UNIVERSITY OF LIVERPOOL

Incorporating time-dimension in ROC curve methodology for event-time outcomes

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy

by

Adina Najwa Kamarudin

March 2019

Acknowledgements

Firstly, I would like to express my sincere gratitude to my supervisors Dr Ruwanthi Kolamunnage-Dona and Dr Trevor Cox for the continuous support during my PhD study, for their patience, motivation, and immense knowledge. Their guidance helped me in all the time of research and writing of this thesis. I have been extremely lucky to have supervisors who cared so much about my work, and who responded to my questions so promptly. I could not have imagined having better advisors for my PhD study.

I would like to acknowledge the generous support from the Malaysia government sponsorship, Majlis Amanah Rakyat Malaysia (MARA) for providing me funding these past four years. I am also grateful to have my PhD friends and the staff in the Department of Biostatistics who have supported me directly or indirectly throughout my PhD study.

I dedicate this thesis to my loving husband Khairul Fadhli for his continuous support throughout this experience and has been the source of strength and inspiration. This dedication also goes to my daughter Qaisara and my son Khaleef for securing their love and patience throughout my PhD life. Special thanks to my close friends Norazliani, Ulfa, Nadia, Saidatul, and Ruhil for always listening, encouraging each other to complete this journey, and for all the fun we have had in the last four years.

Last but not least, I would like to thank my family: my parents and my brothers and sisters for supporting me spiritually throughout writing this thesis and my life in general. Alhamdulillah (All Praises to God).

Abstract

ROC (receiver operating characteristic) curve analysis is well established for assessing how well a continuous biomarker is capable to distinguish between healthy and diseased (event) individuals. The classical ROC curve approach is based on binary (case/control) disease outcome. However, many disease outcomes are time dependent as disease status is changing over time. Thus, estimating an ROC curve as a function of event-time is more appropriate and is a more effective tool in measuring the diagnostic accuracy of a biomarker.

This thesis develops and applies novel time-dependent ROC curve analysis approaches for evaluating the diagnostic efficacy of a biomarker at the baseline level. Two major findings of the comprehensive review undertaken on the time-dependent ROC curve has motivated the methodological developments of this thesis. Firstly, lack of parametric approaches to estimate the biomarker efficacy, and secondly, although biomarkers are often measured with an error due to contamination and variable storage conditions, the current estimation methods ignores this error. The thesis develops a parametric time-dependent ROC curve exploring a range of combination of distributions for event-time and biomarker. The closed form formulae of ROC curve summaries are derived from the joint distribution of event-time and biomarker whenever possible, while numerical solutions are implemented otherwise. A joint modelling approach is proposed to adjust for measurement error of the biomarker. Individual-level deviations of the baseline biomarker measurement from the population mean is linked with the event-time within the proposed joint model. A measurement error adjusted estimator is derived from estimated random effects and association between baseline biomarker and event-time. The proposed methods are evaluated through a range of simulation studies, and illustrated using Mayo Clinic primary biliary cirrhosis (PBC) data. Software is developed in the R language to implement the methodologies.

The results show that although the closed form formulae for parametric time-dependent ROC curve cannot be established for many distributional combinations due to complexity of the joint density, numerical solutions can be readily derived with the current advances in computing and software. The proposed parametric method provides equally precise estimates even when the sample size is small. The observed biomarker measurement could underestimate the true diagnostic effectiveness due to measurement error and hence useful biomarkers might go unnoticed. The proposed methodology effectively adjusts for measurement error when evaluating the diagnostic effectiveness of a biomarker.

List of Tables

List of Figures

List of Publications

1. Kolamunnage-Dona R, Kamarudin AN (2019). **Estimating time-dependent ROC curve of a biomarker subjected to measurement error**. Statistics in Medicine, under review
2. Kamarudin AN, Kolamunnage-Dona R (2018). **Evaluation of time-dependent diagnostic efficacy of a baseline marker accounting for measurement error**. Diagnostic and Prognostic Research, 2(Suppl 1):12
3. Kamarudin AN, Cox T, Kolamunnage-Dona R (2017). **Time-dependent ROC curve analysis in medical research: current methods and applications**. BMC Medical Research Methodology, **17**(1):53
4. Kamarudin AN, Kolamunnage-Dona R, Cox T (2016). **Incorporating the time-dependency in ROC methodology for censored clinical event**. Methods for Evaluating Medical Tests and Biomarkers. Diagnostic and Prognostic Research. 1(Suppl 1):P11

Table of Contents

1 Introduction

1.1 Scope of thesis

Research on personalised medicine has rapidly gained recognition in recent years leading to clinical studies which are aimed to discover potential quantities, collectively known as "biomarkers" that can signal a specific disease or a condition. The biomarkers can be predictive biomarker or prognostic biomarker. Predictive biomarker predicts the event from a treatment while prognostic biomarker are any clinical measurements or characteristics irrespective the treatment [1]. Among the examples of such clinical studies are single clinical measures such as epithelial cell percentage from the S-phase in breast cancer studies [2, 3], CD4 cell counts in AIDS [4], and EFGR and CK5/6 for breast cancer [5, 6], as well as various predictive and prognostic scores that can serve as biomarkers. Some examples of the predictive and prognostic scores include the Framingham risk score used for detecting cardiovascular events in elderly adults in a population-based observational prospective study [7], and the Karnofsky score used for predicting mortality among lung cancer patients [8, 9].

The main purpose of evaluating a candidate biomarker is to accurately discriminate between diseased (referred as "cases") and healthy (referred as "controls") individuals within a period under study. The cases can also be defined based on the response to a treatment such cases are the individuals that respond to the treatment while controls are the individuals who do not. Receiver operating characteristics (ROC) curve analysis is a well-established tool in medical research for assessing how well a biomarker is capable of effectively discriminating between cases and controls [10]. The standard ROC curve analysis is based on a binary disease outcome of whether or not the individual has the disease (case) or remains disease free (control). However, many disease outcomes are time dependent leading to varying event (disease onset) times between the cases and controls. Healthy individuals may not remain consistently disease free and may develop the disease at any time over the study's follow-up period. In cancer, no apparent symptoms can be identified at an early stage, but it can spread to other parts of the body in time.

Thus, considering that the disease status change over time, it is more appropriate to evaluate the discriminant capability of a biomarker. Therefore, a range of time-

dependent ROC curve analyses has been proposed in the past decade to determine the accuracy of a biomarker at specific times of interest. For example, time-dependent ROC curve methodology is used for breast cancer screening to investigate whether the individual is free of subclinical disease after two years of screening [7]. However, the standard ROC approach is still increasingly used in diagnostic clinical research.

Although nonparametric approaches to estimate the time-dependent ROC curve have been extensively proposed in the current literature, parametric approaches may be more efficient when the sample size is small (usually occurs in clinical biomarker development studies) and also since the event-time distributions are often highly skewed [11]. Moreover, clinical biomarkers are usually measured with an error due to contamination during specimen or sample (e.g. blood, urine) collection or variable storage conditions. Failing to adjust for measurement error may hinder the explanatory power of the biomarker causing the ROC curve to be underestimated [12, 13].

1.2 Thesis objectives

The broad aim of this thesis is to explore and extend the methodology for ROC curve analysis for evaluating the diagnostic efficacy of a biomarker when disease outcome is time dependent.

The specific objectives of the thesis are to:

1. Conduct a comprehensive review of a time-dependent ROC curve methodology for various definitions of time dependency in order to explore current approaches, limitations and use in clinical research.
2. Develop a novel parametric approach to estimate the time-dependent ROC curve allowing for varying distributions of event-times and small sample sizes.
3. Develop a data-efficient novel methodology of time-dependent ROC curve to account for the measurement error of clinical biomarkers.
4. Illustrate the existing time-dependent ROC curve methodologies and novel approaches developed in this thesis in a real clinical application.

The rest of this chapter is organised in the following sections. The background information on the standard ROC curve analysis is discussed in Section 1.3. Time-dependent ROC curves include the disease outcome as an event-time, and they use the

longitudinally repeated biomarker measurements. Therefore, the introduction to event-time and longitudinal data and relevant analysis methods for the thesis are provided in Section 1.4 and Section 1.5 respectively. The possible measurement error of a biomarker is discussed in Section 1.6. Section 1.7 describes the details of a dataset from the Mayo Clinic trial in primary biliary cirrhosis (PBC) of the liver, which is used to illustrate methodologies discussed and developed in the thesis. The organisation of the rest of the thesis is presented in Section 1.8.

1.3 Background on ROC curve analysis

1.3.1 Diagnostic test

A diagnostic test is used to classify individuals as diseased or not diseased. For a test that produces a binary result (e.g. presence or absence of a specific methylated DNA sequence in serum [10]), the classification rule is simple; the test is positive if disease present and it is negative if disease absent. However, for a continuous test, the classification rule is based on a predefined threshold value [10]. The threshold value is needed to be defined before classifying an individual as diseased or non-diseased. Once the continuous diagnostic test results are dichotomised on the threshold value to define a positive or negative test, the test result is binary. Thus, individuals can be classified accordingly.

Four possible classification probabilities can be calculated from a diagnostic test. These quantities can be best described using a two-by-two table of test results and true disease status as presented in Table 1.1. It illustrates the cross-classification between the true disease status and the diagnostic test result including the true and false probabilities.

Table 1.1: Classification of test results by disease status

Test Result	**True disease status**	
	Diseased	**Not Diseased**
Positive	True Positives (TP)	False Positives (FP)
Negative	False Negatives (FN)	True Negatives (TN)

A true positive (TP) result occurs when a diseased individual is correctly classified with a positive test while a true negative (TN) result occurs when a healthy or non-diseased individual is correctly classified with a negative test. A false positive (FP) result occurs when a healthy individual is incorrectly classified with a positive test while a false negative (FN) result occurs when a diseased individual is incorrectly classified with a negative test.

A test can have two true probabilities. The True Positive Rate (TPR) is the probability of an individual with TP among all diseased individuals (TP + FN), i.e. $^{TP}/_{(TP+FN)}$ and it is also called *sensitivity*. While the True Negative Rate (TNR) is the probability of an individual with TN among all the healthy individuals (FP + TN), i.e. $^{TN}/_{(FP+TN)}$ and it is called *specificity*.

A test can also have two false probabilities, False Positive Rate (FPR) and False Negative Rate (FNR). FPR is the probability of an individual with FP among all non-diseased individuals (FP + TN), i.e. $^{FP}/_{(FP+TN)}$ and FNR is the probability of an individual with FN among all the diseased individuals (TP + FN), i.e. $^{FN}/_{(TP+FN)}$.

1.3.2 Selecting a threshold

A threshold is a specific value of a continuous biomarker used to indicate the presence or absence of disease. Practically, a threshold value is decided based on the disease's severity and the availability of healthcare resources [10]. A lower threshold value can be assumed for a disease with a higher level of severity, and if healthcare resources are limited, it is important to have more sensitive disease detection. This will subsequently allow individuals who need healthcare assistance to be prioritised.

Usually, a higher biomarker value is considered more indicative of the presence of disease. For example, higher prostate specific antigen (PSA) level indicates higher risk of prostate cancer. However, in some studies, it is the opposite; individuals with liver diseases, for example, tend to have lower albumin levels as a damaged liver that fails to produce albumin or a lower platelet count is linked to a higher risk of death [8, 14]. Among cystic fibrosis (CF) patients, lower levels on pulmonary function test values such as forced expiratory volume in one second (FEV1) predicts the progression to

death [15]. Thus, the background of the disease area and complete understanding of related biomarkers are needed before a threshold value can be decided. A set of the possible threshold values is more efficient than just a single value so the variability of the true positive and true negative rates can be observed across different threshold values.

1.3.3 Standard ROC curve

The ROC curve is used to investigate the performance of a biomarker. It plots sensitivity (TPR) as the y-axis and one minus specificity (FPR) as the x-axis, as presented in Figure 1.1, for all possible threshold values. Plotting TPR versus FPR produces a curve that essentially describes the relationship between the biomarker's performance (correctly or falsely classifying individuals) with the individuals' true disease status.

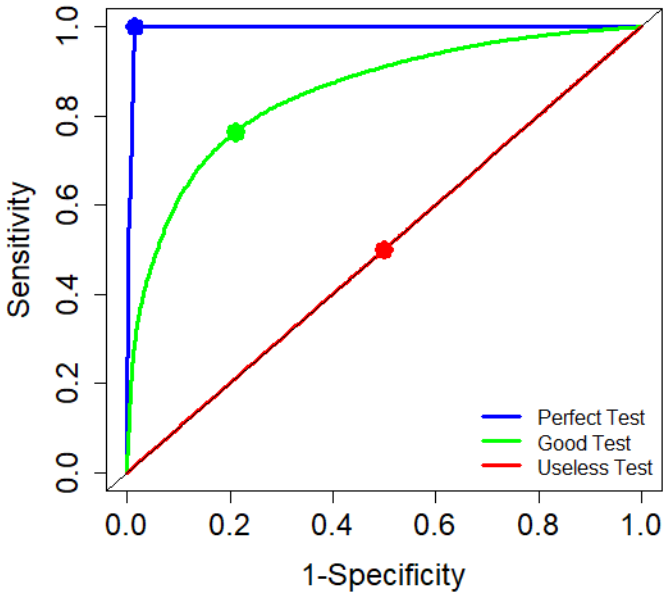

Figure 1.1: ROC curves

The area under the ROC curve (usually abbreviated as AUC) is used as the summary index for a biomarker's performance. AUC estimates the probability of a diseased individual has a higher biomarker value compared to a healthy individual, and it takes a value between 0.5 to 1, with a higher value reflecting a better biomarker performance. A perfect biomarker will have the highest TPR and lowest FPR that the ROC curve

passing through the upper quadrant point (0, 1) (blue line with the solid point indicates the respective optimal threshold in Figure 1.1). A perfect test is able to discriminate between the healthy and diseased with sensitivity = 1 (or 100%) and specificity = 1. If the biomarker is useless (or worthless), then TPR=FPR for all possible thresholds, hence the ROC curve falls on the diagonal line, leading to AUC = 0.5 (red line with the solid point indicates the respective optimal threshold in Figure 1.1). In this case, the test results for the healthy and diseased overlap completely, and they include the point of sensitivity = 0.5 (or 50%) and specificity = 0.5. A good biomarker steepens the gradient in the (0, 1) quadrant, widening the area under the ROC curve and making the AUC approach 1 (the green line with the solid point indicates the respective optimal threshold in Figure 1.1). There is no cut off for AUC value in order to classify the goodness of the biomarker. If the ROC curve close to the diagonal line (AUC approaches 0.5), the biomarker is not good in classifying the cases and controls, while when the ROC curve further from the diagonal line (AUC approaches 1) the biomarker is assumed as good. The point where the highest TPR and lowest FPR are located on the ROC curve describes the optimal threshold value where the biomarker powerfully discriminates between individuals with disease from individuals without disease.

1.4 Event-time data and analysis methods

Event-time is a set of times recorded when individuals have an event. It is called survival time when the event is death and failure time when it is used to describe the progression or development of disease [11]. In the standard ROC curve analysis, the disease is represented by a binary outcome. However, in the time-dependent ROC analysis, the disease is represented by an event-time outcome.

To investigate the relationship between the event-time and the occurrence of the event across individuals, the starting time has to be similar for all individuals; it may be the time when the disease is diagnosed or the starting point of a treatment. From this starting time until the end of the study, the individuals are observed (also called followed-up). The time when an event occurs, loss occurs during the follow-up or the withdrawal from the study will be recorded. When the individuals are lost within the period of a follow-up or have withdrawn from the study, the exact event-time is unknown, and only the lost of follow-up or withdrawal time is recorded. Also if the

study ends before the event has occurred, this latest time is recorded. This is called right censoring. Only right censoring is assumed throughout the thesis.

Event-time data can be analysed using parametric, semiparametric or nonparametric modelling approaches. Parametric modelling is when the event-times are assumed to follow a parametric family distribution such as Weibull, exponential, log-logistic, lognormal or generalised gamma [11]. The most widely used approaches to analyse event-time data are the Cox proportional hazard models and Kaplan Meier estimation of the survival functions.

Following the standard notation, we use T_i to denote the observed event-time where $T_i = \min(T_i^*, C_i)$, and T_i^* is the true event-time and C_i is a potential right censoring time. The event indicator is denoted by δ_i and it takes the value of 1 when the event is observed ($T_i^* < C_i$) or 0 otherwise.

1.4.1 Cox proportional hazard model

The Cox proportional hazard model is a semiparametric modelling approach of the event-time data. The event-time distribution and baseline survival function are not specified; only the regression parameters are known. Thus, this approach is semiparametric. [11]. The Cox proportional hazard model can be defined by

$$\lambda_i(t, \boldsymbol{Z}) = \lambda_{0i}(\mathrm{t})\exp\left(\sum_{l=1}^{p} \beta_l Z_l\right)$$

where $\lambda(t, \boldsymbol{Z})$ is the hazard of an individual at time t and β_l are the corresponding regression coefficients of the baseline covariates Z_l. The term $\lambda_0(\mathrm{t})$ is the baseline hazard function and the final term is the exponential with the power of the linear predictor of the p regression covariates. The term, $\exp(\beta_l)$ is usually interpreted as the hazard ratio which refers to the relative risk of an event. For example, if the hazard ratio is 0.5, the relative risk of having the event in one group is half of the risk of having the event in the other group.

1.4.2 Kaplan-Meier estimation

Kaplan-Meier survival estimation is a nonparametric approach since it does not require any distributional assumptions.

The Kaplan-Meier estimate of the survival function can be defined by

$$\widehat{S}(t) = \prod_{j:T_{(j)} \leq t} \left(1 - \frac{d_j}{r_j}\right)$$

where $T_{(j)}$is the jth ordered event-time in the data, r_j is the number of individuals at risk of the event and d_j is the number of individuals with the event at that time. At each jth ordered event-time $T_{(j)}$, the set of individuals at risk is called the "risk set".

1.5 Longitudinal data and analysis methods

Longitudinal data comprises repeated measurements of biomarkers at a number of time points. Most current studies collect repeated biomarker values, but usually, only the baseline value is considered for the analysis. Despite adding complexity to the methods of analysing such data, the longitudinal biomarker measurements are preferable in the time-dependent setting since the information of an individual is updated over time. The biomarker value that is nearest to the disease onset is assumed to have the most predictive power about the onset of the disease compared to the baseline value [16]. In this thesis, two models will be considered with the longitudinally recorded biomarker data; the linear mixed effect (LME) model and the joint model. While the LME model considers longitudinal biomarker measurements only, the joint model simultaneously links the longitudinal biomarker measurements and event-times.

1.5.1 Linear mixed effect model

As the linear regression model is commonly used for single time-point data, the linear mixed effect model is widely used for analysing longitudinal data. The main purpose of this modelling approach is to capture the unobserved individual heterogeneity. It models the repeated measurements of the biomarker through a specification in the regression model [17]. The model consists of both fixed and random effects. Fixed

effects remain constant across individuals while random effects vary; so that the fixed effects estimate at the population-level and random effects estimate the individual-specific variability.

The random effects can be defined by random intercept only or by both random intercept and random slope. The random intercept only model can be defined by

$$X_{ij} = \beta_{00} + U_{0i} + \varepsilon_{ij},$$

where X_{ij} is the observed biomarker measurement for individual i at time j and β_{00} is the fixed effect of the intercept estimating the population-level biomarker value at $t = 0$ (baseline), U_{0i} is the individual-specific random effect for the intercept and ε_{ij} is the measurement error. The measurement error ε_{ij} and random effects U_{0i} are assumed to be independent, and $\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$ and $U_{0i} \sim N\left(0, \sigma_{u_0}^2\right)$.

The random intercept and random slope model can be defined by

$$X_{ij} = \beta_{00} + \beta_{10} t_{ij} + U_{0i} + U_{1i} t_{ij} + \varepsilon_{ij},$$

with β_{00} is the fixed effect for the intercept, $\beta_{10}$is the fixed effect for the slope of time that estimates the rate of change at the population-level, U_{0i} is the individual-specific random intercept, U_{1i} is the individual-specific random slope of time and ε_{ij} is the measurement error. The random effect components are distributed as bivariate normal distribution.

$$\begin{pmatrix} U_{0i} \\ U_{1i} \end{pmatrix} \sim N\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix} \begin{pmatrix} \sigma_{u_0}^2 & \sigma_{u_0,u_1} \\ \sigma_{u_0,u_1} & \sigma_{u_1}^2 \end{pmatrix}\right].$$

1.5.2 Joint model

A joint model is formulated by two submodels; a longitudinal data submodel and an event-time data submodel, and the two components are linked together through some random effects [18]. Longitudinal data is typically modelled by linear mixed effect models (see Section 1.5.1), while the event-time data are assumed to follow a Cox proportional hazards model (as introduced in Section 1.4.1) [18]. A typical joint model takes the form of

$$X_{ij} = \beta_{00} + \beta_{10} t_{ij} + U_{0i} + U_{1i} t_{ij} + \varepsilon_{ij},$$
$$\lambda_i\big(t, X_i(t)\big) = \lambda_{0i}(\mathrm{t}) \exp\big(W_{2i}(t)\big),$$
$$W_{2i}(t) = \gamma\, W_{1i}(t) \text{ where } W_{1i}(t) = U_{0i} + U_{1i} t.$$

The parameters for the longitudinal submodel are defined similar to those in Section 1.5.1. Typically, the individual-specific random effects are incorporated through $W_{1i}(t_{ij}) = U_{0i} + U_{1i} t_{ij}$. In this component, the measurement error process ε_{ij} is accounted for and it is assumed that $\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$. In the event-time submodel, $X_i(t)$ is the true unknown biomarker value at time t, $\lambda_{0i}(t)$ is an unspecified baseline hazard as defined in Section 1.4.1. This submodel links the true biomarker value at time t through the hazard of an event at time t for the ith individual. The event-time process is assumed to be associated with the longitudinal response through shared random effects $\{W_{1i}(t), W_{2i}(t)\}$. Typically, the joint model includes the proportional association $W_{2i}(t) = \gamma\, W_{1i}(t)$ and γ estimates the level of association between the event-time and longitudinal biomarker processes [19].

1.6 Measurement error

Measurement error is the error induced when measuring a clinical biomarker due to various sources, including contamination during sample collection or variable storage conditions [20]. The method of processing the samples and recording of the biomarker measurements must be standardised to minimise the measurement error. In randomised controlled trials, the protocols for the length of time and temperature for the samples are usually written in advance, and the quality is controlled. The maximum storage duration of the samples is also adhered to avoid variations between the batches of the samples. Thus, it is essential to take into account the measurement error in order to accurately estimate the predictive ability of a biomarker. Failing to adjust to such measurement error in a statistical model may weaken the explanatory power of the biomarker, and the failure to select important biomarkers can occur [12, 13].

1.7 Primary Biliary Cirrhosis (PBC) sequential data

The data comes from the Mayo Clinic trial in primary biliary cirrhosis (PBC) of the liver conducted between 1974 and 1984. PBC is a fatal, but rare liver disease. Patients often present abnormalities in their blood tests, such as elevated serum bilirubin. If PBC is not treated or reaches an advanced stage, it can lead to several major complications, including death.

A total of 424 PBC patients was referred to the Mayo Clinic during that ten-year interval, and met eligibility criteria for the randomised placebo-controlled trial of the drug D-penicillamine. The first 312 cases in the data set participated in the randomised trial and contained largely complete data. The additional 112 cases did not participate in the clinical trial but consented to have their basic measurements recorded and to be followed to measure their rate of survival. Six of those cases were lost during the follow-up period shortly after diagnosis, so the data here are based on the remaining 106 cases as well as the 312 randomised participants.

The results of the clinical trial of the 312 patients have been established that the D-penicillamine drug is not effective in PBC in spite of the immunosuppressive properties [21, 22]. Although the preliminary results were observed promising which showed better survival on treated group [23, 24], the treatment caused severe adverse reactions and even if the treatment was beneficial, the effect is almost certainly small [25]. Thus, the data from the trial has been used to develop a natural history model to understand the course of PBC in untreated patients and to provide historical control information for evaluation of efficacy of new therapeutic interventions.

The data were used to develop a Cox proportional hazards model providing the historical control information to evaluate the performance of a new intervention by Fleming and Harrington [21]. Among many biomarkers, bilirubin was the strongest univariate predictor of survival. When building the model, some biomarkers were log transformed to create a more significant impact on the prognosis when the values are small [21], including albumin, bilirubin and prothrombin time. The final model consists of age, edema, log (bilirubin), log (prothrombin time) and log (albumin). These variables were found biologically reasonable, and albumin provided an exchangeable use as the original measurement or the log-transformed measurement in

biomedical studies. In this thesis, following Heagerty and Zheng [27], the original albumin measurements are used. In Chapters 3 and 4, a model score derived from five covariates (age, edema, log (bilirubin), log (prothrombin time) and albumin) [27] is considered, and in Chapter 5, longitudinal measurements of individual biomarkers transformed as log (bilirubin), $(0.1 \times \text{prothrombin time})^{-4}$ and albumin (in original scale) [28] are used to illustrate the proposed methodologies.

The data are available to be freely downloaded at http://lib.stat.cmu.edu/datasets/pbcseq and have been described in Fleming and Harrington [21] and Murtaugh, et al. [26]. Table 1.2 shows the variables for the full dataset.

Table 1.2: Variables in the PBC data

Variables	**Description**
id	Case number
age	Age in years
sex	0 for male and 1 for female
trt	Treatment code; 1 for D-penicillamine, 2 for placebo and NA for not randomised
time	Number of days between registration and the earlier of death, transplantation, or study analysis in July, 1986
status	Status at endpoint; 0 for censored, 1 for transplant and dead
day	Number of days between enrolment and visit date
albumin	Serum albumin (mg/dl)
alk.phos	Alkaline phosphatase (U/litre)
ascites	Presence of ascites, 0 for no, 1 for yes
ast	Aspartate aminotransferase, once called SGOT (U/ml)
bilirubin	Serum bilirubin (mg/dl)
chol	Serum cholesterol (mg/dl)
copper	Urine copper (ug/day)

edema	Presence of edema, 0 for no edema and no diuretic therapy for edema, 0.5 for edema present without diuretic, or resolved by diuretics and 1 = edema despite diuretic therapy
hepato	Presence of hepatomegaly or enlarged liver, 0 for no and 1 for yes
platelet	Platelet count per cubic ml / 1000
prothrombin time	Standardised blood clotting time (seconds)
spiders	Blood vessel malformations in the skin, 0 for no and 1 for yes
stage	Histologic stage of disease (needs biopsy)
trig	Triglycerides (mg/dl)

1.8 Thesis layout

Chapter 2 is aimed at explaining the foundation of this thesis in detail by discussing the three key definitions of the time-dependent ROC curve analysis. Chapter 3 aims at providing a comprehensive review of the current time-dependent ROC curve approaches. The findings of this review motivate the proposed methodological developments of this thesis. In this chapter, the methods that can be used with the three time-dependent ROC curve definitions are described. The performance of several current methodologies and simple extensions to use longitudinally collected biomarker measurements are illustrated using a widely used prognostic score based on PBC data.

Chapter 4 is aimed at developing a parametric time-dependent ROC curve. Assuming a range of combinations of parametric distributions for the event-time and biomarker including exponential, Weibull and normal distributions, the closed form formulae of cumulative sensitivity, dynamic specificity and the corresponding AUC are derived from the joint distribution of event-time and biomarker whenever possible. Numerical approximations are considered when the closed form estimators are not available. Application to the PBC data is used to illustrate the proposed parametric approach.

In Chapter 6, a novel data-efficient method is proposed within the joint modelling framework to adjust for measurement errors when estimating the time-dependent ROC curve for a continuous biomarker. The methodological review undertaken in Chapter 3 reveals that the current approaches directly use the observed value of the clinical biomarkers in estimating the time-dependent ROC curve or AUC, ignoring the measurement error. Therefore, this chapter develops a methodology that takes into account the measurement error when evaluating the time-dependent performance of a clinical biomarker. The proposed methodology is illustrated using several sequential clinical biomarkers from the Mayo Clinic PBC study.

Chapter 5 and Chapter 7 intend to undertake the simulation studies to evaluate the proposed methodologies in Chapter 4 (parametric approach) and Chapter 5 (measurement error adjusted approach) respectively.

Chapter 8 critically appraises all the findings, discusses the limitations, and suggests avenues for future research.

2 Time-dependent ROC curve analysis

2.1 Introduction

This chapter is aimed to construct the foundation of the thesis. In the standard ROC curve analysis, as discussed in Chapter 1, the individual's disease status is assumed to be fixed for the whole study period. However, the study period usually involves a long follow-up, and during the follow-up, an individual who may not have a disease earlier may develop the disease during the follow-up period. In contrast to the standard ROC curve analysis, the disease status of an individual is observed and updated at each time point in the time-dependent ROC curve analysis. With additional information of the time of disease onset for each individual, the ROC curve can be constructed at several time points, and the predictive ability of the biomarker can be compared. Thus, the time-dependent ROC curve is an efficient tool for measuring the performance of a candidate's biomarker given the true disease status of the individuals at certain time points. In general, the biomarker value at the baseline ($t = 0$) is used for computing the predictive ability at a pre-specified time $t > 0$, but the predictive ability can become weaker as t gets further from the baseline. In longitudinal studies, the biomarker is measured at several time points within a fixed follow-up. If a biomarker measurement has the ability to signify a pending change in the disease status of a patient, then a time-dependent ROC curve on a time-varying biomarker can be used to efficiently guide key medical decisions.

In a time-dependent ROC curve analysis, the sensitivity and specificity are defined at a pre-specified time point t. Each individual is given a different weight that contributes to the definition of sensitivity and specificity at different time points as a case or as a control. This contribution of cases and controls depends on the aim of classification, whether the researcher desires to discriminate between the diseased individuals at or up to time t and healthy individuals beyond that time or within a fixed follow-up time. This has been the basis for developing three definitions of time-dependent ROC curve, namely cumulative/dynamic (abbreviated as C/D), incident/dynamic (I/D) and incident/static (I/S) [27].

The organisation of Chapter 2 is as follows. In Section 2.2, the general notation for the time-dependent ROC curve is defined. In Sections 2.3-2.5, the definitions of the three time-dependent ROC curves are discussed.

2.2 General notation for time-dependent ROC curve

As defined in Chapter 1, let T_i denote the true time of the event and X_i denote the biomarker value (usually the value at the baseline) for individual i, $i = 1, \dots, n$.

For a given time point t (called "target time"), each individual i is classified as a case or control. Let $D_i(t)$ be the disease status for individual i at time t, taking values 1 if it is a case or 0 if it is a control.

Let t^* be a fixed follow-up time, and it depends on the definition of time-dependency.

For a given threshold value c, the time-dependent sensitivity and specificity can be defined respectively by $Se(c,t)$ and $Sp(c,t)$ such that

$$Se(c,t) = P(X_i > c | D_i(t) = 1); Sp(c,t) = P(X_i \leq c | D_i(t) = 0).$$

Then, the corresponding time-dependent ROC curve at time t, $ROC(t)$ plots $Se(c,t)$ against $1 - Sp(c,t)$ for all possible thresholds $c \in (-\infty, +\infty)$. The area under the $ROC(t)$ leads to a time-dependent AUC, which can be defined by

$$AUC(t) = \int_{-\infty}^{\infty} Se(c,t) d[1 - Sp(c,t)],$$

where $[1 - Sp(c,t)] = \frac{\partial[1-Sp(c,t)]}{\partial c} dc$. The AUC computes the probability that the diagnostic test results from a randomly selected pair of one diseased and one non-diseased individuals are correctly ordered with the diseased individual having an earlier event-time and a higher biomarker value than the non-diseased individual [29, 30].

2.3 Cumulative sensitivity and dynamic specificity (C/D)

The time-dependency of the C/D definition can be represented by Figure 2.1, with closed circles indicating individuals who had an event, open circles indicate individuals who had censored event-times. Under this definition, a case is defined by an individual experiencing the event between the baseline (when $t = 0$) and time t (individuals A, B or E in Figure 2.1) and a control by an individual remaining event-free at time t (individuals C, D or F in Figure 2.1). The cases and controls change over time, and each individual may play the role of control at the earlier time (when their event time is greater than the target time, i.e. $T_i > t$) but then contributes as a case at a later times (when the event time is less than or equal to the target time, i.e. $T_i \leq t$).

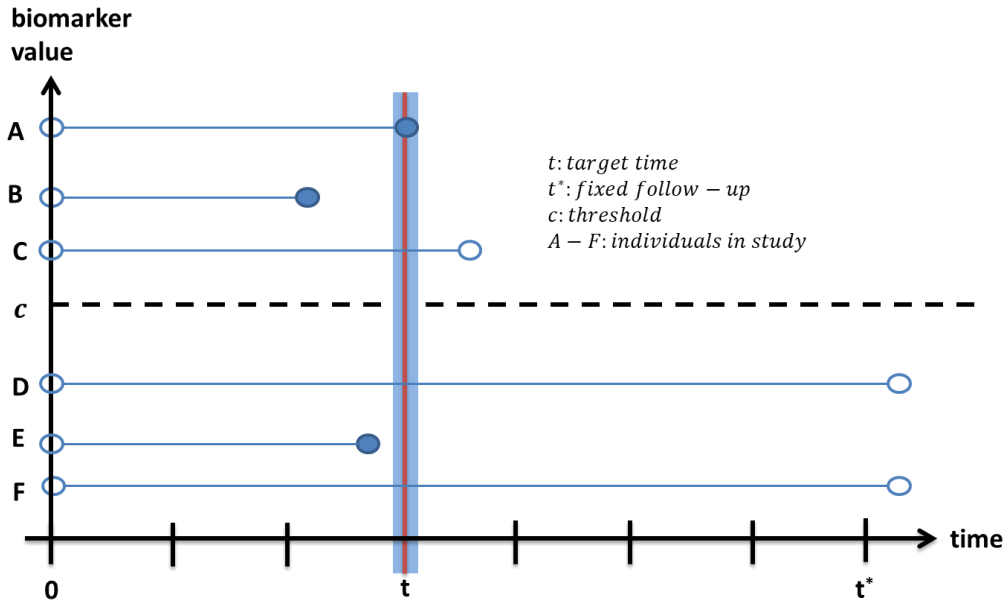

Figure 2.1: Illustration of time-dependency for C/D , I/D and I/S (baseline) definitions

Under the C/D definition, the *cumulative* sensitivity is defined by the probability that an individual has a biomarker value greater than the threshold c among the individuals who experienced the event **before time t** (individuals A or B in Figure 2.1). The *dynamic* specificity is the probability that an individual has a biomarker value less than or equal to c among those event-free individuals **beyond time t** (individuals D or F in Figure 2.1). The term "cumulative" is used because all the diseased individuals from

the baseline up to the target time t are considered in the defining cases, while the term "dynamic" describes the controls that had changed based on t.

Thus, sensitivity and specificity at time t and the resulting AUC(t) can be defined respectively as

$$Se^C(c,t) = P(X_i > c|T_i \leq t), \quad (2.1)$$

$$Sp^D(c,t) = P(X_i \leq c|T_i > t), \quad (2.2)$$

$$AUC^{C,D}(t) = P(X_i > X_j|T_i \leq t, T_j > t), i \neq j. \quad (2.3)$$

It is more appropriate to apply the C/D definition when there is a specific time of interest that is used to discriminate between the individuals experiencing the event and those who are event-free prior to the specific time. This type of discrimination has more clinical relevance than the other two definitions of time dependency (Sections 2.4 and 2.5 below), and hence the C/D definition is commonly used by clinical applications [14, 31]. However, since some individuals may contribute as controls at an earlier time and then contribute as cases later, this definition uses the redundant information in separating the cases from the controls [14].

2.4 Incident sensitivity and dynamic specificity (I/D)

The time-dependency of the I/D definition can also be illustrated in Figure 2.1. Under the I/D definition, a case is defined as an individual with an event at time t (individual A in Figure 2.1) while a control is an event-free individual at time t (individuals C, D or F in Figure 2.1). In this definition, there are individuals who are neither a control nor a case (when the event time is less than the target time, i.e. $T_i < t$, individual B or E in Figure 2.1). Each individual who had an event may have played the role of a control at an earlier time (when the event time is greater than target time, i.e. $T_i > t$) but then contributes as a case at the later incident time (when the event time is the same as the target time, i.e. $T_i = t$).

The term *incident* sensitivity is the probability that an individual has a biomarker value greater than c among the individuals who experience the event **at time t** (individual A in Figure 2.1) and the *dynamic* specificity is the probability that an individual has a

biomarker value less than or equal to c among the individuals that remain event-free **at time t** (individual D or F in Figure 2.1). The term "incident" is used because only diseased individuals at target time t are considered in defining the cases. As in the C/D definition, the term "dynamic" describes the situation of as the t changes, the controls also change.

The sensitivity, specificity and resulting AUC(t) are respectively defined as

$$Se^I(c,t) = P(X_i > c|T_i = t), \tag{2.4}$$

$$Sp^D(c,t) = P(X_i \leq c|T_i > t), \tag{2.5}$$

$$AUC^{I,D}(t) = P(X_i > X_j|T_i = t, T_j > t), i \neq j. \tag{2.6}$$

The I/D definition is more appropriate when the exact target time t is known, and when the researcher wants to discriminate between the individuals experiencing the event and those event-free at a $t = T_i$. For example, Heagerty and Zheng [27] investigated how well a model-based score discriminates between lung cancer patients who are likely to die at pre-specified t = 30, 60, 90 and 120 days within the study's follow-up period and those who survived beyond these times.

The *incident* sensitivity and *dynamic* specificity are defined by dichotomising the risk set at time t into cases and controls (see definition in Section 1.4.2), and this is a natural companion to hazard models such as the Cox proportional hazard model (see Chapter 1 Section 1.4.1) [27]. In addition, the definitions above allow an extension to the time-dependent covariates and time-averaged summaries that are directly related to a familiar concordance measure C-statistic [27]. This is a special advantage of the I/D definition, since in many clinical applications, no priori time t is identified or known, thus a global or concordance accuracy summary is usually desired. The concordance summary is a weighted average of the area under the time-dependent ROC curve, and it can be defined by

$$C^\tau = \int_0^\tau AUC^{I,D}(t) w^\tau(t) dt$$

where $w^{\tau}(t) = 2f(t)S(t)/W^{\tau}$, $W^{\tau} = \int_0^{\tau} 2f(t)S(t)dt = 1 - S^2(\tau)$. W^{τ} are the weights at time t for a fixed follow-up τ, $f(t)$ is the density function of the event time and $S(t)$ is the survival function of the event time. The C^{τ} has a slightly different interpretation from the usual c-statistic and it is the probability that the individual who experienced the event at an earlier time has a higher biomarker value, given that the smaller event time occurs in $(0, \tau)$ Heagerty and Zheng [27].

2.5 Incident sensitivity and static specificity (I/S)

The time-dependency of the I/S definition can be illustrated in Figure 2.1 for a biomarker value at the baseline. Under the I/S definition, a case is defined as an individual with an event at time t (individual A in Figure 2.1), while a control is an event-free individual within a fixed follow-up period, $(0, t^*)$ (individuals D or F in Figure 2.1). The term "incident" is used based on the same reason as in the I/D definition where it considers individuals at the target time only to define cases. The term "static" describes a fix set of healthy individuals (controls) who do not change throughout the follow-up period. As illustrated in Figure 2.1, the controls are "static" and do not change (individuals D and F), and each individual only contributes once as a case or as an event-free individual within the fixed follow-up period $(0, t^*)$.

The *incident* sensitivity and *static* specificity is usually used when a researcher attempts to distinguish between individuals who have an event at time t and those who are 'long term survivors' who are event-free after a suitably long follow-up time, characterised by $T_i \geq t^*$. The rationale of using the fixed follow-up is because the end point t^* is pre-specified and it is considered a long enough time to observe the event. For example, $t^* = 2$ years is typically used in screening for breast cancer since it is assumed that the individual is free from subclinical disease if the clinical disease does not emerge by two years after screening [7].

The sensitivity and specificity can be defined respectively by

$$Se^I(c, t) = P(X_i > c | T_i = t), \tag{2.7}$$

$$Sp^S(c, t^*) = P(X_i \leq c | T_i > t^*), \tag{2.8}$$

$$AUC^{I,S}(t) = P(X_i > X_j | T_i = t, T_j > t^*). \quad (2.9)$$

The I/S definition can also be used in studies in which individuals are followed up for a fixed time period with longitudinally repeated biomarker measurements. However, not all longitudinally measured biomarker values of the individual will be used. Only a biomarker value at a particular visit time s is used instead of using the biomarker value at the baseline [7, 16]. Since some studies may not have a regular visit time schedule, the visit times may differ for each individual. Thus, the time lag between the visit time and the time of disease onset, i.e. $T_i - s$ which is commonly termed as the "time prior to event", is the main interest. The I/S definition with a longitudinally measured biomarker can be illustrated in Figure 2.2, assuming that a biomarker value is measured at the visit time s. The sensitivity and specificity are defined based on a time lag $t = T_i - s$.

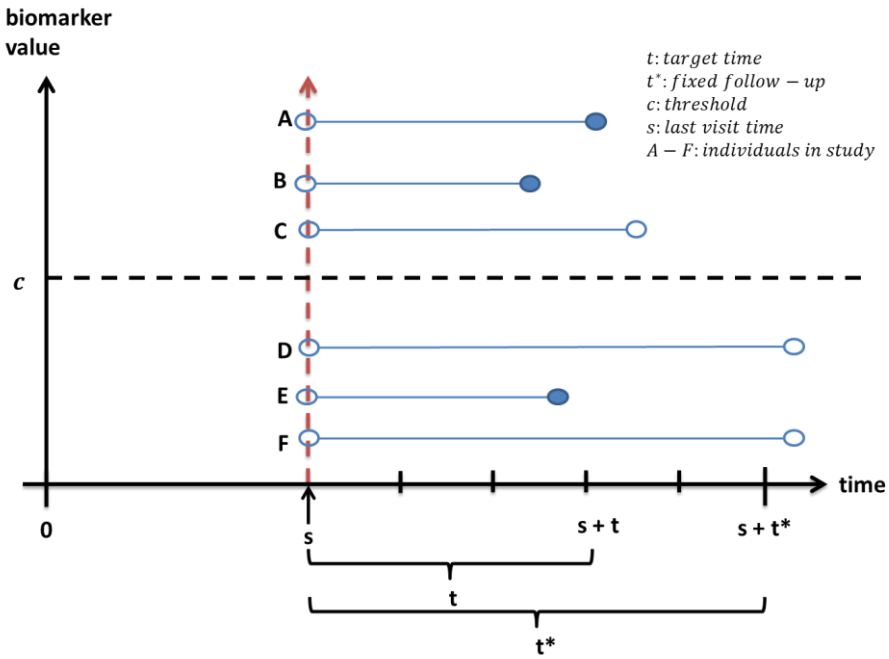

Figure 2.2: Illustration of time-dependency for I/S definition with a longitudinal biomarker.

In this case, the *incident* sensitivity is the probability of an individual with the biomarker value greater than c among individuals having an event at t time units after

the biomarker is measured at the last visit time s (individual A in Figure 2.2). The *static* specificity is the probability that an individual remains event free by t^* time units after the biomarker is measured (individual D or F in Figure 2.2).

If X_i is the biomarker value obtained from individual i at s, then the sensitivity and specificity are defined by

$$Se^I(c,t) = P(X_i > c | T_i - s = t) \tag{2.10}$$

$$Sp^S(c,t^*) = P(X_i \leq c | T_i - s > t^*) \tag{2.11}$$

The above definitions facilitate the use of standard regression approaches for characterising sensitivity and specificity because the time prior to the event $T_i - s$ can simply be used as a covariate [7].

2.6 Discussion

In this chapter, the foundation of the time-dependent ROC curves was presented along with the three key definitions. The generic challenge for a time-dependent ROC curve is the censoring of event-times, as some individuals may be lost during the follow-up period. If the censored individuals are ignored, and the analysis is based on the complete cases only, the estimation of the sensitivity and specificity may be biased, as the information from the individuals prior to the censoring has been ignored, but it had otherwise contributed to the estimation. The three definitions introduced in this chapter take the censoring in event-times into consideration when calculating the ROC curve. Furthermore, consideration of the censored event-times offers more relevant estimates because the censoring of event-times is inevitable in real practice.

A longitudinally repeated biomarker brings an additional challenge to the time-dependent ROC curve when the biomarker measurements at a number of visits are available for each individual. In the I/S definition, not all the biomarker values are used but only the most recent, which is assumed to be more reliable for predicting the disease status [16]. However, many time-dependent ROC curve approaches currently

proposed for a longitudinal biomarker either assume the non-censored event-times or ignore the censored individuals' records [31, 32].

The current time-dependent ROC curve approaches will be discussed in further detail in Chapter 3.

3 Review of current time-dependent ROC curve approaches and applications in medicine

3.1 Introduction

Although the three time-dependent ROC curve definitions (see Chapter 2) were introduced over a decade ago by Heagerty and Zheng [27], and the superiority of a time-dependent analysis over the standard ROC curve was evaluated in subsequent publications [2, 32], these methods are currently underused in clinical research. At the time of writing up this thesis, only one review on time-dependent ROC curve methodologies was available, which was conducted by Blanche, P., et al. [31]. However, their review was restricted to the C/D definition.

The main objective of this chapter is to comprehensively review all currently available ROC curve analysis methodologies under each definition of time dependency. It is aimed to critically evaluate the pros and cons of each methodology, identify software that implements the methods, demonstrate their use in clinical research, and highlight any necessity for the development of further methodologies.

This chapter also extends two current methods to allow for longitudinal measurements of the biomarker. The implementation of each method incorporates a time-varying disease status or a time course (longitudinal record) of a biomarker and is illustrated using the sequential Mayo Clinic PBC data which was introduced in Chapter 1, Section 1.7. The findings of this comprehensive review as at 2016 are published in Kamarudin, et al. [33].

The rest of the chapter is organised as below: The methods used to conduct the review are discussed in Section 3.2. Section 3.3 provides the details of current methodologies, software and proposed extensions. In Section 3.4, results from the review on clinical application are discussed. Some of the methods and proposed extensions are illustrated using the PBC data in Section 3.5, followed by the discussion in Section 3.6.

3.2 Review Methods

The searches for relevant papers for the review have been conducted through MEDLINE (Ovid), Scopus and the internet. The published papers were restricted to English language between years 1995 to August 2016 to ensure all the methodology and clinical application papers of time-dependent ROC curves analysis were included. The common terms and keywords including ROC, AUC, time-dependent, time-specific and accuracy have been used in the search. The number of papers identified for each search is reported in Table 3.1 below after removing duplicates.

At the time of writing up this thesis, a further search has been conducted through MEDLINE (Ovid) and internet/references only (due to time limitation) restricting the publications between August 2016 to August 2018. The same keywords are used. Table 3.1 shows the findings from the updated searches which resulted in an additional 109 papers, of which 9 are methodological and 100 are clinical applications. Only 100 applications from the updated review are discussed in this thesis together with the current review.

Table 3.1: Number of articles from the searches

Search	**Keyword**	**Limitation**	**Current review (Jan 1995 – Aug 2016)**	**Updated review (Aug 2016 – Aug 2018)**
MEDLINE (Ovid)				
1	ROC and Time-dependent	Abstract	108	81
2	ROC and Time-dependent	Title	0	2
3	ROC and Time-specific	Abstract	2	0
4	AUC and Time-dependent	Abstract	208	18
5	AUC and Time-dependent	Title	2	5
6	Accuracy and Time-dependent	Title	4	2
Scopus			8	-
Internet & References			9	1
Total number of articles			**341**	**109**

The title and abstract of each paper are reviewed to decide whether it is related to the methodology of time-dependent ROC curve or only a clinical application. Eight papers were found from the Scopus search using the same keywords. The search through the internet (Google) using the same keywords resulted in five additional papers and four further papers were found after checking the list of references in each paper. A total of 341 papers were found and 33 of these published papers discussed time-dependent ROC curve methodologies. The remaining 308 papers included only an application of the standard or time-dependent ROC curves. If there were any ambiguities or confusion whether to include the studies or the extracted data, my PhD supervisors were consulted. There were 17 papers which were excluded beyond the scope of this review because they did not propose the estimation method of time-dependent ROC curve but focused on different perspective under the time-dependent ROC curve context. For each methodology paper (n=16), the following details were extracted: the definition of sensitivity and specificity (whether C/D, I/D, I/S or other), estimation method, type of estimation (non-parametric, semi-parametric or parametric), limitations and availability of software. Out of the 16 methodology papers, 10 (63%) discussed methodologies along the lines of the C/D definition. Three papers (19%) proposed methodologies based on the I/D definition, and only one paper (6%) proposed methodology along the I/S definition. Two further papers (12%) proposed other methodologies for longitudinal biomarker measurements. The details of the review process are described in Figure 3.3.

3.3 Results from the methodological review

Table 3.2 summarises the estimation methods for each definition with their respective advantages and disadvantages as well as their software tools. The methodologies proposed under each definition are discussed in detail in the subsequent sub-sections.

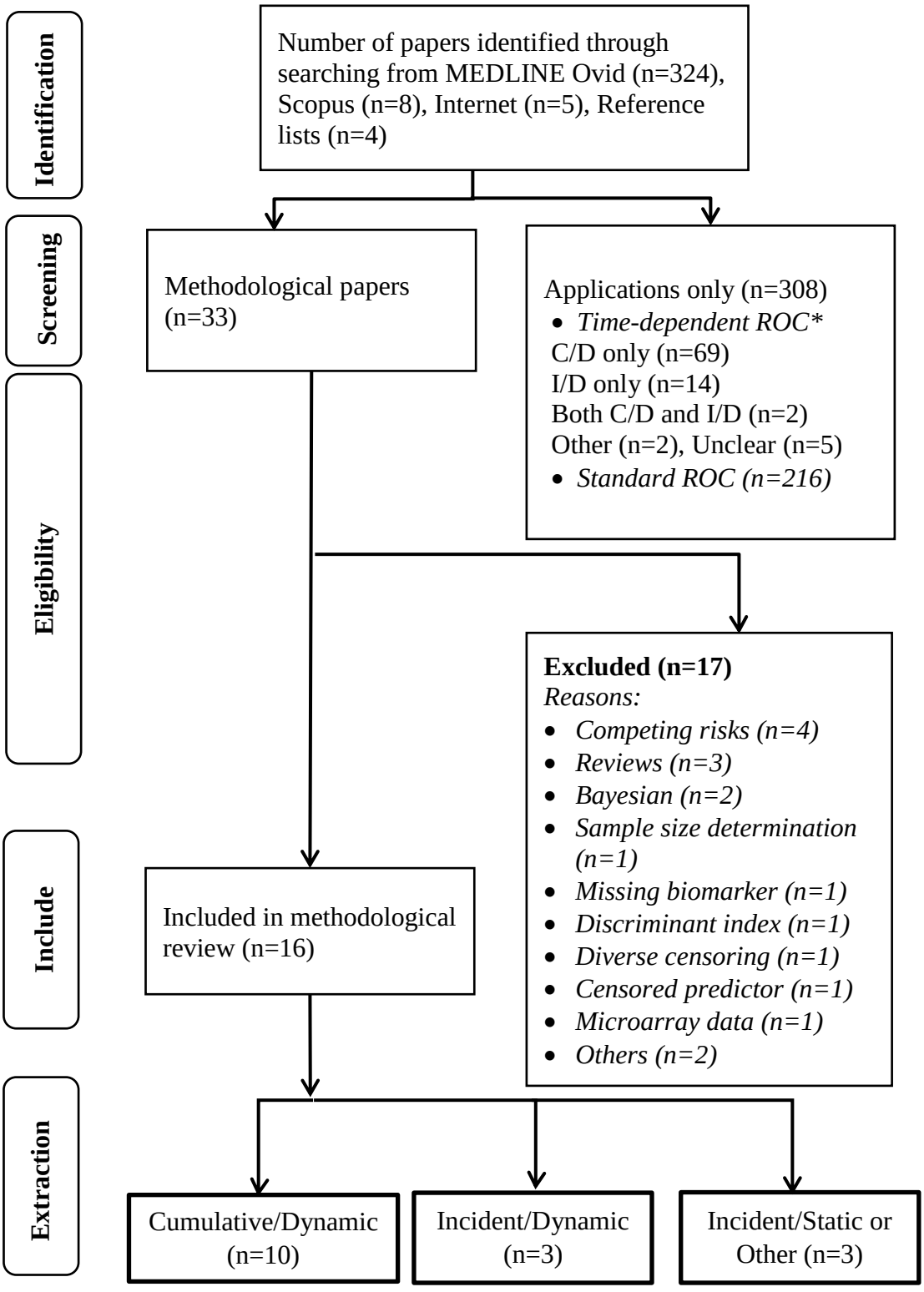

Figure 3.1: CONSORT diagram
** reviewed separately (Other and Unclear: n=7 excluded)*

Table 3.2: Summary of current methods f or each definition

Definition and biomarker time	Sensitivity	Specificity	Estimation method and R software (when available)	Pros / Cons
C/D $t = 0$	$Se^C(c,t)$ $= P(X_i > c \mid T_i \leq t)$	$Sp^D(c,t)$ $= P(X_i \leq c \mid T_i > t)$	CD1 survivalROC CD2 survivalROC CD3 Programme code CD4 survAUC CD5 timeROC CD6 timeROC CD8, VL Cox survival VL Aalen timereg VL KM prodlim	**Pro**: Clinically relevant since many clinical experiments aim to discriminate individuals with disease prior to the specific time and healthy individual beyond that time **Con**: Use redundant information in separating cases and controls

C/D A longitudinal time point	$Se^C(c,t)$ $= P(Y_{ik} > c \mid T_i - s_{ik} \leq t)$	$Sp^D(c,t^*)$ $= P(Y_{ik} \leq c \mid T_i - s_{ik} > t)$	AD4	**Pro**: Use the most recent biomarker value prior to prediction time **Con**: Just use a biomarker value at a particular time instead of using all the serial of biomarker values
I/D $t = 0$	$Se^I(c,t)$ $= P(X_i > c \mid T_i = t)$	$Sp^D(c,t)$ $= P(X_i \leq c \mid T_i > t)$	ID1 risksetROC ID2 ID3 Programme code	**Pro**: Allow time-averaged summaries that are directly related to familiar concordance measures such as Kendall's tau or c-index **Con**: Require an exact time of interest which is often just a few individuals having an event at a particular point
I/S $t = 0$	$Se^I(c,t)$ $= P(Y_i > c \mid T_i = t)$	$Sp^S(c,t^*)$ $= P(Y_i \leq c \mid T_i > t^*)$	IS1	**Pro**: Allow separation of long-term survivors from a healthy individual within a fixed follow-up **Con**: Require an exact time of interest with often just a few individuals having an event at a particular point
I/S A longitudinal time point	$Se^I(c,t)$ $= P(Y_{ik} > c \mid T_i - s_{ik} = t)$	$Sp^S(c,t^*)$ $= P(Y_{ik} \leq c \mid T_i - s_{ik} > t^*)$	IS2	**Pro**: Use the most recent biomarker value prior to prediction time **Con**: Just use the most recent of biomarker value instead of all biomarker values

Other All longitudinal time points	$ROC(t,p) = S[a_0(T_{ik}) + a_1(T_{ik})S^{-1}(p)]$	AD1 Programme code	**Pro**: Use all biomarker values throughout the visit times in the estimation of ROC curve **Con**: Do not incorporate censored outcomes

3.3.1 Naïve estimator of time-dependent ROC curve analysis

Many studies have used an empirical estimator as a basis for comparison with other estimation methods. This estimator only considers observed events and, the sensitivity and specificity are calculated by the observed proportions of true-positives and true-negatives respectively.

If a dataset does not have any censored events (that is, if all individuals have either experienced the event or remained event-free over the study follow-up and not left the study), the sensitivity at time t is estimated as the proportion of the individuals with a biomarker value greater than threshold c, (i.e. $X_i > c$) among individuals who experienced the event before t. The specificity at time t is given by the proportion of the individuals with biomarker value that is less than or equal to c, (i. e. $X_i \leq c$) among event-free individuals beyond time t. When there are censored event-times, the above estimators are computed by removing all the censored individuals before the time point t. The sensitivity and specificity and the resulting AUC(t) can be estimated as follows

$$\widehat{Se}(c,t) = \frac{\sum_{i=1}^{n} \delta_i I\,(X_i > c, T_i \leq t)}{\sum_{i=1}^{n} \delta_i I(T_i \leq t)}$$

$$\widehat{Sp}(c,t) = \frac{\sum_{i=1}^{n} I\,(X_i \leq c, T_i > t)}{\sum_{i=1}^{n} I(T_i > t)}$$

$$\widehat{AUC}(t) = \frac{\sum_{i=1}^{n}\sum_{j=1}^{n} \delta_i I\left(T_i \leq t, T_j > t\right) I(X_i > X_j)}{\sum_{i=1}^{n} \delta_i I\,(T_i \leq t)\sum_{j=1}^{n} I(T_j > t)}$$

where *i* and *j* are the indexes of two independent individuals, and $I(.)$ is an indicator function. However, this estimation is often biased as it ignores the censoring distribution. The specificity estimate is consistent if censoring is independent of X_i and T_i, while the sensitivity and AUC estimates may be biased since T_i will usually depend on X_i [31].

3.3.2 Cumulative sensitivity and dynamic specificity (C/D)

Ten estimation methods have been proposed under C/D definition, and these are discussed in CD1 – CD8 below. CD8 describes three estimation methods.

3.3.2.1 (CD1) Kaplan-Meier estimator of Heagerty, et al. [2]

Heagerty, et al. [2] used the Kaplan-Meier estimator of the survival function [34] to estimate the time-dependent sensitivity and specificity. Using Bayes' Theorem, the two quantities are defined by

$$\widehat{Se}(c,t) = \frac{\{1-\hat{S}(t|X_i > c)\}\left(1-\hat{F}_X(c)\right)}{1-\hat{S}(t)}, \widehat{Sp}(c,t) = \frac{\hat{S}(t|X_i \leq c)\hat{F}_X(c)}{\hat{S}(t)}$$

where $\hat{S}(t)$ is the estimated survival function, $\hat{S}(t|X_i > c)$ is the estimated conditional survival function for the subset defined by $X > c$ and $\hat{F}_X(c)$ is the empirical distribution function of the biomarker, X.

However, this estimator yields non-monotone sensitivity and specificity and is not bounded in [0, 1]. This problem is illustrated by the authors using a hypothetical dataset and is due to the quadrant probability estimator $\hat{P}(X_i > c, T_i > t) = \hat{S}(t|X_i > c)\left(1-\hat{F}_X(c)\right)$, not necessarily producing a valid bivariate distribution as the redistribution to the right of the probability mass is associated with censored observations that will change as the conditioning set $(X > c)$ changes. Another problem is that it is not robust to biomarker-dependent censoring since the conditional Kaplan-Meier estimator, $\hat{S}(t|X_i > c)$ assumes that the censoring process does not depend on the biomarker.

Biomarker- dependent censoring is usually occur in epidemiology study which is when individuals with lower biomarker values tend to be censored earlier. This problem frequently happens when a prognostic biomarker is available, and the frequency of follow-up is influenced by the biomarker value measured at baseline. For example, in

many AIDS studies, an individual's censoring status may be related to his or her CD4 cell count, a well-accepted marker for survival [35].

3.3.2.2 (CD2) Nearest neighbour estimator of Heagerty, et al. [2]

The problems of the CD1 estimators motivated Heagerty, et al. [2] to develop an alternative approach based on a bivariate survival function. This improved methodology uses the nearest neighbour estimator of the bivariate distribution of (X, T), introduced by Akritas [36]. As mentioned earlier, CD1 is not robust to biomarker-dependent censoring; however, censoring often depends on the biomarker. Thus, the independence of time-to-event and censoring time cannot be assumed and they are more likely independent conditionally on the biomarker. In this model-based approach, the probability of each individual is modelled for a case by $1 - S(t|X_i)$ and for a control by $S(t|X_i)$ [31]. Akritas [36] proposed using the following model-based estimator for the conditional survival probability called the weighted Kaplan-Meier estimator and it is defined by

$$\hat{S}_{\lambda_n}(t|X_i) = \prod_{a \in T_n, a \le t} \left\{ 1 - \frac{\sum_j K_{\lambda_n}(X_j, X_i) \boldsymbol{I}(T_j = a)\delta_j}{\sum_j K_{\lambda_n}(X_j, X_i) \boldsymbol{I}(T_j \ge a)} \right\}$$

where $K_{\lambda_n}(X_j, X_i)$ is a kernel function that depends on a smoothing parameter λ_n. Akritas [36] uses a 0/1 nearest neighbour kernel, $K_{\lambda_n}(X_j, X_i) = I(-\lambda_n < \hat{F}_X(X_i) - \hat{F}_X(X_j) < \lambda_n)$ where $2\lambda_n \in (0,1)$ represents the percentage of individuals that are included in each neighbourhood (boundaries). The resulting sensitivity and specificity are defined by

$$\widehat{Se}(c,t) = \frac{\left(1 - \hat{F}_X(c)\right) - \hat{S}_{\lambda_n}(c,t)}{1 - \hat{S}_{\lambda_n}(t)}, \; \widehat{Sp}(c,t) = 1 - \frac{\hat{S}_{\lambda_n}(c,t)}{\hat{S}_{\lambda_n}(t)}$$

where $\hat{S}_{\lambda_n}(t) = \hat{S}_{\lambda_n}(-\infty, t)$. The above estimates of the sensitivity and specificity will produce ROC curve estimates that are invariant to monotone transformations of the biomarker. Both sensitivity and specificity are monotone and bounded in [0, 1]. In contrast with CD1, this nonparametric method is efficient as a semi-parametric method

and allows the censoring to depend on the biomarker space [36]. Heagerty, et al. [2] used bootstrap resampling to estimate the confidence interval for this estimator. Motivated by the results gained by Akritas [36], Cai, Tianxi, et al. [37], Hung and Chiang [4] and Hung and Chiang [38] discussed the asymptotic properties of CD2. They established the usual $\sqrt{n}$-consistency and asymptotic normality and concluded that the bootstrap resampling technique can be used to estimate the variances. In practice, it is suggested that the value for $\lambda_n$is chosen to be $\mathcal{O}(n^{-\frac{1}{3}})$ [2].

3.3.2.3 (CD3) Kaplan-Meier like estimator of Chambless and Diao [39]

Chambless and Diao [39] highlighted the problem with the direct estimation of time-dependent sensitivity, specificity and AUC when the event status is not known at time t for individuals censored prior to t. They proposed a "Kaplan-Meier like" estimator that needs recursive computation using the riskset at each ordered event time, and mimics the Kaplan-Meier estimator. Blanche, P., et al. [31] slightly revised the original estimation for the ease of computation. Let t_k be the k^{th} observed ordered event time and t_m be the last observed event time before target time t. The sensitivity and specificity are defined by

$$\widehat{Se}(c,t) = \frac{\sum_{k=1}^{m} I\big(X_{d(k)} > c\big)\big\{\hat{S}(t_{k-1}) - \hat{S}(t_k)\big\}}{1 - \hat{S}(t_m)}$$

$$\widehat{Sp}(c,t) = \frac{\hat{F}_X(c) - \sum_{k=1}^{m} I\big(X_{d(k)} \le c\big)\big\{\hat{S}(t_{k-1}) - \hat{S}(t_k)\big\}}{\hat{S}(t_m)}$$

where $d(k)$ is the index of the individual who experiences an event at time t_k, $I\big(X_{d(k)} > c\big)$ estimates $P(X_i > c | t_{k-1} < T_i \le t_k)$ and $I\big(X_{d(k)} \le c\big)$ estimates $P(X_i \le c | t_{k-1} < T_i \le t_k)$. $\hat{S}(t_k)$ is the Kaplan-Meier survival function at time t_k and $\hat{S}(t_{k-1}) - \hat{S}(t_k)$ estimates $P(t_{k-1} < T_i \le t_k)$.

An advantage of this method is the sensitivity is monotone and bounded in [0, 1]. A nice property of this nonparametric estimator is that it does not involve any smoothing parameter, unlike CD2. Chambless and Diao [39] compared CD3 with the c-statistic gained from the logistic regression model of the baseline values in a simulation study and apparently it showed little bias. In order to compute variances and confidence

intervals of this estimator, Chambless and Diao [39] suggested using bootstrap re-sampling.

3.3.2.4 (CD4) Alternative estimator of Chambless and Diao [39]

CD1 estimates the conditional survival functions $S(t|X > c)$ using the Kaplan-Meier method under the subset defined by $X > c$. Thus, for a large threshold value c, the subset for $X > c$ may be small for estimating the conditional Kaplan-Meier estimate. However, in clinical applications, this "tail" survival function is often of interest, which is when the distribution is skewed and only few individuals with higher biomarker values, for example in presenting 10 year predicted risk of heart disease. [39]. In order to solve this problem, Chambless and Diao [39] proposed an alternative estimator, CD4, which is a model-based estimator like CD2, but differs in the way of estimating the survival function. CD4 estimates the coefficients of the risk factors from a Cox proportional hazards model and then these coefficients are used to estimate the survival function while CD2 uses the nearest neighbour estimator of $S(t|X > c)$. The proposed sensitivity and specificity are defined by

$$\widehat{Se}(c,t) = \frac{E\left[\left(1 - S(t|X_i)\right)I(X_i > c)\right]}{E[1 - S(t|X_i)]}, \widehat{Sp}(c,t) = \frac{E[S(t|X_i)I(X_i < c)]}{E[S(t|X_i)]}$$

where X here is a score from a survival function. This estimator requires the use of a score X from a survival function [39] instead of the raw biomarker value or score from another model. Hence, CD4 is readily available if X is a score produced from a survival model, however, if X is from an external source, then a survival model can be fitted to produce the equivalent score [39].

Chambless and Diao [39] suggested estimating the conditional survival function $S(t|X_i)$ under a Cox model and replacing the expected values by sample means. Therefore, CD4 is immediately available at any given time. Further, CD4 also produces monotone sensitivity and specificity given the survival function holds the property that the score is produced from a survival model.

A simulation study by Chambless and Diao [39] showed that CD4 is more efficient than CD3, as long as the survival model is not misspecified [40]. As with CD2, this

model-based estimator also allows censoring to depend on the biomarker. The disadvantage of CD4 is that it is not invariant to an increasing transformation of the biomarker (as the score X from a survival function) which is a desirable property of ROC curve estimator [31] and for this reason Blanche, P., et al. [31] choose not to compare this method to the others and the authors will not compare this method with other in this thesis either.

3.3.2.5 (CD5) Inverse probability of censoring weighting

CD5 was proposed by Uno, et al. [41] and Hung and Chiang [38] and modified the naïve estimator by adding weights to the observed biomarker values and time of disease onset in a subsample of uncensored individuals before time t. The weights are the probabilities of being uncensored when calculating the sensitivity:

$$\widehat{Se}(c,t) = \frac{\sum_{i=1}^{n} I\,(X_i > c, T_i \leq t)\{\delta_i / n\hat{S}_c(T_i)\}}{\sum_{i=1}^{n} I(T_i \leq t)\,\{\delta_i / n\hat{S}_c(T_i)\}}$$

where $\hat{S}_c(Z_i)$ is the Kaplan-Meier estimator of the survival function of the censoring time C_i at the i^{th} observed event-time T_i. As discussed by Blanche, P., et al. [31], the above estimate of sensitivity is the same as in CD3 although this is not mentioned by the authors. The specificity remains the same as in the naïve estimator as specified above. CD5 produces monotone sensitivity and specificity and are bounded in [0,1] [31].

3.3.2.6 (CD6) Conditional IPCW

CD6 is a modified version of IPCW that uses the weights that are the conditional probability of being uncensored given the biomarker, instead of the marginal probability of being uncensored [31]. This nonparametric estimator is robust to biomarker dependent censoring similar to previous model-based estimators CD2 and CD4. The sensitivity and specificity are estimated by

$$\widehat{Se}(c,t) = \frac{\sum_{i=1}^{n} I\,(X_i > c, T_i \le t)\{\delta_i / n\hat{S}_c(T_i|X_i)\}}{\sum_{i=1}^{n} I(T_i \le t)\{\delta_i / n\hat{S}_c(T_i|X_i)\}}$$

$$\widehat{Sp}(c,t) = \frac{\sum_{i=1}^{n} I\,(X_i \le c, T_i > t)\{1 / n\hat{S}_c(t|X_i)\}}{\sum_{i=1}^{n} I(T_i > t)\{1 / n\hat{S}_c(t|X_i)\}}$$

where $S_c(t|X_i) = P(C_i > t|X_i)$ is the censoring survival probability that may be estimated using a Cox model. However, Blanche, P., et al. [31] suggested using the nonparametric weighted KM estimator as discussed in CD2, in order to estimate the survival function $S_c(t|X)$ which is also monotone and bounded in [0, 1].

3.3.2.7 (CD7) Weighted AUC (t)

Lambert and Chevret [14] used a similar approach to Heagerty and Zheng [27] and proposed a time-dependent weighted AUC estimator which is restricted to a fixed time interval (τ_1, τ_2) and defined as:

$$\widehat{AUC}^{C,D}_{\omega_{\tau_1\tau_2}} = \frac{1}{\hat{S}(\tau_1) - \hat{S}(\tau_2)}\left[\sum_{\tau_1 \le (i) \le \tau_2} \widehat{AUC}^{C,D}\left(t^{(i)}\right)\left\{\hat{S}\left(t^{(i)}\right) - \hat{S}\left(t^{(i-1)}\right)\right\}\right],$$

where $t^{(i)}$ are the ordered distinct failure times for which, if $t^{(1)} > \tau_1$, it is assumed that $t^{(0)} = \tau_1$, $\hat{S}(t)$ is the Kaplan-Meier estimate of the survival function and $\widehat{AUC}^{C,D}(t)$ is a nonparametric estimator of a C/D time-dependent AUC such as CD2 or CD5 or any other estimators. The value τ_2 can be allocated as the value slightly below the maximum expected follow-up time if no clinically motivated choice is specified [42]. Bootstrap resampling is used to compute the confidence intervals of CD7. Since this weighted AUC is defined under C/D, it is not directly related to concordance measures, unlike the integrated AUC that will be discussed under I/D definition. However, the proposed estimator is better understood by physicians and is also closer to the clinical setting since most clinical studies want to distinguish between individuals who failed and individuals who survived the disease from the baseline to any particular time t. It is easy to implement since it can use any C/D estimators.

3.3.2.8 (CD8) Viallon and Latouche [40] Estimators

Viallon and Latouche [40] proposed several estimators of the time-dependent AUC relying on different estimators of the conditional absolute risk function. The conditional absolute risk function is estimated under the standard Cox proportional hazard model (VL Cox), the Aalen additive model (VL Aalen) or using the conditional Kaplan-Meier estimator (VL KM). The estimator of the time-dependent AUC is defined by

$$AUC_n(t) = \frac{\sum_{i=1}^{n} \frac{i}{n} \hat{F}_n(t; X_i) - \left\{\sum_{i=1}^{n} \hat{F}_n(t; X_i)\right\}^2 / 2}{\sum_{i=1}^{n} \hat{F}_n(t; X_i)\left\{1 - \sum_{i=1}^{n} \hat{F}_n(t; X_i)\right\}}$$

where n is the number of individuals and X_k denotes the k^{th} order statistic attached to the biomarker $X_1, X_2, \dots, X_n$. The conditional absolute risk is defined by $F(t; X = x) = P(T \leq t | X = x)$ and its estimator denoted by $\hat{F}_n(t; X = x)$ is estimated as below.

VL Cox: Consider the Cox model [43] under the conditional hazard rate $\lambda(t; X = x) = \lambda_0(t) \exp(\alpha_0 + \alpha x)$ where λ_0 denotes the baseline hazard rate, α_0 is an intercept and α is the log hazard ratio pertaining to $X = x$. The conditional cumulative hazard rate of $T = t$ given that X is denoted by $\Lambda(t; X = x) = \int_0^t \lambda(u; X = x) du$. Then the estimator of the conditional absolute risk function for VL Cox is given by

$$\hat{F}_{n,Cox}(t; X = x) = 1 - exp\left\{-\hat{\Lambda}_0(t) \exp(\hat{\alpha}_0 + \hat{\alpha} x)\right\}.$$

VL Cox is very similar to the estimator proposed by Heagerty and Zheng [27] that will be introduced in method ID1 but it does not involve the computation of the bivariate expectation [40].

