($p<0.05$). In case of median of time-points of the biomarkers is used as cut-off point, no statistically significant difference between single and serial CRP values is observed ($p=0.180$), while there found to be a statistically significant difference between single and serial values of PCT ($p<0.05$). For the comparison of repeated biomarker values, there is no statistically significant difference between serial values of CRP

($p=0.064$), however for PCT biomarker, statistically significance was found between serial values ($p<0.05$) (Table 4.11a)

Moreover, there exist a statistically significant difference between time-dependent AUC values obtained from the single measurement of CRP and PCT($p<0.05$). For serial measurements, even though it seems that diagnostic accuracy of serial CRP measurements slightly higher than PCT, no statistically significant difference is found between these values ($p=0.619$) when median of survival times is taken as cut-off point. In case of median of time-points is taken as cut-off, also no statistically significant difference between time-dependent AUC of serial CRP and PCT values is found ($p=0.352$) (Table 4.11b).

Numerical results are visualized to make easier to interpret. The following two figures also suggest that there is no difference in diagnosing between taking a single biomarker value or utilizing serial values for CRP biomarker. On the other hand, a single PCT value seems sufficient to predict the death at ICU at the end of follow-up. However, biomarker-based figure indicates that PCT is a better biomarker in terms of diagnostic accuracy at the end of follow-up period than CRP in cases of using single measurement, while serial CRP values have better diagnostic accuracy comparing to serial PCT values in predicting the event of interest in case of median of survival times is used as cut-off point. Moreover, the lowest diagnostic accuracies are observed when cut-off point is taken as median of time-points for both biomarkers in both single and serial measurement cases. (Figure 4.1.)

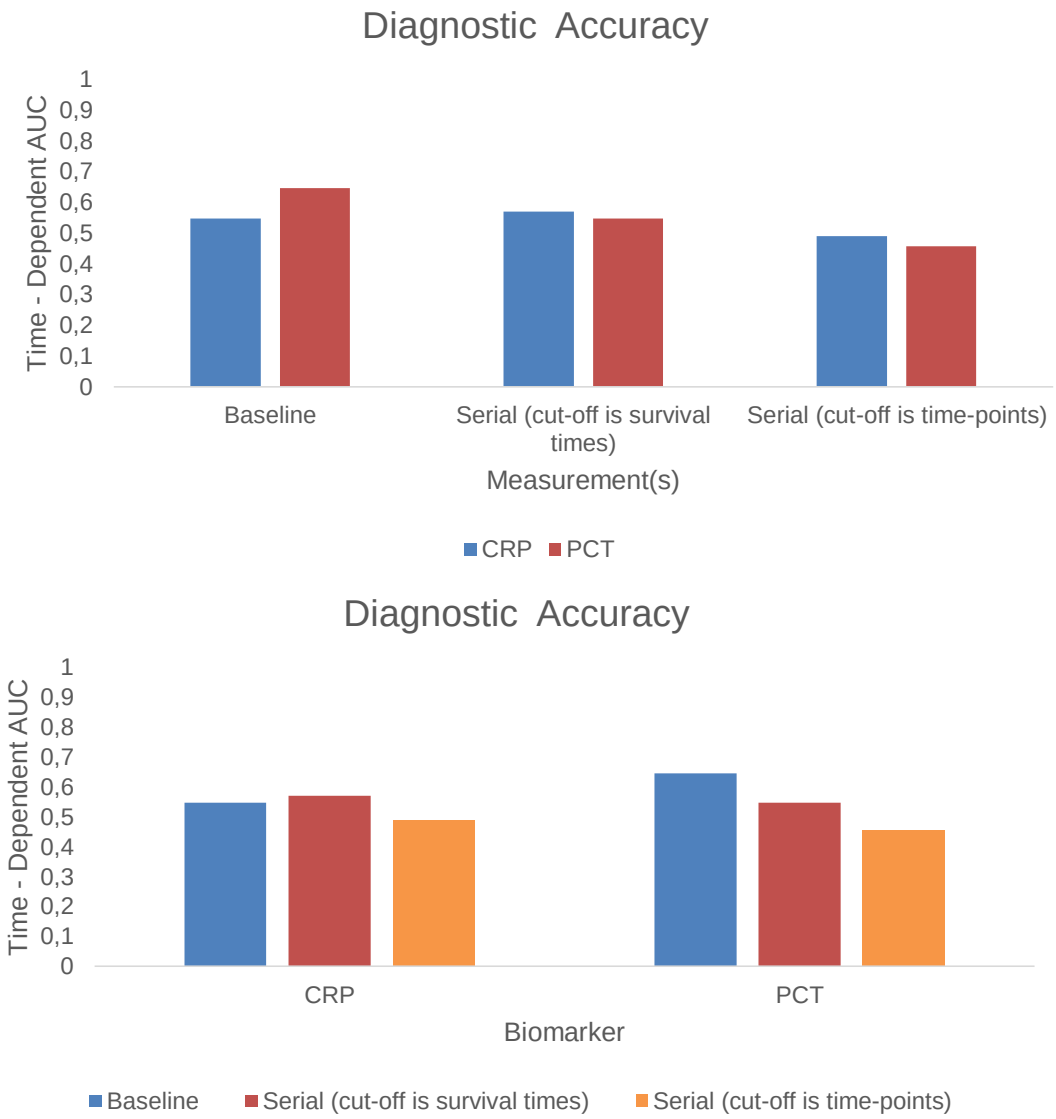

Figure 4.2. Diagnostic Performances of Baseline and Serial Measurements of CRP and PCT

4.3. Assessing the Diagnostic Performance Throughout the Follow-up Period

Another objective in this study is to evaluate the diagnostic performances of serial biomarker values taken throughout the follow-up period. By this way assessing the change of the diagnostic accuracies for both of the biomarkers along the period is aimed. For this reason the basic descriptive statistics (first quantile-Q_1, second quantile (median)-Q_2, mean and third quantile-Q_3) for the time points that the repeated measurements were taken are obtained. Since these descriptive statistics of the time-points can be interpreted as cut-off point on which to base td-AUC

calculations, this section can be thought of the extension of Section 4.1, which has the results of time-dependent diagnostic accuracies of two cut-off points within the period. However, unlike the section 4.1, this section focus mostly on the change in time-dependent diagnostic accuracies of each biomarker within the period. Therefore no attempt was made to focus on to statistically compare these values between biomarkers. In taking these descriptive statistics, baseline measurements that were taken at time t=0 are excluded for both of the biomarkers and these basic descriptives are calculated with the remaining time-points. The reason for excluding the baseline measurements is to better analyze the densely-measured time-points within the follow-up period. In other words, it would be possible to determine the time-points where the most of the measurements are collected more clearly with the exclusion of baseline measurements. For example, if baseline CRP measurements of 457 subjects, in other words each t=0 of 457 subjects included into the calculation, it will enlarge the total number of measurements, then the mean of time-points that the measurements are taken will be calculated smaller than which was supposed to be. As for the PCT biomarker, including the baseline measurements of each 534 subjects into the calculation will reduce the mean of the time-points. In other words, since the arithmetic mean is affected by the outliers in the dataset, including the baseline measurements, namely 0 of 457 subjects from CRP sample and 0 of 534 subjects from PCT sample is considered to affect the results of descriptive statistics of the time-points. Besides, other than the arithmetic mean, inclusion of these baseline measurements would also be considered to have an effect on calculation of especially earlier time-points, for example, the first quantile of the time-points will be calculated smaller than which was supposed to be for both CRP and PCT, since too many 0's will be included into the calculation of this statistic.

Basic descriptive statistics of the time-points that repeated measurements are taken are calculated in an attempt to better evaluate the time-dependent diagnostic accuracies of CRP and PCT biomarkers at these aforementioned time-points. Following table (Table 4.12.) includes mean and median values of repeated biomarker measurements and discrimination abilities of CRP and PCT on the 30^{th} day by using measurements up to time t. t refers to quartiles and mean values of

time-points which repeated measurements are taken, after excluding baseline measurements of both of the biomarkers. As mentioned before, these descriptive statistics for time-points are calculated solely to better evaluate densely-measured time-points. However, joint models are constructed using all time-points -including baseline measurements- for assessing the diagnostic values at these aforementioned time points.

Table 4.12. Basic Descriptive Statistics for Number of Repeated Measurements of CRP and PCT Biomarkers and Corresponding Time-Dependent Diagnostic Accuracies along with standard errors 95% Confidence Intervals

Biomarker	Statistics	time (t)	Mean	Median	td-AUC ± SE	%95 CI of td-AUC
CRP	**Q_1**	4	1.424	1	0.455 ± 0.024	0.396 - 0.497
	Q_2	9	2.389	2	0.504 ± 0.027	0.451 - 0.554
	Mean	11	2.733	3	0.524 ± 0.029	0.472 - 0.590
	Q_3	16	3.299	3	0.530 ± 0.032	0.474 - 0.603
PCT	**Q_1**	4	1.460	1	0.412 ± 0.020	0.380 - 0.464
	Q_2	8	2.293	2	0.509 ± 0.022	0.458 - 0.545
	Mean	10	2.623	2	0.502 ± 0.024	0.460 - 0.559
	Q_3	15	3.307	3	0.553 ± 0.029	0.505 - 0.622

It's observed that 25% of the CRP measurements are taken within the 4 days of the follow-up. Until the first 4 days, mean of 1.424 and median of 1 CRP measurements are taken from per subject. On the other hand half of the measurements of CRP are taken within the 9 days with mean of 2.389 and median of 2 per subject. Mean of time-points for CRP is found as 11 days. and until 11^{th} day. mean of 2.733 and median of 3 CRP measurements are taken from per subject. 75% of the CRP measurements are taken within the 16 days with mean of 3.299 and median of 3 per subject.

The same-increasing-pattern are observed also for the PCT biomarker. That is, 25% of the measurements are taken within the 4 days of the follow-up. Until the 4 days, mean of 1.46 and median of 1 PCT measurements are taken from per subject. Moreover, half of the measurements are taken within the 8 days, with mean of 2.293 and median of 2 from per subject . Mean of time-points for PCT is found as 10 days. and until 10^{th} day, mean of 2.623 and median of 2 PCT measurements are taken from

subjects. Within the 15 days, 75% of the PCT measurements are taken with mean of 3.307 and median of 3 per subject.

After analysing the mean and median values for both of the biomarkers, it is observed that longitudinal information is in increasing-trend throughout the period. With the help of the basic descriptives for the time-point of CRP and PCT, it could be possible to determine the diagnostic performances of serial biomarker values in predicting death in ICU throughout the follow-up period, in this manner it could be also possible to indicate which biomarker is better in predicting ICU mortality at pre-specified time-points. As seen in previous parts, predictive abilities of the biomarkers are determined by means of time-dependent AUC values. Moreover, corresponding 95% confidence intervals along with standard errors are given for these time-dependent diagnostic accuracies to indicate their statistical significances.

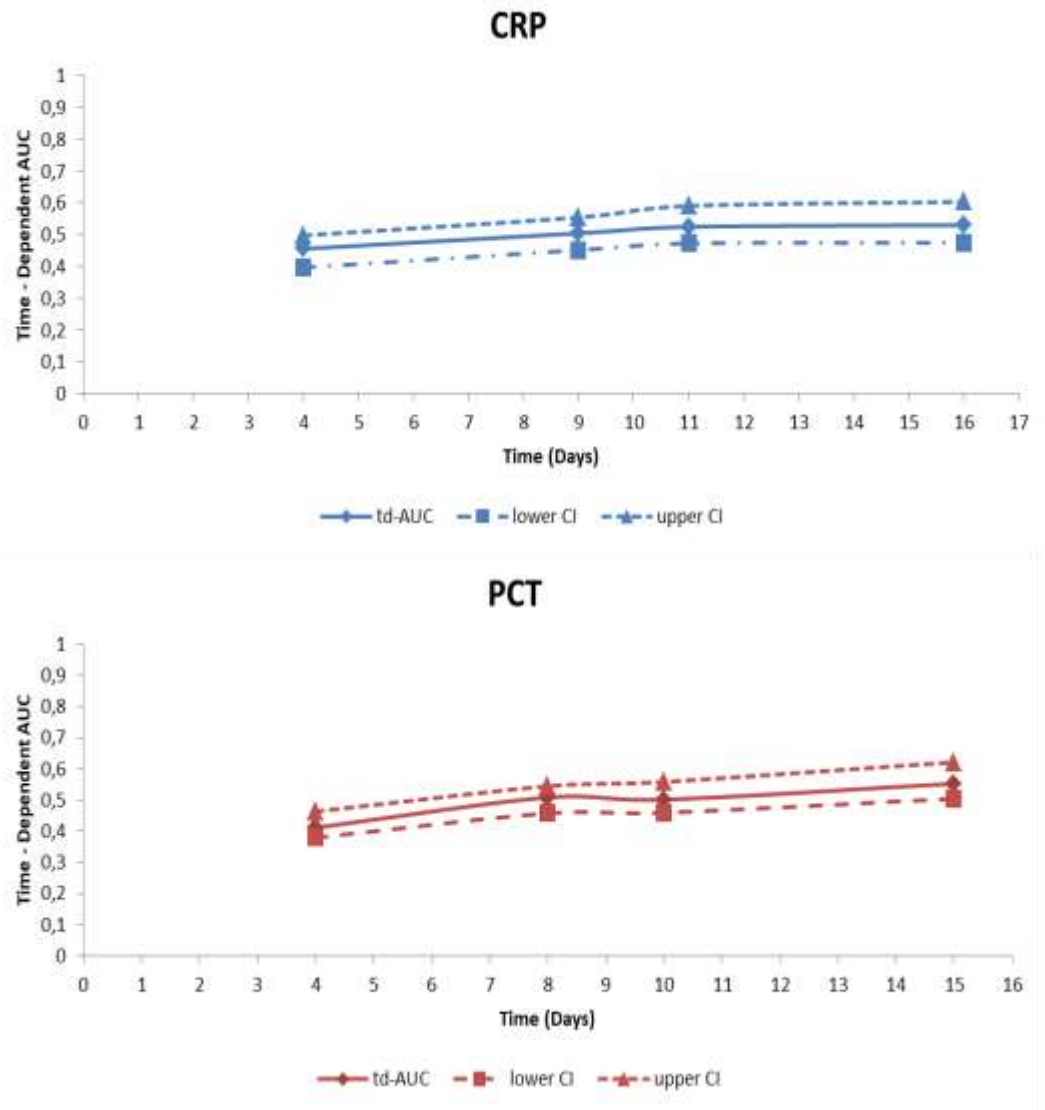

Figure 4.3. Time-Dependent Diagnostic Accuracies of CRP and PCT Biomarkers throughout the Follow-up Period

Table 4.12 and Figure 4.3. suggest that diagnostic accuracies for both biomarkers within the follow-up period are in moderate level they are in increasing trend as longitudinal information increases. However, the increase in time-dependent AUC value of PCT is clearer compared to CRP. Earlier time-points and central time-points of the period, time-dependent diagnostic accuracies are found almost the same for both of the biomarkers, however at later time-points serial PCT values are observed to have better diagnostic performance compared to CRP. Moreover, the increase in diagnostic values of PCT biomarker within the follow-up period are higher than that of CRP, which indicates more stable profile for CRP than PCT in

terms of diagnostic accuracies over the period. Even though serial PCT values give higher diagnostic values at later time-points, by combining the results of the Section 4.1, we reach the conclusion that the highest diagnostic performance is observed in case of using serial CRP measurements when cut-off point is taken as median of survival times. Therefore, we limit taking serial measurements of PCT biomarker to later time-points, while no restriction can be defined for repeated measurements of CRP since they are observed to perform better compared to serial measurements of PCT in overall. Moreover, confidence intervals reveal that none of the diagnostic performances of CRP throughout the follow-up period are statistically significant (all of them include 0.5); on the other hand confidence intervals of PCT suggest that earlier time-dependent diagnostic accuracies are not statistically significant (confidence intervals include 0.5), on the other hand last time-dependent AUC which is the closest one to the end of follow-up period is statistically significant, since its interval does not include 0.5. Results suggest that as the longitudinal information increases, the confidence intervals become wider for CRP; however widths of intervals are almost the same throughout the period for PCT. (Table 4.12 and Figure 4.3.).

These results suggest that as the longitudinal information increases, diagnostic accuracy in predicting the risk of death at the end of follow-up period is observed to increase for both CRP and PCT. However, these results also suggest that diagnostic perfomances are increasing throughout the follow-up period, which means that time-points closer to end of the follow-up period have higher diagnostic performance compared to earlier time-points. Therefore, there is no clear explanation about whether increasing-trend in longitudinal information or closer time-points to the end-of follow-up period increases the diagnostic accuracy. Hence, this topic is considered to need further study.

As mentioned at the beginning of this section, the increase of both of the biomarkers within the period are not statistically tested on the grounds that the focus is mostly on the evaluation of accuracies over the period rather than comparison.

Therefore, results for this section can be thought of intuitive and open-to-interpretation.

4.4. Obtaining the Optimum Cut-Off Value

One of the objectives in using ROC Curves is to obtain cut-off values to distinguish event and event-free subjects. When time dimension is incorporated into classical ROC Curve, it could be possible to obtain time-dependent cut-off values. In this section time-dependent cut-off values for discriminating subjects at risk and without the risk of death at the end of follow-up period are determined for both biomarkers.. Given the previously fitted joint model (4.1) and covariate information x_i for i[th] subject in the sample, Monte Carlo Simulation Scheme is performed in the calculation of the cut-off value. The Monte Carlo simulation steps are explained below:

1. Simulating new parameter values, θ^*, from $N(\widehat{\theta},\ C(\hat{\theta}))$. $\hat{\theta}$s are Maximum Likelihood Estimates and C($\hat{\theta}$) is the covariance matrix, and both parameter estimates and covariance matrix are taken from previously fitted joint model given in (4.1).
2. Simulating possible longitudinal history, $\tilde{y}_i(t)$, based on the previous fitted joint model given in (4.1)
3. Simulating random effects, b_i^* , using longitudinal information and parameter estimates which were calculated in the previous steps and conditioning on $T_i^* > t$. Estimation of these random-effects are based on Metropolis-Hastings algorithm (25).
4. Based on θ^* , $\tilde{y}_i(t)$, b_i^* and x_i , survival probabilities $\Pr(T_i > u | T_i > t,\ b_i^*, x_i; \theta^*)$ are calculated for each subject in the sample.
5. With the help of survival probabilities, time-dependent sensitivity, time-dependent specificity and corresponding cut-off values are calculated for each subject.

This scheme is repeated 1000 times. Means of time-dependent sensitivity, time-dependent specificity metrics and cut-off values that were obtained by

maximizing the product of those mean-of- time-dependent sensitivity and mean-of-time-dependent specificity are also given for either CRP or PCT biomarker (4, 25).

rocJM function in JM package (4) is used to calculate the cut-off values and corresponding time-depending sensitivity and time-dependent specificity values with the help of Monte Carlo simulation process. Even though the simulation procedure needs only the covariate information of the subjects, following figures and tables are given in order to either explain the longitudinal information and longitudinal profile of each biomarker in detail or to help select the most appropriate subject with the covariate information for which prediction of cut-off values and time-dependent diagnostic accuracy metrics are required.

Following tables (Table 4.13. and Table 4.14.) includes descriptive statistics for number of repeated biomarkers along with basic descriptive statistics for these repeated biomarker measurements Table 12 revealed that minimum 2, maximum 18 CRP measurements are taken within 30 days, while for PCT biomarker they are 2 and 19, respectively. Means of approximately 5 measurements are taken from both of the biomarkers, whereas medians of the measurements taken within the follow-up period are found as 4 for either CRP or PCT. 25% of the both CRP and PCT measurements are equal or less than 3, while 75% of the measurements are equal or less than 7 for both of the biomarkers (Table 4.13.).

On the other hand, 2430 CRP and 2858 PCT measurements are taken within the follow-up period (indicated as k in Table 4.14.) with mean of 11.059 and 5.168 for CRP and PCT, respectively. The medians of these all - measurements are found as 8.725 for CRP and 0.314 for PCT. The standard deviations of these measurements are calculated as 9.759 for CRP and it’s 26.234 for PCT. Within the follow-up period, minimum and maximum value of CRP measurements are found as 0.138 and 57.500 respectively. For PCT, they are 0.001 and 568.9, respectively (Table 4.14.).

Table 4.13. Basic descriptive statistics for number of repeated measurements of CRP and PCT

Biomarker	Min	Q_1	Mean	Median	Q_3	Max
CRP	2	3	5.319	4	7	18
PCT	2	3	5.352	4	7	19

Table 4.14. Basic descriptive statistics for serial measurements of CRP and PCT

Biomarker	k	Mean	SD	Median	Min	Max
CRP	2430	11.059	9.759	8.725	0.138	57.500
PCT	2858	5.168	26.234	0.314	0.001	568.9

Results revealed that mean of 5 and median of 4 measurements are taken from both of the biomarkers throughout the follow-up period. Previous tables suggest that representative subject must have 5 serial CRP measurements taken within the follow up period, while for the PCT biomarker, representative subject must also have 5 serial PCT measurements taken within the follow up period (Table 4.13) .

Under these longitudinal information of CRP and PCT samples, 389^{th} subject from CRP sample and 4^{th} subject from PCT sample are chosen as the most appropriate subjects on which to base the calculations. 389^{th} subject has 5 repeated measurements, with mean of 9.008 and median of 8.820 for CRP biomarker. Last time point that the measurement was taken is at time t=15, therefore the interest is in determining the time-dependent cut-off value and corresponding time-dependent sensitivity and time-dependent specificity values at the end of follow-up period, at time t=30, using the longitudinal values measured up to time t=15.On the other hand, 4^{th} subject from PCT sample has also 5 measurements with mean of 1.372 and median of 0.318. The last time point that PCT measurement was taken is at time t=26, therefore it's of interest to determine the time-dependent cut-off value and corresponding time-dependent sensitivity and time-dependent specificity values at the end of follow-up period, at time t=30, using the longitudinal values measured up to time t=26.

Figures, which demonstrate the mean and median values of each time-point for the whole sample over the period for CRP and PCT, and longitudinal trajectories of representative subjects of CRP and PCT are given in an attempt to help better understand the representative-subject selection process prior to calculation of the cut-off values for both biomarker samples (Figure 4.4., Figure 4.5., Table 4.12. and Table 4.13.)

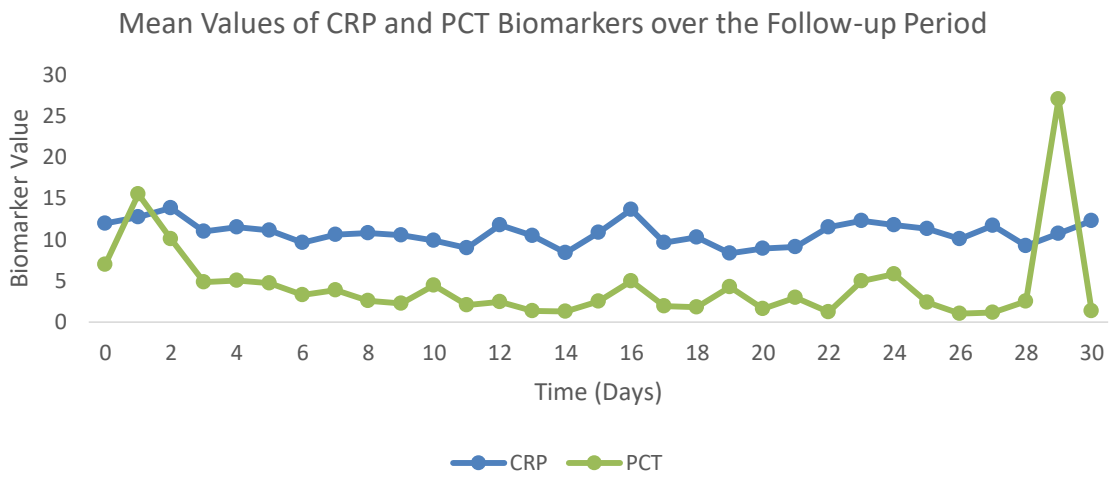

Figure 4.4. Mean Values of CRP and PCT Biomarkers throughout the Follow-up Period

Figures indicate that the serial CRP values are slightly decreasing through the 12th day, then the values show fluctuations through the end of the follow-up period. For PCT, it can also be said that its profile shows more stability between 3rd and 28th days, however its values reach the maximum level on 29th day. To obtain the cut-off values for both of the biomarkers, 389th subject in the CRP sample and 4th subject in the PCT sample are chosen since their longitudinal profiles are considered as the most suitable ones to represent their own samples. Furthermore, dataset which includes the longitudinal biomarker values for 389th subject in the CRP sample and 4th subject in the PCT sample is given below as an example (Table 4.15.).

Table 4.15. Longitudinal biomarker values and covariate information for the representative subjects of CRP and PCT samples

id	pct	log.pct	survtime	time	status	age	gender
4	0.122	-0.914	30	0	0	84	0
4	5.310	0.725	30	5	0	84	0
4	1.020	0.009	30	9	0	84	0
4	0.089	-1.051	30	19	0	84	0
4	0.318	-0.498	30	26	0	84	0
id	**crp**	**log.crp**	**survtime**	**time**	**status**	**age**	**gender**
389	8.820	0.945	16	0	0	86	0
389	15.300	1.185	16	4	0	86	0
389	15.100	1.179	16	4	0	86	0
389	2.800	0.447	16	11	0	86	0
389	3.020	0.480	16	15	0	86	0

Table 4.15 reveals that representative subject of PCT sample is female (gender variable coded as 0), age of 84 and she is a censored observation. The last time PCT value was taken at day 26 and despite the fact that her exact survival time is unknown, it’s assumed to be 30 days. On the other hand, representative subject of CRP sample is also female (gender variable coded as 0), age of 86 and she is also a censored observation. The last time CRP value was taken from her on day 15 and she is known to dropout from the follow-up at the same day.

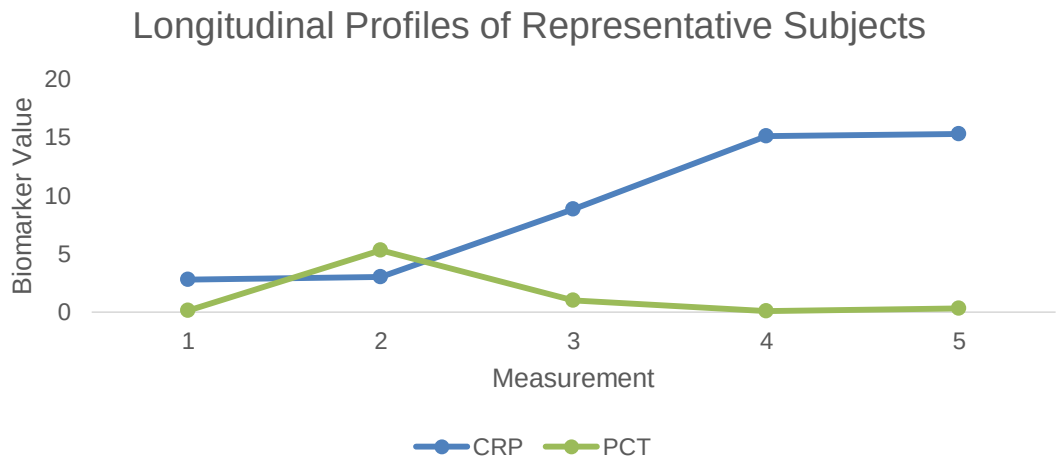

Figure 4.5. Longitudinal Profiles of representative subjects of CRP and PCT samples

Figure 4.5. is given in order to show the longitudinal profiles of the representative subject for both of the biomarkers. It suggests that representative subject of CRP has increasing biomarker values while representative subject of PCT has decreasing profile.