VL Aalen: For the Aalen additive model [44], the conditional hazard rate $\lambda(t; X = x)$ takes the form $\beta_0(t) + \beta_1(t)x$. Thus the estimator of the conditional absolute risk function for VL Aalen is given by

$$\hat{F}_{n,Aalen}(t; X = x) = 1 - \exp\left(-\hat{\beta}_0(t) - \hat{\beta}_1(t)x\right).$$

VL KM: A nearest-neighbour type estimator of conditional absolute risk function is used for VL KM and is defined by

$$\hat{F}_{n,KM}(t; X = x) = 1 - \prod_{Z_{i \le t, \delta_i = 1}} \left\{ \frac{K_{l_n}(X_i, x)}{\sum_j I(Z_j \geq Z_i -) K_{l_n}(X_j, x)} \right\}$$

where l_n is the smoothing parameter of the 0/1 symmetric nearest neighbour kernel K_{l_n} [36].

VL estimators are straightforward to implement since they just plug-in the estimates of the conditional absolute risk function into the time-dependent AUC estimator. This plug-in nature allows their theoretical properties to follow the other established estimators of the conditional absolute risk function. Moreover, it is advisable to use CD8 compared to CD2 in the situations where the independence assumption between the censoring time C, and the pair (T, Z) might be violated [40].

3.3.3 Incident sensitivity and dynamic specificity (I/D)

There are three estimation methods proposed under the I/D definition and these are discussed in ID1 – ID3 below.

Specific notation: Let $R_i(t) = I(Z_i \geq t)$ denote the at-risk indicator. Let $\mathcal{R}_i(t) = (i: R_i(t) = 1)$ denote the individuals that are in the riskset at time t, in which $\mathcal{R}_t^1 = (i; T_i = t)$, are individuals with the event (cases) and $\mathcal{R}_t^0 = (i; T_i > t)$ are individuals without the event (controls). Let $n_t = |\mathcal{R}_t^0|$ be the size of the control set at time t and $d_t = |\mathcal{R}_t^1|$ the size of the case set at time t. Note that the riskset at time t can be represented as $\mathcal{R}_t = (\mathcal{R}_t^1 \cup \mathcal{R}_t^0)$.

3.3.3.1 (ID1) Cox Regression

Heagerty and Zheng [27] used the standard Cox regression model to estimate the sensitivity and specificity by the following three steps:

(i) Fit a Cox model $\lambda_0(t) \exp(X_i \gamma)$ where γ is the proportional hazard regression parameter. In order to relax the proportionality assumption, use a regression-smoothing method to estimate the time-varying coefficient $\hat{\gamma}(t)$ and use it to estimate the sensitivity in (ii) instead of γ.

(ii) The sensitivity can be evaluated using $\hat{\gamma}(t)$ from (i) as follows

$$\widehat{Se}(c,t) = \sum_i I(X_i > c)\pi_k(\hat{\gamma}(t),t).$$

Here $\pi_i(\gamma(t),t) = R_i(t)\exp(X_i\gamma(t))/W(t)$ are the weights under a proportional hazard model and $W(t) = \sum_i R_i(t)\exp(U_i^T\beta)$ are the weights with time-invariant covariates U_i.

(iii) The specificity can be estimated empirically as follow

$$\widehat{Sp}(c,t) = 1 - \sum_k I(X_k > c)\frac{\mathcal{R}_i^0(t)}{n_t}.$$

Heagerty and Zheng [27] suggested using flexible semiparametric methods such as locally weighted maximum partial likelihood (MPL) by Cai, Zongwu and Sun [45] as the regression-smoothing method in (i), and simple local linear smoothing of the scaled Schoenfeld residuals [46] for reducing the bias [27].

The sensitivity is consistent for both the proportional and non-proportional hazards models whenever a consistent estimator of $\hat{\gamma}(t)$ is used [47]. Since the specificity is an empirical distribution function calculated over the control set, it is consistent provided the control set represents an unbiased sample [27]. It is suggested that the computation of the standard errors and confidence intervals is carried out using the nonparametric bootstrap based on the resampling of observations (X_i, T_i, δ_i) [27].

3.3.3.2 (ID2) Weighted mean rank

ID2 was proposed by Saha-Chaudhuri and Heagerty [3] and is based on the idea of ranking the individuals in the riskset by their respective scores. The proposed time-dependent AUC is based on the local rank-based concordance estimation. At any given time t, an estimator of $AUC(t)$ is defined by

$$A(t) = \frac{1}{n_t d_t}\sum_{i\in\mathcal{R}_t^1}\sum_{j=\mathcal{R}_t^0} 1(X_i > X_j).$$

However, frequently, only a small number of individuals experience the event at t, and therefore the information on the neighbourhood is needed in order to estimate the biomarker concordance at t which is defined by

$$WMR(t) = \frac{1}{|\mathcal{N}_t(h_n)|}\sum_{t_j\in\mathcal{N}_t(h_n)} A(t_j) \qquad (3.1)$$

where $\mathcal{N}_t(h_n) = (t_j: |t - t_j| < h_n)$ denotes a neighbourhood around t. This is a nearest-neighbour estimator of the AUC and can be generalized to

$$\widehat{AUC}(t) = \sum_j K_{h_n}(t - t_j).\ A(t_j) \tag{3.2}$$

where K_{h_n} is a standardized kernel function such that $\sum_j K_{h_n}(t - t_j) = 1$. Equation (3.1) is a smoothed version of equation (3.2) and it is based on the local U-statistics summaries. Saha-Chaudhuri and Heagerty [3] suggested the integrated mean square error (IMSE) as a potential method to select an optimal bandwidth.

Under certain conditions, Saha-Chaudhuri and Heagerty [3] showed that $WMR(t)$ follows a normal distribution. It is suggested that this variance estimator for inference can be used in practice since it is simple and does not require resampling methods. Saha-Chaudhuri and Heagerty [3] also provided the details of the large sample properties of this estimator, and then the construction of a confidence interval for $WMR(t)$ using the asymptotic properties is straightforward. Although it is desirable to obtain the simultaneous confidence bands for the function $WMR(t)$, the theory may not be applicable in this case since the limiting process may not possess an independent increment structure. Instead, a simulation of a Gaussian process while keeping the estimates of ID2 fixed is needed to approximate the distribution of the Gaussian process and to estimate the quantiles. ID2 also has the advantage to be potentially robust since the relative bias remains significantly lower than for the ID1estimator.

3.3.3.3 (ID3) Fractional Polynomial

As the ID2 method is computationally intensive, especially in the selection of the bandwidth, Shen, et al. [48] proposed a semi-parametric time-dependent AUC estimator which is easier and more applicable when comparing and screening a large number of candidate biomarkers. The suggested model uses fractional polynomials [49], the parameters of which are estimated using a pseudo partial-likelihood function. Denote $\eta(.)$ as the link function, e.g. the logistic function. $AUC(t)$ is modelled directly as a parametric function of time t using the fractional polynomials of the G degree:

$$\eta\big(AUC(t)\big) = \sum_{g=0}^{G} \beta_g t^{(p_g)} \tag{3.3}$$

where for $g = 1, \ldots, G$, and

$$t^{(p_g)} = \begin{cases} t^{p_g} & if\ p_g \neq 0 \\ \ln(t) & if\ p_g = 0 \end{cases}$$

$p_1 \leq \cdots \leq p_g$ are real-valued powers, and $\beta_0, \ldots, \beta_g$ are unknown regression parameters. The choices of powers are from the set (-2, -1, -1/2, 0, ½, 1, 2) as suggested by Royston, P. and Altman [49]. Unlike the conventional polynomial, the fractional polynomial is flexible and can mimic many function shapes in practice [49]. In order to construct the pseudo partial-likelihood, consider two types of events on each riskset $R(t_k)$ derived from the observed data which are defined by

$$e_1\big(X_i, X_j, T_i, T_j\big) = \big\{X_i > X_j | T_i = t_k, \delta_i = 1, j \in R(t_k)\big\}$$

$$e_2\big(X_i, X_j, T_i, T_j\big) = \big\{X_i \leq X_j | T_i = t_k, \delta_i = 1, j \in R(t_k)\big\}$$

where event $e_1\big(X_i, X_j, T_i, T_j\big)$ and $e_2\big(X_i, X_j, T_i, T_j\big)$ are respectively called concordant and discordant events as $e_1\big(X_i, X_j, T_i, T_j\big)$ occurs if individual *j* has a smaller biomarker value compared to individual i, and $e_2\big(X_i, X_j, T_i, T_j\big)$ occurs if individual j has greater biomarker value compared to individual i, given that individual *j* has longer survival period. For each event time t_k, the counts of the two types of events are given by

$$n_1(t) = \sum_j I\big\{j: X_i > X_j | T_i = t_k, \delta_i = 1, j \in R(t_k)\big\}$$

$$n_2(t) = \textstyle\sum_j I\big\{j: X_i \leq X_j | T_i = t_k, \delta_i = 1, j \in R(t_k)\big\}.$$

Note that at each time point t_k, conditioned on riskset $R(t_k)$, the count $n_1(t_k)$ follows a distribution with probability equal to $AUC(t_k)$. The pseudo partial-likelihood is constructed by multiplying all the probabilities of observing concordant and discordant counts over all of the risksets from the observed event times as shown below

$$L(\beta) \alpha \prod_{k=1}^{K} AUC(t_k; \beta)^{n_1(t_k)} \{1 - AUC(t_k; \beta)\}^{n_2(t_k)}.$$

Maximizing this pseudo partial-likelihood yields parameter estimates $\hat{\beta}$. Then the time-dependent AUC estimate is obtained from equation (3.3) as a smooth function of

time t and β. In practice, the integrated AUC is always of interest for the I/D definition and it can be defined by $\int_0^\tau \omega\,(t;\tau)AUC\big(t;\hat{\beta}\big)dt$. When the weight function $\omega(t;\tau)$is invariant to time, the integrated AUC can be viewed as the global average of the AUC curve [48]. One major advantage of this estimator compared to ID2 is that the proposed method estimates the entire curve as a function of t and β while ID2 just uses a point-wise approach to estimate AUC. Further, this method is understandable and it is easier to make inference since it is a "regression-type" method, with covariates being the functions of time. In estimating the integrated AUC, the ID3 method is more convenient since it uses an analytical expression while the ID2 computation is more complex since the kernel-based estimation procedure has to be repeated N times, and also the selection of bandwidths has to be considered. However, Saha-Chaudhuri and Heagerty [3] decreased the computational burden by calculating the integrated AUC as an average of $AUC(t)$ at 10 time points, which can lead to approximation errors.

3.3.4 Incident sensitivity and static specificity (I/S)

There is only one estimation method proposed under the I/S definition found from the methodological review and one extended method which will be discussed below.

3.3.4.1 (IS1) Marginal regression modelling approach

Cai, Tianxi, et al. [7] proposed an estimation approach using the marginal regression modelling which was first proposed by Leisenring, et al. [50] that accommodates censoring. Let the data for analysis be given by $((X_{ik}, \boldsymbol{U}_i, Z_i, \delta_i, s_{ik}),\ i = 1, \dots, n;\ k = 1, \dots, K_i)$, where $\boldsymbol{U}_i$ denotes the vector of covariates associated with X_{ik} and let T_{ik} be the time lag between the measurement time and the event time, i.e. $T_{ik} = T_i - s_{ik}$. Cai, Tianxi, et al. [7] modelled the marginal probability associated with $(X_{ik}, T_{ik}, \boldsymbol{U}_i)$ and the sensitivity and specificity are defined by the marginal probability models,

$$Se\big(t, s_{ik}, \boldsymbol{U}_{i,}c\big) = P\big(X_{ik} > c \big| T_{ik} = t, \boldsymbol{U}_{i,}s_{ik}\big)$$
$$= g_D\{\eta\boldsymbol{\alpha}_0(t, s_{ik}) + \boldsymbol{\beta}_0'\boldsymbol{U}_i + h_0(c)\}$$

$$Sp(t^*, s_{ik}, \boldsymbol{U}_i, c) = P(X_{ik} \le c | T_{ik} > t^*, \boldsymbol{U}_i, s_{ik})$$
$$= 1 - g_{\bar{D}}\{\xi \boldsymbol{\alpha}_0(s_{ik}) + \boldsymbol{b}_0' \boldsymbol{U}_i + c_0(c)\}$$

where g_D and $g_{\bar{D}}$ are specified inverse link functions, h_0 and c_0 are baseline functions of the threshold c that are completely unspecified. These nonparametric baseline functions of c represent the shape and location of the sensitivity and specificity functions while the parameters $\boldsymbol{\beta}_0$ and $\boldsymbol{b}_0$ quantify the covariate effects on them and $\eta \boldsymbol{\alpha}_0$ and $\xi \boldsymbol{\alpha}_0$ are the time effects. The dependence on time for sensitivity is through the parametric functions $\eta \boldsymbol{\alpha}_0(t, s) = \boldsymbol{\alpha}_0' \boldsymbol{\eta}(t, s)$ and $\xi \boldsymbol{\alpha}_0(s_{ik}) = \boldsymbol{\alpha}_0' \, \xi(s)$ where $\boldsymbol{\eta}$ and ξ are vectors of polynomial or spline basis functions.

Let $\boldsymbol{\Psi}_0 = (\mathbf{H}_0(.) = [h_0(.), c_0(.)]', \boldsymbol{\theta}_0 = [\boldsymbol{\alpha}_0', \boldsymbol{\beta}_0', \boldsymbol{\alpha}_0', \boldsymbol{b}_0'])$ denote all unknown parameters. Cai, Tianxi, et al. [7] considered the marginal binomial likelihood function based on the binary variable $I(X_{ik} \ge c)$ and it is defined by

$$\prod_{i=1}^{n} \prod_{k=1}^{K} \{p_{ik}(x; \boldsymbol{\Psi})\}^{I(X_{ik} Y_{ik} \ge c)} \{1 - p_{ik}(x; \boldsymbol{\Psi})\}^{I(X_{ik} < c)}$$

and the corresponding score equation is solved in order to estimate the nonparametric baseline functions, $\mathbf{H}_0(c)$. Further, $\boldsymbol{\theta}_0$ is estimated by solving the integration of the corresponding score equation. Cai, Tianxi, et al. [7] also proposed an approach that ignores censored observations.

Simulation studies [7] showed that the above method provides reasonably unbiased estimates of the model's parameters of sensitivity and specificity. The approach which includes the censored observations is always more precise than the one that excludes them.

3.3.4.2 (IS2) Proposed extension to ID1 to allow for the baseline and longitudinal biomarker measurements

The main difference between I/D and I/S definitions is related to the controls. The controls in I/D are changing based on the target time whereas in I/S, the controls are static survivors beyond a fixed time. Motivated by this difference, the Cox Regression method ID1 is extended to incorporate a longitudinally repeated biomarker under the I/S definition. Following the I/S definition, a biomarker value at a particular visit time

s is considered. Thus, the time prior to disease is calculated and has been used instead of using the event-time in ID1. The proposed method can readily be used with the baseline value by using just the event time. However, as I/S is not based on classification of the riskset at time t like I/D, this extended method cannot be said as a natural companion to the hazard models. The current software code for ID1 (see Section 3.3.6) has also been updated by redefining the riskset according to the I/S definition. The extended software can also be used with the baseline value of the biomarker.

3.3.5 Additional methods for longitudinal outcomes

Three estimation methods have been proposed for a longitudinal biomarker in addition to those described above under the I/S definition, although some do not incorporate censoring. These estimation methods are discussed below. An extension of the C/D definition for a longitudinally repeated biomarker is suggested as the fourth method.

Specific notation: Let $n = n_D + n_{\bar{D}}$ denote the total number of individuals which is the summation of the where n_D is the total number of cases and $n_{\bar{D}}$ is the total number of controls. Let $\boldsymbol{U}_{ik}^T = vec(T_i, s_{ik}) = \boldsymbol{U}_D$ denotes the vector of covariates associated with X_{ik}. The total number of longitudinally repeated biomarker values for cases is $N_D = \sum_i^{n_D} K_i$. The time prior to an event is defined as the time lag between the measurement time and the event time: $T_{ik} = T_i - s_{ik}$ as above. Similarly for controls, let X_{jl} be the biomarker value obtained from individual j at the l^{th} visit time s_{jl} with $j = n_D + 1, \dots, n_D + n_{\bar{D}}$ and $l = 1, \dots, L_j$. Let $\boldsymbol{U}_{jl}^T = vec(s_{jl}) = \boldsymbol{U}_{\bar{D}}$ denote the vector of covariates associated with Y_{jl}. The total number of longitudinally repeated biomarker values for the controls is $N_{\bar{D}} = \sum_j^{n_{\bar{D}}} L_j$. Thus, the total number longitudinally repeated biomarker values in the study is $N = N_D + N_{\bar{D}}$.

3.3.5.1 (AD1) Linear mixed-effect regression model

Etzioni, et al. [32] proposed the use of a linear random-effect regression model of the serial biomarker measurements as a function of time prior to the event, which was

originally proposed by Tosteson, Anna N Angelos and Begg [51] using the ordinal regression models in order to estimate the time-dependent ROC curve statistics. This approach involves modelling the biomarker values and using the model parameter estimates to induce a ROC curve at a particular time. The ROC is defined by

$$ROC(t,p) = S_D[a_0(t) + a_1(t)S_{\bar{D}}^{-1}(p)] \tag{3.4}$$

where t is the time prior to the event, p is the false positive rate, S_D is one minus the cumulative distribution function for cases and $S_{\bar{D}}$ is one minus the cumulative distribution function for controls. Suppose cases and controls are from the same location-scale family S, μ_D and s_D are the mean and standard deviation of X_{ik}, and $\mu_{\bar{D}}$ and $s_{\bar{D}}$ are the mean and standard deviation of Y_{jl}. Then $a_0(t)$ and $a_1(t)$ are defined by

$$a_0(t) = \frac{\mu_{\bar{D}} - \mu_D}{s_D}$$

$$a_1(t) = \frac{s_{\bar{D}}}{s_D}.$$

To estimate $a_0(t)$ and $a_1(t)$, Zheng, Y. and Heagerty [15] fitted the following linear mixed effect models for cases and controls :

$$Case: X_{ik} = b_{0i} + b_{1i}s_{ik} + \beta_0 + \beta_1 s_{ik} + \beta_2 T_{ik} + \beta_3 s_{ik}T_{ik} + \varepsilon_{ik} \tag{3.5}$$

$$Control: X_{jl} = b_{0j} + b_{1j}s_{jl} + \beta_0 + \beta_1 s_{jl} + \varepsilon_{jl} \tag{3.6}$$

where $\varepsilon_{ik} \sim N(0, \sigma_D^2)$ and $(\beta_0, \beta_1, \beta_2, \beta_3) \sim N[(\beta_0^D, \beta_1^D, \beta_2^D, \beta_3^D), \boldsymbol{V}^D]$ for cases and $\varepsilon_{jl} \sim N(0, \sigma_{\bar{D}}^2)$ and $(\beta_0, \beta_1) \sim N[(\beta_0^{\bar{D}}, \beta_1^{\bar{D}}), \boldsymbol{V}^{\bar{D}}]$ for controls. $\boldsymbol{V}^D$ and $\boldsymbol{V}^{\bar{D}}$ are variance-covariance matrices for cases and controls respectively. It should be noted that, only equation (3.5) includes the time prior to the event (T_{ik}) but not equation (3.6) since the controls are those individuals who do not experience the event. Parameter estimates from equations (3.5) and (3.6) are used to induce the ROC estimates in equation (3.4) using the estimated $a_0(t)$ and $a_1(t)$. For a given s and t, $\mu_D, \mu_{\bar{D}}$, $s_D$and $s_{\bar{D}}$ are estimated by

$\hat{\mu}_D = \boldsymbol{U}_D\, \boldsymbol{\beta}^D$, $\hat{\mu}_{\bar{D}} = \boldsymbol{U}_{\bar{D}}\, \boldsymbol{\beta}^{\bar{D}}$, $\hat{s}_D = \sqrt{\sigma_D^2 + \boldsymbol{U}_D\, \boldsymbol{V}^D\, \boldsymbol{U}_D^T}$ and $\hat{s}_{\bar{D}} = \sqrt{\sigma_{\bar{D}}^2 + \boldsymbol{U}_{\bar{D}}\, \boldsymbol{V}^{\bar{D}}\, \boldsymbol{U}_{\bar{D}}^T}$

where $\boldsymbol{U_D} = [1 \quad s \quad t \quad st]$, $\boldsymbol{\beta^D} = \left[\hat{\beta}_0 \quad \hat{\beta}_1 \quad \hat{\beta}_2 \quad \hat{\beta}_3\right]^{\boldsymbol{T}}$, $\boldsymbol{U_{\bar{D}}} = [1 \quad s]$ and $\boldsymbol{\beta^{\bar{D}}} = [\hat{\beta}_0 \quad \hat{\beta}_1]^{\boldsymbol{T}}$.

3.3.5.2 (AD2) Model of ROC as a function of time prior to disease

Pepe, M. S. [52] proposed the use of a regression model for the ROC curve itself, and similarly, Etzioni, et al. [32] proposed using a ROC model directly as a function of time prior to event. The model is defined by

$$ROC(t,p) = \Phi[\gamma_0 + \gamma_1 \Phi^{-1}(p) + \alpha t]$$

where p is the false positive rate, Φ is one minus the normal cumulative distribution function. At each time t, it is assumed that the ROC is of the binormal form as in equation (3.4) and the ROC curves at different t are related through a linear effect on the intercept. In terms of (3.4), $a_0(t) = \gamma_0 + \alpha t$ and $a_1(t) = \gamma_1$. The parameters γ_0, γ_1 and α can be estimated by the following steps

(i) Construct a dataset of $\{(X_{ik}, X_{jl}),\ D = I(X_{ik} \geq X_{jl})\}$.

(ii) Calculate the quantile p in the control population (control observations in each pair as defined in Step 1 above). It can be estimated by the empirical cumulative distribution function in the control sample.

(iii) The indicator $I(.)$ in Step 1 is estimated conditional on p in Step 2. Thus, the $ROC(p)$ is estimated by fitting a generalized linear model to data $I(.)$, where the family is binomial, the link is probit and the covariates are $\Phi^{-1}(p)$ and T_{ik}.

There are a few advantages of this method compared to the first method in which the range of setting of this method is much broader [52]; the range of models that allowed for the ROC curve is broader; the model can include the interactions between p and U; the distributions of the test result in cases and controls do not need to be derived from the same family. Indeed, no assumptions are made regarding the distribution of biomarker for the controls but only on the relationship between the cases and controls which are made through the ROC curve model.

3.3.5.3 (AD3) Semi-parametric regression quantile estimation

Zheng, Y. and Heagerty [15] proposed a semi-parametric regression quantile approach which is an extension to the parametric approach by Heagerty and Pepe [53] to

construct time-dependent ROC curves. The definition of the ROC curve at time t has the same form as equation (3.4) but since in [15], the positive test is defined as a biomarker value less than c, thus true positive is defined in terms of the cumulative distribution function instead of the survival function. The ROC at time t is estimated by the conditional empirical quantile function of $[X_{ik}|U_{ik}]$, as from a location-scale family and defined as follow:

$$ROC(t,p) = F[a_0(t) + a_1(t)G^{-1}(p)]$$

where F and G are the baseline distribution functions of case and control models as follow

$$Case: X_{ik} = \mu_D(\boldsymbol{U}_{ik}) + \sigma_D(\boldsymbol{U}_{ik})\epsilon_D(\boldsymbol{U}_{ik})$$

$$Control: X_{jl} = \mu_{\bar{D}}(\boldsymbol{U}_{jl}) + \sigma_{\bar{D}}(\boldsymbol{U}_{jl})\epsilon_{\bar{D}}(\boldsymbol{U}_{jl})$$

where μ_D, σ_D, $\mu_{\bar{D}}$ and $\sigma_{\bar{D}}$ are the location and scale functions. Instead of using a quasi-likelihood method to estimate μ_D, σ_D, $\mu_{\bar{D}}$ and $\sigma_{\bar{D}}$ [53], Zheng, Y. and Heagerty [15] used regression splines. In order to estimate the conditional baseline distribution function F and G, Zheng, Y. and Heagerty [15] proposed using an empirical distribution function of the standardized residuals if the baseline functions are independent of covariates, and to consider the symmetrized nearest neighbour (SNN) estimator [54] if the baseline functions are the smooth functions of covariates. Thus, this semi-parametric estimation method gives greater flexibility than the parametric method [32] by allowing separate model choices for each of the key distributional aspects.

3.3.5.4 (AD4) Proposed extension to CD2 to allow for longitudinal biomarker measurements

Zheng, Yingye and Heagerty [16] proposed a generalisation of CD1 by Heagerty, et al. [2] for the longitudinal biomarker measurements. The key idea was similar to the IS2 method in which the most recent biomarker is used to discriminate between cases prior to time t from the controls after time t. In contrast with CD1, it is no longer just use the baseline biomarker or prognostic information but also consider the updated information. The proposed sensitivity and specificity take the same form of CD1. In

order to estimate the distribution function $\hat{F}_Y(c)$ (see CD1), Zheng, Yingye and Heagerty [16] used the semi-parametric regression quantile method for the longitudinal data [53]. For the bivariate survival function, $S(c,t)$, and the marginal survival function, $S(t)$, Zheng, Yingye and Heagerty [16] used a partly conditional hazard model as proposed by Zheng, Yingye and Heagerty [55].

Motivated by the above methodology, CD2 has been extended to incorporate the most recent biomarker value from the longitudinal biomarker record instead of the baseline biomarker value. CD2 is chosen rather than CD1 because CD1 produces a non-monotone sensitivity or specificity. The sensitivity and specificity are defined similar to CD2. The extended CD2 (denoted as AD4) is assumed to have all the advantages of CD2 with an extra advantage of using the most recent biomarker value which is more reliable in depicting the current status of an individual.

3.3.6 Software

The current software for computing the time-dependent ROC curves are available as R packages. These are briefly described below.

3.3.6.1 survivalROC

The "survivalROC" [56] package estimates both the CD1 and CD2. The R documentation includes worked examples using the built-in dataset called *mayo* (Primary Biliary Cirrhosis (PBC) dataset from Mayo Clinic). The estimators can be chosen by the type of either the "KM" or "NNE" methods in the function syntax.

3.3.6.2 survAUC

The package [57] provides a variety of functions to estimate the time-dependent true/false positive rates and AUC for the censored data. The AUC.cd can be used to calculate CD4 and it is restricted to the Cox regression. The estimates obtained from this function are valid as long as the Cox model is specified correctly. The values

returned by this function are AUC, integrated AUC and the times at which the AUC are evaluated.

3.3.6.3 timeROC

The package [58] provides the functions to compute the confidence intervals of AUC and tests for comparing the AUC of two biomarkers measured on the same individuals. Both CD5 and CD6 estimators can be computed using this package. It is also capable of allowing for competing risks event times.

3.3.6.4 survival, timereg and prodlim

The Basehaz function in the "survival" package [59] in R is used to obtain the VL Cox estimates which uses the baseline hazard under a Cox model. The Aalen function in the "timereg" package [60] can be used to estimate the conditional absolute risk under VL Aalen; it returns the estimated coefficients β_0 and β_1. The VL KM estimator can be computed using the "prodlim" package [61]. For the selection of the smoothing parameter l_n, a direct plug-in method can be used by setting l_n to $0.25\ n^{-1/5}$.

3.3.6.5 risksetROC

This "risksetROC" package [62] estimates the time-dependent ROC curves under I/D definition and produces the accuracy measures for the censored data under proportional or non-proportional hazard assumption of the ID1 estimator.

3.4 Results from the clinical applications review

Among the three definitions for sensitivity and specificity, C/D has been the most commonly applied in clinical papers (126/157, 80%). The I/D definitions have been applied in 29 papers (18.5%) while none was found for the I/S definitions. Since the publication by Heagerty and Zheng [27] who introduced the three definitions, the number of clinical papers that used the I/D methodology has increased (Figure 3.2).

Lung, breast and liver cancer are the most common areas for the application of C/D and I/D (Figure 3.3). Some of the applications of C/D and I/D from cancer are described below.

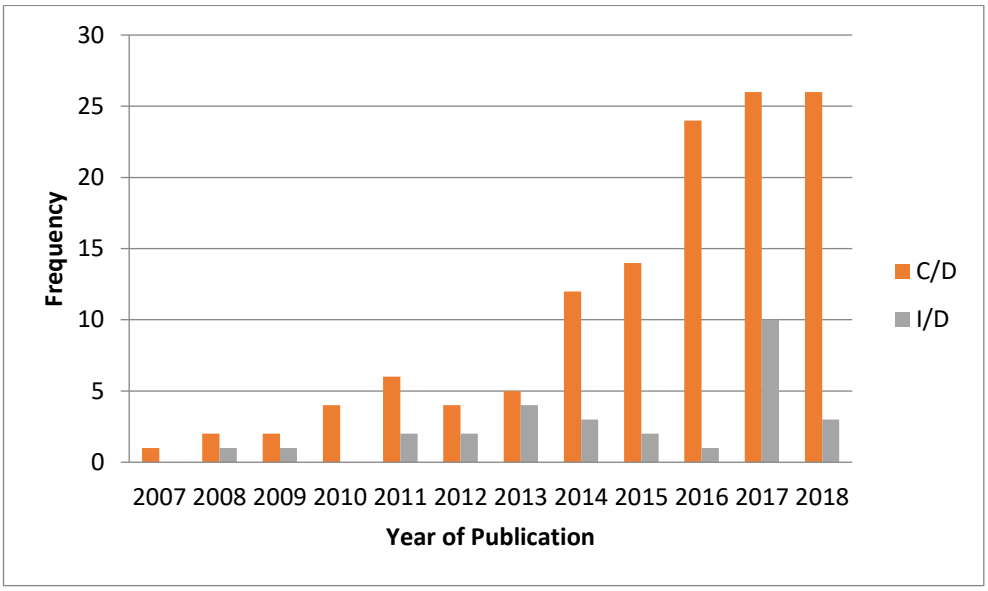

Figure 3.2: Year of publication for clinical applications under C/D and I/D definitions

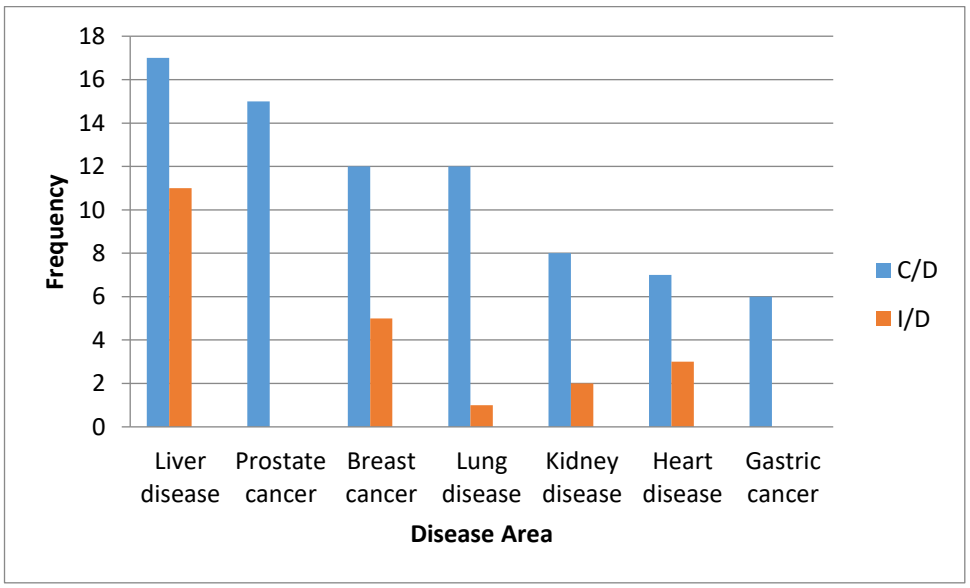

Figure 3.3: Disease area for clinical applications under C/D and I/D definitions

Lu, et al. [63] aimed to determine a robust prognostic biomarker for tumour recurrence as 30% of Stage I non-small cell lung cancer (NSCLC) patients will experience the tumour recurrence after therapy. They used the time-dependent ROC curve analysis to assess the predictive ability of the gene expression signatures. The recurrence-related genes were identified by performing a Cox proportional hazards analysis. A 51-gene expression signature was validated to be highly predictive for recurrence in Stage I NSCLC with the AUC values greater than 0.85 from the baseline up to 100 months of follow-up. The highest AUC values have been seen after 60 months to 100 months of the follow-up with AUC(t) = 0.90, implying that the 51-gene expression signature is a better biomarker in discriminating between Stage 1 NSCLC patients who will experience tumour recurrence up to 60 months and patients who will not experience tumour recurrence beyond 60 months of follow-up. Lu, et al. [63] concluded that this gene expression signature has important prognostic and therapeutic implications for the future management of these patients.

Tse, et al. [64] has developed a prognostic risk prediction model for silicosis among workers exposed to silica in China using a Cox regression analysis to screen the potential predictors. The score from this model was then developed as a unique score system which includes 6 covariates: age at entry, mean concentration of respirable silica, net years of dust exposure, smoking illiteracy and number of jobs. This scoring system is regarded as accurate in discriminating the workers with silicosis and healthy workers up to 600 months of follow-up since the AUC values are more than 0.80. These AUC values seem to decrease from baseline AUC($t = 0$) = 0.96 to the end of follow-up AUC($t = 600$) = 0.83 which indicates the discrimination potential of the baseline score had diminished across the study's follow-up. This study provides scientific guidance for the clinicians to identify high-risk workers.

Yue, Yong, et al. [5], Yue, Y., et al. [6] used the pre-treatment 18F-FDG-PET/CT imaging and combinatorial biomarkers respectively to stratify the risk of TNBC (Triple-negative breast cancer) patients. TNBC is considered as a high-risk disease and normally associated with poor survival. A stratification of prognosis of this disease can help in identifying the patients with good a prognosis for less aggressive therapy. The event-time outcome of the studies was defined as the time to recurrence of TNBC disease. The time-dependent ROC curve was used to assess the prognostic value of the

biomarkers, EFGR and CK5/6 at different cut-off points and the optimal cut-off was obtained based on the AUC values. The cut-off values were estimated by maximising both sensitivity and specificity of the event-time outcome. The optimal values of 15% with AUC=0.675 and 50% with AUC=0.611 for EFGR and CK5/6 were respectively found. AUC values obtained were used as a basis of a decision rule. By using the optimal cut-off value, the patients were stratified into two different risk level groups which helped in selecting the appropriate treatment strategies for patients.

Desmedt, et al. [65] studied the performance of the gene expression index (GGI) in predicting relapses in postmenopausal women who were treated with tamoxifen (T) or letrozole (L) within the BIG 1-98 trial. The predictive ability of GGI was estimated using time-dependent AUC and was plotted as a function of time to characterize temporal changes in the accuracy of the GGI biomarker. They calculated AUC($t = 24$) = 0.73 which implies that 73% of the patients who relapsed at 24^{th} month have greater GGI score than patients who relapse after 24^{th} month. Further, AUC at $t = 27$ was found to be the highest which indicated that the maximal discrimination occured near the median follow-up time.

George, et al. [66] aimed to determine the predictive ability of the lesions texture along with traditional features in order to detect the early tumour response. Texture features are important in detecting the progression of a tumour among cancer patients, e.g. s (18) F-fluorodeoxyglucose (FDG) followed by the positron emission tomography (PET) estimates. The event-time outcome was defined as the time of tumour progression, which is the distance between the subspaces from the baseline scan and the follow-up scan. Time-dependent ROC curve was used to obtain the predictive ability of the weighted subspace-subspace distance from the baseline and the follow-up scan as a biomarker for predicting early tumour response. In a study of 15 patients who had metastatic colorectal cancer, the follow-up scan was taken at the first week after the first dose of the treatment. As a result, a concordance summary of 0.68 is found from the predictive model using weighted subspace-subspace distance metrics. This result helps as an added value in using textural information for therapy response evaluation.

The prognostic role of hepatitis-B virus (HBV) infection in chronic lymphocytic leukemia (CLL) was studied among a Chinese case cohort by Liang, et al. [67]. Three

regression models have been proposed consisting of potential factors of CLL in which Model 1: clinical variables, Model 2: clinical and biological variables and Model 3: clinical, biological and virological variables. The models were evaluated using the time-dependent AUC. The differences across AUC were calculated using a nonparametric approach. Model 3 which was taking account of the HBV status (a virological variable) were found to be the most significant in predicting CLL. This finding provided an additional insight into the virological determinant of CLL prognosis and concluded that the HBV status could be an important risk factor of CLL.

3.5 Illustrative PBC Application

As introduced in Chapter 1 in Section 1.7, the PBC data is used for illustrative purpose for the currently proposed estimation methods discussed in the previous sections. In this chapter, a model score estimated from the Cox model which contained five covariates: log(bilirubin), albumin, log(prothrombin time), edema and age [27] is used as a biomarker.

Table 3.3 shows the estimated AUC from several methods at Year 1, Year 5 and Year 10 based on the baseline value of the biomarker or the most recent value. All methods show decreasing AUCs as the prediction time is further from the biomarker measurement time. This indicated the hypothesis that the discriminative power of the marker becomes weaker with increasing prediction time is proven. The methods involving longitudinal biomarker measurements assume that the value which is closest to the prediction time is better in discriminating between the cases and controls. AD4 used the last value prior to each prediction time as it produces higher values of AUC compared to CD1 which uses the baseline biomarker measurement. This is also true for IS2. The methods involving a longitudinal biomarker measurement are usually interpreted with respect to the time lag between the last visit time and the prediction time because each individual may have a different set of visit times. Thus, the last value prior to each prediction time in the estimation. As the time lag gets longer, the AUC decreases due to the same reason as using the baseline value of a biomarker. The R software previously described was used to estimate these models.

Table 3.3: Estimated time-dependent AUC for Year 1, Year 5 and Year 10

Definitions	Marker time	Method	AUC (SD)		
			Year 1	Year 5	Year 10
C/D	$t = 0$	Naïve	0.846 (0.023)	0.885 (0.022)	0.883 (0.030)
		CD1	0.922 (0.041)	0.921 (0.021)	0.878 (0.027)
		CD2	0.895 (0.056)	0.897 (0.024)	0.869 (0.028)
		CD3	0.922 (0.042)	0.917 (0.020)	0.898 (0.031)
		CD5	0.922 (0.042)	0.915 (0.021)	0.866 (0.028)
		CD6	0.922 (0.038)	0.915 (0.020)	0.870 (0.030)
C/D	Last value prior to:	AD4			
	Year 1		0.926 (0.039)	0.918 (0.019)	0.871 (0.027)
	Year 5		-	0.911 (0.019)	0.910 (0.021)
	Year 10		-	-	0.899 (0.022)
I/D	$t = 0$	ID1	0.845 (0.010)	0.791 (0.028)	0.692 (0.024)
		ID3	0.893 (0.048)	0.757 (0.041)	0.716 (0.143)
I/S	$t = 0$	IS2	0.939 (0.025)	0.836 (0.028)	0.698 (0.034)
I/S	Last value prior to:	IS2			
	Year 1		0.968 (0.003)	0.872 (0.024)	0.698 (0.043)
	Year 5		-	0.957 (0.003)	0.698 (0.031)
	Year 10		-	-	0.768 (0.038)

The AD1 method (Section 3.3.5.1) uses all available longitudinal biomarker values for prediction of the time-dependent ROC curves. The parameter estimates from the two models for the cases and controls are shown in Table 3.4, and the relevant calculations are given below.

Table 3.4: Parameter estimates from linear mixed effect models for cases and controls

Effect	**Coefficient**	**Estimates for Case**	**Estimates for Control**
Fixed Effect	$\beta_0(SE)$	1.139 (8.865× 10^{-2})	-0.569 (0.043)
	$\beta_1(SE)$	-4.813× 10^{-4} (4.419× 10^{-5})	2.906× 10^{-4} (2.502× 10^{-5})
	$\beta_2(SE)$	2.283× 10^{-4} (5.696× 10^{-5})	

	$\beta_3(SE)$	-1.083× 10^{-7}(1.605× 10^{-8})	
Random Effect	σ_{int}	0.593	0.550
	σ_{VT}	3.448×10^{-4}	2.615× 10^{-4}
	$\rho_{int,VT}$	-0.378	0.209
	σ_{Res}	0.293	0.220

SE – Standard error

If the time-dependent ROC curve is estimated at five years prior to death ($i.e.\ T = 5$) for the biomarker measured at visit time which is equal to ten years ($i.e.\ s = 10$), the means and standard deviations for the cases and controls are estimated by

$\hat{\mu}_D = \boldsymbol{U}_D\, \boldsymbol{\beta}^D = 1.1353$, $\hat{\mu}_{\bar{D}} = \boldsymbol{U}_{\bar{D}}\, \boldsymbol{\beta}^{\bar{D}} = -0.5676$,

$\hat{s}_D = \sqrt{\sigma_D^2 + \boldsymbol{U}_D\, \boldsymbol{V}^D\, \boldsymbol{U}_D^T} = 0.6608$, where $\boldsymbol{V}^D = \begin{bmatrix} (0.593)^2 & -7.730 \times 10^{-5} \\ -7.730 \times 10^{-5} & (3.448 \times 10^{-4})^2 \end{bmatrix}$ and

$\hat{s}_{\bar{D}} = \sqrt{\sigma_{\bar{D}}^2 + \boldsymbol{U}_{\bar{D}}\, \boldsymbol{V}^{\bar{D}}\, \boldsymbol{U}_{\bar{D}}^T}$ =0.5924 where $\boldsymbol{V}^{\bar{D}} = \begin{bmatrix} (0.550)^2 & 3.004 \times 10^{-5} \\ 3.004 \times 10^{-5} & (2.615 \times 10^{-4})^2 \end{bmatrix}$.

The corresponding ROC curves are shown in Figure 3.4 for 0, 1, 3 and 5 years prior to death at the visit time of 10 years (year 0 implies that the death occurred at 10 years since the enrolment to the study). Figure 3.4 shows that the discrimination is better when the biomarker is measured at times closer to death.

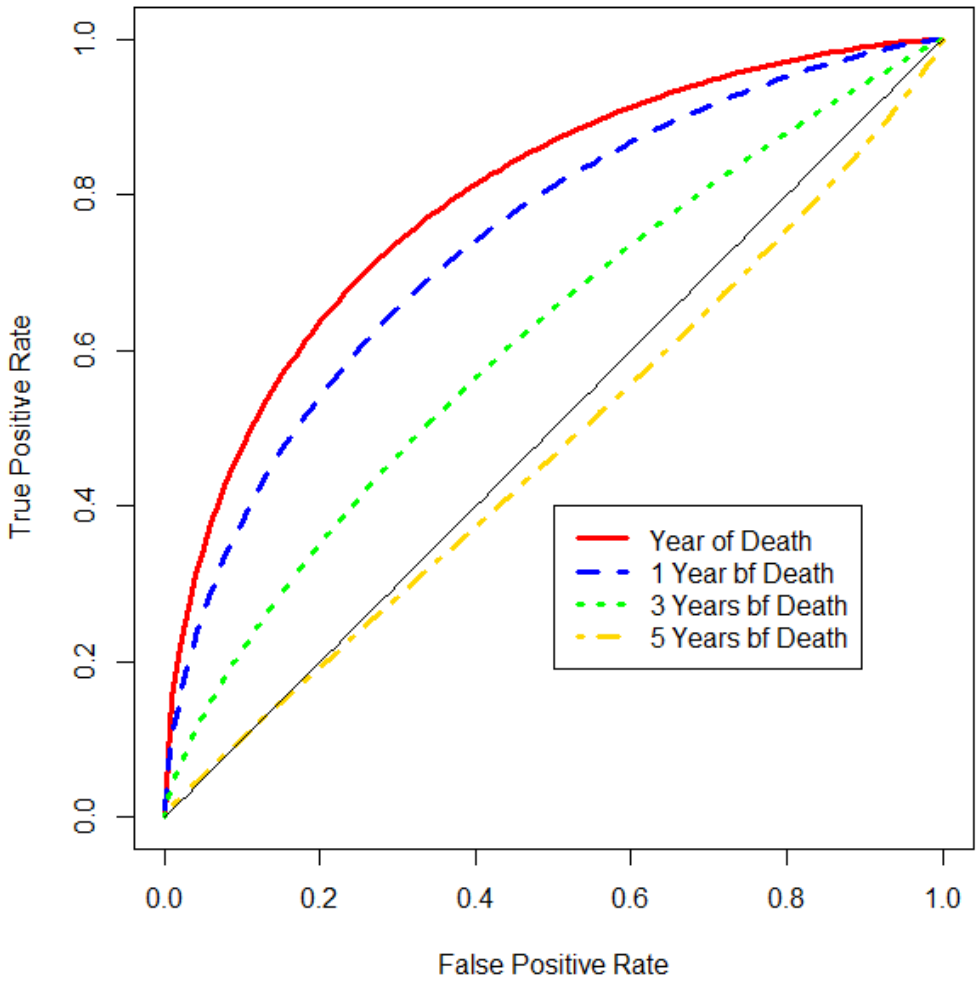

Figure 3.4: Time-dependent ROC curves for 0, 1, 3, 5 years prior to death for the biomarker measured at visit time at ten years.

3.6 Discussion

Although C/D is the most common method being applied, if a researcher has a specific time point of interest in order to distinguish between individuals with an event and individuals without an event at that time point, I/D or I/S is more appropriate. Since I/S requires a fixed follow-up to observe the clinical outcome of interest, it can be applied in long follow-up studies with longitudinally measured biomarkers. C/D and I/D are usually used for a single biomarker value while I/S can include a longitudinal biomarker. As the disease status of an individual may change during the follow-up, the

biomarker values may also change, and hence, the most recent biomarker value may be best related to the current disease status of an individual. Thus, the usage of the most recent biomarker value prior to a target prediction time t is acceptable for the proposed extensions in this chapter.

None of the methods discussed earlier used a complete history of a longitudinal biomarker conditional on the actual event-time. In AD1 method, although all longitudinal biomarker measurements were used, the event-time for the controls was ignored. Therefore, an approach considering a more complete record of each individual when estimating the ROC summaries over time is more appropriate. Further, most current methodologies use nonparametric modelling to estimate the ROC curve, however, when data is following a specific distribution, using a parametric approach is more appropriate and offers more accurate results. Motivated by these findings, this thesis propose two novel methods to estimate the ROC curve, and these will be discussed in detail in the next two chapters; Chapter 4 and Chapter 5.

4 Parametric approach to estimate the time-dependent ROC curve

4.1 Introduction

This chapter is aimed to propose a novel methodology for estimating time-dependent ROC curves based on a parametric approach. In most studies, a nonparametric modelling approach is preferable compared to a parametric approach to avoid any strong assumptions of the data. Some ROC curve studies have concluded that a nonparametric approach has similar performance to a parametric approach [3, 68]. However, in the case when the data is distributed along a specific distribution, treating and modelling such data using the parametric approach is more appropriate and offers more accurate results. Thus, although a parametric approach can induce complexity in terms of model assumptions and specification, exploring possible estimation methods and understanding the difficulties is worth it because it provides models with specific distributions and gives more powerful results.

The semiparametric approach uses a combination of nonparametric and parametric approaches. The parametric part that has been used the most is the linking of these two distributions which requires assumptions and specifications for the model [3]. As discussed in Chapter 3, the main disadvantage of the nonparametric approach is the assumption of independence of the censoring time with the biomarker; the semiparametric model overcomes this problem [2]. However, a fully parametric model will always be efficient and allow biomarker-dependent censoring, as long as the time-to-event model is not misspecified which may lead to dramatic bias [40, 69]. Also analysing a small size of dataset which follows a specific parametric distribution using a parametric approach can produce more precise results. A dataset that has more specifications in terms of the parameter assumptions, provides more useful information to understand in depth the nature of the data.

As discussed extensively in the methodological review in Chapter 3, a parametric approach is uncommon in time-dependent ROC curve estimation. There is one study that has been discussed (AD1) using the most common ROC parametric model which is the binormal model, where it is assumed both cases and controls are normally

distributed with different means [32]. They did not assume any joint distribution of the biomarker value and event time data, and only include the event time term in the model for cases since it does not apply to controls. No study has proposed using the joint event-time and biomarker distribution formulated from parametric distributions. In this chapter, a methodology to estimate the time-dependent ROC curve, specifically the sensitivity, specificity and AUC that uses a joint distribution of the event-time and the biomarker to derive these quantities is proposed. The proposed approach is based on the C/D definition (Section 2.3, Chapter 2) as this is the most commonly used definition in current methods and the most popular in clinical applications [33].

The general framework of the proposed method is presented in Section 4.2 including the formulation of the joint distribution of event time and biomarker value and the derivation of the respective sensitivity, specificity and AUC. The assumptions of the proposed model is introduced in Section 4.3 together with various parametric distribution combinations for event-time and biomarker value, and two different link functions. The formulation of the likelihood function for each combination and link function is discussed in Section 4.3.2. The step-by-step procedure of formulating the joint distribution, likelihood function and the parameter estimation for the simplest distribution combination is shown in Section 4.4 and for the other complex settings are shown in Section 4.5. The application of the proposed method is illustrated in Section 4.6 using Mayo Clinic PBC data.

4.2 General Framework

4.2.1 Joint Distribution Formulation

Let T_i be the event time and X_i be a baseline biomarker value for the ith individual. Denote δ_i as the indicator of the event, taking values 1 if the event occurred at time T_i, and 0 if it did not. The data is observed as $\{X_i, T_i, \delta_i\}$, $i = 1, \dots, n$ for the n individuals in the study dataset.

Both the biomarker values and the event-time data are assumed to follow some parametric distributions and are linked through a linear relationship of the parameters

to form a joint distribution. For the simplest setting, we assume all individuals have the event and no censored observation occurs.

The steps for obtaining the joint distribution of T_i and X_i are as illustrated in Figure 4.1. First, the parametric marginal distributions function for T_i and X_i are defined as $f(t, \boldsymbol{\alpha})$ and $g(x, \boldsymbol{\gamma})$ respectively, where $\boldsymbol{\alpha}$ and $\boldsymbol{\gamma}$ are the sets of parameters for each distribution. Second, these two distributions are linked by modelling X_i on the parameters of T_i, such as $\boldsymbol{\alpha} = h(x, \boldsymbol{\beta})$ where $h(.)$ is a link function and $\boldsymbol{\beta}$ is a set of parameters used in the link function. Third, the conditional distribution of $T_i$given X_i, $f\big(t, h(x, \boldsymbol{\beta})\big)$ is formed. Finally, the conditional distribution, $f\big(t, h(x, \boldsymbol{\beta})\big)$ and the marginal distribution of X_i, $g(x, \boldsymbol{\gamma})$ are multiplied to get the joint density of X_i and T_i such that $f(t, x, \boldsymbol{\gamma}, \boldsymbol{\beta}) = f\big(t, h(x, \boldsymbol{\beta})\big) \times g(x, \boldsymbol{\gamma})$. This formulated joint distribution is then used to derive the sensitivity, specificity and AUC under the C/D definition as in Section 4.2.2 below.

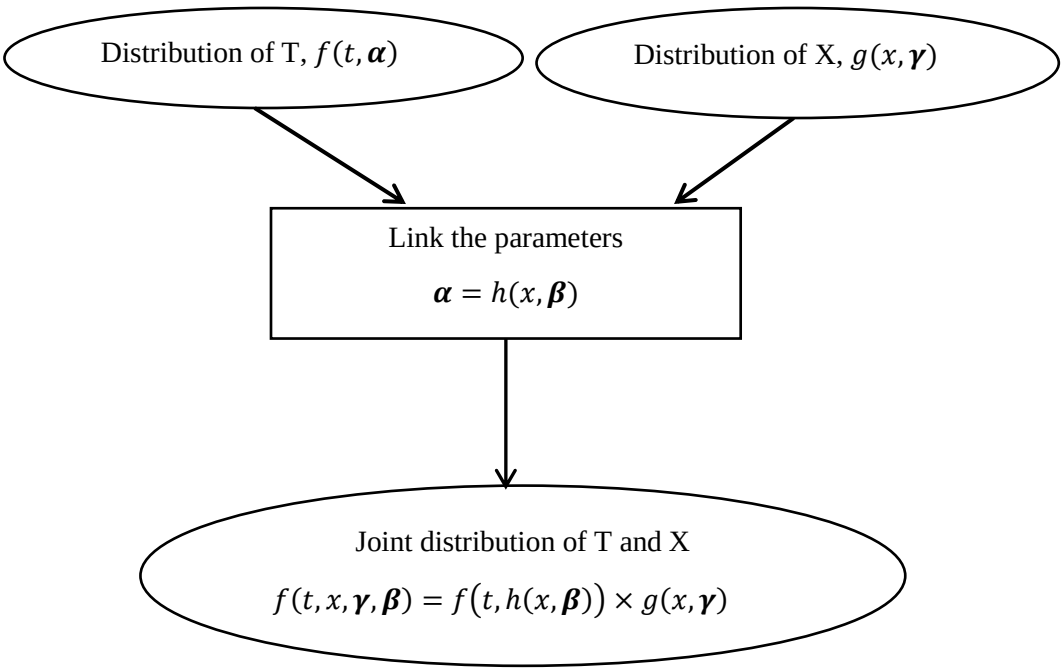

Figure 4.1: Steps for formulating the joint distribution of X_i and T_i

4.2.2 Derivation of Time-Dependent ROC curves

In Chapter 2, the general C/D time-dependent sensitivity, specificity and AUC have been defined in equations (2.1-2.3). Here, the general form of the C/D parametric time-dependent sensitivity, specificity and AUC are derived from the joint distribution of X_i and T_i as formulated in Section 4.2.1 which are as follows:

$$Se(c,t) = P(X_i > c | T_i \leq t) = \frac{\int_c^{\infty}\int_0^t f(t,x,\boldsymbol{\gamma},\boldsymbol{\beta})\, dtdx}{\int_0^{\infty}\int_0^t f(t,x,\boldsymbol{\gamma},\boldsymbol{\beta})\, dtdx},$$

$$Sp(c,t) = P(X_i \leq c | T_i > t) = \frac{\int_0^c\int_t^{\infty} f(t,x,\boldsymbol{\gamma},\boldsymbol{\beta})\, dtdx}{\int_0^{\infty}\int_t^{\infty} f(t,x,\boldsymbol{\gamma},\boldsymbol{\beta})\, dtdx},$$

$$\begin{aligned} AUC(c,T,\boldsymbol{\gamma},\boldsymbol{\beta}) &= P(X_1 > X_2 | T_1 \leq t, T_2 > t) \\ &= \frac{\int_0^{\infty}\int_{x_2}^{\infty}\int_t^{\infty}\int_0^t f(t_1,t_2,x_1,x_2,\boldsymbol{\gamma},\boldsymbol{\beta})\, dt_1dt_2dx_1dx_2}{\int_0^{\infty}\int_0^{\infty}\int_t^{\infty}\int_0^t f(t_1,t_2,x_1,x_2,\boldsymbol{\gamma},\boldsymbol{\beta})\, dt_1dt_2dx_1dx_2}. \end{aligned}$$

When no censoring occurs, the disease status for all individuals is equal to one by the end of the follow up. Thus, in calculating these quantities, the disease status is assessed at the target time based on the event-time. If the event time is less than the target time, the individual has the disease while if it greater than the target time, individual still survives at t.

For a study that includes censoring data, the sensitivity and specificity are calculated separately between cases and controls. The censored individuals are not ignored in this methodology because the available information up to t has been considered through the integration of the joint distribution of X and T at each target time t.

In the current estimation of time-dependent ROC curves methodologies, above quantities are estimated using a bivariate normal distribution (see NNE method in Chapter 3, Section 3.3.2) and modelled nonparametrically. In this chapter, the joint parametric distribution of X and T are used to directly derive the time-dependent ROC curve quantities and these are discussed in detail in the next subsection.

4.3 Modelling proposed parametric approach

4.3.1 Distributional assumptions

The ROC curve is usually modelled separately for cases and controls using a binormal model. Since only cases have the event, the event time is modelled only for the case individuals as a covariate [32]. In the time-dependent approach the bivariate distribution of X and T is required for estimating the sensitivity, specificity and AUC. However, most studies in the literature used a bivariate normal distribution or log normal of event time, followed by a nonparametric approach to estimate the distribution [2, 27]. The proposed approach is different in that some parametric distributions of marginal X and T are assumed to form a joint distribution of X and T and then derive the sensitivity, specificity and AUC.

In event-time or survival data analysis, the event time distribution is usually highly skewed. In parametric methods, it is a common practice to normalise data, however some data give a better understanding if the original distribution is retained. In this chapter, the exponential and Weibull distributions are assumed for event times and the exponential and normal distributions are assumed for biomarker values. The combinations of event time and biomarker value distributions respectively are as follow:

i. exponential / exponential
ii. nxponential / normal
iii. Weibull / normal

For each distribution, the relationship between T and X is varied through the parameters involved. To illustrate how the distributions are linked, the first case (i) which assumes both event time and biomarker value are exponentially distributed, is considered.

Let $T \sim \exp(\lambda)$ and $X \sim \exp(\mu)$ Two link functions are used. The expected value of T is $1/\lambda$, which is modelled in terms of a given biomarker value X by

$$\lambda = \beta x.$$

Thus the ith individual has $T_i \sim \exp(\beta x_i)$. In this thesis, it is always assumed there is a negative relationship between event time and biomarker value, so that higher biomarker values are more indicative of disease [10]. The second link function is

$$\lambda = \beta_0 + \beta_1 x.$$

Thus the ith individual has $T_i \sim \exp(\beta_0 + \beta_1 x_i)$. The most parsimonious linear relationship is used for simplification, but more complex relationships could be used. Among all considered parametric distribution combinations, only the closed-form estimators are available for the Exponential/Exponential case from the first link function. The other distributions and the second link function has involved more complicated statistical computations and required numerical solutions.

4.3.2 Likelihood Formulation

If no censoring occurs and all individuals in the study experience the event by the end of the follow-up, the likelihood function is defined by

$$L(\boldsymbol{\gamma}, x_1, \dots, x_n) = \prod_{i=1}^{n} f(x_i; \boldsymbol{\gamma})$$

where $\boldsymbol{\gamma}$ is the parameter involved. For a study with censored event outcomes, an additional survival function is needed in the likelihood formulation. The observed event-time T_i is defined by $T_i = \min(T_i^*, C_i)$ where T_i^* is the true event-time and C_i is the censoring time for i th individual. Two separate functions are defined which are $f_1(x)$ for the actual events and $f_2(x)$ for censored events, with the respective survival functions, $S_1(t)$ and $S_2(t)$. Thus, the likelihood function can be defined by

$$\begin{aligned} L &= \prod_{i=1}^{n} \{f_1(x_i), S_2(t_i)\}^{\delta_i} \{f_2(x_i), S_1(t_i)\}^{1-\delta_i} \\ &= \prod_{i=1}^{n} \{f_1(x_i), S_2(t_i)\}^{\delta_i} \times \prod_{i=1}^{n} \{f_2(x_i), S_1(t_i)\}^{1-\delta_i} \end{aligned}$$

The joint biomarker and event-time distribution, and the likelihood formulation are as follows:

The joint distribution function is

$$f(t,x) = \left\{f_1(t,x), \int_t^{\infty} S_2(z,x)dz\right\}^{\delta} \left\{f_2(t,x), \int_t^{\infty} S_1(z,x)\,dz\right\}^{1-\delta}$$

$$= \left\{[f_1(t,x)]^{\delta}, \left[\int_t^{\infty} S_1(z,x)dz\right]^{1-\delta}\right\} \times \left\{[f_1(t,x)]^{\delta}, \left[\int_t^{\infty} S_1(z,x)dz\right]^{1-\delta}\right\}$$

Thus, the likelihood can be defined by

$L = \prod_{i=1}^{n} \left\{[f_1(t_i,x_i)]^{\delta_i}\left[\int_t^{\infty} S_1(z_i,x_i)dz\right]^{1-\delta_i}\right\}$ and specifically, in the context of this chapter

$$(\boldsymbol{\gamma},\boldsymbol{\beta};t_1,\dots,t_n;x_1,\dots,x_n) = \prod_{i=1}^{n} f(t_i,x_i;\boldsymbol{\gamma},\boldsymbol{\beta})^{\delta_i} S(t_i|x_i;\boldsymbol{\gamma},\boldsymbol{\beta})^{1-\delta_i}.$$

4.4 Modelling and estimation in the simplest setting

4.4.1 Exponential/Exponential when $\boldsymbol{\lambda = \beta x}$

Adapting the steps that have been discussed in 4.2.1, the joint distribution function is formulated for the Exponential/Exponential case. The event time and the biomarker value are assumed to follow exponential distributions with mean λ and μ respectively. Let $T \sim \exp(\lambda)$ with marginal distribution $f(t) = \lambda e^{-\lambda t}$ and $X \sim \exp(\mu)$ with marginal distribution $g(x) = \mu e^{-\mu x}$. The conditional distribution function can then be defined as $f(t|x) = \beta x e^{-\beta x t}$. The joint distribution function is obtained by multiplying the conditional distribution with the marginal distribution of the biomarker,

$$f(t,x) = f(t|x) \times g(x) = \mu\beta x\, e^{-(\beta t+\mu)x}.$$

The joint distribution function $f(t,x)$is used to determine the closed form of sensitivity, specificity and AUC functions as follows:

$$Se(c,t,\mu,\beta) = P(X_i \geq c | T_i \leq t) = \frac{\int_c^{\infty}\int_0^t \mu\beta x\, e^{-(\beta t+\mu)x}\, dtdx}{\int_0^{\infty}\int_0^t \mu\beta x\, e^{-(\beta t+\mu)x}\, dtdx}$$

$$= e^{-\mu c}\left[1 + \frac{\mu\left(1 - e^{-\beta tc}\right)}{\beta t}\right],$$

$$Sp(c,t,\mu,\beta) = P(X_i < c | T_i > t) = \frac{\int_0^{c}\int_t^{\infty} \mu\beta x\, e^{-(\beta t+\mu)x}\, dtdx}{\int_0^{\infty}\int_t^{\infty} \mu\beta x\, e^{-(\beta t+\mu)x}\, dtdx}$$

$$= 1 - e^{-(\beta t+\mu)c} \text{ and } AUC(\mu,\beta) = \frac{2\mu + 3\beta t}{2\mu + 4\beta t}.$$

Instead of using the above AUC closed form formula, it also can be determined by calculating the area under the plotted sensitivity and specificity using the trapezoidal rule, which is interchangeably used in this thesis.

4.4.2 Estimation of parameters

The parameters for each distribution are estimated using the maximum likelihood estimation (MLE) procedure. As discussed in Section 4.3.2, the likelihood function can be formulated when only joint distribution function is available (for uncensored case) and when it needs an additional survival function (for censored data). The parameters involved in the joint distribution function of the exponential/exponential case include the mean of X (μ) and the coefficient β from the link model that has been used to connect the two distributions.

When there is no censored outcomes, the likelihood function can be defined by

$$L(\mu,\beta; x_1,\dots,x_n; t_1,\dots,t_n) = \prod_{i=1}^{n}\left(\mu\beta x_i e^{-(\beta t_i+\mu)x_i}\right) = (\mu\beta)^n \prod_{i=1}^{n}\left(x_i e^{-(\beta t_i+\mu)x_i}\right).$$

The log-likelihood function is

$$\ln L(\mu,\beta; x_1,\dots,x_n; t_1,\dots,t_n) = n\ln\mu + n\ln\beta + \sum_{i=1}^{n}\ln\left(x_i + e^{-(\beta t_i+\mu)x_i}\right),$$

and it is simplified as

$$\ln L(\mu, \beta; x_1, \dots, x_n; t_1, \dots, t_n) \tag{4.1}$$
$$= n \ln \mu + n \ln \beta + \sum_{i=1}^{n} \ln(x_i) - \left(\beta \sum_{i=1}^{n} t_i + \mu\right) \sum_{i=1}^{n} x_i$$

Thus, the MLE estimator of both parameters can be estimated by maximising the likelihood function in equation (4.1). The log-likelihood function is differentiated with respect to each of the parameters and equated to zero:

$$\frac{\partial \ln L(\mu, \beta; x_1, \dots, x_n; t_1, \dots, t_n)}{\partial \mu} = \frac{n}{\mu} - \sum_{i=1}^{n} x_i = 0 \text{ and}$$

$$\frac{\partial \ln L(\mu, \beta; x_1, \dots, x_n; t_1, \dots, t_n)}{\partial \beta} = \frac{n}{\beta} - \sum_{i=1}^{n} x_i t_i = 0.$$

Thus the MLE for μ and β are respectively $\widehat{\mu} = \frac{n}{\sum_{i=1}^{n} x_i} = \frac{1}{\bar{x}}$ and $\widehat{\beta} = \frac{n}{\sum_{i=1}^{n} x_i t_i}$.

For a study including censored data, the likelihood function is defined by
$L(\mu, \beta; x_1, \dots, x_n) = \prod_{i=1}^{n} f(t_i, x_i; \mu, \beta)^{\delta_i} S(t_i | x_i; \mu, \beta)^{1-\delta_i}$.

The conditional distribution of event time given the biomarker value, $S(t_i | x_i; \mu, \beta)$ is estimated as follow

$$S(t_i | x_i; \mu, \beta) = \int_{t_i}^{\infty} \mu\beta x_i e^{-(\beta x_i u + \mu x_i)} du = \left[\frac{\mu\beta x_i e^{-(\beta x_i u + \mu x_i)}}{-\beta x_i}\right]_{t_i}^{\infty} = -\mu e^{-(\beta t + \mu) x_i},$$

and the likelihood function can be defined by

$$L(\mu, \beta; x_1, \dots, x_n) = \prod_{i=1}^{n} \left(\mu\beta x_i e^{-(\beta t_i + \mu) x_i}\right)^{\delta_i} \left(-\mu e^{-(\beta t + \mu) x_i}\right)^{1-\delta_i}.$$

Since the differentiation of this likelihood is computationally complicated, it is maximised numerically. An R function is written for this maximisation and attached in the Appendix A.1.

4.5 Modelling and estimating in more complex settings

4.5.1 Exponential/Exponential when $\lambda = \beta_0 + \beta_1 x$

In this case, the exponential/exponential case with $\lambda = \beta_0 + \beta_1 x$ is considered. In this case, $T \sim \exp(\lambda)$ with marginal distribution function $f(t) = \lambda e^{-\lambda t}$ and $X \sim \exp(\mu)$ with marginal distribution $g(x) = \mu e^{-\mu x}$. These two functions are linked using $= \beta_0 + \beta_1 x$. Thus the ith individual now has $T_i \sim \exp(\beta_0 + \beta_1 x_i)$ with the conditional distribution function defined as $f(t|x) = (\beta_0 + \beta_1 x) e^{-(\beta_0 + \beta_1 x)t}$. The joint distribution function can be obtained by multiplying the conditional distribution with the marginal distribution of biomarker,

$$f(t, x) = f(t|x) \times g(x) = \mu(\beta_0 + \beta_1 x) e^{-(\mu x + \beta_0 t + \beta_1 x t)}.$$

The closed form of the time-dependent sensitivity, specificity and AUC functions for this case are not derived manually but estimated using numerical integrations in R. The R codes are available in the Appendix A.1.

Estimation of Parameters

The parameters involved in the joint distribution is the parameter for the biomarker value and the link function coefficients. The likelihood function when there is no censored outcome can be defined by

$$L(\mu, \beta_0, \beta_1; x_1, \dots, x_n; t_1, \dots, t_n)$$
$$= \prod_{i=1}^{n} \mu(\beta_0 + \beta_1 x_i) e^{-(\mu x_i + \beta_0 t_i + \beta_1 x_i t_i)} = (\mu\beta_0)^n \prod_{i=1}^{n} \left(\beta_1 x_i e^{-(\mu x_i + \beta_0 t_i + \beta_1 x_i t_i)}\right).$$

Taking the natural log of the likelihood, it becomes

$$\ln L(\mu, \beta_0, \beta_1; x_1, \dots, x_n; t_1, \dots, t_n) = n \ln \mu + n \ln \beta_0 + \sum_{i=1}^{n} \ln\left(\beta_1 x_i e^{-(\mu x_i + \beta_0 t_i + \beta_1 x_i t_i)}\right)$$

And can be written as

$$= n \ln \mu + n \ln \beta_0 + \sum_{i=1}^{n} \ln(\beta_1 x_i) - \left(\mu \sum_{i=1}^{n} x_i + \beta_0 \sum_{i=1}^{n} t_i + \beta_1 \sum_{i=1}^{n} x_i t_i\right)$$

The log likelihood function is then maximised with respect to each parameter. These steps are shown below.

$$\frac{\partial \ln L(\mu, \beta_0, \beta_1; x_1, \dots, x_n; t_1, \dots, t_n)}{\partial \mu} = \frac{n}{\mu} - \sum_{i=1}^{n} x_i = 0 \text{ for } \mu,$$

$$\frac{\partial \ln L(\mu, \beta_0, \beta_1; x_1, \dots, x_n; t_1, \dots, t_n)}{\partial \beta_0} = \frac{n}{\beta_0} - \sum_{i=1}^{n} t_i = 0 \text{ for } \beta_0 \text{ and}$$

$$\frac{\partial \ln L(\mu, \beta_0, \beta_1; x_1, \dots, x_n; t_1, \dots, t_n)}{\partial \beta_1} = \frac{1}{\beta_1 \sum_{i=1}^{n} x_i} \sum_{i=1}^{n} x_i - \sum_{i=1}^{n} x_i t_i = 0 \text{ for } \beta_1.$$

Thus the corresponding ML estimators take the form

$$\widehat{\mu} = \frac{n}{\sum_{i=1}^{n} x_i} = \frac{1}{\bar{x}}, \widehat{\beta}_0 = \frac{n}{\sum_{i=1}^{n} t_i} \text{ and } \widehat{\beta}_1 = \frac{1}{\sum_{i=1}^{n} x_i t_i}.$$

The likelihood function when there exist censored outcomes can be defined by

$$L(\mu, \beta_0, \beta_1; x_1, \dots, x_n) = \prod_{i=1}^{n} f(t_i, x_i, \mu, \beta_0, \beta_1)^{\delta_i} S(t_i | x_i, \mu, \beta_0, \beta_1)^{1-\delta_i}$$

The survival function is estimated by integrating the joint distribution with respect to t,

$$S(t_i | x_i, \mu, \beta_0, \beta_1) = \int_{t_i}^{\infty} \mu(\beta_0 + \beta_1 x)\, e^{-(\beta_0 + \beta_1 x)u - \mu x} du.$$

Thus,

$$S(t_i | x_i, \mu, \beta_0, \beta_1) = \mu(\beta_0 + \beta_1 x) \left[\frac{e^{-(\beta_0 + \beta_1 x)u - \mu x}}{-(\beta_0 + \beta_1 x)} \right]_{t_i}^{\infty} = \mu e^{-(\beta_0 + \beta_1 x)t - \mu x},$$

and the likelihood function finally can be defined by

$$L(\mu, \beta; x_1, \dots, x_n) = \prod_{i=1}^{n} \left(\mu(\beta_0 + \beta_1 x) e^{-(\mu x + \beta_0 t + \beta_1 x t)} \right)^{\delta_i} \left(\mu e^{-(\beta_0 + \beta_1 x)t - \mu x} \right)^{1-\delta_i}.$$

The ML estimation of the parameters is done by using a function written in R and is attached in the Appendix A.1.