Following table includes time-dependent cut-off values and corresponding 95% confidence intervals along with time-dependent diagnostic accuracy values (Table 4.16). Antilog transformation is applied to these cut-off values to ease the interpretation. Maximum of the product of sensitivity and specificity rule is applied to determine the corresponding cut-off values (60). Confidence intervals for the cut-off values are calculated based on nonparametric percentile bootstrap approach. 1000 bootstrap samples are used in the calculation process.

Table 4.16. Time-Dependent Cut-Off Values and Time-Dependent Diagnostic Performance Values along with 95% Confidence Intervals

Biomarker	Statistics			
	td-Cut-Off ± SE	95% CI of td-Cut-Off	td-Sens ± SE	td-Spec ± SE
CRP	7.129 ± 1.130	5.929 - 9.247	0.513 ± 0.001	0.507 ± 0.001
PCT	0.411 ± 1.289	0.269 - 0.700	0.537 ± 0.001	0.563 ± 0.001

To propose a cut-off value for distinguishing subjects at risk and without risk of death in ICU-setting, Coefficient of Quartile Variation CQV measure, which is

considered as an alternative of Coefficient of Variation (CV) measure to compare the variations in different samples when their distributions are non-normal, is calculated for both biomarkers. As for the Coefficient of Variation measure, smaller CQValso implies more stable distribution, whereas larger coefficient is considered as there are more dispersed values in the sample. The reason in preferring to calculate this measure is that the distributions of CRP and PCT samples are skewed and even heavy-tailed, which makes CQV measure the most preferable statistic to compare and to standardize these different dispersions with a single-metric.

Since the distributions of serial CRP and PCT values are skewed, semi-interquartile range to median ratio statistic, which can be considered as the robust alternative of Coefficient of Variation is also calculated along with CQV value in order to determine the most relevant cut-off point.

The first and third quartiles and medians of CRP and PCT samples, their CQV metrics along with Robust Coefficient of Variation (RCV) values and histograms of serial CRP and PCT measurements are summarized in the following table and figure (Table 4.17., Figure 4.6. and Figure 4.7.)

Table 4.17. First and Third Quartiles, Robust Coefficients of Variations and Coefficients of Quartile Variations of CRP and PCT samples

Biomarker	Q_1	Q_3	Median	Robust Coefficient of Variation (RCV)	Coefficient of Quartile Variation (CQV)
CRP	3.475	15.2	8.725	0.672	0.628
PCT	0.127	1.531	0.314	2.236	0.847

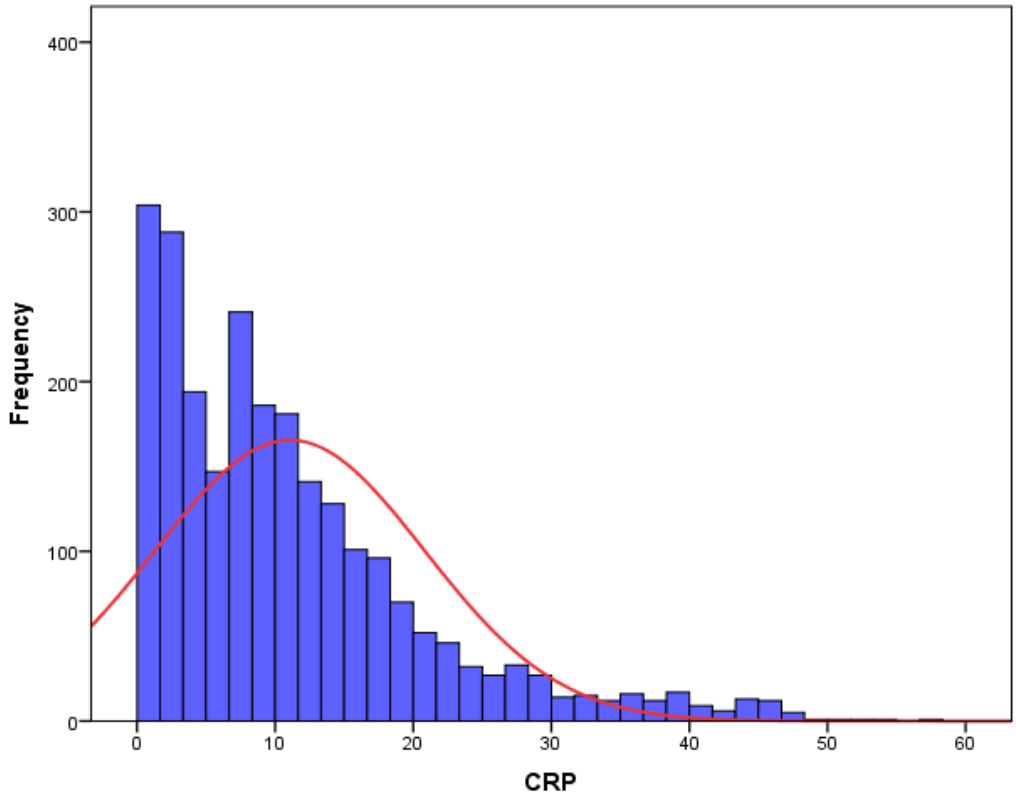

Figure 4.6. Histogram of repeated CRP values

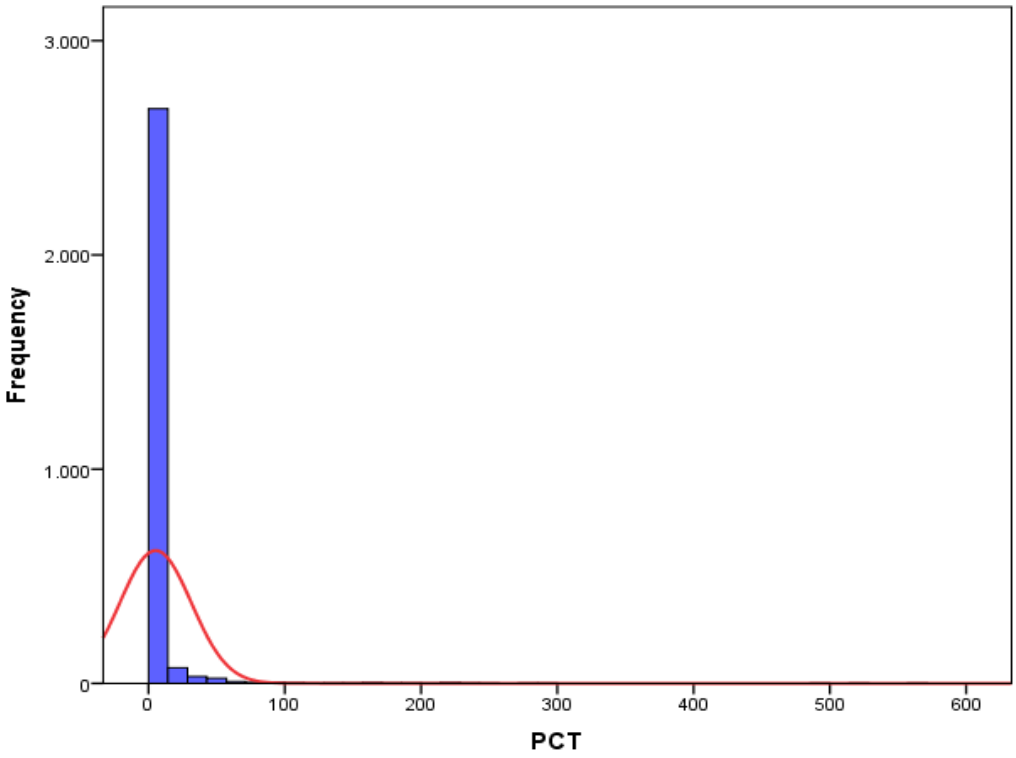

Figure 4.7. Histogram of repeated PCT values

CQV is known to indicate the dispersions in the samples. As observed from the previous table and figures, PCT sample is quite overdispersed than CRP sample, approximately 85% of spread can be observed in this sample. Also, its values are approximately 1.3 times larger than values of CRP. Positively-skewed PCT values are consistent with the CQV statistic, that is, its measurements dispersed in a wide range, the variability of the values are observable throughout the follow-up period.

On the other hand, the CQV of CRP is found as quite reasonable compared to PCT, with approximately 63% of spread is observed in this sample. Although this value is fairly big on its own, when compared to PCT sample, values of CRP show much more stable profile throughout the follow-up period (Figure 4.6 and Figure 4.7).

As for CV, similar interpretations can be made for RCV. That is, subjects in CRP sample show approximately 67% percentage of dispersion around the median, while subjects in PCT sample seems to be approximately 2-times larger from the median. For the comparison of the RCV metrics, subjects in PCT sample are approximately 3 times larger than subjects in CRP sample. This result is consistent with the results of CQV comparison, which depicts PCT values are much more dispersed compared to those of CRP values.

At the end of the analysis, cut-off value of CRP sample is recommended to differentiate the subjects since both its CQV and RCV values are smaller than those of PCT, indicating its values exhibit more consistent distribution during the follow-up period unlike PCT, whose CQV and RCV values demonstrate more variability, indicating inconsistency of the PCT vlaues over the period. Therefore stability of serial CRP values throughout the period are considered to be more reliable than serial PCT measurements in the decision of choosing the appropriate cut-off value.

In this part of the application section, we evaluate diagnostic performances of serial CRP and PCT biomarkers and compare the diagnostic accuracies of single and serial CRP and PCT measurements. A single PCT value is concluded to be more

reliable in discriminating risky and non-risky subjects at the end of follow-up period. Therefore it is suggested to utilize a single PCT value taken at baseline in predicting the risk of death at the end of follow-up for ICU subjects. It is also found that serial CRP measurements have slightly higher diagnostic accuracy when compared to only a single value of this biomarker. Although there is statistically no difference between single and serial measurements of CRP, taking serial CRP values in predicting the risk of death at ICU is recommended, to be able to assess the longitudinal profiles of subjects throughout the follow-up period. Moreover, as more measurements are taken, diagnostic performance of PCT increases more especially at later time-points, which are close to the end of foloow-up period, compared to CRP throughout the period and it makes this biomarker more reliable especially at later time-points of the follow-up in discriminating event and event-free subjects staying in Intensive Care Units. However, serial CRP values are suggested to be taken since they are observed to have the highest diagnostic performance in overall. Besides, cut-off values and corresponding 95% confidence intervals of CRP and PCT are given to distinguish event and event-free subjects in ICU-setting. CQV and RCV statistics are calculated for both of the CRP and PCT samples to propose the cut-off value for utilizing in clinic, and cut-off value of CRP is chosen since measurements of this biomarker taken within the period are observed to have stable longitudinal trajectory, which leads to smaller CQV and RCV values. Furthermore, from time-dependent diagnostic accuracy metrics-perspective, even though both of the biomarkers have the-moderate-level time-dependent sensitivity and time-dependent specificity, results suggest that PCT is more sensitive and specific biomarker compared to CRP.

In this study, finding the most representative subject of the CRP and PCT samples and therefore determining cut-off value is based on mean of CRP and PCT measurements taken within the follow-up period. Other options, such as focusing on the median of the biomarker measurements which were taken within the follow-up period for finding the most representative subject would be considered an alternative when determining the appropriate subject for calculating cut-off values.

4.5. Investigating Factors Affecting the Diagnostic Performance of Serial CRP and PCT Measurements

In this thesis, joint modeling approach is utilized to assess the diagnostic performances of CRP and PCT biomarkers. Within the context of this part, two different random effects structure in longitudinal sub-model; two different distribution options for survival times and four different parameterization types indicating the association between longitudinal and survival data structures are compared in terms of time-dependent AUC values to determine the best joint model combination that gives the maximum-discriminative ability at the end of follow-up-period.

For both CRP and PCT, fixed-effects part of the longitudinal sub-model is modeled with main effects of age and time variables and their interaction term. However for the random-effects part, two different random-effects structure, namely random intercept and random slope (Model-I) and Quadratic Random Effects (Model-II) are compared. The formulas for the two different joint models are given below:

Model-I: $h_i(t) = h_0(t)[\alpha\{\beta_0 + \beta_1 * \text{time} + \beta_2 * \text{age} + \beta_3 * \text{time} * \text{age} + b_0 + b_1 * \text{time}\}]$ (4.6)

Model-II: $h_i(t) = h_0(t)[\alpha\{\beta_0 + \beta_1 * \text{time} + \beta_2 * \text{age} + \beta_3 * \text{time} * \text{age} + b_0 + b_1 * \text{time} + b_2 * (time)^2\}]$ (4.7)

Parameter estimates, standard errors and p-values for the coefficients of the joint models are given in Appendix-IV.

Two different distribution options in survival sub-model are utilized. One of them is baseline hazard unspecified option, for the alternative, a parametric survival model is used and survival times are assumed to follow Piecewise-Constant Distribution.

Other than standard joint model, three more parameterization options, namely slope, current value and slope and cumulative effects are included in the analysis.

The cut-off point to evaluate the diagnostic performances is chosen as the median of survival times, which are 18 and 17 for CRP and PCT, respectively. Mean of 3.735 and median of 3 measurements are taken until the 18^{th} day for CRP biomarker. For PCT, mean of 3.808 and median of 3 measurements are taken until the 17^{th} day. Therefore, by utilizing these measurements, diagnostic performances of CRP and PCT biomarkers in predicting ICU mortality at the end of follow-up period (30^{th} day) are investigated.

Results are given with table and graphic (Table 4.18., Table 4.19., Figure 4.8., Figure 4.9a., Figure 4.9b., Figure 4.10.).

Table 4.18. Time-Dependent AUC values, their standard errors and 95% confidence intervals for CRP under different joint modeling combinations

Random Effects Structure	Parameterization	Baseline Hazard	td-AUC ± SE	95% CI for td-AUC
Model-I	Current Value	Unspecified	0.635 ± 0.027	0.533 - 0.660
	Slope		0.549 ± 0.047	0.403 - 0.591
	Both		0.634 ± 0.027	0.549 - 0.659
	Cumulative Effects		0.571 ± 0.031	0.487 - 0.610
	Current Value	Piecewise-Constant	0.686 ± 0.027	0.617 - 0.723
	Slope		0.553 ± 0.047	0.403 - 0.587
	Both		0.639 ± 0.027	0.554 - 0.659
	Cumulative Effects		0.566 ± 0.031	0.479 - 0.606
Model-II	Current Value	Unspecified	0.615 ± 0.024	0.540 - 0.638
	Slope		0.522 ± 0.046	0.467 - 0.648
	Both		0.614 ± 0.026	0.539 - 0.639
	Cumulative Effects		0.573 ± 0.036	0.475 - 0.619
	Current Value	Piecewise-Constant	0.610 ± 0.026	0.530 - 0.636
	Slope		0.524 ± 0.047	0.394 - 0.579
	Both		0.610 ± 0.026	0.538 - 0.635
	Cumulative Effects		0.570 ± 0.034	0.476 - 0.615

Table 4.19. Time-Dependent AUC values, their standard errors and 95% confidence intervals for PCT under different joint modeling combinations

Random Effects Structure	Parameterization	Baseline Hazard	td-AUC ± SE	95% CI for td-AUC
Model-I	Current Value	Unspecified	0.680 ± 0.022	0.643 - 0.729
	Slope		0.492 ± 0.042	0.428 - 0.596
	Both		0.677 ± 0.022	0.637 - 0.725
	Cumulative Effects		0.517 ± 0.035	0.490 - 0.630
	Current Value	Piecewise Constant	0.674 ± 0.022	0.641 - 0.722
	Slope		0.494 ± 0.045	0.431 - 0.604
	Both		0.666 ± 0.023	0.631 - 0.722
	Cumulative Effects		0.525 ± 0.033	0.494 - 0.630
Model-II	Current Value	Unspecified	0.703 ± 0.021	0.655 - 0.738
	Slope		0.562 ± 0.042	0.489 - 0.648
	Both		0.703 ± 0.030	0.653 - 0.738
	Cumulative Effects		0.551 ± 0.032	0.509 – 0.638
	Current Value	Piecewise Constant	0.696 ± 0.022	0.652 - 0.735
	Slope		0.567 ± 0.026	0.477 - 0.644
	Both		0.694 ± 0.023	0.649 - 0.739
	Cumulative Effects		0.547 ± 0.032	0.509 - 0.632

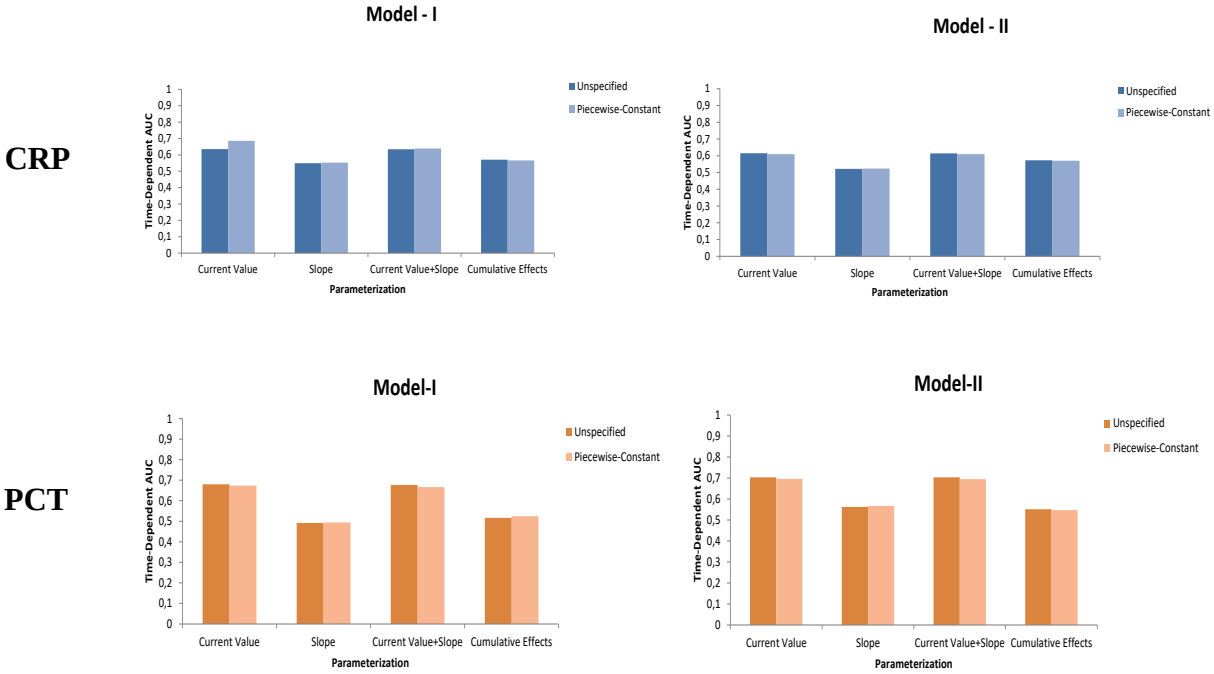

Figure 4.8. Time-Dependent AUC Values in terms of random-effects model structure

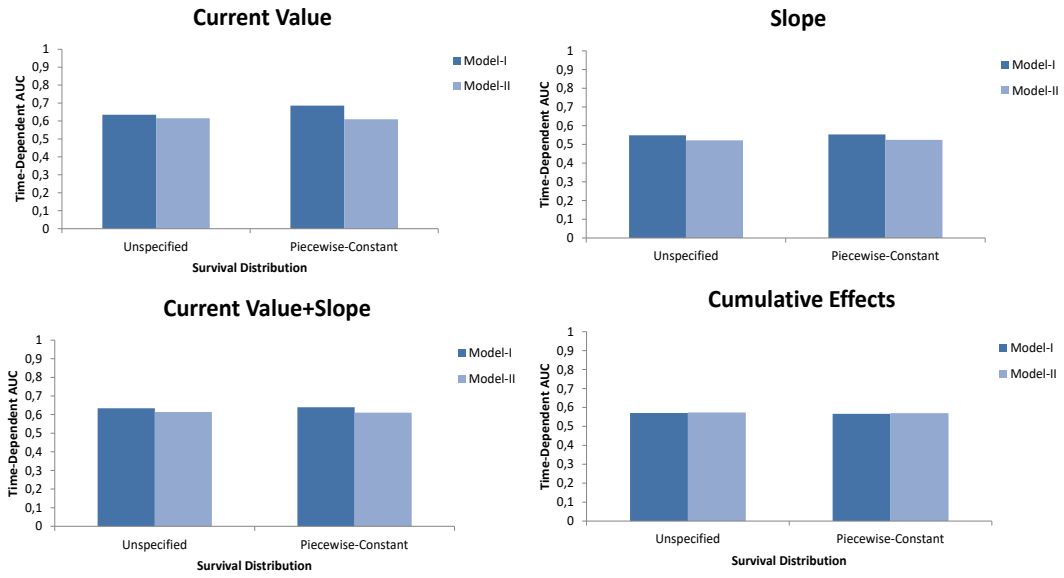

Figure 4.9a.Time-Dependent AUC Values for CRP in terms of different parameterization structures

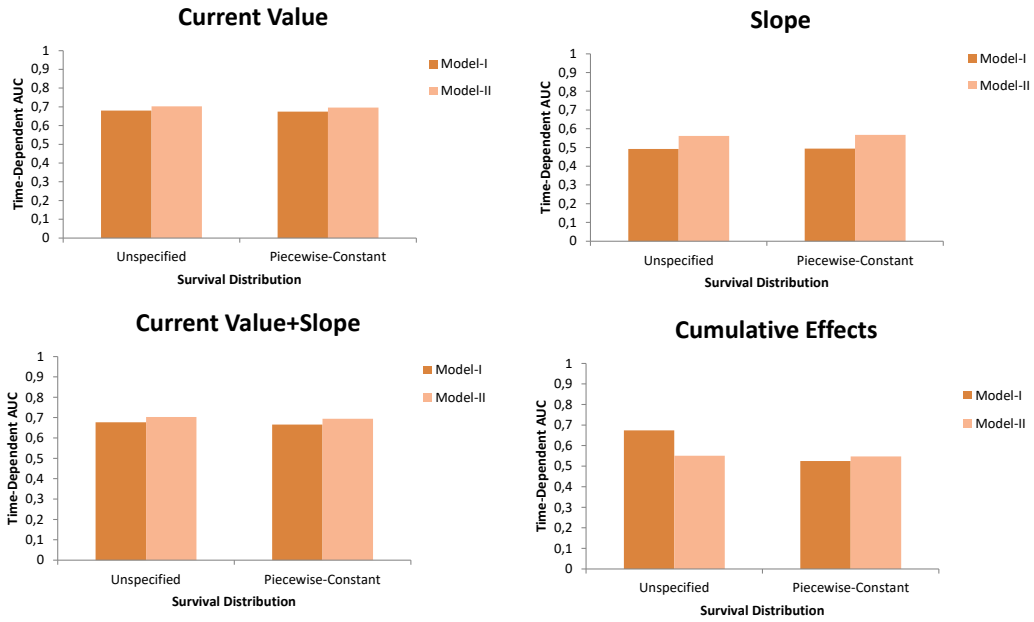

Figure 4.9b. Time-Dependent AUC Values for PCT in terms of different parameterization structures

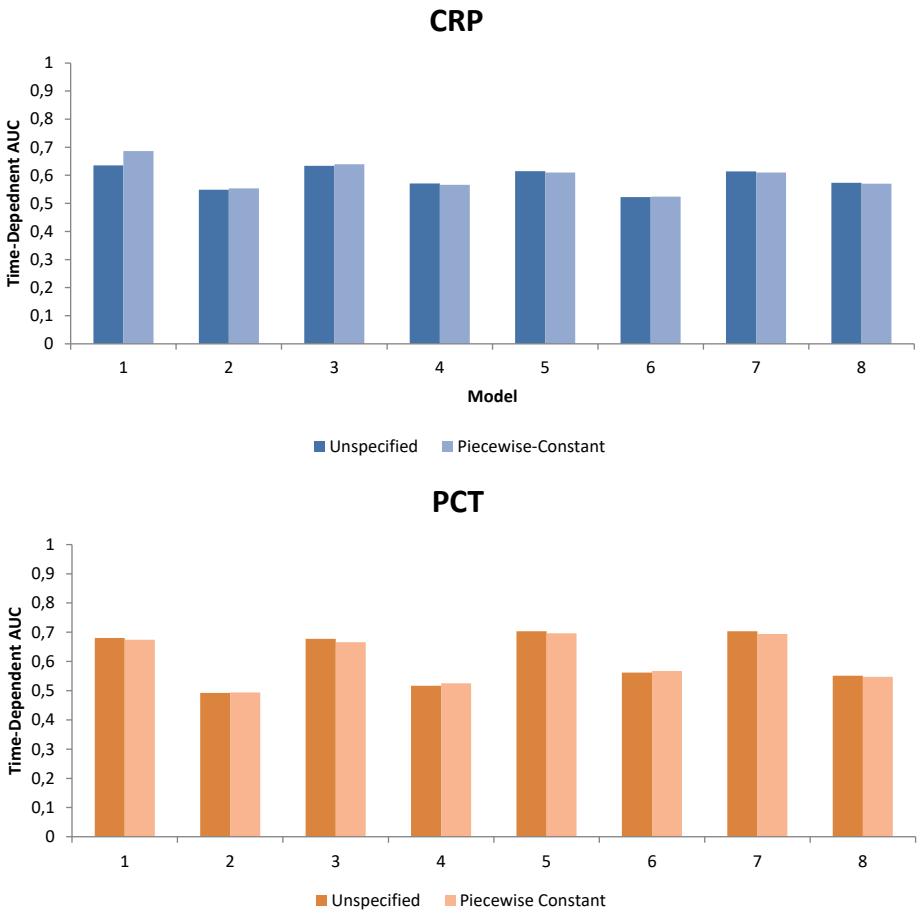

Figure 4.10. Time-Dependent AUC Values in terms of different survival distribution options

In Figure 4.10, joint models are shown as coded 1 to 8. **1** refers to standard joint model-Model-I combination, 2 is joint model with slope parameterization-Model-I, 3 stands for joint model with current value and slope parameterization-Model-I,, 4 refers to joint model with cumulative-effects parameterization-Model-I combination, 5 is standard joint model-Model-II, 6 is joint model with slope parameterization-Model-II, 7 refers to joint model with current value and slope parameterization parameterization-Model-II abd 8 is joint model with cumulative-effects parameterization-Model-II combination.