4.5.2 Exponential/Normal

In most studies, the biomarker value is assumed to have a normal distribution especially when the sample size is large, or if not, it will be transformed to the normal distribution for simplification during the analysis part. Let $T \sim \exp(\lambda)$ with marginal distribution of $f(t) = \lambda e^{-\lambda t}$ and $X \sim N(\mu, \sigma^2)$ with marginal distribution $g(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$. When these two distributions are linked through the expected value of T by $\lambda = \beta x$, thus the ith individual has $T_i \sim \exp(\beta x_i)$, where the conditional distribution function can be defined as $f(t|x) = (\beta x) e^{-(\beta x)t}$. The joint distribution function can be obtained by multiplying the conditional distribution with the marginal distribution of the biomarker,

$$f(t,x) = f(t|x) \times g(x) = \frac{\beta x}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2} - \beta x t}.$$

Considering the second link function, $\lambda = \beta_0 + \beta_1 x$ leads to the ith individual having $T_i \sim \exp(\beta_0 + \beta_1 x_i)$, where the conditional distribution function can be defined as $f(t|x) = (\beta_0 + \beta_1 x) e^{-(\beta_0 + \beta_1 x)t}$. The joint distribution function is obtained by multiplying the conditional distribution with the marginal distribution of the biomarker,

$$f(t,x) = f(t|x) \times g(x) = \frac{\beta_0 + \beta_1 x}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2} - (\beta_0 + \beta_1 x)t}.$$

Estimation of Parameters

There are two parameters from the biomarker value distribution, μ and σ^2 while $\boldsymbol{\beta}$ parameters are from the link function. The likelihood function for the first link function $\lambda = \beta x$ is as follow

$$L(\mu,\sigma,\beta;x_1,\dots,x_n;t_1,\dots,t_n)=\prod_{i=1}^{n}\frac{\beta x}{\sigma\sqrt{2\pi}}e^{-\frac{(x-\mu)^2}{2\sigma^2}-\beta xt}.$$

While the likelihood function for the second link function $\lambda = \beta_0 + \beta_1 x$ is

$$L(\mu,\sigma,\beta_0,\beta_1;x_1,\dots,x_n;t_1,\dots,t_n)=\prod_{i=1}^{n}\frac{\beta_0+\beta_1 x}{\sigma\sqrt{2\pi}}e^{-\frac{(x-\mu)^2}{2\sigma^2}-(\beta_0+\beta_1 x)t}.$$

The corresponding likelihood function for censored outcome for the first link function is defined by

$$L(\mu,\beta;x_1,\dots,x_n)=\prod_{i=1}^{n}f(t_i,x_i;\mu,\sigma,\beta)^{\delta_i}S(t_i|x_i;\mu,\sigma,\beta)^{1-\delta_i},$$

and the survival function, $S(t_i|x_i;\mu,\sigma,\beta)$ can be estimated by

$$\begin{aligned}S(t_i|x_i,\mu,\sigma,\beta)&=\int_{t_i}^{\infty}\frac{\beta x_i}{\sigma\sqrt{2\pi}}e^{-\left[\frac{(x-\mu)^2}{2\sigma^2}-\beta x_i u\right]}du\\&=\frac{\beta x_i}{\sigma\sqrt{2\pi}}\left[\frac{e^{-\left[\frac{(x-\mu)^2}{2\sigma^2}-\beta x_i u\right]}}{-\beta x_i}\right]_{t_i}^{\infty}\\&=\frac{e^{-\left[\frac{(x-\mu)^2}{2\sigma^2}-\beta x_i t_i\right]}}{\sigma\sqrt{2\pi}},\end{aligned}$$

and thus,

$$\begin{aligned}L(\mu,\beta;x_1,\dots,x_n)&=\prod_{i=1}^{n}f(t_i,x_i;\mu,\sigma,\beta)^{\delta_i}S(t_i|x_i;\mu,\sigma,\beta)^{1-\delta_i}\\&=\prod_{i=1}^{n}\left(\frac{\beta x}{\sigma\sqrt{2\pi}}e^{-\frac{(x-\mu)^2}{2\sigma^2}-\beta xt}\right)^{\delta_i}\left(\frac{e^{-\left[\frac{(x-\mu)^2}{2\sigma^2}-\beta x_i t_i\right]}}{\sigma\sqrt{2\pi}}\right)^{1-\delta_i}.\end{aligned}$$

For the second link function, the likelihood function takes the form

$$L(\mu,\sigma,\beta_0,\beta_1;x_1,\dots,x_n)=\prod_{i=1}^{n}f(t_i,x_i,\mu,\sigma,\beta_0,\beta_1)^{\delta_i}\,S(t_i|x_i,\mu,\sigma,\beta_0,\beta_1)^{1-\delta_i}$$

where the $S(t_i|x_i,\mu,\sigma,\beta_0,\beta_1)$ is estimated by

$$S(t_i|x_i,\mu,\beta_0,\beta_1)=\frac{\beta_0+\beta_1x}{\sigma\sqrt{\pi}}\left[\frac{e^{-\left[\frac{(x-\mu)^2}{2\sigma^2}+(\beta_0+\beta_1x)u\right]}}{-(\beta_0+\beta_1x)}\right]_{t_i}^{\infty}=\frac{e^{-\left[\frac{(x-\mu)^2}{2\sigma^2}+(\beta_0+\beta_1x)t_i\right]}}{\sigma\sqrt{\pi}}.$$

Thus the likelihood function can be defined by

$$L(\mu,\sigma,\beta_0,\beta_1;x_1,\dots,x_n;t_1,\dots,t_n)$$
$$=\prod_{i=1}^{n}\left(\frac{\beta_0+\beta_1x}{\sigma\sqrt{2\pi}}e^{-\frac{(x-\mu)^2}{2\sigma^2}-(\beta_0+\beta_1x)t}\right)^{\delta_i}\left(\frac{e^{-\left[\frac{(x-\mu)^2}{2\sigma^2}+(\beta_0+\beta_1x)t_i\right]}}{\sigma\sqrt{\pi}}\right)^{1-\delta_i}.$$

The parameter are estimated using the maximisation numerically procedure and the R code is attached in the Appendix A.2.

4.5.3 Weibull/Normal

Now, the distribution of event time is considered as having Weibull distribution with two parameters which are λ and k. Let $T\sim$Weibull(λ,k) with marginal distribution $f(t)=\lambda k(\lambda t)^{k-1}e^{-(\lambda t)^k}$and $X\sim N(\mu,\sigma^2)$ with marginal distribution $g(x)=\frac{1}{\sigma\sqrt{2\pi}}e^{-\frac{(x-\mu)^2}{2\sigma^2}}$. Considering the first link function $\lambda=\beta x$, the ith individual has $T_i\sim$Weibull(βx$_i,k$) where the conditional distribution function can be defined as $f(t|x)=\beta xk(\beta xt)^{k-1}e^{-\frac{(x-\mu)^2}{2\sigma^2}-(\beta xt)^k}$. The joint distribution function is obtained by multiplying the conditional distribution with the marginal distribution of biomarker,

$$f(t,x)=f(t|x)\times g(x)=\frac{\beta xk(\beta xt)^{k-1}}{\sigma\sqrt{2\pi}}e^{-\frac{(x-\mu)^2}{2\sigma^2}-(\beta xt)^k}.$$

Considering the second link function $\lambda=\beta_0+\beta_1x$, the ith individual has $T_i\sim$Weibull$(\beta_0+\beta_1x_i,k)$ where the conditional distribution function can be defined as

$$f(t|x)=(\beta_0+\beta_1x)k[(\beta_0+\beta_1x)t]^{k-1}e^{-[(\beta_0+\beta_1x)t]^k}.$$

The joint distribution function is obtained by multiplying the conditional distribution with the marginal distribution of biomarker,

$$f(t,x) = f(t|x) \times g(x) = \frac{(\beta_0 + \beta_1 x)k[(\beta_0 + \beta_1 x)t]^{k-1} e^{-\left[\frac{(x-\mu)^2}{2\sigma^2} + (\beta_0 t + \beta_1 xt)^k\right]}}{\sigma\sqrt{2\pi}}.$$

Estimation of Parameters

Parameters involved in the joint distribution are μ and σ^2 from the biomarker value distribution and $\boldsymbol{\beta}$ which represent the coefficients of the link function. These parameters are estimated using MLE and the derivation of the likelihood functions are for the first link function $\lambda = \beta x$ is

$$L(\mu, \sigma, \beta; x_1, \dots, x_n; t_1, \dots, t_n) = \prod_{i=1}^{n} \frac{\beta x k(\beta x t)^{k-1}}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2} - (\beta x t)^k},$$

while the likelihood function for the second link function $\lambda = \beta_0 + \beta_1 x$ is

$$L(\mu, \sigma, \beta_0, \beta_1; x_1, \dots, x_n; t_1, \dots, t_n)$$
$$= \prod_{i=1}^{n} \frac{(\beta_0 + \beta_1 x)k[(\beta_0 + \beta_1 x)t]^{k-1} e^{-\left[\frac{(x-\mu)^2}{2\sigma^2} + (\beta_0 t + \beta_1 xt)^k\right]}}{\sigma\sqrt{2\pi}}.$$

The corresponding likelihood function for censored outcome is defined by

$$L(\mu, \beta; x_1, \dots, x_n) = \prod_{i=1}^{n} f(t_i, x_i; \mu, \sigma, \beta)^{\delta_i} S(t_i|x_i; \mu, \sigma, \beta)^{1-\delta_i},$$

and the conditional survival function $S(t_i|x_i; \mu, \sigma, \beta)$ function is estimated by

$$S(t_i|x_i, \mu, \sigma, \beta, k) = \int_{t_i}^{\infty} \frac{\beta x k(\beta x t)^{k-1}}{\sigma\sqrt{2\pi}} e^{-\frac{(x-\mu)^2}{2\sigma^2} - (\beta x t)^k}.$$

For the second link

$$S(t_i|x_i, \mu, \beta_0, \beta_1, k) = \int_{t_i}^{\infty} \frac{(\beta_0 + \beta_1 x)k[(\beta_0 + \beta_1 x)t]^{k-1} e^{-\left[\frac{(x-\mu)^2}{2\sigma^2} + (\beta_0 t + \beta_1 xt)^k\right]}}{\sigma\sqrt{2\pi}}.$$

The survival functions and the likelihood functions are maximised numerically and the R code is attached in the Appendix A.3.

4.6 Application on Mayo Clinic PBC data

For the illustration of the proposed methodology in a real application, the model score estimated from the Cox model as discussed in Chapter 1 is used as a biomarker. The distributions of event time and biomarker and their scatter plots for the Mayo Clinic PBC data are shown in Figure 4.2 and Figure 4.3 respectively. Figure 4.2 shows that the distributions of the biomarker value and the event time are slightly skewed to the right with very few individuals have higher biomarker value and higher event time. Figure 4.3 displays the relationship between the event time and the biomarker value. A negative relationship is observed between the event time and biomarker value that indicates individual with higher biomarker value tend to have higher risk of death, and this parallel with the assumption of this thesis.

The histograms and the scatter plots for all three combination of the distributions proposed in Section 4.3.1 when the parameters are assumed as close as in Mayo Clinic PBC data, are displayed in Figure 4.4. Based on Figure 4.4, the scatter plot for the first case (when $\mu = 6$, $\beta = 1$ and n=321), is extremely skewed with very few individuals with higher event time (>250) and higher biomarker value (>0.7). However, it can be observed that individuals with low biomarker value have lower risk of event (high event time) while individuals with high biomarker value have higher risk of event (low event time). The negative relationship is also observed in the second case (when $\mu = 6$, $\beta = 1$ and n=321) but not in the last case when the biomarker is assumed normal and when the Weibull event time is assumed. Thus, it may be useful to use a negative link function for the last case so that the assumption is achieved. Among all cases, the second case which assumed normal biomarker value and exponential event time has the closest distribution with the Mayo Clinic PBC data.

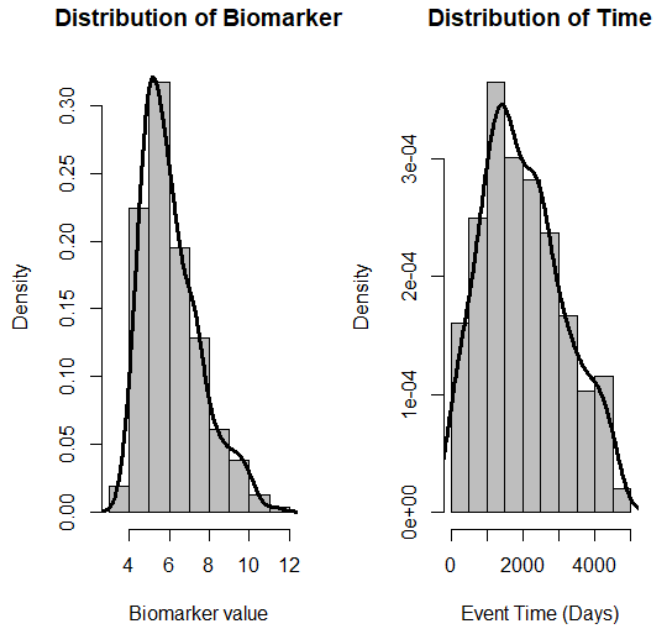

Figure 4.2: Histograms for biomarker and event times

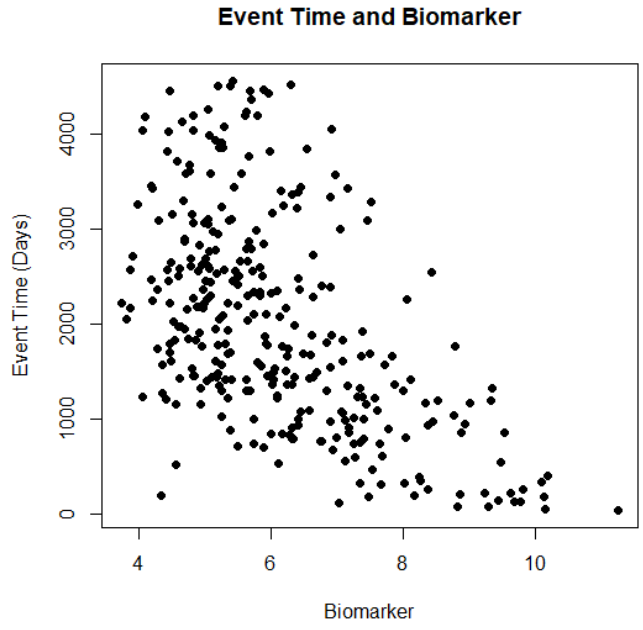

Figure 4.3: Scatter plot for biomarker versus event times

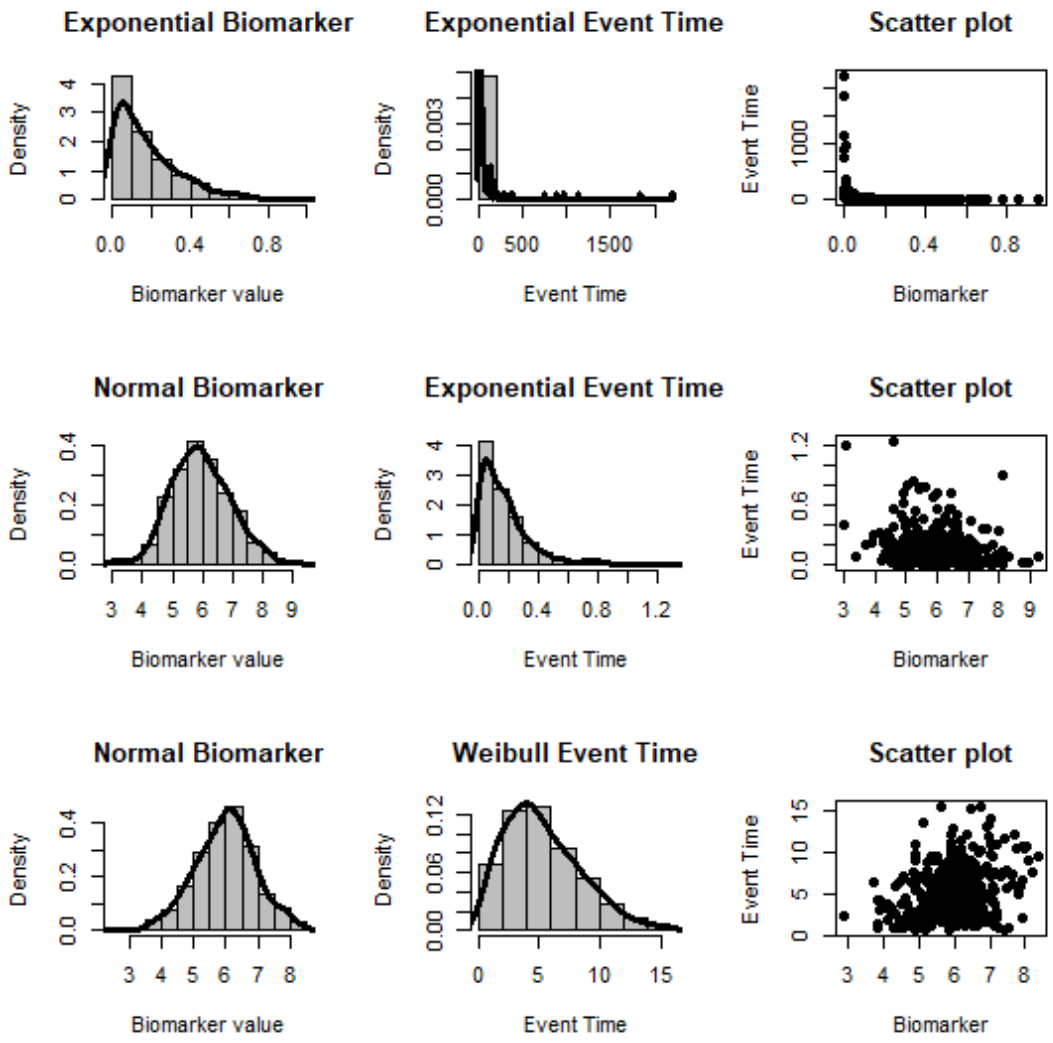

Figure 4.4: Histograms and scatter plots for all distribution combinations (simulated data)

Although the distribution of the biomarker and the event-time in Mayo Clinic PBC data isnot similar with any of the distributions assumed, this data is still used for illustrative purposes of the proposed methodology. The time-dependent AUC is estimated for Year 1, Year 5 and Year 10 as at the same prediction times used in the methodological review in Chapter 3 for each combination of distributions and link functions, and the results are presented in the Table 4.1.

Table 4.1: Estimated time-dependent AUC for proposed methodology

Distribution of Time	Distribution of Biomarker	Link function $\lambda = \beta_0 + \beta_1 x$		AUC(t)		
		β_0	β_1	Year 1	Year 5	Year 10
Exponential	Exponential		1	0.7549	0.7244	0.7379
		1	1	0.8733	0.9612	0.9782
Exponential	Normal		1	0.6920	0.9937	0.9996
		1	1	0.6917	0.9938	0.9999
Weibull	Normal		1	0.9992	0.9999	0.9999
		1	1	0.9999	0.9999	0.9999

Table 4.1 shows the estimated time-dependent AUC for six different scenarios from all three distribution combinations for both link functions. When assume the event-time and biomarker value distributed from an exponential distribution, the AUC values indicate that the model score is good in discriminating the diseased and healthy individuals at all different prediction times. There is no obvious pattern observed for the first link function, but an increasing pattern has shown for the second link function over prediction time. When the biomarker values assumed normal, the AUC values are higher for prediction time are Year 5 and Year 10 for both link functions. When event times are assumed a Weibull distribution and biomarker values are normally distributed, the diagnostic accuracy of the model score is estimated as almost perfect.

4.7 Discussion

In this chapter, six scenarios considering three parametric distributions (exponential, Weibull and normal) of event-times and biomarker values, and two link functions were proposed to estimate the time-dependent ROC curve. The joint distribution and likelihood formulation for complete (no censoring) and incomplete (censored) data were outlined for each scenario. However, the closed form formula for sensitivity, specificity and AUC could only be derived for the simplest scenario

(exponential/exponential). For other scenarios, the estimation of the time-dependent ROC curve summaries were derived numerically. The software was written in R language for the derivations. The proposed method is illustrated using Mayo Clinic PBC data for all 6 scenarios. All estimates of the time-dependent AUC values are between 0.7 to 0.9 which describe a good discriminative power of the model score in discriminating healthy individuals and diseased individuals. Although the underlying distribution of the Mayo PBC data is different with the assumed distribution, the diagnostic accuracy of the model score still can be estimated. However, the AUC value may not indicate the real discriminative power but considering the distribution of the second case as the closest to the distribution of the PBC data, thus the AUC values may be acceptable.

Since this parametric approach used a model score from a Cox model, it is suggested to explore the distribution of other individual biomarkers such as bilirubin, albumin and prothrombin time. If the distributions of the biomarkers are almost similar with the distribution assumed thus the diagnostic accuracy may be more relevant.

5 Simulation Study I: Parametric approach

5.1 Introduction

This chapter is aimed to demonstrate whether the proposed parametric approach to estimate the ROC curve analysis in Chapter 4 is an appropriate framework for estimating the time-dependent accuracies. In Chapter 4, the detailed calculations of estimating the joint distribution of the parametric event-time and biomarker, and likelihood formulation and estimation from various combinations of parametric distributions for censored and uncensored data were proposed. Two aims have been set for this chapter,

1) To demonstrate the validity of the proposed approach to estimate the time-dependent AUC for varying sample sizes with complete data (when event-times are not censored)
2) To estimate the time-dependent AUC with censored event-times (incomplete data)

The rest of this chapter is organised as below. The first aim of the Chapter is investigated in Section 5.2. Section 5.3 considers censored event-times. The results are discussed in Section 5.4.

5.2 Time-dependent AUC for complete data

This simulation is aimed to demonstrate the validity of the proposed approach to estimate the time-dependent AUC for varying sample sizes when the event-time is not censored. The biomarker values (X_i) and event times (T_i) are generated using both link functions discussed in Chapter 4. The sample sizes n are varied at 30, 50, 100, 150, 200 and 500. The disease status is generated from a binomial distribution with probability not having the event is set at 0.3. The biomarker values and event times are generated from 6 scenarios as presented in Table 5.1.

Table 5.1: Complete event data generation

Scenario	Distribution of Marker	Link function	Distribution of event-time	μ	σ^2	β_0	β_1	K
1	Exponential $X \sim \exp(\mu = 1)$	$\lambda = \beta_1 x$	Exponential $T \sim \exp(\lambda = \beta_1 x)$	1			1	
2	Exponential $X \sim \exp(\mu = 1)$	$\lambda = \beta_0 + \beta_1 x$	Exponential $T \sim \exp(\lambda = \beta_0 + \beta_1 x)$	1		1	1	
3	Normal $X \sim \mathrm{N}(\mu = 3, \sigma^2 = 1)$	$\lambda = \beta_1 x$	Exponential $T \sim \exp(\lambda = \beta_1 x)$	3	1		1	
4	Normal $X \sim \mathrm{N}(\mu = 3, \sigma^2 = 1)$	$\lambda = \beta_0 + \beta_1 x$	Exponential $T \sim \exp(\lambda = \beta_0 + \beta_1 x)$	3	1	1	1	
5	Normal $X \sim \mathrm{N}(\mu = 3, \sigma^2 = 1)$	$\lambda = \beta_1 x$	Weibull $T \sim \mathrm{weibull}(\lambda = \beta_1 x)$	3	1		1	2
6	Normal $X \sim \mathrm{N}(\mu = 3, \sigma^2 = 1)$	$\lambda = \beta_0 + \beta_1 x$	Weibull $T \sim \mathrm{weibull}(\lambda = \beta_0 + \beta_1 x)$	3	1	1	1	2

**Darken cells are not applicable for the scenario.*

The biomarker value is generated from an exponential distribution with mean $1/\mu$ or a normal distribution with $\mu = 3$ and $\sigma^2 = 1$ for all sample sizes. For Weibull event times, K is assumed 2. For each simulated dataset, the time-dependent AUCs are estimated at four different prediction times t which are different for exponential and Weibull event time distributions. The parameter values for the exponential, normal and Weibull distributions are randomly chosen for simple illustrative purposes. Any other values of μ, λ, σ^2, β and K can also be used. The prediction times for both exponential and Weibull distributions are selected based on the distribution of the most event time values for each distribution. Prediction times of 0.01, 0.05, 0.07 and 0.10 have been set for event times generated from the exponential distribution because most of the event times are greater than these values while the values of 1.0, 1.5, 1.7 and 2.0 are chosen for event times generated form the Weibull distribution because of the same reason.

The results from this simulation are presented in Table 5.2-5.7 and in Figure 5.1 – 5.3. Table 5.2-5.7 show the estimated parameters and AUC(t) for each scenario (Scenario 1 to Scenario 6 as described in Table 5.1) for various sample sizes allowing small to large sample size. The accuracy of all parameters involved in each scenario are assessed, but only the accuracy of AUC estimates for Scenario 1 is calculated since the closed form formula is only available for Scenario 1.

For Scenario 1, the model parameters μ and β_1, and also AUC(t) are estimated close to the true values with smaller biases and MSEs across all sample sizes and prediction times. The AUC(t) are estimated fairly high at each prediction time t. It is also observed that AUC(t) slightly increases as the prediction time increases. Considering the second link function (Scenario 2), the model parameters μ, β_0 and β_1 are estimated close to the true values with smaller biases and MSEs across all sample sizes and prediction times. Figure 5.1 shows the estimates AUC(t) across all sample sizes for Scenario 1 and 2.

In Scenarios 3, when considering normally distributed biomarker and exponential event-times, the AUC(t) are estimated close to 0.5, however the model parameters are estimated close to the true values with smaller biases and MSEs across all sample sizes

and prediction times. In Scenario 4, not all model parameters are estimated close to the true values. The diagnostic potential for the scenarios is not discussed in this chapter but the effect of different sample size on the magnitude of the AUC are investigated. Figure 5.2 shows the estimates of AUC(t) across all sample sizes for the two scenarios.

In Scenario 5 and 6, when considering normally distributed biomarker and Weibull event-times, AUC(t) are estimated close to 1. Similar with Scenario 3 and 4, only the trend of the AUC(t) across difference sample size is investigated in this simulation. The model parameters are estimated close to the true values with smaller biases and MSEs across all sample sizes and prediction times. Figure 5.3 shows the estimates of AUC(t) across all sample sizes for the two scenarios.

In each scenario (shown in Table 5.2-5.7), it can be observed that, the MSE for the estimated parameters decrease as the sample size increases. However, the estimated AUC(t) are not significantly different when the sample size increases, and the decrease in corresponding SE is also marginal. Figure 5.1 – 5.3 clearly show that any change in AUC for increasing sample sizes is insignificant. This finding indicates that the proposed parametric approach can provide accurate AUC(t) even when the sample size is small.

Table 5.2: Estimated parameters and AUC(t) for Scenario 1

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	True AUC(t)	Estimated AUC (SE)	Bias	MSE
n=30									
μ	1	1.0271 (0.1961)	0.0271	0.0392	0.01	0.7512	0.7577 (0.0019)	0.0065	0.0000
					0.05	0.7561	0.7631 (0.0013)	0.0070	0.0001
β_1	1	1.0336 (0.1936)	0.0336	0.0386	0.07	0.7585	0.7657 (0.0012)	0.0072	0.0001
					0.10	0.7619	0.7695 (0.0013)	0.0076	0.0001
n=50									
μ	1	1.0250 (0.1611)	0.0250	0.0266	0.01	0.7512	0.7593 (0.0014)	0.0081	0.0001
					0.05	0.7561	0.7646 (0.0008)	0.0085	0.0001
β_1	1	1.0155 (0.1431)	0.0155	0.0207	0.07	0.7585	0.7672 (0.0007)	0.0087	0.0001
					0.10	0.7619	0.7710 (0.0009)	0.0091	0.0001
n=100									
μ	1	1.0057 (0.0964)	0.0057	0.0093	0.01	0.7512	0.7601 (0.0008)	0.0089	0.0001
					0.05	0.7561	0.7654 (0.0005)	0.0093	0.0001
β_1	1	1.0124 (0.1058)	0.0124	0.0113	0.07	0.7585	0.7680 (0.0004)	0.0095	0.0001
					0.10	0.7619	0.7718 (0.0005)	0.0099	0.0001

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	True AUC(t)	Estimated AUC (SE)	Bias	MSE
n=150									
μ	1	1.0007 (0.0831)	0.0007	0.0069	0.01	0.7512	0.7604 (0.0006)	0.0092	0.0001
					0.05	0.7561	0.7656 (0.0004)	0.0095	0.0001
β_1	1	1.0046 (0.0859)	0.0046	0.0074	0.07	0.7585	0.7682 (0.0003)	0.0097	0.0001
					0.10	0.7619	0.7720 (0.0003)	0.0101	0.0001
n=200									
μ	1	1.0083 (0.0687)	0.0083	0.0048	0.01	0.7512	0.7605 (0.0006)	0.0093	0.0001
					0.05	0.7561	0.7657 (0.0003)	0.0096	0.0001
β_1	1	1.0041 (0.0729)	0.0041	0.0053	0.07	0.7585	0.7683 (0.0003)	0.0098	0.0001
					0.10	0.7619	0.7721 (0.0003)	0.0102	0.0001
n=500									
μ	1	1.0021 (0.0441)	0.0021	0.0019	0.01	0.7512	0.7605 (0.0004)	0.0093	0.0001
					0.05	0.7561	0.7658 (0.0003)	0.0097	0.0001
β_1	1	1.0015 (0.0449)	0.0015	0.0020	0.07	0.7585	0.7683 (0.0002)	0.0098	0.0001
					0.10	0.7619	0.7721 (0.0002)	0.0102	0.0001

Table 5.3: Estimated parameters and AUC(t) for Scenario 2

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	Estimated AUC (SE)
n=30						
μ	1	1.0406 (0.1912)	0.0406	0.0382	0.01	0.6234 (0.0114)
					0.05	0.6271 (0.0121)
β_0	1	1.0594 (0.4052)	0.0594	0.1677	0.07	0.6289 (0.0124)
β_1	1	1.1058 (0.5953)	0.1058	0.3656	0.10	0.6316 (0.0129)
n=50						
μ	1	1.0273 (0.1464)	0.0273	0.0222	0.01	0.6244 (0.0089)
					0.05	0.6281 (0.0094)
β_0	1	1.0248 (0.2964)	0.0248	0.0885	0.07	0.6299 (0.0096)
β_1	1	1.0531 (0.4285)	0.0531	0.1864	0.10	0.6326 (0.0100)
n=100						
μ	1	1.0182 (0.1062)	0.0182	0.0116	0.01	0.6250 (0.0066)
					0.05	0.6287 (0.0069)
β_0	1	1.0197 (0.2155)	0.0197	0.0468	0.07	0.6305 (0.0071)
β_1	1	1.0322 (0.3138)	0.0322	0.0995	0.10	0.6332 (0.0074)

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	Estimated AUC (SE)
n=150						
$\boldsymbol{\mu}$	1	1.0127 (0.0839)	0.0127	0.0072	0.01	0.6254 (0.0052)
					0.05	0.6291 (0.0055)
$\boldsymbol{\beta_0}$	1	1.0179 (0.1695)	0.0179	0.0291	0.07	0.6309 (0.0057)
$\boldsymbol{\beta_1}$	1	1.0101 (0.2338)	0.0101	0.0548	0.10	0.6336 (0.0059)
n=200						
$\boldsymbol{\mu}$	1	1.0106 (0.0706)	0.0106	0.0051	0.01	0.6254 (0.0044)
					0.05	0.6291 (0.0047)
$\boldsymbol{\beta_0}$	1	1.0113 (0.1521)	0.0113	0.0233	0.07	0.6309 (0.0048)
$\boldsymbol{\beta_1}$	1	1.0154 (0.2112)	0.0154	0.0448	0.10	0.6336 (0.0049)
n=500						
$\boldsymbol{\mu}$	1	1.0023 (0.0450)	0.0023	0.0020	0.01	0.6258 (0.0029)
					0.05	0.6296 (0.0030)
$\boldsymbol{\beta_0}$	1	1.0026 (0.0943)	0.0026	0.0089	0.07	0.6314 (0.0031)
$\boldsymbol{\beta_1}$	1	0.9977 (0.1250)	-0.0023	0.0156	0.10	0.6341 (0.0032)

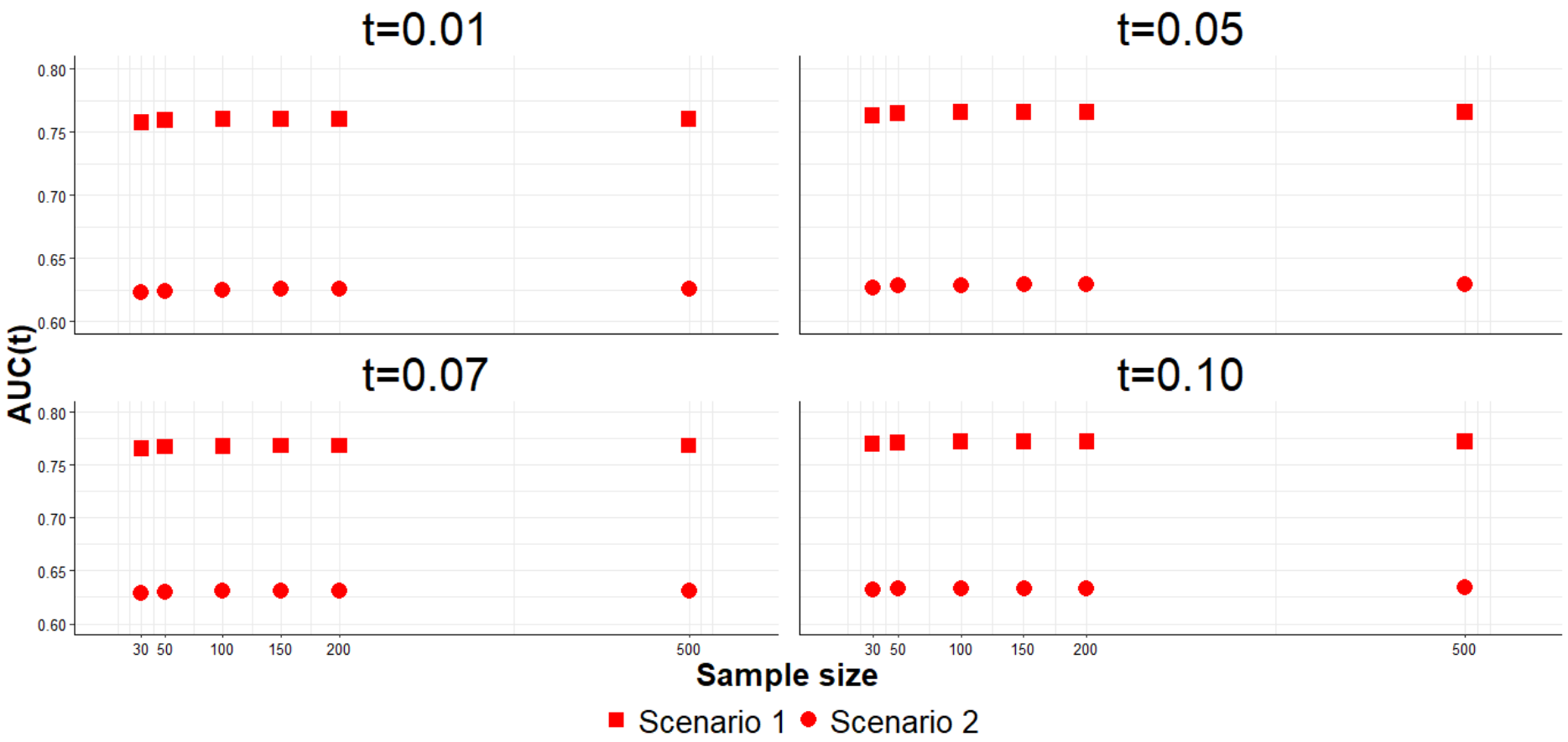

Figure 5.1: Estimates of AUC(t) across various sample sizes for Scenario 1 and 2

Table 5.4: Estimated parameters and AUC(t) for Scenario 3

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	Estimated AUC (SE)
n=30						
μ	3	3.0017 (0.1746)	0.0017	0.0305	0.01	0.5671 (0.0039)
σ^2	1	1.0366 (0.0600)	0.0366	0.0049	0.05	0.5714 (0.0039)
β_1	1	1.0851 (0.1359)	0.0851	0.0257	0.07	0.5736(0.0042)
					0.10	0.5769(0.0052)
n=50						
μ	3	2.9954 (0.1383)	-0.0046	0.0191	0.01	0.5674 (0.0039)
σ^2	1	1.0354 (0.0520)	0.0354	0.0040	0.05	0.5719 (0.0031)
β_1	1	1.0684 (0.1011)	0.0684	0.0149	0.07	0.5740 (0.0031)
					0.10	0.5774 (0.0032)
n=100						
μ	3	3.0038 (0.0998)	0.0038	0.0100	0.01	0.5674 (0.0023)
σ^2	1	1.0230 (0.0354)	0.0230	0.0018	0.05	0.5718 (0.0022)
β_1	1	1.0487 (0.0675)	0.0487	0.0069	0.07	0.5740 (0.0023)
					0.10	0.5774 (0.0023)

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	Estimated AUC (SE)
n=150						
μ	3	2.9961 (0.0834)	-0.0039	0.0070	0.01	0.5676 (0.0019)
σ^2	1	1.0173 (0.0298)	0.0173	0.0012	0.05	0.5719 (0.0019)
β_1	1	1.0357 (0.0532)	0.0357	0.0041	0.07	0.5742 (0.0019)
					0.10	0.5776 (0.0019)
n=200						
μ	3	3.0016 (0.0687)	0.0016	0.0047	0.01	0.5675 (0.0016)
σ^2	1	1.0168 (0.0272)	0.0168	0.0010	0.05	0.5718 (0.0016)
β_1	1	1.0329 (0.0467)	0.0329	0.0033	0.07	0.5740 (0.0016)
					0.10	0.5774 (0.0015)
n=500						
μ	3	3.0015 (0.0454)	0.0015	0.0021	0.01	0.5675 (0.0011)
σ^2	1	1.0105 (0.0168)	0.0105	0.0004	0.05	0.5718 (0.0010)
β_1	1	1.0177 (0.0274)	0.0177	0.0011	0.07	0.5740 (0.0010)
					0.10	0.5774 (0.0010)

Table 5.5: Estimated parameters and AUC(t) for Scenario 4

Parameter	True value	Estimated Parameters (SE)	Bias	MSE	t	Estimated AUC (SE)
n=30						
μ	3	3.0021 (0.1332)	0.0021	0.0177	0.01	0.5505 (0.0023)
σ^2	1	0.9752 (0.1333)	-0.0248	0.0184	0.05	0.5548 (0.0023)
β_0	1	1.3607 (0.9224)	0.3607	0.9809	0.07	0.5570 (0.0023)
β_1	1	0.9542 (0.3701)	-0.0458	0.1391	0.10	0.5603 (0.0024)
n=50						
μ	3	2.9986 (0.1453)	-0.0014	0.0211	0.01	0.5508 (0.0019)
σ^2	1	0.9880 (0.0969)	-0.0120	0.0095	0.05	0.5551 (0.0018)
β_0	1	1.2818 (0.8158)	0.2818	0.7449	0.07	0.5572 (0.0026)
β_1	1	0.9431 (0.3197)	-0.0569	0.1054	0.10	0.5607 (0.0019)
n=100						
μ	3	3.0018 (0.1022)	0.0018	0.0104	0.01	0.5508 (0.0016)
σ^2	1	0.9874 (0.0662)	-0.0126	0.0045	0.05	0.5551 (0.0013)
β_0	1	1.2095 (0.6814)	0.2095	0.5082	0.07	0.5573 (0.0013)
β_1	1	0.9505 (0.2577)	-0.0495	0.0689	0.10	0.5607 (0.0015)

Parameter	True value	Estimated Parameters (SE)	Bias	MSE	t	Estimated AUC (SE)
n=150						
$\boldsymbol{\mu}$	3	2.9934 (0.0812)	-0.0066	0.0066	0.01	0.5509 (0.0012)
$\boldsymbol{\sigma^2}$	1	0.9923 (0.0608)	-0.0077	0.0038	0.05	0.5552 (0.0014)
$\boldsymbol{\beta_0}$	1	1.1373 (0.5849)	0.1373	0.3610	0.07	0.5574 (0.0011)
$\boldsymbol{\beta_1}$	1	0.9722 (0.2243)	-0.0278	0.0511	0.10	0.5608 (0.0012)
n=200						
$\boldsymbol{\mu}$	3	3.0044 (0.0718)	0.0044	0.0052	0.01	0.5508 (0.0010)
$\boldsymbol{\sigma^2}$	1	0.9938 (0.0484)	-0.0062	0.0024	0.05	0.5550 (0.0012)
$\boldsymbol{\beta_0}$	1	1.1587 (0.5753)	0.1587	0.3562	0.07	0.5573 (0.0011)
$\boldsymbol{\beta_1}$	1	0.9487 (0.2118)	-0.0513	0.0475	0.10	0.5607 (0.0010)
n=500						
$\boldsymbol{\mu}$	3	2.9998 (0.0415)	-0.0002	0.0017	0.01	0.5509 (0.0006)
$\boldsymbol{\sigma^2}$	1	0.9954 (0.0306)	-0.0046	0.0010	0.05	0.5551 (0.0006)
$\boldsymbol{\beta_0}$	1	1.0796 (0.3900)	0.0796	0.1584	0.07	0.5573 (0.0006)
$\boldsymbol{\beta_1}$	1	0.9765 (0.1483)	-0.0235	0.0225	0.10	0.5608 (0.0005)

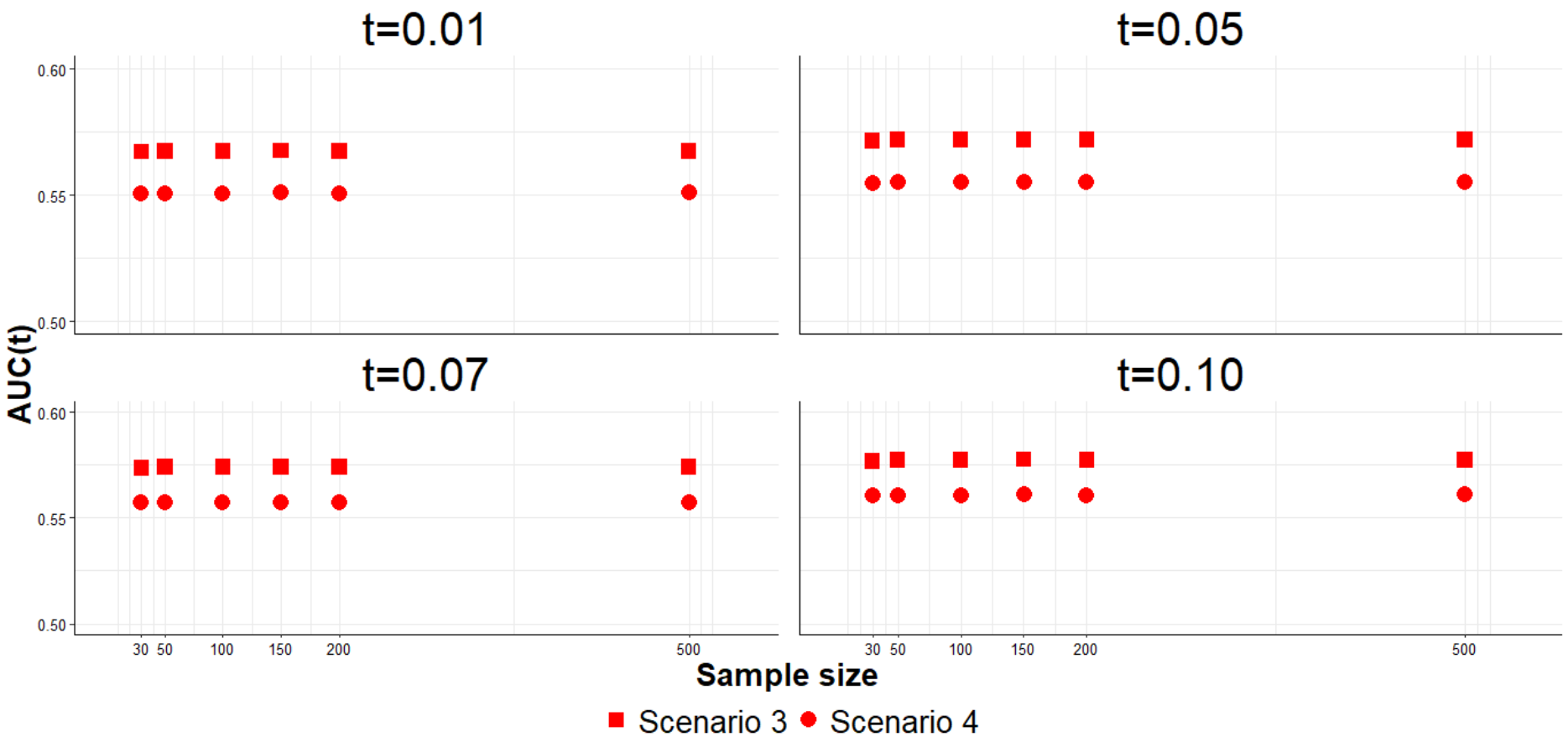

Figure 5.2: Estimates of AUC(t) across various sample sizes for Scenario 3 and 4

Table 5.6: Estimated parameters and AUC(t) for Scenario 5

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	Estimated AUC (SE)
n=30						
μ	3	2.9957 (0.1812)	-0.0043	0.0329	1.0	0.6602 (0.0457)
σ^2	1	0.9697 (0.1256)	-0.0303	0.0167	1.5	0.9263 (0.0290)
β_1	1	1.0149 (0.0997)	0.0149	0.0102	1.7	0.9669 (0.0341)
K	2	2.0775 (0.3205)	0.0775	0.1087	2.0	0.9987 (0.0455)
n=50						
μ	3	2.9996 (0.1346)	-0.0004	0.0181	1.0	0.6585 (0.0337)
σ^2	1	0.9824 (0.0989)	-0.0176	0.0101	1.5	0.9260 (0.0090)
β_1	1	1.0025 (0.0711)	0.0025	0.0051	1.7	0.9671 (0.0061)
K	2	2.0612 (0.2325)	0.0612	0.0578	2.0	0.9982 (0.0050)
n=100						
μ	3	3.0019 (0.1008)	0.0019	0.0102	1.0	0.6572 (0.0250)
σ^2	1	0.9928 (0.0704)	-0.0072	0.0050	1.5	0.9268 (0.0063)
β_1	1	1.0028 (0.0539)	0.0028	0.0029	1.7	0.9680 (0.0039)
K	2	2.0227 (0.1615)	0.0227	0.0266	2.0	0.9995 (0.0038)

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	Estimated AUC (SE)
n=150						
$\boldsymbol{\mu}$	3	3.0027 (0.0763)	0.0027	0.0058	1.0	0.6562 (0.0187)
$\boldsymbol{\sigma^2}$	1	0.9946 (0.0598)	-0.0054	0.0036	1.5	0.9272 (0.0046)
$\boldsymbol{\beta_1}$	1	1.0045 (0.0449)	0.0045	0.0020	1.7	0.9682 (0.0028)
K	2	2.0095 (0.1267)	0.0095	0.0161	2.0	0.9998 (0.0025)
n=200						
$\boldsymbol{\mu}$	3	2.9986 (0.0664)	-0.0014	0.0044	1.0	0.6559 (0.0166)
$\boldsymbol{\sigma^2}$	1	0.9963 (0.0463)	-0.0037	0.0022	1.5	0.9276 (0.0041)
$\boldsymbol{\beta_1}$	1	1.0043 (0.0382)	0.0043	0.0015	1.7	0.9680 (0.0098)
K	2	2.0154 (0.1095)	0.0154	0.0122	2.0	0.9999 (0.0022)
n=500						
$\boldsymbol{\mu}$	3	3.0042 (0.0461)	0.0042	0.0021	1.0	0.6552 (0.0113)
$\boldsymbol{\sigma^2}$	1	0.9943 (0.0309)	-0.0057	0.0010	1.5	0.9273 (0.0027)
$\boldsymbol{\beta_1}$	1	1.0015 (0.0243)	0.0015	0.0006	1.7	0.9683 (0.0017)
K	2	2.0026 (0.0694)	0.0026	0.00483	2.0	0.9999 (0.0015)

Table 5.7: Estimated parameters and AUC(t) for Scenario 6

Parameter	True value	Estimated parameter (SE)	Bias	MSE	Time	Estimated AUC (SE)
n=30						
μ	3	2.9806 (0.1847)	-0.0194	0.0345	1.0	0.9844 (0.0049)
σ^2	1	0.9705 (0.1261)	-0.0295	0.0168	1.5	0.9958 (0.0046)
β_0	1	1.2074 (0.8688)	0.2074	0.7978	1.7	0.9963 (0.0046)
β_1	1	0.9535 (0.3272)	-0.0465	0.1092	2.0	0.9965 (0.0047)
K	2	2.1167 (0.3273)	0.1167	0.1207		
n=50						
μ	3	3.0013 (0.1443)	0.0013	0.0208	1.0	0.9874 (0.0029)
σ^2	1	0.9864 (0.0907)	-0.0136	0.0084	1.5	0.9980 (0.0021)
β_0	1	1.1414 (0.6774)	0.1414	0.4789	1.7	0.9983 (0.0021)
β_1	1	0.9651 (0.2484)	-0.0349	0.0629	2.0	0.9985 (0.0021)
K	2	2.0814 (0.2348)	0.0814	0.0618		
n=100						
μ	3	2.9993 (0.1023)	-0.0007	0.0105	1.0	0.9887 (0.0020)
σ^2	1	0.9947 (0.0666)	-0.0053	0.0045	1.5	0.9991 (0.0006)
β_0	1	1.0809 (0.4707)	0.0809	0.2281	1.7	0.9994 (0.0006)

Parameter	True value	Estimated parameter (SE)	Bias	MSE	Time	Estimated AUC (SE)
$\boldsymbol{\beta_1}$	1	0.9839 (0.1796)	-0.0161	0.0325	2.0	0.9995 (0.0006)
K	2	2.0464 (0.1640)	0.0464	0.0290		
n=150						
$\boldsymbol{\mu}$	3	2.9986 (0.0801)	-0.0014	0.0064	1.0	0.9890 (0.0014)
$\boldsymbol{\sigma^2}$	1	0.9926 (0.0568)	-0.0074	0.0033	1.5	0.9993 (0.0004)
$\boldsymbol{\beta_0}$	1	1.0563 (0.3552)	0.0563	0.1293	1.7	0.9996 (0.0004)
$\boldsymbol{\beta_1}$	1	0.9915 (0.1363)	-0.0085	0.0186	2.0	0.9997 (0.0004)
K	2	2.0177 (0.1343)	0.0177	0.0183		
n=200						
$\boldsymbol{\mu}$	3	3.0020 (0.0651)	0.0020	0.0042	1.0	0.9892 (0.0011)
$\boldsymbol{\sigma^2}$	1	0.9925 (0.0481)	-0.0075	0.0024	1.5	0.9995 (0.0002)
$\boldsymbol{\beta_0}$	1	1.0327 (0.2999)	0.0327	0.0910	1.7	0.9997 (0.0002)
$\boldsymbol{\beta_1}$	1	0.9908 (0.1181)	-0.0092	0.0140	2.0	0.9998 (0.0002)
K	2	2.0247 (0.1100)	0.0247	0.0127		
n=500						
$\boldsymbol{\mu}$	3	3.0013 (0.0448)	0.0013	0.0020	1.0	0.9894 (0.0007)
$\boldsymbol{\sigma^2}$	1	0.9950 (0.0320)	-0.0050	0.0010	1.5	0.9996 (0.0001)

Parameter	True value	Estimated parameter (SE)	Bias	MSE	Time	Estimated AUC (SE)
$\boldsymbol{\beta_0}$	1	1.0069 (0.1910)	0.0069	0.0365	1.7	0.9998 (0.0001)
$\boldsymbol{\beta_1}$	1	0.9998 (0.0742)	-0.0002	0.0055	2.0	0.9999 (0.0001)
K	2	2.0053 (0.0677)	0.0053	0.0046		

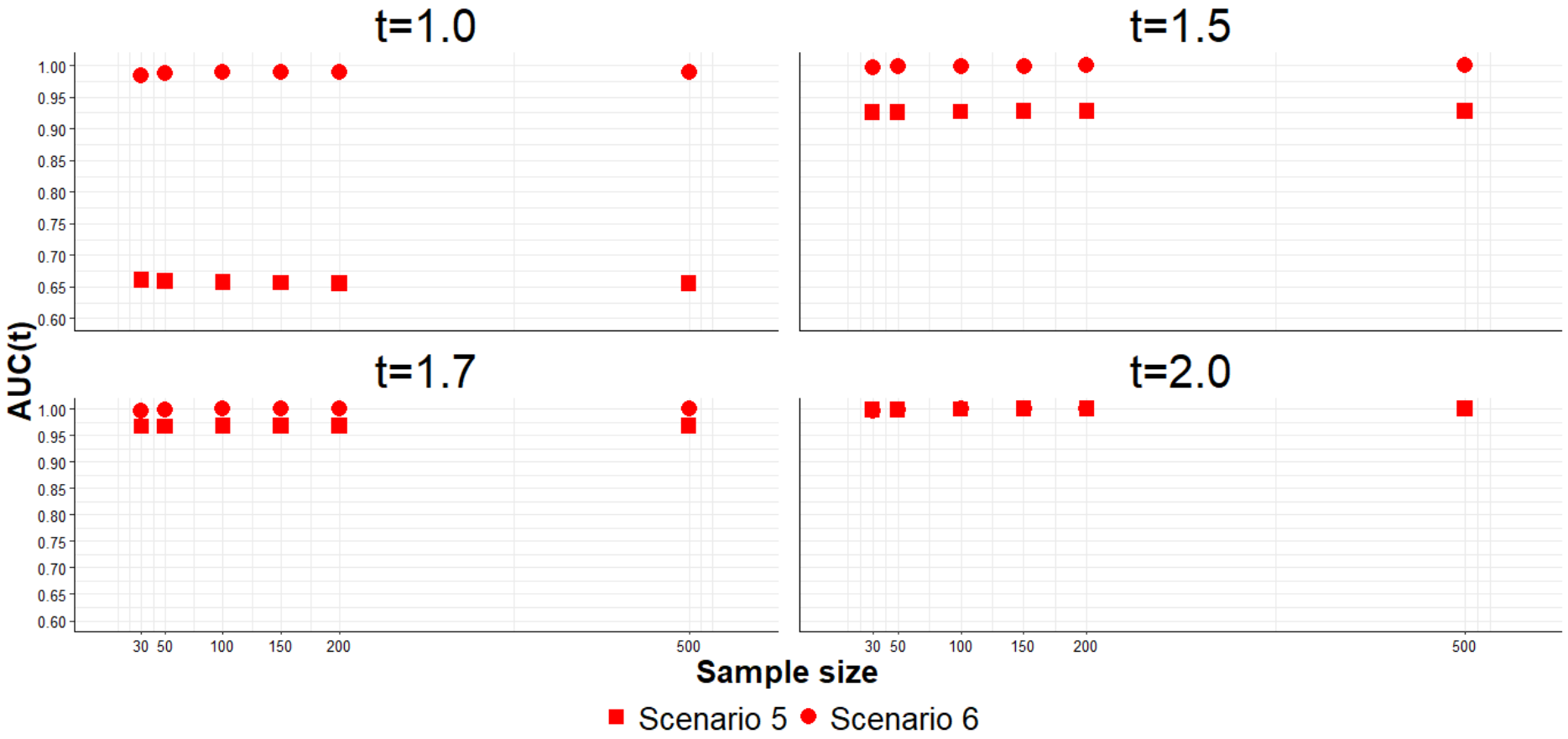

Figure 5.3: Estimates of AUC(t) across various sample sizes for Scenario 5 and 6

5.3 Time-dependent AUC for incomplete data (censored event-times)

The data are simulated similarly as in Section 5.1, and here we consider a moderate sample size of n=50 and 30% censoring of the event-times. The disease status is generated from a binomial distribution with probability of having the event set at 0.7. The results are shown in Table 5.8 – 5.13 for the same 6 scenarios in Table 5.1.

The estimated AUC(t) shown in Table 5.8 and Table 5.9 are slightly low compared to the estimates shown in Table 5.2 and Table 5.3 for Scenario 1 and 2 respectively and have slightly higher MSEs. Results for other scenarios are presented in Table 5.10-5.13 are also almost similar to the results from non-censored event times in Section 5.1. These results suggest that the proposed parametric method can be applied for censored event-times and it can provide estimates as accurate as the data with complete (non-censored) event times.

Table 5.8: Estimated parameters and AUC(t) for Scenario 1

Parameter	True value	Estimated Parameters (SE)	Bias	MSE	t	True AUC(t)	Estimated AUC (SE)	Bias	MSE
μ	1	1.0194 (0.1522)	0.0932	0.0236	0.01	0.7512	0.7293 (0.0031)	-0.0219	0.0005
					0.05	0.7561	0.7338 (0.0038)	-0.0223	0.0005
β_1	1	0.7208 (0.1234)	-0.2792	0.0194	0.07	0.7585	0.7359 (0.0041)	-0.0226	0.0005
					0.10	0.7619	0.7391 (0.0046)	-0.0228	0.0005

Table 5.9: Estimated parameters and AUC(t) for Scenario 2

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	Estimated AUC (SE)
μ	1	1.0192 (0.1391)	0.0192	0.3329	0.01	0.6248 (0.0085)
					0.05	0.6285 (0.0090)
β_0	1	0.7295 (0.2456)	-0.2705	0.1335	0.07	0.6304 (0.0092)
β_1	1	0.7320 (0.3333)	-0.2680	0.1829	0.10	0.6331 (0.0096)

Table 5.10: Estimated parameters and AUC(t) for Scenario 3

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	Estimated AUC (SE)
μ	3	3.0044 (0.1399)	0.0044	0.0196	0.01	0.5674 (0.0031)
σ^2	1	0.9881 (0.1004)	-0.0119	0.0102	0.05	0.5717 (0.0031)
β_1	1	0.5100 (0.1046)	-0.4900	0.2510	0.07	0.5739 (0.0031)
					0.10	0.5773 (0.0032)

Table 5.11: Estimated parameters and AUC(t) for Scenario 4

Parameter	True value	Estimated Parameters (SE)	Bias	MSE	t	Estimated AUC (SE)
μ	3	2.9972 (0.1443)	-0.0028	0.0208	0.01	0.5508 (0.0018)
σ^2	1	0.9867 (0.0968)	-0.0133	0.0096	0.05	0.5551 (0.0018)
β_0	1	0.9404 (0.0842)	-0.0596	0.0106	0.07	0.5573 (0.0018)
β_1	1	0.6439 (0.3196)	-0.3561	0.2290	0.10	0.5607 (0.0018)

Table 5.12: Estimated parameters and AUC(t) for Scenario 5

Parameter	True value	Estimated Parameters (SE)	Bias	MSE	Time	Estimated AUC (SE)
μ	3	3.0062 (0.1402)	0.0062	0.0197	1.0	0.9602 (0.0058)
σ^2	1	0.9878 (0.1002)	-0.0122	0.0102	1.5	0.9932 (0.0027)
β_1	1	0.8428 (0.0746)	-0.1572	0.0303	1.7	0.9957 (0.0026)
K	2	2.0715 (0.2787)	0.0715	0.0828	2.0	0.9972 (0.0027)

Table 5.13: Estimated parameters and AUC(t) for Scenario 6

Parameter	True value	Estimated parameter (SE)	Bias	MSE	t	Estimated AUC (SE)
μ	3	2.9979 (0.1546)	-0.0021	0.0239	1.0	0.9874 (0.0029)
σ^2	1	0.7582 (0.0886)	-0.2418	0.0663	1.5	0.9980 (0.0021)
β_0	1	0.9239 (0.7481)	-0.0761	0.5655	1.7	0.9984 (0.0022)
β_1	1	0.7270 (0.2945)	-0.0273	0.1613	2.0	0.9986 (0.0022)
K	2	1.5355 (0.5353)	-0.4645	0.5023		

5.4 Discussion

This chapter demonstrated the appropriateness of the proposed framework of the parametric time-dependent ROC curve approach. The performance of the proposed method is investigated for data complete and incomplete data with censoring. The estimation of the parameters and AUC(t) are explored for different sample sizes. As the sample size increases, the parameters are estimated closer to the true parameter values with decreasing MSE. However, the changes in estimated AUC(t) are marginal. Thus, AUC(t) are not affected by the sample size when considering the correct parametric distributions or event times and biomarker. This observation provides a valuable information especially for biomarker development and evaluation studies because these studies are usually relying on small sample size to assess the diagnostic accuracy.

When data are incomplete (includes censored event-times), the AUC(t) are estimated slightly lower than the complete data, but the difference is marginal. Hence, the proposed parametric approach to estimate the time-dependent ROC can be applied to incomplete data by taking account of the censored event-times, but still provides as accurate estimates of AUC(t) as complete data.

For complete data, when censoring is not occurs, the definition of the individual's disease status is defined by the event time. It is assumed that at a particular predict time, all individuals with event time lower than the predict time ($T_i \leq t$) are having the disease, and vice versa. Thus, the number of diseased individuals is depending on the distribution of event time and the biomarker. To observe the distribution closely, Figure 5.4 – Figure 5.9 displayed the scatter plots for all scenarios considering all sample size.

In Figure 5.4 and 5.5, the scatter plots show that most of the individuals with higher biomarker value have lower event time. A few individuals with higher event time and at the same time have lower biomarker value. For these scenarios, the true positive fraction (TPR) is higher than false positive fraction (FPR) which resulted stable and good discriminating power of the biomarker with AUC values between are 0.6 and 0.77 as shown in Table 5.2 and 5.3.

The scatter plot for Scenario 3 and 4 are shown in Figure 5.6 and 5.7. The AUC values computed for these distribution combinations are quite low and approach to 0.5 which indicates a useless biomarker in predicting the individual's disease status. Based on the scatter plots, the negative relationship is observed between the biomarker and the event time. However, in calculating the TPR and FPR for all possible threshold and all prediction times, the TPR and FPR are quite low and almost similar with each other thus resulted in low AUC values. The number of diseased and healthy individuals with high biomarker values are almost the same for all cases. Thus, it can be said that these combinations of the distributions or the link functions may not suitable in this study.

For the last distribution combinations, the scatter plots for Scenario 5 and 6 are shown in Figure 5.8 and 5.9. A positive relationship is obviously seen in the scatter plots which is deviated from our assumption. Thus, the resulted AUC values can not be used to interpret the powerfulness of the biomarker in discriminating between healthy and disease individuals. A negative link function between the event time and biomarker value is suggested to have a more relevant AUC values in future study.

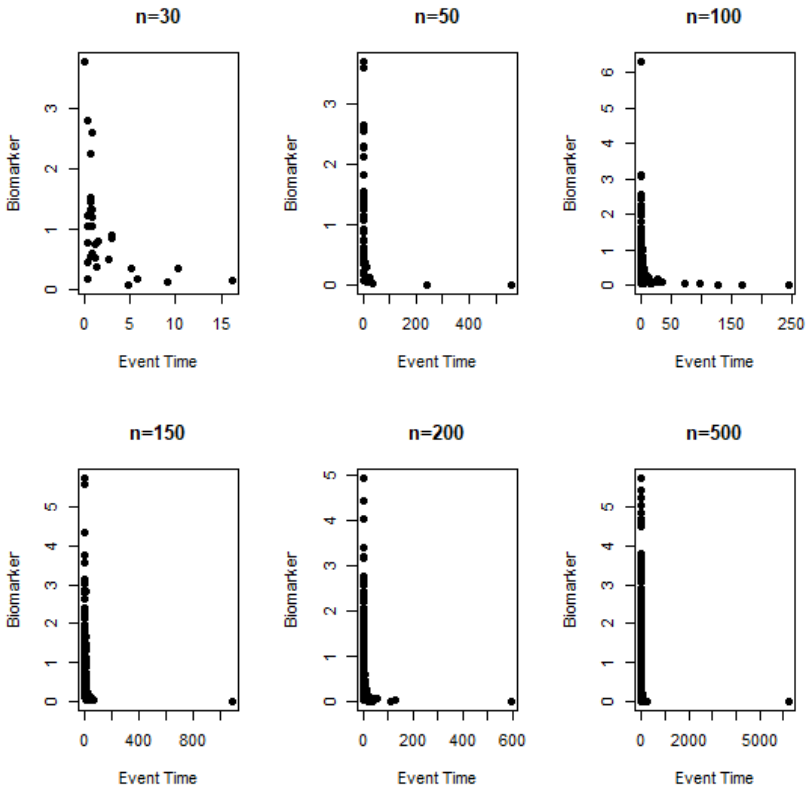

Figure 5.4: Scatter plots for Scenario 1

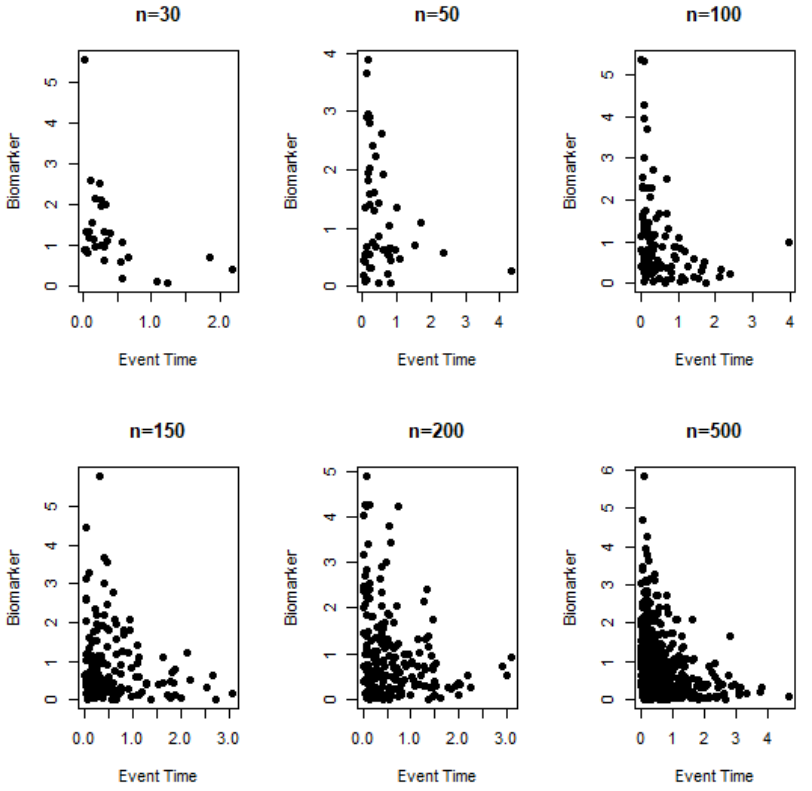

Figure 5.5: Scatter plot for Scenario 2

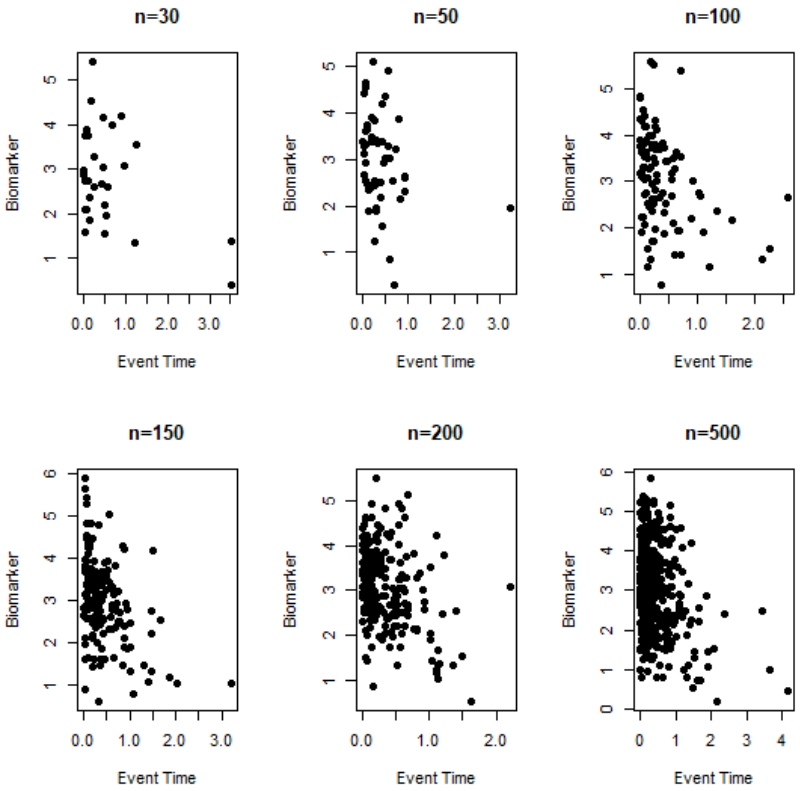

Figure 5.6: Scatter plots for Scenario 3

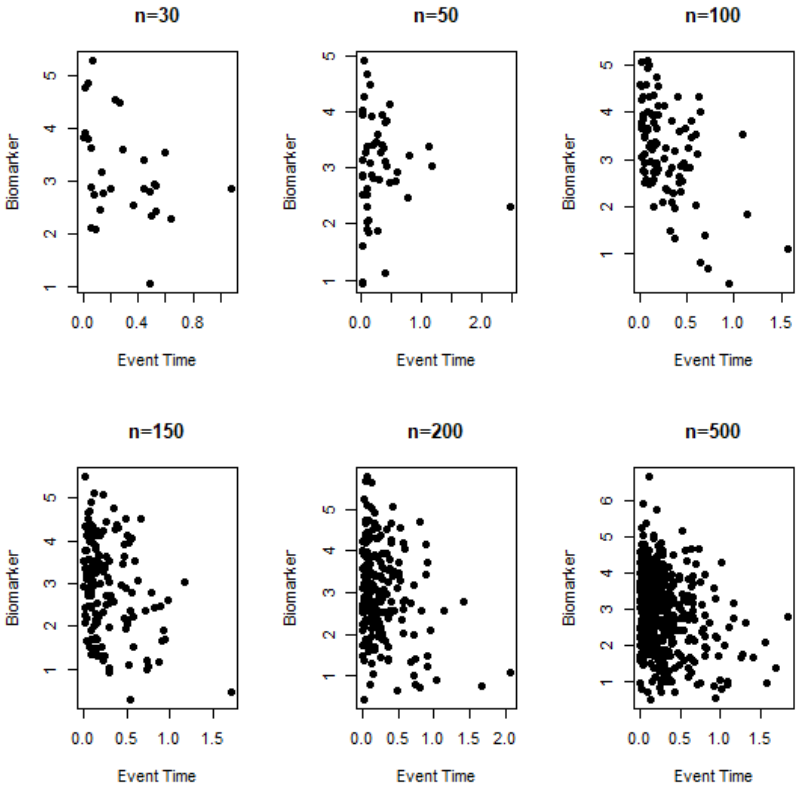

Figure 5.7: Scatter plots for Scenario 4

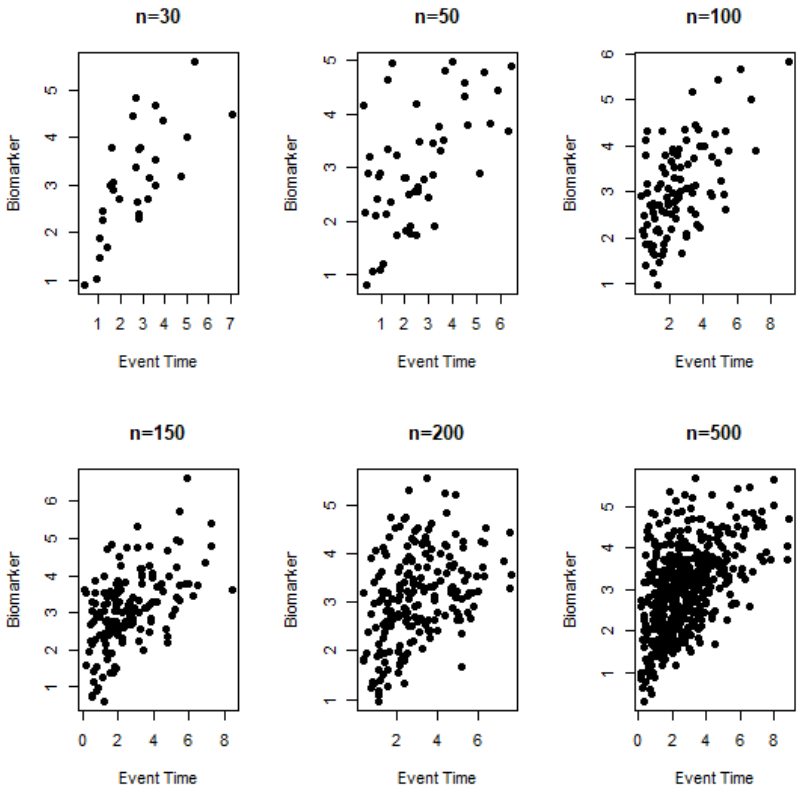

Figure 5.8: Scatter plot for Scenario 5

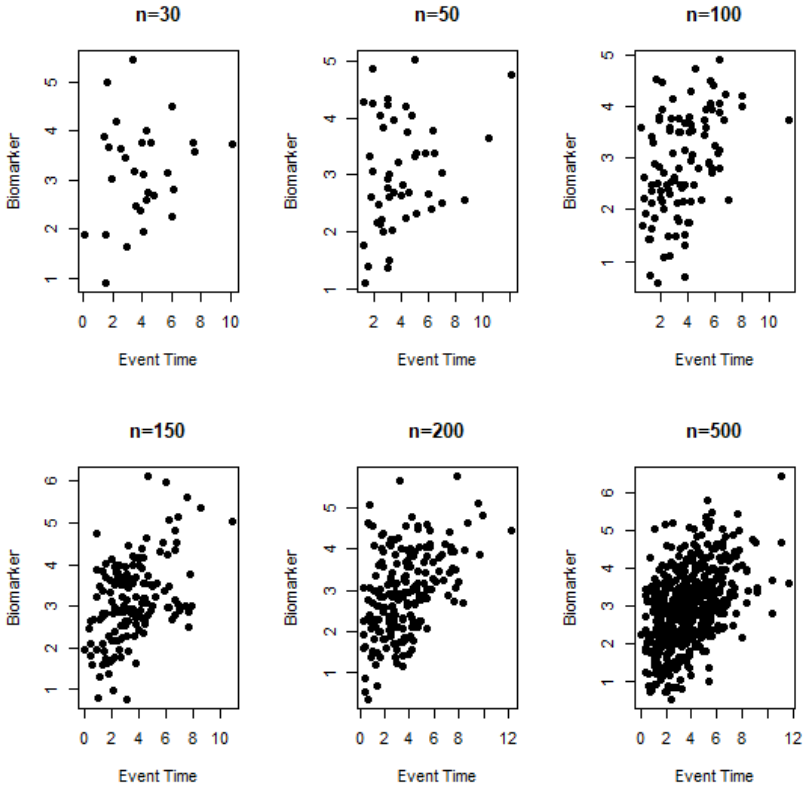

Figure 5.9: Scatter plots for Scenario 6

6 Time-dependent ROC curve analysis adjusted for measurement error in the baseline biomarker

6.1 Introduction

Measurement error in a biomarker is the error induced when measuring the biomarker. It includes the laboratory error and variations during measurement collection or storage condition, and is a random variation within the true biomarker value that can be estimated using repeated measurements [70]. All currently proposed methods of time-dependent ROC curve, as discussed in Chapter 3, directly use the observed value of a biomarker and ignore the possible measurement error. However, in standard ROC curve context, the effect of measurement error on estimating the AUC has been extensively discussed [71-83]. Ignoring the measurement error may underestimate the AUC and useful biomarkers may be overlooked [19].