Analysis results revealed that time-dependent diagnostic accuracies are found as moderate and almost similar for both biomarkers. Maximum diagnostic performance for CRP is observed with standard joint model (current value parameterization)-random intercept and random slope structure-Piecewise Constant distribution combination (Table 4.18). On the other hand for PCT, standard joint model-quadratic random effects structure and baseline hazard unspecified combination has the highest diagnostic performance. (Table 4.19.)

For random-effects structure model comparison, CRP seems to perform better in Model-I, whereas PCT has higher diagnostic performance in Model-II. Therefore constructing the joint model with more detailed functional form of random-effects part increases time-dependent AUC values for PCT in this study. However in general there is no exact answer about which model structure should be used in random effects part of LME model. It is changeable in accordance with the purpose of the research. (Figure 4.8)

In parameterization perspective, the highest diagnostic performance is reached when standard joint model is used for both CRP and PCT. On the other hand slope parameterization type has the minimum time-dependent AUC values for both biomarkers. In general standard joint model (current value parameterization) and both parameterization types have higher performance than cumulative effects and slope parameterization types for either CRP or PCT. (Figure 4.9a and 4.9b)

For survival distribution comparison, it seems there is no noteworthy difference between these two options for neither CRP nor PCT. The most remarkable difference is observed for CRP biomarker with standard joint model. In that case Piecewise-Constant Distribution gives higher diagnostic accuracy than its alternative. Even though these diagnostic accuracies are similar, Piecewise-Constant Distribution is recommended to use since it's a parametric survival distribution and allows flexibility while modeling survival times. (Figure 4.10.)

In this part, determination of predictive abilities of the biomarkers are based on the cut-off point which uses median of the survival times. Other cut-off alternatives can also be considered in order to make a comparison of their diagnostic performances in predicting the risk of death at the end of the period.

4.6. Evaluating Cut-Off Values for Longitudinal Data

Other than assessing the diagnostic performance of biomarkers and comparing these performances, one of the objectives in using classical ROC Analysis is obtaining cut-off values to discriminate subjects who are at risk and who are not. However when time dimension is incorporated this ROC curve analysis, a single cut-off value becomes insufficient to distinguish the two groups. In longitudinal studies, as long as new measurements are taken from the subjects within the follow-up period, cut-off values can be updated and this property gives cut-off values dynamic characteristics. Therefore in these studies, rather than utilizing a single cut-off value, time-dependent cut-off values are obtained to discriminate event and event-free subjects within the time interval $t+\Delta t$, using measurements up to time t.

In this part of the application, diagnostic accuracies of CRP and PCT biomarkers are evaluated and their performances in distinguishing the subjects on the 1^{st}, 2^{nd} and 3^{rd} day after the last measurement was taken are demonstrated by time-dependent ROC curves and time-dependent cut-off values.

To obtain the cut-off values, first of all sub-groups are created for both gender and for each biomarker. Joint models with current value parameterization (standard

joint models) are constructed based on the same formula (4.1) in order to evaluate the contribution of each biomarker value taken at time t for both women and men datasets of CRP and PCT biomarkers. Coefficients, standard errors, p-values and goodness of fit statistics of these models are given below (Table 4.20a., Table 4.20b., Table 4.21a. and Table 4.21b.).

Table 4.20a. Coefficients, standard errors, p-values, standard deviation of linear mixed-effects model and goodness of fit statistics of joint models for each gender for CRP

Gender	Process	Variable	β	SE (β)	p-value
Female	Longitudinal	**Intercept**	0.7449	0.115	<0.0001
		time	-0.0177	0.0087	0.0426
		age	0.0007	0.0017	0.6737
		time*age	0.0002	0.0001	0.0459
	Survival	**α**	1.1209	0.3802	0.0032
		log(xi.1)	-5.8971	0.4771	
		log(xi.2)	-6.1428	0.6170	
		log(xi.3)	-5.0438	0.4873	
		log(xi.4)	-4.7400	0.4477	
		log(xi.5)	-4.6323	0.4581	
		log(xi.6)	-4.4053	0.6326	
		log(xi.7)	10.9631	0.5173	
σ = 0.264					
AIC = 1467.087, **BIC** = 1531.823					
Male	Longitudinal	**Intercept**	0.8544	0.1239	<0.0001
		time	-0.018	0.0094	0.0564
		age	0.0001	0.0019	0.9817
		time*age	0.0002	0.0001	0.1258
	Survival	**α**	1.7195	0.4741	0.0003
		log(xi.1)	-7.1443	0.6571	
		log(xi.2)	-5.2196	0.5456	
		log(xi.3)	-6.1239	0.6025	
		log(xi.4)	-5.9011	0.6012	
		log(xi.5)	-5.3772	0.5660	
		log(xi.6)	-5.6883	0.7289	
		log(xi.7)	10.1973	0.6663	
σ = 0.241					
AIC = 1339.39, **BIC** = 1405.045					

Table 4.20b. Variance-covariance matrix of random-effects in joint models for each gender for CRP

		Intercept	time	time^2
Female	**Intercept**	0.252	-0.019	0.000502
	time	-0.019	0.0037	-0.000104
	time^2	0.000502	-0.0001	0.00000319
		Intercept	**time**	**time^2**
Male	**Intercept**	0.225	-0.016	0.0004
	time	-0.016	0.0037	-0.000104
	time^2	0.0004	-0.0001	0.00000386

Table 4.21a. Coefficients, standard errors, p-values, standard deviation of linear mixed-effects model and goodness of fit statistics of joint models for each gender for PCT

Gender	Process	Variable	β	SE (β)	p-value
Female	**Longitudinal**	**Intercept**	-0.1277	0.1786	0.4746
		time	-0.0376	0.0112	0.0008
		age	-0.0034	0.0026	0.1876
		time*age	0.0006	0.0002	0.0005
	Survival	**α**	1.1659	0.1923	<0.0001
		log(xi.1)	-4.6695	0.2862	
		log(xi.2)	-4.1848	0.3181	
		log(xi.3)	-3.8624	0.3039	
		log(xi.4)	-3.8624	0.2908	
		log(xi.5)	-3.3635	0.2403	
		log(xi.6)	-3.9859	0.5845	
		log(xi.7)	11.6124	0.4272	
σ = 0.408					
AIC = 2939.857, **BIC** = 3006.840					
Male	**Longitudinal**	**Intercept**	-0.1745	0.2052	0.3949
		time	-0.0261	0.0166	0.1166
		age	-0.0011	0.0031	0.7333
		time*age	0.0003	0.0002	0.2915
	Survival	**α**	1.2621	0.1813	<0.0001
		log(xi.1)	-5.6228	0.3948	
		log(xi.2)	-3.6995	0.2301	
		log(xi.3)	-4.3462	0.3362	
		log(xi.4)	-3.4009	0.2647	
		log(xi.5)	-3.5690	0.2635	
		log(xi.6)	-4.3608	0.5310	
		log(xi.7)	11.1473	0.4896	
σ = 0.409					
AIC = 3304.563, **BIC** = 3373.826					

Table 4.21b. Variance-covariance matrix of random-effects in joint models for each gender for PCT

		Intercept	time	time^2
Female	**Intercept**	0.628	-0.037	0.000702
	time	-0.037	0.0087	-0.0003
	time^2	0.000702	-0.0003	0.00000938
		Intercept	**time**	**time^2**
Male	**Intercept**	0.720	-0.053	0.00124
	time	-0.053	0.0111	-0.0004
	time^2	0.00124	-0.0004	0.0000152

For each sub-group, median of age and number of repeated biomarker measurements are given as basic descriptive statistics. For a new-coming subject who admitted to the any intensive care unit, these values are considered to represent that subject. And with the help of these values, time-dependent ROC curves are drawn and time-dependent cut-off values for 1st, 2nd and 3rd day after the last measurement was taken are calculated. For example, for CRP biomarker, median age of men is 67 and on average, 4 measurements are taken from per-subject in this group within the follow-up period. Therefore, for a new-coming subject to this sub-group, it's assumed that his age is 67 and total of 4 measurements from this subject will be taken. Also, fixed-visit times are considered for all cases, for example, the time-points for these measurements are considered to be taken as t=0, 1, 2 and 3. For each sub-group, this procedure is considered and representative descriptive statistics are given in the following table (Table 4.22.).

Table 4.22. Characteristics of representative subjects for each sub-groups of CRP and PCT

Biomarker	Gender	Age	Number of Measurements
CRP	**Female**	73	4
	Male	67	5
PCT	**Female**	72	4
	Male	67	4

Based on the Monte-Carlo simulation scheme described in Section 4.4, time-dependent cut-off values are determined as the values which has the maximum value

of product of time-dependent specificity and time – dependent specificity at Δt = 1, 2, 3 (60).

All the results are given with time-dependent ROC Curves, time-dependent AUC and time-dependent cut-off values for CRP and PCT biomarkers, separately. Results are demonstrated below:

4.6.1. Diagnostic Accuracy of CRP Biomarker

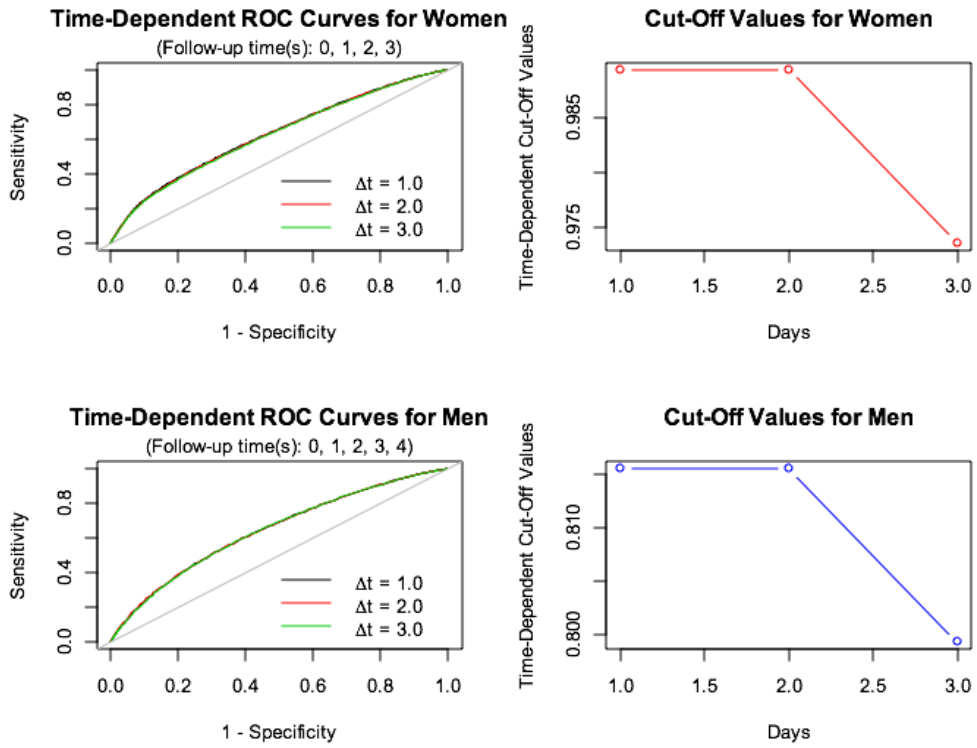

Figure 4.11. Time-Dependent ROC Curves and Time-Dependent Cut-Off values of CRP for Δt=1, 2 and 3 after the last measurement

Table 4.23. Time-Dependent AUC Values and Time-Dependent Cut-Off values of CRP for Δt=1, 2 and 3 after the last measurement

Gender	Time - Dependent AUC			Time-Dependent Cut-Off Values		
	Δt = 1	Δt = 2	Δt = 3	Δt = 1	Δt = 2	Δt = 3
Female	0.624	0.621	0.618	0.989	0.989	0.974
Male	0.640	0.640	0.639	0.816	0.816	0.799

The left side of the table indicates the time-dependent AUC values for the first 3 days after the last measurement was taken from the representative subject. In other words they can be defined as the indicator of the discriminative ability of the biomarker in Intensive Care Units on the 1st, 2nd and 3rd day after the last measurement was taken. The right hand side demonstrates the time – dependent cut – off values that are utilized for discriminating the subjects who will be at risk and who will be risk-free on the 1st, 2nd and 3rd day after the last measurement.

Results revealed that discriminative ability of CRP biomarker is in moderate level on the 1st, 2nd and 3rd day after the last measurement. Also it is observed that the time-dependent cut-off values remain the same on the first 2 days after the last measurement for both women and men, while on the 3rd day they decrease. CRP biomarker has almost the same diagnostic performances on these first 3 days in both gender groups, however this performance is better in men than women. On the other hand, contrary to time-dependent diagnostic accuracy values, cut-off values obtained for women are higher than cut-off values obtained for men on the first 3 days after the last measurement. (Figure 4.11. and Table 4.23.)

4.6.2. Diagnostic Accuracy of PCT Biomarker

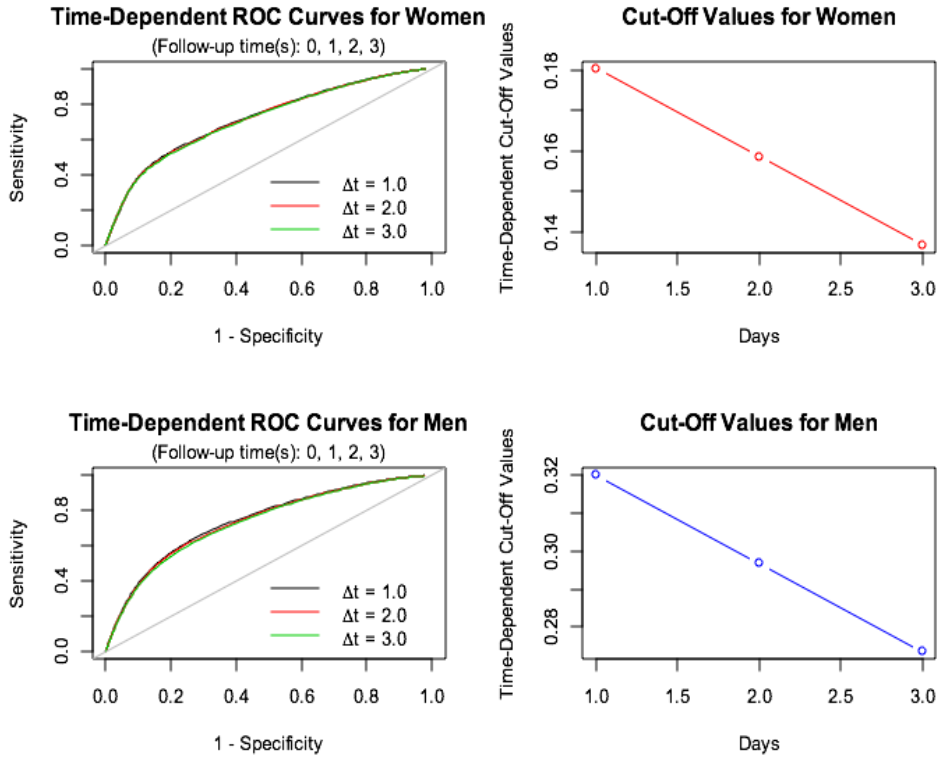

Figure 4.12. Time-Dependent ROC Curves and Time-Dependent Cut-Off values of PCT for Δt=1, 2 and 3 after the last measurement

Table 4.24. Time-Dependent AUC Values and Time-Dependent Cut-Off values of PCT for Δt=1, 2 and 3 after the last measurement

Gender	Time - Dependent AUC			Time-Dependent Cut-Off Values		
	Δt = 1	**Δt = 2**	**Δt = 3**	**Δt = 1**	**Δt = 2**	**Δt = 3**
Female	0.697	0.694	0.691	0.180	0.159	0.137
Male	0.718	0.712	0.707	0.320	0.297	0.274

For PCT biomarker, it's revealed that diagnostic accuracy of PCT in men is better than the diagnostic accuracy of PCT in women on the 1st, 2nd and 3rd day after the last measurement. However for both gender groups, this diagnostic performances are prone to decrease through the 3rd day. For the time - dependent cut-off values, for both genders they are in decreasing trend through the 3rd day after the last measurement was taken.

Likewise CRP, it can be said that the discriminative ability and time-dependent cut-off values of PCT biomarker decreases through the 3rd day, that is, they reach the minimum values on this day (Figure 4.12. and Table 4.24.). Contrary to CRP, cut-off values for men are found to be higher than those of women on the first 3 days after the last measurement.

In summary, it's observed that PCT biomarker has better discriminative ability compared to CRP on the first 3 days after the last measurement, both in men and women. For gender comparison, it should be noted that both biomarkers have slightly higher predictive ability in men than in women. The trajectory of these time-dependent AUC values is the same in all cases. That is, they reach the highest value on the first day after the last measurement and decreases slightly on the 2nd and 3rd days for both biomarkers and in both genders. For the time-dependent cut-off values, they are in decreasing trend in women and men for PCT, however for CRP, they remain constant on the first two days and then decrease on the 3rd day after the last measurement.

These time-dependent ROC curves and time-dependent cut-off values suggest that the risk of death in Intensive Care Units on the first 3 days after the last measurement is prone decrease for all cases-for both biomarkers and for both genders-in this study.

4.7. Time-Dependent Diagnostic Accuracy Metrics

In this section, corresponding time-dependent diagnostics accuracy values, time-dependent sensitivity and time-dependent specificity, are given for each cut-off value to determine more specific and more sensitive markers (Table 4.25.).

Table 4.25. Time-Dependent Sensitivity and Time-Dependent Specificity Measures

Gender	Biomarker	Td-Cut-Off	Td-Sens-Δ_1	Td-Sens-Δ_2	Td-Sens-Δ_3	Td-Spec-Δ_1	Td-Spec-Δ_2	Td-Spec-Δ_3
Female	CRP	0.989	0.562	0.556	0.551	0.612	0.614	0.615
		0.989	0.562	0.556	0.551	0.612	0.614	0.615
		0.974	0.575	0.569	0.564	0.598	0.600	0.601
	PCT	0.180	0.609	0.601	0.593	0.713	0.716	0.720
		0.159	0.618	0.609	0.602	0.703	0.706	0.710
		0.137	0.626	0.618	0.610	0.693	0.696	0.699
Male	CRP	0.816	0.585	0.585	0.582	0.622	0.623	0.626
		0.816	0.585	0.585	0.582	0.622	0.623	0.626
		0.799	0.599	0.598	0.596	0.608	0.608	0.612
	PCT	0.320	0.651	0.639	0.63	0.718	0.719	0.721
		0.297	0.659	0.648	0.639	0.709	0.710	0.712
		0.274	0.667	0.656	0.647	0.700	0.701	0.703

Table 4.25 indicates that time-dependent diagnostic accuracy metrics are very close to each other as corresponding time-dependent AUC values. Almost all time-dependent diagnostic accuracy measures are found in moderate level. On the other hand for biomarker comparison, PCT is found to be more sensitive and specific biomarker compared to CRP during the first 3 days after the last measurement was taken.

4.8. Evaluating the Diagnostic Performance throughout the Follow-up Period

In both classical ROC Curves and time-dependent ROC Curves obtained by the baseline measurement taken at t=0, a single ROC Curve, a single AUC value and a single cut-off value to distinguish subjects who are at risk and who are risk-free, is sufficient to assess the diagnostic accuracy. However a single AUC value or a single cut - off value is not sufficient when serial biomarker measurements are taken within the follow-up period. In such cases, it could be possible to update the diagnostic accuracy after each serial biomarker value taken within this period. Also in this way the contribution to diagnostic performance of each serial measurement could be determined.

In this part, the diagnostic performances throughout the follow-up period for CRP and PCT biomarkers are investigated and updated time-dependent AUC values along with updated time-dependent cut-off values are given. Time-dependent cut-off

values are calculated based on fitted joint models with log-transformed biomarker values. Therefore figuresare drawn with log-transformed CRP and log-transformed PCT values.

4.8.1. Diagnostic Accuracy of CRP Biomarker in terms of Genders

4.8.1.1. Diagnostic Accuracy of CRP in Women

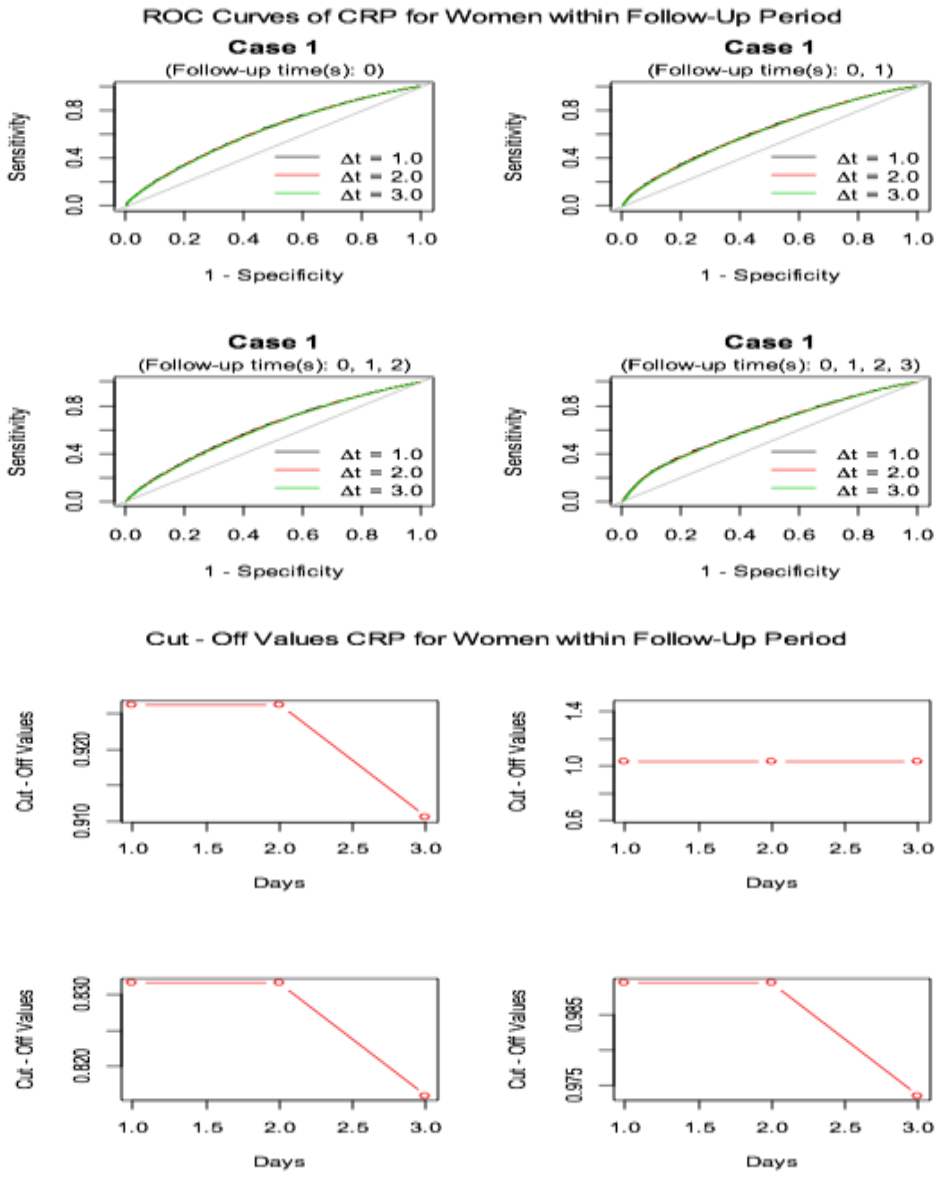

Figure 4.13. Time-Dependent ROC Curves and Time-Dependent Cut-Off values of CRP for Women for Δt=1, 2 and 3 after the last measurement

Table 4.26. Time-Dependent AUC Values and Time-Dependent Cut-Off values of CRP for Women for Δt=1, 2 and 3 after the last measurement

Time of Measurements	Time-Dependent AUC			Time-Dependent Cut-Off Values		
	Δt = 1	**Δt = 2**	**Δt = 3**	**Δt = 1**	**Δt = 2**	**Δt = 3**
t=0	0.617	0.615	0.612	0.926	0.926	0.911
t=1	0.616	0.612	0.609	1.037	1.037	1.037
t=2	0.609	0.606	0.603	0.832	0.832	0.816
t=3	0.624	0.621	0.618	0.989	0.989	0.974

It is revealed that in general the diagnostic performance of CRP is fairly moderate in women, the contributions of time points t=1 and t=2 to the discriminative ability are almost the same. The contribution of the baseline measurement (t=0) is higher compared to these aforementioned time points, t=1 and t=2; however the biggest contribution comes out of the last time point, namely time=3, so that with the help of this measurement, discriminative power of the biomarker increases about 3%, compared to previous time point, namely t=2. In overall, for the time-dependent AUC values, it should be noted that they are quite similar for the first 3 days after the last measurement and they are slightly decreasing through the 3rd day.

For the time-dependent cut-off values, these values either remain constant or decrease through the 3rd day after the last measurement. In detail, after the first measurement (taken at t=0), these cut-off values remain constant on the first two days and decrease on the third day. After the second measurement, which is taken at t=1, time-dependent cut-off values are observed to increase compared to cut-off values after the baseline measurement, and these cut-off values remain the same all the first three days. After the third measurement, time-dependent cut-off values decrease considerably compared to previous time-dependent cut-off values, which means the risk of death decrease after the third measurement taken at t=2, and they remain constant after the two days, and then decrease on the 3rd day after the last measurement. On the other hand, last measurement taken at t=3 seems to increase the cut-off values compared to t=2. However they are the same on the first two days, but decrease on the 3rd day. (Figure 4.13. and Table 4.26.).

4.8.1.2. Diagnostic Accuracy of CRP in Men

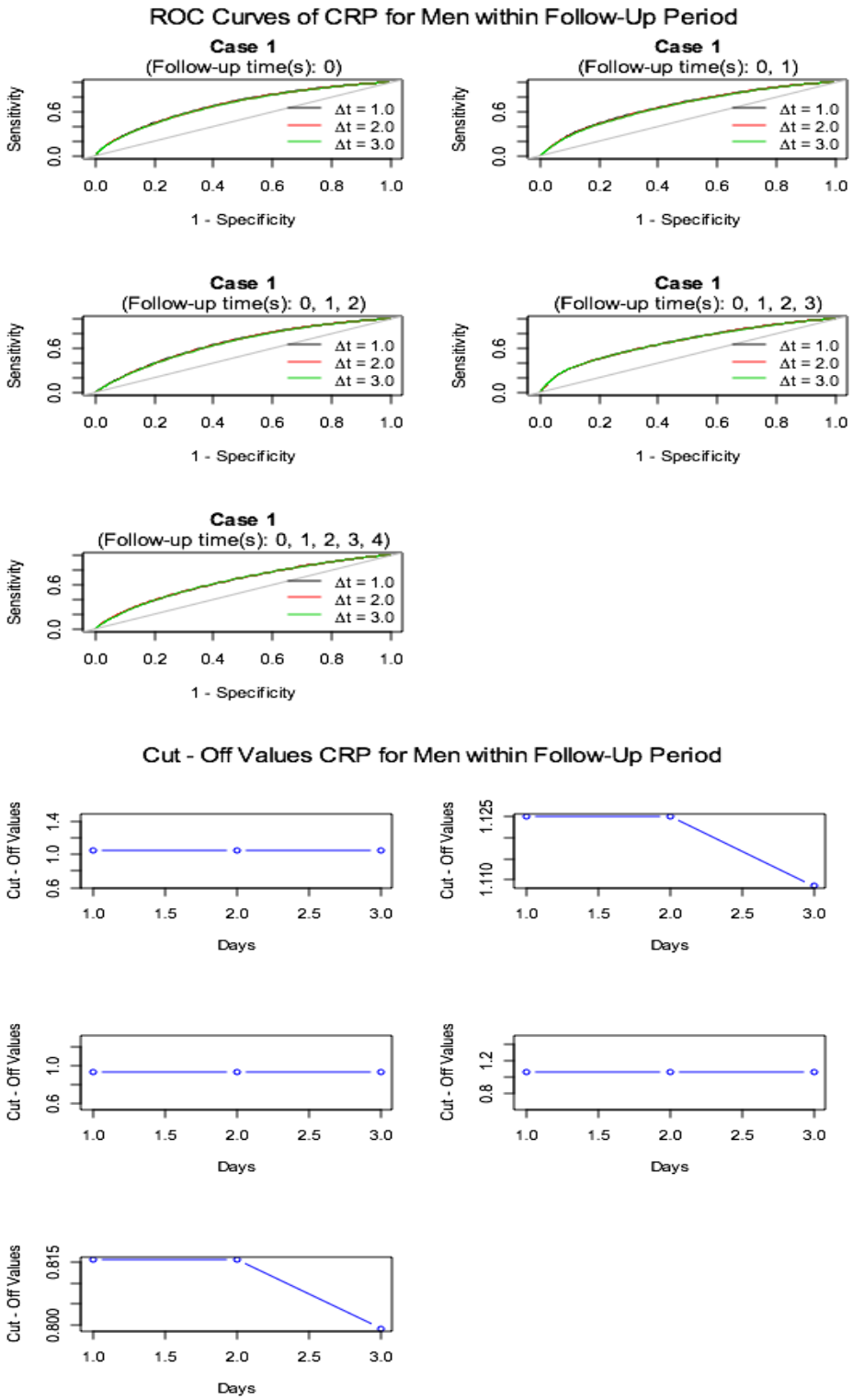

Figure 4.14. Time-Dependent ROC Curves and Time-Dependent Cut-Off values of CRP for Men for Δt=1, 2 and 3 after the last measurement

Table 4.27. Time-Dependent AUC Values and Time-Dependent Cut-Off values of CRP for Men for Δt=1, 2 and 3 after the last measurement

Time of Measurements	Time-Dependent AUC			Time-Dependent Cut-Off Values		
	Δt = 1	**Δt = 2**	**Δt = 3**	**Δt = 1**	**Δt = 2**	**Δt = 3**
t=0	0.690	0.687	0.683	1.0435	1.0435	1.0435
t=1	0.678	0.674	0.670	1.125	1.125	1.109
t=2	0.662	0.659	0.656	0.930	0.930	0.930
t=3	0.677	0.677	0.676	1.0598	1.0598	1.0598
t=4	0.640	0.640	0.639	0.816	0.816	0.799

Results for men of CRP suggest that the diagnostic accuracy is prone to decrease through the 3rd day for all time points, namely t=0, 1, 2, 3 and 4. The maximum contribution to the diagnostic performance comes from the baseline measurement, taken at t=3, while the minimum contribution belongs to the last time point, taken at t=4. Contribution of the 4th measurement that was taken at t=3 is second biggest, comes after the baseline measurement, on the other hand the lowest contribution to the predictive ability comes out of the measurement taken at t=4. In overall, for the time-dependent AUC values, they are almost in decreasing trend through the 3rd day, also it seems as long as new measurements are taken, they are prone to decrease on Δt =1, 2 and 3.

For the time-dependent cut-off values of CRP in men, these values either remain constant or decrease through the 3rd day after the last measurement. In detail, after the first measurement (taken at t=0), these cut-off values remain constant on the first three days. After the second measurement, which is taken at t=1, time-dependent cut-off values are observed to be increase compared to previous measurement time and they are found as the same for the first two days and then decrease on the 3rd. For the next time-point, t=2, they are observed to be decrease compared to previous time-point, t=1, and also remain constant on the 1st, 2nd and 3rd days. However time-dependent cut-off values from the following measurement, namely from t=3, increases considerably compared to t=2 and as for the time-point t=2, they remain constant on the first three days. Cut-off values obtained from the last measurement, taken at t=4, are however decreases compared to previous time point considerably. Therefore it must be mentioned that time-dependent cut-off values in men seem to

have fluctuations for the 1st, 2nd and 3rd days, so that the minimum cut-off values are obtained from the last measurement taken at t=4, while the maximum ones are obtained from the previous time point, taken at t=3. (Figure 4.14.. and Table 4.27.)

In overall, CRP biomarker has higher diagnostic performance in men than women, in all time points (t) and in all future time points (Δt), in terms of time-dependent AUC values. On the other hand the contribution of time points to the diagnostic accuracy changes, that is, the maximum contribution comes from the last time point taken at t=3 and minimum contribution belongs to time point t=2, which is last but one measurement for women, while for men the maximum contribution belong to the baseline measurement taken at t=0, and the minimum contribution comes out of the last measurement taken at time-point t=4. For the time-dependent cut-off values however, minimum cut-off value comes after the third measurement taken at t=2 and maximum one from the previous measurement, taken at t=1, in women, while for men, minimum and maximum threshold values come after the measurements taken at t=4 and t=3, respectively.

4.8.2. Diagnostic Accuracy of PCT Biomarker in terms of Genders

4.8.2.1. Diagnostic Accuracy of PCT in Women

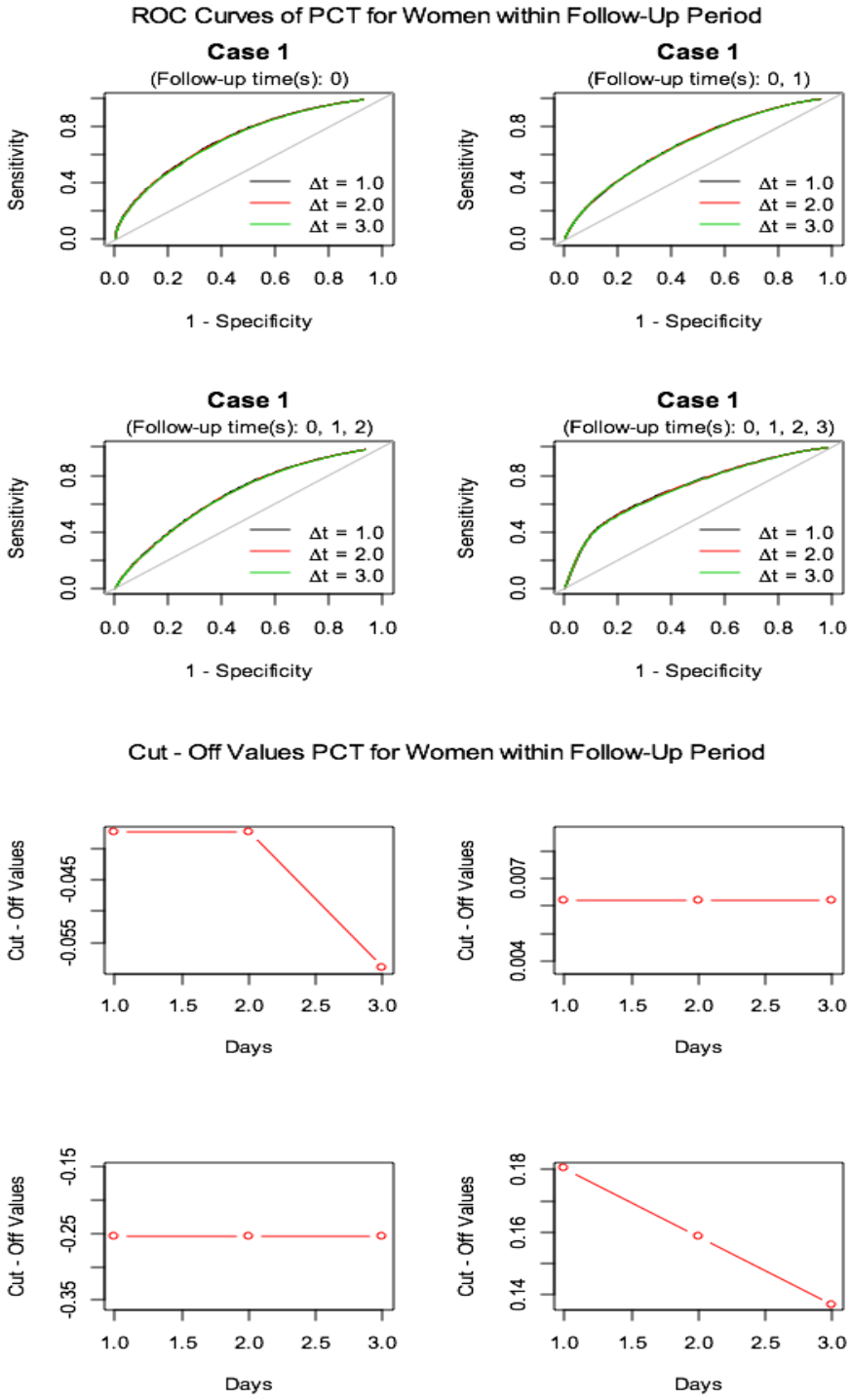

Figure 4.15. Time-Dependent ROC Curves and Time-Dependent Cut-Off values of PCT for Women for Δt=1, 2 and 3 after the last measurement

Table 4.28. Time-Dependent AUC Values and Time-Dependent Cut-Off values of PCT for Women for Δt=1, 2 and 3 after the last measurement

Time of Measurements	Time-Dependent AUC			Time-Dependent Cut-Off Values		
	Δt = 1	**Δt = 2**	**Δt = 3**	**Δt = 1**	**Δt = 2**	**Δt = 3**
t=0	0.648	0.645	0.640	-0.037	-0.037	-0.059
t=1	0.629	0.628	0.627	0.006	0.006	0.006
t=2	0.606	0.603	0.600	-0.255	-0.255	-0.255
t=3	0.697	0.694	0.691	0.180	0.159	0.137

Results of women revealed that time-dependent accuracies of PCT are almost similar through the 3rd day after the last measurement. Maximum contribution come from the last measurement, which is taken at t=3. On the other hand relatively minimum contribution belongs to measurement taken at t=2. It can be observed that as longitudinal information increase, in other words as new measurements are taken from the subjects, the discriminative power is prone to increase. However it should be noted that this discriminative power are in decreasing trend throughout the 3rd day for all time-points.

For the time-dependent cut-off values of PCT biomarker in women, these values either remain constant or decrease through the 3rd day after the last measurement. After the baseline measurement, which is taken at t=0, cut-off values are prone to decrease through the 3rd day. However they increase after the second measurement and remain constant. Following longitudinal measurement, which is taken at t=2, decrease these time-dependent cut-off values considerably on the 1st, 2nd and 3rd days compared to measurement time t=1. On the other hand the last measurement seems to increase these time-dependent cut-off values so that they reach the maximum levels compared to other cut-off values. (Figure 4.15.. and Table 4.28.)

4.8.2.2. Diagnostic Accuracy of PCT in Men

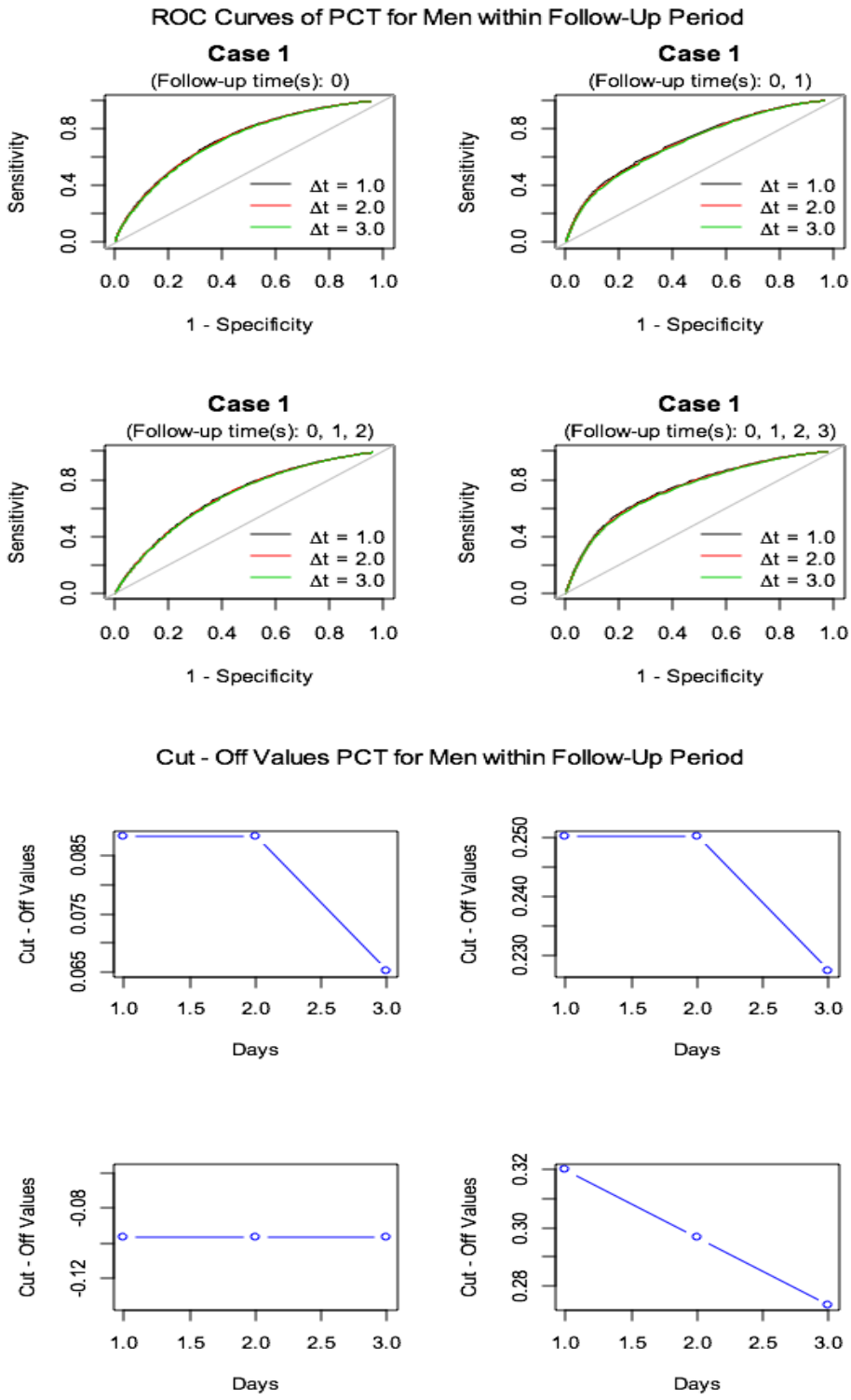

Figure 4.16. Time-Dependent ROC Curves and Time-Dependent Cut-Off values of PCT for Men for Δt=1, 2 and 3 after the last measurement

Table 4.29. Time-Dependent AUC Values and Time-Dependent Cut-Off values of PCT for Men for Δt=1, 2 and 3 after the last measurement

Time of Measurements	Time-Dependent AUC			Time-Dependent Cut-Off Values		
	Δt = 1	**Δt = 2**	**Δt = 3**	**Δt = 1**	**Δt = 2**	**Δt = 3**
t=0	0.675	0.672	0.667	0.088	0.088	0.065
t=1	0.674	0.669	0.663	0.250	0.250	0.227
t=2	0.650	0.647	0.643	-0.097	-0.097	-0.097
t=3	0.718	0.712	0.707	0.320	0.297	0.274

Results for men revealed that time-dependent accuracies of PCT biomarker are similar through the 3rd day after the last measurement, like other cases. Maximum contribution comes from the last measurement, which is taken at t=3.On the other hand it's observed that third measurement decreases this diagnostic performance so that time-dependent AUC value reaches its minimum value after t=2. It can be observed that as longitudinal information increases, generally the discriminative accuracies are prone to increase. Also it should be noted that this discriminative power is in decreasing trend throughout the 3rd day.

For the time-dependent cut-off values, the trajectory for men is similar for all time points, t=0, 1, 2 and 3. That is, these values either remain constant or decrease throughout 3rd day after the last measurement. After the baseline measurement, time-dependent cut-off values remain the same the first two days but on the 3rd day it decreases. Following measurement taken at t=1 increases the cut-off values compared to baseline measurement, t=0, however it decreases on the 2nd day and remain constant on the first three days after the last measurement. Contrary to previous cut-off profiles, the trajectory of the last measurement taken at t=3 is neither remain constant on the first three days nor remain constant on the first two days and then decrease on the 3rd day after the last measurement. The thresholds are decreasing gradually throughout the 3rd day after the measurement taken at t=3. (Figure 4.16. and Table 4.29.)

In overall, PCT has higher diagnostic performance in men than women, in all time points (t) and in all future time points (Δt), in terms of time-dependent AUC

values, like CRP. On the other hand the contributions of time points to the diagnostic accuracy are the same, that is, maximum contributions come from the last time point taken at t=3 and minimum contributions are observed after the second measurement taken at t=2 in both men and women. As for the time-dependent cut-off values, they depict fluctuations for both groups, that is, they decrease after relatively big cut-off values and increase after relatively small cut-off values in both men and women. Maximum time-dependent cut-off values are obtained after the last measurement which is taken at t=3, in both women and men. However minimum cut-off values are observed on t=2, which is last but one measurement for both of the groups.

To sum up, time-dependent AUC values are observed to decrease through the 3rd day after each biomarker value in both gender groups and in both of the biomarkers. Moreover, in general as long as new measurements are taken from subjects within the follow-up period, time-dependent diagnostic accuracies are prone to increase. On the other hand in both gender groups and in both biomarkers, it's found that time-dependent cut-off values either remain constant or decrease through the 3rd day, but these values never increase through the 3rd day. This result also proves that the risk of death in ICU-setting is decreasing over the further time-points after the last measurement was taken.

5. DISCUSSION

Area Under Curve (AUC) obtained from the classical ROC Curve is the most common measure to determine the diagnostic accuracy of a biomarker. There is no time interval between the measurement and the diagnosis in classical ROC Curve. However in many situations in clinics a single biomarker measurement taken within the follow-up is utilized to make diagnosis of the event at the end of follow-up period. When the time dimension is incorporated to the classical ROC Curve, diagnostic accuracy is determined by time-dependent AUC values obtained from time-dependent ROC Curves. But in many situations in clinics, a single value is insufficient to make a diagnosis. Therefore, evaluating longitudinal profile of a biomarker is considered as a more effective way for diagnosing. As in the single measurement-case, diagnostic accuracy of serial biomarker measurements taken within the follow-up period is determined by time-dependent AUC values. In literature, the first study evaluating the diagnostic performance of longitudinal data was published in 2004 (13); however studies including the diagnostic performance of serial biomarkers have gained much attention starting 2010s. (3, 6, 10-12, 15-22)

Studies investigating the diagnostic accuracy of serial biomarker values have focused mostly on HIV studies (3, 14), dementia researches (17, 19), cancer research (10, 11) and cardiovascular diseases (15, 18, 21). Therefore longer follow-up periods are taken such as months and years. Since the event is defined as ICU mortality in this thesis, the survival time is taken as 30 days. There are several studies modeling ICU biomarkers with joint modeling approach, Deslandes and Chevret analyzed the relationship between serial SOFA scores and ICU mortality in competing-risk-setting (61). Khoundabi et al. investigated repeated Urine Output measurements along with other risk factors on the occurrence of Acute Kidney Injure (AKI) in ICU patients (62). In these studies, only the relationship between serial biomarker values and the event of interest is analyzed, however the diagnostic values of these biomarkers are not investigated. To the best of our knowledge, there is no other study in literature to analyze the diagnostic performances of serial CRP and PCT biomarkers using joint models. In this thesis, short follow-up period is taken – 30 days – and two different

joint models are constructed for CRP and PCT biomarkers and their discriminative abilities in predicting ICU mortality at the end of follow-up period are evaluated and compared. Moreover, diagnostic accuracies of these serial biomarker measurements are assessed throughout the follow-up period, hence it would be possible to determine in which time points which biomarker should be preferred to predict the event of interest. 95% confidence intervals are given along with these time-dependent AUC values to determine whether these diagnostic accuracies are statistically significant. Karaismailoglu et.al assessed the diagnostic performances of cardiac panel biomarkers over the follow-up period but they have utilized single biomarker values in the analysis (63). Fournier et al. proposed R^2 curve to assess the predictive accuracy of longitudinal data (12). They compared this proposed metric and Brier Score in predicting the event of interest throughout the follow-up period using serial Serum Creatinine measurements cumulatively from DIVAT data. They also presented 95% confidence intervals for these metrics throughout the follow-up period. Musoro et.al evaluated diagnostic performances of serial SOFA scores along the follow-up period in competing risk setting by using joint modeling approach. Standard joint modeling has been performed to obtain time-dependent diagnostic accuracy values. Time-dependent AUC values and Brier Score as diagnostic performance measures for predicting the risk of death in hospital has been reported (21).

In this thesis cut-off values for both biomarkers are determined over a representative subject of the each sample of CRP and PCT. Time-dependent sensitivity and time-dependent specificity values are given for these cut-off values. *CQV* and *RCV* statistics are calculated for both of the biomarkers to determine which biomarker should be preferred to discriminate subjects at risk and subjects without at risk of death at the end of follow- up period in ICU setting. Smaller *CQV* and *RCV* are proposed to determine the relevant cut-off value for discrimination. To the best of our knowledge, this thesis is the first in proposing the *CQV* and *RCV* statistics together in the decision of the most appropriate cut-off point when there are several threshold alternatives for the pre-specified event of interest in the study. Moreover,

calculating the cut-off values over representative subjects of the sample of the biomarkers is considered to be firstly applied in this thesis.

Rather than taking a single biomarker value to make a diagnosis, clinicians mostly prefer taking serial biomarker measurements to investigate the longitudinal trajectory of the subjects in detail on either the most appropriate treatment decision or the diagnosis. Kurz et al. compared single and serial Troponin-T values in patients with acute STEMI to predict major adverse cardiac event (MACE). They have found that single Troponin-T value is as effective as serial Troponin-T values and may be useful in predicting future events (64). Wolff and Bouadma (65) and Samsudin and Vasikaran (66) reported that utilizing serial PCT values over single PCT value is recommended in most situations in clinic. On the other hand, several studies have stated that serial CRP values are valuable compared to single CRP taken at the time of admission to diagnose sepsis (49), while other studies have defined using serial CRP values over single value as helpful for diagnosis (67). In this thesis, diagnostic accuracies of the biomarker values taken at baseline (t=0) and repeated measurements of CRP and PCT biomarkers taken within the follow-up period are evaluated and compared in terms of time-dependent AUC values. Also 95% confidence intervals obtained from nonparametric percentile bootstrap method are given in this study. Moreover, to the first, this study is considered to be unique in comparing diagnostic accuracies of single and serial biomarker values performing joint modeling, giving p-values as a comparison criteria. There are several other studies in literature which give 95% confidence intervals by using nonparametric bootstrap approach for time-dependent AUC, time-dependent sensitivity and time-dependent specificity values. In this study percentile method is applied for 95% confidence intervals for both time-dependent AUC values and time-dependent cut-off values.

For each biomarker, different combinations of joint models are compared and interpreted in terms of their diagnostic performances in predicting ICU mortality at the end of the period. The aim is to find out the best joint model combination for obtaining the optimal diagnostic accuracy for both CRP and PCT. Within the context

of this analysis, two different random-effects model structure in longitudinal sub-model, two different survival distribution in survival sub-model and four different parameterization options to link between longitudinal and survival sub-models are included and compared. To the best of our knowledge, it's the most comprehensive study that analyses different combinations such in detail, compares the diagnostic accuracies of these ICU biomarkers under these combinations, gives the best-combination for both of the biomarkers that has the maximum-diagnostic-accuracy. Several other studies in literature have also investigated different joint model combinations. But in these studies different joint models are either compared in terms of dynamic survival probabilities or in terms of diagnostic accuracies of the models (21) or some studies have used goodness-of-fit measures to compare different combinations of joint models (15).

In classical ROC Curve Analysis, a single cut-off value is sufficient to differentiate diseased and non-diseased subjects. When time dimension is incorporated into the ROC Curve, a single cut-off value becomes inadequate to distinguish the two groups since new measurements of biomarkers are taken throughout the follow-up period. As long as new measurements are taken from the subjects, cut-off values for distinguishing risky and non-risky groups are updated in follow-up studies. This property gives cut-off values dynamic characteristics. In literature, there are several studies including cut-off values obtaining from a single biomarker value taken within the follow-up period (63, 68). However, a few studies have investigated the cut-off values in time-dependent setting. Abdi et al. used joint modeling approach to investigate the relationship between serial mycophenolic acid (MPA) and acute rejection (AR). They have obtained time-dependent threshold values for serial MPA values based on fitted joint models along with 95% confidence intervals obtained by nonparametric bootstrap method (16). In this thesis, time-dependent cut-off values for discriminating the subjects for the first three days after the last measurement was taken are calculated and interpreted for each gender group for both CRP and PCT biomarkers. Also diagnostic accuracies are updated after each serial biomarker value taken within this period. By this way it's intended to evaluate the contribution of each biomarker value in the discrimination of subjects at risk and

subjects without risk of death for the 1st, 2nd and 3rd days after the last measurement. To the best of our knowledge there is no study in literature to investigate the time-dependent cut-off values for longitudinal data such in detailed way.

6. CONCLUSION

Time-dependent AUC value evaluates the diagnostic performance of longitudinal biomarker at the end of follow-up period. This measure should be utilized in assessing the diagnostic performance of serial biomarker measurements rather than determining the diagnostic accuracy of each time-point by classical ROC Curve.

In application part of the thesis, C-reactive Protein and Procalcitonin measurements taken from Adult Intensive Care Units(ICU)' (Emergency, Brain Surgery, General Surgery, Intensive Care Units, Cardiology, Neurology Units) diagnostic performances in predicting death in ICU at the end of follow-up were assessed by time-dependent AUC values.

Within the context of this thesis;

1. Joint Modeling Approach, which enables to model longitudinal and survival data simultaneously and time-dependent diagnostic accuracy metrics, namely time-dependent AUC, time-dependent ROC Curves, time-dependent sensitivity and time-dependent specificity metrics, which are obtained by performing joint modeling approach are introduced.

2. Survival time is taken as 30 days and diagnostic performances of serial CRP and PCT biomarkers in predicting the risk of death at the end of follow-up period are investigated by time-dependent AUC values. At the end of the analysis, which biomarker is better in predicting the event of interest is determined.