Motivated from the findings of the methodological review conducted in Chapter 3, a novel methodology is proposed to estimate the time-dependent diagnostic accuracy of a biomarker adjusted for measurement error. In most clinical studies, although biomarker measurements are collected longitudinally over patients' follow-up, only the baseline measurement of the biomarker is used in analyses. Thus, a novel data-efficient method is proposed that considers all available longitudinal measurements of the biomarker to adjust for the measurement error when estimating the diagnostic accuracy at the baseline level.

The organisation of the chapter is as follows. The current measurement error adjusted methodologies for the standard ROC curve are briefly discussed in Section 6.2. Adopting regression calibration, a measurement error adjusted time-dependent ROC curve is proposed in Section 6.3. However, this methodology was found to be inefficient, and hence, a second method is proposed along the joint modelling framework in Section 6.4. The proposed joint model, derivation of the likelihood and estimation based on EM algorithm are discussed in sections 6.4.1 to 6.4.3. The proposed time-dependent ROC curve approach is discussed in Section 6.4.4, and the proposed methodology is illustrated using PBC data in Section 6.4.5.

6.2 Current measurement error adjusted methods for standard ROC curve

To investigate the degree of biomarker measurement error, validity or reliability studies can be conducted [20]. A validity study requires the true biomarker measurements so that the comparison can be made with the observed biomarker measurements. Since in most cases the true biomarker measurements are unknown, the reliability study is preferable, in which repeated measurements of biomarkers are taken from the same individual in a study. The reliability study is commonly used in biomarker evaluation and considered in this chapter to adjust for measurement error in biomarkers. Although error can be estimated using resampling methods such bootstrap in statistical modelling, a resampling method is not appropriate when a biomarker is measured with an error [80]. Following the methodological review conducted in Chapter 3, using additional keywords "measurement error" and "ROC curve", 13 methodological papers were found which discussed the adjustment of measurement error in the context of standard ROC curve. However, no study was found adjusting the measurement error in biomarker in the context of time-dependent ROC curve.

The methods discussed in standard ROC curve approach mostly studied the effect of random measurement error on the confidence interval of AUC. Ignoring the measurement error may lead to serious misleading results on the effectiveness of the biomarker and having the coverage less than nominal values [73, 74]. Vexler, et al. [76] proposed an estimation of ROC curve based on stably distributed biomarkers subject to measurement error and pooling mixtures. Coffin and Sukhatme [71, 72] proposed estimation of bias due to measurement error derived from nonparametric and parametric AUC estimation method respectively. These methodologies require the distribution function of the true biomarker which is unknown in practice. However, the distribution function can be estimated based on the observed biomarker distribution function but may cause a deconvolution problem because it involved reconstructing a distribution by the distribution of their sums. Therefore, not all distribution functions can be reconstructed. Prokhorov and Ushakov [84] have solved this problem by using infinite divisible distributions such as Normal, Cauchy, Exponential or gamma for the biomarker [76]. Coffin and Sukhatme [72] used kernel density estimation to estimate

the observed biomarker density with normal kernel functions, and then estimate the probability distribution function of the true biomarkers by deconvolving the two densities.

Faraggi [74], Reiser [73], Li, Yanhong, et al. [80], Schisterman, et al. [83] and Rosner, et al. [82] consider separate distribution functions for cases and controls where $X_i \sim N(\mu_X, \sigma_X^2)$ and $X_j^* \sim N(\mu_{X^*}, \sigma_{X^*}^2)$ denote distributions of the true biomarker value for cases and controls respectively. In situations where the true biomarkers X_i and X_j^* are not directly observable, using Q_X and Q_X^* as the observed biomarker values for the cases and controls respectively, additive error models were assumed such that $Q_i = X_i + \varepsilon_i$ and $Q_j^* = X_j^* + \varepsilon_j^*$ where $\varepsilon_i \sim N(0, \sigma_\varepsilon^2)$ and $\varepsilon_j^* \sim N(0, \sigma_{\varepsilon^*}^2)$ respectively, and X, X^*, ε and ε^* are all assumed independent of each other. The subscripts i and j are the indexes for individuals in the m cases and n controls respectively. Using the general definition $AUC = \Phi(\delta)$ where $\delta = \frac{\mu_X - \mu_{X^*}}{\sqrt{\sigma_X^2 + \sigma_{X^*}^2}}$, the corrected AUC is defined by

$$AUC^* = \Phi(\delta^*)$$

where Φ denotes the standard normal cumulative distribution function.

Faraggi [74] assumed the true biomarker follows normal distributions with common variances $\sigma_X^2 = \sigma_{X^*}^2 = \sigma^2$, and common variances of measurement error $\sigma_\varepsilon^2 = \sigma_{\varepsilon^*}^2 = \sigma_{error}^2$ such that

$$X_i \sim N\left(\mu_X, \sigma^2\left(1+\theta^2\right)\right); X_j^* \sim N\left(\mu_{X^*}, \sigma^2\left(1+\theta^2\right)\right) \qquad (6.1)$$

where $\theta = \sigma_{error}^2/\sigma^2$ is a known measurement error index and AUC^* is defined with $\delta^* = \frac{\delta}{\sqrt{1+\theta^2}}$ such that $AUC^* = \Phi\left(\delta^*\sqrt{1+\theta^2}\right)$. A confidence interval for δ^* and thus for AUC^* are obtained following Owen, et al. [85] numerically. Faraggi [74] has also proposed a method to account for different variances between cases and controls.

By assuming similar parametric distributions for true biomarker value for cases and control as in equation 6.1, Reiser [73] proposed an interval estimation of AUC which depends on the availability of repeated measurements from internal experimentation,

i.e. repeated biomarker values for each individual. Since longitudinal follow-up exposes to irregular schedule and unequal number of biomarker measurements between individuals, Reiser [73] provided ANOVA-based approach for equal replicates while an alternative method following Searle, et al. [86] for unequal replicates. Two approaches are proposed to estimate $var(\delta)$ based on Reiser and Guttman [87] method and the delta method [88]. The confidence interval for δ^* is defined by $\widehat{\delta}^* \pm z_{\alpha/2}\sqrt{\widehat{\text{var}}\left(\widehat{\delta}^*\right)}$ where $z_{\alpha/2}$ denotes the $1-\frac{\alpha}{2}$ quantile of the standard normal distribution. A simulation study shows that the delta method is preferable because the coverage probability is close to nominal value [73].

Li, Yanhong, et al. [80] developed an approach which is adjusted for measurement error using either external (i.e. study conducted alongside the main study) or internal replicated biomarker measurements based on MOVER (Method Of Variance Estimates Recovery). Assuming that AUC is a function of normal means and variances, δ is defined by

$$\delta^* = \frac{\mu_{Q_X} - \mu_{Q_X^*}}{\sqrt{\sigma_{Q_X}^2 - \sigma_\varepsilon^2 + \sigma_{Q_X^*}^2 - \sigma_{\varepsilon^*}^2}}$$

and therefore, inferences for δ^* and AUC^* can be conducted using the observed data. For internal replication, the point estimate of mean and variance are estimated following Thomas and Hultquist [89], and an asymmetric confidence interval for δ^* is obtained by applying MOVER. For external replication, a confidence interval is obtained using the delta-method.

Schisterman, et al. [83] used an external repeated biomarker measurement to estimate the variance of measurement error $\hat{\sigma}_\varepsilon^2$. The AUC^* is estimated by

$$\widehat{AUC^*} = \Phi\left(\widehat{\delta^*}\right),$$

and

$$\widehat{\delta^*} = \frac{\bar{X} - \overline{X^*}}{\sqrt{(S_X^2 + S_{X^*}^2 - 2\hat{\sigma}_\varepsilon^2)}}$$

where S_X^2 and $S_{X^*}^2$ are the sample variances, and $\overline{X}$ and $\overline{X^*}$ are sample means for cases and controls respectively. If the denominator $\left(S_X^2 + S_{X^*}^2 - 2\hat{\sigma}_\varepsilon^2\right)$ is negative, following Rao [90], suggested replacing the negative S_X^2 or $S_{X^*}^2$ by a very small number. The confidence interval for AUC^* and δ^* are estimated by using the delta method; $\widehat{\delta^*} \pm z_{\alpha/2}\sqrt{var\left(\widehat{\delta^*}\right)}$ and the corresponding interval for AUC^* is

$$\left\{\Phi\left(\widehat{\delta^*} - z_{\alpha/2}\sqrt{var\left(\widehat{\delta^*}\right)}\right), \Phi\left(\widehat{\delta^*} + z_{\alpha/2}\sqrt{var\left(\widehat{\delta^*}\right)}\right)\right\}.$$

Rosner, et al. [82] aims to extend Reiser [73] method for non-normality of the biomarker by using probit-shift model with a parameter μ. The corrected AUC is estimated approximately by

$$AUC^*(\mu) \approx \Phi\left(\frac{\mu}{\sqrt{2}}\right)$$

while the derivation for the confidence interval is discussed in detail in Rosner, et al. [82].

6.3 Proposed Method 1: Regression calibration to adjust for measurement error in time-dependent ROC curve

Regression calibration is the most common method used to adjust for error of covariates in the Cox model [91]. It replaces the true covariate X by its regression on observed covariate W in the standard analysis to obtain parameter estimates. The true and observed biomarkers are modelled in an additive error model by

$W = X + \varepsilon$ where W is the observed value, X is the true value and ε is the error associated with X. The inference of the corresponding β parameter from the Cox model is based on the likelihood function

$$L(\beta) = \prod_{i=1}^{n}\left\{\frac{e^{\beta' W_i}}{\sum_{j\in R_i} e^{\beta' W_j}}\right\}^{\Delta_i}.$$

Then when X and ε are both normally distributed with mean zero and unknown σ_x^2 and known σ_ε^2 respectively, the expected value of X conditional on W is given by

$$\mathrm{E}(X_i|W_i) = \left(\frac{\hat{\sigma}_x}{\hat{\sigma}_x + \sigma_\varepsilon}\right) W_i, i = 1, \dots, n \tag{6.2}$$

and the σ_x^2 can be estimated by substracting the σ_ε^2 from σ_W^2 while σ_ε^2 can be estimated from longitudinal measurements of biomarker. Regression calibration improves the estimation of β parameter but still exhibit some bias. Although regression calibration is easiest to implement and offers improvements, it is not efficient when the error associated with X is high, and is also sensitive to the normality assumption [91]. Thus Hu, et al. [91] suggest to use more sophisticated method such as the likelihood based approaches [91].

This method is adopted to develop a measurement-error adjusted ROC curve under I/D definition. However, it was found that the regression calibration approach is not suitable to adjust for the measurement error in estimating the diagnostic accuracy of a biomarker. For the completeness of this thesis, the relevant findings from the conducted simulation study is presented below.

The longitudinal data were simulated using the same linear mixed effect model $\boldsymbol{x_i}(t) = 1 - t + U_{0i} + U_{1i}t + \varepsilon_i$. The variance of measurement error $\hat{\sigma}_\varepsilon^2$ is estimated from the longitudinal values X_i and the adjusted biomarker values Z_i can be computed by equation 5.2.

$$Z_i = W_i * (\hat{\sigma}_x^2/(\hat{\sigma}_x^2 + \hat{\sigma}_\varepsilon^2))$$

where $\hat{\sigma}_\varepsilon^2 = \frac{\sum_{i=1}^{n}\sum_{j=1}^{k_i}(W_{ij} - \overline{W}_{i.})^2}{\sum_{i=1}^{n}(k_i - 1)}$ and $\hat{\sigma}_x^2 = \hat{\sigma}_w^2 - \hat{\sigma}_\varepsilon^2$ where $\hat{\sigma}_w^2$ is the estimated sample variance of the observed biomarker. The estimated Cox model parameter associated with the baseline values of true, observed and adjusted biomarker are shown as in Table 6.1. The bias for the coefficient from the Cox model using the measurement error adjusted biomarker is lower than the bias for the observed biomarker, hence regression calibration method improves the coefficient estimates of the observed biomarker. This is parallel with the hypothesis that the observed biomarker always underestimates the effect of the covariates in the Cox model [91]. However, the estimated time-dependent $AUC(t)$ from the adjusted biomarker shows a higher bias

and MSE than the observed biomarker. Thus, it is concluded that regression calibration is inefficient to adjust for the measurement error when estimating the diagnostic accuracy of a biomarker.

Table 6.1: Estimated β from Cox model and AUC(t=2) from I/D method ID1 for varying error variance

σ_ε^2	True $\widehat{\beta}$ (SE)	$\widehat{\beta}_W$ (SE)	Bias for $\widehat{\beta}_W$	$\widehat{\beta}_Z$ (SE)	Bias for $\widehat{\beta}_Z$	True AUC (SE)	AUC_W (SE)	Bias for AUC_W	MSE	AUC_Z (SE)	Bias for AUC_Z	MSE
1.5	0.4149 (0.0661)	0.1517 (0.0365)	-0.2632	0.4187 (0.0429)	0.0019	0.6792 (0.0278)	0.6141 (0.0302)	-0.0651	0.0052	0.5596 (0.0717)	-0.1196	0.0194
2.0	0.4096 (0.0682)	0.1246 (0.0349)	-0.2850	0.3874 (0.0401)	0.0021	0.6770 (0.0241)	0.6111 (0.0251)	0.0659	0.0050	0.5351 (0.0288)	-0.1419	0.0210
2.5	0.4112 (0.0682)	0.1073 (0.0319)	-0.3039	0.3661 (0.0382)	0.0035	0.6437 (0.0282)	0.5903 (0.0286)	0.0534	0.0037	0.5287 (0.0336)	-0.1150	0.0144

**SE - standard error; MSE - mean square error*

6.4 Proposed Method 2: Joint modelling to adjust for measurement error in time-dependent ROC curve

A novel more data-efficient method within the joint modelling framework [18] is proposed to adjust for measurement error when estimating the time-dependent ROC curve.

6.4.1 General formulation of the joint model

A joint model is formulated by two submodels which are; a longitudinal submodel for $\boldsymbol{x}_i$ and an event-time submodel for (T_i,δ_i), and the two components are linked together through some shared parameters. Longitudinal trajectory is typically modelled by linear mixed effect models, while the event-time assumes various choice of modelling approaches through shared latent effects [18]. Following Henderson, et al. [18] a Gaussian linear model is assumed for biomarker measurement, and proportional hazards is assumed for event-times:

$$x_{ij} = \beta_0 + \beta_1 t_{ij} + W_{1i}(t_{ij}) + \varepsilon_{ij}$$
$$\lambda_i(t|X_i(t)) = \lambda_{0i}(t)\mathrm{e}^{W_{2i}(t)}.$$

In longitudinal data submodel, β_0 and β_1 are regression coefficients related to intercept and slope. Individual-specific random effects are incorporated through $W_{1i}(t_{ij})$ where $W_1(.)$ is an unobserved zero-mean Gaussian random process. In this component, measurement error process ε_{ij} is accounted for and ε_{ij} assumes Gaussian distribution with mean zero and variance σ_ε^2. In event-time submodel, $X_i(t)$ is the true unknown biomarker value at time t, $\lambda_{0i}(t)$ is an unspecified baseline hazard and $W_{2i}(t)$ is a second unobserved zero-mean Gaussian random process. The event-time process is associated with the longitudinal response through the shared random effect of $W_{1i}(t)$ and $W_{2i}(t)$. This model links the true biomarker value at time t through the hazard of event at time t for the ith individual. Further, $W_{1i}(t_{ij})$ and the measurement error process ε_{ij} are assumed to be mutually independent [18]. Many authors assume $W_{1i}(t) = U_{0i} + U_{1i}t$ in conjunction with a proportionality assumption $W_{2i}(t) = \gamma\, W_{1i}(t)$ where U_{0i} and U_{1i} are individual-level random intercept and random slope

respectively, and (U_{0i}, U_{1i}) assume a multivariate normal distribution with mean 0 and variance $\Sigma_u = \begin{pmatrix} \sigma_{u_0}^2 & \sigma_{u_0,u_1} \\ \sigma_{u_0,u_1} & \sigma_{u_1}^2 \end{pmatrix}$ [13].

6.4.2 Proposed joint modelling formulation

It is assumed that biomarker data $\boldsymbol{x}_i$ are available for each individual at times t_{ij}, $i = 1, \dots, n$; $j = 1, \dots, m_i$, and allow the possibility of different numbers and timing of longitudinal measurements for different individuals. To link the individual-specific baseline biomarker value (at $t = 0$) to the risk of event, following joint model is proposed:

$$x_{ij} = \beta_0 + \beta_1 t_{ij} + U_{0i} + U_{1i} t + \varepsilon_{ij}$$
$$\lambda_i(t|X_i(t)) = \lambda_{0i}(t) \exp(\gamma U_{0i}) \quad (6.3)$$

with $W_{1i}(t) = U_{0i} + U_{1i} t$ and $W_{2i} = U_{0i}$. In this specification, U_{0i} and U_{1i} reflect individual-level deviations of the longitudinal profile from the population mean at baseline and from the population mean slope at time t respectively, and the random intercept term alone in the event-time submodel links the risk of event directly on the true individual-specific value of the biomarker at baseline. The parameter γ estimates the level of association between biomarker value at baseline and hazard for the event.

The model is estimated by maximising the joint likelihood of the observed data via the EM algorithm, and any integration is performed using the Gauss-Hermite quadrature [18]. It involves taking expectations with respect to the unobserved latent process $\{W_{1i}(t), W_{2i}\}$. The EM algorithm iterates between two steps until convergence is achieved. E-step determines expected values $E[U_{0i}]$ conditional on observed joint outcome $\{T_i, \delta_i, \boldsymbol{x_i}\}$. M-step maximises the complete data log-likelihood by W_{2i} replaced by corresponding expectation. These steps are described in Section 6.4.3.1.

6.4.3 Joint likelihood formulation

The joint density of observed longitudinal and event-time outcomes derives the joint likelihood function. Let $\boldsymbol{\theta} = \{\beta, \Sigma_u, \sigma_\varepsilon^2, \gamma, \lambda_0(.)\}$ denote all unknown parameters to be estimated.

The random effects $W_i(t) = \{W_{1i}(t), W_{2i}(t)\}$ underlie both the longitudinal and event-time outcome processes [13] and the longitudinal and event-time processes are assumed to be independent conditional on $W_i = \{W_{1i}, W_{2i}\}$ where $W_{1i}(t) = U_{0i} + U_{1i}t$ and $W_{2i} = U_{0i}$.

Then, the joint density for any individual i can be conveniently defined by

$$f(x_i, T_i, \delta_i) = \int_{-\infty}^{\infty} f\,(x_i, T_i, \delta_i | W_i) f(W_i) dW_i$$
$$= \int_{-\infty}^{\infty} f(x_i | W_{1i})\, f(T_i, \delta_i | W_{2i}) f(W_i) dW_i$$

where the individual functions in $f(x_i, T_i, \delta_i)$ can be defined by

$$f(x_{ij}|W_{1i}) = \frac{1}{\sqrt{2\pi\sigma_\varepsilon^2}} \exp\left\{-\frac{1}{2\sigma_\varepsilon^2}(x_{ij} - \beta Z_{ij} - W_{1i})'(x_{ij} - \beta Z_{ij} - W_{1i})\right\}$$

is the standard multivariate normal density of longitudinal data x_{ij} with $Z_{ij} = \{1, t_{ij}\}$,

$$f(T_i, \delta_i | W_{2i}) = [\lambda_0(T_i) e^{\gamma W_{2i}}]^{\delta_i} \exp\left\{-\int_0^{T_i} \lambda_0(v)\, e^{\gamma W_{2i}} dv\right\}$$

is the usual event-time distribution for $\{T_i, \delta_i\}$, and

$$f(W_i) = (|\Sigma_u|)^{-1/2} \exp\left\{\frac{-W_i' \Sigma_u^{-1} W_i}{2}\right\}$$

is the Gaussian density of W_i with zero mean and variance Σ_u. Thus, the complete data likelihood can be defined as the product of these quantities over all individuals

$$\prod_{i=1}^{n} \left[\int_{-\infty}^{\infty} \left\{\prod_{j=1}^{m_i} f(x_{ij}|W_{1i})\right\} f(T_i, \delta_i | W_{2i}) f(W_i) dW_{1i}\right]$$

Complication arises in maximising this likelihood because of incomplete information of W_i since the random effects are being unobserved. To solve this problem of missing random effects, EM algorithm is used. As shown by Wulfsohn and Tsiatis [13], in this setting EM algorithm gives an efficient method for maximum likelihood estimation. More details of the EM algorithm is given in section below.

6.4.3.1 EM estimation algorithm

The algorithm is described by Wulfsohn and Tsiatis [13], and the procedure involves iterating between the following E and M steps until convergence is achieved. E-step computes the expected log-likelihood of the complete data conditional on the observed data and the current estimate of the parameters, and M-step computes new parameter estimates by maximizing this expected log-likelihood.

E-step

Considering $W_i = \{W_{1i}, W_{2i}\}$ as missing data, this step calculates the expected log-likelihood of the complete data conditional on the observed data $\{x_{ij}, t_{ij}, T_i, \delta_i\}$ and the current parameter estimates $\widehat{\theta}$. It estimates conditional expectations of the form $E\left[h(W_i)|x_{ij}, t_{ij}, T_i, \delta_i, \widehat{\theta}\right]$ for some $h(W_i)$ as required below.

Let $\mathbb{Z} = \left\{\left(x_{ij}, t_{ij}, T_i, \delta_i\right), i = 1, \dots, n;\ j = 1, \dots, m_i\right\}$ be the observed biomarker data which includes the observed longitudinal measurements with recorded measurement times, and event-time data.

The expected log-likelihood related to longitudinal outcome data:

$$L\left(\sigma_\varepsilon^2, \beta|\mathbb{Z}, \hat{\theta}\right) =$$

$$\prod_{i=1}^{n}\prod_{j=1}^{m_i}\frac{1}{\sqrt{2\pi\sigma_\varepsilon^2}}\exp\left\{-\frac{1}{2\sigma_\varepsilon^2}\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)'\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)|\mathbb{Z}, \widehat{\theta}\right\}$$

and hence

$$E\left[\log\left(L\left(\sigma_\varepsilon^2,\beta|\mathbb{Z},\hat{\theta}\right)\right)\right]=$$

$$-\frac{1}{2\sigma_\varepsilon^2}\sum_{i=1}^{n}\sum_{j=1}^{m_i}E_i\left[\left(x_{ij}-\beta Z_{ij}-W_{1i}(t_{ij})\right)'\left(x_{ij}-\beta Z_{ij}-W_{1i}(t_{ij})\right)|\mathbb{Z},\hat{\theta}\right]$$

$$+\sum_{i=1}^{n}\log\left(\frac{1}{(2\pi\sigma_\varepsilon^2)^{\frac{m_i}{2}}}\right)$$

The expected log-likelihood related to event-time data:

$$L\left(\lambda_0(v),\gamma|\mathbb{Z},\hat{\theta}\right)=\prod_{i=1}^{n}[\lambda_0(T_i)e^{\gamma W_{2i}}]^{\delta_i}\exp\left\{-\int_0^{T_i}\lambda_0(v)\,e^{\gamma W_{2i}}dv\right\}$$

and hence

$$E\left[\log\left(L\left(\lambda_0,\gamma|\mathbb{Z},\hat{\theta}\right)\right)\right]=$$

$$\sum_{i=1}^{n}\delta_i\log[\lambda_0(T_i)]+\sum_{i=1}^{n}\delta_i\log\left(\gamma E_i[W_{2i}|\mathbb{Z},\hat{\theta}]\right)-\sum_{i=1}^{n}\int_0^{T_i}\lambda_0(v)\,E_i\left[e^{\gamma W_{2i}}|\mathbb{Z},\hat{\theta}\right]dv$$

The expected log-likelihood related to random effects:

$$L\left(\Sigma_u|\mathbb{Z},\hat{\theta}\right)=\prod_{i=1}^{n}|\Sigma_u|^{-1/2}\exp\left\{\frac{-W_{1i}{}'\Sigma_u{}^{-1}W_{1i}}{2}\right\}$$

and hence

$$E\left[\log L\left(\Sigma_u|\mathbb{Z},\hat{\theta}\right)\right]=\frac{\sum_{i=1}^{n}E_i\left[-W_{1i}{}'\Sigma_u{}^{-1}W_{1i}|\mathbb{Z},\hat{\theta}\right]}{2}+\log\left(|\Sigma_u|^{-n/2}\right)$$

Using transformation $\mathrm{H}=\Sigma_u{}^{-1}$, the expected log-likelihood is revised by

$$E\left[\log L\left(H|\mathbb{Z},\hat{\theta}\right)\right]=\frac{\sum_{i=1}^{n}E_i\left[-W_{1i}{}'\mathrm{H}W_{1i}|\mathbb{Z},\hat{\theta}\right]}{2}+\log\left(|H|^{n/2}\right)$$

Therefore, four specific forms of expectations are required; $E_i\left(W_{1i}(t_{ij})|\mathbb{Z},\hat{\theta}\right)$, $E_i\left(W_{2i}|\mathbb{Z},\hat{\theta}\right)$, $E_i\left(e^{\gamma W_{2i}}|\mathbb{Z},\hat{\theta}\right)$ and $E_i\left[(W_iW_i{}')|\mathbb{Z},\hat{\theta}\right]$.

The conditional density of W_i given the observed data and the current estimates of the parameters is equal to

$$f(W_i|\mathbb{Z},\hat{\theta}) = \frac{f(W_i|x_i,T_i,\hat{\Sigma}_u,\hat{\sigma}_\varepsilon^2)f(T_i,\delta_i|W_i,\hat{\lambda}_0,\hat{\gamma})}{\int_{-\infty}^{\infty} f(W_i|x_i,T_i,\hat{\Sigma}_u,\hat{\sigma}_\varepsilon^2)f(T_i,\delta_i|W_i,\hat{\lambda}_0,\hat{\gamma})}.$$

Thus, the conditional expectation of any function of W_i can be written by

$$E_i[h(W_i)|\mathbb{Z},\hat{\theta}] = \frac{\int_{-\infty}^{\infty} h(W_i)f(W_i|x_i,T_i,\hat{\Sigma}_u,\hat{\sigma}_\varepsilon^2)f(T_i,\delta_i|W_i,\hat{\lambda}_0,\hat{\gamma})}{\int_{-\infty}^{\infty} f(W_i|x_i,T_i,\hat{\Sigma}_u,\hat{\sigma}_\varepsilon^2)f(T_i,\delta_i|W_i,\hat{\lambda}_0,\hat{\gamma})}. \quad (6.4)$$

The conditional distribution function of W_i given y_i, $f(W_i|\boldsymbol{x_i},T_i,\hat{\Sigma}_u,\hat{\sigma}_\varepsilon^2)$ can be derived from the joint bivariate normal distribution of W_i and $\boldsymbol{x_i}$

$$\begin{pmatrix} x_i \\ W_i \end{pmatrix} \sim MVN\left[\begin{pmatrix} \beta Z_{ij} \\ 0 \end{pmatrix}, \begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix}\right]$$

and the components of covariance matrix are given by

$$B_{11} = \begin{Bmatrix} Z_{i1}\Sigma_u {Z_{i1}}', & \cdots, & Z_{i1}\Sigma_u {Z_{im_i}}' \\ \vdots & \ddots & \vdots \\ Z_{imi}\Sigma_u {Z_{i1}}', & \ldots, & Z_{im_i}\Sigma_u {Z_{im_i}}' \end{Bmatrix} + I_{m_i}\sigma_\varepsilon^2,$$

where I_{m_i} is an identity matrix with dimensions $m_i \times m_i$ as $\Sigma_u$for each individual i, and

$$B_{21} = \begin{pmatrix} \sigma_{u_0}^2 + \sigma_{u_0,u_1}t_{i1}, \ldots, \sigma_{u_0}^2 + \sigma_{u_0,u_1}t_{im_i} \\ \sigma_{u_0,u_1} + \sigma_{u_1}^2 t_{i1}, \ldots, \sigma_{u_0,u_1} + \sigma_{u_1}^2 t_{im_i} \end{pmatrix},$$

$B_{21} = {B_{21}}'$ and

$B_{22} = \Sigma_u$

Using the standard theory of normal distribution and information from above multivariate distribution, the mean and variance of W_i given y_i can be define as

$$E[W_i|x_i] = E[W_i] + \rho\frac{B_{22}}{B_{11}}\left[x_i - E[x_i]\right] = B_{12}{B_{11}}^{-1}[x_i - \beta Z_i - W_{1i}(t)]$$

$$\mathrm{Var}(W_i|x_i) = \mathrm{Var}(W_i)(1-\rho^2) = B_{22} - B_{21}{B_{11}}^{-1}B_{12}$$

where ρ is the correlation between W_i and y_i and $Z_i = \{1, t_i\}$. Thus,

$$W_i|y_i \sim N\left(B_{12}{B_{11}}^{-1}[x_i - \beta Z_i - W_{1i}(t)], B_{22} - B_{21}{B_{11}}^{-1}B_{12}\right)$$

and for simplicity we write it as $W_i|x_i \sim N\left(\mu_{x_i}, B_{x_i}\right)$ with the distribution function

$$f(W_i|x_i) = (2\pi)^{-\frac{1}{2}}{B_{x_i}}^{-1/2}\exp\left\{-\frac{1}{2}\left(W_{1i}-\mu_{x_i}\right)'{B_{x_i}}^{-1}\left(W_{1i}-\mu_{x_i}\right)\right\}$$

where μ_{x_i} and B_{x_i} represent the mean and variance of the above transformed variable which are equal to $B_{12}{B_{11}}^{-1}[x_i - \beta Z_i - W_{1i}(t)]$ and $B_{22} - B_{21}{B_{11}}^{-1}B_{12}$ respectively.

The evaluation of the expectations of the form in (6.4) requires numerical integration. Wulfsohn and Tsiatis [13] adopts a p-point Gauss Hermite quadrature approximation.

A p-point Gauss-Hermite quadrature formula can be defined by

$$\int_{-\infty}^{\infty} e^{-\emptyset^2} f(\emptyset)\, d\emptyset = \sum_{j=1}^{p} g_j f(h_j) \qquad (6.5)$$

where $h_j (j = 1, \ldots, p)$ are tabulated abscissa values for $\emptyset$ and $g_j (j = 1, \ldots, p)$ are the associated weights. Equation (6.5) can be define as a distribution function of $\emptyset$ which follows a normal distribution with mean zero and variance ½. Thus, the parameter $\emptyset$ can be defined in terms of W_i as follow

$$\emptyset_i = \left(W_i - W_{x_i}\right)\left(2B_{x_i}\right)^{-\frac{1}{2}}$$

where W_{x_i} is the conditional variable of W_i given x_i and $\left(2B_{x_i}\right)^{-\frac{1}{2}}$ is the inverted Cholesky decomposition of $2B_{x_i}$ and $\emptyset_i = (\emptyset_{1i}, \emptyset_{2i})$ are independent and normally distributed. All functions in Equation (6.4) are transformed to the quadrature formula in Equation (6.5) using the following definition

$$W_i^{'} = \emptyset_i\left(2B_{x_i}\right)^{\frac{1}{2}} + W_{x_i}.$$

So, the non-constant term of the numerator in Equation (6.46.) can be write as follow

$$\int_{-\infty}^{\infty} h(W_i^{'}) \left[e^{\gamma W_{2i}^{'}}\right]^{\delta_i} \exp\left\{-\int_0^{T_i} \lambda_0(v)\, e^{\gamma W_{2i}^{'}} dv\right\} \times \exp\left\{-\left(\emptyset_{1i}^2 + \emptyset_{2i}^2\right)\right\} d\emptyset_i$$

and after the transformation, it becomes

$$\sum_{j=1}^{p}\sum_{k=1}^{p} h\left(W_i^{'}\right)\left[e^{\gamma W_{2i}^{'}}\right]^{\delta_i} \exp\left\{-\int_0^{T_i} \lambda_0(v)\, e^{\gamma W_{2i}^{'}} dv\right\} \times g_j g_k$$

where $W_i^{'}$and $W_{2i}^{'}$ now in the functions of $\emptyset_{1i}$ and $\emptyset_{2i}$ which respectively take on p abscissa values $h_j(j = 1, \ldots, p)$ and $h_k(k = 1, \ldots, p)$. With this transformation, the estimates of all expectations are calculated and ready to be used in the M-step.

M-step

The expected log-likelihood is maximised to compute the parameter estimates $\widehat{\theta}$. Each function of W_i is replaced by its corresponding expectation calculated using quadrature approximation. This involves setting the first derivative of each expected log likelihood with respect to the corresponding parameter equal to zero. This would lead to closed form maximum likelihoods estimates for $\beta, \sigma_\varepsilon^2, \lambda_0$ and Σ_u. However, no closed form estimate of γ can be computed by this step alone, and is estimated numerically by one-step Newton Raphson algorithm. The maximisation procedure for each parameter is described below.

The estimated measurement error variance σ_ε^2:

$$\frac{\partial E\left[log\left(L(\sigma_\varepsilon^2, \beta|\mathbb{Z}, \widehat{\theta})\right)\right]}{\partial \sigma_\varepsilon^2} =$$

$$\frac{1}{2(\sigma_\varepsilon^2)^2}\sum_{i=1}^{n}\sum_{j=1}^{m_i} E_i\left[\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)^{'}\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)|\mathbb{Z}, \widehat{\theta}\right] - \frac{\sum_{i=1}^{n} m_i}{2\sigma_\varepsilon^2}$$

$$= 0$$

$$\frac{\sum_{i=1}^{n} m_i}{2\sigma_\varepsilon^2} = \frac{1}{2(\sigma_\varepsilon^2)^2}\sum_{i=1}^{n}\sum_{j=1}^{m_i} E_i\left[\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)^{'}\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)|\mathbb{Z}, \widehat{\theta}\right]$$

and thus

$$\sigma_{\varepsilon}^{2} = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m_i} E_i\left[\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)'\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)|\mathbb{Z}, \widehat{\theta}\right]}{\sum_{i=1}^{n} m_i}$$

The estimated fixed effect coefficients for the longitudinal submodel β:

$$\frac{\partial E\left[log\left(L(\sigma_{\varepsilon}^{2}, \beta|\mathbb{Z}, \widehat{\theta})\right)\right]}{\partial \beta}$$

$$= -\frac{1}{2(\sigma_{\varepsilon}^{2})^{2}}\sum_{i=1}^{n}\sum_{j=1}^{m_i} E_i\left[\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)'\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)|\mathbb{Z}, \hat{\theta}\right]$$

and by setting

$$\sum_{i=1}^{n}\sum_{j=1}^{m_i} E_i\left[\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)'\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)|\mathbb{Z}, \widehat{\theta}\right] = 0$$

then compute

$$\beta Z_{ij} = \sum_{i=1}^{n}\sum_{j=1}^{m_i} E_i\left[\left(x_{ij} - W_{1i}(t_{ij})\right)|\mathbb{Z}, \widehat{\theta}\right]$$

$$\beta = {Z_{ij}}^{-1}\sum_{i=1}^{n}\sum_{j=1}^{m_i} E_i\left[\left(x_{ij} - W_{1i}(t_{ij})\right)|\mathbb{Z}, \widehat{\theta}\right]$$

The estimated baseline hazard $\lambda_0(T_i)$:

$$\frac{\partial E\left[\log\left(L(\lambda_0, \gamma|\mathbb{Z}, \widehat{\theta})\right)\right]}{\partial \lambda_0} = \frac{\delta_i}{\lambda_0(T_i)} - E_i\left[e^{\gamma W_{2i}}|\mathbb{Z}, \widehat{\theta}\right] = 0$$

and thus

$$\lambda_0(T_i) = \frac{\delta_i}{E_i\left[e^{\gamma W_{2i}}|\mathbb{Z}, \widehat{\theta}\right]}$$

The estimated variance covariance matrix for random effects Σ_u: The revised expected log-likelihood are differentiated with respect to H.

$$\frac{\partial E\left[logL(H|\mathbb{Z},\widehat{\theta})\right]}{\partial H} = \frac{\partial E}{\partial H}\left[\frac{n}{2}\log|H| - \frac{1}{2}H\sum_{i=1}^{n} E_i\left[W_{1i}\,W_{1i}{}'\right]\right] = 0$$

$$\frac{n}{2}H^{-1} - \frac{1}{2}\sum_{i=1}^{n} E_i\left[W_{1i}W_{1i}{}'\right] = 0$$

$$\frac{n}{2}\Sigma_u - \frac{1}{2}\sum_{i=1}^{n} E_i\left[W_{1i}W_{1i}{}'\right] = 0$$

Thus $n\Sigma_u = \sum_{i=1}^{n} E_i[W_{1i}W_{1i}{}']$ and

$$\Sigma_u = \frac{\sum_{i=1}^{n} E_i\left[W_{1i}W_{1i}{}'\right]}{n}$$

The estimated association parameter γ:

$$\frac{\partial E\left[\log\left(L(\lambda_0,\gamma|\mathbb{Z},\widehat{\theta})\right)\right]}{\gamma} = \sum_{i=1}^{n}\frac{\delta_i}{\gamma} - \lambda_0(T_i)\,E\left[e^{\gamma W_{2i}}|\mathbb{Z},\widehat{\theta}\right]E\left[W_{2i}|\mathbb{Z},\widehat{\theta}\right] = 0$$

Solving the above expression for γ leads to a function of λ_0, thus no closed form estimate of γ can be computed. Therefore, to estimate γ, one-step Newton Raphson algorithm is used which will explained in detail in section below.

The following are all closed-form estimators available for parameters except for γ.

$$\widehat{\beta} = {Z_i}^{-1}\ \sum_{i=1}^{n}\sum_{j=1}^{m_i} E_i\left[\left(x_{ij} - W_{1i}(t_{ij})\right)|\mathbb{Z},\widehat{\theta}\right]$$

$$\widehat{\Sigma}_u = \frac{1}{n}\sum_{i=1}^{n} E_i\left[W_{1i}{W_{1i}}'|\mathbb{Z},\widehat{\theta}\right]$$

$$\hat{\sigma}_{\varepsilon}^{2} = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m_i} E_i\left[\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)'\left(x_{ij} - \beta Z_{ij} - W_{1i}(t_{ij})\right)|\mathbb{Z}, \hat{\theta}\right]}{\sum_{i=1}^{n} m_i}$$

$$\hat{\lambda}_0(v) = \sum_{i=1}^{n} \frac{\delta_i I(X_i = v)}{\sum_{j=1}^{n} E_j[\exp\{\gamma W_{2i}\}|\mathbb{Z}, \hat{\theta}]R_j(v)}$$

where $R_j(.)$ is an at risk indicator, taking value 1 when the jth individual is at risk at v, and 0 otherwise. The baseline hazard $\hat{\lambda}_0(v)$ is evaluated at each of the ordered event times, denoted by $v_1, v_2, \ldots, v_k$.

<u>One-step Newton-Raphson</u>

The purpose of this numerical method is to find successive values of γ using the first derivative of a function of γ. In general, the successive value can be defined by

$$\hat{\gamma}_{current} = \hat{\gamma}_{initial} - \frac{f(\hat{\gamma}_{initial})}{f'(\hat{\gamma}_{initial})} \tag{6.6}$$

The first derivative of the function f' measures the instantaneous rate of change of the function. The second term in Equation (6.6) approximates the difference between these two successive values. In this case, the difference is approximated by a multiplication of information and score functions of a parameter, in which at the m th iteration, the $\hat{\gamma}$ can be defined by

$$\hat{\gamma}_m = \hat{\gamma}_{m-1} + I_{\hat{\gamma}_{m-1}}^{-1} S_{\hat{\gamma}_{m-1}}$$

where $S_{\hat{\gamma}_{m-1}}$ and $I_{\gamma_{m-1}}^{-1}$ are the score and information at the $(m-1)$th iteration value respectively. Score $S_{\hat{\gamma}}$ and information $I_{\hat{\gamma}}$ are determined by taking the first and second derivatives of the expected log-likelihood with respect to γ respectively:

$$S_{\hat{\gamma}} = \frac{\partial E\left[\log\left(L(\hat{\lambda}_0, \gamma|\mathbb{Z}, \hat{\theta})\right)\right]}{\partial \gamma} = \sum_{i=1}^{n}\left\{\frac{\delta_i}{\gamma} - \sum_{j=1}^{k} \hat{\lambda}_0(v_j)\, E_i[W_{2i} e^{\gamma W_{2i}}|\mathbb{Z}, \hat{\theta}]\right\}$$

$$I_{\hat{\gamma}} = \frac{\partial^2 E\left[\log\left(L(\hat{\lambda}_0, \gamma|\mathbb{Z}, \hat{\theta})\right)\right]}{\partial \gamma^2} = -\sum_{i=1}^{n} \frac{\delta_i}{\gamma^2} + \sum_{j=1}^{k} \hat{\lambda}_0(v_j)\, E_i\left[(W_{2i})^2 e^{\gamma W_{2i}} | \mathbb{Z}, \hat{\theta}\right]$$

To begin the EM algorithm, initial parameters are needed. These parameters can be estimated from separate maximum likelihood process of longitudinal measurements on event-time, by ignoring any association exist between them. Separate linear mixed models are fitted for each longitudinal measure to get estimate for parameters β, Σ_u, and σ_ε^2 using "lme" function in "nlme" package in R. The estimated random effects obtained from the fitted models (random intercept only for baseline model) are then included in the Cox proportional hazard model for event-time outcome. The initial parameter of hazards λ_0 are obtained from the Cox proportional hazards model for survival outcome using the "coxph" function in "survival" package in R.

6.4.4 Proposed time-dependent ROC curve methodology

A novel, but computationally simple approach is proposed to estimate the time-dependent ROC curve for a biomarker at baseline level that is subject to measurement error. The best linear unbiased estimates of the individual-specific deviation U_{0i} related to true biomarker value at baseline is estimated from the above EM algorithm.

The proposed approach includes 4 steps:

Step 1: Using the available longitudinal measurements of the biomarker and event-times, the joint model specified in (6.3) is fitted, and the measurement error-adjusted estimator is estimated from the linear predictor

$$\widehat{\mathrm{M}}_i = \hat{\gamma}\widehat{U}_{0i}$$

where $\widehat{U}_{0i}$ is the estimated deviation of the true biomarker value from the population mean at baseline for the ith individual, and $\hat{\gamma}$ is the estimated level of association between true biomarker and hazard for the event value at baseline. Further, $\exp(\hat{\gamma})$ is the hazard ratio associated with a unit increase in the value of biomarker at baseline with respect to the population mean. The validity of $\widehat{\mathrm{M}}_i$ as the measurement error-

adjusted estimator in time dependent ROC curve analysis is extensively explored in our simulation studies.

Step 2: At any time t_h (> 0), use the counting process $D_i(t_h)$ such that each diseased individual plays a role as *control* for an early time $t_h < T_i$ but then play the role of *case* when $t_h = T_i$. $D_i(t) = 1$ indicates that ith individual has experienced the event at time t_h or prior to time t_h. Here, the failure time is represented through the counting process $N(t_h) = I(T_i \leq t_h)$, and the corresponding increment is defined by $dN(t_h) = N(t_h) - N(t_h -)$ in terms of the failure time T_i alone. Note this definition is different from the usual counting process notation $N(t_h) = I(X_i \leq t_h, \delta_i = 1)$, and it adopts the incident/dynamic ROC curve terminology discussed by Heagerty and Zheng [27].

Step 3: Define the set of individuals at risk at time t_h (riskset) by at-risk indicator $R_i(t_h) = I(X_i \geq t_h)$. Then, dichotomise the riskset at time t_h into two mutually exclusive groups: *cases* (experienced event at time t_h) and *controls* (survived event beyond time t_h).

For simplicity in the notation, t is used instead of t_h in the rest of this section.

Step 4: Based on $\widehat{\mathrm{M}}_k$ of the individuals in the riskset, the discriminatory potential of the biomarker at time t conditional on a threshold value c is assessed which determines the *test* positive if $\widehat{\mathrm{M}}_k \geq c$ and *test* negative if $\widehat{\mathrm{M}}_k < c$. The sensitivity and specificity at t are then defined by

$$\text{sensitivity}(c, t)\text{: } Pr\{\widehat{\mathrm{M}}_i > c |\, dN(t) = 1\}$$

$$\text{specificity}(c, t)\text{: } Pr\{\widehat{\mathrm{M}}_i \leq c |\, N(t) = 0\}$$

where $c \in (-\infty, +\infty)$. $\text{Sensitivity}\,(c, t)$ estimates the fraction of individuals with $\widehat{\mathrm{M}}_k > c$ among those who experience the event (disease onset) at t, while $\text{specificity}(c, t)$ estimates the fraction of individuals with $\widehat{\mathrm{M}}_k \leq c$ among those who survived disease-free beyond time t.

To estimate the above probabilities of $\widehat{\mathrm{M}}_k$ conditional on incident/dynamic failure times defined in Step 3, we can use the proportional hazards properties of the joint likelihood function related to the event-time submodel in (6.36.). Xu and O'Quigley [47] has proposed estimating the proportion of variation in the covariate that is explained by failure times. Xu and O'Quigley [47] estimated the distribution of the covariate conditional on failure at time t based on the weights $\pi_k(t)$ from the Cox proportional hazards model, and the same approach was later used by Heagerty and Zheng [27] to estimate the time-dependent sensitivities and specificities. Following Heagerty and Zheng [27], for a given threshold value c, we estimate the sensitivity (TPF) by

$$\text{sensitivity}\,(c,t) = Pr\big(\widehat{\mathrm{M}}_i > c | T_i = t\big) = \sum_k I\left(\widehat{\mathrm{M}}_k > c\right)\pi_k(t)$$

where $\pi_k(t) = R_k(t)\exp\big(\widehat{\mathrm{M}}_k\big)/W(t)$, with $W(t) = \sum_k R_k(t)\exp\big(\widehat{\mathrm{M}}_k\big)$ is the total weight of the riskset individuals, are the weights under a proportional hazards, and $I(.)$ is an indicator.

The specificity $(1 - \text{FPF})$ can be calculated empirically by

$$\text{specificity}\,(c,t) = P\big(\widehat{\mathrm{M}}_i \le c | T_i > t\big) = \frac{\sum_k I\big(\widehat{\mathrm{M}}_k \le c\big)R_k^0(t)}{\sum_k R_k^0(t)}$$

where $R_k^0(t)$ is the set of event-free individuals in the riskset at time t and $\sum_k R_k^0(t)$ is the size of that control-set.

Bansal and Heagerty [92] has used the above definition when there exists time-specific *cases* of interest at a particular time t. However, this definition is applied to estimate the diagnostic accuracy at any time $t > 0$ with no prior information on the predicted time. The proportional hazard assumption does not require any *case* to exist at time t to produce the sensitivity but only will force the FPF equal to zero and specificity equal to one. Thus, although there is no *case* exists at time t (which usually happens in practice), the discriminatory potential of the biomarker can still be estimated at time t.

Once the above incident sensitivity (semiparametric) and dynamic specificity (nonparametric) are defined, the time-dependent ROC curve at time t for all $c \in$

$(-\infty, +\infty)$ can be computed by kernel (density) smoothing which follows closely the details of the original data [93]. The kernel estimate is obtained by smoothing the corresponding histograms of $\widehat{\mathrm{M}}_k$ for the *cases* and *controls* at time t. Let the smoothed version of TPF and FPF be $\widehat{S}_D(t)$ and $\widehat{S}_{\bar{D}}(t)$ respectively. The smoothed time-dependent ROC function at time t is given by $\{\hat{S}_D(t,c),\ \hat{S}_{\bar{D}}(t,c)\}$ for $c \in (-\infty, +\infty)$ or equivalently

$$\mathrm{ROC}_t(\rho) = S_D\left[S_{\bar{D}}^{-1}(\rho)\right],\ \ \rho \in (0,1)$$

where ρ is the abscissa axis (FPF) and $\mathrm{ROC}_t(\rho)$ the ordinate axis (TPF) of the ROC plot [93].

The AUC(t) is simply $\widehat{AUC}(t) = \int \widehat{\mathrm{ROC}}_t(\rho)d\rho$ the area under the ROC curve for time t, and estimates the probability of a random pair of individuals, who experiences the event at time t has a larger biomarker value than the individual who remains event-free beyond time t.

In practice, there is no specific time t of interest usually, but restricted to a fixed follow-up period $(0, \tau)$. In that case, a global summary is preferable, and the above AUC(t) can be modified to provide a survival concordance index (C-index) to account for finite follow-up by

$$\mathrm{C}^{\tau} = \int_0^{\tau} \mathrm{AUC(t)w}^{\tau}(t)dt$$

where $\mathrm{w}^{\tau}(t) = 2f(t)S(t)/\{1 - S^2(\tau)\}$with $f(t)$ is the density function of event time and $S(t)$ is the survival function of the event time. This defines the probability that the predictions for the random pair of individuals are concordant with their outcomes, given that the smaller event time occurs in $(0, \tau)$.

6.4.5 Calculation of the 95% confidence intervals for sensitivity and specificity

In the proposed approach, $\widehat{\mathrm{M}}_i$ is computed from model parameter estimates, which is then used as the input to ROC analysis. Hence the 95% confidence intervals (CIs) of sensitivity and specificity must account for uncertainty due to the estimation processes.

Therefore, the 95% CIs for accuracy summaries are estimated by the bootstrap sampling with replacement [94]. The previously suggested time-dependent ROC models for censored event based on a single biomarker value were also suggested bootstrap approaches to estimate the corresponding CIs [2, 27, 39].

6.5 Application

The proposed approach is applied to the PBC sequential data using three selected biomarkers. The longitudinally recorded serum bilirubin measurements (in mg/dl), albumin (in mg/dl) and prothrombin time (in seconds) are used in the analysis with the aim of assessing the predictively accuracy of the initial (baseline). The range of the longitudinal measurements and timing of the measurements differ between patients. The bilirubin measurements were log-transformed and the prothrombin time were transformed by $(0.1\times\text{prothrombin time})^{-4}$. Albumin was not transformed and original value is used in the analysis [28].

Table 6.2 presents the estimates of association parameter $\hat{\gamma}$ and C-index C^{τ} at fixed follow-up (0, 3650 days or 10 years) from the joint model and Cox model for the three biomarkers. The proposed measurement error adjusted biomarker from the joint model consistently provides higher association parameter estimates than the baseline observed biomarker that lead to higher C-Index for all three biomarkers.

Table 6.2: Estimated association parameter and C-Index for the adjusted and observed baseline biomarkers

Biomarker	Adjusted		Observed	
	Association	**C-Index**	**Association**	**C-Index**
Log (bilirubin)	1.4073 (0.1508)	0.7848 (0.0212)	1.0674 (0.1040)	0.7532 (0.0195)
$(0.1 \times \text{Prothrombin Time})^{-4}$	6.4252 (0.8648)	0.7613 (0.0248)	3.3653 (0.5343)	0.6977 (0.0258)

Albumin	4.7720 (0.8037)	0.7910 (0.0247)	1.7126 (0.2453)	0.6727 (0.0221)

Table 6.3 shows the estimated time-dependent AUC, sensitivity and specificity at prediction times Year 1, Year 5 and Year 10. The proposed measurement error adjusted biomarker performs well with higher time-dependent AUC estimates than the observed biomarker at all prediction times and across all three biomarkers. This can be supported with the graphical presentation of the estimated time-dependent ROC curve in Figure 6.1-6.3, that show the consistent performance of the adjusted biomarker. Among the three biomarkers, the time-dependent AUC for log (bilirubin) biomarker is the highest which means it has the best predictive ability in detecting the presence of the disease among PBC patients.

Table 6.3: Estimated time-dependent AUC(t), sensitivity and specificity of the adjusted and observed baseline biomarkers

Biomarker	Prediction Time	Adjusted			Observed		
		AUC (SE)	Sensitivity (SE)	Specificity (SE)	AUC (SE)	Sensitivity (SE)	Specificity (SE)
Log (bilirubin)	Year 1	0.8295 (0.0098)	0.7692 (0.0124)	0.7517 (0.0131)	0.7953 (0.0204)	0.7275 (0.0199)	0.7274 (0.0182)
	Year 5	0.7686 (0.0126)	0.6911 (0.0124)	0.7164 (0.0149)	0.7355 (0.0161)	0.6600 (0.0156)	0.6974 (0.0164)
	Year 10	0.6878 (0.0195)	0.6393 (0.0216)	0.6460 (0.0238)	0.6584 (0.0260)	0.6037 (0.0210)	0.6278 (0.0259)
$(0.1 \times \text{Prothrombin Time})^{-4}$	Year 1	0.8174 (0.0089)	0.7526 (0.0089)	0.7331 (0.0122)	0.7060 (0.0252)	0.6593 (0.0223)	0.6423 (0.0188)
	Year 5	0.7679 (0.0116)	0.7018 (0.0134)	0.7078 (0.0133)	0.6973 (0.0229)	0.6458 (0.0182)	0.6392 (0.0190)
	Year 10	0.6465 (0.0148)	0.6160 (0.0172)	0.5990 (0.0188)	0.6497 (0.0218)	0.5980 (0.0192)	0.6121 (0.0225)
Albumin	Year 1	0.8174 (0.0089)	0.7526 (0.0089)	0.7331 (0.0122)	0.6871 (0.0220)	0.6248 (0.0161)	0.6420 (0.0185)
	Year 5	0.7679 (0.0116)	0.7018 (0.0134)	0.7078 (0.0133)	0.6644 (0.0205)	0.6125 (0.0146)	0.6218 (0.0177)
	Year 10	0.6464 (0.0148)	0.6160 (0.0172)	0.5990 (0.0188)	0.6188 (0.0165)	0.6000 (0.0167)	0.5707 (0.0158)

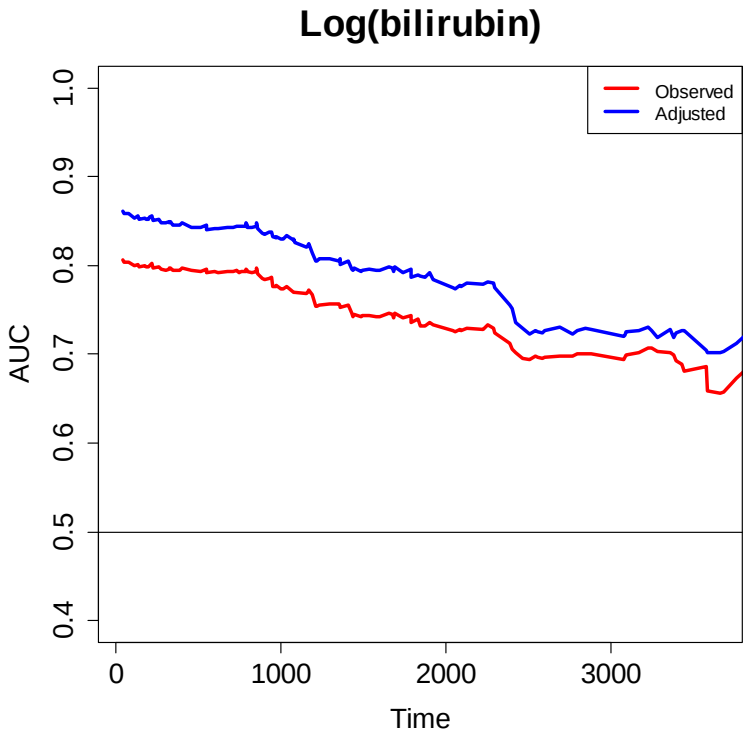

Figure 6.1: Estimated AUC over time for log (bilirubin)

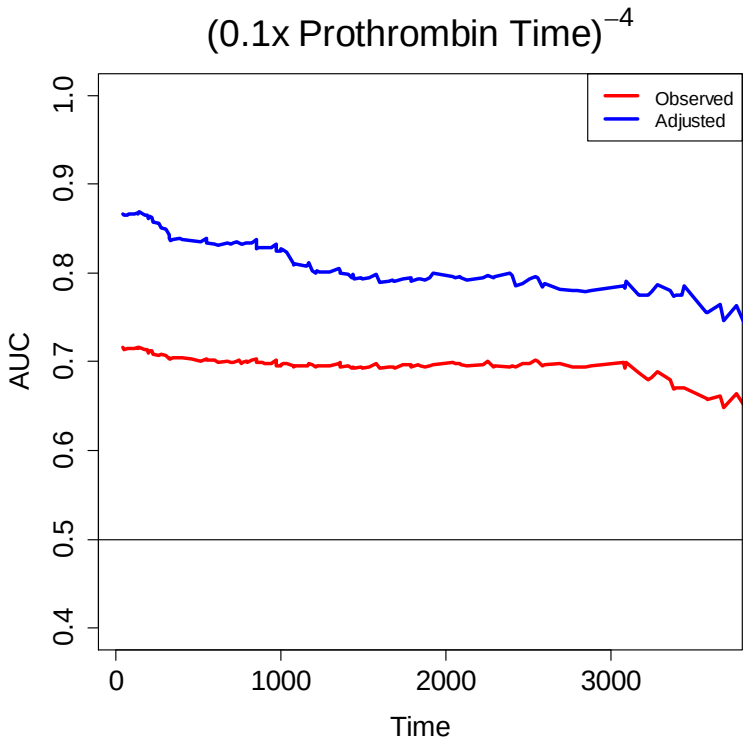

Figure 6.2: Estimated AUC over time for transformed prothrombin time

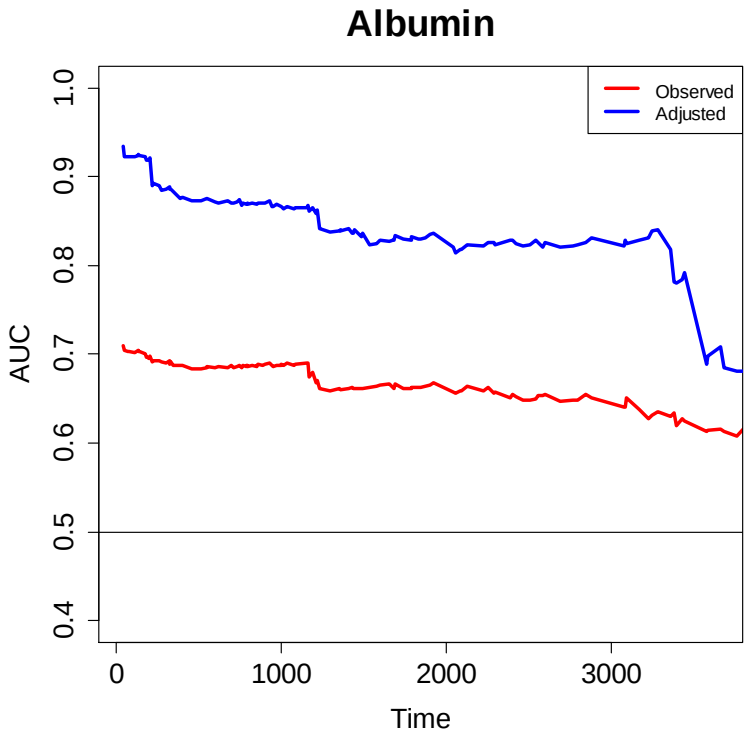

Figure 6.3: Estimated AUC over time for Albumin

Table 6.4 shows the time-dependent AUC of the observed and adjusted values estimated from several current approaches. It shows that across all approaches, the proposed measurement error adjusted biomarker performs well at all prediction times with higher AUC(t).

Table 6.4: Time-dependent AUC (Standard Error) for current methods

Biomarker	Prediction Time	NNE		KMCD		IPCW		CIPCW		FP	
		Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Log (bilirubin)	Year 1	0.9055 (0.0355)	0.8557 (0.0386)	0.8985 (0.0315)	0.8581 (0.0359)	0.8985 (0.0315)	0.8581 (0.0359)	0.8985 (0.0315)	0.8520 (0.0565)	0.8510 (0.0383)	0.7815 (0.0514)
	Year 5	0.9066 (0.0201)	0.8615 (0.0244)	0.8988 (0.0183)	0.8586 (0.0232)	0.9155 (0.0165)	0.8722 (0.0219)	0.9132 (0.0169)	0.8350 (0.0326)	0.7801 (0.0345)	0.7305 (0.0397)
	Year 10	0.8333 (0.0318)	0.8128 (0.0300)	0.7964 (0.0329)	0.7854 (0.0341)	0.8529 (0.0300)	0.8386 (0.0302)	0.8407 (0.0312)	0.6928 (0.0560)	0.6406 (0.0754)	0.6078 (0.0842)
$(0.1\times\text{Prothrombin Time})^{-4}$	Year 1	0.9213 (0.0430)	0.9023 (0.0252)	0.9288 (0.0367)	0.9052 (0.0228)	0.9288 (0.0367)	0.9052 (0.0228)	0.9288 (0.0367)	0.9029 (0.0377)	0.9093 (0.0300)	0.8524 (0.0384)
	Year 5	0.9215 (0.0181)	0.7533 (0.0368)	0.9143 (0.0187)	0.7608 (0.0350)	0.9241 (0.0163)	0.7552 (0.0341)	0.9189 (0.0167)	0.6825 (0.0475)	0.8377 (0.0262)	0.5634 (0.0439)
	Year 10	0.8902 (0.0256)	0.7622 (0.0314)	0.8536 (0.0308)	0.8259 (0.0454)	0.9677 (0.0126)	0.6664 (0.0415)	0.9706 (0.0117)	0.4409 (0.0484)	0.7795 (0.0578)	0.6608 (0.0777)
Albumin	Year 1	0.9213 (0.0431)	0.8356 (0.0557)	0.9288 (0.0367)	0.8326 (0.0529)	0.9288 (0.0367)	0.8326 (0.0529)	0.9288 (0.0367)	0.8258 (0.0843)	0.9092 (0.0300)	0.7764 (0.0513)
	Year 5	0.9215 (0.0181)	0.7418 (0.0386)	0.9143 (0.0186)	0.7384 (0.0324)	0.9241 (0.0163)	0.7507 (0.0318)	0.9189 (0.0167)	0.7211 (0.0414)	0.8377 (0.0262)	0.6530 (0.0401)
	Year 10	0.8902 (0.0256)	0.6922 (0.0421)	0.8536 (0.0308)	0.6522 (0.0450)	0.9677 (0.0126)	0.7476 (0.0376)	0.9706 (0.0117)	0.6864 (0.0412)	0.7795 (0.0578)	0.4596 (0.0854)

7 Simulation Study II: Measurement Error Adjusted ROC curve Approach

7.1 Introduction

This chapter is aimed to demonstrate whether the proposed joint model (in Section 6.4.2) and the measurement error adjusted time-dependent ROC curve approach (in Section 6.4.3) that were discussed in Chapter 6 are appropriate frameworks for estimating the time-dependent diagnostic accuracies of a biomarker at the baseline. Four simulation studies are conducted. A software is written in R language to estimate the proposed joint model by modifying the current "joint" function in joineR library, see Appendix B.

The rest of this chapter is organised as below. The details on generating the simulated data is discussed in Section 7.2. The accuracy of the estimation of the association parameter from the proposed joint model is investigated in Section 7.3. In Section 7.4, how the strength of association between the biomarker and event-time process modifies the diagnostic accuracy is determined. The accuracy of the proposed time-dependent ROC curve methodology is evaluated in Section 7.5. The performance of the proposed measurement error adjusted biomarker is demonstrated further using several current methods (from Chapter 3) of C/D and I/D definitions of time-dependency in Section 7.6.

7.2 Simulating the data

The longitudinal values of a biomarker (x) were simulated for 500 individuals under a linear mixed model with fixed (population-level) intercept and slope with coefficients $\beta_0 = 1$ and $\beta_1 = -1$ respectively, random intercept U_0 and random slope U_1 terms, and measurement error ε_{ij} using $x_i(t_{ij}) = \beta_0 + \beta_1 t_{ij} + U_{0i} + U_{1i} t_{ij} + \varepsilon_{ij}$. The random intercept U_0 and random slope U_1 terms were generated from a bivariate normal distribution $N(\mathbf{0}, \Sigma_U)$ with variances 1 and covariance 0.5, and measurement error ε_{ij} was generated from a normal distribution with mean zero and known variance

$N(0, \sigma_e^2)$. The positive variances and covariance in Σ_U and the negative slope β_1 induce a negative correlation between random effects U_0 and U_1. This setting simulates longitudinal trajectories with larger intercepts to have smaller slopes or vice versa. Hence an individual with a low biomarker value (poor prognosis) at the baseline will have a more rapid decline in their biomarker profile over time, and vice versa, which reflects the convention for ROC curve analysis. Longitudinal times were set at 0, 1, 2, 3, 4, 5, so a maximum of 6 longitudinal observations recorded at these time points up to individual's event time in the final dataset. The true longitudinal biomarker values were generated by excluding the measurement error ε_{ij} from $x_i(t_{ij})$.

Based on the association structure $W_2(t) = \gamma W_1(t) = \gamma U_0$, event times T_i were generated under Gompertz distribution with scale parameter θ_0 and shape parameter θ_1 assuming Cox proportional hazards model $\lambda(t) = \lambda_0(t) \exp(\gamma U_0)$ (see Bender, et al. [95] for more details). The event times T_i were simulated by

$$T_i = \frac{1}{\theta_{1i}} \log\left\{1 - \frac{\theta_{1i} \log(X_i)}{\lambda_i}\right\}$$

where X_i is derived from the uniform [0,1] distribution, $\lambda_i = \exp(\theta_0 + \gamma U_{0i})$ where the value of θ_0 and θ_1 are set to -3 and 1 respectively. Exponential distribution is used to control the censoring rate in the simulated data.

The strength of associations were varied at $\gamma = \{0.25, 0.50, 0.75, 1\}$ to allow weak (0.25) to strong (1) association between the baseline biomarker value and event-time outcomes. The % event was varied at 70, 50 and 30 by controlling the exponential distribution parameter for censoring. Exponential distribution parameter was set at $\exp(-2)$, $\exp(-1.3)$ and $\exp(-0.6)$ to get the censoring rate approximately at 30%, 50% and 70% respectively. The variance of measurement error were varied $\sigma_e^2 = 0.25$, 0.5, 1.0, 1.5, 2.0 and 2.5 to allow lower to higher measurement error in biomarker values to assess the impact of measurement error.

The true and observed (with measurement error) biomarker values at baseline are extracted from the simulated longitudinal datasets. The joint model specified in equation (5.3) in Chapter 5 is fitted to obtain $\widehat{U}_{0i}$ for each individual. Only positive associations ($\gamma > 0$) are examined, however, the behaviour for negative associations with the same strength would be the same, but in opposite direction, and will not impact on biases and other characteristics.

7.3 Accuracy of the proposed association parameter estimation

This simulation study is aimed to explore the accuracy of estimation of association parameter γ from the proposed joint model (see equation 5.3 in Section 5.4.2) which is crucial for estimating the correct ROC summaries from the proposed time-dependent approach. To compare the joint modelling estimate of γ with standard approaches, Cox proportional hazards (PH) model is also fitted including the observed biomarker value x_{i0} at baseline $\lambda_i(t) = \lambda_0(t)\exp\{\alpha x_{i0}\}$. The Cox PH regression parameter α indicates the association between risk of the event and baseline value of the biomarker; hence α is comparable to γ in the proposed joint modelling formulation [19]. The linear mixed effect (LME) model $x_{ij} = \beta_0 + \beta_1 t_{ij} + U_{0i} + U_{1i}t + \varepsilon_{ij}$ is also fitted and used the estimated random intercept term in place of x_{i0} in the above Cox model (this is comparable to a two-stage approach rather than a joint model). The bias, mean square error (MSE) and coverage percentage are calculated from 500 simulated datasets.

Table 7.1 presents the estimated association parameter from the proposed joint model and the two Cox PH models with their standard error (SE), MSE, bias, and coverage percentages (Cov) across varying measurement error variances for 30% censorings. The results for other percentages of censoring are tabulated and presented in Appendix C (Table C.1-C.2). Figure 7.1-7.3 show the graphical presentations for the estimated association parameter against the measurement error variance for 30%, 50% and 70% censoring respectively.

Based on Table 7.1, it can be observed that the proposed joint model provides the most accurate estimation of the association with smaller MSE and biases, and the coverage

percentages are closer to 95% for all settings, and this observation is consistent with the previous simulation study results [19, 96]. Further, proposed joint model estimates γ fairly close to the true value even when the measurement error is high; indicating that the joint model makes the proper adjustment of measurement error when estimating the underlying association at the baseline level. The Cox model including the observed biomarker value underestimates the level of association to a great extent especially when the true association is fairly strong, and a high measurement error substantially affects the estimation of association. Figure 7.1-7.3 show the same patterns across all percentages of censoring that the observed biomarker underestimates the association parameter as the variance of measurement error increases. Modelling baseline biomarker value as a covariate in the Cox regression model is simpler and most current time-dependent ROC curves are based on this model; however, it fails to account for the measurement error.

The two-stage approach which fits the estimated random intercept term from linear mixed effect model as a covariate in the Cox regression model improves the estimation of the association parameter to some extent from the observed value, however it underestimates the parameter severely especially when the association is stronger. These simulation results strengthened the case for using the joint modelling framework for estimating the efficacy of a biomarker at baseline level that is subject to measurement error.