3. Diagnostic performances of single and serial CRP and PCT values in predicting death at the end of follow-up period were assessed using time-dependent AUC values. At the end of the analysis, more efficient marker in predicting the event of interest is determined and suggested to use this

biomarker in practice. Furthermore, diagnostic accuracies of these biomarkers are evaluated throughout the follow-up period to determine which biomarker should be opted to predict the event of interest at pre-specified time-points by means of their diagnostic performances. Also cut-off values for discriminating subjects with and without risk of death are determined for both CRP and PCT, by using the longitudinal information of the most appropriate subjects to represent the sample of the biomarker. Coefficient of Quartile Variation and Robust Coefficient of Variation statistics are proposed for choosing the most appropriate cut-off value to discriminate the groups when there are several threshold alternatives for the event.

4. Time-dependent cut-off values utilized for distinguishing subjects at risk and subjects without risk of death for ICU mortality after the last measurement was taken are identified. For both biomarkers, these cut-off values are calculated for both women and men. These cut-off values and time-dependent ROC curves are presented with relevant graphics to visualize the results. Also updated time-dependent cut-off values are determined to investigate the contribution of each biomarker value taken during the follow-up period. At the end of this analysis, all the time-dependent accuracy measures, including time-dependent sensitivity and time-dependent specificity metrics are determined for the first, second and third day after the last measurement was taken.

5. Diagnostic performances of serial CRP and PCT measurements are assessed and compared in detail. For the comparison, two different random-effects model options in longitudinal model, two different survival distribution options in survival model and four different parameterization options to link longitudinal and survival data are utilized. Time-dependent AUC values are used as comparison criteria. At the end of the analysis, the best combination, which gives the optimum diagnostic accuracy is determined for each

biomarker and these combinations are suggested to utilize to obtain better predictive accuracy at the end of follow-up period.

6. 95% confidence intervals of time-dependent AUC values are given by performing nonparametric percentile bootstrap method in order to determine whether the observed time-dependent diagnostic accuracy is statistically significant. 1000 bootstrapped samples are used in the analysis. p-values are also given as comparison criteria to compare the time-dependent AUC values obtained by either single and serial biomarker measurements or serial biomarker values with different cut-off options.

Data were collected retrospectively from Hacettepe University Hospital database. Risk factors other than age, gender and ICU where patients stay were not recorded in the database, therefore could not be included in the study. A prospective study which enables to include other risk factors such as smoking status, family history, race and so on would be more informative since it would lead to study the effects of all the risk factors under a comprehensive research.

Diagnostic accuracy could be increased by combining biomarkers with relevant statistical methods. In this study, two different models are constructed for either CRP or PCT to obtain their diagnostic accuracies. Consideration of combining of the serial measurements of the biomarkers by proper statistical methods could be future-work alternative.

7. REFERENCES

1. Fawcett, T. An introduction to ROC Analysis. Pattern Recognit Lett. 2006;27(8):861-874.
2. Heagerty, P., Lumley, T. ve Pepe M. Time-Dependent ROC Curves for Censored Survival Data and a Diagnostic Marker. Biometrics. 2000;56(2):337-344.
3. Rizopoulos, D. Dynamic Predictions and Prospective Accuracy in Joint Models for Longitudinal and Time-to-Event Data. Biometrics. 2011;67(3):819-829.
4. Rizopoulos, D. JM: An R package for the joint modelling of longitudinal and time-to-event data. J Stat Softw (Online). 2010;35(9):1-33.
5. Rizopoulos, D. (2016). The R Package JMbayes for Fitting Joint Models for Longitudinal and Time-to-Event Data Using MCMC. J Stat Softw. 2016;72(7):1-45.
6. Proust-Lima C, Philipps V, Diakite A and Liquet B. Estimation of Extended Mixed Models Using Latent Classes and Latent Processes: The R Package lcmm. J Stat Softw. 2017;78(2):1-56.
7. Zhou XH, Obuchowski NA, McClish DK. Statistical methods in diagnostic medicine, 1st ed. New York: John Wiley & Sons; 2002.
8. Etzioni, R., Pepe, M., Longton, G., Hu, C., Goodman, G. Incorporating the time dimension in receiver operating characteristic curves: a case study of prostate cancer. Med Decis Making.1999;19(3):242-251.
9. Blanche, P., Dartigues, J. F., Jacqmin-Gadda, H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. Stat Med. 2013;32(30): 5381-5397..
10. Król, A., Ferrer, L., Pignon, J. P., Proust-Lima, C., Ducreux, M., Bouché et al. Joint model for left-censored longitudinal data, recurrent events and terminal event: Predictive abilities of tumor burden for cancer evolution with application to the FFCD 2000–05 trial. Biometrics. 2016;72(3):907-916.
11. Sène, M., Taylor, J. M., Dignam, J. J., Jacqmin-Gadda, H., & Proust-Lima, C. Individualized dynamic prediction of prostate cancer recurrence with and without the initiation of a second treatment: Development and validation. Stat Methods Med Res. 2016;25(6):2972-2991.
12. Fournier, M. C., Dantan, E., & Blanche, P. An R^2-curve for evaluating the accuracy of dynamic predictions. Stat Med. 2018;37(7):1125-1133
13. Zheng, Y., Heagerty, P. J. Semiparametric estimation of time-dependent ROC curves for longitudinal marker data. Biostatistics. 2004;5(4):615-632.
14. Zheng, Y., Heagerty, P. J. Prospective accuracy for longitudinal markers. Biometrics. 2007;63(2):332-341.

15. Njagi, E. N., Rizopoulos, D., Molenberghs, G., Dendale, P., Willekens, K. A joint survival-longitudinal modelling approach for the dynamic prediction of rehospitalization in telemonitored chronic heart failure patients. Stat. Model. 2013;13(3):179-198.

16. Abdi, Z. D., Essig, M., Rizopoulos, D., Le Meur, Y., Prémaud, A., Woillard, J. B et. al. Impact of longitudinal exposure to mycophenolic acid on acute rejection in renal-transplant recipients using a joint modeling approach. Pharmacol. Res. 2013;72:52-60.

17. Blanche, P., Proust-Lima, C., Loubère, L., Berr, C., Dartigues, J. F., Jacqmin-Gadda, H. Quantifying and comparing dynamic predictive accuracy of joint models for longitudinal marker and time-to-event in presence of censoring and competing risks. Biometrics. 2105;71(1):102-113.

18. Yang, L., Yu, M., Gao, S. Joint models for multiple longitudinal processes and time-to-event outcome. J Stat Comput Simul. 2016;86(18): 3682-3700.

19. Li, K., Chan, W., Doody, R. S., Quinn, J., & Luo, S. Prediction of conversion to Alzheimer's disease with longitudinal measures and time-to-event data. J. Alzheimers Dis. 2017;58(2):361-371.

20. Mauff, K., Steyerberg, E. W., Nijpels, G., Heijden, A. A., Rizopoulos, D. Extension of the association structure in joint models to include weighted cumulative effects. Stat Med. 2017;36(23):3746-3759.

21. Rizopoulos, D., Molenberghs, G., Lesaffre, E. M. Dynamic predictions with time-dependent covariates in survival analysis using joint modeling and landmarking. Biom J. 2017;59(6):1261-1276.

22. Musoro, J. Z., Zwinderman, A. H., Abu-Hanna, A., Bosman, R., Geskus, R. B. Dynamic prediction of mortality among patients in intensive care using the sequential organ failure assessment (SOFA) score: a joint competing risk survival and longitudinal modeling approach. Stat Neerl. 2018;72(1):34-47.

23. Lim, HJ., Mondal, P., Skinner, S. Joint modeling of longitudinal and event time data: application to HIV study. J Med Inform. 2013;1(1):1

24. Rizopoulos, D., Takkenberg, J. J. Tools & techniques--statistics: Dealing with time-varying covariates in survival analysis--joint models versus Cox models. EuroIntervention.2014; 10(2): 285-287.

25. Rizopoulos D. Joint Models for Longitudinal and Time-to-Event Data: with Applications in R. 1st ed.Boca Raton, FL: CRC Press; 2012.

26. Elashoff RM, Li G, Li N. Joint Modelling of Longitudinal and Time-to-Event Data. 1st ed.Boca Raton, FL: CRC Press; 2017 .

27. Cox, DR.. Regression Models and Life-Tables. J R Stat Soc Series B Stat Methodol. 1972;34(2):187-220.

28. Schluchter MD. Methods for the analysis of informatively censored longitudinal data. Stat Med. 1992;11(14-15):1861-70.

29. Katki HA, Cheung LC, Fetterman B, Castle PE, Sundaram R. A joint model of persistent human papilloma virus infection and cervical cancer risk: implications for cervical cancer screening. J R Stat Soc Ser A Stat Soc. 2015;178(4):903-23.

30. Huang Y, Yan C, Xing D, Zhang N, Chen H. Jointly modeling event time and skewed-longitudinal data with missing response and mismeasured covariate for AIDS studies. J Biopharm Stat. 2015;25(4):670-94.

31. Piccorelli AV, Schluchter MD. Jointly modeling the relationship between longitudinal and survival data subject to left truncation with applications to cystic fibrosis. Stat Med. 2012;31(29):3931-45.

32. Andrinopoulou ER, Rizopoulos D, Jin R, Bogers AJ, Lesaffre E, Takkenberg JJ. An introduction to mixed models and joint modeling: analysis of valve function over time. Ann Thorac Surg. 2012;93(6):1765-72.

33. Ivanova A, Molenberghs G, Verbeke G. Mixed models approaches for joint modeling of different types of responses. J Biopharm Stat. 2016;26(4):601-18.

34. Ferrer L, Rondeau V, Dignam J, Pickles T, Jacqmin-Gadda H, Proust-Lima C. Joint modelling of longitudinal and multi-state processes: application to clinical progressions in prostate cancer. Stat Med. 2016;35(22):3933-48.

35. Rizopoulos, D. Fast fitting of joint models for longitudinal and event time data using a pseudo-adaptive Gaussian quadrature rule. Comput. Statist. Data Anal. 2012; 56(3): 491-501.

36. Fisher, LD., Lin, DY. Time-dependent covariates in the Cox proportional-hazards regression model. Annu Rev Public Health. 1999;20(1): 145-157.

37. Vacek, PM. Assessing the effect of intensity when exposure varies over time. Stat Med. 1997;16(5):505-513.

38. Wolkewitz, M., Allignol, A., Schumacher, M., Beyersmann, J. Two pitfalls in survival analyses of time-dependent exposure: a case study in a cohort of Oscar nominees. Am Stat. 2010;64(3):205-211.

39. Hauptmann M, Wellmann J, Lubin JH, Rosenberg PS, Kreienbrock L. Analysis of exposure-time-response relationships using a spline weight function. Biometrics. 2000;56(4):1105-8.

40. Sylvestre MP, Abrahamowicz M. Flexible modeling of the cumulative effects of time-dependent exposures on the hazard. Stat Med. 2009;28(27):3437-53.

41. Hayat EA, Suner A, Uyar B, Dursun Ö, Orman MN, Kitapçıoğlu G. Comparison of five survival models: breast cancer registry data from Ege University Cancer Research Center. Turkiye Klinikleri J Med Sci. 2010;30(5):1665-74.

42. Akram M, Aman Ullah M, Taj R. Survival analysis of cancer patients using parametric and non-parametric approaches. Pakistan Vet J. 2007;27(4):194-8.

43. Harrell, F. E., Lee, K. L., Mark, D. B. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15(4):361-387.

44. Gosling, P., Dickson, G. R. Serum C-reactive protein in patients with serious trauma. Injury. 1992;23(7):483-486.

45. Povoa, P., Coelho, L., Almeida, E., Fernandes, A., Mealha, R., Moreira, P. et al. C-reactive protein as a marker of infection in critically ill patients. Clin. Microbiol. Infect. 2005;11(2):101-108.

46. Valkanova, V., Ebmeier, K. P., & Allan, C. L. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2013;150(3):736-744.

47. Lagrand, W. K., Visser, C. A., Hermens, W. T., Niessen, H. W., Verheugt, F. W., Wolbink, G. J. et al. C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? Circulation. 1999;100(1):96-102.

48. Koenig, W. Update on C-reactive protein as a risk marker in cardiovascular disease. Kidney Int. Suppl. 2003;63:S58-S61.

49. Póvoa, P. C-reactive protein: a valuable marker of sepsis. Intensive Care Med. 2002;*28*(3):235-243.

50. Li, H. X., Liu, Z. M., Zhao, S. J., Zhang, D., Wang, S. J., Wang, Y. S. Measuring both procalcitonin and C-reactive protein for a diagnosis of sepsis in critically ill patients. J. Int. Med. Res. 2014;42(4):1050-1059.

51. Schuetz, P., Albrich, W., & Mueller, B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. BMC Med. 2011;9(1):107.

52. Lee, H. Procalcitonin as a biomarker of infectious diseases. Korean J. Intern. Med. 2013;*28*(3):285.

53. Sudhir, U., Venkatachalaiah, R. K., Kumar, T. A., Rao, M. Y., Kempegowda, P. Significance of serum procalcitonin in sepsis. Indian J Crit Care Med. 2011;15(1):1.

54. Vijayan, A. L., Ravindran, S., Saikant, R., Lakshmi, S., Kartik, R. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. J Intensive Care. 2017;5(1):51.

55. El-Azeem, A. A., Hamdy, G., Saraya, M., Fawzy, E., Anwar, E., Abdulattif, S. The role of procalcitonin as a guide for the diagnosis, prognosis, and decision of antibiotic therapy for lower respiratory tract infections. Egypt J Chest Dis Tuberc. 2013;*62*(4):687-695.

56. Patrick J. Heagerty and packaging by Paramita Saha-Chaudhuri (2013). survivalROC: Time-dependent ROC curve estimation from censored survival data. R package version 1.0.3. https://CRAN.R-project.org/package=survivalROC

57. Canty A, Ripley B. boot: Bootstrap R (S-Plus) Functions. R Package Version 1.3-20. 2017.

58. Davison AC, Hinkley DV. Confidence intervals. Bootstrap Methods and Their Application. 1st ed. Cambridge: Cambridge University Press; 1997. p.582

59. Bonett, DG. Confidence interval for a coefficient of quartile variation. Comput Stat Data Anal.2006;50(11):2953-2957

60. Liu, X. Classification accuracy and cut point selection. Stat Med. 2012;31(23): 2676-2686.

61. Deslandes E, Chevret S. Joint modeling of multivariate longitudinal data and the dropout process in a competing risk setting: application to ICU data. BMC Med Res Methodol. 2010;10(1):69.

62. Khoundabi B, Kazemnejad A, Mansourian M, Hashemian SM, Kazempoor Dizaji M. Acute kidney injury risk factors for ICU patients following cardiac surgery: the application of joint modeling. Trauma Mon. 2016;21(4):e23749.

63. Karaismailoglu E., Dikmen ZG., Akbiyik F., Karaagaoglu AE. A statistical approach to evaluate the performance of cardiac biomarkers in predicting death due to acute myocardial infarction: time-dependent ROC curve. Turk J Med Sci. 2018;48(2):237-245.

64. Kurz, K., Schild, C., Isfort, P., Katus, HA., Giannitsis, E. Serial and single time-point measurements of cardiac troponin T for prediction of clinical outcomes in patients with acute ST-segment elevation myocardial infarction. Clin Res Cardiol.2009;98(2):94-100.

65. Wolff, M., Bouadma, L What procalcitonin brings to management of sepsis in the ICU. Crit Care. 2010;14(6);1007.

66. Samsudin, I., Vasikaran, SD. Clinical Utility and Measurement of Procalcitonin. Clin Biochem Rev.2017;38(2):59.

67. Medeiros, I. L., Terra, R. M., Choi, E. M., Pego-Fernandes, P. M., Jatene, F. B. Evaluation of serial C-reactive protein measurements after surgical treatment of pleural empyema. Clinics. 2012;67(3): 243-247.

68. Sigirli, D., Ercan, I., Jin, Y., Paksoy, E., Tolunay, S., Tasdelen, I. Evaluatıng cut-off values wıth tıme-dependent roc curves for Kİ67. Pakistan J. Statist. 2010;26(4).

APPENDICES

I - ETHICAL APPROVAL FORM OF HACETTEPE UNIVERSITY

T.C.
HACETTEPE ÜNİVERSİTESİ
Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu

Sayı : 16969557 – 387
Konu : ARAŞTIRMA PROJESİ DEĞERLENDİRME RAPORU

Toplantı Tarihi : 14 MART 2017 SALI
Toplantı No : 2017/07
Proje No : GO 17/233 (Değerlendirme Tarihi: 14.03.2017)
Karar No : GO 17/233- 27

Üniversitemiz Tıp Fakültesi Biyoistatistik Anabilim Dalı öğretim üyelerinden Prof. Dr. Ahmet Ergun KARAAĞAOĞLU' nun sorumlu araştırmacı olduğu, Prof. Dr. Zeliha Günnur DİKMEN, Doç. Dr. Aslı PINAR, Doç. Dr. Oytun PORTAKAL ile birlikte çalışacakları ve Arş. Gör. Naime Meriç KONAR' ın doktora tezi olan, GO 17/233 kayıt numaralı, ***"Uzunlamasına Verilerde Zamana Bağlı Roc Eğrilerinin Performansını Etkileyen Faktörler"*** başlıklı proje önerisi araştırmanın gerekçe, amaç, yaklaşım ve yöntemleri dikkate alınarak incelenmiş olup, idari izinlerin tamamlanması kaydı ile etik açıdan uygun bulunmuştur.

1.Prof. Dr. Nurten AKARSU	(Başkan)	10 Prof. Dr. Oya Nuran EMİROĞLU	(Üye)
2. Prof. Dr. Sevda F. MÜFTÜOĞLU	(Üye)	11 Yrd. Doç. Dr. Özay GÖKÖZ	(Üye)
3. Prof. Dr. M. Yıldırım SOKA	(Üye)	12. Doç. Dr. Gözde GİRGİN	(Üye)
4. Prof. Dr. Neşlet SAĞLAM	(Üye)	13. Doç. Dr. Fatma Visal OKUR	(Üye)
5. Prof. Dr. Hatice Doğan BUZOĞLU	(Üye)	14.Yrd. Doç. Dr. Can Ebru KURT	(Üye)
6. Prof. Dr. R. Köksal ÖZGÜL	(Üye)	15. Yrd. Doç. Dr. H. Hüsrev TURNAGÖL	(Üye)
7. Prof. Dr. Ayşe Lale DOĞAN	(Üye)	16. Öğr. Gör. Dr. Müge DEMİR	(Üye)
8. Prof. Dr. Elmas Ebru KALÇIN	(Üye)	17. Öğr. Gör. Meltem ŞENGELEN	(Üye)
9. Prof. Dr. Mintaze Kerem GÜNEL	(Üye)	18. Av. Meltem ONURLU	(Üye)

Hacettepe Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu
06100 Sıhhiye-Ankara
Telefon: 0 (312) 305 1082 • Faks: 0 (312) 310 0580 • E-posta: goetik@hacettepe.edu.tr

Ayrıntılı Bilgi için:

II -PART OF CRP DATASET

id	crp	lcrp	survtime	time	status	age	unit	gender
1	20.1	1.303	4	0	0	24	3	0
1	1.33	0.124	4	4	0	24	3	0
2	12.4	1.093	6	0	1	61	3	1
2	11.4	1.057	6	1	1	61	3	1
2	11.2	1.049	6	2	1	61	3	1
2	10.3	1.013	6	2	1	61	3	1
2	9.82	0.992	6	5	1	61	3	1
2	9	0.954	6	5	1	61	3	1
3	14.6	1.164	12	0	1	60	4	1
3	7.56	0.879	12	2	1	60	4	1
3	10.3	1.013	12	3	1	60	4	1
3	15.8	1.199	12	4	1	60	4	1
3	17.7	1.248	12	6	1	60	4	1
3	23.3	1.367	12	6	1	60	4	1
3	46.6	1.668	12	8	1	60	4	1
3	44.9	1.652	12	12	1	60	4	1
4	8.29	0.919	13	0	0	61	4	0
4	8.2	0.914	13	2	0	61	4	0
4	6.05	0.782	13	3	0	61	4	0
5	0.913	-0.040	30	0	0	60	4	1
5	0.666	-0.177	30	2	0	60	4	1
5	5.4	0.732	30	8	0	60	4	1
5	6.72	0.827	30	10	0	60	4	1
5	7.66	0.884	30	13	0	60	4	1
5	5.78	0.762	30	14	0	60	4	1
5	11.2	1.049	30	16	0	60	4	1
5	14.4	1.158	30	20	0	60	4	1
5	13.4	1.127	30	23	0	60	4	1
5	13.1	1.117	30	27	0	60	4	1
5	11.4	1.057	30	30	0	60	4	1

Data for the first 5 subjects were shown for CRP biomarker.

Variables:

crp: Repeated C-Reactive Proitein Measurements (untransformedvalues)

lcrp: Repeated C-Reactive Proitein Measurements (after logarithmic transformation)

gender : 0:Female, 1:Male

age : age of the subjects (Years)

survtime : survival time of each subject (Days)

time : time-points at which the repeated measurements are taken

status : 0: Censored, 1: Event

unit : 1:Emergency ICU, 2:General Surgery ICU, 3:Brain Surgery ICU, 4:Internal Diseases ICU, 5:Cardiology ICU, 6:Neurology ICU

III - PART OF PCT DATASET

id	pct	lpct	survtime	time	status	age	unit	gender
1	54.57	1.737	11	0	1	60	4	1
1	6.19	0.792	11	3	1	60	4	1
1	2.32	0.365	11	4	1	60	4	1
1	6.26	0.797	11	5	1	60	4	1
1	19.48	1.29	11	5	1	60	4	1
2	0.141	-0.851	12	0	0	61	4	0
2	0.189	-0.724	12	3	0	61	4	0
2	0.213	-0.672	12	5	0	61	4	0
3	7.71	0.887	5	0	1	61	3	1
3	8.44	0.926	5	1	1	61	3	1
3	7.73	0.888	5	2	1	61	3	1
3	8.38	0.923	5	2	1	61	3	1
3	10.78	1.033	5	5	1	61	3	1
3	11.92	1.076	5	5	1	61	3	1
4	0.122	-0.914	30	0	0	84	6	0
4	5.31	0.725	30	5	0	84	6	0
4	1.02	0.009	30	9	0	84	6	0
4	0.089	-1.051	30	19	0	84	6	0
4	0.318	-0.498	30	26	0	84	6	0
5	0.127	-0.896	30	0	0	60	6	1
5	56.94	1.755	30	9	0	60	6	1
5	0.343	-0.465	30	19	0	60	6	1
5	5.89	0.77	30	26	0	60	6	1
5	1.76	0.246	30	29	0	60	6	1

Data for the first 5 subjects were shown for PCT biomarker.

Variables:

pct: repeated Procalcitonin Measurements (untransformed values)

lpct: repeated Procalcitonin Measurements (after logarithmic transformation)

gender : 0:Female, 1:Male

age: age of the subjects (Years)

survtime : survival time of each subject (Days)

time : time-points at which the repeated measurements are taken

status : 0: Censored, 1: Event

unit : 1:Emergency ICU, 2:General Surgery ICU, 3:Brain Surgery ICU, 4:Internal Diseases ICU, 5:Cardiology ICU, 6:Neurology ICU.

IV – PARAMETER ESTIMATES OF JOINT MODEL COMBINATIONS

Total of 16 different joint models (8 of them are for Model-I and the other 8 models for Model-II) are constructed for each biomarker. These combinations are named as JM_1, JM_2,…JM_8 and listed below:

JM	Joint Model Combination
JM_1	Standard Joint Model with Unspecified Baseline Hazard Function
JM_2	Standard Joint Model with Piecewise-Constant Function
JM_3	Joint Model with Slope Parameterization with Unspecified Baseline Hazard Function
JM_4	Joint Model with Slope Parameterization with Piecewise Constant Function
JM_5	Joint Model with Both Parameterization with Unspecified Baseline Hazard Function
JM_6	Joint Model with Both Parameterization with Piecewise-Constant Function
JM_7	Joint Model with Cumulative-Effects Parameterization with Unspecified Baseline Hazard Function
JM_8	Joint Model with Cumulative-Effects Parameterization with Piecewise-Constant Function

Table 1: Parameter estimates, standard errors and p-values of joint models and measurement error for linear mixed effects model of joint models for Model-I for CRP biomarker

Joint Model	Process	Variable	β	SE (β)	p-value
JM_1	Longitudinal	Intercept	0.8341	0.0851	<0.0001
		time	-0.0207	0.0068	0.0025
		age	0.0001	0.0013	0.9736
		time*age	0.0003	0.0001	0.0088
	Survival	α	1.436	0.2961	<0.0001
		σ = 0.2746608			
JM_2	Longitudinal	Intercept	0.8337	0.0851	<0.0001
		time	-0.0207	0.0067	0.0024
		age	0.0001	0.0013	0.9731
		time*age	0.0003	0.0001	0.0084
	Survival	α	1.3789	0.2916	<0.0001
		log (xi.1)	-6.2542	0.3691	
		log (xi.2)	-5.3515	0.3728	
		log (xi.3)	-5.5957	0.3689	
		log (xi.4)	-5.1809	0.3503	
		log (xi.5)	-5.0042	0.3646	
		log (xi.6)	-4.9809	0.4516	
		log (xi.7)	10.7068	0.3871	
		σ = 0.2746560			
JM_3	Longitudinal	Intercept	0.8351	0.0854	<0.0001
		time	-0.0219	0.007	0.0016
		age	0.0001	0.0013	0.9984
		time*age	0.0003	0.0001	0.0086
	Survival	α	2.4533	5.2215	0.6385
		σ = 0.2745663			
JM_4	Longitudinal	Intercept	0.8351	0.0854	<0.0001
		time	-0.0219	0.0069	0.0016
		age	0.0001	0.0013	0.9989
		time*age	0.0003	0.0001	0.0085
	Survival	α	2.5866	5.1918	0.6183
		log (xi.1)	-4.9655	0.2186	
		log (xi.2)	-4.0895	0.2361	
		log (xi.3)	-4.3391	0.2299	
		log (xi.4)	-3.9229	0.1929	
		log (xi.5)	-3.7354	0.2090	
		log (xi.6)	-3.6916	0.3329	
		log (xi.7)	11.9954	0.2360	
		σ = 0.2745624			

JM_5	**Longitudinal**	**Intercept**	0.8346	0.0852	<0.0001
		time	-0.0208	0.0069	0.0025
		age	0.0001	0.0013	0.9713
		time*age	0.0003	0.0001	0.0088
	Survival	**α_1**	1.442	0.3008	<0.0001
		α_2	-0.9508	6.1022	0.8762
		$\sigma = 0.2746283$			
JM_6	**Longitudinal**	**Intercept**	0.834	0.0851	<0.0001
		time	-0.0208	0.0069	0.0025
		age	0.0001	0.0013	0.9731
		time*age	0.0003	0.0001	0.0085
	Survival	**α_1**	1.3823	0.2923	<0.0001
		α_2	-0.4423	5.8745	0.940
		log (xi.1)	-6.1286	0.3644	
		log (xi.2)	-5.2282	0.3644	
		log (xi.3)	-5.4735	0.3585	
		log (xi.4)	-5.0562	0.3375	
		log (xi.5)	-4.8785	0.3520	
		log (xi.6)	-4.8484	0.4400	
		log (xi.7)	10.8441	0.3719	
		$\sigma = 0.2746482$			
JM_7	**Longitudinal**	**Intercept**	0.8351	0.0848	<0.0001
		time	-0.0216	0.0069	0.002
		age	0.0001	0.0013	0.981
		time*age	0.0003	0.001	0.009
	Survival	**α**	0.0718	0.0247	0.004
		$\sigma = 0.2745185$			
JM_8	**Longitudinal**	**Intercept**	0.8363	0.0849	<0.0001
		time	-0,0219	0,0069	0.0014
		age	0,0001	0,0013	0.976
		time*age	0,0003	0,0001	0.008
	Survival	**α**	0.0601	0.0233	0.010
		log (xi.1)	-5.0242	0.2191	
		log (xi.2)	-4.1431	0.2364	
		log (xi.3)	-4.3872	0.2302	
		log (xi.4)	-3.9727	0.1946	
		log (xi.5)	-3.8005	0.2148	
		log (xi.6)	-3.7870	0.3422	
		log (xi.7)	11.8933	0.2522	
		$\sigma = 0.2744885$			

Table 2. Variance-covariance matrix of random-effects for joint model combinations for Model-I for CRP biomarker

JM_1		**Intercept**	**time**
	Intercept	0.202	-0.006
	time	-0.006	0.001
JM_2		**Intercept**	**time**
	Intercept	0.201	-0.006
	time	-0.006	0.001
JM_3		**Intercept**	**time**
	Intercept	0.203	-0.006
	time	-0.006	0.001
JM_4		**Intercept**	**time**
	Intercept	0.203	-0.006
	time	-0.006	0.001
JM_5		**Intercept**	**time**
	Intercept	0.202	-0.006
	time	-0.006	0.001
JM_6		**Intercept**	**time**
	Intercept	0.207	-0.006
	time	-0.006	0.001
JM_7		**Intercept**	**time**
	Intercept	0.201	-0.006
	time	-0.006	0.001
JM_8		**Intercept**	**time**
	Intercept	0.201	-0.006
	time	-0.006	0.001

Table 3. Parameter estimates, standard errors and p-values of joint models and measurement error for linear mixed effects model of joint models for Model-II for CRP biomarker

Joint Model	Process	Variable	β	SE (β)	p-value
JM_1	Longitudinal	Intercept	0.8044	0.0842	<0.0001
		time	-0.017	0.0064	0.0074
		age	0.0003	0.0012	0.8167
		time*age	0.0002	0.0001	0.0153
	Survival	α	1.612	0.3215	<0.0001
		σ = 0.2517925			
JM_2	Longitudinal	Intercept	0.8046	0.0841	<0.0001
		time	-0.0171	0.0064	0.0072
		age	0.0003	0.0012	0.8085
		time*age	0.0002	0.0001	0.0162
	Survival	α	1.4134	0.2975	<0.0001
		log (xi.1)	-6.2941	0.3766	
		log (xi.2)	-5.3879	0.3794	
		log (xi.3)	-5.6383	0.3769	
		log (xi.4)	-5.2145	0.3556	
		log (xi.5)	-5.0310	0.3673	
		log (xi.6)	-5.0284	0.4608	
		log (xi.7)	10.6257	0.4076	
		σ = 0.2520769			
JM_3	Longitudinal	Intercept	0.8069	0.0847	<0.0001
		time	-0.0182	0.0065	0.0047
		age	0.0003	0.0012	0.7845
		time*age	0.0002	0.0001	0.0181
	Survival	α	-1.4106	5.6165	0.8017
		σ = 0.2521585			
JM_4	Longitudinal	Intercept	0.807	0.0847	<0.0001
		time	-0.0183	0.0065	0.0047
		age	0.0003	0.0012	0.7848
		time*age	0.0002	0.0001	0.0176
	Survival	α	-1.0769	3.7142	0.7719
		log (xi.1)	-4.9828	0.2203	
		log (xi.2)	-4.1056	0.2367	
		log (xi.3)	-4.3533	0.2301	
		log (xi.4)	-3.9342	0.1930	
		log (xi.5)	-3.7463	0.2088	
		log (xi.6)	-3.7066	0.3338	
		log (xi.7)	11.9846	0.2362	
		σ = 0.2521291			

JM_5	**Longitudinal**	**Intercept**	0.8042	0.0842	<0.0001
		time	-0.017	0.0064	0.0081
		age	0.0003	0.0012	0.8116
		time*age	0.0002	0.0001	0.0156
	Survival	**α_1**	1.6255	0.3267	<0.0001
		α_2	0.2596	5.1612	0.9599
			$\sigma = 0.2518011$		
JM_6	**Longitudinal**	**Intercept**	0.8046	0.0841	<0.0001
		time	-0.0171	0.0064	0.0075
		age	0.0003	0.0012	0.808
		time*age	0.0002	0.0001	0.0161
	Survival	**α_1**	1.4149	0.3005	<0.0001
		α_2	-0.1562	4.1159	0.9697
		log (xi.1)	-6.0974	0.3592	
		log (xi.2)	-5.1807	0.3593	
		log (xi.3)	-5.4274	0.3565	
		log (xi.4)	-5.0013	0.3344	
		log (xi.5)	-4.8108	0.3483	
		log (xi.6)	-4.7900	0.4461	
		log (xi.7)	10.8839	0.3909	
			$\sigma = 0.252076$		
JM_7	**Longitudinal**	**Intercept**	0.8075	0.0845	<0.0001
		time	-0.018	0.0065	0.0054
		age	0.0003	0.0012	0.7989
		time*age	0.0002	0.0001	0.0179
	Survival	**α**	0.0348	0.0274	0.0274
			$\sigma = 0.2521361$		
JM_8	**Longitudinal**	**Intercept**	0.8082	0.0845	<0.0001
		time	-0.0181	0.0065	0.0049
		age	0.0003	0.0012	0.8025
		time*age	0.0002	0.0001	0.0171
	Survival	**α**	0.0338	0.0156	0.0296
		log (xi.1)	-5.0018	0.2186	
		log (xi.2)	-4.1232	0.236	
		log (xi.3)	-4.3704	0.2298	
		log (xi.4)	-3.9563	0.1937	
		log (xi.5)	-3.7720	0.2113	
		log (xi.6)	-3.7413	0.3365	
		log (xi.7)	11.9553	0.2401	
			$\sigma = 0.2521199$		

Table 4. Variance-covariance matrix of random-effects for joint model combinations for Model-II for CRP biomarker

		Intercept	**time**	**time^2**
JM_1	**Intercept**	0.240	-0.017	0.000449
	time	-0.017	0.0036	-0.00011
	time^2	0.0004	-0.0001	0.00000356
		Intercept	**time**	**time^2**
JM_2	**Intercept**	0.239	-0.017	0.00044
	time	-0.017	0.004	-0.0001
	time^2	0.00044	-0.0001	0.0000034
		Intercept	**time**	**time^2**
JM_3	**Intercept**	0.240	-0.017	0.00043
	time	-0.017	0.004	-0.000106
	time^2	0.00043	-0.0001	0.0000034
		Intercept	**time**	**time^2**
JM_4	**Intercept**	0.240	-0.017	0.00043
	time	-0.017	0.0036	-0.0001
	time^2	0.00043	-0.0001	0.0000034
		Intercept	**time**	**time^2**
JM_5	**Intercept**	0.240	-0.017	0.00045
	time	-0.017	0.0036	-0.0001
	time^2	0.00045	-0.0001	0.0000036
		Intercept	**time**	**time^2**
JM_6	**Intercept**	0.244	-0.017	0.00045
	time	-0.017	0.0035	-0.0001
	time^2	0.00045	-0.0001	0.0000034
		Intercept	**time**	**time^2**
JM_7	**Intercept**	0.238	-0.0168	0.00042
	time	-0.0168	0.00359	-0.000104
	time^2	0.00042	-0.0001	0.0000034
		Intercept	**time**	**time^2**
JM_8	**Intercept**	0.238	-0.0168	0.000423
	time	-0.0168	0.0036	-0.000105
	time^2	0.00042	-0.00011	0.0000034

Table 5. Parameter estimates, standard errors and p-values of joint models and measurement error for linear mixed effects model of joint models for Model-I for PCT biomarker

Joint Model	Process	Variable	β	SE (β)	p-value
JM_1	Longitudinal	Intercept	-0.1509	0.1345	0.2619
		time	-0.0314	0.0102	0.0022
		age	-0.0021	0.002	0.2882
		time*age	0.0004	0.0001	0.010
	Survival	α	1.1988	0.1331	<0.0001
			σ = 0.4568325		
JM_2	Longitudinal	Intercept	-0.15196	0.1343	0.2579
		time	-0.0314	0.0103	0.0022
		age	-0.0021	0.002	0.2871
		time*age	0.0004	0.0002	0.0098
	Survival	α	1.1724	0.1294	<0.0001
		log (xi.1)	-5.0573	0.2305	
		log (xi.2)	-3.8740	0.1842	
		log (xi.3)	-4.0180	0.2249	
		log (xi.4)	-3.6768	0.1947	
		log (xi.5)	-3.7373	0.1937	
		log (xi.6)	-3.1986	0.2821	
		log (xi.7)	11.8429	0.2948	
			σ = 0.4566912		
JM_3	Longitudinal	Intercept	-0.4358	3.2696	0.263
		time	-0.152	0.1358	0.0014
		age	-0.0328	0.0103	0.3333
		time*age	-0.002	0.002	0.0154
	Survival	α	-0.9199	3.2525	0.894
			σ = 0.4586285		
JM_4	Longitudinal	Intercept	-0.1527	0.1358	0.263
		time	-0.0328	0.0103	0.0014
		age	-0.002	0.002	0.3333
		time*age	0.0004	0.0002	0.0154
	Survival	α	-0.1527	0.1358	0.7773
		log (xi.1)	-5.0344	0.2257	
		log (xi.2)	-4.0254	0.1848	
		log (xi.3)	-4.2240	0.2255	
		log (xi.4)	-3.9112	0.1944	
		log (xi.5)	-3.9545	0.1911	
		log (xi.6)	-3.5150	0.2793	
		log (xi.7)	11.4887	0.2915	

			σ = 0.4584787		
JM_5	**Longitudinal**	**Intercept**	-0.1524	0.1344	0.2569
		time	-0.0308	0.0103	0.0027
		age	-0.0021	0.002	0.2892
		time*age	0.0004	0.0001	0.0105
	Survival	**α_1**	1.205	0.1353	<0.0001
		α_2	1.5581	2.6488	0.5564
			σ = 0.4567036		
JM_6	**Longitudinal**	**Intercept**	-0.2819	0.1096	0.0101
		time	-0.0199	0.0072	0.0057
		age	-0.0007	0.0016	0.6624
		time*age	0.0002	0.0001	0.0183
	Survival	**α_1**	1.2072	0.13	<0.0001
		α_2	3.4182	2.5326	0.1771
		log (xi.1)	-4.9941	0.2330	
		log (xi.2)	-3.8636	0.1849	
		log (xi.3)	-4.0270	0.2258	
		log (xi.4)	-3.7199	0.1990	
		log (xi.5)	-3.7816	0.1999	
		log (xi.6)	-3.2182	0.2846	
		log (xi.7)	11.8442	0.2966	
			σ = 0.4642654		
JM_7	**Longitudinal**	**Intercept**	-0.1492	0.1348	0.2686
		time	-0.0327	0.0103	0.0014
		age	-0.002	0.002	0.309
		time*age	0.0004	0.0002	0.0133
	Survival	**α**	0.0243	0.0158	0.1231
			σ = 0.457796		
JM_8	**Longitudinal**	**Intercept**	-0.1481	0.1348	0.2179
		time	-0.0328	0.0103	0.0014
		age	-0.0021	0.002	0.3043
		time*age	0.0004	0.0002	0.0128
	Survival	**α**	0.0259	0.0152	0.0886
		log (xi.1)	-5.0253	0.2237	
		log (xi.2)	-4.0112	0.1827	
		log (xi.3)	-4.2039	0.2238	
		log (xi.4)	-3.8862	0.1927	
		log (xi.5)	-3.9253	0.1894	
		log (xi.6)	-3.4634	0.2780	
		log (xi.7)	11.5629	0.2896	
			σ = 0.457751		

Table 6. Variance-covariance matrix of random-effects for joint model combinations for Model-I for PCT biomarker

JM_1		**Intercept**	**time**
	Intercept	0.599	-0.021
	time	-0.021	0.002
JM_2		**Intercept**	**time**
	Intercept	0.597	-0.021
	time	-0.021	0.002
JM_3		**Intercept**	**time**
	Intercept	0.611	-0.02
	time	-0.02	0.002
JM_4		**Intercept**	**time**
	Intercept	0.609	-0.022
	time	-0.022	0.002
JM_5		**Intercept**	**time**
	Intercept	0.598	-0.02
	time	-0.02	0.002
JM_6		**Intercept**	**time**
	Intercept	0.594	-0.02
	time	-0.02	0.002
JM_7		**Intercept**	**time**
	Intercept	0.601	-0.02
	time	-0.02	0.002
JM_8		**Intercept**	**time**
	Intercept	0.600	-0.020
	time	-0.020	0.002

Table 7. Parameter estimates, standard errors and p-values of joint models and measurement error for linear mixed effects model of joint models for Model-II for PCT biomarker

Joint Model	Process	Variable	β	SE (β)	p-value
JM_1	Longitudinal	Intercept	-0.1357	0.1338	0.3106
		time	-0.0346	0.0098	0.0004
		age	-0.0025	0.002	0.2057
		time*age	0.0005	0.0001	0.0013
	Survival	α	1.3145	0.1349	<0.0001
		σ = 0.4097275			
JM_2	Longitudinal	Intercept	-0.1368	0.1337	0.3062
		time	-0.0346	0.0098	0.0004
		age	-0.0025	0.002	0.2082
		time*age	0.0005	0.0001	0.0013
	Survival	α	1.2191	0.131	<0.0001
		log (xi.1)	-5.1025	0.2332	
		log (xi.2)	-3.8835	0.1852	
		log (xi.3)	-4.0179	0.2255	
		log (xi.4)	-3.6582	0.1949	
		log (xi.5)	-3.7370	0.1939	
		log (xi.6)	-3.4396	0.2936	
		log (xi.7)	11.4648	0.3193	
		σ = 0.4103118			
JM_3	Longitudinal	Intercept	-0.1341	0.1363	0.3252
		time	-0.0358	0.01	0.0004
		age	-0.0023	0.002	0.2647
		time*age	0.0004	0.0001	0.0046
	Survival	α	-1.8244	2.1468	0.3954
		σ = 0.4101474			
JM_4	Longitudinal	Intercept	-0.1347	0.1362	0.3227
		time	-0.0356	0.01	0.0004
		age	-0.0023	0.002	0.2644
		time*age	0.0004	0.0001	0.0047
	Survival	α	-1.3106	1.9257	0.4961
		log (xi.1)	-5.0535	0.2276	
		log (xi.2)	-4.0369	0.1845	
		log (xi.3)	-4.2321	0.2245	
		log (xi.4)	-3.9139	0.1929	
		log (xi.5)	-3.9495	0.1892	
		log (xi.6)	-3.5016	0.2775	
		log (xi.7)	11.5031	0.2888	
		σ = 0.4100207			

JM_5	**Longitudinal**	**Intercept**	-0.136	0.1338	0.3091
		time	-0.0344	0.0098	0.0004
		age	-0.0025	0.002	0.2053
		time*age	0.0005	0.0001	0.0013
	Survival	**α_1**	1.3194	0.1366	<0.0001
		α_2	0.2648	1.6099	<0.0001
		$\sigma = 0.4098769$			
JM_6	**Longitudinal**	**Intercept**	-0.2385	0.1027	0.0202
		time	-0.0215	0.0075	0.0045
		age	-0.0009	0.0015	0.5579
		time*age	0.0003	0.0001	0.0038
	Survival	**α_1**	1.2795	0.1396	<0.0001
		α_2	1.8523	1.8558	0.3182
		log (xi.1)	-5.0623	0.2366	
		log (xi.2)	-3.9031	0.1874	
		log (xi.3)	-4.0357	0.2266	
		log (xi.4)	-3.6976	0.1978	
		log (xi.5)	-3.8202	0.2081	
		log (xi.6)	-3.6054	0.3306	
		log (xi.7)	11.3088	0.3429	
		$\sigma = 0.4159172$			
JM_7	**Longitudinal**	**Intercept**	-0.131	0.1353	0.331
		time	-0.0358	0.01	0.0004
		age	-0.0024	0.002	0.242
		time*age	0.0004	0.0001	0.0035
	Survival	**α**	0.0237	0.0107	0.0265
		$\sigma = 0.4094571$			
JM_8	**Longitudinal**	**Intercept**	-0.1301	0.1353	0.3363
		time	-0.0358	0.010	0.0003
		age	-0.0024	0.002	0.2394
		time*age	0.0004	0.0001	0.0034
	Survival	**α**	0.0247	0.0109	0.0235
		log (xi.1)	-5.0257	0.2236	
		log (xi.2)	-4.0087	0.1826	
		log (xi.3)	-4.1978	0.2238	
		log (xi.4)	-3.8772	0.1927	
		log (xi.5)	-3.9117	0.1895	
		log (xi.6)	-3.4461	0.2782	
		log (xi.7)	11.5741	0.2899	
		$\sigma = 0.4094836$			

Table 8. Variance-covariance matrix of random-effects for joint model combinations for Model-II for PCT biomarker

		Intercept	time	time^2
JM$_1$	**Intercept**	0.684	-0.047	0.00106
	time	-0.047	0.0103	-0.00033
	time^2	0.00106	-0.0003	0.000012
		Intercept	**time**	**time^2**
JM$_2$	**Intercept**	0.679	-0.046	0.001
	time	-0.0457	0.0099	-0.0003
	time^2	0.001	-0.0003	0.000011
		Intercept	**time**	**time^2**
JM$_3$	**Intercept**	0.678	-0.043	0.00081
	time	-0.043	0.0097	-0.0003
	time^2	0.00081	-0.0003	0.0000125
		Intercept	**time**	**time^2**
JM$_4$	**Intercept**	0.678	-0.044	0.000821
	time	-0.044	0.0097	-0.0003
	time^2	0.0008	-0.0003	0.0000125
		Intercept	**time**	**time^2**
JM$_5$	**Intercept**	0.684	-0.0471	0.0011
	time	-0.0471	0.0103	-0.0003
	time^2	0.0011	-0.0003	0.0000122
		Intercept	**time**	**time^2**
JM$_6$	**Intercept**	0.685	-0.0464	0.00106
	time	-0.046	0.0099	-0.0003
	time^2	0.001	-0.0003	0.000011
		Intercept	**time**	**time^2**
JM$_7$	**Intercept**	0.67	-0.043	0.000833
	time	-0.043	0.0098	-0.0003
	time^2	0.000833	-0.0003	0.0000125
		Intercept	**time**	**time^2**
JM$_8$	**Intercept**	0.669	-0.043	0.000833
	time	-0.043	0.0098	-0.0003
	time^2	0.000833	-0.0003	0.0000125

V - R CODES

```
# R Code to obtain subject-specific longitudinal profiles of randomly selected 16
patients from  CRP sample #

########################################
### DOWNLOADING THE CRP DATASET ###
########################################
library(foreign)
crp=read.csv2("C:/Users/Meriç/Desktop/crp457.csv", header=TRUE)
head(crp,10)

######################
### Preparing the Data ###
######################
#data=data[,-4]
#we include an indicator for the baseline measurement#
#crp$t0 <- as.numeric(crp$time == 0)
library(JM)
crp$id=as.numeric(crp$id)
crp$trsf=as.numeric(crp$trsf)
crp$time=as.integer(crp$time)
crp$gender=as.factor(crp$gender)
crp$gender <- factor(crp$gender,
levels = c(1,2),
labels = c("female", "male"))
crp$survtime=as.numeric(crp$survtime)
crp$status=as.integer(crp$status)
crp$status <- factor(crp$status,
levels = c(0,1),
labels = c("censored", "dead"))
crp$stime=as.numeric(crp$stime)
crp$stime1=as.numeric(crp$stime1)
nrow(crp)
head(crp)

class(crp$id)
class(crp$trsf)
class(crp$time)
class(crp$gender)
class(crp$survtime)
class(crp$stime)
class(crp$stime1)
class(crp$status)


#########################################################################
#########################################################################
```

```
# R Code to obtain subject-specific longitudinal profiles of randomly selected 16
patients from  CRP sample #

set.seed(123)
## we take a sample of patients with more than six measurements
library(lattice)
crp$id=as.factor(crp$id)
long_ids <- names(which(table(crp$id) > 6))
length(long_ids)
ids <- sample(long_ids, 16)
crp.random=xyplot(lcrp ~ time | id, data = crp, col="blue",
      subset = id %in% ids, type = c("b"),
      lwd = 2, xlab="Days",ylab="Log-Transformed CRP" ,layout = c(4,4))
crp.random

# R Code to obtain subject-specific longitudinal profiles of randomly selected 16
patients from  PCT sample #

########################################
### DOWNLOADING THE CRP DATASET ###
########################################
library(foreign)
pct=read.csv2("C:/Users/Meriç/Desktop/pct534.csv", header=TRUE)
head(pct,10)

##########################
### Preparing the Data ###
##########################
pct$id=as.numeric(pct$id)
pct$trsf=as.numeric(pct$trsf)
pct$time=as.integer(pct$time)
pct$gender=as.factor(pct$gender)
pct$gender <- factor(pct$gender,
levels = c(1,2),
labels = c("female", "male"))
pct$survtime=as.numeric(pct$survtime)
pct$status=as.integer(pct$status)
pct$status <- factor(pct$status,
levels = c(0,1),
labels = c("censored", "dead"))
pct$stime=as.numeric(pct$stime)
pct$stime1=as.numeric(pct$stime1)
pct$yas=as.numeric(pct$yas)
nrow(pct)
head(pct)

class(pct$id)
class(pct$trsf)
```

```
class(pct$time)
class(pct$gender)
class(pct$survtime)
class(pct$stime)
class(pct$stime1)
class(pct$status)
class(pct$yas)


#########################################################################
#########################################################################
######
set.seed(123)
## we take a sample of patients with more than six measurements
library(lattice)
pct$id=as.factor(pct$id)
long_ids <- names(which(table(pct$id) > 6))
length(long_ids)
ids <- sample(long_ids, 16)
pct.random=xyplot(lpct ~ time | id, data = pct, col="red",
      subset = id %in% ids, type = c("b"),
      lwd = 2, xlab="Days",ylab="Log-Transformed PCT" ,layout = c(4,4))
pct.random
```