Table 7.1: Association parameters for varying measurement error with 30% censoring

True γ	Proposed joint model					Cox regression model with the observed biomarker					Cox regression model with estimated random intercept term from LME model				
	$\hat{\gamma}_t$	SE	MSE	Bias	Cov	$\hat{\alpha}$	SE	MSE	Bias	Cov	$\hat{\alpha}$	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 0.25$															
0	-0.0008	0.0569	0.003	-0.001	95.8	-0.0002	0.0481	0.002	-0.000	96.4	-0.0008	0.0570	0.003	-0.001	95.8
0.25	0.2507	0.0602	0.004	0.001	95.6	0.1997	0.0496	0.005	-0.050	81.2	0.2494	0.0591	0.004	-0.001	95.6
0.50	0.4995	0.0684	0.005	-0.001	94.6	0.3884	0.0532	0.015	-0.112	43.2	0.4888	0.0641	0.004	-0.011	95.2
0.75	0.7455	0.0774	0.006	-0.005	95.2	0.5609	0.0564	0.039	-0.189	9.6	0.7130	0.0688	0.006	-0.037	93.2
1	0.9891	0.0876	0.008	-0.011	94.8	0.7166	0.0601	0.084	-0.283	0.6	0.9194	0.0724	0.012	-0.081	80.2
Measurement error $\sigma_e^2 = 0.5$															
0	-0.0006	0.0598	0.008	-0.001	95.2	0.0002	0.0441	0.002	0.000	96.0	-0.0006	0.0596	0.004	-0.001	95.2
0.25	0.2504	0.0642	0.005	0.000	95.2	0.1657	0.0454	0.018	-0.084	52.8	0.2465	0.0618	0.004	-0.004	95.4
0.50	0.4981	0.0748	0.006	-0.002	95.4	0.3171	0.0481	0.036	-0.183	4.6	0.4775	0.0671	0.005	-0.023	94.4
0.75	0.7430	0.0872	0.008	-0.007	95.6	0.4499	0.0506	0.093	-0.300	0.0	0.6870	0.0720	0.009	-0.063	86.8
1	0.9832	0.1010	0.011	-0.017	94.8	0.5625	0.0536	0.194	-0.438	0.0	0.8704	0.0759	0.023	-0.130	56.4
Measurement error $\sigma_e^2 = 1.0$															
0	-0.0004	0.0636	0.004	-0.000	95.0	0.0006	0.0384	0.002	0.001	96.0	-0.0005	0.0624	0.004	-0.001	95.2
0.25	0.2494	0.0698	0.005	-0.001	96.0	0.1238	0.0392	0.018	-0.126	10.2	0.2401	0.0648	0.004	-0.010	94.8
0.50	0.4943	0.0829	0.007	-0.006	95.6	0.2317	0.0404	0.074	-0.268	0.0	0.4578	0.0699	0.007	-0.042	91.6
0.75	0.7364	0.1006	0.010	-0.014	94.8	0.3222	0.0423	0.185	-0.428	0.0	0.6482	0.0764	0.016	-0.102	71.4
1	0.9669	0.1223	0.016	-0.033	95.0	0.3940	0.0447	0.371	-0.608	0.0	0.8018	0.0818	0.046	-0.198	31.2
Measurement error $\sigma_e^2 = 1.5$															
0	-0.0003	0.0662	0.004	-0.000	95.2	0.0007	0.0343	0.001	0.001	95.8	-0.0003	0.0640	0.004	-0.000	95.4
0.25	0.2481	0.0717	0.005	-0.002	94.6	0.0955	0.0328	0.025	-0.155	0.0	0.2340	0.0648	0.004	-0.016	94.2
0.50	0.4935	0.0913	0.008	-0.007	96.2	0.1833	0.0361	0.102	-0.317	0.0	0.4438	0.0737	0.009	-0.056	87.6
0.75	0.7323	0.1119	0.013	-0.018	95.6	0.2513	0.0371	0.250	-0.499	0.0	0.6205	0.0806	0.023	-0.130	63.8

True γ	Proposed joint model					Cox regression model with the observed biomarker					Cox regression model with estimated random intercept term from LME model				
	$\hat{\gamma}_t$	SE	MSE	Bias	Cov	$\hat{\alpha}$	SE	MSE	Bias	Cov	$\hat{\alpha}$	SE	MSE	Bias	Cov
1	0.9605	0.1469	0.023	-0.040	96.0	0.3024	0.0389	0.488	-0.698	0.0	0.7602	0.0876	0.065	-0.240	21.8
Measurement error $\sigma_e^2 = 2.0$															
0	-0.0002	0.0682	0.005	0.000	95.4	0.0008	0.0313	0.001	0.001	95.6	-0.0002	0.0651	0.004	-0.000	95.6
0.25	0.2480	0.0760	0.006	-0.002	90.0	0.0791	0.0300	0.030	-0.171	0.0	0.2296	0.0671	0.005	-0.020	94.0
0.50	0.4918	0.0980	0.010	-0.008	96.2	0.1516	0.0327	0.123	-0.348	0.0	0.4317	0.0765	0.011	-0.068	84.6
0.75	0.7175	0.1719	0.031	-0.033	96.0	0.2061	0.0335	0.297	-0.544	0.0	0.5987	0.0848	0.030	-0.151	54.6
1	0.9502	0.1602	0.028	-0.050	96.0	0.2466	0.0347	0.569	-0.753	0.0	0.7301	0.0933	0.082	-0.270	17.6
Measurement error $\sigma_e^2 = 2.5$															
0	-0.0002	0.0700	0.005	-0.000	95.4	0.0008	0.0290	0.001	0.001	95.0	-0.0001	0.0660	0.004	-0.000	95.4
0.25	0.2418	0.0825	0.007	-0.008	94.4	0.0686	0.0293	0.034	-0.181	0.0	0.2208	0.0713	0.006	-0.029	94.0
0.50	0.4900	0.1044	0.011	-0.010	96.4	0.1292	0.0300	0.138	-0.371	0.0	0.4215	0.0793	0.013	-0.079	82.8
0.75	0.7227	0.1311	0.018	-0.027	95.6	0.1748	0.0307	0.332	-0.575	0.0	0.5816	0.0893	0.036	-0.168	49.0
1	0.9391	0.1714	0.033	-0.061	95.8	0.2083	0.0317	0.628	-0.792	0.0	0.7054	0.0995	0.097	-0.295	16.0

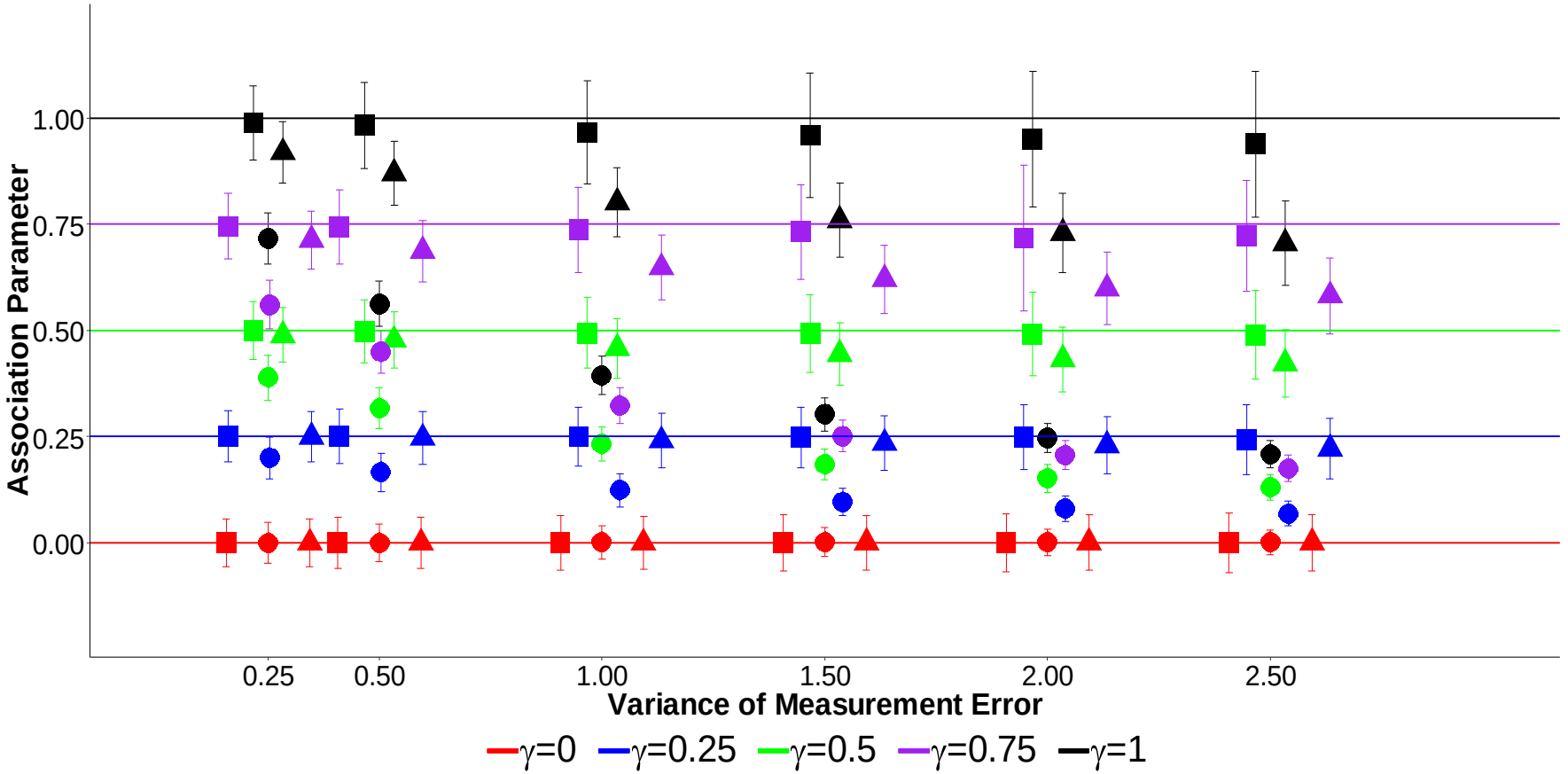

Figure 7.1: Association parameter estimates for 30% censoring. Square indicates the estimate from the proposed joint model, circle the Cox model with observed biomarker and triangle the Cox model with estimated random intercept from LME model. The horizontal lines are the true value of the association parameter.

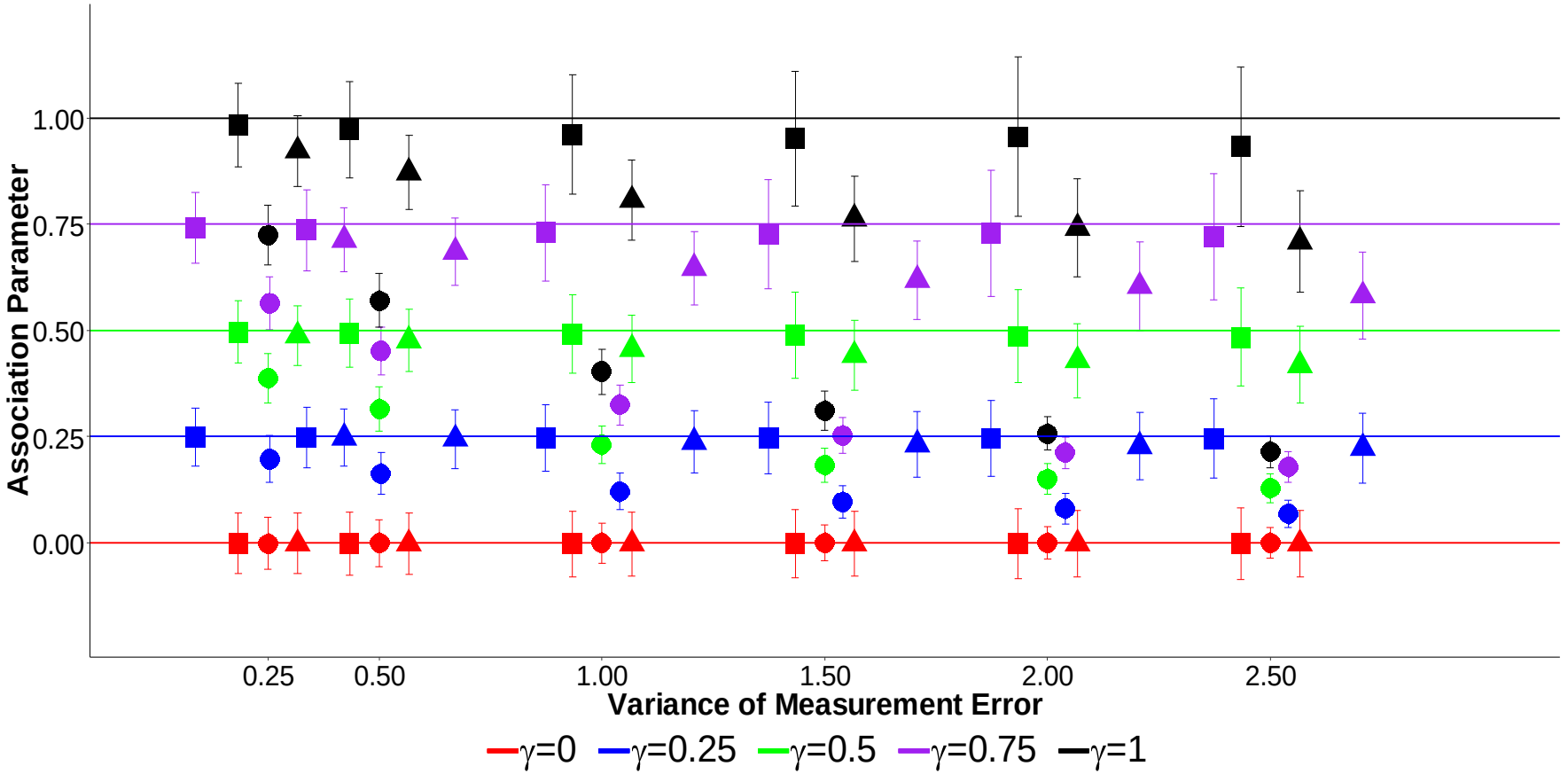

Figure 7.2: Association parameter estimates for 50% censoring. Square indicates the estimate from the proposed joint model, circle the Cox model with observed biomarker and triangle the Cox model with estimated random intercept from LME model. The horizontal lines are the true value of the association parameter.

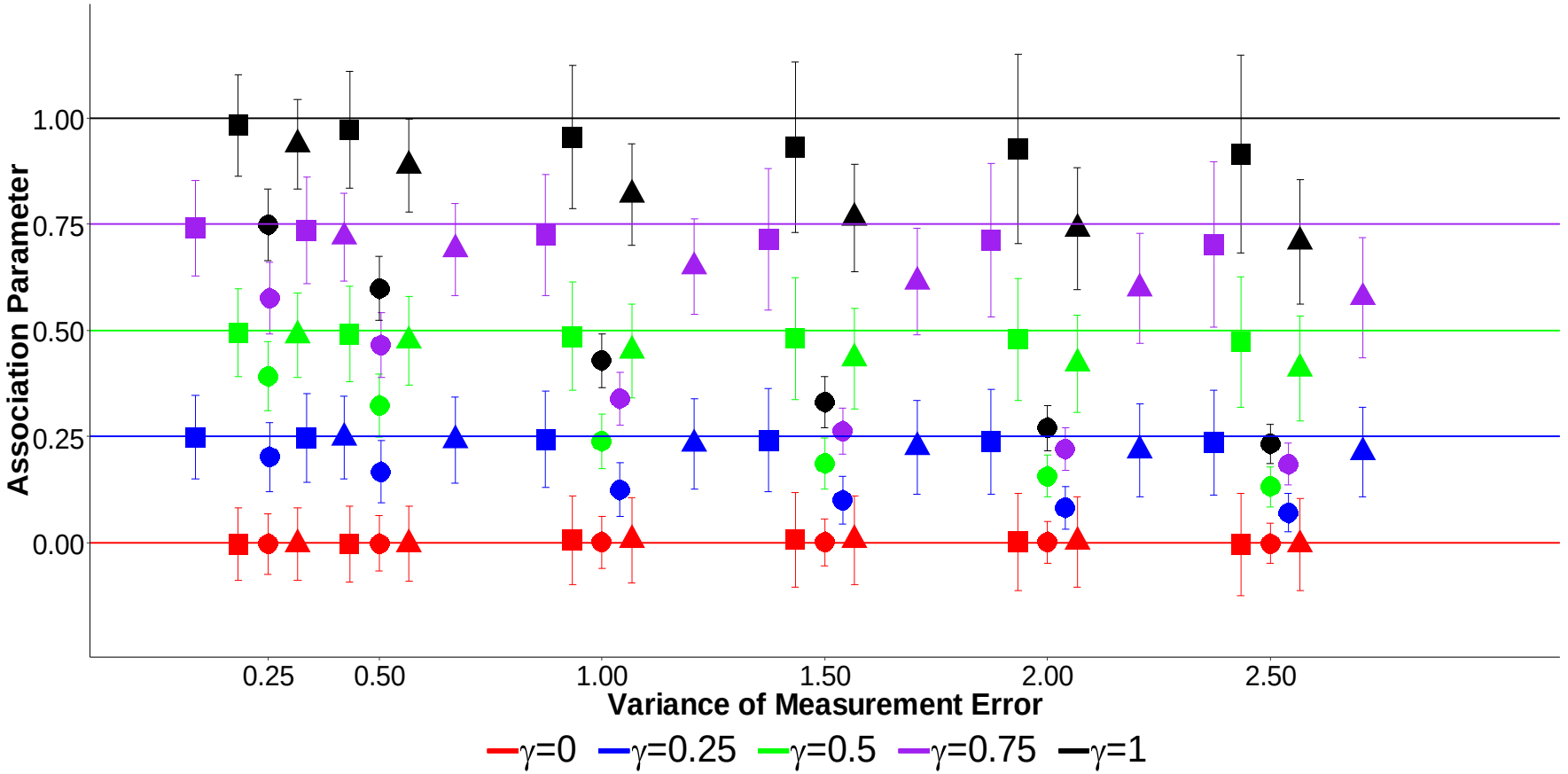

Figure 7.3: Association parameter estimates for 70% censoring. Square indicates the estimate from the proposed joint model, circle the Cox model with observed biomarker and triangle the Cox model with estimated random intercept from LME model. The horizontal lines are the true value of the association parameter.

7.4 Relationship between association parameter and C-index

This simulation is aimed to explore how the strength of association between the biomarker and event-time process modifies the diagnostic accuracy of the biomarker. The C-index for follow-up period of (0, 2) for the proposed measurement error adjusted biomarker $\widehat{M} = \hat{\gamma}\widehat{U}_0$ is compared with the true C-index (based on the "true" baseline biomarker value x_0). To explore further, the C-index of the observed baseline biomarker x_0 and the estimated random intercept term from LME model $(\widehat{U}_0)_{\text{lme}}$ are estimated. The estimates of C-index are evaluated by bias, MSE and coverage percentage, and are calculated from 500 simulated datasets. The "risksetROC" library in R is used to estimate the C-index for the true, observed and LME values of the biomarkers. The risksetROC software also uses the corresponding linear predictor of the Cox PH model to estimate the ROC curve summaries, hence its estimates are comparable to the proposed approach.

Table 7.2 presents the bias, MSE and coverage estimates for C-index at follow-up (0, 2) from the joint model and Cox models for 30% censoring. The results for other percentages of censoring are tabulated and presented in Appendix C (Table C.3-C.4). Figure 7.4-7.6 show the graphical presentations for the estimated C-index against the measurement error variance for 30%, 50% and 70% censoring respectively.

When $\gamma = 0$, that is when there is no association between the baseline biomarker and disease process, the C-index is estimated fairly close to the null value of 0.5 (which indicates biomarker shows no discriminatory potential) across all settings. As strength of the association becomes stronger (γ moves towards 1.0), the estimated C-indexes are also increased by acceptable margins. It is observed that the proposed measurement error adjusted biomarker $\widehat{\mathrm{M}}_i$ from the joint model provides the most accurate C-index estimation with smaller MSE and biases, and higher coverage probabilities across all settings. For all biomarkers, as the association parameter becomes stronger, the biases increase that leads to decreasing value of coverage percentages. As expected, the observed biomarker dramatically underestimates the discriminatory potential of the biomarker with the highest bias and coverage percentages close to zero especially when the association is stronger and measurement error is high. The LME model

estimate performs better than observed biomarker. As shown in Figure 7.4-7.6, the same patterns can be observed across all percentages of censoring.

Table 7.2: C-Index for varying measurement error with 30% censoring

True γ	True C-Index (SE)	Proposed measurement error adjusted estimator $\widehat{M}$					Observed biomarker x_0					LME estimator $(\widehat{U}_0)_{\text{lme}}$				
		C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 0.25$																
0	0.5117 (0.0089)	0.5117	0.0090	0.000	0.000	95.4	0.5120	0.0091	0.000	0.000	96.0	0.5118	0.0570	0.000	0.000	95.6
0.25	0.5698 (0.0148)	0.5649	0.0152	0.000	-0.005	94.0	0.5623	0.0152	0.000	-0.008	92.4	0.5646	0.0150	0.000	-0.005	93.8
0.50	0.6353 (0.0151)	0.6256	0.0162	0.000	-0.010	91.8	0.6185	0.0157	0.001	-0.017	80.4	0.6235	0.0155	0.000	-0.012	88.6
0.75	0.6928 (0.0148)	0.6788	0.0165	0.001	-0.014	85.6	0.6652	0.0156	0.001	-0.028	56.6	0.6734	0.0155	0.001	-0.019	73.8
1	0.7415 (0.0147)	0.7228	0.0167	0.001	-0.019	80.8	0.7025	0.0157	0.002	-0.039	32.4	0.7132	0.0155	0.001	-0.028	53.4
Measurement error $\sigma_e^2 = 0.5$																
0	0.5117 (0.0089)	0.5118	0.0090	0.000	0.000	95.2	0.5120	0.0092	0.000	0.000	95.6	0.5117	0.0090	0.000	-0.001	95.4
0.25	0.5697 (0.0148)	0.5620	0.0155	0.000	-0.008	92.6	0.5567	0.0153	0.000	-0.013	85.0	0.5611	0.0150	0.000	-0.009	92.0
0.50	0.6353 (0.0151)	0.6203	0.0169	0.001	-0.015	85.8	0.6066	0.0157	0.001	-0.029	54.4	0.6159	0.0155	0.001	-0.019	74.2
0.75	0.6929 (0.0151)	0.6714	0.0176	0.001	-0.022	74.8	0.6471	0.0159	0.002	-0.046	17.4	0.6611	0.0157	0.001	-0.032	47.0
1	0.7415 (0.0147)	0.7141	0.0180	0.001	-0.028	64.4	0.6785	0.0161	0.004	-0.063	2.2	0.6964	0.0157	0.002	-0.045	17.0

True γ	True C-Index (SE)	Proposed measurement error adjusted estimator $\widehat{M}$					Observed biomarker x_0					LME estimator $(\widehat{U}_0)_{\text{lme}}$				
		C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 1.0$																
0	0.5117 (0.0089)	0.5116	0.0093	0.000	-0.000	95.0	0.5119	0.0094	0.000	0.000	95.8	0.5114	0.0090	0.000	-0.000	94.6
0.25	0.5697 (0.0148)	0.5584	0.0158	0.000	-0.011	89.2	0.5490	0.0153	0.001	-0.021	72.4	0.5561	0.0147	0.000	-0.014	84.2
0.50	0.6352 (0.0151)	0.6136	0.0176	0.001	-0.022	76.2	0.5907	0.0155	0.002	-0.045	16.2	0.6054	0.0152	0.001	-0.030	49.2
0.75	0.6929 (0.0151)	0.6621	0.0189	0.001	-0.031	61.6	0.6236	0.0158	0.005	-0.069	1.2	0.6445	0.0157	0.003	-0.048	13.4
1	0.7415 (0.0147)	0.7023	0.0200	0.002	-0.039	48.4	0.6479	0.0162	0.009	-0.094	0.0	0.6479	0.0157	0.005	-0.068	1.0
Measurement error $\sigma_e^2 = 1.5$																
0	0.5117 (0.0089)	0.5115	0.0093	0.000	-0.000	94.6	0.5119	0.0094	0.000	0.000	95.8	0.5112	0.0089	0.000	-0.001	95.0
0.25	0.5695 (0.0149)	0.5556	0.0152	0.000	-0.014	83.8	0.5423	0.0144	0.001	-0.027	53.0	0.5523	0.0138	0.001	-0.017	77.6
0.50	0.6353 (0.0151)	0.6091	0.0183	0.001	-0.026	69.2	0.5804	0.0156	0.003	-0.055	6.4	0.5979	0.0151	0.002	-0.037	30.4
0.75	0.6929 (0.0151)	0.6560	0.0200	0.002	-0.037	53.0	0.6087	0.0158	0.007	-0.084	0.0	0.6330	0.0157	0.004	-0.060	2.8
1	0.7415 (0.0147)	0.6952	0.0221	0.003	-0.046	42.8	0.6293	0.0162	0.013	-0.112	0.0	0.6579	0.0157	0.007	-0.084	0.0
Measurement error $\sigma_e^2 = 2.0$																
0	0.5117 (0.0089)	0.5115	0.0094	0.000	-0.000	95.4	0.5119	0.0095	0.000	0.000	96.2	0.5110	0.0089	0.000	-0.001	95.6

True γ	True C-Index (SE)	Proposed measurement error adjusted estimator $\widehat{M}$					Observed biomarker x_0					LME estimator $(\widehat{U}_0)_{\text{lme}}$				
		C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov
0.25	0.5695 (0.0149)	0.5538	0.0154	0.001	-0.016	81.8	0.5385	0.0145	0.001	-0.031	42.2	0.5496	0.0136	0.001	-0.020	68.6
0.50	0.6353 (0.0151)	0.6055	0.0188	0.001	-0.030	65.0	0.5730	0.0155	0.004	-0.062	2.4	0.5921	0.0150	0.002	-0.043	19.2
0.75	0.6929 (0.0151)	0.6508	0.0280	0.003	-0.042	45.6	0.5981	0.0157	0.009	-0.095	0.0	0.6241	0.0158	0.005	-0.069	0.4
1	0.7415 (0.0146)	0.6892	0.0235	0.003	-0.052	35.8	0.6164	0.0161	0.016	-0.125	0.0	0.6465	0.0157	0.009	-0.095	0.0
Measurement error $\sigma_e^2 = 2.5$																
0	0.5117 (0.0089)	0.5115	0.0093	0.000	-0.000	95.4	0.5119	0.0095	0.000	0.000	96.6	0.5108	0.0087	0.000	-0.001	95.4
0.25	0.5697 (0.0158)	0.5515	0.0169	0.001	-0.018	81.2	0.5363	0.0152	0.001	-0.033	41.2	0.5467	0.0146	0.001	-0.023	65.8
0.50	0.6353 (0.0151)	0.6026	0.0193	0.001	-0.033	59.6	0.56774	0.0154	0.005	-0.068	1.2	0.5874	0.0148	0.003	-0.048	11.0
0.75	0.6929 (0.0151)	0.6469	0.0219	0.003	-0.046	41.0	0.5902	0.0156	0.011	-0.103	0.0	0.6171	0.0158	0.006	-0.076	0.0
1	0.7415 (0.0147)	0.6843	0.0249	0.004	-0.057	33.4	0.6068	0.0161	0.018	-0.135	0.0	0.6374	0.0160	0.011	-0.104	0.0

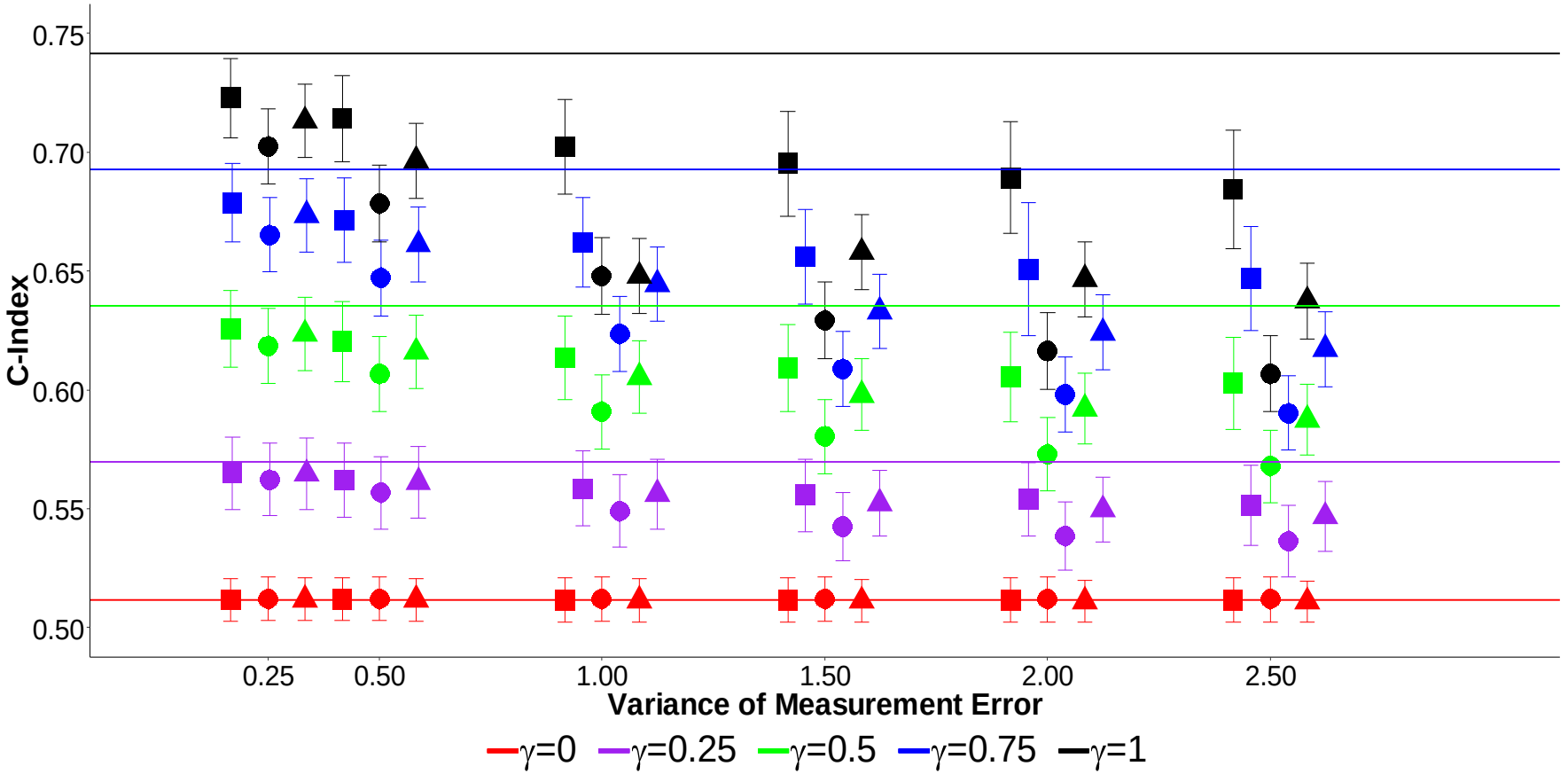

Figure 7.4: C-Index estimates for 30% censoring. Square indicates the estimate from the proposed joint model, circle the Cox model with observed biomarker and triangle the Cox model with estimated random intercept from LME model. The horizontal lines are the true value of the association parameter.

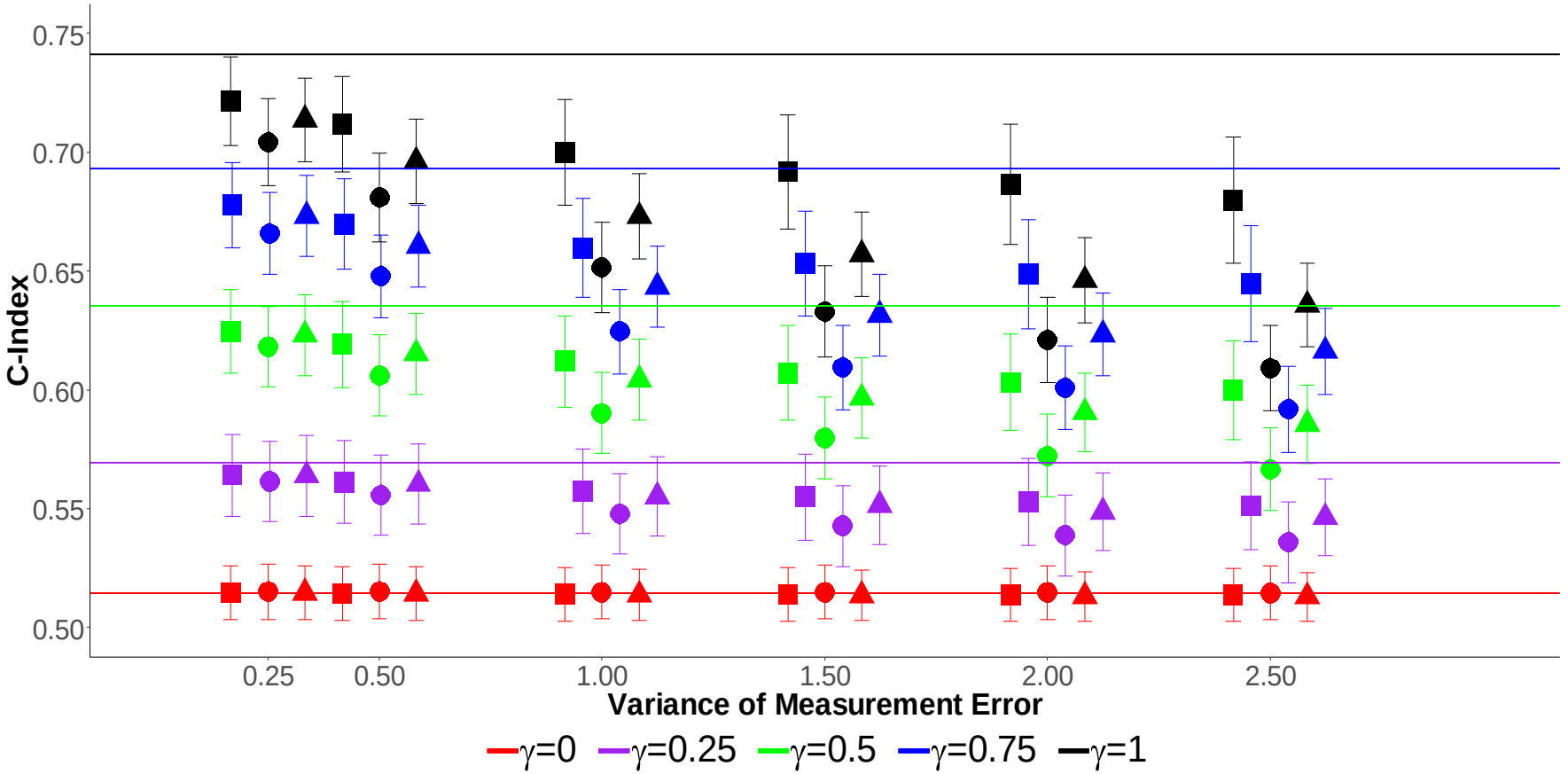

Figure 7.5: C-Index estimates for 50% censoring. Square indicates the estimate from the proposed joint model, circle the Cox model with observed biomarker and triangle the Cox model with estimated random intercept from LME model. The horizontal lines are the true value of the association parameter.

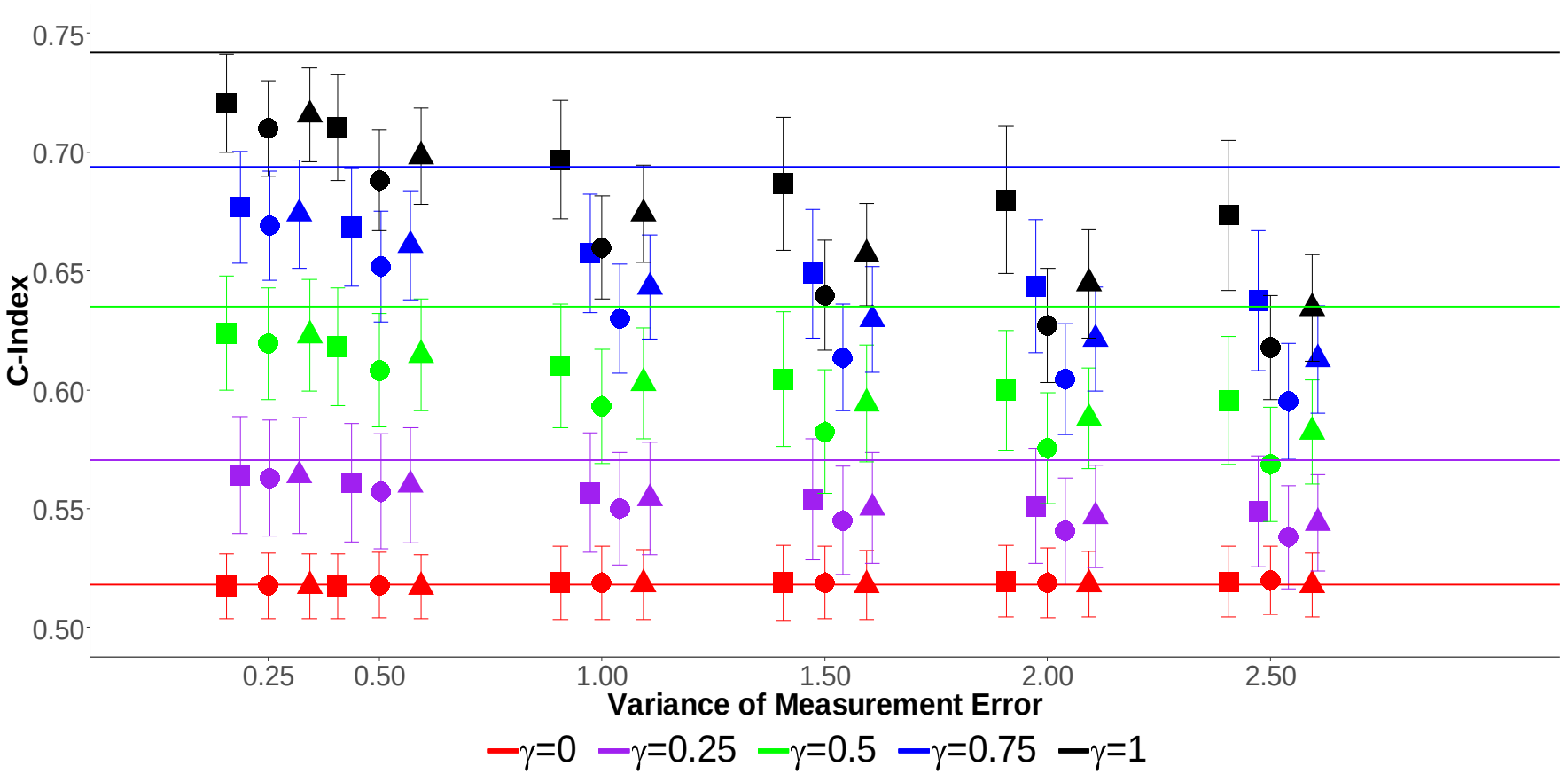

Figure 7.6: C-Index estimates for 70% censoring. Square indicates the estimate from the proposed joint model, circle the Cox model with observed biomarker and triangle the Cox model with estimated random intercept from LME model. The horizontal lines are the true value of the association parameter.

7.5 Evaluate the accuracy of the proposed measurement-error adjusted ROC curve

This simulation is aimed to evaluate the accuracy of the proposed time-dependent ROC curve methodology by comparing the estimates of AUC(t), and sensitivity(t) and specificity(t) at the optimal threshold value at $t = t_h = 1, 2, 3, 4$ for varying settings of γ, σ_e^2 and percentage of censoring. The validity of the proposed measurement error-adjusted estimator $\widehat{\mathrm{M}}$ was evaluated by bias, MSE and coverage percentage with respect to the true summaries at time t, and compared further with the ROC curve summaries of the observed baseline biomarker value. To estimate the summaries for the true and observed values, "risksetROC" library in R is used as in Section 7.4.

Table 7.3 - 7.7 present the bias, MSE and coverage percentage (from 500 simulated datasets) for AUC(t), and sensitivity(t) and specificity(t) at the optimal threshold value at $t = t_h = 1, 2, 3, 4$ for 30% of censoring across varying association parameters. The results for other percentages of censoring are tabulated and presented in Appendix C (Table C.5-C.14). Figure 7.7 to 7.9 show the estimated AUC(t) graphically. The ROC curve summary estimates from the proposed measurement error adjusted biomarker provides more accurate estimates of AUC(t) with lower MSE and bias, and higher coverage percentages across most settings of γ. When there is no association between the baseline biomarker and event-time $\gamma = 0$, the AUC(t) is estimated fairly close to the null value of 0.5 for both proposed model and the observed biomarker. As expected, the AUC(t) decreases as the prediction time increases because of weaker discriminatory potential as departing from the baseline. In some settings, different pattern of coverage percentages can be observed as the prediction time increases. However, the coverage percentage as displayed in Table 7.3 – 7.7 may depend on the bias as higher bias produces narrow confidence interval while lower bias produces wider confidence interval. It is also noted that, as the association parameter becomes stronger, the coverage percentages decreases across all settings.

Table 7.3: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0 and 30% censoring

t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.5114 (0.0089)	0.5111 (0.0086)	0.0001	-0.0003	95.2	0.5079 (0.0061)	0.5079 (0.0062)	0.5112 (0.0083)	0.0001	-0.0002	94.2	0.5079 (0.0060)	0.5079 (0.0059)
2	0.5114 (0.0089)	0.5111 (0.0086)	0.0001	-0.0003	95.4	0.5079 (0.0063)	0.5079 (0.0061)	0.5112 (0.0083)	0.0001	-0.0002	94.2	0.5078 (0.0061)	0.5080 (0.0059)
3	0.5113 (0.0088)	0.5111 (0.0085)	0.0001	-0.0003	95.0	0.5078 (0.0067)	0.5079 (0.0063)	0.5111 (0.0082)	0.0001	-0.0002	94.0	0.5079 (0.0065)	0.5078 (0.0061)
4	0.5107 (0.0082)	0.5106 (0.0082)	0.0001	0.0000	94.8	0.5022 (0.0175)	0.5130 (0.0139)	0.5105 (0.0078)	0.0001	-0.0001	95.2	0.5020 (0.0173)	0.5131 (0.0141)
Measurement error $\sigma_e^2 = 0.5$													
1	0.5114 (0.0089)	0.5111 (0.0087)	0.0001	-0.0003	95.0	0.5079 (0.0062)	0.5078 (0.0062)	0.5112 (0.0082)	0.0001	-0.0002	95.0	0.5079 (0.0059)	0.5080 (0.0059)
2	0.5114 (0.0089)	0.5111 (0.0087)	0.0001	-0.0003	95.2	0.5079 (0.0063)	0.5078 (0.0062)	0.5112 (0.0082)	0.0001	-0.0002	94.8	0.5079 (0.0060)	0.5079 (0.0059)
3	0.5113 (0.0088)	0.5111 (0.0086)	0.0001	-0.0003	95.4	0.5078 (0.0067)	0.5078 (0.0064)	0.5111 (0.0082)	0.0001	-0.0002	95.0	0.5080 (0.0064)	0.5078 (0.0060)
4	0.5107 (0.0082)	0.5106 (0.0083)	0.0001	0.0000	95.2	0.5020 (0.0175)	0.5132 (0.0140)	0.5106 (0.0079)	0.0001	-0.0001	95.2	0.5020 (0.0175)	0.5132 (0.0142)
Measurement error $\sigma_e^2 = 1.0$													
1	0.5114 (0.0089)	0.5112 (0.0088)	0.0001	-0.0003	94.8	0.5079 (0.0064)	0.5079 (0.0062)	0.5113 (0.0083)	0.0001	-0.0001	95.0	0.5080 (0.0059)	0.5080 (0.0059)
2	0.5114 (0.0089)	0.5112 (0.0088)	0.0001	-0.0002	95.2	0.5079 (0.0064)	0.5080 (0.0063)	0.5113 (0.0082)	0.0001	-0.0001	95.0	0.5079 (0.0060)	0.5081 (0.0059)
3	0.5113 (0.0088)	0.5111 (0.0088)	0.0001	-0.0002	95.0	0.5078 (0.0070)	0.5080 (0.0065)	0.5113 (0.0082)	0.0001	-0.0001	95.2	0.5079 (0.0063)	0.5081 (0.0063)

t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
4	0.5107 (0.0082)	0.5108 (0.0084)	0.0001	0.0000	95.4	0.5020 (0.0177)	0.5133 (0.0141)	0.5107 (0.0080)	0.0001	0.0000	95.4	0.5021 (0.0178)	0.5132 (0.0141)
Measurement error $\sigma_e^2 = 1.5$													
1	0.5114 (0.0089)	0.5112 (0.0088)	0.0001	-0.0002	95.2	0.5080 (0.0064)	0.5079 (0.0062)	0.5114 (0.0083)	0.0001	0.0000	95.0	0.5081 (0.0060)	0.5082 (0.0059)
2	0.5114 (0.0089)	0.5114 (0.0089)	0.0001	0.0000	95.4	0.5080 (0.0064)	0.5081 (0.0064)	0.5114 (0.0083)	0.0001	0.0000	95.0	0.5080 (0.0060)	0.5082 (0.0060)
3	0.5113 (0.0088)	0.5113 (0.0088)	0.0001	0.0000	95.2	0.5080 (0.0070)	0.5080 (0.0064)	0.5114 (0.0082)	0.0001	0.0000	94.8	0.5079 (0.0063)	0.5082 (0.0063)
4	0.5107 (0.0082)	0.5108 (0.0085)	0.0001	0.0001	95.0	0.5022 (0.0178)	0.5133 (0.0141)	0.5108 (0.0080)	0.0001	0.0001	95.8	0.5022 (0.0179)	0.5133 (0.0142)
Measurement error $\sigma_e^2 = 2.0$													
1	0.5114 (0.0089)	0.5113 (0.0088)	0.0001	-0.0001	95.4	0.5080 (0.0063)	0.5080 (0.0063)	0.5115 (0.0083)	0.0001	0.0001	95.2	0.5081 (0.0060)	0.5082 (0.0059)
2	0.5114 (0.0089)	0.5115 (0.0089)	0.0001	0.0001	95.4	0.5081 (0.0065)	0.5082 (0.0063)	0.5115 (0.0083)	0.0001	0.0001	95.2	0.5081 (0.0061)	0.5082 (0.0060)
3	0.5113 (0.0088)	0.5115 (0.0089)	0.0001	0.0001	95.2	0.5082 (0.0071)	0.5081 (0.0064)	0.5115 (0.0083)	0.0001	0.0001	94.8	0.5081 (0.0064)	0.5081 (0.0063)
4	0.5107 (0.0082)	0.5109 (0.0085)	0.0001	0.0002	94.6	0.5024 (0.0179)	0.5132 (0.0141)	0.5109 (0.0081)	0.0001	0.0002	96.2	0.5023 (0.0179)	0.5133 (0.0142)
Measurement error $\sigma_e^2 = 2.5$													
1	0.5121 (0.0089)	0.5115 (0.0089)	0.0001	-0.0006	95.6	0.5081 (0.0064)	0.5081 (0.0063)	0.5117 (0.0086)	0.0001	-0.0004	96.4	0.5082 (0.0061)	0.5084 (0.0062)
2	0.5120 (0.0088)	0.5117 (0.0091)	0.0001	-0.0003	94.8	0.5082 (0.0066)	0.5083 (0.0065)	0.5117 (0.0086)	0.0001	-0.0004	96.2	0.5083 (0.0062)	0.5082 (0.0062)
3	0.5120 (0.0088)	0.5118 (0.0091)	0.0001	-0.0003	95.4	0.5082 (0.0071)	0.5085 (0.0068)	0.5117 (0.0086)	0.0001	-0.0004	96.0	0.5082 (0.0066)	0.5083 (0.0064)

t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
4	0.5115 (0.0088)	0.5112 (0.0089)	0.0001	-0.0003	95.0	0.5030 (0.0179)	0.5130 (0.0145)	0.5110 (0.0084)	0.0001	-0.0005	95.8	0.5033 (0.0174)	0.5125 (0.0142)

Table 7.4: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0.25 and 30% censoring

Predicted Time t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.5701 (0.0146)	0.5652 (0.0144)	0.0002	-0.0049	93.0	0.5464 (0.0105)	0.5460 (0.0104)	0.5630 (0.0141)	0.0003	-0.0071	91.4	0.5447 (0.0102)	0.5446 (0.0102)
2	0.5694 (0.0143)	0.5646 (0.0141)	0.0002	-0.0048	93.4	0.5461 (0.0105)	0.5456 (0.0103)	0.5625 (0.0138)	0.0002	-0.0070	91.6	0.5444 (0.0101)	0.5442 (0.0101)
3	0.5677 (0.0139)	0.5630 (0.0137)	0.0002	-0.0047	92.8	0.5450 (0.0106)	0.5446 (0.0104)	0.5611 (0.0135)	0.0002	-0.0066	91.2	0.5436 (0.0106)	0.5433 (0.0101)
4	0.5626 (0.0154)	0.5581 (0.0147)	0.0002	-0.0045	94.4	0.5425 (0.0189)	0.5410 (0.0183)	0.5568 (0.0150)	0.0029	-0.0520	93.4	0.5408 (0.0184)	0.5410 (0.0192)
Measurement error $\sigma_e^2 = 0.5$													
1	0.5701 (0.0146)	0.5623 (0.0147)	0.0003	-0.0077	92.0	0.5444 (0.0107)	0.5441 (0.0105)	0.5574 (0.0141)	0.0004	-0.0126	85.2	0.5408 (0.0102)	0.5407 (0.0102)
2	0.5694 (0.0143)	0.5618 (0.0143)	0.0003	-0.0077	92.4	0.5441 (0.0106)	0.5436 (0.0105)	0.5571 (0.0138)	0.0003	-0.0124	85.4	0.5405 (0.0100)	0.5404 (0.0101)
3	0.5677 (0.0139)	0.5601 (0.0139)	0.0002	-0.0076	92.4	0.5430 (0.0109)	0.5425 (0.0104)	0.5560 (0.0136)	0.0003	-0.0117	86.0	0.5399 (0.0106)	0.5397 (0.0101)
4	0.5626 (0.0154)	0.5552 (0.0144)	0.0003	-0.0074	93.4	0.5402 (0.0181)	0.5390 (0.0187)	0.5523 (0.0147)	0.0003	-0.0103	90.0	0.5376 (0.0177)	0.5376 (0.0190)

Predicted Time t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 1.0$													
1	0.5701 (0.0146)	0.5587 (0.0151)	0.0004	-0.0114	87.8	0.5417 (0.0112)	0.5415 (0.0107)	0.5498 (0.0142)	0.0006	-0.0203	70.0	0.5353 (0.0101)	0.5353 (0.0103)
2	0.5694 (0.0143)	0.5583 (0.0148)	0.0003	-0.0111	87.6	0.5415 (0.0109)	0.5412 (0.0107)	0.5495 (0.0140)	0.0006	-0.0199	70.2	0.5352 (0.0101)	0.5350 (0.0102)
3	0.5677 (0.0139)	0.5566 (0.0142)	0.0003	-0.0111	87.0	0.5406 (0.0110)	0.5399 (0.0107)	0.5487 (0.0137)	0.0005	-0.0190	70.6	0.5348 (0.0184)	0.5344 (0.0103)
4	0.5626 (0.0154)	0.5515 (0.0141)	0.0003	-0.0111	88.4	0.5374 (0.0183)	0.5366 (0.0177)	0.5458 (0.0145)	0.0005	-0.0168	76.8	0.5329 (0.0184)	0.5330 (0.0186)
Measurement error $\sigma_e^2 = 1.5$													
1	0.5701 (0.0146)	0.5561 (0.0155)	0.0004	-0.0140	83.8	0.5400 (0.0113)	0.5397 (0.0111)	0.5446 (0.0143)	0.0009	-0.0255	59.4	0.5361 (0.0102)	0.5316 (0.0103)
2	0.5694 (0.0143)	0.5561 (0.0152)	0.0004	-0.0133	84.8	0.5399 (0.0112)	0.5397 (0.0110)	0.5443 (0.0141)	0.0008	-0.0251	59.2	0.5315 (0.0102)	0.5314 (0.0102)
3	0.5677 (0.0139)	0.5544 (0.0145)	0.0004	-0.0132	84.0	0.5387 (0.0112)	0.5387 (0.0108)	0.5437 (0.0139)	0.0008	-0.0239	60.8	0.5310 (0.0103)	0.5311 (0.0104)
4	0.5626 (0.0154)	0.5494 (0.0141)	0.0004	-0.0132	84.2	0.5364 (0.0180)	0.5345 (0.0176)	0.5412 (0.0144)	0.0007	-0.0214	66.4	0.5295 (0.0181)	0.5298 (0.0187)
Measurement error $\sigma_e^2 = 2.0$													
1	0.5701 (0.0146)	0.5542 (0.0156)	0.0005	-0.0159	81.0	0.5386 (0.0115)	0.5382 (0.0111)	0.5407 (0.0143)	0.0011	-0.0294	47.8	0.5290 (0.0103)	0.5288 (0.0103)
2	0.5694 (0.0143)	0.5545 (0.0154)	0.0005	-0.0150	82.4	0.5387 (0.0114)	0.5386 (0.0110)	0.5406 (0.0142)	0.0010	-0.0289	49.2	0.5288 (0.0102)	0.5287 (0.0103)
3	0.5677 (0.0139)	0.5529 (0.0148)	0.0004	-0.0147	81.6	0.5379 (0.0113)	0.5373 (0.0178)	0.5401 (0.0140)	0.0010	-0.0276	52.0	0.5284 (0.0106)	0.5285 (0.0103)
4	0.5626 (0.0154)	0.5479 (0.0141)	0.0004	-0.0147	79.8	0.5349 (0.0180)	0.5339 (0.0178)	0.5379 (0.0143)	0.0008	-0.0247	58.4	0.5275 (0.0177)	0.5269 (0.0183)

Predicted Time t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 2.5$													
1	0.5701 (0.0146)	0.5525 (0.0158)	0.0006	-0.0175	78.8	0.5375 (0.0116)	0.5370 (0.0111)	0.5378 (0.0144)	0.0013	-0.0323	38.0	0.5269 (0.0103)	0.5267 (0.0103)
2	0.5694 (0.0143)	0.5531 (0.0157)	0.0005	-0.0163	80.2	0.5378 (0.0116)	0.5376 (0.0112)	0.5376 (0.0143)	0.0012	-0.0318	39.4	0.5268 (0.0103)	0.5266 (0.0102)
3	0.5677 (0.0139)	0.5517 (0.0150)	0.0005	-0.0159	80.4	0.5370 (0.0115)	0.5366 (0.0111)	0.5372 (0.0140)	0.0011	-0.0305	41.8	0.5268 (0.0104)	0.5260 (0.0104)
4	0.5626 (0.0154)	0.5467 (0.0141)	0.0005	-0.0159	79.0	0.5346 (0.0176)	0.5325 (0.0180)	0.5352 (0.0143)	0.0010	-0.0274	50.6	0.5264 (0.0180)	0.5242 (0.0179)

Table 7.5: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0.5 and 30% censoring

Predicted Time t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.6366 (0.0154)	0.6267 (0.0154)	0.0003	-0.0099	90.2	0.5908 (0.0115)	0.5900 (0.0117)	0.6194 (0.0147)	0.0005	-0.0172	79.8	0.5853 (0.0110)	0.5851 (0.0110)
2	0.6324 (0.0144)	0.6225 (0.0143)	0.0003	-0.0099	89.2	0.5884 (0.0113)	0.5865 (0.0110)	0.6166 (0.0138)	0.0004	-0.0158	79.4	0.5836 (0.0108)	0.5827 (0.0105)
3	0.6239 (0.0133)	0.6143 (0.0130)	0.0003	-0.0096	89.4	0.5832 (0.0112)	0.5802 (0.0108)	0.6107 (0.0130)	0.0003	-0.0132	83.4	0.5801 (0.0111)	0.5780 (0.0107)
4	0.6096 (0.0174)	0.6001 (0.0164)	0.0004	-0.0095	91.2	0.5732 (0.0183)	0.5705 (0.0198)	0.5996 (0.0143)	0.0003	-0.0100	90.2	0.5726 (0.0186)	0.5709 (0.0200)

Predicted Time t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.5$													
1	0.6366 (0.0154)	0.6214 (0.0160)	0.0005	-0.0152	83.4	0.5869 (0.0120)	0.5863 (0.0120)	0.6073 (0.0146)	0.0011	-0.0293	48.8	0.5767 (0.0108)	0.5763 (0.0109)
2	0.6324 (0.0144)	0.6172 (0.0147)	0.0004	-0.0152	81.4	0.5843 (0.0114)	0.5829 (0.0111)	0.6052 (0.0138)	0.0009	-0.0272	51.4	0.5753 (0.0105)	0.5747 (0.0105)
3	0.6239 (0.0133)	0.6088 (0.0132)	0.0004	-0.0151	80.0	0.5793 (0.0111)	0.5761 (0.0111)	0.6008 (0.0131)	0.0007	-0.0231	58.0	0.5724 (0.0112)	0.5714 (0.0103)
4	0.6096 (0.0174)	0.5945 (0.0158)	0.0005	-0.0151	83.8	0.5694 (0.0171)	0.5661 (0.0184)	0.5918 (0.0161)	0.0006	-0.0178	80.0	0.5670 (0.0190)	0.5653 (0.0186)
Measurement error $\sigma_e^2 = 1.0$													
1	0.6366 (0.0154)	0.6147 (0.0170)	0.0008	-0.0220	74.2	0.5821 (0.0128)	0.5814 (0.0124)	0.5913 (0.0146)	0.0023	-0.0454	13.0	0.5652 (0.0108)	0.5647 (0.0108)
2	0.6324 (0.0144)	0.6109 (0.0155)	0.0007	-0.0215	71.0	0.5797 (0.0120)	0.5785 (0.0117)	0.5899 (0.0141)	0.0020	-0.0425	14.6	0.5642 (0.0106)	0.5638 (0.0105)
3	0.6239 (0.0133)	0.6024 (0.0137)	0.0006	-0.0215	68.4	0.5744 (0.0115)	0.5781 (0.0111)	0.5870 (0.0135)	0.0015	-0.0369	23.6	0.5622 (0.0108)	0.5617 (0.0107)
4	0.6096 (0.0174)	0.5881 (0.0152)	0.0007	-0.0215	68.2	0.5645 (0.0170)	0.5618 (0.0180)	0.5804 (0.0155)	0.0011	-0.0292	51.2	0.5591 (0.0172)	0.5567 (0.0173)
Measurement error $\sigma_e^2 = 1.5$													
1	0.6366 (0.0154)	0.6101 (0.0177)	0.0010	-0.0265	67.0	0.5789 (0.0134)	0.5780 (0.0129)	0.5808 (0.0147)	0.0033	-0.0558	3.6	0.5576 (0.0108)	0.5573 (0.0107)
2	0.6324 (0.0144)	0.6071 (0.0162)	0.0009	-0.0254	66.2	0.5771 (0.0126)	0.5756 (0.0119)	0.5798 (0.0142)	0.0030	-0.0526	4.8	0.5571 (0.0106)	0.5565 (0.0105)
3	0.6239 (0.0133)	0.5988 (0.0142)	0.0008	-0.0251	58.4	0.5717 (0.0118)	0.5692 (0.0112)	0.5776 (0.0137)	0.0023	-0.0463	8.2	0.5554 (0.0107)	0.5551 (0.0108)
4	0.6096 (0.0174)	0.5845 (0.0150)	0.0009	-0.0251	59.0	0.5617 (0.0178)	0.5595 (0.0174)	0.5724 (0.0152)	0.0016	-0.0372	33.4	0.5525 (0.0165)	0.5516 (0.0166)

Predicted Time t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 2.0$													
1	0.6366 (0.0154)	0.6064 (0.0183)	0.0012	-0.0302	62.4	0.5764 (0.0138)	0.5753 (0.0133)	0.5733 (0.0147)	0.0042	-0.0633	1.0	0.5522 (0.0109)	0.5520 (0.0106)
2	0.6324 (0.0144)	0.6042 (0.0168)	0.0011	-0.0283	61.4	0.5749 (0.0128)	0.5735 (0.0124)	0.5726 (0.0143)	0.0042	-0.0633	1.8	0.5517 (0.0107)	0.5514 (0.0105)
3	0.6239 (0.0133)	0.5962 (0.0147)	0.0010	-0.0277	54.2	0.5699 (0.0122)	0.5673 (0.0112)	0.5708 (0.0138)	0.0038	-0.0599	2.6	0.5504 (0.0106)	0.5503 (0.0108)
4	0.6096 (0.0174)	0.5821 (0.0150)	0.0010	-0.0275	52.6	0.5603 (0.0180)	0.5574 (0.0164)	0.5664 (0.0150)	0.0030	-0.0531	18.4	0.5480 (0.0165)	0.5474 (0.0168)
Measurement error $\sigma_e^2 = 2.5$													
1	0.6366 (0.0154)	0.6033 (0.0188)	0.0015	-0.0333	55.8	0.5745 (0.0141)	0.5727 (0.0136)	0.5676 (0.0147)	0.0050	-0.0691	0.2	0.5480 (0.0107)	0.5480 (0.0107)
2	0.6324 (0.0144)	0.6017 (0.0173)	0.0012	-0.0308	58.0	0.5732 (0.0133)	0.5717 (0.0126)	0.5670 (0.0144)	0.0045	-0.0655	0.6	0.5476 (0.0106)	0.5476 (0.0105)
3	0.6239 (0.0133)	0.5942 (0.0151)	0.0011	-0.0297	49.0	0.5685 (0.0126)	0.5658 (0.0161)	0.5655 (0.0139)	0.0036	-0.0584	0.8	0.5498 (0.0107)	0.5464 (0.0106)
4	0.6096 (0.0174)	0.5804 (0.0151)	0.0011	-0.0292	47.2	0.5588 (0.0182)	0.5564 (0.0161)	0.5617 (0.0148)	0.0025	-0.0480	11.0	0.5438 (0.0167)	0.5447 (0.0168)

Table 7.6: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0.75 and 30% censoring

Predicted Time t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity	AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity
Measurement error $\sigma_e^2 = 0.25$													
1	0.6955 (0.0153)	0.6815 (0.0161)	0.0005	-0.0141	86.2	0.6320 (0.0125)	0.6297 (0.0129)	0.6673 (0.0149)	0.0010	-0.0282	53.6	0.6211 (0.0115)	0.6197 (0.0118)
2	0.6839 (0.0145)	0.6694 (0.0145)	0.0004	-0.0145	83.4	0.6248 (0.0121)	0.6195 (0.0117)	0.6597 (0.0138)	0.0008	-0.0242	59.0	0.6162 (0.0114)	0.6134 (0.0111)
3	0.6677 (0.0136)	0.6531 (0.0134)	0.0004	-0.0147	83.0	0.6138 (0.0120)	0.6067 (0.0115)	0.6487 (0.0131)	0.0005	-0.0190	71.0	0.6085 (0.0118)	0.6054 (0.0118)
4	0.6468 (0.0182)	0.6318 (0.0172)	0.0005	-0.0150	85.2	0.5984 (0.0180)	0.5913 (0.0195)	0.6335 (0.0177)	0.0005	-0.0133	88.8	0.5992 (0.0174)	0.5934 (0.0192)
Measurement error $\sigma_e^2 = 0.5$													
1	0.6955 (0.0153)	0.6742 (0.0172)	0.0007	-0.0213	76.2	0.6268 (0.0135)	0.6243 (0.0133)	0.6485 (0.0150)	0.0024	-0.0471	12.0	0.6069 (0.0114)	0.6061 (0.0117)
2	0.6839 (0.0145)	0.6621 (0.0152)	0.0007	-0.0218	70.4	0.6192 (0.0125)	0.6142 (0.0120)	0.6429 (0.0139)	0.0019	-0.0410	14.4	0.6035 (0.0108)	0.6015 (0.0112)
3	0.6677 (0.0136)	0.6454 (0.0136)	0.0007	-0.0223	62.6	0.6085 (0.0121)	0.6009 (0.011)	0.6348 (0.0133)	0.0013	-0.0329	31.6	0.5979 (0.0114)	0.5955 (0.0116)
4	0.6468 (0.0182)	0.6239 (0.0165)	0.0008	-0.0228	70.6	0.5933 (0.0174)	0.5913 (0.0179)	0.6231 (0.0167)	0.0008	-0.0236	70.8	0.5902 (0.0167)	0.5873 (0.0186)
Measurement error $\sigma_e^2 = 1.0$													
1	0.6955 (0.0153)	0.6651 (0.0189)	0.0013	-0.0304	63.0	0.6201 (0.0149)	0.6175 (0.0142)	0.6244 (0.0151)	0.0053	-0.0711	0.4	0.5893 (0.0112)	0.5885 (0.0116)
2	0.6839 (0.0145)	0.6539 (0.0164)	0.0012	-0.0300	56.2	0.6131 (0.0133)	0.6081 (0.0126)	0.6209 (0.0142)	0.0042	-0.0630	0.4	0.5870 (0.0108)	0.5858 (0.0110)
3	0.6677 (0.0136)	0.6371 (0.0142)	0.0011	-0.0307	42.6	0.6020 (0.0125)	0.5950 (0.0117)	0.6158 (0.0136)	0.0029	-0.0519	4.0	0.5835 (0.0112)	0.5822 (0.0113)

Predicted Time t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity	AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity
4	0.6468 (0.0182)	0.6154 (0.0156)	0.0012	-0.0314	45.8	0.5865 (0.0175)	0.5793 (0.0173)	0.6078 (0.0156)	0.0018	-0.0389	29.6	0.5791 (0.0159)	0.5761 (0.0173)
Measurement error $\sigma_e^2 = 1.5$													
1	0.6955 (0.0153)	0.6589 (0.0203)	0.0018	-0.0366	55.2	0.6158 (0.0159)	0.6127 (0.0150)	0.6092 (0.0151)	0.0077	-0.0863	0.0	0.5781 (0.0112)	0.5776 (0.0114)
2	0.6839 (0.0145)	0.6489 (0.0175)	0.0015	-0.0350	48.6	0.6094 (0.0143)	0.6044 (0.0130)	0.6068 (0.0144)	0.0062	-0.0771	0.0	0.5765 (0.0109)	0.5758 (0.0109)
3	0.6677 (0.0136)	0.6324 (0.0148)	0.0015	-0.0353	34.0	0.5986 (0.0131)	0.5917 (0.0118)	0.6031 (0.0138)	0.0044	-0.0647	0.6	0.5739 (0.0112)	0.5733 (0.0112)
4	0.6468 (0.0182)	0.6108 (0.0154)	0.0015	-0.0360	35.2	0.5834 (0.0172)	0.5758 (0.0170)	0.5970 (0.0151)	0.0027	-0.0497	9.8	0.5706 (0.0154)	0.5688 (0.0166)
Measurement error $\sigma_e^2 = 2.0$													
1	0.6955 (0.0153)	0.6540 (0.0214)	0.0022	-0.0416	48.2	0.6125 (0.0168)	0.6087 (0.0156)	0.5985 (0.0151)	0.0096	-0.0970	0.0	0.5705 (0.0112)	0.5699 (0.0112)
2	0.6839 (0.0145)	0.6451 (0.0185)	0.0018	-0.0388	43.6	0.6067 (0.0149)	0.6017 (0.0137)	0.5967 (0.0145)	0.0078	-0.0872	0.0	0.5692 (0.0109)	0.5686 (0.0109)
3	0.6677 (0.0136)	0.6293 (0.0154)	0.0017	-0.0384	29.4	0.5963 (0.0134)	0.5893 (0.0121)	0.5938 (0.0139)	0.0057	-0.0739	0.0	0.5672 (0.0114)	0.5666 (0.0110)
4	0.6468 (0.0182)	0.6079 (0.0153)	0.0017	-0.0389	28.8	0.5829 (0.0172)	0.5721 (0.0162)	0.5889 (0.0148)	0.0036	-0.0579	3.2	0.5644 (0.0147)	0.5631 (0.0155)
Measurement error $\sigma_e^2 = 2.5$													
1	0.6955 (0.0152)	0.6495 (0.0224)	0.0026	-0.0459	44.4	0.6096 (0.0174)	0.6052 (0.0163)	0.5906 (0.0151)	0.0112	-0.1049	0.0	0.5646 (0.0111)	0.5643 (0.0111)
2	0.6839 (0.0145)	0.6419 (0.0193)	0.0021	-0.0420	38.8	0.6044 (0.0155)	0.5991 (0.0140)	0.5891 (0.0145)	0.0092	-0.0948	0.0	0.5636 (0.0108)	0.5632 (0.0109)
3	0.6678 (0.0136)	0.6269 (0.0159)	0.0019	-0.0409	27.4	0.5944 (0.0140)	0.5875 (0.0124)	0.5868 (0.0140)	0.0068	-0.0810	0.0	0.5620 (0.0112)	0.5617 (0.0109)

Predicted Time t	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity	AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity
4	0.6468 (0.0182)	0.6058 (0.0155)	0.0019	-0.0410	24.4	0.5810 (0.0179)	0.5710 (0.0154)	0.5826 (0.0145)	0.0043	-0.0641	1.0	0.5593 (0.0144)	0.5591 (0.0151)

Table 7.7: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=1.0 and 30% censoring

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity	AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity
Measurement error $\sigma_e^2 = 0.25$													
1	0.7433 (0.0148)	0.7256 (0.0160)	0.0006	-0.0176	81.0	0.6676 (0.0132)	0.6620 (0.0134)	0.7045 (0.0152)	0.0017	-0.0388	27.4	0.6499 (0.0120)	0.6470 (0.0127)
2	0.7230 (0.0139)	0.7046 (0.0143)	0.0005	-0.0184	75.8	0.6538 (0.0125)	0.6439 (0.0121)	0.6915 (0.0138)	0.0012	-0.0315	36.2	0.6413 (0.0115)	0.6361 (0.0117)
3	0.7007 (0.0139)	0.6816 (0.0136)	0.0005	-0.0191	70.6	0.6380 (0.0128)	0.6253 (0.0122)	0.6767 (0.0135)	0.0008	-0.0240	57.0	0.6306 (0.0122)	0.6248 (0.0128)
4	0.6769 (0.0195)	0.6570 (0.0181)	0.0007	-0.0199	79.8	0.6202 (0.0190)	0.6067 (0.0184)	0.6599 (0.0185)	0.0006	-0.0170	84.4	0.6191 (0.0173)	0.6123 (0.0201)
Measurement error $\sigma_e^2 = 0.5$													
1	0.7433 (0.0148)	0.7171 (0.0173)	0.0010	-0.0262	67.0	0.6609 (0.0142)	0.6554 (0.0139)	0.6797 (0.0154)	0.0043	-0.0635	1.8	0.6308 (0.0119)	0.6287 (0.0126)
2	0.7230 (0.0139)	0.6960 (0.0150)	0.0010	-0.0270	57.6	0.6471 (0.0132)	0.6374 (0.0123)	0.6705 (0.0141)	0.0030	-0.0525	4.4	0.6247 (0.0114)	0.6210 (0.0115)
3	0.7007 (0.0139)	0.6726 (0.0138)	0.0010	-0.0281	47.0	0.6312 (0.0132)	0.6187 (0.0121)	0.6597 (0.0136)	0.0019	-0.0410	13.2	0.6172 (0.0120)	0.6128 (0.0122)
4	0.6769 (0.0195)	0.6475 (0.0173)	0.0012	-0.0294	60.2	0.6125 (0.0182)	0.6002 (0.0171)	0.6470 (0.0172)	0.0012	-0.0299	58.4	0.6088 (0.0165)	0.6035 (0.0180)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity	AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity
Measurement error $\sigma_e^2 = 1.0$													
1	0.7433 (0.0148)	0.7062 (0.0192)	0.0017	-0.0370	49.8	0.6530 (0.0158)	0.6470 (0.0149)	0.6490 (0.0157)	0.0091	-0.0943	0.0	0.6076 (0.0119)	0.6062 (0.0122)
2	0.7230 (0.0139)	0.6866 (0.0165)	0.0016	-0.0364	39.0	0.6399 (0.0143)	0.6305 (0.0129)	0.6434 (0.0145)	0.0066	-0.0796	0.0	0.6037 (0.0113)	0.6019 (0.0115)
3	0.7007 (0.0139)	0.6633 (0.0146)	0.0016	-0.0374	27.8	0.6242 (0.0136)	0.611 (0.0122)	0.6366 (0.0138)	0.0043	-0.0641	0.4	0.5989 (0.0117)	0.5970 (0.0121)
4	0.6769 (0.0195)	0.6375 (0.0166)	0.0018	-0.0394	35.2	0.6058 (0.0174)	0.5923 (0.0164)	0.6281 (0.0158)	0.0026	-0.0488	14.6	0.5937 (0.0157)	0.5909 (0.0160)
Measurement error $\sigma_e^2 = 1.5$													
1	0.7433 (0.0148)	0.6987 (0.0209)	0.0024	-0.0445	43.4	0.6477 (0.0174)	0.6408 (0.0157)	0.6301 (0.0157)	0.0130	-0.1132	0.0	0.5935 (0.0118)	0.5926 (0.0120)
2	0.7230 (0.0139)	0.6809 (0.0178)	0.0021	-0.0421	32.4	0.6358 (0.0152)	0.6259 (0.0136)	0.6262 (0.0147)	0.0096	-0.0968	0.0	0.5910 (0.0113)	0.5896 (0.0115)
3	0.7007 (0.0139)	0.6583 (0.0154)	0.0020	-0.0424	21.8	0.6203 (0.0141)	0.6082 (0.0126)	0.6213 (0.0140)	0.0065	-0.0793	0.0	0.5873 (0.0117)	0.5863 (0.0117)
4	0.6769 (0.0195)	0.6324 (0.0164)	0.0022	-0.0445	21.6	0.6020 (0.0177)	0.5886 (0.0157)	0.6150 (0.0152)	0.0041	-0.0619	1.8	0.5840 (0.0144)	0.5812 (0.0165)
Measurement error $\sigma_e^2 = 2.0$													
1	0.7433 (0.0148)	0.6925 (0.0221)	0.0031	-0.0508	35.4	0.6436 (0.0183)	0.6357 (0.0164)	0.6170 (0.0157)	0.0162	-0.1263	0.0	0.5840 (0.0118)	0.5831 (0.0117)
2	0.7230 (0.0139)	0.6764 (0.0188)	0.0025	-0.0466	30.2	0.6323 (0.0159)	0.6226 (0.0141)	0.6226 (0.0141)	0.0121	-0.1089	0.0	0.5819 (0.0112)	0.5810 (0.0114)
3	0.7007 (0.0139)	0.6547 (0.0161)	0.0024	-0.0460	19.4	0.6173 (0.0147)	0.6058 (0.0127)	0.6058 (0.0127)	0.0084	-0.0904	0.0	0.5791 (0.0115)	0.5785 (0.0116)
4	0.6770 (0.0194)	0.6291 (0.0164)	0.0026	-0.0478	16.0	0.6001 (0.0179)	0.5859 (0.0152)	0.5859 (0.0152)	0.0054	-0.0718	1.0	0.5763 (0.0140)	0.5746 (0.0150)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity	AUC(SE)	MSE	Bias	Cov	Sensitivity	Specificity
Measurement error $\sigma_e^2 = 2.5$													
1	0.7433 (0.0148)	0.6971 (0.0232)	0.0037	-0.0562	30.2	0.6397 (0.0193)	0.6315 (0.0170)	0.6073 (0.0157)	0.0187	-0.1360	0.0	0.5770 (0.0117)	0.5762 (0.0116)
2	0.7230 (0.0139)	0.6725 (0.0197)	0.0029	-0.0505	27.2	0.6297 (0.0167)	0.6193 (0.0146)	0.6050 (0.0149)	0.0142	-0.1180	0.0	0.5752 (0.0112)	0.5745 (0.0114)
3	0.7006 (0.0141)	0.6520 (0.0168)	0.0027	-0.0487	17.8	0.6154 (0.0154)	0.6035 (0.0128)	0.6019 (0.0143)	0.0100	-0.0987	0.0	0.5732 (0.0114)	0.5722 (0.0118)
4	0.6768 (0.0194)	0.6268 (0.0164)	0.0028	-0.0500	14.0	0.5992 (0.0180)	0.5835 (0.0152)	0.5976 (0.0148)	0.0065	-0.0792	0.0	0.5704 (0.0141)	0.5695 (0.0149)

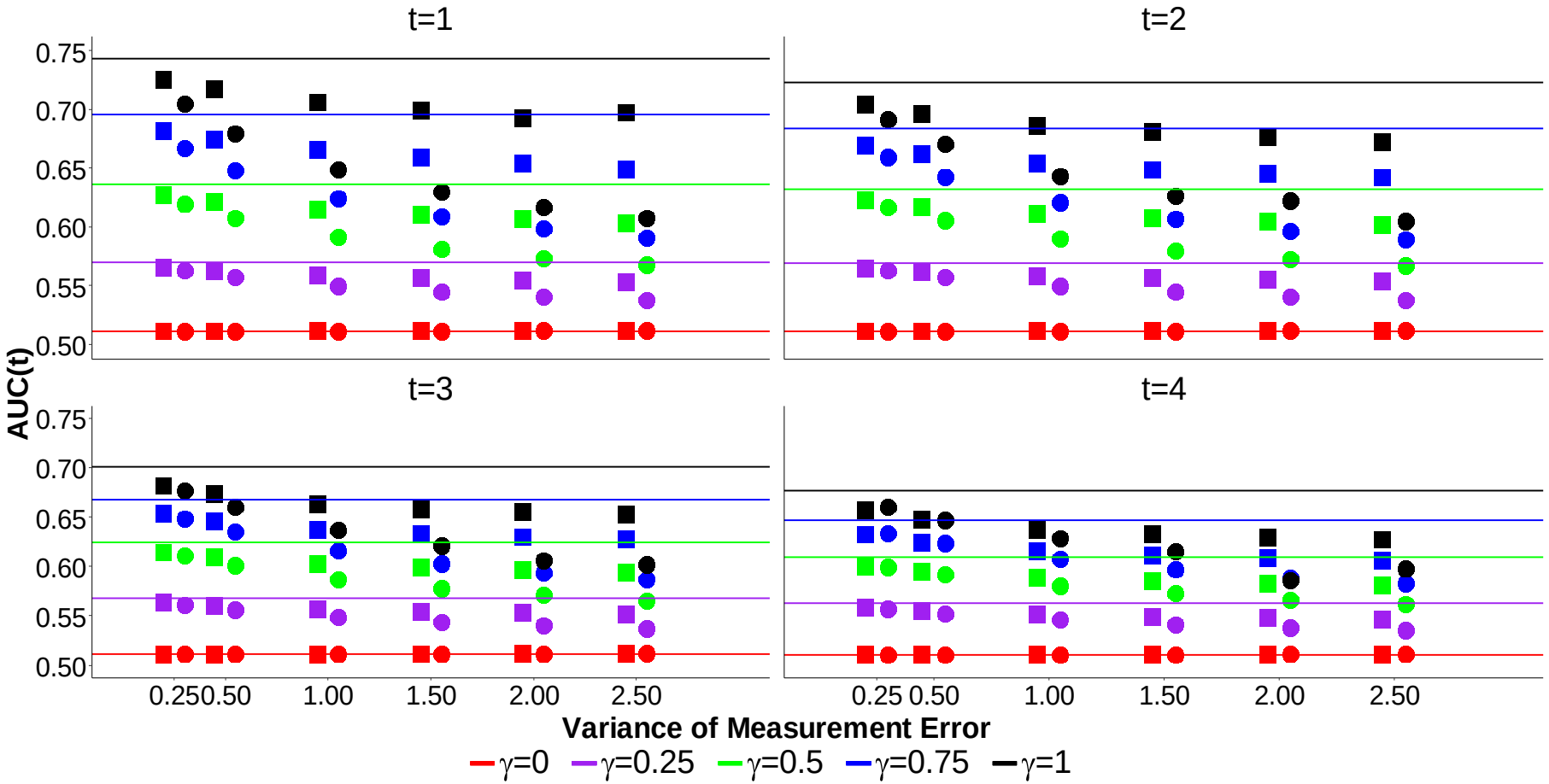

Figure 7.7: AUC(t) estimates for 30% censoring. Square is the estimate from the proposed approach, and circle is from the Cox model with observed biomarker. The horizontal lines are the true value of the association parameter.

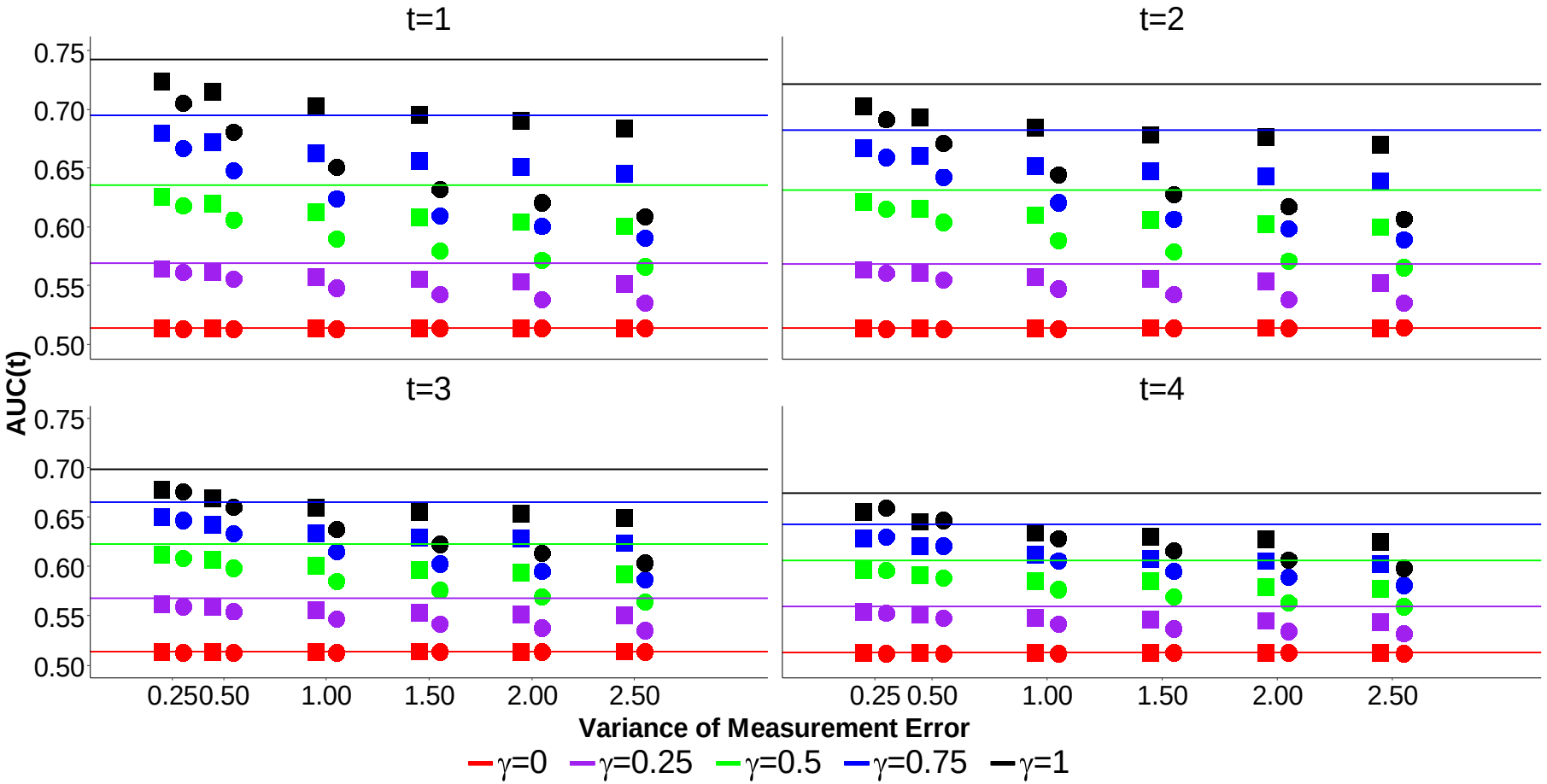

Figure 7.8: AUC(t) estimates for 50% censoring. Square is the estimate from the proposed approach, and circle is from the Cox model with observed biomarker. The horizontal lines are the true value of the association parameter.

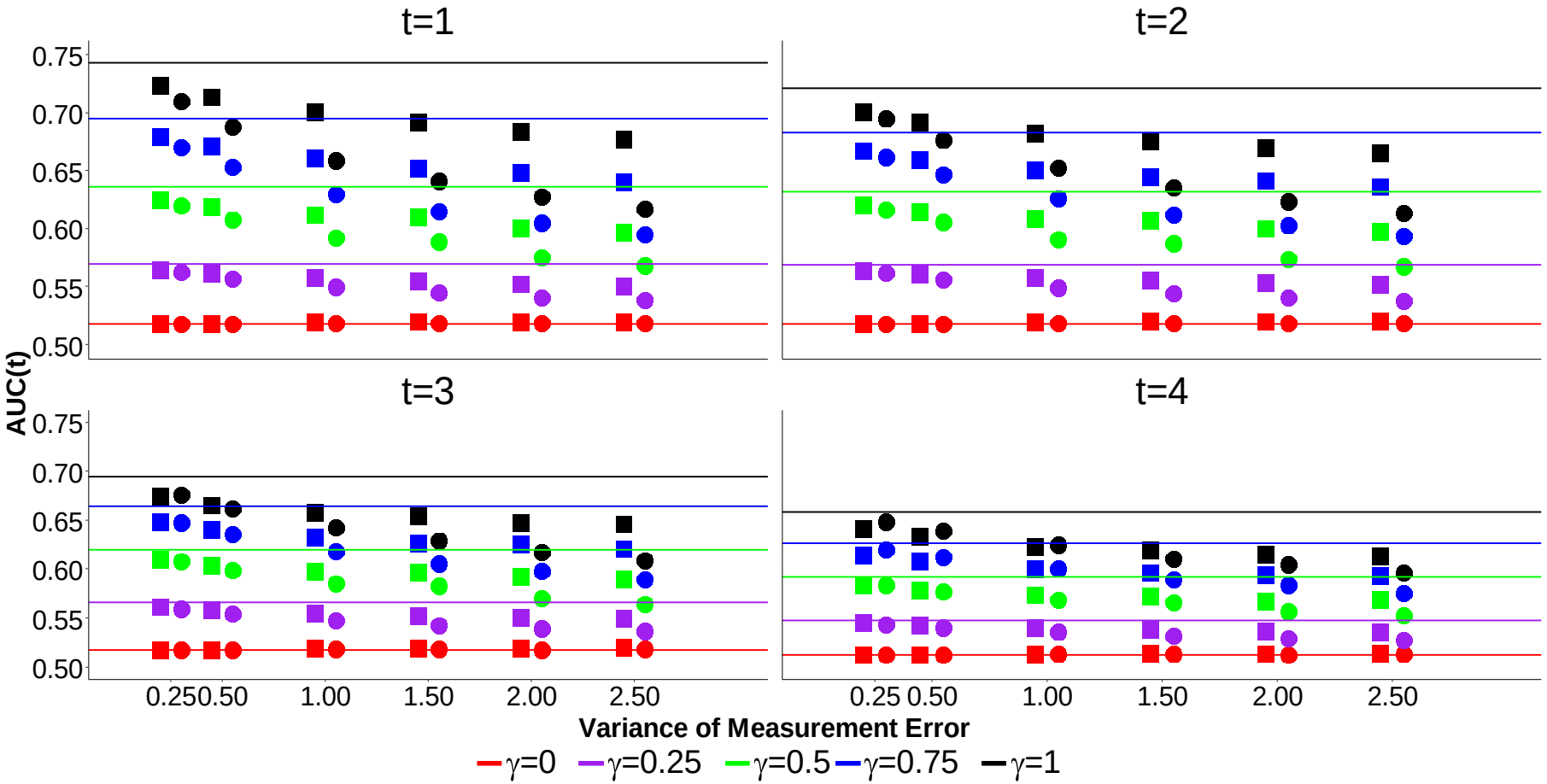

Figure 7.9: AUC(t) estimates for 70% censoring. Square is the estimate from the proposed approach, and circle is from the Cox model with observed biomarker. The horizontal lines are the true value of the association parameter.

7.6 Use of the proposed estimator within some current methods

This simulation is aimed to demonstrate the use of proposed time-dependent ROC curve approach within five time-dependent ROC curve approaches proposed under I/D and C/D definitions [33], that were presented in Chapter 2 and 3. It is also aimed to evaluate the implication of measurement error further. AUC(t) under C/D definition (methods CD2, CD3, CD5, CD6) are estimated using "survivalROC" and"timeROC" libraries in R and R codes provided by the authors [31, 48]. Under I/D definition (method ID3), the R code provided by the authors [48] is used.

Tables 7.8 – 7.12 present the estimated AUC(t) for the above 5 methodologies at $t = t_h = 1, 2, 3, 4$ based on 500 simulated datasets for 30% censoring across varying γ. The results for other percentages of censoring are presented in Appendix C (Table C.15-C.24). In each methodology, AUC(t) is estimated for the observed biomarker at baseline and measurement error adjusted $\widehat{\mathrm{M}}$. Similar to previous simulation results (see Section 7.4 in Tables 7.3-7.7), the AUC(t) is estimated fairly close to the null value of 0.5 for both observed and adjusted values of the biomarker when $\gamma = 0$, and as strength of the association becomes stronger (γ moves towards 1.0), the estimated AUC(t) are also increased by acceptable margins. As expected, AUC(t) estimated from the observed value is lower across all settings.

It is observed that the estimated AUC(t) for methods under C/D have been increased over prediction time as expected. However, that decreases for FP method, since under I/D definition, the number of cases are defined only at the incident time (t in this case).

Table 7.8: Time-dependent AUC, sensitivity and specificity for all current method when γ=0 with 30% censoring

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.4980 (0.0292)	0.4995 (0.0289)	0.4985 (0.0461)	0.4988 (0.0456)	0.4988 (0.0459)	0.4991 (0.0455)	0.4987 (0.0459)	0.4990 (0.0455)	0.5000 (0.0358)	0.4999 (0.0353)
2	0.4986 (0.0208)	0.4995 (0.0197)	0.4986 (0.0327)	0.4990 (0.0307)	0.4993 (0.0321)	0.4997 (0.0304)	0.4992 (0.0321)	0.4996 (0.0303)	0.5007 (0.0253)	0.5015 (0.0242)
3	0.4999 (0.0205)	0.5005 (0.0190)	0.5009 (0.0370)	0.5013 (0.0351)	0.5017 (0.0316)	0.5021 (0.0294)	0.5016 (0.0317)	0.5020 (0.0295)	0.5011 (0.0261)	0.5008 (0.0247)
4	0.4957 (0.0451)	0.4952 (0.0428)	0.4958 (0.1412)	0.4973 (0.1404)	0.5031 (0.0709)	0.5032 (0.0680)	0.5032 (0.0710)	0.5034 (0.0681)	0.5007 (0.0783)	0.5018 (0.0779)
Measurement error $\sigma_e^2 = 0.5$										
1	0.4975 (0.0298)	0.4997 (0.0293)	0.4992 (0.0470)	0.4995 (0.0466)	0.4995 (0.0467)	0.4999 (0.0465)	0.4993 (0.0467)	0.4998 (0.0465)	0.4999 (0.0368)	0.5009 (0.0345)
2	0.4983 (0.0216)	0.4997 (0.0196)	0.4988 (0.0340)	0.4995 (0.0303)	0.4996 (0.0335)	0.5001 (0.0302)	0.4995 (0.0334)	0.5000 (0.0301)	0.5009 (0.0265)	0.5012 (0.0242)
3	0.4998 (0.0218)	0.5004 (0.0191)	0.5011 (0.0389)	0.5018 (0.0351)	0.5019 (0.0337)	0.5024 (0.0295)	0.5018 (0.0338)	0.5024 (0.0296)	0.5014 (0.0271)	0.5014 (0.0255)
4	0.4958 (0.0463)	0.4954 (0.0435)	0.4960 (0.1412)	0.4988 (0.1397)	0.5033 (0.0732)	0.5037 (0.0681)	0.5033 (0.0733)	0.5039 (0.0681)	0.4981 (0.0744)	0.5014 (0.0786)
Measurement error $\sigma_e^2 = 1.0$										
1	0.4967 (0.0302)	0.5003 (0.0308)	0.4998 (0.0483)	0.5001 (0.0479)	0.5001 (0.0476)	0.5004 (0.0479)	0.5000 (0.0476)	0.5004 (0.0478)	0.4997 (0.0376)	0.5019 (0.0351)
2	0.4978 (0.0229)	0.4998 (0.0197)	0.4992 (0.0364)	0.4999 (0.0300)	0.5000 (0.0355)	0.5004 (0.0300)	0.4998 (0.0354)	0.5003 (0.0299)	0.5016 (0.0279)	0.5010 (0.0240)

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
3	0.4995 (0.0236)	0.5004 (0.0193)	0.5012 (0.0420)	0.5023 (0.0353)	0.5021 (0.0370)	0.5028 (0.0297)	0.5019 (0.0372)	0.5027 (0.0298)	0.5009 (0.0279)	0.5016 (0.0246)
4	0.4953 (0.0482)	0.4949 (0.0445)	0.4961 (0.1423)	0.5010 (0.1390)	0.5037 (0.0772)	0.5043 (0.0680)	0.5037 (0.0773)	0.5044 (0.0680)	0.5020 (0.0771)	0.5022 (0.0762)
Measurement error $\sigma_e^2 = 1.5$										
1	0.4966 (0.0302)	0.5006 (0.0314)	0.5003 (0.0492)	0.5005 (0.0486)	0.5005 (0.0482)	0.5008 (0.0485)	0.5004 (0.0482)	0.5008 (0.0485)	0.5001 (0.0385)	0.5016 (0.0352)
2	0.4974 (0.0234)	0.5000 (0.0197)	0.4994 (0.0382)	0.5001 (0.0298)	0.5003 (0.0371)	0.5006 (0.0299)	0.5001 (0.0370)	0.5005 (0.0297)	0.5014 (0.0290)	0.5014 (0.0239)
3	0.4991 (0.0249)	0.5006 (0.0194)	0.5013 (0.0445)	0.5026 (0.0355)	0.5022 (0.0396)	0.5029 (0.0299)	0.5021 (0.0398)	0.5029 (0.0300)	0.5013 (0.0297)	0.5016 (0.0259)
4	0.4952 (0.0503)	0.4950 (0.0442)	0.4965 (0.1436)	0.5026 (0.1386)	0.5039 (0.0808)	0.5047 (0.0682)	0.5038 (0.0809)	0.5048 (0.0681)	0.4999 (0.0763)	0.5026 (0.0759)
Measurement error $\sigma_e^2 = 2.0$										
1	0.4968 (0.0305)	0.5009 (0.0319)	0.5006 (0.0499)	0.5008 (0.0491)	0.5009 (0.0487)	0.5011 (0.0491)	0.5007 (0.0487)	0.5010 (0.0490)	0.5010 (0.0393)	0.5023 (0.0352)
2	0.4972 (0.0239)	0.5000 (0.0196)	0.4997 (0.0398)	0.5003 (0.0297)	0.5005 (0.0384)	0.5007 (0.0298)	0.5003 (0.0384)	0.5007 (0.0296)	0.5010 (0.0300)	0.5010 (0.0240)
3	0.4989 (0.0260)	0.5008 (0.0197)	0.5015 (0.0468)	0.5027 (0.0356)	0.5023 (0.0419)	0.5030 (0.0300)	0.5021 (0.0421)	0.5029 (0.0302)	0.5015 (0.0305)	0.5020 (0.0253)
4	0.4950 (0.0520)	0.4956 (0.0440)	0.4973 (0.1456)	0.5034 (0.1385)	0.5041 (0.0843)	0.5048 (0.0680)	0.5039 (0.0843)	0.5050 (0.0679)	0.5005 (0.0752)	0.5018 (0.0767)
Measurement error $\sigma_e^2 = 2.5$										
1	0.4968 (0.0317)	0.5008 (0.0329)	0.5009 (0.0515)	0.5002 (0.0500)	0.5009 (0.0498)	0.5003 (0.0499)	0.5011 (0.0499)	0.5005 (0.0499)	0.5017 (0.0416)	0.5009 (0.0381)

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
2	0.4976 (0.0234)	0.5001 (0.0202)	0.5021 (0.0400)	0.5008 (0.0308)	0.5019 (0.0383)	0.5007 (0.0308)	0.5020 (0.0383)	0.5008 (0.0307)	0.5027 (0.0313)	0.5000 (0.0247)
3	0.4984 (0.0272)	0.4977 (0.0205)	0.5036 (0.0496)	0.4993 (0.0361)	0.5028 (0.0456)	0.4985 (0.0311)	0.5029 (0.0455)	0.4986 (0.0311)	0.5010 (0.0309)	0.4990 (0.0257)
4	0.4938 (0.0557)	0.4908 (0.0437)	0.5073 (0.1505)	0.5035 (0.1446)	0.5025 (0.0878)	0.4968 (0.0664)	0.5027 (0.0878)	0.4967 (0.0664)	0.5015 (0.0742)	0.4971 (0.0765)

Table 7.9: Time-dependent AUC, sensitivity and specificity for all current method when γ=0.25 with 30% censoring

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.5486 (0.0332)	0.5408 (0.0323)	0.5790 (0.0470)	0.5646 (0.0469)	0.5790 (0.0469)	0.5649 (0.0469)	0.5789 (0.0468)	0.5648 (0.0468)	0.5760 (0.0365)	0.5630 (0.0352)
2	0.5536 (0.0227)	0.5451 (0.0214)	0.5880 (0.0326)	0.5733 (0.0310)	0.5884 (0.0320)	0.5739 (0.0305)	0.5883 (0.0318)	0.5738 (0.0304)	0.5749 (0.0240)	0.5628 (0.0232)
3	0.5674 (0.0206)	0.5568 (0.0189)	0.6150 (0.0360)	0.5959 (0.0337)	0.6153 (0.0310)	0.5966 (0.0283)	0.6152 (0.0310)	0.5965 (0.0283)	0.5745 (0.0247)	0.5623 (0.0244)
4	0.6069 (0.0349)	0.5891 (0.0336)	0.6956 (0.1228)	0.6641 (0.1234)	0.6975 (0.0576)	0.6662 (0.0561)	0.6976 (0.0578)	0.6664 (0.0563)	0.5726 (0.0703)	0.5588 (0.0703)
Measurement error $\sigma_e^2 = 0.5$										
1	0.5510 (0.0336)	0.5377 (0.0324)	0.5848 (0.0475)	0.5595 (0.0475)	0.5844 (0.0472)	0.5598 (0.0474)	0.5843 (0.0471)	0.5597 (0.0474)	0.5802 (0.0366)	0.5586 (0.0352)

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
2	0.5557 (0.0237)	0.5412 (0.0210)	0.5928 (0.0341)	0.5673 (0.0307)	0.5928 (0.0334)	0.5680 (0.0305)	0.5927 (0.0333)	0.5679 (0.0303)	0.5780 (0.0255)	0.5569 (0.0230)
3	0.5704 (0.0220)	0.5521 (0.0187)	0.6209 (0.0378)	0.5881 (0.0335)	0.6207 (0.0331)	0.5886 (0.0283)	0.6207 (0.0331)	0.5886 (0.0283)	0.5780 (0.0260)	0.5574 (0.0249)
4	0.6117 (0.0366)	0.5814 (0.0345)	0.7049 (0.1226)	0.6508 (0.1227)	0.7062 (0.0595)	0.6528 (0.0571)	0.7063 (0.0598)	0.6530 (0.0572)	0.5754 (0.0693)	0.5537 (0.0666)
Measurement error $\sigma_e^2 = 1.0$										
1	0.5550 (0.0343)	0.5333 (0.0333)	0.5935 (0.0482)	0.5519 (0.0484)	0.5924 (0.0475)	0.5522 (0.0483)	0.5923 (0.0475)	0.5522 (0.0482)	0.5862 (0.0378)	0.5511 (0.0357)
2	0.5586 (0.0254)	0.5359 (0.0208)	0.5997 (0.0366)	0.5586 (0.0304)	0.5990 (0.0358)	0.5592 (0.0303)	0.5989 (0.0356)	0.5591 (0.0301)	0.5820 (0.0277)	0.5501 (0.0239)
3	0.5739 (0.0238)	0.5455 (0.0187)	0.6292 (0.0410)	0.5770 (0.0334)	0.6279 (0.0369)	0.5774 (0.0286)	0.6279 (0.0369)	0.5773 (0.0286)	0.5819 (0.0273)	0.5489 (0.0248)
4	0.6172 (0.0381)	0.5701 (0.0352)	0.7182 (0.1229)	0.6321 (0.1225)	0.7170 (0.0633)	0.6333 (0.0585)	0.7171 (0.0635)	0.6335 (0.0587)	0.5803 (0.0681)	0.5478 (0.0693)
Measurement error $\sigma_e^2 = 1.5$										
1	0.5588 (0.0349)	0.5301 (0.0334)	0.6002 (0.0490)	0.5467 (0.0487)	0.5983 (0.0481)	0.5471 (0.0487)	0.5982 (0.0480)	0.5470 (0.0486)	0.5905 (0.0383)	0.5462 (0.0352)
2	0.5608 (0.0268)	0.5322 (0.0206)	0.6051 (0.0389)	0.5527 (0.0302)	0.6035 (0.0378)	0.5532 (0.0301)	0.6035 (0.0376)	0.5531 (0.0299)	0.5851 (0.0296)	0.5445 (0.0231)
3	0.5761 (0.0258)	0.5410 (0.0187)	0.6352 (0.0441)	0.5694 (0.0334)	0.6328 (0.0401)	0.5696 (0.0287)	0.6328 (0.0401)	0.5696 (0.0287)	0.5841 (0.0291)	0.5444 (0.0257)

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
4	0.6205 (0.0412)	0.5627 (0.0351)	0.7281 (0.1240)	0.6195 (0.1227)	0.7238 (0.0665)	0.6200 (0.0595)	0.7239 (0.0668)	0.6202 (0.0596)	0.5840 (0.0688)	0.5421 (0.0697)
Measurement error $\sigma_e^2 = 2.0$										
1	0.5623 (0.0356)	0.5277 (0.0335)	0.6057 (0.0499)	0.5429 (0.0490)	0.6030 (0.0487)	0.5432 (0.0490)	0.6029 (0.0487)	0.5432 (0.0490)	0.5946 (0.0402)	0.5421 (0.0346)
2	0.5625 (0.0280)	0.5294 (0.0205)	0.6096 (0.0410)	0.5483 (0.0300)	0.6072 (0.0397)	0.5488 (0.0300)	0.6071 (0.0395)	0.5487 (0.0298)	0.5872 (0.0310)	0.5408 (0.0228)
3	0.5776 (0.0277)	0.5377 (0.0189)	0.6400 (0.0470)	0.5638 (0.0334)	0.6365 (0.0431)	0.5639 (0.0289)	0.6365 (0.0431)	0.5639 (0.0288)	0.5856 (0.0301)	0.5407 (0.0248)
4	0.6229 (0.0435)	0.5579 (0.0357)	0.7358 (0.1257)	0.6098 (0.1229)	0.7286 (0.0700)	0.6101 (0.0599)	0.7287 (0.0703)	0.6103 (0.0601)	0.5868 (0.0665)	0.5396 (0.0675)
Measurement error $\sigma_e^2 = 2.5$										
1	0.5655 (0.0363)	0.5258 (0.0335)	0.6104 (0.0508)	0.5399 (0.0492)	0.6069 (0.0494)	0.5402 (0.0491)	0.6068 (0.0494)	0.5402 (0.0491)	0.5973 (0.0410)	0.5391 (0.0348)
2	0.5643 (0.0292)	0.5273 (0.0203)	0.6135 (0.0430)	0.5449 (0.0299)	0.6103 (0.0415)	0.5453 (0.0299)	0.6102 (0.0413)	0.5453 (0.0297)	0.5893 (0.0322)	0.5380 (0.0231)
3	0.5790 (0.0293)	0.5351 (0.0190)	0.6442 (0.0497)	0.5593 (0.0334)	0.6397 (0.0459)	0.5594 (0.0289)	0.6396 (0.0458)	0.5594 (0.0289)	0.5869 (0.0315)	0.5374 (0.0252)
4	0.6246 (0.0464)	0.5539 (0.0359)	0.7427 (0.1275)	0.6022 (0.1231)	0.7323 (0.0734)	0.6024 (0.0603)	0.7324 (0.0737)	0.6026 (0.0604)	0.5887 (0.0683)	0.5370 (0.0669)

Table 7.10: Time-dependent AUC, sensitivity and specificity for all current method when γ=0.5 with 30% censoring

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.6028 (0.0359)	0.5844 (0.0345)	0.6557 (0.0446)	0.6279 (0.0451)	0.6553 (0.0444)	0.6281 (0.0450)	0.6553 (0.0443)	0.6281 (0.0449)	0.6483 (0.0349)	0.6233 (0.0340)
2	0.6090 (0.0235)	0.5905 (0.0218)	0.6726 (0.0304)	0.6436 (0.0294)	0.6726 (0.0297)	0.6441 (0.0288)	0.6725 (0.0295)	0.6440 (0.0286)	0.6421 (0.0229)	0.6182 (0.0225)
3	0.6256 (0.0221)	0.6046 (0.0204)	0.7146 (0.0344)	0.6775 (0.0330)	0.7142 (0.0289)	0.6780 (0.0275)	0.7142 (0.0290)	0.6780 (0.0276)	0.6360 (0.0244)	0.6109 (0.0243)
4	0.6737 (0.0327)	0.6434 (0.0309)	0.8087 (0.0950)	0.7587 (0.0964)	0.8097 (0.0396)	0.7616 (0.0419)	0.8098 (0.0398)	0.7617 (0.0421)	0.6277 (0.0551)	0.5996 (0.0549)
Measurement error $\sigma_e^2 = 0.5$										
1	0.6085 (0.0364)	0.5771 (0.0339)	0.6657 (0.0448)	0.6173 (0.0456)	0.6647 (0.0444)	0.6175 (0.0455)	0.6646 (0.0443)	0.6175 (0.0454)	0.6551 (0.0346)	0.6135 (0.0339)
2	0.6143 (0.0242)	0.5826 (0.0212)	0.6814 (0.0316)	0.6316 (0.0294)	0.6806 (0.0308)	0.6321 (0.0289)	0.6806 (0.0307)	0.6321 (0.0287)	0.6479 (0.0239)	0.6075 (0.0223)
3	0.6313 (0.0229)	0.5956 (0.0199)	0.7252 (0.0362)	0.6620 (0.0332)	0.7236 (0.0310)	0.6624 (0.0280)	0.7237 (0.0310)	0.6624 (0.0281)	0.6432 (0.0248)	0.6004 (0.0247)
4	0.6820 (0.0336)	0.6310 (0.0308)	0.8223 (0.0937)	0.7364 (0.0956)	0.8214 (0.0406)	0.7395 (0.0442)	0.8215 (0.0408)	0.7397 (0.0443)	0.6314 (0.0549)	0.5887 (0.0537)
Measurement error $\sigma_e^2 = 1.0$										
1	0.6183 (0.0377)	0.5670 (0.0337)	0.6812 (0.0452)	0.6021 (0.0462)	0.6788 (0.0446)	0.6023 (0.0460)	0.6787 (0.0446)	0.6022 (0.0460)	0.6658 (0.0359)	0.5985 (0.0336)
2	0.6218 (0.0266)	0.5717 (0.0206)	0.6943 (0.0344)	0.6144 (0.0295)	0.6919 (0.0335)	0.6149 (0.0290)	0.6919 (0.0334)	0.6148 (0.0288)	0.6558 (0.0262)	0.5930 (0.0222)

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
3	0.6389 (0.0251)	0.5832 (0.0197)	0.7399 (0.0396)	0.6403 (0.0334)	0.7360 (0.0351)	0.6405 (0.0286)	0.7361 (0.0351)	0.6405 (0.0287)	0.6499 (0.0268)	0.5860 (0.0245)
4	0.6932 (0.0367)	0.6138 (0.0305)	0.8410 (0.0927)	0.7054 (0.0951)	0.8355 (0.0432)	0.7081 (0.0471)	0.8357 (0.0433)	0.7083 (0.0472)	0.6433 (0.0539)	0.5742 (0.0559)
Measurement error $\sigma_e^2 = 1.5$										
1	0.6266 (0.0390)	0.5601 (0.0333)	0.6933 (0.0463)	0.5916 (0.0467)	0.6895 (0.0455)	0.5918 (0.0465)	0.6894 (0.0455)	0.5918 (0.0465)	0.6741 (0.0377)	0.5885 (0.0343)
2	0.6275 (0.0290)	0.5643 (0.0204)	0.7042 (0.0373)	0.6027 (0.0295)	0.7002 (0.0363)	0.6031 (0.0291)	0.7001 (0.0362)	0.6030 (0.0289)	0.6608 (0.0287)	0.5832 (0.0227)
3	0.6440 (0.0276)	0.5745 (0.0195)	0.7503 (0.0432)	0.6255 (0.0335)	0.7443 (0.0390)	0.6257 (0.0290)	0.7443 (0.0390)	0.6257 (0.0290)	0.6544 (0.0288)	0.5760 (0.0245)
4	0.7007 (0.0398)	0.6020 (0.0307)	0.8539 (0.0928)	0.6843 (0.0951)	0.8438 (0.0461)	0.6866 (0.0488)	0.8440 (0.0463)	0.6868 (0.0489)	0.6494 (0.0538)	0.5670 (0.0550)
Measurement error $\sigma_e^2 = 2.0$										
1	0.6342 (0.0405)	0.5550 (0.0333)	0.7028 (0.0476)	0.5838 (0.0469)	0.6977 (0.0467)	0.5841 (0.0468)	0.6976 (0.0467)	0.5840 (0.0468)	0.6808 (0.0393)	0.5815 (0.0343)
2	0.6323 (0.0314)	0.5588 (0.0203)	0.7121 (0.0403)	0.5940 (0.0296)	0.7065 (0.0392)	0.5944 (0.0291)	0.7065 (0.0390)	0.5943 (0.0289)	0.6647 (0.0311)	0.5757 (0.0225)
3	0.6480 (0.0301)	0.5683 (0.0196)	0.7584 (0.0468)	0.6146 (0.0335)	0.7502 (0.0427)	0.6148 (0.0291)	0.7502 (0.0427)	0.6147 (0.0291)	0.6572 (0.0307)	0.5691 (0.0250)
4	0.7063 (0.0433)	0.5937 (0.0310)	0.8639 (0.0935)	0.6685 (0.0951)	0.8491 (0.0494)	0.6707 (0.0499)	0.8493 (0.0495)	0.6708 (0.0500)	0.6519 (0.0545)	0.5604 (0.0536)
Measurement error $\sigma_e^2 = 2.5$										
1	0.6407 (0.0422)	0.5509 (0.0331)	0.7103 (0.0492)	0.5778 (0.0471)	0.7041 (0.0482)	0.5781 (0.0470)	0.7039 (0.0483)	0.5780 (0.0470)	0.6860 (0.0406)	0.5747 (0.0342)

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
2	0.6362 (0.0339)	0.5545 (0.0201)	0.7186 (0.0432)	0.5872 (0.0296)	0.7115 (0.0420)	0.5875 (0.0292)	0.7114 (0.0418)	0.5875 (0.0290)	0.6677 (0.0339)	0.5704 (0.0228)
3	0.6509 (0.0328)	0.5633 (0.0197)	0.7648 (0.0502)	0.6061 (0.0336)	0.7544 (0.0462)	0.6062 (0.0293)	0.7544 (0.0462)	0.6062 (0.0293)	0.6591 (0.0339)	0.5637 (0.0254)
4	0.7104 (0.0474)	0.5870 (0.0309)	0.8723 (0.0945)	0.6561 (0.0952)	0.8524 (0.0526)	0.6582 (0.0507)	0.8526 (0.0528)	0.6584 (0.0508)	0.6551 (0.0545)	0.5561 (0.0532)

Table 7.11: Time-dependent AUC, sensitivity and specificity for all current method when γ=0.75 with 30% censoring

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.6609 (0.0370)	0.6305 (0.0349)	0.7282 (0.0394)	0.6893 (0.0403)	0.7276 (0.0392)	0.6894 (0.0401)	0.7275 (0.0391)	0.6894 (0.0400)	0.7112 (0.0298)	0.6765 (0.0302)
2	0.6600 (0.0250)	0.6311 (0.0227)	0.7463 (0.0279)	0.7043 (0.0274)	0.7458 (0.0266)	0.7048 (0.0261)	0.7458 (0.0266)	0.7047 (0.0261)	0.6978 (0.0216)	0.6622 (0.0209)
3	0.6706 (0.0243)	0.6404 (0.0220)	0.7905 (0.0320)	0.7391 (0.0314)	0.7893 (0.0260)	0.7394 (0.0256)	0.7894 (0.0260)	0.7395 (0.0257)	0.6856 (0.0223)	0.6468 (0.0231)
4	0.7125 (0.0307)	0.6725 (0.0285)	0.8682 (0.0689)	0.8077 (0.0710)	0.8673 (0.0276)	0.8098 (0.0325)	0.8675 (0.0276)	0.8100 (0.0326)	0.6693 (0.0405)	0.6284 (0.0433)
Measurement error $\sigma_e^2 = 0.5$										
1	0.6707 (0.0384)	0.6184 (0.0341)	0.7409 (0.0397)	0.6735 (0.0410)	0.7393 (0.0393)	0.6736 (0.0408)	0.7393 (0.0393)	0.6736 (0.0408)	0.7212 (0.0316)	0.6609 (0.0303)

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
2	0.6687 (0.0263)	0.6192 (0.0218)	0.7581 (0.0295)	0.6866 (0.0281)	0.7564 (0.0282)	0.6872 (0.0269)	0.7565 (0.0281)	0.6871 (0.0268)	0.7055 (0.0233)	0.6470 (0.0214)
3	0.6794 (0.0252)	0.6280 (0.0212)	0.8041 (0.0332)	0.7174 (0.0320)	0.8011 (0.0276)	0.7177 (0.0266)	0.8012 (0.0276)	0.7178 (0.0267)	0.6943 (0.0238)	0.6321 (0.0235)
4	0.7245 (0.0322)	0.6568 (0.0282)	0.8835 (0.0679)	0.7808 (0.0716)	0.8797 (0.0281)	0.7830 (0.0358)	0.8798 (0.0281)	0.7832 (0.0358)	0.6825 (0.0413)	0.6088 (0.0429)
Measurement error $\sigma_e^2 = 1.0$										
1	0.6867 (0.0408)	0.6021 (0.0336)	0.7600 (0.0407)	0.6507 (0.0419)	0.7566 (0.0402)	0.6509 (0.0418)	0.7566 (0.0402)	0.6509 (0.0418)	0.7345 (0.0332)	0.6406 (0.0309)
2	0.6815 (0.0289)	0.6030 (0.0212)	0.7749 (0.0326)	0.6616 (0.0287)	0.7708 (0.0313)	0.6621 (0.0277)	0.7709 (0.0312)	0.6621 (0.0277)	0.7159 (0.0253)	0.6255 (0.0218)
3	0.6917 (0.0272)	0.6109 (0.0208)	0.8223 (0.0358)	0.6874 (0.0327)	0.8157 (0.0307)	0.6877 (0.0278)	0.8158 (0.0307)	0.6877 (0.0278)	0.7044 (0.0254)	0.6114 (0.0241)
4	0.7416 (0.0356)	0.6359 (0.0282)	0.9039 (0.0669)	0.7432 (0.0727)	0.8937 (0.0293)	0.7454 (0.0396)	0.8938 (0.0293)	0.7456 (0.0396)	0.6948 (0.0407)	0.5919 (0.0428)
Measurement error $\sigma_e^2 = 1.5$										
1	0.6995 (0.0428)	0.5910 (0.0330)	0.7746 (0.0421)	0.7746 (0.0421)	0.6353 (0.0424)	0.7695 (0.0416)	0.7694 (0.0416)	0.6353 (0.0424)	0.7446 (0.0351)	0.6263 (0.0313)
2	0.6908 (0.0316)	0.5920 (0.0212)	0.7875 (0.0356)	0.7875 (0.0356)	0.6451 (0.0283)	0.7812 (0.0343)	0.7812 (0.0342)	0.6450 (0.0282)	0.7226 (0.0280)	0.6119 (0.0220)
3	0.6997 (0.0293)	0.5993 (0.0206)	0.8348 (0.0384)	0.8348 (0.0384)	0.6674 (0.0284)	0.8248 (0.0338)	0.8249 (0.0337)	0.6675 (0.0284)	0.7101 (0.0272)	0.5973 (0.0244)
4	0.7531 (0.0388)	0.6218 (0.0286)	0.9176 (0.0665)	0.9176 (0.0665)	0.7198 (0.0418)	0.9013 (0.0315)	0.9015 (0.0314)	0.7200 (0.0418)	0.7019 (0.0422)	0.5819 (0.0428)

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 2.0$										
1	0.7102 (0.0451)	0.5828 (0.0329)	0.7858 (0.0440)	0.6236 (0.0430)	0.7792 (0.0434)	0.6238 (0.0429)	0.7791 (0.0434)	0.6237 (0.0429)	0.7527 (0.0372)	0.6153 (0.0316)
2	0.6982 (0.0344)	0.5839 (0.0211)	0.7974 (0.0387)	0.6321 (0.0295)	0.7890 (0.0373)	0.6325 (0.0287)	0.7890 (0.0371)	0.6325 (0.0286)	0.7275 (0.0311)	0.6019 (0.0224)
3	0.7058 (0.0316)	0.5909 (0.0206)	0.8443 (0.0414)	0.6524 (0.0334)	0.8312 (0.0369)	0.6526 (0.0288)	0.8313 (0.0369)	0.6526 (0.0288)	0.7139 (0.0303)	0.5882 (0.0250)
4	0.7616 (0.0419)	0.6116 (0.0288)	0.9280 (0.0670)	0.6990 (0.0742)	0.9060 (0.0343)	0.7008 (0.0432)	0.9061 (0.0342)	0.7009 (0.0432)	0.7057 (0.0439)	0.5733 (0.0429)
Measurement error $\sigma_e^2 = 2.5$										
1	0.7183 (0.0472)	0.5764 (0.0329)	0.7941 (0.0458)	0.6145 (0.0433)	0.7862 (0.0453)	0.6147 (0.0433)	0.7861 (0.0452)	0.6146 (0.0433)	0.7585 (0.0394)	0.6063 (0.0317)
2	0.7039 (0.0371)	0.5774 (0.0210)	0.8049 (0.0415)	0.6222 (0.0297)	0.7945 (0.0401)	0.6226 (0.0289)	0.7945 (0.0399)	0.6226 (0.0288)	0.7309 (0.0333)	0.5943 (0.0217)
3	0.7102 (0.0340)	0.5842 (0.0206)	0.8513 (0.0443)	0.6409 (0.0336)	0.8353 (0.0400)	0.6411 (0.0291)	0.8354 (0.0399)	0.6411 (0.0291)	0.7159 (0.0329)	0.5814 (0.0253)
4	0.7676 (0.0453)	0.6037 (0.0288)	0.9363 (0.0676)	0.6845 (0.0745)	0.9086 (0.0371)	0.6862 (0.0441)	0.9087 (0.0371)	0.6863 (0.0441)	0.7097 (0.0471)	0.5658 (0.0434)

Table 7.12: Time-dependent AUC, sensitivity and specificity for all current method when γ=1.0 with 30% censoring

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.7132 (0.0351)	0.6719 (0.0329)	0.7897 (0.0335)	0.7420 (0.0350)	0.7887 (0.0333)	0.7421 (0.0348)	0.7887 (0.0333)	0.7420 (0.0347)	0.7626 (0.0257)	0.7185 (0.0256)
2	0.7020 (0.0268)	0.6640 (0.0245)	0.8067 (0.0258)	0.7538 (0.0260)	0.8058 (0.0247)	0.7542 (0.0249)	0.8058 (0.0246)	0.7542 (0.0248)	0.7414 (0.0206)	0.6945 (0.0203)
3	0.7057 (0.0254)	0.6673 (0.0232)	0.8462 (0.0292)	0.7844 (0.0298)	0.8444 (0.0227)	0.7848 (0.0238)	0.8445 (0.0227)	0.7848 (0.0238)	0.7238 (0.0225)	0.6728 (0.0226)
4	0.7391 (0.0306)	0.6917 (0.0280)	0.9036 (0.0546)	0.8370 (0.0583)	0.9016 (0.0221)	0.8391 (0.0287)	0.9017 (0.0220)	0.8393 (0.0286)	0.7063 (0.0325)	0.6494 (0.0348)
Measurement error $\sigma_e^2 = 0.5$										
1	0.7267 (0.0370)	0.6558 (0.0328)	0.8039 (0.0343)	0.7220 (0.0363)	0.8018 (0.0340)	0.7221 (0.0362)	0.8018 (0.0340)	0.7221 (0.0361)	0.7735 (0.0266)	0.7000 (0.0265)
2	0.7136 (0.0278)	0.6487 (0.0234)	0.8204 (0.0273)	0.7313 (0.0269)	0.8178 (0.0262)	0.7318 (0.0259)	0.8178 (0.0261)	0.7318 (0.0259)	0.7509 (0.0218)	0.6743 (0.0210)
3	0.7170 (0.0262)	0.6519 (0.0222)	0.8611 (0.0299)	0.7582 (0.0306)	0.8567 (0.0237)	0.7585 (0.0252)	0.8569 (0.0237)	0.7586 (0.0253)	0.7348 (0.0228)	0.6525 (0.0235)
4	0.7534 (0.0315)	0.6735 (0.0274)	0.9193 (0.0532)	0.8070 (0.0591)	0.9131 (0.0221)	0.8093 (0.0322)	0.9132 (0.0221)	0.8095 (0.0321)	0.7195 (0.0322)	0.6307 (0.0344)
Measurement error $\sigma_e^2 = 1.0$										
1	0.7479 (0.0396)	0.6339 (0.0325)	0.8249 (0.0361)	0.6931 (0.0381)	0.8207 (0.0358)	0.6932 (0.0380)	0.8207 (0.0357)	0.6932 (0.0379)	0.7885 (0.0284)	0.6730 (0.0273)
2	0.7306 (0.0298)	0.6280 (0.0226)	0.8393 (0.0302)	0.6999 (0.0280)	0.8335 (0.0290)	0.7003 (0.0271)	0.8335 (0.0289)	0.7003 (0.0270)	0.7624 (0.0244)	0.6486 (0.0214)

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
3	0.7323 (0.0276)	0.6314 (0.0216)	0.8803 (0.0315)	0.7220 (0.0316)	0.8711 (0.0258)	0.7223 (0.0267)	0.8712 (0.0258)	0.7223 (0.0267)	0.7464 (0.0239)	0.6264 (0.0235)
4	0.7735 (0.0334)	0.6498 (0.0271)	0.9393 (0.0516)	0.7652 (0.0602)	0.9254 (0.0225)	0.7675 (0.0361)	0.9256 (0.0225)	0.7676 (0.0360)	0.7354 (0.0317)	0.6058 (0.0357)
Measurement error $\sigma_e^2 = 1.5$										
1	0.7632 (0.0416)	0.6187 (0.0325)	0.8398 (0.0378)	0.6732 (0.0392)	0.8338 (0.0375)	0.6733 (0.0392)	0.8338 (0.0374)	0.6732 (0.0391)	0.7993 (0.0312)	0.6549 (0.0284)
2	0.7423 (0.0322)	0.6140 (0.0220)	0.8524 (0.0330)	0.6786 (0.0286)	0.8439 (0.0316)	0.6790 (0.0279)	0.8439 (0.0315)	0.6790 (0.0278)	0.7694 (0.0269)	0.6314 (0.0221)
3	0.7420 (0.0293)	0.6175 (0.0213)	0.8927 (0.0338)	0.6979 (0.0322)	0.8791 (0.0285)	0.6981 (0.0276)	0.8793 (0.0284)	0.6981 (0.0276)	0.7521 (0.0274)	0.6109 (0.0243)
4	0.7862 (0.0355)	0.6339 (0.0270)	0.9521 (0.0516)	0.7371 (0.0610)	0.9314 (0.0248)	0.7391 (0.0382)	0.9316 (0.0248)	0.7393 (0.0381)	0.7427 (0.0362)	0.5919 (0.0362)
Measurement error $\sigma_e^2 = 2.0$										
1	0.7742 (0.0430)	0.6074 (0.0323)	0.8502 (0.0394)	0.6580 (0.0396)	0.8429 (0.0391)	0.6581 (0.0395)	0.8428 (0.0390)	0.6580 (0.0395)	0.8073 (0.0333)	0.6408 (0.0285)
2	0.7508 (0.0341)	0.6037 (0.0215)	0.8620 (0.0354)	0.6627 (0.0288)	0.8510 (0.0339)	0.6631 (0.0281)	0.8510 (0.0337)	0.6631 (0.0280)	0.7742 (0.0294)	0.6192 (0.0219)
3	0.7488 (0.0308)	0.6073 (0.0211)	0.9014 (0.0358)	0.6800 (0.0327)	0.8841 (0.0306)	0.6801 (0.0281)	0.8842 (0.0305)	0.6802 (0.0281)	0.7551 (0.0296)	0.5998 (0.0246)
4	0.7950 (0.0375)	0.6225 (0.0269)	0.9616 (0.0520)	0.7162 (0.0615)	0.9347 (0.0271)	0.7180 (0.0395)	0.9349 (0.0270)	0.7182 (0.0393)	0.7475 (0.0393)	0.5816 (0.0366)
Measurement error $\sigma_e^2 = 2.5$										
1	0.7825 (0.0449)	0.5991 (0.0325)	0.8580 (0.0410)	0.6467 (0.0400)	0.8496 (0.0409)	0.6468 (0.0401)	0.8495 (0.0408)	0.6467 (0.0400)	0.8132 (0.0356)	0.6304 (0.0293)

Predicted Time t	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
2	0.7573 (0.0362)	0.5958 (0.0214)	0.8693 (0.0375)	0.6508 (0.0291)	0.8562 (0.0360)	0.6512 (0.0285)	0.8562 (0.0358)	0.6512 (0.0284)	0.7777 (0.0316)	0.6102 (0.0222)
3	0.7534 (0.0323)	0.5994 (0.0210)	0.9078 (0.0377)	0.6665 (0.0331)	0.8873 (0.0326)	0.6666 (0.0287)	0.8874 (0.0325)	0.6666 (0.0286)	0.7571 (0.0318)	0.5913 (0.0248)
4	0.8012 (0.0396)	0.6137 (0.0268)	0.9689 (0.0526)	0.6998 (0.0622)	0.9366 (0.0290)	0.7018 (0.0403)	0.9367 (0.0290)	0.7019 (0.0402)	0.7488 (0.0424)	0.5740 (0.0371)

7.7 Discussion

This chapter demonstrated the appropriateness and performance of the proposed measurement error adjusted time-dependent ROC curve approach. The proposed joint model estimated the true association parameter accurately with lower biases and MSE, and higher coverage percentages across different settings of the association, measurement error variance and percentage of censoring. It is clearly observed that as the variance of measurement error increases, the bias increases dramatically for association parameters if the Cox model is used.

A strong association (higher association parameter) between biomarker value and event time implies high diagnostic accuracy, and this is observed in the above simulation results. The proposed measurement error adjusted biomarker is consistently powerful in discriminating between diseased individuals and healthy individuals. Although the estimated standard error of the proposed approach is high, the diagnostic accuracy estimates are the closest to the true values. The proposed time-dependent ROC curve decreases over the prediction time as expected as discrimination power is weaker as the prediction time is far from baseline. In other words, as the prediction time increases, the potential of the baseline value of the biomarker becomes weaker in describing the current true status (diseased or not) of the individual. This is consistent with other studies that investigate the performance of the biomarker with respect to the prediction time [33]. However, this is not always true for the methods under C/D definition. These results evidenced that the proposed joint model approach can properly adjust the possible measurement error of a biomarker when estimating the time-dependent ROC curve.

8 Conclusion and Future Work

8.1 Introduction

In this thesis, methodologies and software have been developed and extended for the estimation of the time-dependent ROC curve. The methods have been assessed through simulation and application to a real clinical dataset. This chapter is aimed to summarise the thesis by highlighting the original contributions and discuss the implication of the research and suggest future research. Section 8.2 provides a summary of thesis chapters, outlining the original contributions to the current research, while section 8.3 describes the limitations of proposed approaches and possible future extensions. This chapter is concluded by making final remarks in Section 8.4.

8.2 Summary of thesis

The work presented in this thesis focused on the development, application and assessment of the time-dependent ROC curve. It comprised four main objectives as described in Chapter 1, and made several contributions to the current literature.

As the foundation of thesis, the background of time-dependent ROC curve analysis was extensively given in Chapter 2 describing three key definitions of time-dependency providing illustrations to enhance understanding.

The first objective was achieved in Chapter 3 in which a comprehensive review of the methodology for estimating the time-dependent ROC curve was conducted. The definitions, advantages and limitations of each methods whenever available, were given. Most of the methodologies discussed in the current literature were restricted to a single baseline biomarker value. One method considered longitudinally recorded biomarker values but ignored the censored event-time data (AD1 in Chapter 3). Motivated by the limited methodology in the current literature to allow the longitudinal values of a biomarker, two current methods had been extended in this chapter (IS2 and AD4). From the review of clinical applications, the number publications on time-dependent ROC curve analysis are increasing by year, while the cumulative/dynamic (C/D) definition has mostly been used. This definition is more relevant in clinical

practice since most studies aimed at discriminating between the diseased individual up to a particular time and healthy individuals beyond that time. The chapter has provided the software and illustrated the calculations of the ROC curve summaries for most methods across all 3 definitions. Overall, the findings of this review highlighted two main points which had motivated the work of this thesis; firstly the lack of parametric ROC curve approaches and secondly, ignorance of the measurement error of a biomarker in assessing the diagnostic accuracy.

A novel parametric approach to estimate the time-dependent ROC curve was proposed in Chapter 4. Parametric approaches can be valuable when the sample size is small. The development studies of biomarkers rely on small sample sizes to evaluate the diagnostic accuracy, especially when the biomarkers are more expensive. The chapter has considered six possible scenarios and derived closed-form formula for the ROC curve summaries whenever possible, otherwise derived numerically. The simulation study conducted in Chapter 6 concluded that the time-dependent estimate of AUC is not essentially affected by sample size, and is estimated accurately for smaller sample sizes such as 30. Although not all the scenarios provided realistic estimates of AUC as expected, the proposed methodology initiated a valuable platform for the potential future development of parametric approaches. The proposed approaches could be improved to have more stable estimates of AUC by considering other forms of parametric distributions and link functions driven by real data.

The third objective was achieved in Chapter 5 in which a measurement error adjusted time-dependent ROC curve analysis was proposed within the joint longitudinal data and event-time modelling framework. A joint model has been derived to provide an estimate at the baseline level, and a novel time-dependent ROC curve approach was proposed along the incident/dynamic (I/D) definition. As concluded from the simulation studies conducted in Chapter 7, the proposed measurement error adjusted estimate for the biomarker at baseline level accurately performed in the context of ROC curve by estimating AUC at its nominal level when there is no association between the biomarker and event, and as the strength of association increases, the estimated AUC also increases by the acceptable margins. The proposed measurement error adjusted estimator of the baseline biomarker consistently performed more accurately than the observed biomarker and the two-stage estimator. Ignoring the

measurement error severely underestimates the true association between the biomarker and event, and hence misleading results and conclusions can be drawn on the performance of a biomarker. The proposed joint model and the ROC curve approach are currently being developed to be included in the joineR library in R.

Most current approaches and both the proposed approaches were illustrated using real data in order to enhance the application of the time-dependent ROC curve rather than the standard ROC curve in main stream clinical research.

8.3 Limitations and Future Works

In developing the parametric approach, a limited number of parametric distributions were considered in this thesis, with two link functions across several scenarios. Not all the scenarios derived close-form estimators of ROC curve summaries, and hence numerical integration was required which resulted in computational difficulties including convergence issues. More flexible approaches allowing a wide range of parametric distributions and the link functions which derive closed-form estimators would be useful in clinical research.

This thesis is restricted to single right-censored event-times. However, in practice, many other events can affect the occurrence of the primary event which are called competing risks, with other forms of censoring. In addition, the current research on these aspects has been relatively limited. Jacqmin-Gadda, et al. [97] proposed a methodology to allow for semicompeting risks with interval censored data. However, they found that this approach is less efficient than the current IPCW method (CD5 in Chapter 3). Li, Shanshan [98] proposed nonparametric and semiparametric methodologies with left truncation, but the ROC curve was estimated under prevalent sampling (consists of individuals who have experienced the initial events but not the failure events). A more recent study has adapted the time-dependent ROC curve analysis within a multi-state competing risk framework [99]. The authors have assessed the prognostic ability of the multistate structured additive regression (STAR) model at each transition. In this approach, the time-dependent ROC curve provides a common scale to compare the risk scores at different transitions although the

measuring unit of the biomarkers is different. This is a unique application of the time-dependent ROC curve.

Further, the joint model with competing risks event-time has been studied by many researchers [100-102], and the proposed time-dependent ROC curve approach can be readily applied to account for the measurement error when the primary event is affected by competing risks or informative censoring. It can also be extended along the multiple biomarkers following the methodological developments in multivariate joint models [103] and software [28].

8.4 Conclusion

In conclusion, this thesis has presented the development and applications of time-dependent ROC curve analysis approach in medical research. The significance of using time-dependent ROC curve approach over standard approach has been discussed and findings from clinical application evidenced the appropriateness. The proposed methodologies in this thesis suggest that measurement error associated with a biomarker could lead to misleading conclusions of the diagnostic performance summaries, and parametric approaches are particularly useful when the sample size is restricted. Overall, the research presented in this thesis is of great value in enhancing the research area of time-dependent ROC curve.

References

1. Brown G, Papangelou K, Sechidis K, Svensson D, Weatherall J, Metcalfe PD: **Distinguishing prognostic and predictive biomarkers: an information theoretic approach**. *Bioinformatics* 2018, **34**(19):3365-3376.

2. Heagerty PJ, Lumley T, Pepe MS: **Time-dependent ROC curves for censored survival data and a diagnostic marker**. *Biometrics* 2000, **56**(2):337-344.

3. Saha-Chaudhuri P, Heagerty PJ: **Non-parametric estimation of a time-dependent predictive accuracy curve**. *Biostatistics* 2013, **14**(1):42-59.

4. Hung H, Chiang CT: **Estimation methods for time-dependent AUC models with survival data**. *CANADIAN JOURNAL OF STATISTICS-REVUE CANADIENNE DE STATISTIQUE* 2010, **38**(1):8-26.

5. Yue Y, Astvatsaturyan K, Cui X, Zhang X, Fraass B, Bose S: **Stratification of Prognosis of Triple-Negative Breast Cancer Patients Using Combinatorial Biomarkers**. *PloS one* 2016, **11**(3):e0149661.

6. Yue Y, Cui X, Bose S, Audeh W, Zhang X, Fraass B: **Stratifying triple-negative breast cancer prognosis using 18 F-FDG-PET/CT imaging**. *Breast Cancer Res Treat* 2015, **153**.

7. Cai T, Pepe MS, Zheng Y, Lumley T, Jenny NS: **The sensitivity and specificity of markers for event times**. *Biostatistics* 2006, **7**(2):182-197.

8. Kalbfleisch JD, Prentice RL: **The statistical analysis of failure time data**, vol. 360. New Jersey: John Wiley & Sons; 2011.

9. Schemper M, Henderson R: **Predictive Accuracy and Explained Variation in Cox Regression**. *Biometrics* 2000, **56**(1):249-255.

10. Pepe MS: **The statistical evaluation of medical tests for classification and prediction**: Oxford University Press, USA; 2003.

11. Kleinbaum DG, Klein M: **Survival Analysis: A Self-Learning Text**: Springer New York; 2006.

12. Tsiatis AA, DeGruttola V, Wulfsohn MS: **Modeling the Relationship of Survival to Longitudinal Data Measured with Error. Applications to Survival and CD4 Counts in Patients with AIDS**. *Journal of the American Statistical Association* 1995, **90**(429):27-37.

13. Wulfsohn MS, Tsiatis AA: **A Joint Model for Survival and Longitudinal Data Measured with Error**. *Biometrics* 1997, **53**(1):330-339.

14. Lambert J, Chevret S: **Summary measure of discrimination in survival models based on cumulative/dynamic time-dependent ROC curves**. *Statistical Methods In Medical Research* 2014, **25**(5):2088-2102.

15. Zheng Y, Heagerty PJ: **Semiparametric estimation of time-dependent ROC curves for longitudinal marker data**. *Biostatistics* 2004, **5**(4):615-632.

16. Zheng Y, Heagerty PJ: **Prospective accuracy for longitudinal markers**. *Biometrics* 2007, **63**(2):332-341.

17. Liu X: **Methods and Applications of Longitudinal Data Analysis**: Elsevier Science; 2015.

18. Henderson R, Diggle P, Dobson A: **Joint modelling of longitudinal measurements and event time data**. *Biostatistics* 2000, **1**(4):465-480.

19. Kolamunnage-Dona R, Williamson PR: **Time-dependent efficacy of longitudinal biomarker for clinical endpoint**. *Statistical Methods in Medical Research* 2018, **27**(6):1909-1924.

20. White E: **Measurement error in biomarkers: sources, assessment, and impact on studies**. *IARC scientific publications* 2011(163):143-161.

21. Fleming TR, Harrington DP: **Counting processes and survival analysis**, vol. 169. New Jersey: John Wiley & Sons; 2011.

22. James OF: **D-penicillamine for primary biliary cirrhosis**. *Gut* 1985, **26**(2):109-113.

23. Dickson ER, Wiesner, R.H., Baldus, W.P.: **D-penicillamine improves survival and retards histologic progression in primary biliary cirrhosis**. *Gastroenterology* 1982, **82**.

24. Epstein O, Lee R, Boss AM, Jain S, Cook D, Scheuer P, Sherlock S: **D-PENICILLAMINE TREATMENT IMPROVES SURVIVAL IN PRIMARY BILIARY CIRRHOSIS**. *The Lancet* 1981, **317**(8233):1275-1277.

25. Neuberger J, Christensen E, Portmann B, Caballeria J, Rodes J, Ranek L, Tygstrup N, Williams R: **Double blind controlled trial of d-penicillamine in patients with primary biliary cirrhosis**. *Gut* 1985, **26**(2):114-119.

26. Murtaugh PA, Dickson ER, Van Dam GM, Malinchoc M, Grambsch PM, Langworthy AL, Gips CH: **Primary biliary cirrhosis: Prediction of short-term survival based on repeated patient visits**. *Hepatology* 1994, **20**(1):126-134.

27. Heagerty PJ, Zheng Y: **Survival model predictive accuracy and ROC curves**. *Biometrics* 2005, **61**(1):92-105.

28. Hickey GL, Philipson P, Jorgensen A, Kolamunnage-Dona R: **joineRML: a joint model and software package for time-to-event and multivariate longitudinal outcomes**. *BMC Medical Research Methodology* 2018, **18**(1):50.

29. Bamber D: **The area above the ordinal dominance graph and the area below the receiver operating characteristic graph**. *Journal of mathematical psychology* 1975, **12**(4):387-415.

30. Hanley JA, McNeil BJ: **The meaning and use of the area under a receiver operating characteristic (ROC) curve**. *Radiology* 1982, **143**(1):29-36.

31. Blanche P, Dartigues JF, Jacqmin-Gadda H: **Review and comparison of ROC curve estimators for a time-dependent outcome with marker-dependent censoring**. *Biometrical Journal* 2013, **55**(5):687-704.

32. 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**. *Medical Decision Making* 1999, **19**(3):242-251.

33. Kamarudin AN, Cox T, Kolamunnage-Dona R: **Time-dependent ROC curve analysis in medical research: current methods and applications**. *BMC Medical Research Methodology* 2017, **17**(1):53.

34. Kaplan EL, Meier P: **Nonparametric estimation from incomplete observations**. *Journal of the American statistical association* 1958, **53**(282):457-481.

35. Zheng Y, Cai T, Pepe MS, Levy WC: **Time-dependent Predictive Values of Prognostic Biomarkers with Failure Time Outcome**. *Journal of the American Statistical Association* 2008, **103**(481):362-368.

36. Akritas MG: **Nearest neighbor estimation of a bivariate distribution under random censoring**. *The Annals of Statistics* 1994:1299-1327.

37. Cai T, Gerds TA, Zheng Y, Chen J: **Robust Prediction of t-Year Survival with Data from Multiple Studies**. *Biometrics* 2011, **67**(2):436-444.

38. Hung H, Chiang CT: **Optimal Composite Markers for Time-Dependent Receiver Operating Characteristic Curves with Censored Survival Data**. *Scandinavian Journal of Statistics* 2010, **37**(4):664-679.

39. Chambless LE, Diao G: **Estimation of time-dependent area under the ROC curve for long-term risk prediction**. *Statistics in Medicine* 2006, **25**(20):3474-3486.

40. Viallon V, Latouche A: **Discrimination measures for survival outcomes: connection between the AUC and the predictiveness curve**. *Biometrical Journal* 2011, **53**(2):217-236.

41. Uno H, Cai TX, Tian L, Wei LJ: **Evaluating prediction rules for t-year survivors with censored regression models**. *Journal of the American Statistical Association* 2007, **102**(478):527-537.

42. Royston P, Parmar MK: **The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt**. *Statistics in medicine* 2011, **30**(19):2409-2421.

43. Cox DR: **lRegression Models and Life Tables, mJournal of the Royal Statistical Society**. *Series B* 1972, **34**(2):187&220.

44. Aalen OO: **A linear regression model for the analysis of life times**. *Statistics in medicine* 1989, **8**(8):907-925.

45. Cai Z, Sun Y: **Local Linear Estimation for Time-Dependent Coefficients in Cox's Regression Models**. *Scandinavian Journal of Statistics* 2003, **30**(1):93-111.

46. Grambsch PM, Therneau TM: **Proportional hazards tests and diagnostics based on weighted residuals**. *Biometrika* 1994, **81**(3):515-526.

47. Xu R, O'Quigley J: **Proportional hazards estimate of the conditional survival function**. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 2000, **62**(4):667-680.

48. Shen W, Ning J, Yuan Y: **A direct method to evaluate the time-dependent predictive accuracy for biomarkers**. *Biometrics* 2015, **71**(2):439-449.

49. Royston P, Altman DG: **Regression Using Fractional Polynomials of Continuous Covariates - Parsimonious Parametric Modeling**. *Applied Statistics-Journal of the Royal Statistical Society Series C* 1994, **43**(3):429-467.

50. Leisenring W, Pepe MS, Longton G: **A marginal regression modelling framework for evaluating medical diagnostic tests**. *Statistics in medicine* 1997, **16**(11):1263-1281.

51. Tosteson ANA, Begg CB: **A general regression methodology for ROC curve estimation**. *Medical Decision Making* 1988, **8**(3):204-215.

52. Pepe MS: **Three approaches to regression analysis of receiver operating characteristic curves for continuous test results**. *Biometrics* 1998, **54**(1):124-135.

53. Heagerty PJ, Pepe MS: **Semiparametric estimation of regression quantiles with application to standardizing weight for height and age in US children**. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 1999, **48**(4):533-551.

54. Yang S-S: **Linear combination of concomitants of order statistics with application to testing and estimation**. *Annals of the Institute of Statistical Mathematics* 1981, **33**(1):463-470.

55. Zheng Y, Heagerty PJ: **Partly conditional survival models for longitudinal data**. *Biometrics* 2005, **61**(2):379-391.

56. Heagerty PJ, Saha-Chaudhuri P, Saha-Chaudhuri MP: **Package 'survivalROC'**. 2013.

57. Potapov S, Adler W, Schmid M: **survAUC: Estimators of Prediction Accuracy for Time-to-Event Data. R package version 1.0-5**. In.; 2012.

58. Blanche P: **TimeROC: Time-dependent ROC curve and AUC for censored survival data**. *R package version 02, URL http://CRAN R-project org/package= timeROC* 2013.

59. Therneau TM, Lumley T: **Package 'survival'**. In.: Verze; 2015.

60. Scheike T: **Timereg Package**. In.: R Package Version; 2009.

61. Gerds TA, Rcpp I, Rcpp L, Gerds MTA: **Package 'prodlim'**. 2015.

62. Heagerty PJ, Saha-Chaudhuri P, Saha-Chaudhuri MP: **Package 'risksetROC'**. 2012.

63. Lu Y, Wang L, Liu P, Yang P, You M: **Gene-expression signature predicts postoperative recurrence in stage I non-small cell lung cancer patients**. *PLoS One* 2012, **7**(1):e30880.

64. Tse LA, Dai JC, Chen MH, Liu YW, Zhang H, Wong TW, Leung CC, Kromhout H, Meijer E, Liu S *et al*: **Prediction models and risk assessment for silicosis using a retrospective cohort study among workers exposed to silica in China**. *Scientific Reports* 2015, **5**.