*** R codes for Figure 4.1 and Figure 4.2 are taken from web page of JM package (4).

```
################################
# R Codes for Section s 4.1 and 4.2 #
################################

############################
### R Codes for Section 4.1 ###
############################

library(JM)
library(survivalROC)

##################################
 DOWNLOADING THE CRP DATASET
##################################
crp=read.csv2("C:/Users/Meric/Desktop/crp457.csv", header=TRUE)
head(crp,10)
```

```
######################
### Preparing the Data ###
######################

crp$id=as.factor(crp$id)
crp$crp=as.numeric(crp$crp)
crp$trsf=as.numeric(crp$trsf)
crp$score=as.numeric(crp$score)
crp$time=as.integer(crp$time)
crp$gender=as.factor(crp$gender)
crp$unit=as.factor(crp$unit)
crp$gender=factor(crp$gender, levels=c(0,1), labels=c("female", "male"))
crp$survtime=as.numeric(crp$survtime)
crp$status=as.numeric(crp$status)
#crp$status=factor(crp$status, levels=c(0,1), labels=c("censored", "dead"))
#crp$stime=as.numeric(crp$stime)
#crp$stime1=as.numeric(crp$stime1)
crp$age=as.numeric(crp$age)

lcrp=log(crp$crp)
lcrp=as.numeric(lcrp)
crp=cbind(crp,lcrp)

nrow(crp)

### SURVIVAL PART ###
surv.data=crp[crp$time==0,]
surv <-coxph(Surv(survtime, status)~1, data=surv.data, x=TRUE)
summary(surv)

summary(surv.data$survtime)


#LINEAR MIXED EFFECTS MODELLING#

ctrl <- lmeControl(maxIter=100,msMaxIter=100,niterEM=100,tolerance=1e-
7,msTol=1e-3, opt='optim')
lme.model2=lme(lcrp~time*age, random = ~time+I(time^2)|id ,
control='ctrl',na.action = na.omit,data = crp)
summary(lme.model2)


### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION #####
### COMPUTING SLOPE ###
dform.cum <- list(fixed= ~I(time^2/2)+~I((time^2/2)*age), indFixed=c(1:2,4),
random = ~I(time^2/2)+I(time^3/3), indRandom = 1:3)
```

```
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
jm.model2.cum.piece<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform.cum,
method="piecewise-PH-aGH")

################################################
#### TIME - DEPENDENT AUC CALCULATION ###
################################################
### td-AUC for survival time cut-off point ###
set.seed(123)
auc.crp.1=aucJM(jm.model2.cum.piece, crp,  18, 30)

### td-AUC for time-points cut-off point ###
set.seed(123)
auc.crp.2=aucJM(jm.model2.cum.piece, crp,  6, 30)

#######################################################
######## Calculating Confidence Interval for td-AUC #########
#######################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(jm.model2.cum.piece, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.crp.1=boot.ci(bt, type="perc")
sd.crp.1=sd(bt$t)

all.crp.18=bt$t

#########################################################
### Calculating Confidence Interval and p-value for td-AUC ###
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(jm.model2.cum.piece, d, Tstart=7, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.crp.2=boot.ci(bt, type="perc")
sd.crp.2=sd(bt$t)

all.crp.7=bt$t
```

```
########################################
### DOWNLOADING THE PCT DATASET ###
########################################
pct=read.csv2("C:/Users/Meric/Desktop/pct534.csv", header=TRUE)
head(pct,10)

#########################
### Preparing the Data ###
#########################
library(JM)
pct$id=as.factor(pct$id)
pct$pct=as.numeric(pct$pct)
pct$time=as.integer(pct$time)
pct$gender=as.factor(pct$gender)
pct$unit=as.factor(pct$unit)
pct$gender=factor(pct$gender, levels=c(0,1), labels=c("female", "male"))
pct$survtime=as.numeric(pct$survtime)
pct$status=as.numeric(pct$status)
pct$status=factor(pct$status, levels=c(0,1), labels=c("censored", "dead"))
pct$age=as.numeric(pct$age)
nrow(pct)

nrow(crp)

### SURVIVAL PART ###
surv.data=pct[pct$time==0,]
surv <-coxph(Surv(survtime, status)~1, data=surv.data, x=TRUE)
summary(surv)
summary(surv.data$survtime)


#LINEAR MIXED EFFECTS MODELLING#

ctrl <- lmeControl(maxIter=100,msMaxIter=100,niterEM=100,tolerance=1e-
7,msTol=1e-3, opt='optim')
lme.model2=lme(lpct~time*age, random = ~time+I(time^2)|id ,
control='ctrl',na.action = na.omit,data = pct)
summary(lme.model2)


### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION #####
### COMPUTING SLOPE ###
dform.cum <- list(fixed= ~I(time^2/2)+~I((time^2/2)*age), indFixed=c(1:2,4),
random = ~I(time^2/2)+I(time^3/3), indRandom = 1:3)


ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
```

```
jm.model2.cum.piece<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform.cum,
method="piecewise-PH-aGH")

################################################
#### TIME - DEPENDENT AUC CALCULATION ####
################################################
### td-AUC for survival time cut-off point ###
set.seed(123)
auc.pct.1=aucJM(jm.model2.cum.piece, crp,  17, 30)

### td-AUC for time-points cut-off point ###
set.seed(123)
auc.pct.2=aucJM(jm.model2.cum.piece, crp,  7, 30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(jm.model2.cum.piece, d, Tstart=17,  Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.pct.1=boot.ci(bt, type="perc")
sd.pct.1=sd(bt$t)
all.pct.17=bt$t

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(jm.model2.cum.piece, d, Tstart=7, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.pct.2=boot.ci(bt, type="perc")
sd.pct.2=sd(bt$t)

all.pct.7=bt$t
```

```
######################
# R Codes for Section 4.2 #
######################

#####################################################################
######  Diagnostic Performance of a Single Measurement of CRP  ###########
#####################################################################

cutoff <- 30
crp.auc= survivalROC(Stime=surv.data$survtime,
status=surv.data$status,
marker=surv.data$lcrp,
predict.time=cutoff, method="KM")
crp.auc$AUC


#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return( survivalROC(Stime=d$survtime,
status=d$status,
marker=d$lcrp,
predict.time=cutoff, method="KM")$AUC)
}
bt<- boot(surv.data, f, R=1000)
bt
mean=mean(bt$t, na.rm=T)
mean
ci.uns=boot.ci(bt, type="perc")
sd.crp=sd(bt$t)

all.crp.0.30 = bt$t

#####################################################################
######  Diagnostic Performance of a Single Measurement of PCT  ###########
#####################################################################


### SURVIVAL PART ###
surv.data=pct[pct$time==0,]
#surv.data
surv <-coxph(Surv(survtime, status)~1, data=surv.data, x=TRUE)
summary(surv)
```

```
summary(surv.data$survtime)

####################################
#######  Diagnostic Performance #######
####################################

#attach(surv.data)
cutoff <- 30
pct.auc= survivalROC(Stime=surv.data$survtime,
status=surv.data$status,
marker=surv.data$lpct,
predict.time=cutoff, method="KM")
pct.auc$AUC

all.pct.0.30 = bt$t


#########################################################
######## Calculating Confidence Interval for td-AUC ########
#########################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return( survivalROC(Stime=d$survtime,
status=d$status,
marker=d$lcrp,
predict.time=cutoff, method="KM")$AUC)
}
bt<- boot(surv.data, f, R=1000)
bt
mean=mean(bt$t, na.rm=T)
mean
plot(bt)
ci.uns=boot.ci(bt, type="perc")
sd.pct=sd(bt$t)

#####################################

#### Comparison of Time  - Dependent AUC Values of Baseline  CRP and PCT
Measurements ###

var.crp.single =(sd.crp)^2
var.pct.single =(sd.pct)^2

z=(crp.auc – pct.auc)/sqrt(var.pct.single+var.crp.single)
z
p=2*pnorm(-abs(z))
```

```
p


#### Comparison of Time  - Dependent AUC Values of Serial  CRP and PCT
Measurements ###

var.crp.serial.1=(sd.crp.1)^2
var.pct.serial.1=(sd.pct.1)^2

z1=(auc.crp.1-auc.pct.1)/sqrt(var.crp.serial.1+var.pct.serial.1)
z1
p1=2*pnorm(-abs(z1))
p1


#########################################################################

var.crp.serial.2=(sd.crp.2)^2
var.pct.serial.2=(sd.pct.2)^2

z2=(auc.crp.2-auc.pct.2)/sqrt(var.crp.serial.2+var.pct.serial.2)
z2
p2=2*pnorm(-abs(z2))
p2

#########################################################################

z3=(auc.crp.2-auc.pct.1)/sqrt(var.crp.serial.2+var.pct.serial.1)
z3
p3=2*pnorm(-abs(z3))
p3

#########################################################################

z4=(auc.crp.1-auc.pct.2)/sqrt(var.crp.serial.1+var.pct.serial.2)
z4
p4=2*pnorm(-abs(z4))
p4

#########################################################################


#### Comparison of Time  - Dependent AUC Values of Single and Serial  CRP
Measurements ###

Z5 =(crp.auc-auc.crp.1)/ sqrt(var.crp.single+var.crp.serial.1)
Z5
p5=2*pnorm(-abs(z5))
```

```
p5


Z6 =(crp.auc-auc.crp.2)/ sqrt(var.crp.single+var.crp.serial.2)
Z6
P6=2*pnorm(-abs(z6))
p6

#### Comparison of Time  - Dependent AUC Values of Single and Serial PCT
Measurements ###

Z7 =(pct.auc-auc.pct.1)/ sqrt(var.pct.single+var.pct.serial.1)
Z7
P7=2*pnorm(-abs(z7))
P7


Z8=(pct.auc-auc.pct.2)/ sqrt(var.pct.single+var.pct.serial.2)
Z8
P8=2*pnorm(-abs(z8))
P8

######################
#R Codes for Section 4.3 #
######################

#######################################
### DOWNLOADING THE DATASET #####
#######################################
crp1=read.csv2("C:/Users/Meriç/Desktop/crp1.csv", header=TRUE)
head(crp1,10)
quantile(crp1$time)

crp1 is the dataset that were created after excluding baseline CRP measurements.

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
### AUC ###
set.seed(123)
auc.crp.1=aucJM(jm.model2.cum.piece, crp, 4,30)

### AUC ###
set.seed(123)
auc.crp.2=aucJM(jm.model2.cum.piece, crp, 9,30)
```

```
### AUC ###
set.seed(123)
auc.crp.3=aucJM(jm.model2.cum.piece, crp, 11,30)

### AUC ###
set.seed(123)
auc.crp.4=aucJM(jm.model2.cum.piece, crp, 16,30)

auc.crp=rbind(auc.crp.1$auc,auc.crp.2$auc,auc.crp.3$auc,auc.crp.4$auc)
auc.crp


#### CALCULATING THE CONFIDENCE INTERVALS FOR TD-AUC
VALUES ###

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(jm.model2.cum.piece, d, Tstart=4, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.Q1=boot.ci(bt, type="perc")
ci.Q1


#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(jm.model2.cum.piece, d, Tstart=9, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.Q2=boot.ci(bt, type="perc")
ci.Q2
```

```
#######################################################
######## Calculating Confidence Interval for td-AUC #########
#######################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(jm.model2.cum.piece, d, Tstart=11, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.mean=boot.ci(bt, type="perc")
ci.mean

#######################################################
######## Calculating Confidence Interval for td-AUC #########
#######################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(jm.model2.cum.piece, d, Tstart=16,  Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.Q3=boot.ci(bt, type="perc")
ci.Q3


#######################################
### DOWNLOADING THE PCT DATASET #
#######################################
pct1=read.csv2("C:/Users/Meriç/Desktop/pct1.csv", header=TRUE)
head(pct1,10)
quantile(pct1$time)
```

pct1 is the dataset that were created after excluding baseline CRP measurements.

```
#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
### AUC ###
set.seed(123)
auc. pct.1=aucJM(jm.model2.cum.piece, pct, 4,30)

### AUC ###
set.seed(123)
auc. pct.2=aucJM(jm.model2.cum.piece, pct, 8,30)
```

```
### AUC ###
set.seed(123)
auc. pct.3=aucJM(jm.model2.cum.piece, pct, 10,30)

### AUC ###
set.seed(123)
auc. pct.4=aucJM(jm.model2.cum.piece, pct, 15,30)

auc. pct =rbind(auc. pct.1$auc, auc. pct.2$auc, auc. pct.3$auc, auc. pct.4$auc)
auc. pct


#### CALCULATING THE CONFIDENCE INTERVALS FOR TD-AUC
VALUES ###

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(jm.model2.cum.piece, d, Tstart=4, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.Q1=boot.ci(bt, type="perc")
ci.Q1


#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(jm.model2.cum.piece, d, Tstart=8, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.Q2=boot.ci(bt, type="perc")
ci.Q2


#########################################################
######## Calculating Confidence Interval for td-AUC #########
```

```
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(jm.model2.cum.piece, d, Tstart=10, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.mean=boot.ci(bt, type="perc")
ci.mean

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(jm.model2.cum.piece, d, Tstart=15,  Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.Q3=boot.ci(bt, type="perc")
ci.Q3

#########################
### R Codes for Section 4.4 ###
#########################
```

Based on the same formula (4.1) of the fitted joint models in Section 4 under the name of jm.model2.cum.piece, time-dependent diagnostic accuracy values and corresponding cut-off values are calculated as explained in using 1000 Monte Carlo samples for CRP biomarker for both genders.

```
# for the longitudinal process

# number of measurements per patient
ni <- with(crp, tapply(lcrp, id, length))
summary(ni)

lcrp=describe(crp$lcrp)

summary.crp=as.data.frame(tapply(crp$lcrp, crp$id,summary))
colnames(summary.crp)<-c("Min","1st Q", "Median", "Mean", "3rd Q", "Max")
summarycrp=as.matrix(summary.crp,ncol=6, nrow=457)
write.table(summary.crp, "C:/Users/Meriç/Desktop/summarycrp.txt", sep="")
```

```
###Time - Dependent Sensitivity and Specificity and Cut- Off Values ####
crp.389=crp[crp$id==389,]
set.seed(123)
roc.crp.389 <- rocJM(jm.model2.cum.piece, dt=c(13,14,15), crp.389, idVar = "id",
directionSmaller=FALSE)
roc.crp.389$optThr[[1]][3]

auc=roc.crp.389$AUCs
cutoff=roc.crp.389$optThr

tdsens=t(roc.crp.389$MCresults[[1]])
tdspec=t(roc.crp.389$MCresults[[2]])

se_tdsens=t(roc.crp.389$MCresults[[3]])
se_tdspec=t(roc.crp.389$MCresults[[4]])
cc=roc.crp.389$cc

daccuracy=cbind(cc,tdsens, tdspec, se_tdsens, se_tdspec)
dim(daccuracy)

write.table(daccuracy, "C:/Users/Meriç/Desktop/dac.txt", quote=F, sep=" ")

########## BOOTSTRAP PROCEDURE ##########
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return( rocJM(jm.model2.cum.piece, dt=c(13,14,15), d, idVar = "id",
directionSmaller=FALSE)$optThr[[1]][3])
}
bt<- boot(crp.389, f, R=1000)
bt
ci.uns=boot.ci(bt, type="perc")
ci.uns
```