65. Desmedt C, Giobbie-Hurder A, Neven P, Paridaens R, Christiaens M-R, Smeets A, Lallemand F, Haibe-Kains B, Viale G, Gelber RD: **The Gene expression Grade Index: a potential predictor of relapse for endocrine-treated breast cancer patients in the BIG 1–98 trial**. *BMC medical genomics* 2009, **2**(1):1.

66. George J, Claes P, Vunckx K, Tejpar S, Deroose C, Nuyts J, Loeckx D, Suetens P: **A textural feature based tumor therapy response prediction model for longitudinal evaluation with PET imaging**. In: *Biomedical Imaging (ISBI), 2012 9th IEEE International Symposium on: 2012*: IEEE; 2012: 1048-1051.

67. Liang J-H, Gao R, Dai J-C, Gale RP, Li W, Fan L, Hu Z-B, Xu W, Li J-Y: **The prognostic role of HBV infection in chronic lymphocytic leukemia**. *Journal of Cancer Research and Clinical Oncology* 2018, **144(**7):1309-1315.

68. Hajian-Tilaki KO, Hanley JA, Joseph L, Collet J-P: **A Comparison of Parametric and Nonparametric Approaches to ROC Analysis of Quantitative Diagnostic Tests**. *Medical Decision Making* 1997, **17**(1):94-102.

69. Blanche P, Latouche A, Viallon V: **Time-Dependent AUC with Right-Censored Data: A Survey**. In*: 2013; New York, NY*: Springer New York; 2013: 239-251.

70. Bennett DA, Landry D, Little J, Minelli C: **Systematic review of statistical approaches to quantify, or correct for, measurement error in a continuous exposure in nutritional epidemiology**. *BMC medical research methodology* 2017, **17**(1):146-146.

71. Coffin M, Sukhatme S: **A Parametric Approach to Measurement Errors in Receiver Operating Characteristic Studies**. In: *Lifetime Data: Models in*

Reliability and Survival Analysis. edn. Edited by Jewell NP, Kimber AC, Lee M-LT, Whitmore GA. Boston, MA: Springer US; 1996: 71-75.

72. Coffin M, Sukhatme S: **Receiver Operating Characteristic Studies and Measurement Errors**. *Biometrics* 1997, **53**(3):823-837.

73. Reiser B: **Measuring the effectiveness of diagnostic markers in the presence of measurement error through the use of ROC curves**. *Stat Med* 2000, **19**(16):2115-2129.

74. Faraggi D: **The effect of random measurement error on receiver operating characteristic (ROC) curves**. *Stat Med* 2000, **19**(1):61-70.

75. Tosteson TD, Buonaccorsi JP, Demidenko E, Wells WA: **Measurement Error and Confidence Intervals for ROC Curves**. *Biometrical Journal* 2005, **47**(4):409-416.

76. Vexler A, Schisterman EF, Liu A: **Estimation of ROC curves based on stably distributed biomarkers subject to measurement error and pooling mixtures**. *Stat Med* 2008, **27**(2):280-296.

77. Vexler A, Liu A, Eliseeva E, Schisterman EF: **Maximum likelihood ratio tests for comparing the discriminatory ability of biomarkers subject to limit of detection**. *Biometrics* 2008, **64**(3):895-903.

78. Perkins NJ, Schisterman EF, Vexler A: **Generalized ROC curve inference for a biomarker subject to a limit of detection and measurement error**. *Statistics in medicine* 2009, **28**(13):1841-1860.

79. Long Q, Flanders WD, Fedirko V, Bostick RM: **Robust statistical methods for analysis of biomarkers measured with batch/experiment-specific errors**. *Statistics in medicine* 2010, **29**(3):361-370.

80. Li Y, Koval JJ, Donner A, Zou GY: **Interval estimation for the area under the receiver operating characteristic curve when data are subject to error**. *Statistics in Medicine* 2010, **29**(24):2521-2531.

81. Perkins NJ, Schisterman EF: **The Youden Index and the Optimal Cut-Point Corrected for Measurement Error**. *Biometrical Journal* 2005, **47**(4):428-441.

82. Rosner B, Tworoger S, Qiu W: **Correcting AUC for Measurement Error**. *Journal of biometrics & biostatistics* 2015, **6**(5):270.

83. Schisterman EF, Faraggi D, Reiser B, Trevisan M: **Statistical Inference for the Area under the Receiver Operating Characteristic Curve in the Presence of Random Measurement Error**. *American Journal of Epidemiology* 2001, **154**(2):174-179.

84. Prokhorov AV, Ushakov NG: **On the Problem of Reconstructing a Summands Distribution by the Distribution of Their Sum**. *Theory of Probability & Its Applications* 2002, **46**(3):420-430.

85. Owen DB, Craswell KJ, Hanson DL: **Nonparametric Upper Confidence Bounds for Pr{Y < X} and Confidence Limits for Pr{Y < X} When X and Y are Normal**. *Journal of the American Statistical Association* 1964, **59**(307):906-924.

86. Searle SR, Casella G, McCulloch CE: **Variance Components**: Wiley; 2009.

87. Reiser B, Guttman I: **Statistical Inference for Pr(Y < X): The Normal Case**. *Technometrics* 1986, **28**(3):253-257.

88. Miller RG: **Survival Analysis**: Wiley; 2011.

89. Thomas JD, Hultquist RA: **Interval Estimation for the Unbalanced Case of the One-Way Random Effects Model**. *The Annals of Statistics* 1978, **6**(3):582-587.

90. Rao PSRS: **Variance Components: Mixed Models, Methodologies and Applications**: Taylor & Francis; 1997.

91. Hu P, Tsiatis AA, Davidian M: **Estimating the Parameters in the Cox Model When Covariate Variables are Measured with Error**. *Biometrics* 1998, **54**(4):1407-1419.

92. Bansal A, Heagerty PJ: **A tutorial on evaluating time-varying discrimination accuracy for survival models used in dynamic decision-making**. In: *ArXiv e-prints.* 2017.

93. Zou KH, Hall WJ, Shapiro DE: **Smooth non-parametric receiver operating characteristic (ROC) curves for continuous diagnostic tests**. *Stat Med* 1997, **16**(19):2143-2156.

94. Efron B, Tibshirani RJ: **An Introduction to the Bootstrap**: Taylor & Francis; 1994.

95. Bender R, Augustin T, Blettner M: **Generating survival times to simulate Cox proportional hazards models**. *Stat Med* 2005, **24**(11):1713-1723.

96. Crowther MJ, Lambert PC, Abrams KR: **Adjusting for measurement error in baseline prognostic biomarkers included in a time-to-event analysis: a joint modelling approach**. *BMC medical research methodology* 2013, **13**(1):146.

97. Jacqmin-Gadda H, Blanche P, Chary E, Touraine C, Dartigues J-F: **Receiver operating characteristic curve estimation for time to event with semicompeting risks and interval censoring**. *Statistical Methods in Medical Research* 2016, **25**(6):2750-2766.

98. Li S: **Estimating time-dependent ROC curves using data under prevalent sampling**. *Statistics in Medicine* 2017, **36**(8):1285-1301.

99. Teixeira L, Cadarso-Suárez C, Rodrigues A, Mendonça D: **Time-dependent ROC methodology to evaluate the predictive accuracy of semiparametric multi-state models in the presence of competing risks: An application to peritoneal dialysis programme**. *Statistical Modelling* 2016, **16**(5):409-428.

100. Hickey GL, Philipson P, Jorgensen A, Kolamunnage-Dona R: **A comparison of joint models for longitudinal and competing risks data, with application to an epilepsy drug randomized controlled trial**. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 2018, **181**(4):1105-1123.

101. Hickey Graeme L, Philipson P, Jorgensen A, Kolamunnage-Dona R: **Joint Models of Longitudinal and Time-to-Event Data with More Than One Event Time Outcome: A Review**. In: *The International Journal of Biostatistics.* vol. 14; 2018.

102. Williamson PR, Kolamunnage-Dona R, Philipson P, Marson AG: **Joint modelling of longitudinal and competing risks data**. *Statistics in Medicine* 2008, **27**(30):6426-6438.

103. Hickey GL, Philipson P, Jorgensen A, Kolamunnage-Dona R: **Joint modelling of time-to-event and multivariate longitudinal outcomes: recent developments and issues**. *BMC medical research methodology* 2016, **16**(1):117-117.

Appendix A R code for parametric approach

Appendix A.1 Exponential/Exponential

```
##First link

library(cubature)
##Multiplication of two functions
Multiply=function(a,b){
  force(a)
  force(b)
  function(x){a(x)*b(x)}
}

Para1 <- function(marker,time,param.t2,pt){
ft <- function (t){(1/mean(time))*exp(-(1/mean(time))*t)}
gx <- function (x){(1/mean(marker))*exp(-(1/mean(marker))*x[2])}
ftx<-function(x){param.t2*x[2]*exp(-param.t2*x[2]*x[1])}

##Define the joint distribution
IG <- Multiply(ftx,gx)
ooo <- order(time)
t <- time[ooo]
x <- marker[ooo]

cut.values <- unique(x)
cut.values <- cut.values[order(cut.values)]
ncuts <- length(cut.values)

roc.matrix <- matrix(NA, ncuts, 2)
roc.matrix[ncuts, 1] <- 0
roc.matrix[ncuts, 2] <- 1

for (i in 1:(ncuts - 1)) {
   Limit <- c(0,cut.values[i],pt,10)
   Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
            upperLimit=c(Limit[3],Limit[4]))
   Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
            upperLimit=c(Limit[3],Limit[4]))
   Se <- Se1$integral/Se2$integral

   Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
```

```
            upperLimit = c(Limit[4],Limit[2]))
  Sp2 <-adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
           upperLimit = c(Limit[4], Limit[4]))
  Sp <- Sp1$integral/Sp2$integral

   roc.matrix[i, 1] <- Se
   roc.matrix[i, 2] <- Sp   }

##Calculation of Area under the ROC curve  for each time point
sensitivity = roc.matrix[, 1]
specificity = roc.matrix[, 2]
x <- 1 - c(0,specificity)
y <- c(1,sensitivity)
n <- length(x)
dx <- x[-n] - x[-1]
mid.y <- (y[-n] + y[-1])/2
area <- sum(dx * mid.y)
list(cut.values = c(-Inf, cut.values), TP = y, FP = x, predict.time = pt,AUC = area)}


##second link

library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
  force(a)
  force(b)
  function(x){a(x)*b(x)}
}

#exp/exp
Para11 <- function(marker,time,param.t2,param.t3,pt){
ft <- function (t){(1/mean(time))*exp(-(1/mean(time))*t)}
gx <- function (x){(1/mean(marker))*exp(-(1/mean(marker))*x[2])}
ftx<-function(x){(param.t2+param.t3*x[2])*
exp(-(param.t2+param.t3*x[2])*x[1])}
predict.time <- pt
IG <- Multiply(ftx,gx)
ooo <- order(time)
t <- time[ooo]
x <- marker[ooo]
cut.values <- unique(x)
cut.values <- cut.values[order(cut.values)]
ncuts <- length(cut.values)
```

```
roc.matrix <- matrix(NA, ncuts, 2)
roc.matrix[ncuts, 1] <- 0
roc.matrix[ncuts, 2] <- 1


for (i in 1:(ncuts - 1)) {
Limit <- c(0,cut.values[i],pt,500)
Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
        upperLimit=c(Limit[3],Limit[4]))
Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
        upperLimit=c(Limit[3],Limit[4]))
Se <- Se1$integral/Se2$integral

Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
        upperLimit = c(Limit[4],Limit[2]))
Sp2 <-adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
        upperLimit = c(Limit[4], Limit[4]))
Sp <- Sp1$integral/Sp2$integral

roc.matrix[i, 1] <- Se
 roc.matrix[i, 2] <- Sp}

##Calculation of Area under the ROC curve  for each time point
sensitivity = roc.matrix[, 1]
specificity = roc.matrix[, 2]
x <- 1 - c(0,specificity)
y <- c(1,sensitivity)
n <- length(x)
dx <- x[-n] - x[-1]
mid.y <- (y[-n] + y[-1])/2
area <- sum(dx * mid.y)
list(cut.values = c(-Inf, cut.values), TP = y, FP = x,
predict.time = pt,AUC = area)}
```

Appendix A.2 Exponential/Normal

```
##First link

library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
force(a)
force(b)
function(x){a(x)*b(x)}
}

Para2 <- function(marker,time,param.t2,pt){
ft <- function (t){(1/mean(time))*exp(-(1/mean(time))*t)}
gx <- function (x){(1/(sd(marker)*(sqrt(2*pi))))*(exp(-((x[2]-
mean(marker))^2))/(2*sd(marker)^2))}
ftx<-function(x){param.t2*x[2]*exp(-param.t2*x[2]*x[1])}

IG <- Multiply(ftx,gx)
ooo <- order(time)
 t <- time[ooo]
 x <- marker[ooo]

cut.values <- unique(x)
cut.values <- cut.values[order(cut.values)]
ncuts <- length(cut.values)

roc.matrix <- matrix(NA, ncuts, 2)
roc.matrix[ncuts, 1] <- 0
roc.matrix[ncuts, 2] <- 1

for (i in 1:(ncuts - 1)) {
   Limit <- c(0,cut.values[i],pt,500)
   Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
          upperLimit=c(Limit[3],Limit[4]))
  Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
           upperLimit=c(Limit[3],Limit[4]))
  Se <- Se1$integral/Se2$integral
  Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
           upperLimit = c(Limit[4],Limit[2]))
  Sp2 <-adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
```

```
        upperLimit = c(Limit[4], Limit[4]))
  Sp <- Sp1$integral/Sp2$integral

  roc.matrix[i, 1] <- Se
  roc.matrix[i, 2] <- Sp
  }

##Calculation of Area under the ROC curve  for each time point
sensitivity = roc.matrix[, 1]
specificity = roc.matrix[, 2]
x <- 1 - c(0,specificity)
y <- c(1,sensitivity)
n <- length(x)
dx <- x[-n] - x[-1]
mid.y <- (y[-n] + y[-1])/2
area <- sum(dx * mid.y)
list(cut.values = c(-Inf, cut.values), TP = y, FP = x, predict.time = pt,AUC = area)
}



##Parameter estimation
#Define the joint pdf
ftx <- function(t,x,param.t,param.x1,param.x2)
{param.t*x/(param.x2*sqrt(2*pi))*exp(-(x-param.x1)^2/(2*(param.x2)^2)-
param.t*x*t)}
load("observations.dat")
LL <- function(param.t,param.x1,param.x2) {
  R =(ftx(data[,1],data[,2],param.t,param.x1,param.x2))
  #print(c(param.t,param.x1,param.x2,R))
  -sum(log(R))}

library(stats4)
LH<-mle(LL, start = list(param.t = 1, param.x1=1, param.x2=1),
        method = "L-BFGS-B", lower = c(1,1,1),
        upper = c(Inf, Inf,Inf))

Parameters<-matrix(LH@coef,1,3)
save( Parameters, file="resultsParameterLH.dat" )



##second link
```

```
library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
  force(a)
  force(b)
  function(x){a(x)*b(x)}
}

##exp/normal
Para22 <- function(marker,time,param.t2,param.t3,pt){
ft <- function (t){(1/mean(time))*exp(-(1/mean(time))*t)}
gx <- function (x){(1/(sd(marker)*(sqrt(2*pi))))*(exp(-((x[2]-
mean(marker))^2))/(2*sd(marker)^2))}
ftx<- function(x){(param.t2+param.t3*x[2])*
exp(-(param.t2+param.t3*x[2])*x[1])}
predict.time <- pt

IG <- Multiply(ftx,gx)
ooo <- order(time)
t <- time[ooo]
x <- marker[ooo]

cut.values <- unique(x)
cut.values <- cut.values[order(cut.values)]
ncuts <- length(cut.values)

roc.matrix <- matrix(NA, ncuts, 2)
roc.matrix[ncuts, 1] <- 0
roc.matrix[ncuts, 2] <- 1

for (i in 1:(ncuts - 1)) {
Limit <- c(0,cut.values[i],pt,500)

Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
          upperLimit=c(Limit[3],Limit[4]))
Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
          upperLimit=c(Limit[3],Limit[4]))
Se <- Se1$integral/Se2$integral

Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
          upperLimit = c(Limit[4],Limit[2]))
```

```
Sp2 <-adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
        upperLimit = c(Limit[4], Limit[4]))
Sp <- Sp1$integral/Sp2$integral
roc.matrix[i, 1] <- Se
roc.matrix[i, 2] <- Sp}

##Calculation of Area under the ROC curve  for each time point
sensitivity = roc.matrix[, 1]
specificity = roc.matrix[, 2]
x <- 1 - c(0,specificity)
y <- c(1,sensitivity)
n <- length(x)
dx <- x[-n] - x[-1]
mid.y <- (y[-n] + y[-1])/2
area <- sum(dx * mid.y)
list(cut.values = c(-Inf, cut.values), TP = y, FP = x,
predict.time = pt,AUC = area)}

##Parameter estimation

#Define the joint pdf
ftx <- function(t,x,param.t1,param.t2,param.x1,param.x2)
{(param.t1+param.t2*x)/(param.x2*sqrt(2*pi))*exp(-(x-
param.x1)^2/(2*(param.x2)^2)-(param.t1+param.t2*x)*t)}

load("observations.dat")
LL <- function(param.t1,param.t2,param.x1,param.x2) {
        R =(ftx(data[,1],data[,2],param.t1,param.t2,param.x1,param.x2))
        #print(c(param.t1,param.t2,param.x1,param.x2,R))
        -sum(log(R))}
library(stats4)
LH<-mle(LL, start = list(param.t1 = 1, param.t2=1, param.x1=1, param.x2=0.25),
        method = "L-BFGS-B", lower = c(0.5,0.5,0.5,0.5),
    upper = c(Inf, Inf,Inf,Inf))
```

Appendix A.3 Weibull/Normal

```
##First link

library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
force(a)
force(b)
function(x){a(x)*b(x)}}

Para3 <- function(marker,time,param.t3,predt){
ft <- function (t){sqrt(1/mean(time))*2*(sqrt(1/mean(marker))*t)^(2-1)*exp(-
sqrt(1/mean(marker))*t)^2}
gx <- function (x){(1/(sd(marker)*(sqrt(2*pi))))*(exp(-((x[2]-
mean(marker))^2))/(2*sd(marker)^2))}
ftx <- function(x){ (param.t3*x[2]*2)*((param.t3*x[2]*x[1])^(2-1))*
exp(-(param.t3*x[2]*x[1])^2)}

IG <- Multiply(ftx,gx)
ooo <- order(time)
t <- time[ooo]
x <- marker[ooo]

cut.values <- unique(x)
cut.values <- cut.values[order(cut.values)]
ncuts <- length(cut.values)

roc.matrix <- matrix(NA, ncuts, 2)
roc.matrix[ncuts, 1] <- 0
roc.matrix[ncuts, 2] <- 1

  for (i in 1:(ncuts - 1)) {
Limit <- c(0,cut.values[i],predt,100)
Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
          upperLimit=c(Limit[3],Limit[4]))
Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
           upperLimit=c(Limit[3],Limit[4]))
Se <- Se1$integral/Se2$integral
Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
           upperLimit = c(Limit[4],Limit[2]))
```

```
Sp2 <-adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
         upperLimit = c(Limit[4], Limit[4]))
 Sp <- Sp1$integral/Sp2$integral

   roc.matrix[i, 1] <- Se
   roc.matrix[i, 2] <- Sp}

  ##Calculation of Area under the ROC curve  for each time point
  sensitivity = roc.matrix[, 1]
  specificity = roc.matrix[, 2]
  x <- 1 - c(0,specificity)
  y <- c(1,sensitivity)
  n <- length(x)
  dx <- x[-n] - x[-1]
  mid.y <- (y[-n] + y[-1])/2
  area <- sum(dx * mid.y)
  list(cut.values = c(-Inf, cut.values), TP = y, FP = x,
      predict.time = predt,AUC = area) }



##Parameter estimation
load("observations.dat")

#Define the joint pdf
ftx <- function(t,x,param.t1,param.t2,param.x1,param.x2)
{(param.t1*x*param.t2*(param.t1*x*t)^(param.t2-1))/
 (param.x2*sqrt(2*pi))*
 exp(-((x-param.x1)^2/(2*param.x2^2))-(param.t1*x*t)^param.t2)}

LL <- function(param.t1,param.t2,param.x1,param.x2) {
 R =ftx(data[,1],data[,2],param.t1,param.t2,param.x1,param.x2)
  -sum(log(R))}


library(stats4)
LH<-mle(LL, start = list(param.t1 = 0.1, param.t2=1,param.x1=1, param.x2=0.5),
    method = "L-BFGS-B", lower = c(0.1,1,1,0.5),
    upper = c(Inf, Inf,Inf,Inf))

Parameters<-matrix(LH@coef,1,4)
save( Parameters, file="resultsParameterLH.dat" )
```

```
##second link

library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
  force(a)
  force(b)
  function(x){a(x)*b(x)}
}

#weibull/normal
Para33 <- function(marker,time,param.t3,param.t4,predt)
{ ft <- function (t){sqrt(1/mean(time))*2*(sqrt(1/mean(time))*t)^(2-1)*exp(-
sqrt(1/mean(time))*t)^2}
gx <- function (x){(1/(sd(marker)*sqrt(2*pi)))*(exp(-((x[2]-
mean(marker))^2))/(2*(sd(marker))^2)) }
ftx <- function(x){ ((param.t3+param.t4*x[2])*2)*
(((param.t3+param.t4*x[2])*x[1])^(2-1))*
 exp(-((param.t3+param.t4*x[2])*x[1])^2)}
  predict.time <- predt

  IG <- Multiply(ftx,gx)
  ooo <- order(time)
  t <- time[ooo]
  x <- marker[ooo]

  cut.values <- unique(x)
  cut.values <- cut.values[order(cut.values)]
  ncuts <- length(cut.values)

  roc.matrix <- matrix(NA, ncuts, 2)
  roc.matrix[ncuts, 1] <- 0
  roc.matrix[ncuts, 2] <- 1

  for (i in 1:(ncuts - 1)) {
    Limit <- c(0,cut.values[i],predt,100)
    Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
                          upperLimit=c(Limit[3],Limit[4]))
    Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
                          upperLimit=c(Limit[3],Limit[4]))
```

```
   Se <- Se1$integral/Se2$integral
   Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
                    upperLimit = c(Limit[4],Limit[2]))
   Sp2 <-adaptIntegrate(IG,  lowerLimit = c(Limit[3],Limit[1]),
                   upperLimit = c(Limit[4], Limit[4]))
   Sp <- Sp1$integral/Sp2$integral

   roc.matrix[i, 1] <- Se
   roc.matrix[i, 2] <- Sp }

  ##Calculation of Area under the ROC curve  for each time point
  sensitivity = roc.matrix[, 1]
  specificity = roc.matrix[, 2]
  x <- 1 - c(0,specificity)
  y <- c(1,sensitivity)
  n <- length(x)
  dx <- x[-n] - x[-1]
  mid.y <- (y[-n] + y[-1])/2
  area <- sum(dx * mid.y)
  list(cut.values = c(-Inf, cut.values), TP = y, FP = x,
      predict.time = predt,AUC = area)

}

##Parameter estimation

load("observations.dat")
#Define the joint pdf
ftx <- function(t,x,param.t1,param.t2,param.t3,param.x1,param.x2) {
  (((param.t1+param.t2*x)*param.t3))*(((param.t1+param.t2*x)*t)^(param.t3-1))*
    (exp(-((x-param.x1)^2)/(2*param.x2^2)-((param.t1+param.t2*x)*t)^param.t3))/
    (param.x2*sqrt(2*pi))}
LL <- function(param.t1,param.t2,param.t3,param.x1,param.x2) {
  R =(ftx(data[,1],data[,2],param.t1,param.t2,param.t3,param.x1,param.x2))
  #print(c(param.t1,param.t2,param.t3,param.x1,param.x2,R))
  -sum(log(R))}

library(stats4)
LH<-mle(LL, start = list(param.t1 = 0.1, param.t2=0.1, param.t3=1,
                    param.x1=1, param.x2=0.5),
        method = "L-BFGS-B", lower = c(0.1,0.1,1,1,0.5),
        upper = c(Inf, Inf,Inf,Inf,Inf))
```

```
Parameters<-matrix(LH@coef,1,5)
save( Parameters, file="resultsParameterLH.dat" )
```

Appendix A.4 Exponential/Exponential- censored outcome

```
##First link

library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
  force(a)
  force(b)
  function(x){a(x)*b(x)}
}

Para1cens <- function(marker,time,status,param.t2,pt){
ft <- function (t){(1/mean(time))*exp(-(1/mean(time))*t)}
gx <- function (x){(1/mean(marker))*exp(-(1/mean(marker))*x[2])}
ftx<-function(x){param.t2*x[2]*exp(-param.t2*x[2]*x[1])}


IG <- Multiply(ftx,gx)
ooo <- order(time)
t <- time[ooo]
x <- marker[ooo]
d<- status[ooo]

data<- cbind(x,t,d)
censored=ifelse(data[,2]<=pt&data[,3]==0,1,0)
data<-cbind(data,censored)
data <- subset(data,censored==0)

cut.values <- unique(x)
cut.values <- cut.values[order(cut.values)]
ncuts <- length(cut.values)

roc.matrix <- matrix(NA, ncuts, 2)
roc.matrix[ncuts, 1] <- 0
roc.matrix[ncuts, 2] <- 1
```

```
for (i in 1:(ncuts - 1)) {
  Limit <- c(0,cut.values[i],pt,12)
  Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
           upperLimit=c(Limit[3],Limit[4]))
  Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
            upperLimit=c(Limit[3],Limit[4]))
  Se <- Se1$integral/Se2$integral

  Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
            upperLimit = c(Limit[4],Limit[2]))
  Sp2 <-adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
          upperLimit = c(Limit[4], Limit[4]))
  Sp <- Sp1$integral/Sp2$integral

   roc.matrix[i, 1] <- Se
   roc.matrix[i, 2] <- Sp
    }

##Calculation of Area under the ROC curve  for each time point
sensitivity = roc.matrix[, 1]
specificity = roc.matrix[, 2]
x <- 1 - c(0,specificity)
y <- c(1,sensitivity)
n <- length(x)
dx <- x[-n] - x[-1]
mid.y <- (y[-n] + y[-1])/2
area <- sum(dx * mid.y)
list(cut.values = c(-Inf, cut.values), TP = y, FP = x,
predict.time = pt,AUC = area)
}

##Parameter estimation
load("observations.dat")
ftx <- function(t,x,param.t,param.x)
{param.x*param.t*x*exp(-(param.t*x*t+param.x*x))}
#Define the survival function
st <- function(t,x,param.t,param.x)
{param.x*exp(-(param.t*x*t+param.x*x))}

LL <- function(param.t,param.x) {
          #param.x = log (param.x)
```

```
  R
=(ftx(data[,1],data[,2],param.t,param.x)^(data[,3]))*(st(data[,1],data[,2],param.t,pa
ram.x)^(1-data[,3]))
   -sum(log(R))}

library(stats4)
LH<- mle(LL, start = list(param.t = 1, param.x=1), method = "L-BFGS-B", lower
= c(0.5, 0.5), upper = c(Inf, Inf))

Parameters<-matrix(LH@coef,1,2)
save( Parameters, file="resultsParameterLH.dat" )

##Second link
library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
  force(a)
  force(b)
  function(x){a(x)*b(x)}
}
#Second link
Para11cens<- function(marker,time,status,param.t2,param.t3,pt){
ft <- function (t){(1/mean(time))*exp(-(1/mean(time))*t)}
gx <- function (x){(1/mean(marker))*exp(-(1/mean(marker))*x[2])}
ftx<-function(x){(param.t2+param.t3*x[2])*
exp(-(param.t2+param.t3*x[2])*x[1])}
IG <- Multiply(ftx,gx)
ooo <- order(time)
t <- time[ooo]
x <- marker[ooo]
d<- status[ooo]

data<- cbind(x,t,d)
censored=ifelse(data[,2]<=pt&data[,3]==0,1,0)
data<-cbind(data,censored)
data <- subset(data,censored==0)
library(cubature)
cut.values <- unique(x)
cut.values <- cut.values[order(cut.values)]
ncuts <- length(cut.values)
roc.matrix <- matrix(NA, ncuts, 2)
```

```
roc.matrix[ncuts, 1] <- 0
 roc.matrix[ncuts, 2] <- 1

for (i in 1:(ncuts - 1)) {

Limit <- c(0,cut.values[i],pt,12)
Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
          upperLimit=c(Limit[3],Limit[4]))
Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
          upperLimit=c(Limit[3],Limit[4]))
Se <- Se1$integral/Se2$integral

Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
          upperLimit = c(Limit[4],Limit[2]))
Sp2 <-adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
          upperLimit = c(Limit[4], Limit[4]))
Sp <- Sp1$integral/Sp2$integral

roc.matrix[i, 1] <- Se
roc.matrix[i, 2] <- Sp}

##Calculation of Area under the ROC curve  for each time point
sensitivity = roc.matrix[, 1]
specificity = roc.matrix[, 2]
x <- 1 - c(0,specificity)
y <- c(1,sensitivity)
n <- length(x)
dx <- x[-n] - x[-1]
mid.y <- (y[-n] + y[-1])/2
area <- sum(dx * mid.y)
list(cut.values = c(-Inf, cut.values), TP = y, FP = x,
predict.time = pt,AUC = area)}

##Parameter estimation
load("observations.dat")
ftx <- function(t,x,param.t1,param.t2,param.x)
{param.x*(param.t1+param.t2*x)*exp(-((param.t1+param.t2*x)*t+param.x*x))}
#Define the survival function
st <- function(t,x,param.t1,param.t2,param.x)
{param.x*exp(-((param.t1+param.t2*x)*t+param.x*x))}
LL <- function(param.t1,param.t2,param.x) {
  #param.x = log (param.x)
```

```
  R =(ftx(data[,1],data[,2],param.t1,param.t2,param.x)^(data[,3]))*
    (st(data[,1],data[,2],param.t1,param.t2,param.x)^(1-data[,3]))
  print(c(param.t1,param.t2,param.x))
  -sum(log(R))}

library(stats4)
LH<-mle(LL, start = list(param.t1 = 1, param.t2=1, param.x=1), method = "L-
BFGS-B", lower = c(0.1, 0.1,0.1),upper = c(Inf, Inf, Inf))

Parameters<-matrix(LH@coef,1,3)
save( Parameters, file="resultsParameterLH.dat" )
```

Appendix A.5 Exponential/Normal- censored outcome

```
##First link

library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
  force(a)
  force(b)
  function(x){a(x)*b(x)}
}

Para2cens <- function(marker,time,status,param.t2,pt){
ft <- function (t){(1/mean(time))*exp(-(1/mean(time))*t)}
gx <- function (x){(1/(sd(marker)*(sqrt(2*pi))))*(exp(-((x[2]-
mean(marker))^2))/(2*sd(marker)^2))}
ftx<-function(x){param.t2*x[2]*exp(-param.t2*x[2]*x[1])}



IG <- Multiply(ftx,gx)
ooo <- order(time)
t <- time[ooo]
x <- marker[ooo]
d<- status[ooo]

data<- cbind(x,t,d)
censored=ifelse(data[,2]<=pt&data[,3]==0,1,0)
data<-cbind(data,censored)
data <- subset(data,censored==0)
```

```
cut.values <- unique(x)
cut.values <- cut.values[order(cut.values)]
ncuts <- length(cut.values)

roc.matrix <- matrix(NA, ncuts, 2)
roc.matrix[ncuts, 1] <- 0
roc.matrix[ncuts, 2] <- 1

for (i in 1:(ncuts - 1)) {
  Limit <- c(0,cut.values[i],pt,15)
  Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
            upperLimit=c(Limit[3],Limit[4]))
  Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
            upperLimit=c(Limit[3],Limit[4]))
  Se <- Se1$integral/Se2$integral
  Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
            upperLimit = c(Limit[4],Limit[2]))
  Sp2 <-adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
           upperLimit = c(Limit[4], Limit[4]))
  Sp <- Sp1$integral/Sp2$integral

  roc.matrix[i, 1] <- Se
  roc.matrix[i, 2] <- Sp
  }

##Calculation of Area under the ROC curve  for each time point
sensitivity = roc.matrix[, 1]
specificity = roc.matrix[, 2]
x <- 1 - c(0,specificity)
y <- c(1,sensitivity)
n <- length(x)
dx <- x[-n] - x[-1]
mid.y <- (y[-n] + y[-1])/2
area <- sum(dx * mid.y)
list(cut.values = c(-Inf, cut.values), TP = y, FP = x, predict.time = pt,AUC = area)
}

##Parameter estimation
load("observations.dat")
ftx <- function(t,x,param.t,param.x1,param.x2)
```

```
{param.t*x/(param.x2*sqrt(2*pi))*exp(-(x-param.x1)^2/(2*(param.x2)^2)-
param.t*x*t)}

#Define the survival function
st <- function(t,x,param.t,param.x1,param.x2)
{exp(-(x-param.x1)^2/(2*(param.x2)^2)-param.t*x*t)/(param.x2*sqrt(2*pi))}



LL <- function(param.t,param.x1,param.x2) {
R =(ftx(data[,1],data[,2],param.t,param.x1,param.x2)^(data[,3]))*
 (st(data[,1],data[,2],param.t,param.x1,param.x2)^(1-data[,3]))
-sum(log(R))}

library(stats4)
LH<-mle(LL, start = list(param.t = 1, param.x1=1, param.x2=0.25),
method = "L-BFGS-B", lower = c(0.1,0.1,0.1),upper = c(Inf, Inf,Inf))

Parameters<-matrix(LH@coef,1,3)
save( Parameters, file="resultsParameterLH.dat" )

##Second link
library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
  force(a)
  force(b)
  function(x){a(x)*b(x)}}

Para22cens<- function(marker,time,status,param.t2,param.t3,pt){
ft <- function (t){(1/mean(time))*exp(-(1/mean(time))*t)}
gx <- function (x){1/(sd(marker)*sqrt(2*pi))*exp(-(x[2]-
mean(marker))^2)/2*(sd(marker)^2)}
ftx<- function(x){(param.t2+param.t3*x[2])*
exp(-(param.t2+param.t3*x[2])*x[1])}
predict.time <- pt



IG <- Multiply(ftx,gx)
ooo <- order(time)
t <- time[ooo]
x <- marker[ooo]
```

```
d<- status[ooo]

data<- cbind(x,t,d)
censored=ifelse(data[,2]<=pt&data[,3]==0,1,0)
data<-cbind(data,censored)
data <- subset(data,censored==0)

library(cubature)
cut.values <- unique(x)
cut.values <- cut.values[order(cut.values)]
ncuts <- length(cut.values)
roc.matrix <- matrix(NA, ncuts, 2)
 roc.matrix[ncuts, 1] <- 0
 roc.matrix[ncuts, 2] <- 1

for (i in 1:(ncuts - 1)) {
Limit <- c(0,cut.values[i],pt,15)
 Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
          upperLimit=c(Limit[3],Limit[4]))
Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
          upperLimit=c(Limit[3],Limit[4]))
Se <- Se1$integral/Se2$integral
Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
          upperLimit = c(Limit[4],Limit[2]))
Sp2 <-adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
          upperLimit = c(Limit[4], Limit[4]))
Sp <- Sp1$integral/Sp2$integral

roc.matrix[i, 1] <- Se
roc.matrix[i, 2] <- Sp}

##Calculation of Area under the ROC curve  for each time point
sensitivity = roc.matrix[, 1]
specificity = roc.matrix[, 2]
x <- 1 - c(0,specificity)
y <- c(1,sensitivity)
n <- length(x)
dx <- x[-n] - x[-1]
mid.y <- (y[-n] + y[-1])/2
area <- sum(dx * mid.y)
list(cut.values = c(-Inf, cut.values), TP = y, FP = x,
predict.time = pt,AUC = area)}
```

```
##Parameter estimation
#Define the joint pdf
ftx <- function(t,x,param.t1,param.t2,param.x1,param.x2)
{(param.t1+param.t2*x)/(param.x2*sqrt(2*pi))*exp(-(x-
param.x1)^2/(2*(param.x2)^2)-(param.t1+param.t2*x)*t)}

#Define the survival function
st <- function(t,x,param.t1,param.t2,param.x1,param.x2)
{exp(-(x-param.x1)^2/(2*(param.x2)^2)-
(param.t1+param.t2*x)*t)/(param.x2*sqrt(2*pi))}



load("observations.dat")
LL <- function(param.t1,param.t2,param.x1,param.x2) {
  R =(ftx(data[,1],data[,2],param.t1,param.t2,param.x1,param.x2)^(data[,3]))*
    (st(data[,1],data[,2],param.t1,param.t2,param.x1,param.x2)^(1-data[,3]))
  print(c(param.t1,param.t2,param.x1,param.x2,R))
  -sum(log(R))}

library(stats4)
LH<-mle(LL, start = list(param.t1 = 0.1, param.t2=0.1, param.x1=1,
param.x2=0.25),  method = "L-BFGS-B", lower = c(0.1,0.1,0.1,0.1),
 upper = c(Inf, Inf,Inf,Inf))

Parameters<-matrix(LH@coef,1,4)
save( Parameters, file="resultsParameterLH.dat" )
```

Appendix A.6 Weibull/Normal- censored outcome

```
##First link
library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
  force(a)
  force(b)
  function(x){a(x)*b(x)}
}
```

```
#weibull/normal
Para3cens<- function(marker,time,status,param.t3,predt){
  ft <- function (t){sqrt(1/mean(time))*2*(sqrt(1/mean(marker))*t)^(2-1)*exp(-
sqrt(1/mean(marker))*t)^2}
  gx <- function (x){(1/(sd(marker)*(sqrt(2*pi))))*(exp(-((x[2]-
mean(marker))^2))/(2*sd(marker)^2))}
  ftx <- function(x){ (param.t3*x[2]*2)*((param.t3*x[2]*x[1])^(2-1))*
      exp(-(param.t3*x[2]*x[1])^2)}


  IG <- Multiply(ftx,gx)
  ooo <- order(time)
  t <- time[ooo]
  x <- marker[ooo]
  d<- status[ooo]


  data<- cbind(x,t,d)
  censored=ifelse(data[,2]<=predt&data[,3]==0,1,0)
  data<-cbind(data,censored)
  data <- subset(data,censored==0)

  library(cubature)

  cut.values <- unique(x)
  cut.values <- cut.values[order(cut.values)]
  ncuts <- length(cut.values)

  roc.matrix <- matrix(NA, ncuts, 2)
  roc.matrix[ncuts, 1] <- 0
  roc.matrix[ncuts, 2] <- 1

  for (i in 1:(ncuts - 1)) {
    Limit <- c(0,cut.values[i],predt,15)
    Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
                          upperLimit=c(Limit[3],Limit[4]))
    Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
                          upperLimit=c(Limit[3],Limit[4]))
    Se <- Se1$integral/Se2$integral
    Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
                          upperLimit = c(Limit[4],Limit[2]))
```

```
   Sp2 <-adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
                    upperLimit = c(Limit[4], Limit[4]))
   Sp <- Sp1$integral/Sp2$integral

   roc.matrix[i, 1] <- Se
   roc.matrix[i, 2] <- Sp
  }

  ##Calculation of Area under the ROC curve  for each time point
  sensitivity = roc.matrix[, 1]
  specificity = roc.matrix[, 2]
  x <- 1 - c(0,specificity)
  y <- c(1,sensitivity)
  n <- length(x)
  dx <- x[-n] - x[-1]
  mid.y <- (y[-n] + y[-1])/2
  area <- sum(dx * mid.y)
  list(cut.values = c(-Inf, cut.values), TP = y, FP = x,
      predict.time = predt,AUC = area)}

##Parameter estimation
load("observations.dat")
#Define the joint pdf
ftx <- function(t,x,param.t1,param.t2,param.x1,param.x2)
{param.t1*x*param.t2*(param.t1*x*t)^(param.t2-1)*
exp(-(x-param.x1)^2/2*param.x2^2-(param.t1*x*t)^param.t2)/
(param.x2*sqrt(2*pi))}

#Define the survival function
st <- function(t,x,param.t1,param.t2,param.x1,param.x2)
{(exp(-(param.t1*x*t)^param.t2-
(x-param.x1)^2/2*param.x2^2))/(param.x2*sqrt(2*pi))}



LL <- function(param.t1,param.t2,param.x1,param.x2) {
R =(ftx(data[,1],data[,2],param.t1,param.t2,param.x1,param.x2)^(data[,3]))*
 (st(data[,1],data[,2],param.t1,param.t2,param.x1,param.x2)^(1-data[,3]))
-sum(log(R))}

library(stats4)
LH<-   mle(LL, start = list(param.t1 = 0.1, param.t2=1,param.x1=1,
param.x2=0.5), method = "L-BFGS-B", lower = c(0.1,1,1,1),
```

```
upper = c(Inf, Inf,Inf,Inf))

Parameters<-matrix(LH@coef,1,5)
save( Parameters, file="resultsParameterLH.dat" )

##Second link
library(cubature)

##Multiplication of two functions
Multiply=function(a,b){
  force(a)
  force(b)
  function(x){a(x)*b(x)}}

Para33cens <- function(marker,time,status,param.t3,param.t4,predt)
{ft <- function (t){sqrt(1/mean(time))*2*(sqrt(1/mean(time))*t)^(2-1)*exp(-
sqrt(1/mean(time))*t)^2}
  gx <- function (x){1/(sd(marker)*sqrt(2*pi))*exp(-(x[2]-
mean(marker))^2)/2*(sd(marker)^2)}
  ftx <- function(x){ ((param.t3+param.t4*x[2])*2)*
 (((param.t3+param.t4*x[2])*x[1])^(2-1))*
exp(-((param.t3+param.t4*x[2])*x[1])^2)}


  IG <- Multiply(ftx,gx)
  ooo <- order(time)
  t <- time[ooo]
  x <- marker[ooo]
  d<- status[ooo]

  data<- cbind(x,t,d)
  censored=ifelse(data[,2]<=predt&data[,3]==0,1,0)
  data<-cbind(data,censored)
  data <- subset(data,censored==0)

  library(cubature)

  cut.values <- unique(x)
  cut.values <- cut.values[order(cut.values)]
  ncuts <- length(cut.values)

  roc.matrix <- matrix(NA, ncuts, 2)
```

```
  roc.matrix[ncuts, 1] <- 0
  roc.matrix[ncuts, 2] <- 1

  for (i in 1:(ncuts - 1)) {
  Limit <- c(0,cut.values[i],predt,100)
  Se1 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[2]),
  upperLimit=c(Limit[3],Limit[4]))
  Se2 <- adaptIntegrate(IG,lowerLimit=c(Limit[1],Limit[1]),
  upperLimit=c(Limit[3],Limit[4]))
  Se <- Se1$integral/Se2$integral
  Sp1 <- adaptIntegrate(IG, lowerLimit = c(Limit[3],Limit[1]),
  upperLimit = c(Limit[4],Limit[2]))
  Sp2 <-adaptIntegrate(IG,  lowerLimit = c(Limit[3],Limit[1]),
  upperLimit = c(Limit[4], Limit[4]))
  Sp <- Sp1$integral/Sp2$integral

 roc.matrix[i, 1] <- Se
 roc.matrix[i, 2] <- Sp
   }

  ##Calculation of Area under the ROC curve  for each time point
  sensitivity = roc.matrix[,1]
  specificity = roc.matrix[,2]
  x <- 1 - c(0,specificity)
  y <- c(1,sensitivity)
  n <- length(x)
  dx <- x[-n] - x[-1]
  mid.y <- (y[-n] + y[-1])/2
  area <- sum(dx * mid.y)
  list(cut.values = c(-Inf, cut.values), TP = y, FP = x,
  predict.time = predt,AUC = area)
}

##Parameter estimation

#Define the joint pdf
ftx <- function(t,x,param.t1,param.t2,param.x1,param.x2)
{param.t1*x*param.t2*(param.t1*x*t)^(param.t2-1)*
exp(-(x-param.x1)^2/2*param.x2^2-(param.t1*x*t)^param.t2)/
(param.x2*sqrt(2*pi))}

#Define the survival function
```

```
st <- function(t,x,param.t1,param.t2,param.x1,param.x2)
{(exp(-(param.t1*x*t)^param.t2-
(x-param.x1)^2/2*param.x2^2))/(param.x2*sqrt(2*pi))}
LL <- function(param.t1,param.t2,param.x1,param.x2) {
R =(ftx(data[,1],data[,2],param.t1,param.t2,param.x1,param.x2)^(data[,3]))*
 (st(data[,1],data[,2],param.t1,param.t2,param.x1,param.x2)^(1-data[,3]))
 -sum(log(R))}
library(stats4)
LH<-   mle(LL, start = list(param.t1 = 0.1, param.t2=1,param.x1=1,
param.x2=0.5), method = "L-BFGS-B", lower = c(0.1,1,1,1), upper = c(Inf,
Inf,Inf,Inf))

Parameters<-matrix(LH@coef,1,5)
save( Parameters, file="resultsParameterLH.dat" )
```

Appendix B R code for proposed joint function

```
##############################################################################
#This is simdat2 function that has been edited  from the simdat function.


simdat2 <- function(n, model, sepassoc, ntms, ran, b1, b2, gamma, sigu,
                vare, theta0, theta1, censoring, censlam, truncation,
                trunctime, gridstep) {

  ctsx <- rnorm(n)
  binx <- rbinom(n, 1, 0.5)
  X2 <- cbind(ctsx, binx)
  id <- 1:n
  idl <- rep(id, each = ntms)
  ctsxl <- rep(ctsx, each = ntms)
  binxl <- rep(binx, each = ntms)
  time <- rep(0:(ntms-1), length = n*ntms)
  X1 <- cbind(intercept = 1, ctsxl, binxl, ltime = time)
  U <- MASS::mvrnorm(n, mu = rep(0, ran), Sigma = sigu)
  Ul <- U[rep(1:n, each = ntms), ]
  D <- getD(ran, time)
  DU <- t(D) * Ul
  Y1 <- (X1 %*% b1) + rowSums(DU) + sqrt(vare) * rnorm(n*ntms)
  Y2 <- (X1 %*% b1) + rowSums(DU)
  u0 <- U[, 1]
  if (model == "intslope") {
    u1 <- U[, 2]
  } else {
    u1 <- rep(0, n)
  }
  b2x <- X2 %*% b2
  #b2x <- matrix(0,nrow=n)
  cens <- rep(1, n)
  if (!sepassoc) {
    gamma <- rep(gamma[1], ran)
  }
  if (model != "quad") {
    if (model == "int") {
      gamma <- c(gamma[1], 0)
    }
    uu <- runif(n)
    if (model == "int") {
      survtime <- -log(uu) / exp(theta0 + b2x + gamma[1]*u0)
    } else {
      ii <- ((theta1 + gamma[2]*u1) < 0) & (uu < exp(exp(theta0 + b2x + gamma[1]*u0) /
                                          (theta1 + gamma[2]*u1)))
      survtime <- rep(0, n)
      survtime[ii] <- Inf
      survtime[!ii] <- log(1 - (theta1 + gamma[2]*u1[!ii]) * log(uu[!ii]) /
                         exp(theta0 + b2x[!ii] + gamma[1]*u0[!ii])) / (theta1 +
gamma[2]*u1[!ii])
    }
```

```
  } else {
    tau <- trunctime
    tgrid <- seq(runif(1, 0, gridstep), tau, gridstep)
    lam0 <- exp(theta0 + theta1 * tgrid)
    hazt <- gridstep * exp(b2x) %*% lam0
    gD2 <- gamma * getD(ran, tgrid)
    hmat <- exp(U %*% gD2) * hazt
    uu <- matrix(runif(length(hmat)), n, length(tgrid))
    tmat <- matrix(tgrid, n, length(tgrid), byrow = TRUE)
    tmat[hmat < uu] <- tau
    survtime <- apply(tmat, 1, min)
    cens[survtime == tau] <- 0
  }

  if (censoring) {
    censtime <- -log(runif(n)) / censlam
  } else {
    censtime <- rep(Inf, n)
  }
  if (model != "quad") {
    if (truncation) {
      censtime <- pmin(censtime, trunctime)
    }
  }
  ii <- (censtime < survtime)
  survtime[ii] <- censtime[ii]
  cens[ii] <- 0
  ls <- rep(survtime, each = ntms)
  Y1 <- Y1[ls > time]
  Y2 <- Y2[ls > time]
  X1 <- X1[ls > time, ]
  idl <- idl[ls > time]
  time <- time[ls > time]
  cat(paste0(round(100 * sum(cens) / n, 1), "% experienced event\n"))

  list(longdat = data.frame(id = idl, Y1, Y2, time, X1),
       survdat = data.frame(id, survtime, cens, X2),
            c=round(100 * sum(cens) / n, 1))

}


##############################################################################
#
##simjoint

simjoint2<-function(n = 500, model = c("intslope", "int", "quad"), sepassoc = FALSE,
    ntms = 5, b1 = c(1, 0, 0, -1), b2 = c(1, 1), gamma = c(1,
        0.1), sigu, vare = 0.01, theta0 = -3, theta1 = 1, censoring = TRUE,
    censlam = exp(-3), truncation = FALSE, trunctime = max(ntms),
    gridstep = 0.01)
{
    model <- match.arg(model)
```

```
  if (model != "intslope" && model != "int" && model != "quad") {
    stop(paste("Unknown model:", model))
  }
  ran <- 2
  if (model == "int") {
    ran <- 1
  }
  else if (model == "quad") {
    ran <- 3
  }
  lat <- ran
  if (!sepassoc) {
    lat <- 1
  }
  if (length(gamma) != lat) {
    warning("Number of association parameters do not match model choice\n")
  }
  gamma <- rep(gamma, length = ran)
  if (missing(sigu)) {
    sigu <- diag(ran)
  }
  if (length(sigu) != ran^2) {
    warning("Dimension of covariance matrix does not match chosen model\n")
    if (length(sigu) > ran^2) {
      sigu <- sigu[1:ran, 1:ran]
    }
    else {
      sigu <- diag(ran) * sigu[1]
    }
  }
  if (model == "int") {
    if (sigu < 0) {
      stop("Variance must be positive")
    }
  }
  else {
    if (!isSymmetric(sigu)) {
      stop("Covariance matrix is not symmetric")
    }
    if (any(eigen(sigu)$values < 0) || (det(sigu) <= 0)) {
      stop("Covariance matrix must be positive semi-definite")
    }
  }
  sim <- simdat2(n, model, sepassoc, ntms, ran, b1, b2, gamma,
    sigu, vare, theta0, theta1, censoring, censlam, truncation,
    trunctime, gridstep)
  list(longitudinal = sim$longdat, survival = sim$survdat,c=sim$c)
}

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

##edit the predefined longst function in joineR (longst2)
```

```
longst2<-function (longdat, long.formula, model, longdat2)
{
   if (model == "int") {
      rf <- as.formula(paste("~1", colnames(longdat)[1], sep = "|"))
   }else if (model == "intslope") {
      rf <- as.formula(paste(paste0("~", colnames(longdat)[3]),
         colnames(longdat)[1], sep = "|"))
   }else if (model == "baseline") {
      rf <- as.formula(paste(paste0("~", colnames(longdat)[3]),
         colnames(longdat)[1], sep = "|"))
   }else {
      tsq <- paste0(paste0("I(", paste(colnames(longdat)[3],
         "^2", sep = "")), ")")
      rf <- as.formula(paste(paste0("~", paste(colnames(longdat)[3],
         tsq, sep = "+")), colnames(longdat)[1], sep = "|"))
   }
   long.start <- nlme::lme(long.formula, random = rf, method = "ML",
      data = data.frame(longdat2), na.action = na.omit, control = lmeControl(maxIter =
100,
         msMaxIter = 100, opt = "optim"))
   q <- dim(nlme::VarCorr(long.start))[1] - 1
   sigma.u <- as.matrix(nlme::getVarCov(long.start))
   rownames(sigma.u) <- paste("U_", 0:(q - 1), sep = "")
   colnames(sigma.u) <- paste("U_", 0:(q - 1), sep = "")
   if (model == "intslope") {
      corr <- as.numeric(nlme::VarCorr(long.start)[2, 3])
   }else if (model == "baseline"){
           corr <- as.numeric(nlme::VarCorr(long.start)[2, 3])
   }else if (model == "int") {
      corr <- NA
   }else if (model == "quad") {
      corr <- as.numeric(nlme::VarCorr(long.start)[2:3, 3])
   }
   sigma.z <- long.start$sigma^2
   ll <- long.start$logLik
   b1 <- nlme::fixef(long.start)
   list(b1 = data.frame(b1), sigma.z = sigma.z, sigma.u = sigma.u,
      corr = corr, log.like = ll)
}
##############################################################################
#
####emUpdate##
emUpdate.b <- function(longdat, survdat, model, ran, lat, sepassoc,
                paraests, gpt, max.it, tol, loglik, verbose) {

  id <- longdat[, 1]
  Y <- longdat[, 2]
  tt <- longdat[, 3]
  X1 <- as.matrix(longdat[, 4:dim(longdat)[2]])
  n <- length(survdat[, 2])
  s <- survdat[, 2]
  cen <- survdat[, 3]
  p1 <- dim(longdat)[2] - 3
```

```
p2 <- dim(survdat)[2] - 3
X2 <- 0
if (p2 > 0) {
  X2 <- as.matrix(survdat[, 4:dim(survdat)[2]])
} else {
  b2x <- matrix(0, n, 1)
}
b1 <- paraests$b1[, 1]
sigma.u <- paraests$sigma.u
tsigu <- t(sigma.u)
sigma.z <- paraests$sigma.z
if (loglik) {
  b2 <- paraests$b2[, 1]
} else {
  b2 <- c(paraests$b2, rep(0, lat))
}
haz <- paraests$haz
sf <- paraests$sf
rs <- paraests$rs
nev <- paraests$nev
nn <- diff(match(unique(id), id))
nn <- c(nn, length(id) - sum(nn))
N <- sum(nn)
g <- statmod::gauss.quad.prob(gpt, "normal", sigma = sqrt(0.5))
ab <- g$nodes
w <- g$weights * sqrt(pi)
gmat <- matrix(0, gpt^ran, ran)
gmat[, 1] <- rep(ab, each = gpt^(ran - 1))
if (model != "int") {
  gmat[, 2] <- rep(ab, gpt)
  w <- as.vector(w %x% w)
}
if (model == "quad") {
  gmat[, 3] <- rep(ab, each = gpt)
  w <- as.vector(w %x% g$weights * sqrt(pi))
}
EU <- matrix(0, n, ran)
EUU <- matrix(0, n, sum(1:ran))
EexpU <- matrix(0, n, length(haz))
EUexpU <- matrix(0, n, ran)
EUUexpU <- matrix(0, n, sum(1:ran))
r <- Y - X1 %*% b1
Dtt <- getD(ran, tt)
Dtt2 <- t(Dtt)
if (model != "int") {
  Dttc <- t(getD(sum(1:ran) - ran, tt)) * tt
}
Ds <- getD(ran, s)
Dst <- t(Ds)
Dsf <- getD(ran, sf)
Dsf2 <- Dsf^2
Dsfc <- t(t(Dsf) * sf)
Dnsf <- matrix(1, ran, length(sf))
```

```
s1 <- rep(1:(ran - 1), (ran - 1):1)
s2 <- sequence((ran - 1):1) + rep(1:(ran - 1), (ran - 1):1)
cnn <- c(0, cumsum(nn))
Inn <- diag(max(nn))
conv <- FALSE
if (loglik) {
  l1 <- 0
  l2 <- 0
}

# main loop over EM iterations begins here
for (it in 1:max.it) {

  if (p2 > 0) {
    b2x <- X2 %*% b2[1:p2]
  }
  eb2x <- exp(b2x)
  sigma.zi <- sigma.z * Inn
  cov <- sigma.u %*% Dtt
  tcov <- Dtt2 %*% sigma.u
  DH <- Dnsf * rep(haz, each = ran)

  # main loop over subjects begins here
  for (i in 1:n) {

    rv <- r[(cnn[i] + 1):cnn[i + 1]]
    ttv <- Dtt2[(cnn[i] + 1):cnn[i + 1], ]
    W21 <- cov[, (cnn[i] + 1):cnn[i + 1]]
    W12 <- tcov[(cnn[i] + 1):cnn[i + 1], ]
    if (model == "int") {
      W11 <- tcrossprod(ttv, W21) + sigma.zi[1:nn[i], 1:nn[i]]
    } else {
      W11 <- ttv %*% W21 + sigma.zi[1:nn[i], 1:nn[i]]
    }
    if (nn[i] == 1) {
      W3 <- W12 / as.vector(W11)
      if (model == "int") {
        cvch <- sqrt((sigma.u - tcrossprod(W21, W3)) * 2)
      } else {
        cvch <- chol((sigma.u - tcrossprod(W21, W3)) * 2)
      }
      cm <- matrix(W3 * rv, gpt^ran, ran, byrow = TRUE)
    } else {
      W3 <- solve(W11, W12)
      if (model == "int") {
        cvch <- sqrt((sigma.u - W21 %*% W3) * 2)
      } else {
        cvch <- chol((sigma.u - W21 %*% W3) * 2)
      }
      cm <- matrix(rv %*% W3, gpt^ran, ran, byrow = TRUE)
    }
    newu <- gmat %*% cvch + cm
    newu2 <- newu^2
```

```
  if (model != "int") {
    newu2 <- cbind(newu2, newu[, s1] * newu[, s2])
  }
  egDUs <- 1
  if (cen[i] == 1) {
    egDUs <- exp(newu %*% (Dst[i, ] * b2[(p2 + 1):(p2 + lat)]) +
                 b2x[i, ]) * haz[rs[i]]

  }
  egDUsf <- exp(newu %*% (Dsf[, 1:rs[i]] * b2[(p2 + 1):(p2 + lat)]))
  ess <- exp(-(eb2x[i, ] * egDUsf) %*% haz[1:rs[i]])
  f <- egDUs * ess * w
  den <- sum(f)


  EU[i, 1:ran] <- f[, 1] %*% newu / den
  EUU[i, 1:sum(1:ran)] <- f[, 1] %*% newu2 / den
  C <- egDUsf[, 1:rs[i]]
  EexpU[i, 1:rs[i]] <- f[, 1] %*% C / den
  if (model == "int") {
    EUexpU[i, 1] <- sum(f[, 1] %*% (newu[, 1] * C) * haz[1:rs[i]]) / den
    EUUexpU[i, 1] <- sum(f[, 1] %*% (newu[, 1]^2 * C) * haz[1:rs[i]]) / den
  } else {
    EUexpU[i, 1:ran] <- rowSums(crossprod(newu * f[, 1], C) *
                                Dsf[, 1:rs[i]] * DH[, 1:rs[i]]) / den
    EUUexpU[i, 1:ran] <- rowSums(crossprod(newu2[, 1:ran] * f[, 1], C) *
                                 Dsf2[, 1:rs[i]] * DH[, 1:rs[i]]) / den
    if (model == "intslope" ){
      EUUexpU[i, ran + 1] <- 2 * sum(f[, 1] %*% (newu2[, ran + 1] * C) *
                                     haz[1:rs[i]] * sf[1:rs[i]]) / den
    } else if( model == "baseline"){
            EUUexpU[i, ran + 1] <- 2 * sum(f[, 1] %*% (newu2[, ran + 1] * C) *
                                     haz[1:rs[i]] * sf[1:rs[i]]) / den

          }else {
      EUUexpU[i, (ran + 1):sum(1:ran)] <- 2 *
        rowSums(crossprod(newu2[, (ran + 1):sum(1:ran)] * f[, 1], C) *
                  Dsfc[, 1:rs[i]] * DH[, 1:rs[i]]) / den
    }
  }

  # calculate the log-likelihood
  if (loglik) {
    if (den > 0) {
      l2 <- l2 + log(den)
    }
    l1 <- l1 - nn[i] * 0.5 * log(2 * pi) - 0.5 * log(det(W11)) -
      0.5 * sum(rv * solve(W11, rv))
  }

} # end loop over subjects

parac <- data.frame(c(b1,  b2, sigma.z, sigma.u))
```

```
    EexpUi <- colSums(t(EexpU) * haz)
    haz <- nev / colSums(EexpU * eb2x[, 1])
    EUmat <- apply(EU, 2, rep, nn)
    EUUmat <- apply(EUU, 2, rep, nn)
    Ut <- rowSums(EUmat * Dtt2)
    UUt <- rowSums(EUUmat[, 1:ran] * Dtt2^2)
    UUt2 <- 0
    if (model != "int") {
      UUt2 <- rowSums(EUUmat[, (ran + 1):sum(1:ran)] * Dttc)
    }
    b1 <- solve(crossprod(X1), crossprod(X1, Y - Ut))
    r <- Y - X1 %*% b1
    sigma.z <- sum(r^2 - 2 * r * Ut + UUt + 2 * UUt2) / N
    diag(sigma.u) <- colMeans(EUU)[1:ran]
    if (model != "int") {
      sigma.u[lower.tri(sigma.u)] <- colMeans(EUU)[-(1:ran)]
      sigma.u[upper.tri(sigma.u)] <- t(sigma.u)[upper.tri(sigma.u)]
    }
    fd <- vector("numeric", p2 + ran)
    sd <- matrix(0, p2 + ran, p2 + ran)
    fd[(p2 + 1):(p2 + ran)] <- colSums(cen * (EU * t(Ds))) -
      colSums(eb2x[, 1] * EUexpU)
    if (model != "int") {
      inds1 <- (p2 + 1):(p2 + ran)
      inds2 <- upper.tri(sd[(p2 + 1):(p2 + ran), inds1])
      sd[inds1, inds1][inds2] <- -colSums(eb2x[, 1] * 0.5 * EUUexpU)[(ran +
1):sum(1:ran)]
    }
    if (p2 > 0) {
      fd[1:p2] <- c(colSums((cen * X2) - (X2 * eb2x[, 1] * EexpUi)))
      sd[(1:p2), (p2 + 1):(p2 + ran)] <- -t(X2) %*% (eb2x[, 1] * EUexpU)
      sd <- sd + t(sd)
      for (i in 1:p2) {
        for (j in 1:p2) {
          sd[i, j] <- -(sum(X2[, i] * X2[, j] * eb2x[, 1] * EexpUi))
        }
      }
    }
    if (model == "int") {
      sd[(p2 + 1), (p2 + 1)] <- -colSums(eb2x[, 1] * EUUexpU)[1:ran]
    } else {
      diag(sd[(p2 + 1):(p2 + ran), (p2 + 1):(p2 + ran)]) <-
        -colSums(eb2x[, 1] * EUUexpU)[1:ran]
    }
    if (!sepassoc) {
      if (model == "int") {
        fd <- fd
        sd <- sd
      } else {
        fd[p2 + 1] <- sum(fd[(p2 + 1):(p2 + ran)])
        fd <- fd[1:(p2 + 1)]
        if (p2 > 1) {
          sd[1:p2, p2 + 1] <- rowSums(sd[(1:p2), (p2 + 1):(p2 + ran)])
```

```
      } else {
        sd[1:p2, p2 + 1] <- sum(sd[(1:p2), (p2 + 1):(p2 + ran)])
      }
      sd[p2 + 1, 1:p2] <- sd[1:p2, p2 + 1]
      sd[p2 + 1, p2 + 1] <- sum(sd[(p2 + 1):(p2 + ran), (p2 + 1):(p2 + ran)])
      sd <- sd[1:(p2 + 1), 1:(p2 + 1)]
    }
  }

if (model=="baseline"){
          fd <- fd[-length(fd)]
          sd <- sd[-nrow(sd),-ncol(sd)]
          b2 <- b2[-length(b2)]
          b2 <- b2 - solve(sd, fd)
          b2<-c(b2,0)
          } else{b2 <- b2 - solve(sd, fd)}

  para <- data.frame(c(b1,  b2, sigma.z, sigma.u))
  if (verbose) {
    print(paste("Iter:", it))
    print(as.numeric(c(b1, b2, sigma.z, sigma.u)))
  }
  dd <- abs(parac - para)

  if (max(dd) < tol) {
    conv <- TRUE
    break
  }

 }

 if ((conv != TRUE) & !loglik) {
  print("Not converged ")
 }

 if (loglik) {
  ll <- l1 + l2 - 0.5 * ran * n * log(pi)
  list("log.like" = ll,
       "longlog.like" = l1,
       "survlog.like" = ll - l1)
 } else {
  list("b1" = data.frame(b1),
       "b2" = data.frame(b2),
       "sigma.z" = sigma.z,
       "sigma.u" = sigma.u,
       "haz" = haz,
       "random" = EU,
       "conv" = conv,
       "iters" = it)
 }

}
```

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

joint.b <- function (data, long.formula, surv.formula, model = c("intslope",
   "int", "quad", "baseline"), sepassoc = FALSE, longsep = FALSE, survsep = FALSE,
   gpt, lgpt, max.it, tol, verbose = FALSE)
{
   if (!inherits(data, "jointdata")) {
      stop("Data must be of class 'jointdata'\n")
   }
   id <- data$subj.col
   time.long <- data$time.col
   if (missing(gpt)) {
      gpt <- 3
   }
   if (missing(lgpt)) {
      lgpt <- 10
   }
   if (missing(max.it)) {
      max.it <- 200
   }
   if (missing(tol)) {
      tol <- 0.001
   }
   Call <- match.call()
   if (any(sapply(data$baseline, "class") == "factor")) {
      data$baseline <- droplevels(data$baseline)
   }
   ldatList <- joineR:::prepLongData(long.formula, data, id, time.long)
   longdat <- ldatList$longdat
   long.data <- ldatList$long.data
   sdatList <- joineR:::prepSurvData(surv.formula, data, id, time.long)
   survdat <- sdatList$survdat
   survdat2 <- sdatList$survdat2
   p2 <- sdatList$p2
   compRisk <- sdatList$compRisk
   sort.dat <- function(longdat, survdat) {
      longid <- longdat[, 1]
      nn <- diff(match(unique(longid), longid))
      nn[length(nn) + 1] <- length(longid) - sum(nn)
      svec <- rep(survdat[, 2], nn)
      sort.long <- longdat[order(svec), ]
      os <- order(survdat[, 2])
      sort.surv <- survdat[os, ]
      list(long.s = data.frame(sort.long), surv.s = data.frame(sort.surv))
   }
   sort <- sort.dat(longdat, survdat)
   longdat <- sort$long.s
   survdat <- sort$surv.s
   model <- match.arg(model)
   if ((model == "int" || model == "quad" || model == "baseline") && compRisk) {
      warning("Competing risks models are only fitted with model = 'intslope'")
      model <- "intslope"
```

```
    }
    if (model != "intslope" && model != "int" && model != "quad" && model !=
"baseline") {
        stop(paste("Unknown model:", model))
    }
    ran <- 2
    if (model == "int") {
        ran <- 1
    }
    if (model == "quad") {
        ran <- 3
    }
    lat <- ran
    if (sepassoc && compRisk) {
        warning("Competing risks models are only fitted with sepassoc = FALSE")
        sepassoc <- FALSE
    }
    if (!sepassoc) {
        lat <- 1
    }

    ldaests <- longst2(longdat, long.formula, model, long.data)
    if (!compRisk) {
        survests <- joineR:::survst(survdat, surv.formula, survdat2)
        paraests <- c(ldaests, survests)
    }else {
        survests.a <- joineR:::survstCR(survdat, surv.formula, survdat2,
            event = 1)
        survests.b <- joineR:::survstCR(survdat, surv.formula, survdat2,
            event = 2)
        paraests <- c(ldaests, survests.a, survests.b)
    }
    if (!compRisk) {
        sep.ll <- ldaests$log.like + survests$log.like[2]
        sep.loglik <- list(seplhood = sep.ll, sepy = ldaests$log.like,
            sepn = survests$log.like[2])
    }else {
        sep.ll <- ldaests$log.like + survests.a$log.like[2] +
            survests.b$log.like[2]
        sep.loglik <- list(seplhood = sep.ll, sepy = ldaests$log.like,
            sepn = survests.a$log.like[2] + survests.b$log.like[2])
    }
    if (!compRisk) {
        jointfit <- emUpdate.b(longdat = longdat, survdat = survdat,
            model = model, ran = ran, lat = lat, sepassoc = sepassoc,
            paraests = paraests, gpt = gpt, max.it = max.it,
            tol = tol, loglik = FALSE, verbose = verbose)
    }else {
        jointfit <- joineR:::emUpdateCR(longdat = longdat, survdat = survdat,
            paraests = paraests, gpt = gpt, max.it = max.it,
            tol = tol, loglik = FALSE, verbose = verbose)
    }
    b1 <- jointfit$b1
```

```
    rownames(b1) <- rownames(paraests$b1)
    random <- jointfit$random
    colnames(random) <- paste0("U_", 0:(ran - 1))
    rownames(random) <- survdat[, 1]
    sigma.u <- jointfit$sigma.u
    rownames(sigma.u) <- colnames(sigma.u) <- rownames(ldaests$sigma.u)
    if (!compRisk) {
        hazard <- jointfit$haz
        likeests <- c(jointfit, list(rs = survests$rs, sf = survests$sf))
        if (p2 > 0) {
            b2 <- jointfit$b2[1:p2, ]
            names(b2) <- names(paraests$b2)
        }else {
            b2 <- NULL
        }
        fixed <- list(longitudinal = b1, survival = b2)
        latent <- jointfit$b2[(p2 + 1):(p2 + lat), ]
        names(latent) <- paste0("gamma_", 0:(lat - 1))
    }else {
        hazard <- list(haz.a = jointfit$haz.a, haz.b = jointfit$haz.b)
        likeests <- c(jointfit, list(s.dist.a = survests.a$s.dist.a,
            id.a = survests.a$id.a, s.dist.b = survests.b$s.dist.b,
            id.b = survests.b$id.b))
        if (p2 > 0) {
            b2.a <- jointfit$b2.a[1:p2, ]
            b2.b <- jointfit$b2.b[1:p2, ]
            names(b2.a) <- names(b2.b) <- names(paraests$b2.a[1:p2])
        }else {
            b2.a <- b2.b <- NULL
        }
        fixed <- list(longitudinal = b1, survival1 = b2.a, survival2 = b2.b)
        latent <- with(jointfit, c(b2.a[(p2 + 1), ], b2.b[(p2 +
            1), ]))
        names(latent) <- paste0("gamma_", 1:2)
    }
    coefficients <- list(fixed = fixed, random = random, latent = latent)
    if (!compRisk) {
        jointll <- emUpdate.b(longdat = longdat, survdat = survdat,
            model = model, ran = ran, lat = lat, sepassoc = sepassoc,
            paraests = likeests, gpt = lgpt, max.it = 1, tol = tol,
            loglik = TRUE, verbose = FALSE)
    }else {
        jointll <- joineR:::emUpdateCR(longdat = longdat, survdat = survdat,
            paraests = likeests, gpt = lgpt, max.it = 1, tol = tol,
            loglik = TRUE, verbose = FALSE)
    }
    loglik <- list(jointlhood = jointll$log.like, jointy = jointll$longlog.like,
        jointn = jointll$survlog.like)
    if (!compRisk) {
        sepests <- list(longests = sep(ldaests, longsep), survests = sep(survests,
            survsep))
    }else {
        sepests <- list(longests = sep(ldaests, longsep), survests1 = sep(survests.a,
```