Based on the same formula (4.1) of the fitted joint models in Section 4 under the name of jm.model2.cum.piece, time-dependent diagnostic accuracy values and corresponding cut-off values are calculated as explained in using 1000 Monte Carlo samples for PCT biomarker for both genders.

```
# for the longitudinal process

# number of measurements per patient
ni <- with(pct, tapply(lpct, id, length))
summary(ni)
```

```
lpct=describe(pct$lpct)

summary.pct=as.data.frame(tapply(pct$lpct, pct$id,summary))
colnames(summary.pct)<-c("Min","1st Q", "Median", "Mean", "3rd Q", "Max")
summarypct=as.matrix(summary.pct,ncol=6, nrow=457)
write.table(summary.pct, "C:/Users/Meriç/Desktop/summarypct.txt", sep="")

####### Time - Dependent Sensitivity and Specificity and Cut- Off Values #######
pct.4=pct[pct$id==4,]
set.seed(123)
roc.pct.4 <- rocJM(jm.model2.cum.piece, dt=c(2,3,4), pct.4, idVar = "id",
directionSmaller=FALSE)
roc.pct.4

auc=roc.pct.4$AUCs
cutoff=roc.pct.4$optThr

tdsens=t(roc.pct.4$MCresults[[1]])
tdspec=t(roc.pct.4$MCresults[[2]])

se_tdsens=t(roc.pct.4$MCresults[[3]])
se_tdspec=t(roc.pct.4$MCresults[[4]])
cc=roc.pct.4$cc

daccuracy=cbind(cc,tdsens, tdspec, se_tdsens, se_tdspec)


######### BOOTSTRAP PROCEDURE ##########
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return( rocJM(jm.model2.cum.piece, dt=c(2,3,4), d, idVar = "id",
directionSmaller=FALSE)$optThr[[1]][3])
}
bt<- boot(pct.4, f, R=1000)
bt
ci.uns=boot.ci(bt, type="perc")
ci.uns
```

```
############################
#### R Codes for Section 4.5####
############################

# Joint Models for CRP for Model – I  Using previously loaded crp dataset #

### SURVIVAL PART ###
surv.data=crp[crp$time==0,]

# SURVIVAL PART #
# survival regression fit #
library(survival)
surv <-coxph(Surv(survtime, status)~ 1, data=surv.data, x=TRUE)
summary(surv)

#LINEAR MIXED EFFECTS MODELLING#
ctrl <- lmeControl(maxIter=200,msMaxIter=200,niterEM=200,tolerance=1e-
7,msTol=1e-3, opt='optim')
#ctrl <- lmeControl(opt='optim')
lme.model1=lme(lcrp~time*age, random = ~time|id , control='ctrl',na.action =
na.omit,data = crp)
summary(lme.model1)
lme.model1

### JOINT MODEL FORMULATION ###
ctrl <- list(iter.EM=300,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM1<- jointModel(lme.model1,surv, timeVar = "time",control='ctrl')

ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM2<- jointModel(lme.model1,surv, timeVar = "time",control='ctrl',
method="piecewise-PH-aGH")

#################################################################
############   TIME - DEPENDENT AUC CALCULATION ############
#################################################################

### AUC ###
set.seed(123)
auc.model1.uns=aucJM(JM1, crp, 18,30)

#######################################################
######## Calculating Confidence Interval for td-AUC #########
#######################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM1, d, Tstart=18, Thoriz=30)$auc)
```

```
}
bt<- boot(crp, f, R=1000)
bt

ci.uns=boot.ci(bt, type="perc")
se=sd(bt$t)


#####################################################################
############   TIME - DEPENDENT AUC CALCULATION ############
#####################################################################
set.seed(123)
auc.model1.piece=aucJM(JM2, crp, Tstart = 18, Thoriz = 30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM2, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt

ci.piece=boot.ci(bt, type="perc")
se=sd(bt$t)

### JM WITH SLOPE PARAMETERIZATION ###
### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-
04)
dform <- list(fixed= ~1+age, indFixed=c(2,4), random = ~1, indRandom = 2)
dform

### JOINT MODEL WITH SLOPE PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM3<- jointModel(lme.model1,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform)


### JOINT MODEL WITH SLOPE PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM4<- jointModel(lme.model1, surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform,
method="piecewise-PH-aGH")
```

```
#######################################################
####### TIME - DEPENDENT AUC CALCULATION #####
#######################################################
### AUC ###
set.seed(123)
auc.model1.slope.uns=aucJM(JM3, crp, 18,30)

#######################################################
######## Calculating Confidence Interval for td-AUC #########
#######################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM3, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt

ci.slope.uns=boot.ci(bt, type="perc")
se=sd(bt$t)

#######################################################
####### TIME - DEPENDENT AUC CALCULATION #####
#######################################################

set.seed(123)
auc.model1.slope.piece=aucJM(JM4, crp, Tstart = 18, Thoriz = 30)

#######################################################
######## Calculating Confidence Interval for td-AUC #########
#######################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM4, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt

ci.slope.piece=boot.ci(bt, type="perc")
ci.slope.piece
se=sd(bt$t)

### JM WITH BOTH PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
```

```
JM5<- jointModel(lme.model1,surv, timeVar =
"time",control='ctrl',derivForm=dform,parameterization="both")


ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM6<- jointModel(lme.model1,surv, timeVar =
"time",control='ctrl',derivForm=dform, parameterization="both",
method="piecewise-PH-aGH")

#####################################################
####### TIME - DEPENDENT AUC CALCULATION #####
#####################################################
### AUC ###
set.seed(123)
auc.model1.both.uns=aucJM(JM5, crp, 18,30)

#####################################################
######## Calculating Confidence Interval for td-AUC #########
#####################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(JM5,  d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.both.uns=boot.ci(bt, type="perc")
se=sd(bt$t)

#####################################################
####### TIME - DEPENDENT AUC CALCULATION #####
#####################################################
set.seed(123)
auc.model1.both.piece=aucJM(JM6, crp, Tstart = 18, Thoriz = 30)

#####################################################
######## Calculating Confidence Interval for td-AUC #########
#####################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(JM6, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.both.piece=boot.ci(bt, type="perc")
```

```
se=sd(bt$t)

 ### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION   ###
### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-08,numeriDeriv="cd",eps.Hes=1e-
04)
dform.cum <- list(fixed= ~I(time^2/2)+I((time^2/2)*age), indFixed=c(1:2,4),
random = ~I(time^2/2), indRandom = 1:2)



### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION  ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM7<- jointModel(lme.model1,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform.cum)


### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION  ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM8<- jointModel(lme.model1,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform.cum,
method="piecewise-PH-aGH")

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
### AUC ###
set.seed(123)
auc.model1.cum.uns=aucJM(JM7, crp, 18,30)


#########################################################
### Calculating Confidence Interval and p-value for td-AUC ###
#########################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(JM7, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.cum.uns=boot.ci(bt, type="perc")
se=sd(bt$t)
```

```
#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
set.seed(123)
auc.model1.cum.piece=aucJM(JM8, crp, Tstart = 18, Thoriz = 30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM8 d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.cum.piece=boot.ci(bt, type="perc")
se=sd(bt$t)

# Joint Models for CRP for Model – II  Using previously loaded crp dataset #

#LINEAR MIXED EFFECTS MODELLING#

ctrl <- lmeControl(maxIter=100,msMaxIter=100,niterEM=100,tolerance=1e-
7,msTol=1e-3, opt='optim')
#ctrl <- lmeControl(opt='optim')
lme.model2=lme(lcrp~time*age, random = ~time+I(time^2)|id ,
control='ctrl',na.action = na.omit,data = crp)
summary(lme.model2)
lme.model2


### JOINT MODEL FORMULATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM1<- jointModel(lme.model2,surv, timeVar = "time",control='ctrl')


### JOINT MODEL WITH SLOPE PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM2<- jointModel(lme.model2,surv, timeVar = "time",control='ctrl',
method="piecewise-PH-aGH")
```

```
#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################

### AUC ###
set.seed(123)
auc.model2.uns=aucJM(JM1, crp, 18,30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM1, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.uns=boot.ci(bt, type="perc")
se=sd(bt$t)


#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
set.seed(123)
auc.model2.piece=aucJM(JM2, crp, Tstart = 18, Thoriz = 30)

#################################################################
### Calculating Confidence Interval and p-value for td-AUC ###
#################################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM2, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1)
bt
mean=mean(bt$t, na.rm=T)
mean
plot(bt)

ci.piece=boot.ci(bt, type="perc")
se=sd(bt$t)
```

```
### JM WITH SLOPE PARAMETERIZATION ###
### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-
04)
dform <- list(fixed= ~1+age, indFixed=c(2,4), random = ~I(2*time), indRandom =
2:3)
dform

ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM3<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform)

### JOINT MODEL WITH SLOPE PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM4<- jointModel(lme.model2, surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform,
method="piecewise-PH-aGH")


#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
### AUC ###
set.seed(123)
auc.model2.slope.uns=aucJM(JM3, crp, 18,30)


#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM3, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt

ci.slope.uns=boot.ci(bt, type="perc ")
se=sd(bt$t)

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################

set.seed(123)
auc.model2.slope.piece=aucJM(JM4, crp, Tstart = 18, Thoriz = 30)
```

```
#######################################################
######## Calculating Confidence Interval for td-AUC ########
#######################################################

library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM4, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt

ci.slope.piece=boot.ci(bt, type="perc")
se=sd(bt$t)


### JM WITH BOTH PARAMETERIZATION ###
### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-
04)
dform <- list(fixed= ~1+age, indFixed=c(2,4), random = ~I(2*time), indRandom =
2:3)
dform


### JM WITH BOTH PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM5<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',derivForm=dform,parameterization="both")

### JM WITH BOTH PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM6<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',derivForm=dform, parameterization="both",
method="piecewise-PH-aGH")

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
### AUC ###
set.seed(123)
auc.model2.both.uns=aucJM(JM5 crp, 18,30)
```

```
#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(JM5,  d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt

ci.both.uns=boot.ci(bt, type="perc")
se=sd(bt$t)

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
set.seed(123)
auc.model2.both.piece=aucJM(JM6, crp, Tstart = 18, Thoriz = 30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(JM6, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt

ci.both.piece=boot.ci(bt, type="perc")
se=sd(bt$t)

### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION   ###
### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-08,numeriDeriv="cd",eps.Hes=1e-
04)
dform.cum <- list(fixed= ~I(time^2/2)+~I((time^2/2)*age), indFixed=c(1:2,4),
random = ~I(time^2/2)+I(time^3/3), indRandom = 1:3)
```

```
### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION  ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM7<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform.cum)

### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION  ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM8<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform.cum,
method="piecewise-PH-aGH")

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
### AUC ###
set.seed(123)
auc.model2.cum.uns=aucJM(JM7uns, crp, 18,30)

###########################################
### Calculating Confidence Interval for td-AUC ###
###########################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM7, d, Tstart=18, Thoriz=30)$auc)
}
bt<- boot(crp, f, R=1000)
bt
ci.cum.uns=boot.ci(bt, type="perc")
se=sd(bt$t)


#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
set.seed(123)
auc.model2.cum.piece=aucJM(JM8, crp, Tstart = 18, Thoriz = 30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM8, d, Tstart=18, Thoriz=30)$auc)
}
```

```
bt<- boot(crp, f, R=1000)
bt
ci.cum.piece=boot.ci(bt, type="perc")
se=sd(bt$t)


# Joint Models for PCT for Model – I  Using previously loaded pct dataset #


### SURVIVAL PART ###
surv.data=pct[pct$time==0,]

# SURVIVAL PART #
# survival regression fit #
library(survival)
surv <-coxph(Surv(survtime, status)~ 1, data=surv.data, x=TRUE)
summary(surv)

#LINEAR MIXED EFFECTS MODELLING#
ctrl <- lmeControl(maxIter=200,msMaxIter=200,niterEM=200,tolerance=1e-
7,msTol=1e-3, opt='optim')
#ctrl <- lmeControl(opt='optim')
lme.model1=lme(lpct~time*age, random = ~time|id , control='ctrl',na.action =
na.omit,data = pct)
summary(lme.model1)
lme.model1

### JOINT MODEL FORMULATION ###
ctrl <- list(iter.EM=300,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM1<- jointModel(lme.model1,surv, timeVar = "time",control='ctrl')

### JOINT MODEL WITH SLOPE PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM2<- jointModel(lme.model1,surv, timeVar = "time",control='ctrl',
method="piecewise-PH-aGH")

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################

### AUC ###
set.seed(123)
auc.model1.uns=aucJM(JM1, pct, 17,30)
```

```
#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(JM1, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt

ci.uns=boot.ci(bt, type="perc")
se=sd(bt$t)


#####################################################################
############   TIME - DEPENDENT AUC CALCULATION ############
#####################################################################
set.seed(123)
auc.model1.piece=aucJM(JM2, pct, Tstart = 17, Thoriz = 30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(JM2, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt

ci.piece=boot.ci(bt, type="perc")
se=sd(bt$t)

### JM WITH SLOPE PARAMETERIZATION ###
### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-
04)
dform <- list(fixed= ~1+age, indFixed=c(2,4), random = ~1, indRandom = 2)
dform

### JOINT MODEL WITH SLOPE PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM3<- jointModel(lme.model1,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform)
```

```
### JOINT MODEL WITH SLOPE PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM4<- jointModel(lme.model1, surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform,
method="piecewise-PH-aGH")

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
### AUC ###
set.seed(123)
auc.model1.slope.uns=aucJM(JM3, pct, 17,30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM3, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt

ci.slope.uns=boot.ci(bt, type="perc")
se=sd(bt$t)

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################

set.seed(123)
auc.model1.slope.piece=aucJM(JM4, pct, Tstart = 17, Thoriz = 30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM4, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
```

```
ci.slope.piece=boot.ci(bt, type="perc")
ci.slope.piece
se=sd(bt$t)

### JM WITH BOTH PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM5<- jointModel(lme.model1,surv, timeVar =
"time",control='ctrl',derivForm=dform,parameterization="both")


ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM6<- jointModel(lme.model1,surv, timeVar =
"time",control='ctrl',derivForm=dform, parameterization="both",
method="piecewise-PH-aGH")

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
### AUC ###
set.seed(123)
auc.model1.both.uns=aucJM(JM5, pct, 17, 30)


#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM5,  d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.both.uns=boot.ci(bt, type="perc")
se=sd(bt$t)


#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
set.seed(123)
auc.model1.both.piece=aucJM(JM6, pct, Tstart = 17, Thoriz = 30)
```

```
#######################################################
######## Calculating Confidence Interval for td-AUC #########
#######################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(JM6, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.both.piece=boot.ci(bt, type="perc")
se=sd(bt$t)

 ### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION   ###
### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-08,numeriDeriv="cd",eps.Hes=1e-
04)
dform.cum <- list(fixed= ~I(time^2/2)+I((time^2/2)*age), indFixed=c(1:2,4),
random = ~I(time^2/2), indRandom = 1:2)


### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION  ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM7<- jointModel(lme.model1,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform.cum)


### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION  ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM8<- jointModel(lme.model1,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform.cum,
method="piecewise-PH-aGH")


#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
### AUC ###
set.seed(123)
auc.model1.cum.uns=aucJM(JM7, pct, 17,30)


#######################################################
######## Calculating Confidence Interval for td-AUC #########
#######################################################
library(boot)
f <- function(data, i){
```

```
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM7, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.cum.uns=boot.ci(bt, type="perc")
se=sd(bt$t)


#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
set.seed(123)
auc.model1.cum.piece=aucJM(JM8, pct, Tstart = 17, Thoriz = 30)


#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM8 d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.cum.piece=boot.ci(bt, type="perc")
se=sd(bt$t)

# Joint Models for PCT for Model – II  Using previously loaded pct dataset #



#LINEAR MIXED EFFECTS MODELLING#

ctrl <- lmeControl(maxIter=100,msMaxIter=100,niterEM=100,tolerance=1e-
7,msTol=1e-3, opt='optim')
#ctrl <- lmeControl(opt='optim')
lme.model2=lme(lpct~time*age, random = ~time+I(time^2)|id ,
control='ctrl',na.action = na.omit,data = pct)
summary(lme.model2)
lme.model2

### JOINT MODEL FORMULATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM1<- jointModel(lme.model2,surv, timeVar = "time",control='ctrl')
```

```
### JOINT MODEL WITH SLOPE PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM2<- jointModel(lme.model2,surv, timeVar = "time",control='ctrl',
method="piecewise-PH-aGH")

#####################################################################
############   TIME - DEPENDENT AUC CALCULATION ############
#####################################################################

### AUC ###
set.seed(123)
auc.model2.uns=aucJM(JM1, pct, 17,30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM1, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.uns=boot.ci(bt, type="perc")
se=sd(bt$t)

#####################################################################
############   TIME - DEPENDENT AUC CALCULATION ############
#####################################################################
set.seed(123)
auc.model2.piece=aucJM(JM2, pct, Tstart = 17, Thoriz = 30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM2, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt

ci.piece=boot.ci(bt, type="perc")
se=sd(bt$t)
```

```
### JM WITH SLOPE PARAMETERIZATION ###
### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-
04)
dform <- list(fixed= ~1+age, indFixed=c(2,4), random = ~I(2*time), indRandom =
2:3)
dform

ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM3<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform)

### JOINT MODEL WITH SLOPE PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM4<- jointModel(lme.model2, surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform,
method="piecewise-PH-aGH")

############################################################
############   TIME - DEPENDENT AUC CALCULATION ######
############################################################
### AUC ###
set.seed(123)
auc.model2.slope.uns=aucJM(JM3, pct, 17,30)


#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
          d <- data[i,]
     set.seed(123)
          return(aucJM(JM3, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt

ci.slope.uns=boot.ci(bt, type="perc ")
se=sd(bt$t)

############################################################
############   TIME - DEPENDENT AUC CALCULATION ######
############################################################

set.seed(123)
auc.model2.slope.piece=aucJM(JM4, pct, Tstart = 17, Thoriz = 30)
```

```
#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM4, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt

ci.slope.piece=boot.ci(bt, type="perc")
se=sd(bt$t)

### JM WITH BOTH PARAMETERIZATION ###
### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-
04)
dform <- list(fixed= ~1+age, indFixed=c(2,4), random = ~I(2*time), indRandom =
2:3)
dform


### JM WITH BOTH PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM5<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',derivForm=dform,parameterization="both")

### JM WITH BOTH PARAMETERIZATION ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM6<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',derivForm=dform, parameterization="both",
method="piecewise-PH-aGH")

#############################################################
############   TIME - DEPENDENT AUC CALCULATION ######
#############################################################
set.seed(123)
auc.model2.both.uns=aucJM(JM5 pct, 17,30)

#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
```

```
    set.seed(123)
        return(aucJM(JM5,  d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt

ci.both.uns=boot.ci(bt, type="perc")
se=sd(bt$t)

############################################################
############   TIME - DEPENDENT AUC CALCULATION ######
############################################################
set.seed(123)
auc.model2.both.piece=aucJM(JM6, pct, Tstart = 17, Thoriz = 30)


#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM6, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt

ci.both.piece=boot.ci(bt, type="perc")
se=sd(bt$t)

### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION   ###
### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-08,numeriDeriv="cd",eps.Hes=1e-
04)
dform.cum <- list(fixed= ~I(time^2/2)+~I((time^2/2)*age), indFixed=c(1:2,4),
random = ~I(time^2/2)+I(time^3/3), indRandom = 1:3)


### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION  ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
JM7<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform.cum)

### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION  ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
```

```
JM8<- jointModel(lme.model2,surv, timeVar =
"time",control='ctrl',parameterization="slope",derivForm=dform.cum,
method="piecewise-PH-aGH")

#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
### AUC ###
set.seed(123)
auc.model2.cum.uns=aucJM(JM7, pct, 17,30)

##########################################
### Calculating Confidence Interval for td-AUC ###
##########################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM7, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.cum.uns=boot.ci(bt, type="perc")
se=sd(bt$t)


#####################################################
####### TIME - DEPENDENT AUC CALCULATION ####
#####################################################
set.seed(123)
auc.model2.cum.piece=aucJM(JM8, pct, Tstart = 17, Thoriz = 30)


#########################################################
######## Calculating Confidence Interval for td-AUC #########
#########################################################
library(boot)
f <- function(data, i){
        d <- data[i,]
    set.seed(123)
        return(aucJM(JM8, d, Tstart=17, Thoriz=30)$auc)
}
bt<- boot(pct, f, R=1000)
bt
ci.cum.piece=boot.ci(bt, type="perc")
se=sd(bt$t)
```

```
######################
# R Codes for Section 4.6 #
######################

# Time- Dependent ROC Curves and Time-dependent cut-off values for CRP #

library(JM)
library(joineR)
library(psych)

################################
  DOWNLOADING THE DATASET
################################
crp=read.csv2("C:/Users/Meriç/Desktop/crp457.csv", header=TRUE)
head(crp,10)


####### Selecting Female Group #######
crp.female=crp[crp$gender=="female",]
head(crp.female)
nrow(crp.female)

########## Survival Part #############
crp.female.t0=crp.female[crp.female$time==0,]
head(crp.female.t0)
nrow(crp.female.t0)


# SURVIVAL PART #
library(survival)
crp.female.t0$status=as.numeric(crp.female.t0$status)
surv<-coxph(Surv(survtime, status)~ 1, data=crp.female.t0, x=TRUE)
summary(surv)

#LINEAR MIXED EFFECTS MODELLING#
ctrl <- lmeControl(maxIter=100,msMaxIter=100,niterEM=100,tolerance=1e-
7,msTol=1e-3, opt='optim')
#ctrl <- lmeControl(opt='optim')
lme.model1=lme(lcrp~time*age, random = ~time+I(time^2)|id ,
control='ctrl',na.action = na.omit,data = crp.female)
summary(lme.model1)
lme.model1

### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-08,numeriDeriv="cd",eps.Hes=1e-
04)
dform.cum <- list(fixed= ~I(time^2/2), indFixed=1:2, random =
~I(time^2/2)+I(time^3/3), indRandom = 1:3)
```

```
### STANDARD JM ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
jm.model2.piece<- jointModel(lme.model1,surv,
timeVar="time",control='ctrl',method="piecewise-PH-aGH")

# data on which to base the ROC calculations
data <- data.frame(
   id = 1,
   age=67,
   time = c(0, 1, 2, 3)
)
data$t0 <- as.numeric(data$time == 0)
data

# ROC estimation for Dt = (1, 2, 3)
set.seed(123)
ROC.1 <- rocJM(jm.model2.piece, dt = c(1, 2, 3), data =data,
directionSmaller=FALSE, M = 1000,  burn.in = 500)

## Time-dependent Cut-off Values ##
Cutoff.1=ROC.1$cc

## Time - dependent sensitivity ##
sens=t(ROC.1$MCresults[[1]])

#### Time - dependent specificity ##
spec=t(ROC.1$MCresults[[2]])

#### Standard error of td-sensitivity ###
sesens=t(ROC.1$MCresults[[3]])

#### Standard error of td-specificity ###
sespec=t(ROC.1$MCresults[[4]])

tdaccuracy=cbind(cutoff.1, sens, spec, sesens, sespec)

write.table(tdaccuracy, "C:/Users/Meriç/Desktop/tdaccuracy.txt", sep=" ",
quote=FALSE)


# ROC curves
P1=plot(ROC.1, legend = TRUE, main="Time-Dependent ROC Curves for
Women")


#Cut-Off Values
C1=plot(Cutoff.1, col="red", main="Cut-Off Values")
```

```
AUCS.1=ROC.1$AUCs
AUCS.1=as.data.frame(AUCS.1)

Cutoff.1=ROC.1$optThr
Cutoff.1=as.data.frame(Cutoff.1)

R1=cbind(AUCS.1, Cutoff.1)
R1=as.matrix(R1, nrow=3, ncol=2)
colnames(R1)<-c("AUCS.1","Cut-Offs.1")


####### Selecting Male Group #######
crp.male=crp[crp$gender=="male",]
head(crp.male)
nrow(crp.male)

########## Survival Part #############
crp.male.t0=crp.male[crp.male$time==0,]
head(crp.male.t0)
nrow(crp.male.t0)


# SURVIVAL PART #
library(survival)
crp.female.t0$status=as.numeric(crp.female.t0$status)
surv<-coxph(Surv(survtime, status)~ 1, data=crp.male.t0, x=TRUE)
summary(surv)

#LINEAR MIXED EFFECTS MODELLING#
ctrl <- lmeControl(maxIter=100,msMaxIter=100,niterEM=100,tolerance=1e-
7,msTol=1e-3, opt='optim')
#ctrl <- lmeControl(opt='optim')
lme.model1=lme(lcrp~time*age, random = ~time+I(time^2)|id ,
control='ctrl',na.action = na.omit,data = crp.male)
summary(lme.model1)
lme.model1

### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-08,numeriDeriv="cd",eps.Hes=1e-
04)
dform.cum <- list(fixed= ~I(time^2/2), indFixed=1:2, random =
~I(time^2/2)+I(time^3/3), indRandom = 1:3)

### STANDARD JM ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
```

```
jm.model2.piece<- jointModel(lme.model1,surv,
timeVar="time",control='ctrl',method="piecewise-PH-aGH")

# data on which to base the ROC calculations
data <- data.frame(
   id = 1,
   age=72,
   time = c(0, 1, 2, 3, 4)
)
data$t0 <- as.numeric(data$time == 0)
data

# ROC estimation for Dt = (1, 2, 3)
set.seed(123)
ROC.2 <- rocJM(jm.model2.piece, dt = c(1, 2, 3), data =data,
directionSmaller=FALSE, M = 1000,  burn.in = 500)

#########################################################################

######################
# R Codes for Section 4.7 #
######################

## Time-dependent Cut-off Values ##
Cutoff.2=ROC.2$cc

## Time - dependent sensitivity ##
sens=t(ROC.2$MCresults[[1]])

#### Time - dependent specificity ##
spec=t(ROC.2$MCresults[[2]])

#### Standard error of td-sensitivity ###
sesens=t(ROC.2$MCresults[[3]])

#### Standard error of td-specificity ###
sespec=t(ROC.2$MCresults[[4]])

tdaccuracy=cbind(cutoff, sens, spec, sesens, sespec)

#########################################################################

# ROC curves
P2=plot(ROC.2, legend = TRUE, main="Time-Dependent ROC Curves for Men")

Cutoff.2=ROC.2$optThr
Cutoff.2=as.data.frame(Cutoff.2)
```

```
#Cut-Off Values
C2=plot(Cutoff.2, col=”blue”, main=”Cut-Off Values”)

AUCS.2=ROC.2$AUCs
AUCS.2=as.data.frame(AUCS.1)

R2=cbind(AUCS.2, Cutoff.2)
R2=as.matrix(R12,  nrow=3, ncol=2)
colnames(R2)<-c("AUCS.2","Cut-Offs.2")

par(mfrow=c(2,2))
plot(ROC.1, legend = TRUE, main=” Time-Dependent ROC Curves for Women”)
plot(ROC.2, legend = TRUE, main=” Time-Dependent ROC Curves for Men”)
plot(Cutoff.1, col=”red”, main=”Cut-Off Values for Women”)
plot(Cutoff.1, col=”red”, main=”Cut-Off Values for  Men”)


# Time- Dependent ROC Curves and Time-dependent cut-off values for PCT #

################################
### DOWNLOADING THE DATASET ###
################################
pct=read.csv2("C:/Users/Meriç/Desktop/pct534.csv", header=TRUE)
head(pct,10)


####### Selecting Female Group #######
pct.female=pct[pct$gender=="female",]
head(pct.female)
nrow(pct.female)

########## Survival Part #############
pct.female.t0=pct.female[pct.female$time==0,]
head(pct.female.t0)
nrow(pct.female.t0)


# SURVIVAL PART #
library(survival)
pct.female.t0$status=as.numeric(pct.female.t0$status)
surv<-coxph(Surv(survtime, status)~ 1, data=pct.female.t0, x=TRUE)
summary(surv)

#LINEAR MIXED EFFECTS MODELLING#
ctrl <- lmeControl(maxIter=100,msMaxIter=100,niterEM=100,tolerance=1e-
7,msTol=1e-3, opt='optim')
#ctrl <- lmeControl(opt='optim')
```

```
lme.model1=lme(lpct~time*age, random = ~time+I(time^2)|id ,
control='ctrl',na.action = na.omit,data = pct.female)
summary(lme.model1)
lme.model1

### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-08,numeriDeriv="cd",eps.Hes=1e-
04)
dform.cum <- list(fixed= ~I(time^2/2), indFixed=1:2, random =
~I(time^2/2)+I(time^3/3), indRandom = 1:3)

### JM WITH CUMULATIVE EFFECTS PARAMETERIZATION  ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
jm.model2.piece<- jointModel(lme.model1,surv,
timeVar="time",control='ctrl',method="piecewise-PH-aGH")


# data on which to base the ROC calculations
data <- data.frame(
   id = 1,
   age=67,
   time = c(0, 1, 2, 3)
)
data$t0 <- as.numeric(data$time == 0)
data

# ROC estimation for Dt = (1, 2, 3)
set.seed(123)
ROC.1 <- rocJM(jm.model2.piece, dt = c(1, 2, 3), data =data,
directionSmaller=FALSE, M = 1000,  burn.in = 500)


## Time-dependent Cut-off Values ##
Cutoff.1=ROC.1$cc

## Time - dependent sensitivity ##
sens=t(ROC.1$MCresults[[1]])

#### Time - dependent specificity ##
spec=t(ROC.1$MCresults[[2]])

#### Standard error of td-sensitivity ###
sesens=t(ROC.1$MCresults[[3]])

#### Standard error of td-specificity ###
sespec=t(ROC.1$MCresults[[4]])

tdaccuracy=cbind(cutoff.1, sens, spec, sesens, sespec)
```

```
write.table(tdaccuracy, "C:/Users/Meriç/Desktop/tdaccuracy.txt", sep=" ",
quote=FALSE)


# ROC curves
P1=plot(ROC.1, legend = TRUE, main=”Time-Dependent ROC Curves for
Women”)


#Cut-Off Values
C1=plot(Cutoff.1, col=”red”, main=”Cut-Off Values”)


AUCS.1=ROC.1$AUCs
AUCS.1=as.data.frame(AUCS.1)

Cutoff.1=ROC.1$optThr
Cutoff.1=as.data.frame(Cutoff.1)

R1=cbind(AUCS.1, Cutoff.1)
R1=as.matrix(R1, nrow=3, ncol=2)
colnames(R1)<-c("AUCS.1","Cut-Offs.1")


####### Selecting Male Group #######
pct.male=pct[pct$gender=="male",]
head(pct.male)
nrow(pct.male)

########## Survival Part #############
pct.male.t0=pct.male[pct.male$time==0,]
head(pct.male.t0)
nrow(pct.male.t0)


# SURVIVAL PART #
library(survival)
pct.female.t0$status=as.numeric(pct.female.t0$status)
surv<-coxph(Surv(survtime, status)~ 1, data=pct.male.t0, x=TRUE)
summary(surv)

#LINEAR MIXED EFFECTS MODELLING#
ctrl <- lmeControl(maxIter=100,msMaxIter=100,niterEM=100,tolerance=1e-
7,msTol=1e-3, opt='optim')
#ctrl <- lmeControl(opt='optim')
lme.model1=lme(lpct~time*age, random = ~time+I(time^2)|id ,
control='ctrl',na.action = na.omit,data = pct.male)
```

```
summary(lme.model1)
lme.model1

### COMPUTING SLOPE ###
ctrl <- list(only.EM=TRUE,iter.EM=200,tol3=1e-08,numeriDeriv="cd",eps.Hes=1e-
04)
dform.cum <- list(fixed= ~I(time^2/2), indFixed=1:2, random =
~I(time^2/2)+I(time^3/3), indRandom = 1:3)

### STANDARD JM ###
ctrl <- list(iter.EM=200,tol3=1e-09,numeriDeriv="cd",eps.Hes=1e-04)
jm.model2.piece<- jointModel(lme.model1,surv,
timeVar="time",control='ctrl',method="piecewise-PH-aGH")


# data on which to base the ROC calculations
data <- data.frame(
   id = 1,
   age=73,
   time = c(0, 1, 2, 3)
)
data$t0 <- as.numeric(data$time == 0)
data

# ROC estimation for Dt = (1, 2, 3 )
set.seed(123)
ROC.2 <- rocJM(jm.model2.piece, dt = c(1, 2, 3), data =data,
directionSmaller=FALSE, M = 1000,  burn.in = 500)

#########################################################################

######################
# R Codes for Section 4.7 #
###################### #


## Time-dependent Cut-off Values ##
Cutoff.2=ROC.2$cc

## Time - dependent sensitivity ##
sens=t(ROC.2$MCresults[[1]])

#### Time - dependent specificity ##
spec=t(ROC.2$MCresults[[2]])

#### Standard error of td-sensitivity ###
sesens=t(ROC.2$MCresults[[3]])
```

```
#### Standard error of td-specificity ###
sespec=t(ROC.2$MCresults[[4]])

tdaccuracy=cbind(cutoff, sens, spec, sesens, sespec)

#########################################################################


# ROC curves
P2=plot(ROC.2, legend = TRUE, main="Time-Dependent ROC Curves for Men")

Cutoff.2=ROC.2$optThr
Cutoff.2=as.data.frame(Cutoff.2)

#Cut-Off Values
C2=plot(Cutoff.2, col="blue", main="Cut-Off Values")

AUCS.2=ROC.2$AUCs
AUCS.2=as.data.frame(AUCS.1)

R2=cbind(AUCS.2, Cutoff.2)
R2=as.matrix(R12,  nrow=3, ncol=2)
colnames(R2)<-c("AUCS.2","Cut-Offs.2")

par(mfrow=c(2,2))
plot(ROC.1, legend = TRUE, main=" Time-Dependent ROC Curves for Women")
plot(ROC.2, legend = TRUE, main=" Time-Dependent ROC Curves for Men")
plot(Cutoff.1, col="red", main="Cut-Off Values for Women")
plot(Cutoff.1, col="red", main="Cut-Off Values for  Men")
```

########################
 # R Codes for Section 4.8 #
########################

Based on previously fitted jm.model2.piece model, time-dependent ROC curves are constructed for both genders and both biomarkers with the help of the code given below:

```
# Time-Dependent ROC Curves and Cut-Off Values for CRP in Women #

# data on which to base the ROC calculations
data <- data.frame(
   id = 1,
   age=67,
   time = c(0, 1, 2, 3, 4)
)
```

```
data$t0 <- as.numeric(data$time == 0)
data

set.seed(123)
ROCs.1 <- rocJM(jm.model2.piece, dt = c(1, 2, 3), data = data,
   M = 1000, burn.in = 500)

ROCs.1

# ROC curves
plot(ROCs.1, legend = TRUE, main="Time –dependent ROC Curves for Women")


Cutoff.Crp.Women=ROCs.1$optThr
Cutoff.Crp.Women =as.data.frame(Cutoff.Crp.Women)
plot(Cutoff.Crp.Women, col="red", main="Cut-off Values" )
```

 # Time-Dependent ROC Curves and Cut-Off Values for CRP in Men #

```
# data on which to base the ROC calculations
data <- data.frame(
   id = 1,
   age=72,
   time = c(0, 1, 2, 3)
)
data$t0 <- as.numeric(data$time == 0)
data

set.seed(123)
ROCs.2 <- rocJM(jm.model2.piece, dt = c(1, 2, 3), data = data,
   M = 1000, burn.in = 500)

ROCs.2

# ROC curves
plot(ROCs.2, legend = TRUE, main="Time –dependent ROC Curves for Women")


Cutoff.Crp.Men=ROCs.2$optThr
Cutoff.Crp.Men =as.data.frame(Cutoff.Crp.Men)
plot(Cutoff.Crp.Men, col="blue", main="Cut-off Values" )
```

 # Time-Dependent ROC Curves and Cut-Off Values for PCT in Women #

```
# data on which to base the ROC calculations
data <- data.frame(
```

```
   id = 1,
   age=67,
   time = c(0, 1, 2, 3)
)
data$t0 <- as.numeric(data$time == 0)
data

set.seed(123)
ROCs.1 <- rocJM(jm.model2.piece, dt = c(1, 2, 3), data = data,
   M = 1000, burn.in = 500)

ROCs.1

# ROC curves
plot(ROCs.1, legend = TRUE, main="Time –dependent ROC Curves for Women")


Cutoff.Crp.Women=ROCs.1$optThr
Cutoff.Crp.Women =as.data.frame(Cutoff.Crp.Women)
plot(Cutoff.Crp.Women, col="red", main="Cut-off Values" )
```

 # Time-Dependent ROC Curves and Cut-Off Values for PCT in Men #

```
# data on which to base the ROC calculations
data <- data.frame(
   id = 1,
   age=67,
   time = c(0, 1, 2, 3, 4)
)
data$t0 <- as.numeric(data$time == 0)
data

set.seed(123)
ROCs.2 <- rocJM(jm.model2.piece, dt = c(1, 2, 3), data = data,
   M = 1000, burn.in = 500)

ROCs.2

# ROC curves
plot(ROCs.2, legend = TRUE, main="Time –dependent ROC Curves for Women")


Cutoff.Crp.Men=ROCs.2$optThr
Cutoff.Crp.Men =as.data.frame(Cutoff.Crp.Men)
plot(Cutoff.Crp.Men, col="blue", main="Cut-off Values" )
```

All other analyses are performed via IBM SPSS Statistics Version 22.0 from Hacettepe University. Some of the figures in the thesis are drawn in Microsoft Excel Program.

9. CURRICULUM VITAE

1. Personal Information

Name Surname : Naime Meric Konar

Date of Birth: 01/01/1990

Place of Birth: Adana, Turkey

Nationality: Turkish

Address: Kirsehir Ahi Evran University , Faculty of Medicine, Department of Biostatistics and Medical Informatics, Bagbasi , Kirsehir

Phone: +90554 518 03 03

2. Education

2013 – 2018 : Hacettepe University, Department of Biostatistics, Combined Master and PhD

2008 - 2012 : Dokuz Eylül University, Department of Statistics, BSc

2004 – 2008 : Konak Anatolian High School

3. Work Experience

2013 – 2017 : Research Assistant, Hacettepe University, Institue of Health Sciences, Department of Biostatistics

2018 - … : Research Assistant, Kirsehir Ahi Evran University, Department of Biostatistics and Medical Informatics

4. Research Experience

1. **June - September 2014** Research Fellow
   German Cancer Research Center (DKFZ)
   Department of Cancer Epidemiology
   Heidelberg, Germany

   Project : Developing a comprehensive statistical model for the prediction of endometrial cancer risk integrating questionnaire and interview derived data on lifestyle and reproductive factors as well as data on pre-diagnostic biomarkers from the European Prospective Investigation into Cancer and Nutrition (EPIC study).

2. **November – December 2017** Visiting PhD Student
   Katholieke Universiteit Leuven

I-Biostat
Leuven, Belgium

Project Title : Developing a risk prediction model using joint modleing approach for Intensive Care Unit (ICU) patients.

5. Scientific Activities

5.1. Articles in International Journals

1. Dag, O., Dolgun, A., Konar, N.M. (2018). onewaytests: An R Package for One-Way Tests in Independent Groups Designs. The R Journal. Accepted

2. Karaismailoglu, E., Konar, N. M., Goksuluk, D., & Karaagaoglu, A. E. (2018). Factors effecting the model performance measures area under the ROC curve, net reclassification improvement and integrated discrimination improvement. Communications in Statistics-Simulation and Computation, 1-13.

3. Baysal, S. S., Koc, S., Kaya, B. C., Gunes, A., Konar, N. M., & Altiparmak, I. H. (2018). Relationship between the endothelium biomarkers endocan and thrombomodulin and slow coronary flow. Biomedical Research, 29(7).

4. Fortner, R. T., Hüsing, A., Kühn, T., Konar, M., Overvad, K., Tjønneland, A., ... & Boeing, H. (2017). Endometrial cancer risk prediction including serum-based biomarkers: results from the EPIC cohort. International journal of cancer, 140(6), 1317-1323.

5.2. Oral Presentations in International Conferences

1. Konar, N.M., Karaismailoğlu, E., Karaağaoğlu, E. (2018). Determination of Risk Factors for ICU Mortality with Single and Serial Biomarker Values. 4th International Researchers, Statisticians and Young Statisticians Congrss, 28-30 April, Izmir, Turkey.

2. Konar, N.M., Karaismailoğlu, E., Karaağaoğlu, E. (2017). Evakuating Time Dependent Cut-Offs for Longitudinal Data. 19th National 2nd International Biostatistics Congress, 25 – 28 October , Antalya, Turkey.

3. Konar, N.M., Karaismailoğlu, E., Karaağaoğlu, E. (2017). The Use of Joint Modeling Approach in Personalized Medicine. IBS-EMR, 8-12 May 2017, Thessaloniki, Greece.

4. Konar, N.M., Karaismailoğlu, E., Karaağaoğlu, E. (2016). Sensitivity Analysis Under Different Parameterizations. 18th National 1st International Biostatistics Congress, 26 – 29 October 2016, Antalya, Turkey.

5. Konar, N.M., Dag, O., Dolgun, A. (2015). Effects of Non-normality and Heterogeneity on Tests for One-Way Independent Groups Design: Type I Error and Power Comparisons. XVth Spanish Biometric Conference, 22-25 September, Bilbao, Spain.

6. Konar, N.M., Dag, O. (2015). Determining the Number of Clusters with an Application in R. European Meeting of Statisticians, 6-10 July, Amsterdam, the Netherlands.

7. Konar, N.M., Karaismailoğlu E., Göksülük, D., Karaağaoğlu, E. (2015). The effect of Correlation Structure Between Diagnostic Tests on Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI). IBS-EMR, 11-15 May, Cappadocia, Turkey.

5.3. Poster Presentations in International Conferences

1. Konar, N.M., Karaismailoğlu, E., Karaağaoğlu, E. (2017). Factors Affecting the Diagnostic Performance of Longitudinal Biomarkers: A Simulation Study. CEN -ISBS, 28 August – 1 September, Vienna, Austria.

2. Konar, N.M., Karaismailoğlu E., Karaağaoğlu E. (2016). Comparison of Diagnostic Performance of Repeated Measurements and Baseline Measurement of Troponin-i in Predicting Death in an Emergency Setting. International Society of Clinical Biostatistics, 21-25 August, Birmingham, Uited Kingdom.

3. Konar, N.M., Dag, O., Basol, M. (2015). Comparison of Multiple Linear Regression and Ridge Regression on a Real Life Data Application. 9th International Statistics Congress, 28 October - 01 November, Antalya, Turkey.

4. Basol, M., Dag, O., Konar, N.M. (2015). Estimation of Ridge Constant in Ridge Regression via K-Fold Cross Validation. 9th International Statistics Congress, 28 October - 01 November, Antalya, Turkey.

5.4. Oral Presentations in National Conferences

1. Konar, N.M., Dag, O., Dolgun, A. (2015). onewaytests: Tek Yonlu Bagimsiz Grup Tasarimi icin Bir R Paketi. 17th National Biostatistics Congress, 5-9 Congress, Girne, Turkish Republic of Northern Cyprus.

6. Grants

TUBITAK –BIDEB - Support for Attending International Conference, for XVth Spanish Biometric Conference, 22-25 September 2015, Bilbao/Spain