```
        survsep), survests2 = sep(survests.b, survsep))
    }
    results <- list(coefficients = coefficients, sigma.z = jointfit$sigma.z,
        sigma.u = sigma.u, hazard = hazard, loglik = loglik,
        numIter = jointfit$iters, convergence = jointfit$conv,
        model = model, sepassoc = sepassoc, sepests = sepests,
        compRisk = compRisk, sep.loglik = sep.loglik, formulae = list(lformula =
long.formula,
            sformula = surv.formula), data = data, call = Call)
    class(results) <- "joint"
    return(results)
}
```

Appendix C Additional simulation results for measurement error approach

Table C. 1: Association parameter for varying measurement error with 50% censoring

True association parameter	Proposed joint model					Cox regression model with the observed biomarker					Cox regression model with estimated random intercept term from LME model				
	$\widehat{\gamma}_t$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 0.25$															
0	-0.0025	0.0713	0.0051	-0.0025	94.2	-0.0018	0.0605	0.0037	-0.0018	95.0	-0.0025	0.0713	0.0051	-0.0025	94.2
0.25	0.2483	0.0677	0.0046	-0.0017	94.6	0.1969	0.0551	0.0059	-0.0531	84.2	0.2473	0.0668	0.0045	-0.0027	94.8
0.50	0.4963	0.0736	0.0054	-0.0037	94.8	0.3869	0.0575	0.0161	-0.1131	50.2	0.4876	0.0699	0.0050	-0.0124	94.6
0.75	0.7414	0.0840	0.0071	-0.0086	95.4	0.5634	0.0624	0.0387	-0.1866	16.4	0.7136	0.0755	0.0070	-0.0364	90.2
1	0.9838	0.0989	0.0100	-0.0162	95.2	0.7243	0.0705	0.0810	-0.2757	3.2	0.9231	0.0835	0.0129	-0.0769	83.6
Measurement error $\sigma_e^2 = 0.5$															
0	-0.0027	0.0738	0.0054	-0.0027	94.6	-0.0015	0.0550	0.0030	-0.0015	94.6	-0.0026	0.0732	0.0054	-0.0026	94.6
0.25	0.2477	0.0718	0.0052	-0.0023	94.8	0.1628	0.0499	0.0101	-0.0872	56.2	0.2440	0.0696	0.0049	-0.0060	94.6
0.50	0.4941	0.0806	0.0065	-0.0059	95.2	0.3156	0.0521	0.0367	-0.1844	6.4	0.4759	0.0733	0.0060	-0.0241	93.6
0.75	0.7362	0.0952	0.0093	-0.0138	93.4	0.4518	0.0564	0.0921	-0.2982	0.0	0.6859	0.0795	0.0104	-0.0641	85.4
1	0.9736	0.1136	0.0136	-0.0264	94.6	0.5705	0.0631	0.1884	-0.4295	0.0	0.8723	0.0871	0.0239	-0.1277	67.6
Measurement error $\sigma_e^2 = 1.0$															
0	-0.0028	0.0773	0.0060	-0.0028	94.4	-0.0011	0.0472	0.0022	-0.0011	95.0	-0.0027	0.0754	0.0057	-0.0027	94.4

True association parameter	Proposed joint model					Cox regression model with the observed biomarker					Cox regression model with estimated random intercept term from LME model				
	$\widehat{\gamma}_t$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov
0.25	0.2466	0.0788	0.0062	-0.0034	95.4	0.1208	0.0431	0.0185	-0.1292	15.8	0.2374	0.0737	0.0056	-0.0126	93.4
0.50	0.4911	0.0920	0.0085	-0.0089	95.2	0.2307	0.0449	0.0745	-0.2693	0.0	0.4565	0.0788	0.0081	-0.0435	90.8
0.75	0.7300	0.1137	0.0133	-0.0200	95.2	0.3240	0.0480	0.1837	-0.4260	0.0	0.6465	0.0866	0.0182	-0.1035	77.8
1	0.9614	0.1400	0.0211	-0.0386	95.4	0.4023	0.0530	0.3601	-0.5977	0.0	0.8067	0.0938	0.0462	-0.1933	43.6
Measurement error $\sigma_e^2 = 1.5$															
0	-0.0028	0.0802	0.0064	-0.0028	94.2	-0.0008	0.0420	0.0018	-0.0008	94.8	-0.0027	0.0768	0.0059	-0.0027	94.6
0.25	0.2459	0.0847	0.0072	-0.0041	94.4	0.0960	0.0386	0.0252	-0.1540	2.0	0.2316	0.0768	0.0062	-0.0184	93.0
0.50	0.4890	0.1014	0.0104	-0.0110	95.2	0.1817	0.0401	0.1029	-0.3183	0.0	0.4413	0.0832	0.0104	-0.0587	88.8
0.75	0.7264	0.1289	0.0172	-0.0236	94.4	0.2527	0.0425	0.2491	-0.4973	0.0	0.6186	0.0929	0.0259	-0.1314	69.6
1	0.9514	0.1594	0.0278	-0.0486	94.0	0.3117	0.0463	0.4759	-0.6883	0.0	0.7634	0.1002	0.0660	-0.2366	32.8
Measurement error $\sigma_e^2 = 2.0$															
0	-0.0028	0.0827	0.0068	-0.0028	95.0	-0.0007	0.0381	0.0015	-0.0007	94.8	-0.0026	0.0779	0.0061	-0.0026	94.4
0.25	0.2453	0.0895	0.0080	-0.0047	94.4	0.0797	0.0353	0.0303	-0.1703	0.2	0.2267	0.0794	0.0068	-0.0233	92.4
0.50	0.4864	0.1088	0.0120	-0.0136	95.2	0.1499	0.0365	0.1239	-0.3501	0.0	0.4289	0.0870	0.0126	-0.0711	86.4
0.75	0.7291	0.1485	0.0225	-0.0209	95.4	0.2115	0.0380	0.2914	-0.5385	0.0	0.6036	0.1042	0.0323	-0.1464	70.2
1	0.9567	0.1876	0.0371	-0.0433	94.0	0.2572	0.0397	0.5533	-0.7428	0.0	0.7421	0.1156	0.0799	-0.2579	33.0

True association parameter	Proposed joint model					Cox regression model with the observed biomarker					Cox regression model with estimated random intercept term from LME model				
	$\widehat{\gamma}_t$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 2.5$															
0	-0.0028	0.0850	0.0072	-0.0028	94.6	-0.0006	0.0352	0.0012	-0.0006	94.2	-0.0025	0.0791	0.0063	-0.0025	94.8
0.25	0.2448	0.0935	0.0088	-0.0052	94.6	0.0680	0.0328	0.0342	-0.1820	0.0	0.2226	0.0816	0.0074	-0.0274	92.6
0.50	0.4839	0.1153	0.0136	-0.0161	94.8	0.1276	0.0338	0.1399	-0.3724	0.0	0.4187	0.0907	0.0149	-0.0813	84.4
0.75	0.7200	0.1484	0.0229	-0.0300	94.8	0.1780	0.0358	0.3285	-0.5720	0.0	0.5820	0.1028	0.0388	-0.1680	60.8
1	0.9331	0.1882	0.0399	-0.0669	94.6	0.2137	0.0368	0.6196	-0.7863	0.0	0.7095	0.1199	0.0988	-0.2905	27.6

Table C. 2: Association parameter for varying measurement error with 70% censoring

True association parameter	Proposed joint model					Cox regression model with the observed biomarker					Cox regression model with estimated random intercept term from LME model				
	$\widehat{\gamma}_t$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 0.25$															
0	-0.0040	0.0850	0.0072	-0.0040	95.2	-0.0028	0.0714	0.0051	-0.0028	94.4	-0.0040	0.0852	0.0073	-0.0040	95.2
0.25	0.2477	0.0986	0.0097	-0.0023	94.4	0.2014	0.0814	0.0090	-0.0486	91.4	0.2472	0.0977	0.0095	-0.0028	95.0
0.50	0.4944	0.1027	0.0106	-0.0056	95.6	0.3920	0.0808	0.0182	-0.1080	72.6	0.4884	0.0990	0.0099	-0.0116	95.4
0.75	0.7408	0.1119	0.0126	-0.0092	94.4	0.5754	0.0846	0.0376	-0.1746	41.8	0.7201	0.1035	0.0116	-0.0299	93.8
1	0.9837	0.1195	0.0145	-0.0163	94.2	0.7491	0.0844	0.0701	-0.2509	16.6	0.9382	0.1051	0.0149	-0.0618	90.6

True association parameter	Proposed joint model					Cox regression model with the observed biomarker					Cox regression model with estimated random intercept term from LME model				
	$\widehat{\gamma}_t$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 0.5$															
0	-0.0036	0.0893	0.0080	-0.0036	95.2	-0.0019	0.0657	0.0043	-0.0019	94.8	-0.0036	0.0884	0.0078	-0.0036	95.4
0.25	0.2458	0.1047	0.0110	-0.0042	94.4	0.1669	0.0739	0.0124	-0.0831	80.8	0.2418	0.1016	0.0104	-0.0082	94.0
0.50	0.4914	0.1129	0.0128	-0.0086	95.8	0.3226	0.0739	0.0369	-0.1774	32.8	0.4753	0.1044	0.0115	-0.0247	94.0
0.75	0.7349	0.1255	0.0160	-0.0151	94.8	0.4655	0.0768	0.0868	-0.2845	4.6	0.6913	0.1084	0.0152	-0.0587	92.0
1	0.9730	0.1384	0.0199	-0.0270	94.0	0.5987	0.0754	0.1667	-0.4013	0.2	0.8886	0.1103	0.0246	-0.1114	82.8
Measurement error $\sigma_e^2 = 1.0$															
0	0.0061	0.1047	0.0110	0.0061	92.8	0.0012	0.0612	0.0037	0.0012	94.0	0.0057	0.1008	0.0102	0.0057	93.0
0.25	0.2430	0.1138	0.0130	-0.0070	94.4	0.1244	0.0636	0.0198	-0.1256	48.8	0.2322	0.1065	0.0117	-0.0178	93.4
0.50	0.4857	0.1276	0.0165	-0.0143	95.2	0.2384	0.0637	0.0725	-0.2616	2.2	0.4523	0.1105	0.0145	-0.0477	92.4
0.75	0.7247	0.1428	0.0210	-0.0253	95.2	0.3394	0.0625	0.1725	-0.4106	0.0	0.6501	0.1130	0.0228	-0.0999	86.6
1	0.9563	0.1685	0.0303	-0.0437	94.0	0.4286	0.0638	0.3306	-0.5714	0.0	0.8200	0.1196	0.0467	-0.1800	67.4
Measurement error $\sigma_e^2 = 1.5$															
0	0.0066	0.1108	0.0123	0.0066	93.2	0.0009	0.0549	0.0030	0.0009	94.4	0.0060	0.1043	0.0109	0.0060	94.2
0.25	0.2410	0.1212	0.0148	-0.0090	95.0	0.0992	0.0566	0.0260	-0.1508	24.6	0.2246	0.1100	0.0128	-0.0254	93.2
0.50	0.4807	0.1428	0.0208	-0.0193	95.2	0.1866	0.0598	0.1018	-0.3134	0.0	0.4336	0.1188	0.0185	-0.0664	91.8

True association parameter	Proposed joint model					Cox regression model with the observed biomarker					Cox regression model with estimated random intercept term from LME model				
	$\widehat{\gamma}_t$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov	$\widehat{\alpha}$	SE	MSE	Bias	Cov
0.75	0.7149	0.1669	0.0741	-0.0351	94.6	0.2631	0.0547	0.2401	-0.4869	0.0	0.6148	0.1259	0.0341	-0.1352	79.8
1	0.9316	0.2011	0.0451	-0.0684	88.6	0.3309	0.0595	0.4513	-0.6691	0.0	0.7650	0.1259	0.0711	-0.2350	51.2
Measurement error $\sigma_e^2 = 2.0$															
0	0.0018	0.1148	0.0132	0.0018	95.6	0.0004	0.0489	0.0024	0.0004	95.4	0.0016	0.1067	0.0114	0.0016	96.4
0.25	0.2380	0.1231	0.0153	-0.0120	94.8	0.0810	0.0500	0.0311	-0.1690	8.4	0.2176	0.1096	0.0131	-0.0324	94.2
0.50	0.4787	0.1434	0.0210	-0.0213	94.2	0.1567	0.0493	0.1203	-0.3433	0.0	0.4219	0.1148	0.0193	-0.0781	90.8
0.75	0.7122	0.1808	0.0341	-0.0378	95.0	0.2198	0.0505	0.2837	-0.5302	0.0	0.5983	0.1296	0.0398	-0.1517	77.4
1	0.9270	0.2231	0.0551	-0.0730	95.6	0.2701	0.0535	0.5357	-0.7299	0.0	0.7397	0.1429	0.0882	-0.2603	50.4
Measurement error $\sigma_e^2 = 2.5$															
0	-0.0047	0.1197	0.0143	-0.0047	95.6	-0.0021	0.0468	0.0022	-0.0021	94.0	-0.0046	0.1086	0.0118	-0.0046	96.4
0.25	0.2360	0.1235	0.0154	-0.0140	95.2	0.0703	0.0450	0.0343	-0.1797	1.6	0.2129	0.1059	0.0126	-0.0371	94.2
0.50	0.4726	0.1531	0.0242	-0.0274	94.6	0.1314	0.0473	0.1381	-0.3686	0.0	0.4094	0.1236	0.0235	-0.0906	90.0
0.75	0.7020	0.1945	0.0401	-0.0480	95.4	0.1847	0.0489	0.3219	-0.5653	0.0	0.5778	0.1416	0.0497	-0.1722	77.2
1	0.9162	0.2332	0.0614	-0.0838	93.2	0.2315	0.0462	0.5928	-0.7685	0.0	0.7094	0.1465	0.1059	-0.2906	46.4

Table C. 3: C-Index for varying measurement error with 50% censoring

γ	True C-Index (SE)	Proposed measurement error adjusted estimator $(\widehat{U}_0)_{adj}$					Observed biomarker x_0					LME model random intercept term estimator $(\widehat{U}_0)_{lme}$				
		C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 0.25$																
0	0.5149 (0.0115)	0.5146	0.0114	0.0001	-0.0003	94.8	0.5150	0.0116	0.0001	0.0001	95.8	0.5146	0.0114	0.0001	-0.0003	94.8
0.25	0.5694 (0.0176)	0.5641	0.0172	0.0003	-0.0053	93.6	0.5614	0.0170	0.0004	-0.0080	91.4	0.5639	0.0170	0.0003	-0.0055	93.2
0.50	0.6352 (0.0173)	0.6247	0.0176	0.0004	-0.0105	91.2	0.6181	0.0170	0.0006	-0.0171	82.2	0.6231	0.0170	0.0004	-0.0121	88.4
0.75	0.6930 (0.0169)	0.6776	0.0179	0.0006	-0.0154	85.6	0.6659	0.0172	0.0010	-0.0271	62.6	0.6732	0.0170	0.0007	-0.0198	78.8
1	0.7412 (0.0169)	0.7215	0.0187	0.0007	-0.0197	81.6	0.7044	0.0183	0.0017	-0.0368	48.4	0.7136	0.0176	0.0011	-0.0276	65.8
Measurement error $\sigma_e^2 = 0.5$																
0	0.5149 (0.0115)	0.5143	0.0114	0.0001	-0.0006	95.2	0.5150	0.0115	0.0001	0.0001	95.0	0.5142	0.0113	0.0001	-0.0007	95.2
0.25	0.5694 (0.0176)	0.5612	0.0174	0.0004	-0.0082	920	0.5557	0.0169	0.0005	-0.0137	87.2	0.5603	0.0169	0.0004	-0.0091	90.8
0.50	0.6352 (0.0173)	0.6191	0.0182	0.0006	-0.0161	85.0	0.6061	0.0170	0.0011	-0.0291	59.0	0.6152	0.0170	0.0007	-0.0200	78.0
0.75	0.6930 (0.0169)	0.6697	0.0190	0.0009	-0.0233	77.2	0.6478	0.0174	0.0023	-0.0452	28.0	0.6605	0.0172	0.0013	-0.0325	52.8
1	0.7412 (0.0169)	0.7118	0.0200	0.0013	-0.0294	68.4	0.6809	0.0188	0.0040	-0.0603	10.8	0.6962	0.0177	0.0023	-0.0450	28.0

γ	True C-Index (SE)	Proposed measurement error adjusted estimator $(\widehat{U}_0)_{adj}$					Observed biomarker x_0					LME model random intercept term estimator $(\widehat{U}_0)_{lme}$				
		C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 1.0$																
0	0.5149 (0.0115)	0.5140	0.0113	0.0001	-0.0009	96.0	0.5149	0.0114	0.0001	0.0000	95.4	0.5137	0.0109	0.0001	-0.0012	96.0
0.25	0.5694 (0.0176)	0.5574	0.0178	0.0005	-0.0120	89.6	0.5479	0.0169	0.0008	-0.0215	75.6	0.5552	0.0167	0.0005	-0.0142	86.2
0.50	0.6352 (0.0173)	0.6120	0.0192	0.0009	-0.0232	76.8	0.5902	0.0171	0.0023	-0.0450	26.8	0.6043	0.0169	0.0012	-0.0309	55.0
0.75	0.6930 (0.0169)	0.6598	0.0207	0.0015	-0.0332	63.0	0.6244	0.0176	0.0050	-0.0686	3.4	0.6434	0.0172	0.0028	-0.0496	19.0
1	0.7412 (0.0169)	0.6999	0.0223	0.0022	-0.0413	53.4	0.6514	0.0191	0.0084	-0.0898	0.4	0.6730	0.0178	0.0050	-0.0682	3.6
Measurement error $\sigma_e^2 = 1.5$																
0	0.5149 (0.0115)	0.5139	0.0112	0.0001	-0.0010	96.2	0.5148	0.0113	0.0001	-0.0001	95.4	0.5134	0.0106	0.0001	-0.0015	96.4
0.25	0.5694 (0.0176)	0.5549	0.0181	0.0005	-0.0145	87.6	0.5426	0.0170	0.0010	-0.0268	64.8	0.5515	0.0165	0.0006	-0.0179	81.0
0.50	0.6352 (0.0173)	0.6071	0.0199	0.0012	-0.0281	70.4	0.5798	0.0172	0.0034	-0.0554	10.6	0.5966	0.0167	0.0018	-0.0386	38.0
0.75	0.6930 (0.0169)	0.6532	0.0221	0.0021	-0.0398	55.4	0.6094	0.0177	0.0073	-0.0836	0.4	0.6315	0.0172	0.0041	-0.0615	3.8
1	0.7412 (0.0169)	0.6918	0.0240	0.0030	-0.0494	44.0	0.6330	0.0191	0.0121	-0.1082	0.0	0.6571	0.0177	0.0074	-0.0841	0.4
Measurement error $\sigma_e^2 = 2.0$																
0	0.5149 (0.0115)	0.5138	0.0112	0.0001	-0.0011	96.2	0.5147	0.0113	0.0001	-0.0002	95.2	0.5131	0.0104	0.0001	-0.0018	97.0

γ	True C-Index (SE)	Proposed measurement error adjusted estimator $(\widehat{U}_0)_{adj}$					Observed biomarker x_0					LME model random intercept term estimator $(\widehat{U}_0)_{lme}$				
		C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov
0.25	0.5694 (0.0176)	0.5529	0.0183	0.0006	-0.0165	85.2	0.5387	0.0170	0.0012	-0.0307	54.2	0.5486	0.0163	0.0007	-0.0208	75.6
0.50	0.6352 (0.0173)	0.6032	0.0204	0.0014	-0.0320	64.0	0.5723	0.0173	0.0043	-0.0629	5.6	0.5905	0.0166	0.0023	-0.0447	24.6
0.75	0.6938 (0.0164)	0.6486	0.0231	0.0026	-0.0452	49.4	0.6008	0.0176	0.0090	-0.0930	0.0	0.6232	0.0174	0.0053	-0.0706	2.4
1	0.7412 (0.0156)	0.6864	0.0253	0.0036	-0.0548	40.0	0.6209	0.0179	0.0148	-0.1203	0.0	0.6461	0.0181	0.0094	-0.0951	0.0
Measurement error $\sigma_e^2 = 2.5$																
0	0.5149 (0.0115)	0.5137	0.0112	0.0001	-0.0012	96.4	0.5146	0.0114	0.0001	-0.0003	95.4	0.5129	0.0102	0.0001	-0.0020	96.8
0.25	0.5694 (0.0176)	0.5512	0.0184	0.0007	-0.0182	83.6	0.5358	0.0169	0.0014	-0.0336	46.0	0.5463	0.0161	0.0008	-0.0231	72.2
0.50	0.6352 (0.0173)	0.5999	0.0209	0.0017	-0.0353	2.8	0.5666	0.0173	0.0050	-0.0686	0.2	0.5856	0.0165	0.0027	-0.0496	0.0
0.75	0.6937 (0.0167)	0.6447	0.0244	0.0030	-0.0490	46.6	0.5918	0.0182	0.0107	-0.1019	0.0	0.6163	0.0181	0.0063	-0.0774	1.0
1	0.7412 (0.0158)	0.6798	0.0266	0.0045	-0.0614	34.8	0.6092	0.0180	0.0178	-0.1320	0.0	0.6357	0.0175	0.0114	-0.1055	0.0

Table C. 4: C-Index for varying measurement error with 70% censoring

Association parameter	True C-Index (SE)	Proposed measurement error adjusted estimator $(\widehat{U}_0)_{adj}$					Observed biomarker x_0					LME model random intercept term estimator $(\widehat{U}_0)_{lme}$				
		C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 0.25$																
0	0.5180 (0.0138)	0.5173	0.0136	0.0002	-0.0007	96.0	0.5176	0.0138	0.0002	-0.0004	95.4	0.5174	0.0136	0.0002	-0.0006	96.0
0.25	0.5075 (0.0245)	0.5640	0.0246	0.0006	-0.0065	93.0	0.5628	0.0245	0.0007	-0.0077	93.0	0.5639	0.0245	0.0006	-0.0066	93.2
0.50	0.6351 (0.0229)	0.6239	0.0240	0.0007	-0.0112	92.0	0.6194	0.0236	0.0008	-0.0157	89.6	0.6229	0.0235	0.0007	-0.0122	91.0
0.75	0.6937 (0.0221)	0.6768	0.0234	0.0008	-0.0169	89.2	0.6690	0.0229	0.0011	-0.0247	83.2	0.6740	0.0227	0.0009	-0.0197	87.0
1	0.7419 (0.0190)	0.7206	0.0206	0.0009	-0.0213	82.6	0.7099	0.0201	0.0014	-0.0320	65.4	0.7157	0.0199	0.0011	-0.0262	74.6
Measurement error $\sigma_e^2 = 0.5$																
0	0.5180 (0.0138)	0.5173	0.0136	0.0002	-0.0007	95.6	0.5178	0.0138	0.0002	-0.0002	94.8	0.5172	0.0134	0.0002	-0.0008	95.8
0.25	0.5075 (0.0245)	0.5609	0.0248	0.0007	-0.0096	91.8	0.5573	0.0243	0.0008	-0.0132	91.0	0.5599	0.0242	0.0007	-0.0106	91.8
0.50	0.6351 (0.0229)	0.6180	0.0248	0.0009	-0.0171	89.0	0.6082	0.0239	0.0013	-0.0269	78.4	0.6147	0.0235	0.0010	-0.0204	85.4
0.75	0.6937 (0.0221)	0.6684	0.0247	0.0013	-0.0253	83.4	0.6519	0.0234	0.0023	-0.0418	56.4	0.6608	0.0228	0.0016	-0.0329	74.0
1	0.7419 (0.0190)	0.7103	0.0222	0.0015	-0.0316	72.6	0.6882	0.0209	0.0033	-0.0537	27.4	0.6983	0.0202	0.0023	-0.0436	44.2

Association parameter	True C-Index (SE)	Proposed measurement error adjusted estimator $(\widehat{U}_0)_{\text{adj}}$					Observed biomarker x_0					LME model random intercept term estimator $(\widehat{U}_0)_{\text{lme}}$				
		C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov
Measurement error $\sigma_e^2 = 1.0$																
0	0.5186 (0.0145)	0.5187	0.0155	0.0002	0.0001	94.6	0.5187	0.0154	0.0002	0.0001	95.0	0.5181	0.0148	0.0002	-0.0005	95.2
0.25	0.5075 (0.0245)	0.5568	0.0251	0.0008	-0.0137	90.6	0.5499	0.0236	0.0010	-0.0206	86.0	0.5542	0.0237	0.0008	-0.0163	89.0
0.50	0.6351 (0.0229)	0.6100	0.0259	0.0013	-0.0251	84.0	0.5930	0.0241	0.0024	-0.0421	59.4	0.6028	0.0233	0.0016	-0.0323	96.0
0.75	0.6934	0.6574	0.0251	0.0019	-0.0360	70.6	0.6299	0.0229	0.0046	-0.0635	22.6	0.6432	0.0218	0.0030	-0.0502	34.8
1	0.7419 (0.0190)	0.6969	0.0248	0.0026	-0.0450	56.8	0.6598	0.0217	0.0072	-0.0821	3.8	0.6740	0.0205	0.0050	-0.0679	8.2
Measurement error $\sigma_e^2 = 1.5$																
0	0.5186 (0.0145)	0.5188	0.0157	0.0002	0.0002	94.0	0.5189	0.0153	0.0002	0.0003	95.0	0.5178	0.0146	0.0002	-0.0008	95.4
0.25	0.5075 (0.0245)	0.5540	0.0254	0.0009	-0.0165	89.6	0.5451	0.0228	0.0012	-0.0254	78.0	0.5503	0.0233	0.0010	-0.0202	86.0
0.50	0.6364 (0.0253)	0.6044	0.0284	0.0018	-0.0320	81.0	0.5823	0.0260	0.0036	-0.0541	45.4	0.5943	0.0245	0.0024	-0.0421	60.4
0.75	0.6922 (0.0210)	0.6489	0.0271	0.0026	-0.0433	64.8	0.6136	0.0224	0.0067	-0.0786	6.8	0.6295	0.0223	0.0044	-0.0627	20.8
1	0.7424 (0.0194)	0.6866	0.0279	0.0039	-0.0558	44.4	0.6398	0.0232	0.0111	-0.1026	1.0	0.6569	0.0214	0.0078	-0.0855	3.0
Measurement error $\sigma_e^2 = 2.0$																
0	0.5199 (0.0157)	0.5194	0.0150	0.0002	-0.0005	95.6	0.5187	0.0146	0.0002	-0.0012	95.5	0.5181	0.0138	0.0002	-0.0018	96.4

Association parameter	True C-Index (SE)	Proposed measurement error adjusted estimator $(\widehat{U}_0)_{adj}$					Observed biomarker x_0					LME model random intercept term estimator $(\widehat{U}_0)_{lme}$				
		C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov	C-Index	SE	MSE	Bias	Cov
0.25	0.5693 (0.0245)	0.5511	0.0242	0.0010	-0.0194	86.4	0.5405	0.0223	0.0014	-0.0300	72.2	0.5467	0.0216	0.0010	-0.0238	78.8
0.50	0.6347 (0.0218)	0.5997	0.0253	0.0019	-0.0350	68.2	0.5755	0.0233	0.0041	-0.0592	24.8	0.5879	0.0211	0.0026	-0.0468	35.2
0.75	0.6935 (0.0207)	0.6435	0.0280	0.0033	-0.0500	55.4	0.6045	0.0234	0.0085	-0.0890	3.4	0.6213	0.0218	0.0057	-0.0722	9.6
1	0.7419 (0.0205)	0.6799	0.0310	0.0048	-0.0620	47.4	0.6270	0.0241	0.0138	-0.1149	0.0	0.6448	0.0230	0.0100	-0.0971	1.2
Measurement error $\sigma_e^2 = 2.5$																
0	0.5194 (0.0146)	0.5193	0.0148	0.0002	-0.0006	96.8	0.5199	0.0143	0.0002	0.0000	94.2	0.5178	0.0134	0.0002	-0.0021	97.4
0.25	0.5686 (0.0225)	0.5488	0.0233	0.0010	-0.0217	87.0	0.5380	0.0216	0.0015	-0.0325	66.6	0.5440	0.0203	0.0011	-0.0265	75.8
0.50	0.6354 (0.0234)	0.5955	0.0270	0.0023	-0.0399	69.4	0.5686	0.0241	0.0050	-0.0668	20.4	0.5823	0.0220	0.0033	-0.0531	32.0
0.75	0.6937 (0.0221)	0.6375	0.0296	0.0040	-0.0562	52.8	0.5953	0.0244	0.0103	-0.0984	1.8	0.6128	0.0225	0.0071	-0.0809	5.2
1	0.7409 (0.0203)	0.6735	0.0316	0.0055	-0.0674	40.2	0.6176	0.0219	0.0157	-0.1233	0.0	0.6343	0.0224	0.0119	-0.1066	0.4

Table C. 5: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0 and 50% censoring

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.5138 (0.0104)	0.5134 (0.0107)	0.0001	-0.0005	94.6	0.5094 (0.0743)	0.5095 (0.0076)	0.5133 (0.0102)	0.0001	-0.0005	95.6	0.5095 (0.0073)	0.5094 (0.0073)
2	0.5138 (0.0103)	0.5134 (0.0107)	0.0001	-0.0004	95.0	0.5094 (0.0079)	0.5096 (0.0075)	0.5133 (0.0102)	0.0001	-0.0005	95.6	0.5094 (0.0073)	0.5095 (0.0074)
3	0.5137 (0.0103)	0.5133 (0.0105)	0.0001	-0.0004	95.2	0.5094 (0.0088)	0.5094 (0.0077)	0.5133 (0.0102)	0.0001	-0.0004	95.6	0.5094 (0.0087)	0.5094 (0.0074)
4	0.5126 (0.0097)	0.5123 (0.0102)	0.0001	-0.0003	95.0	0.4936 (0.0298)	0.5242 (0.0264)	0.5121 (0.0098)	0.0001	-0.0004	94.6	0.4935 (0.0297)	0.5241 (0.0263)
Measurement error $\sigma_e^2 = 0.5$													
1	0.5140 (0.0103)	0.5136 (0.0105)	0.0001	-0.0004	95.4	0.5097 (0.0742)	0.5096 (0.0074)	0.5134 (0.0100)	0.0001	-0.0006	95.6	0.5095 (0.0071)	0.5095 (0.0072)
2	0.5130 (0.0102)	0.5136 (0.0104)	0.0001	-0.0004	95.4	0.5096 (0.0075)	0.5096 (0.0075)	0.5134 (0.0100)	0.0001	-0.0006	95.6	0.5094 (0.0073)	0.5095 (0.0073)
3	0.5139 (0.0102)	0.5135 (0.0103)	0.0001	-0.0004	95.6	0.5094 (0.0083)	0.5097 (0.0080)	0.5133 (0.0100)	0.0001	-0.0006	95.6	0.5092 (0.0084)	0.5098 (0.0075)
4	0.5128 (0.0098)	0.5125 (0.0098)	0.0001	-0.0003	95.4	0.4936 (0.0299)	0.5245 (0.0264)	0.5122 (0.0097)	0.0001	-0.0006	94.6	0.4933 (0.0299)	0.5244 (0.0263)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 1.0$													
1	0.5140 (0.0103)	0.5137 (0.0103)	0.0001	-0.0003	95.0	0.5097 (0.0742)	0.5097 (0.0074)	0.5134 (0.0099)	0.0001	-0.0006	95.4	0.5094 (0.0070)	0.5096 (0.0071)
2	0.5130 (0.0102)	0.5138 (0.0105)	0.0001	-0.0002	95.4	0.5098 (0.0077)	0.5096 (0.0076)	0.5134 (0.0100)	0.0001	-0.0006	95.8	0.5094 (0.0072)	0.5095 (0.0071)
3	0.5139 (0.0102)	0.5136 (0.0103)	0.0001	-0.0003	95.4	0.5093 (0.0082)	0.5100 (0.0079)	0.5133 (0.0098)	0.0001	-0.0006	96.2	0.5093 (0.0082)	0.5096 (0.0073)
4	0.5128 (0.0098)	0.5125 (0.0102)	0.0001	-0.0002	94.6	0.4937 (0.0297)	0.5245 (0.0264)	0.5121 (0.0095)	0.0001	-0.0006	95.8	0.4932 (0.0298)	0.5244 (0.0263)
Measurement error $\sigma_e^2 = 1.5$													
1	0.5144 (0.0105)	0.5138 (0.0108)	0.0001	-0.0006	95.0	0.5098 (0.0755)	0.5097 (0.0077)	0.5141 (0.0100)	0.0001	-0.0003	96.0	0.5099 (0.0071)	0.5100 (0.0071)
2	0.5143 (0.0104)	0.5139 (0.0109)	0.0001	-0.0004	95.6	0.5097 (0.0080)	0.5100 (0.0077)	0.5140 (0.0099)	0.0001	-0.0003	95.4	0.5098 (0.0071)	0.5101 (0.0073)
3	0.5142 (0.0103)	0.5138 (0.0106)	0.0001	-0.0005	94.8	0.5095 (0.0084)	0.5100 (0.0082)	0.5140 (0.0099)	0.0001	-0.0003	96.0	0.5097 (0.0080)	0.5101 (0.0076)
4	0.5130 (0.0097)	0.5126 (0.0103)	0.0001	-0.0004	94.0	0.4941 (0.0299)	0.5243 (0.0266)	0.5126 (0.0093)	0.0001	-0.0004	96.0	0.4940 (0.0299)	0.5243 (0.0266)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 2.0$													
1	0.5142 (0.0111)	0.5137 (0.0111)	0.0001	-0.0005	95.0	0.5097 (0.0706)	0.5096 (0.0079)	0.5142 (0.0105)	0.0001	0.0001	95.2	0.5101 (0.0076)	0.5100 (0.0074)
2	0.5141 (0.0111)	0.5139 (0.0113)	0.0001	-0.0002	95.0	0.5098 (0.0082)	0.5098 (0.0080)	0.5142 (0.0105)	0.0001	0.0001	95.2	0.5100 (0.0075)	0.5101 (0.0077)
3	0.5139 (0.0108)	0.5137 (0.0111)	0.0001	-0.0002	94.6	0.5094 (0.0092)	0.5101 (0.0081)	0.5140 (0.0103)	0.0001	0.0001	95.2	0.5098 (0.0082)	0.5101 (0.0081)
4	0.5128 (0.0105)	0.5126 (0.0106)	0.0001	-0.0002	94.8	0.4942 (0.0298)	0.5241 (0.0257)	0.5130 (0.0103)	0.0001	0.0002	95.4	0.4947 (0.0288)	0.5241 (0.0257)
Measurement error $\sigma_e^2 = 2.5$													
1	0.5138 (0.0104)	0.5135 (0.0105)	0.0001	-0.0003	94.8	0.5096 (0.0696)	0.5095 (0.0074)	0.5137 (0.0102)	0.0001	-0.0001	96.6	0.5097 (0.0073)	0.5097 (0.0073)
2	0.5137 (0.0104)	0.5138 (0.0107)	0.0001	0.0001	94.6	0.5096 (0.0077)	0.5100 (0.0077)	0.5146 (0.0102)	0.0001	-0.0001	96.6	0.5096 (0.0074)	0.5097 (0.0073)
3	0.5136 (0.0103)	0.5138 (0.0106)	0.0001	0.0003	94.2	0.5094 (0.0089)	0.5102 (0.0079)	0.5135 (0.0099)	0.0001	-0.0001	96.6	0.5093 (0.0081)	0.5098 (0.0077)
4	0.5123 (0.0096)	0.5126 (0.0099)	0.0001	0.0003	94.2	0.4931 (0.0319)	0.5253 (0.0253)	0.5122 (0.0095)	0.0001	-0.0002	96.6	0.4925 (0.0310)	0.5251 (0.0288)

Table C. 6: Time-dependent AUC, sensitivity, specificity for adjusted and obsrved biomarkers when γ=0.25 and 50% censoring

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.5693 (0.0176)	0.5642 (0.0172)	0.0003	-0.0052	93.6	0.5455 (0.0125)	0.5456 (0.0124)	0.5613 (0.0170)	0.0004	-0.0080	91.4	0.5435 (0.0122)	0.5436 (0.0124)
2	0.5686 (0.0174)	0.5635 (0.0170)	0.0003	-0.0051	93.8	0.5453 (0.0127)	0.5448 (0.0122)	0.5608 (0.0168)	0.1025	-0.3198	91.4	0.5433 (0.0123)	0.5430 (0.0124)
3	0.5677 (0.0167)	0.5618 (0.0164)	0.0003	-0.0049	93.8	0.5440 (0.0124)	0.5438 (0.0129)	0.5594 (0.0164)	0.0003	-0.0073	92.2	0.5427 (0.0129)	0.5418 (0.0129)
4	0.5591 (0.0179)	0.5542 (0.0167)	0.0003	-0.0049	94.4	0.5400 (0.0296)	0.5388 (0.0287)	0.5525 (0.0169)	0.0003	-0.0065	93.6	0.5399 (0.0294)	0.5365 (0.0282)
Measurement error $\sigma_e^2 = 0.5$													
1	0.5693 (0.0176)	0.5614 (0.0174)	0.0004	-0.0080	92.0	0.5435 (0.0125)	0.5436 (0.0127)	0.5556 (0.0169)	0.0005	-0.0137	86.8	0.5395 (0.0122)	0.5395 (0.0123)
2	0.5686 (0.0174)	0.5608 (0.0172)	0.0004	-0.0078	91.6	0.5432 (0.0126)	0.5431 (0.0125)	0.5552 (0.0167)	0.0005	-0.0134	86.6	0.5393 (0.0124)	0.5391 (0.0121)
3	0.5677 (0.0167)	0.5589 (0.0165)	0.0003	-0.0078	92.2	0.5420 (0.0127)	0.5417 (0.0127)	0.5541 (0.0164)	0.0004	-0.0126	88.2	0.5386 (0.0127)	0.5383 (0.0130)
4	0.5591 (0.0179)	0.5514 (0.0163)	0.0003	-0.0077	93.0	0.5371 (0.0288)	0.5375 (0.0287)	0.5481 (0.0167)	0.0004	-0.0110	90.8	0.5356 (0.0296)	0.5342 (0.0282)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 1.0$													
1	0.5693 (0.0176)	0.5577 (0.0179)	0.0005	-0.0117	90.2	0.5409 (0.0130)	0.5410 (0.0128)	0.5478 (0.0169)	0.0008	-0.0216	75.0	0.5338 (0.0121)	0.5339 (0.0122)
2	0.5686 (0.0174)	0.5574 (0.0176)	0.0004	-0.0112	89.8	0.5409 (0.0131)	0.5405 (0.0126)	0.5475 (0.0168)	0.1025	-0.3198	76.6	0.5336 (0.0121)	0.5338 (0.0122)
3	0.5677 (0.0167)	0.5554 (0.0168)	0.0004	-0.0112	89.8	0.5392 (0.0129)	0.5394 (0.0128)	0.5467 (0.0164)	0.0007	-0.0200	77.7	0.5335 (0.0127)	0.5328 (0.0127)
4	0.5591 (0.0179)	0.5479 (0.0160)	0.0004	-0.0112	89.0	0.5353 (0.0291)	0.5343 (0.0282)	0.5418 (0.0166)	0.0006	-0.0173	81.6	0.5323 (0.0290)	0.5282 (0.0267)
Measurement error $\sigma_e^2 = 1.5$													
1	0.5693 (0.0176)	0.5551 (0.0182)	0.0005	-0.0143	64.2	0.5391 (0.0132)	0.5390 (0.0130)	0.5425 (0.0170)	0.0010	-0.0268	88.0	0.5300 (0.0120)	0.5302 (0.0123)
2	0.5686 (0.0174)	0.5552 (0.0181)	0.0005	-0.0134	65.2	0.5392 (0.0132)	0.5392 (0.0130)	0.5423 (0.0168)	0.0010	-0.0263	88.0	0.5300 (0.0120)	0.5300 (0.0124)
3	0.5677 (0.0167)	0.5533 (0.0172)	0.0005	-0.0133	67.2	0.5377 (0.0134)	0.5380 (0.0129)	0.5417 (0.0165)	0.0009	-0.0250	88.2	0.5295 (0.0125)	0.5297 (0.0126)
4	0.5591 (0.0179)	0.5459 (0.0160)	0.0004	-0.0132	73.4	0.5343 (0.0292)	0.5343 (0.0275)	0.5374 (0.0165)	0.0007	-0.0217	86.4	0.5278 (0.0291)	0.5264 (0.0258)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC(SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 2.0$													
1	0.5693 (0.0176)	0.5530 (0.0184)	0.0006	-0.0163	85.4	0.5377 (0.0133)	0.5375 (0.0132)	0.5386 (0.0170)	0.0012	-0.0307	53.8	0.5273 (0.0120)	0.5275 (0.0123)
2	0.5686 (0.0174)	0.5536 (0.0184)	0.0006	-0.0150	86.4	0.5380 (0.0134)	0.5380 (0.0132)	0.5385 (0.0168)	0.0012	-0.0301	55.2	0.5272 (0.0122)	0.5274 (0.0121)
3	0.5677 (0.0167)	0.5519 (0.0175)	0.0005	-0.0148	87.2	0.5367 (0.0135)	0.5369 (0.0133)	0.5380 (0.0165)	0.0011	-0.0287	59.0	0.5268 (0.0125)	0.5271 (0.0126)
4	0.5591 (0.0179)	0.5445 (0.0161)	0.0005	-0.0146	83.8	0.5333 (0.0296)	0.5313 (0.0272)	0.5342 (0.0165)	0.0009	-0.0249	64.2	0.5242 (0.0290)	0.5253 (0.0254)
Measurement error $\sigma_e^2 = 2.5$													
1	0.5693 (0.0176)	0.5513 (0.0185)	0.0007	-0.0181	84.0	0.5364 (0.0135)	0.5363 (0.0131)	0.5358 (0.0169)	0.0014	-0.0336	45.8	0.5252 (0.0120)	0.5254 (0.0122)
2	0.5686 (0.0174)	0.5522 (0.0186)	0.0006	-0.0164	84.8	0.5371 (0.0136)	0.5369 (0.0134)	0.5356 (0.0167)	0.0014	-0.0330	46.8	0.5252 (0.0120)	0.5253 (0.0121)
3	0.5677 (0.0167)	0.5507 (0.0178)	0.0006	-0.0160	85.4	0.5359 (0.0136)	0.5361 (0.0135)	0.5352 (0.0164)	0.0013	-0.0315	48.6	0.5249 (0.0126)	0.5250 (0.0123)
4	0.5591 (0.0179)	0.5435 (0.0163)	0.0005	-0.0156	83.6	0.5320 (0.0293)	0.5311 (0.0271)	0.5318 (0.0163)	0.0010	-0.0273	56.6	0.5212 (0.0291)	0.5248 (0.0252)

Table C. 7: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0.5 and 50% censoring

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.6356 (0.0174)	0.6253 (0.0178)	0.0004	-0.0103	91.2	0.5897 (0.0135)	0.5894 (0.0133)	0.6182 (0.0171)	0.0006	-0.0174	82.2	0.5845 (0.0128)	0.5843 (0.0130)
2	0.6315 (0.0166)	0.6213 (0.0168)	0.0004	-0.0102	90.6	0.5872 (0.0131)	0.5860 (0.0128)	0.6155 (0.0165)	0.0184	-0.1347	83.0	0.5827 (0.0128)	0.5822 (0.0127)
3	0.6223 (0.0160)	0.6121 (0.0157)	0.0004	-0.0102	90.8	0.5812 (0.0131)	0.5782 (0.0135)	0.6088 (0.0158)	0.0004	-0.0135	85.4	0.5786 (0.0134)	0.5771 (0.0139)
4	0.6062 (0.0208)	0.5966 (0.0193)	0.0005	-0.0095	92.4	0.5739 (0.0268)	0.5668 (0.0286)	0.5959 (0.0201)	0.0005	-0.0102	91.6	0.5720 (0.0269)	0.5673 (0.0272)
Measurement error $\sigma_e^2 = 0.5$													
1	0.6356 (0.0174)	0.6200 (0.0185)	0.0006	-0.0156	85.8	0.5856 (0.0139)	0.5858 (0.0138)	0.6062 (0.0171)	0.0012	-0.0294	59.2	0.5758 (0.0126)	0.5756 (0.0129)
2	0.6315 (0.0166)	0.6159 (0.0173)	0.0005	-0.0155	84.8	0.5832 (0.0136)	0.5823 (0.0129)	0.6042 (0.0166)	0.0184	-0.1347	61.0	0.5744 (0.0127)	0.5741 (0.0126)
3	0.6223 (0.0160)	0.6065 (0.0158)	0.0005	-0.0158	82.6	0.5774 (0.0135)	0.5749 (0.0134)	0.5989 (0.0158)	0.0008	-0.0234	65.2	0.5714 (0.0129)	0.5700 (0.0132)
4	0.6062 (0.0208)	0.5912 (0.0187)	0.0006	-0.0150	85.6	0.5697 (0.0267)	0.5629 (0.0276)	0.5883 (0.0195)	0.0007	-0.0178	84.6	0.5666 (0.0264)	0.5619 (0.0274)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 1.0$													
1	0.6356 (0.0174)	0.6130 (0.0196)	0.0009	-0.0226	79.6	0.5808 (0.0148)	0.5805 (0.0143)	0.5903 (0.0172)	0.0024	-0.0455	26.4	0.5641 (0.0126)	0.5642 (0.0127)
2	0.6315 (0.0166)	0.6097 (0.0183)	0.0008	-0.0218	77.4	0.5786 (0.0141)	0.5778 (0.0135)	0.5889 (0.0167)	0.0184	-0.1347	28.6	0.5631 (0.0123)	0.5633 (0.0128)
3	0.6223 (0.0160)	0.6003 (0.0164)	0.0008	-0.0220	72.0	0.5727 (0.0137)	0.5705 (0.0134)	0.5853 (0.0159)	0.0016	-0.0370	35.8	0.5611 (0.0131)	0.5606 (0.0126)
4	0.6062 (0.0208)	0.5850 (0.0181)	0.0008	-0.0212	77.2	0.5655 (0.0263)	0.5579 (0.0270)	0.5773 (0.0187)	0.0012	-0.0289	65.0	0.5580 (0.0256)	0.5543 (0.0261)
Measurement error $\sigma_e^2 = 1.5$													
1	0.6356 (0.0174)	0.6081 (0.0204)	0.0012	-0.0275	69.4	0.5774 (0.0153)	0.5768 (0.0148)	0.5797 (0.0173)	0.0034	-0.0559	9.8	0.5566 (0.0125)	0.5567 (0.0127)
2	0.6315 (0.0166)	0.6057 (0.0190)	0.0010	-0.0258	77.4	0.5758 (0.0149)	0.5748 (0.0137)	0.5788 (0.0169)	0.0184	-0.1347	12.8	0.5561 (0.0124)	0.5559 (0.0126)
3	0.6223 (0.0160)	0.5966 (0.0169)	0.0009	-0.0257	72.0	0.5703 (0.0145)	0.5676 (0.0137)	0.5761 (0.0161)	0.0024	-0.0462	17.6	0.5547 (0.0128)	0.5537 (0.0130)
4	0.6062 (0.0208)	0.5850 (0.0180)	0.0008	-0.0212	77.2	0.5627 (0.0260)	0.5554 (0.0270)	0.5696 (0.0182)	0.0017	-0.0366	47.4	0.5508 (0.0254)	0.5501 (0.0252)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 2.0$													
1	0.6356 (0.0174)	0.6041 (0.0209)	0.0014	-0.0315	66.2	0.5745 (0.0156)	0.5738 (0.0151)	0.5722 (0.0173)	0.0043	-0.0634	5.6	0.5512 (0.0125)	0.5513 (0.0127)
2	0.6315 (0.0166)	0.6025 (0.0196)	0.0012	-0.0289	67.8	0.5735 (0.0149)	0.5727 (0.0144)	0.5714 (0.0169)	0.0184	-0.1347	6.6	0.5508 (0.0124)	0.5507 (0.0126)
3	0.6223 (0.0160)	0.5941 (0.0174)	0.0011	-0.0282	63.2	0.5688 (0.0146)	0.5655 (0.0138)	0.5693 (0.0162)	0.0031	-0.0530	10.4	0.5498 (0.0129)	0.5498 (0.0129)
4	0.6062 (0.0208)	0.5792 (0.0180)	0.0011	-0.0270	67.2	0.5602 (0.0257)	0.5545 (0.0269)	0.5638 (0.0178)	0.0021	-0.0424	31.4	0.5467 (0.0252)	0.5456 (0.0251)
Measurement error $\sigma_e^2 = 2.5$													
1	0.6356 (0.0174)	0.6006 (0.0214)	0.0017	-0.0350	62.0	0.5723 (0.0160)	0.5711 (0.0154)	0.5665 (0.0174)	0.0051	-0.0692	2.6	0.5480 (0.0107)	0.5480 (0.0107)
2	0.6315 (0.0166)	0.5999 (0.0201)	0.0014	-0.0315	64.4	0.5719 (0.0154)	0.5705 (0.0146)	0.5658 (0.0170)	0.0184	-0.1347	3.2	0.5476 (0.0106)	0.5476 (0.0105)
3	0.6223 (0.0160)	0.5921 (0.0178)	0.0012	-0.0302	61.4	0.5669 (0.0147)	0.5645 (0.0141)	0.5641 (0.0163)	0.0037	-0.0582	5.6	0.5498 (0.0107)	0.5464 (0.0106)
4	0.6062 (0.0208)	0.5776 (0.0181)	0.0011	-0.0286	64.4	0.5590 (0.0262)	0.5535 (0.0270)	0.5592 (0.0176)	0.0025	-0.0470	22.4	0.5438 (0.0167)	0.5447 (0.0168)

Table C. 8: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0.75 and 50% censoring

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.6947 (0.0176)	0.6797 (0.0187)	0.0006	-0.0150	86.4	0.6304 (0.0146)	0.6290 (0.0147)	0.6668 (0.0177)	0.0011	-0.0279	63.6	0.6206 (0.0137)	0.6195 (0.0140)
2	0.6828 (0.0159)	0.6677 (0.0164)	0.0005	-0.0151	85.0	0.6231 (0.0136)	0.6186 (0.0132)	0.6591 (0.0164)	0.0045	0.0652	68.2	0.6153 (0.0130)	0.6134 (0.0135)
3	0.6649 (0.0161)	0.6496 (0.0155)	0.0005	-0.0153	82.0	0.6111 (0.0139)	0.6042 (0.0137)	0.6467 (0.0157)	0.0006	-0.0181	77.0	0.6075 (0.0142)	0.6037 (0.0142)
4	0.6422 (0.0222)	0.6280 (0.0205)	0.0006	-0.0142	89.0	0.5988 (0.0262)	0.5879 (0.0247)	0.6303 (0.0216)	0.0006	-0.0119	93.0	0.5986 (0.0256)	0.5911 (0.0257)
Measurement error $\sigma_e^2 = 0.5$													
1	0.6947 (0.0176)	0.6722 (0.0198)	0.0009	-0.0225	80.2	0.6248 (0.0135)	0.6235 (0.0155)	0.6483 (0.0179)	0.0025	-0.0464	27.8	0.6067 (0.0138)	0.6060 (0.0137)
2	0.6828 (0.0159)	0.6603 (0.0172)	0.0008	-0.0224	73.2	0.6175 (0.0142)	0.6133 (0.0136)	0.6 427 (0.0167)	0.0045	0.0652	32.0	0.6030 (0.0133)	0.6015 (0.0132)
3	0.6649 (0.0161)	0.6419 (0.0157)	0.0008	-0.0229	67.2	0.6055 (0.0142)	0.5985 (0.0138)	0.6335 (0.0156)	0.0012	-0.0314	47.4	0.5974 (0.0140)	0.5942 (0.0135)
4	0.6422 (0.0222)	0.6203 (0.0197)	0.0009	-0.0219	79.6	0.5937 (0.0256)	0.5814 (0.0232)	0.6206 (0.0208)	0.0009	-0.0216	84.0	0.5900 (0.0241)	0.5853 (0.0258)

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 1.0$													
1	0.6947 (0.0176)	0.6626 (0.0216)	0.0015	-0.0321	68.6	0.6179 (0.0169)	0.6162 (0.0163)	0.6245 (0.0179)	0.0052	-0.0702	3.2	0.5892 (0.0134)	0.5887 (0.0136)
2	0.6828 (0.0159)	0.6520 (0.0187)	0.0013	-0.0308	62.4	0.6112 (0.0152)	0.6073 (0.0143)	0.6210 (0.0170)	0.0045	0.0652	4.6	0.5868 (0.0129)	0.5861 (0.0134)
3	0.6649 (0.0161)	0.6337 (0.0164)	0.0012	-0.0312	51.8	0.5997 (0.0148)	0.5922 (0.0140)	0.6151 (0.0157)	0.0027	-0.0498	10.8	0.5834 (0.0134)	0.5813 (0.0136)
4	0.6422 (0.0222)	0.6119 (0.0190)	0.0013	-0.0303	62.8	0.5874 (0.0239)	0.5753 (0.0223)	0.6059 (0.0197)	0.0017	-0.0363	53.2	0.5798 (0.0233)	0.5738 (0.0230)
Measurement error $\sigma_e^2 = 1.5$													
1	0.6947 (0.0176)	0.6560 (0.0230)	0.0020	-0.0387	60.2	0.6134 (0.0177)	0.6110 (0.0172)	0.6094 (0.0179)	0.0076	-0.0853	0.4	0.5780 (0.0133)	0.5780 (0.0134)
2	0.6828 (0.0159)	0.6469 (0.0200)	0.0017	-0.0359	57.6	0.6076 (0.0161)	0.6033 (0.0148)	0.6069 (0.0171)	0.0045	0.0652	0.8	0.5764 (0.0129)	0.5760 (0.0132)
3	0.6649 (0.0161)	0.6292 (0.0172)	0.0016	-0.0357	46.8	0.5958 (0.0149)	0.5894 (0.0147)	0.6026 (0.0159)	0.0041	-0.0622	2.6	0.5744 (0.0133)	0.5722 (0.0132)
4	0.6422 (0.0222)	0.6074 (0.0189)	0.0016	-0.0347	53.8	0.5826 (0.0240)	0.5734 (0.0226)	0.5954 (0.0190)	0.0025	-0.0468	30.4	0.5717 (0.0226)	0.5663 (0.0215)

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 2.0$													
1	0.6947 (0.0176)	0.6514 (0.0240)	0.0025	-0.0442	53.8	0.6103 (0.0186)	0.6072 (0.0177)	0.6009 (0.0177)	0.0093	-0.0947	0.0	0.5722 (0.0132)	0.5715 (0.0129)
2	0.6828 (0.0159)	0.6432 (0.0206)	0.0021	-0.0404	51.8	0.6054 (0.0169)	0.6003 (0.0150)	0.5987 (0.0168)	0.0053	0.0706	0.2	0.5706 (0.0129)	0.5703 (0.0126)
3	0.6649 (0.0161)	0.6277 (0.0179)	0.0019	-0.0392	45.0	0.5947 (0.0155)	0.5888 (0.0143)	0.5955 (0.0163)	0.0054	-0.0714	1.0	0.5683 (0.0137)	0.5681 (0.0131)
4	0.6422 (0.0222)	0.6052 (0.0203)	0.0019	-0.0386	51.8	0.5806 (0.0247)	0.5720 (0.0244)	0.5892 (0.0188)	0.0033	-0.0547	20.8	0.5647 (0.0217)	0.5641 (0.0220)
Measurement error $\sigma_e^2 = 2.5$													
1	0.6947 (0.0176)	0.6450 (0.0246)	0.0031	-0.0496	47.6	0.6058 (0.0190)	0.6024 (0.0180)	0.5908 (0.0180)	0.0111	-0.1039	0.0	0.5646 (0.0133)	0.5646 (0.0133)
2	0.6828 (0.0159)	0.6390 (0.0216)	0.0024	-0.0438	48.2	0.6019 (0.0173)	0.5975 (0.0158)	0.5893 (0.0174)	0.0090	-0.0935	0.2	0.5634 (0.0133)	0.5634 (0.0133)
3	0.6649 (0.0161)	0.6235 (0.0186)	0.0021	-0.0413	40.6	0.5914 (0.0159)	0.5856 (0.0149)	0.5866 (0.0162)	0.0064	-0.0783	0.2	0.5613 (0.0128)	0.5613 (0.0128)
4	0.6422 (0.0222)	0.6026 (0.0194)	0.0019	-0.0394	46.6	0.5791 (0.0240)	0.5699 (0.0223)	0.5813 (0.0182)	0.0040	-0.0607	9.6	0.5570 (0.0217)	0.5570 (0.0217)

Table C. 9: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=1.0 and 50% censoring

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.7429 (0.0169)	0.7239 (0.0185)	0.0007	-0.0191	82.4	0.6658 (0.0869)	0.6614 (0.0153)	0.7053 (0.0176)	0.0017	-0.0377	43.8	0.6506 (0.0141)	0.6476 (0.0145)
2	0.7216 (0.0155)	0.7023 (0.0159)	0.0006	-0.0193	76.4	0.6519 (0.0140)	0.6424 (0.0134)	0.6916 (0.0158)	0.0012	-0.0300	51.8	0.6409 (0.0131)	0.6367 (0.0135)
3	0.6982 (0.0163)	0.6779 (0.0155)	0.0007	-0.0202	75.6	0.6349 (0.0142)	0.6230 (0.0146)	0.6758 (0.0156)	0.0007	-0.0224	71.4	0.6304 (0.0145)	0.6240 (0.0150)
4	0.6743 (0.0239)	0.6547 (0.0213)	0.0008	-0.0196	84.8	0.6201 (0.0235)	0.6052 (0.0232)	0.6591 (0.0228)	0.0008	-0.0152	90.8	0.6200 (0.0234)	0.6120 (0.0258)
Measurement error $\sigma_e^2 = 0.5$													
1	0.7429 (0.0169)	0.7148 (0.0200)	0.0012	-0.0281	69.2	0.6588 (0.0869)	0.6546 (0.0164)	0.6811 (0.0179)	0.0041	-0.0618	5.8	0.6316 (0.0140)	0.6299 (0.0143)
2	0.7216 (0.0155)	0.6935 (0.0170)	0.0011	-0.0281	60.2	0.6450 (0.0147)	0.6360 (0.0139)	0.6713 (0.0162)	0.0028	-0.0504	12.4	0.6251 (0.0132)	0.6218 (0.0134)
3	0.6982 (0.0163)	0.6688 (0.0158)	0.0011	-0.0294	52.8	0.6276 (0.0145)	0.6164 (0.0145)	0.6597 (0.0153)	0.0017	-0.0385	29.0	0.6173 (0.0145)	0.6130 (0.0141)
4	0.6743 (0.0239)	0.6450 (0.0204)	0.0013	-0.0293	68.0	0.6130 (0.0232)	0.5980 (0.0231)	0.6468 (0.0217)	0.0012	-0.0275	74.2	0.6107 (0.0223)	0.6031 (0.0252)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 1.0$													
1	0.7429 (0.0169)	0.7034 (0.0224)	0.0021	-0.0395	57.6	0.6503 (0.0869)	0.6457 (0.0174)	0.6508 (0.0181)	0.0088	-0.0921	0.2	0.6087 (0.0139)	0.6077 (0.0139)
2	0.7216 (0.0155)	0.6840 (0.0189)	0.0018	-0.0376	47.2	0.6376 (0.0160)	0.6290 (0.0149)	0.6447 (0.0165)	0.0062	-0.0769	0.6	0.6047 (0.0131)	0.6029 (0.0132)
3	0.6982 (0.0163)	0.6595 (0.0166)	0.0018	-0.0387	25.0	0.6205 (0.0154)	0.6097 (0.0149)	0.6374 (0.0154)	0.0039	-0.0608	2.2	0.6000 (0.0135)	0.5974 (0.0139)
4	0.6743 (0.0239)	0.6350 (0.0197)	0.0019	-0.0393	48.6	0.6054 (0.0235)	0.5909 (0.0216)	0.6285 (0.0200)	0.0025	-0.0458	38.2	0.5958 (0.0218)	0.5910 (0.0233)
Measurement error $\sigma_e^2 = 1.5$													
1	0.7429 (0.0169)	0.6956 (0.0241)	0.0028	-0.0473	49.4	0.6477 (0.0871)	0.6394 (0.0183)	0.6320 (0.0180)	0.0126	-0.1109	0.0	0.5946 (0.0136)	0.5942 (0.0137)
2	0.7216 (0.0155)	0.6783 (0.0203)	0.0023	-0.0433	41.2	0.6334 (0.0171)	0.6247 (0.0157)	0.6277 (0.0167)	0.0091	-0.0939	0.0	0.5919 (0.0131)	0.5908 (0.0130)
3	0.6982 (0.0163)	0.6546 (0.0175)	0.0022	-0.0436	30.4	0.6167 (0.0159)	0.6063 (0.0151)	0.6225 (0.0155)	0.0060	-0.0757	0.0	0.5889 (0.0136)	0.5866 (0.0133)
4	0.6743 (0.0239)	0.6299 (0.0196)	0.0024	-0.0445	38.2	0.6018 (0.0243)	0.5871 (0.0202)	0.6156 (0.0191)	0.0038	-0.0588	13.4	0.5840 (0.0144)	0.5817 (0.0215)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 2.0$													
1	0.7429 (0.0169)	0.6902 (0.0259)	0.0035	-0.0534	46.2	0.6410 (0.0212)	0.6351 (0.0194)	0.6210 (0.0181)	0.0154	-0.1226	0.0	0.5870 (0.0136)	0.5859 (0.0134)
2	0.7216 (0.0155)	0.6767 (0.0218)	0.0028	-0.0481	41.6	0.6309 (0.0186)	0.6218 (0.0161)	0.6177 (0.0170)	0.0113	-0.1051	0.0	0.5845 (0.0132)	0.5838 (0.0130)
3	0.6982 (0.0163)	0.6532 (0.0187)	0.0025	-0.0468	32.0	0.6155 (0.0171)	0.6057 (0.0152)	0.6135 (0.0165)	0.0078	-0.0866	0.0	0.5815 (0.0142)	0.5809 (0.0139)
4	0.6743 (0.0239)	0.6270 (0.0209)	0.0027	-0.0477	35.2	0.5995 (0.0238)	0.5844 (0.0220)	0.6069 (0.0188)	0.0050	-0.0678	6.0	0.5789 (0.0211)	0.5756 (0.0212)
Measurement error $\sigma_e^2 = 2.5$													
1	0.7429 (0.0169)	0.6836 (0.0275)	0.0042	-0.0589	41.6	0.6364 (0.0222)	0.6297 (0.0205)	0.6093 (0.0182)	0.0181	-0.1333	0.0	0.5780 (0.0134)	0.5778 (0.0135)
2	0.7216 (0.0155)	0.6703 (0.0231)	0.0032	-0.0512	37.8	0.6277 (0.0193)	0.6184 (0.0173)	0.6068 (0.0172)	0.0135	-0.1148	0.0	0.5763 (0.0132)	0.5759 (0.0130)
3	0.6982 (0.0163)	0.6489 (0.0195)	0.0028	-0.0493	28.4	0.6127 (0.0174)	0.6018 (0.0159)	0.6035 (0.0162)	0.0092	-0.0948	0.0	0.5744 (0.0135)	0.5734 (0.0133)
4	0.6743 (0.0239)	0.6248 (0.0203)	0.0029	-0.0502	31.2	0.5983 (0.0243)	0.5832 (0.0202)	0.5986 (0.0183)	0.0062	-0.0764	1.0	0.5723 (0.0191)	0.5703 (0.0206)

Table C. 10: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0 and 70% censoring

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.5180 (0.0139)	0.5175 (0.0135)	0.0002	-0.0005	96.4	0.5124 (0.0097)	0.5124 (0.0096)	0.5178 (0.0138)	0.0002	-0.0002	95.6	0.5126 (0.0099)	0.5126 (0.0099)
2	0.5178 (0.0136)	0.5174 (0.0132)	0.0002	-0.0004	95.4	0.5122 (0.0099)	0.5124 (0.0096)	0.5176 (0.0135)	0.0002	-0.0002	95.6	0.5123 (0.0101)	0.5123 (0.0098)
3	0.5174 (0.0133)	0.5171 (0.0131)	0.0002	-0.0004	95.0	0.5107 (0.0137)	0.5136 (0.0117)	0.5172 (0.0133)	0.0002	-0.0002	95.0	0.5110 (0.0132)	0.5110 (0.0119)
4	0.5126 (0.0119)	0.5123 (0.0110)	0.0001	-0.0003	94.4	0.4554 (0.0732)	0.5641 (0.0708)	0.5124 (0.0111)	0.0001	-0.0002	95.6	0.4556 (0.0726)	0.5641 (0.0708)
Measurement error $\sigma_e^2 = 0.5$													
1	0.5180 (0.0139)	0.5174 (0.0136)	0.0002	-0.0005	95.6	0.5122 (0.0096)	0.5125 (0.0099)	0.5179 (0.0138)	0.0002	0.0000	94.6	0.5126 (0.0099)	0.5128 (0.0099)
2	0.5178 (0.0136)	0.5173 (0.0134)	0.0002	-0.0005	95.6	0.5122 (0.0099)	0.5123 (0.0099)	0.5178 (0.0135)	0.0002	0.0000	94.4	0.5124 (0.0102)	0.5128 (0.0098)
3	0.5174 (0.0133)	0.5170 (0.0133)	0.0002	-0.0004	95.6	0.5108 (0.0134)	0.5133 (0.0115)	0.5174 (0.0133)	0.0002	-0.0001	95.0	0.5114 (0.0133)	0.5133 (0.0117)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
4	0.5126 (0.0119)	0.5123 (0.0111)	0.0001	-0.0003	94.4	0.4555 (0.0728)	0.5641 (0.0708)	0.5125 (0.0111)	0.0001	-0.0001	95.8	0.4558 (0.0720)	0.5641 (0.0708)
Measurement error $\sigma_e^2 = 1.0$													
1	0.5190 (0.0148)	0.5188 (0.0148)	0.0002	-0.0003	96.0	0.5133 (0.0106)	0.5133 (0.0107)	0.5187 (0.0145)	0.0002	-0.0004	95.0	0.5133 (0.0104)	0.5132 (0.0103)
2	0.5188 (0.0145)	0.5187 (0.0145)	0.0002	-0.0001	96.0	0.5131 (0.0107)	0.5135 (0.0106)	0.5185 (0.0141)	0.0002	-0.0003	95.4	0.5130 (0.0104)	0.5132 (0.0104)
3	0.5185 (0.0141)	0.5183 (0.0141)	0.0002	-0.0002	95.8	0.5124 (0.0145)	0.5136 (0.0118)	0.5180 (0.0138)	0.0002	-0.0005	95.2	0.5124 (0.0136)	0.5132 (0.0116)
4	0.5130 (0.0119)	0.5130 (0.0118)	0.0001	0.0000	94.4	0.4558 (0.0733)	0.5648 (0.0707)	0.5131 (0.0121)	0.0001	0.0001	96.0	0.4559 (0.0729)	0.5648 (0.0707)
Measurement error $\sigma_e^2 = 1.5$													
1	0.5201 (0.0160)	0.5192 (0.0148)	0.0002	-0.0009	96.0	0.5134 (0.0105)	0.5138 (0.0106)	0.5184 (0.0143)	0.0002	-0.0016	95.6	0.5132 (0.0102)	0.5129 (0.0103)
2	0.5197 (0.0157)	0.5193 (0.0146)	0.0002	-0.0004	95.4	0.5136 (0.0109)	0.5138 (0.0107)	0.5182 (0.0140)	0.0002	-0.0015	96.0	0.5129 (0.0102)	0.5129 (0.0104)
3	0.5193 (0.0151)	0.5189 (0.0141)	0.0002	-0.0005	95.8	0.5124 (0.0144)	0.5144 (0.0123)	0.5178 (0.0136)	0.0002	-0.0016	95.4	0.5121 (0.0140)	0.5132 (0.0113)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
4	0.5139 (0.0133)	0.5133 (0.0119)	0.0001	-0.0006	95.6	0.4562 (0.0735)	0.5647 (0.0706)	0.5128 (0.0119)	0.0001	-0.0012	96.0	0.4554 (0.0731)	0.5647 (0.0706)
Measurement error $\sigma_e^2 = 2.0$													
1	0.5197 (0.0160)	0.5189 (0.0146)	0.0002	-0.0008	96.4	0.5133 (0.0105)	0.5134 (0.0104)	0.5182 (0.0142)	0.0002	-0.0015	96.4	0.5130 (0.0102)	0.5128 (0.0101)
2	0.5194 (0.0156)	0.5192 (0.0146)	0.0002	-0.0001	95.2	0.5135 (0.0107)	0.5138 (0.0108)	0.5181 (0.0139)	0.0002	-0.0013	95.2	0.5126 (0.0102)	0.5130 (0.0104)
3	0.5189 (0.0149)	0.5188 (0.0141)	0.0002	-0.0001	95.4	0.5125 (0.0140)	0.5143 (0.0122)	0.5176 (0.0134)	0.0002	-0.0013	95.4	0.5117 (0.0137)	0.5133 (0.0114)
4	0.5135 (0.0128)	0.5132 (0.0121)	0.0001	-0.0003	94.6	0.4577 (0.0735)	0.5629 (0.0702)	0.5127 (0.0119)	0.0001	-0.0008	94.6	0.4572 (0.0730)	0.5629 (0.0702)
Measurement error $\sigma_e^2 = 2.5$													
1	0.5194 (0.0153)	0.5190 (0.0151)	0.0002	-0.0004	95.6	0.5135 (0.0108)	0.5134 (0.0108)	0.5188 (0.0147)	0.0002	-0.0006	96.2	0.5133 (0.0105)	0.5133 (0.0105)
2	0.5191 (0.0149)	0.5195 (0.0153)	0.0002	0.0005	94.4	0.5138 (0.0114)	0.5140 (0.0111)	0.5186 (0.0144)	0.0002	-0.0005	95.8	0.5130 (0.0104)	0.5134 (0.0108)
3	0.5187 (0.0145)	0.5192 (0.0149)	0.0002	0.0004	94.8	0.5126 (0.0146)	0.5147 (0.0127)	0.5181 (0.0139)	0.0002	-0.0006	96.0	0.5120 (0.0138)	0.5138 (0.0120)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
4	0.5132 (0.0125)	0.5135 (0.0126)	0.0002	0.0003	94.4	0.4557 (0.0738)	0.5656 (0.0710)	0.5134 (0.0129)	0.0002	0.0002	96.4	0.4555 (0.0736)	0.5656 (0.0710)

Table C. 11: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0.25 and 70% censoring

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.5695 (0.0224)	0.5640 (0.0222)	0.0005	-0.0055	94.2	0.5456 (0.0160)	0.5453 (0.0160)	0.5621 (0.0225)	0.0006	-0.0074	94.0	0.5442 (0.0162)	0.5440 (0.0161)
2	0.5686 (0.0219)	0.5633 (0.0216)	0.0005	-0.0054	94.0	0.5451 (0.0159)	0.5449 (0.0159)	0.5615 (0.0220)	0.0005	-0.0071	93.8	0.5436 (0.0163)	0.5439 (0.0161)
3	0.5663 (0.0219)	0.5610 (0.0211)	0.0005	-0.0054	94.6	0.5445 (0.0181)	0.5425 (0.0183)	0.5594 (0.0215)	0.0005	-0.0069	93.2	0.5427 (0.0185)	0.5420 (0.0180)
4	0.5476 (0.0256)	0.5444 (0.0238)	0.0006	-0.0031	97.2	0.5079 (0.0803)	0.5618 (0.0683)	0.5436 (0.0245)	0.0006	-0.0039	97.4	0.5074 (0.0799)	0.5612 (0.0686)
Measurement error $\sigma_e^2 = 0.5$													

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
1	0.5695 (0.0224)	0.5612 (0.0224)	0.0006	-0.0083	93.4	0.5436 (0.0163)	0.5433 (0.0161)	0.5567 (0.0226)	0.0007	-0.0127	93.4	0.5404 (0.0163)	0.5402 (0.0162)
2	0.5686 (0.0219)	0.5604 (0.0218)	0.0005	-0.0082	91.0	0.5428 (0.0160)	0.5431 (0.0162)	0.5562 (0.0222)	0.0006	-0.0124	93.6	0.5398 (0.0163)	0.5401 (0.0162)
3	0.5663 (0.0219)	0.5580 (0.0211)	0.0005	-0.0083	91.6	0.5418 (0.0182)	0.5410 (0.0181)	0.5544 (0.0215)	0.0006	-0.0120	93.2	0.5390 (0.0181)	0.5386 (0.0183)
4	0.5476 (0.0256)	0.5422 (0.0229)	0.0006	-0.0054	96.8	0.5042 (0.0797)	0.5618 (0.0683)	0.5403 (0.0236)	0.0006	-0.0073	96.4	0.5025 (0.0791)	0.5606 (0.0682)
Measurement error $\sigma_e^2 = 1.0$													
1	0.5695 (0.0224)	0.5572 (0.0229)	0.0007	-0.0122	92.0	0.5408 (0.0166)	0.5405 (0.0165)	0.5493 (0.0226)	0.0009	-0.0202	84.8	0.5350 (0.0163)	0.5350 (0.0162)
2	0.5686 (0.0219)	0.5570 (0.0224)	0.0006	-0.0116	92.4	0.5406 (0.0167)	0.5404 (0.0163)	0.5489 (0.0223)	0.0009	-0.0197	84.6	0.5349 (0.0163)	0.5346 (0.0162)
3	0.5663 (0.0219)	0.5545 (0.0214)	0.0006	-0.0118	90.8	0.5396 (0.0186)	0.5384 (0.0176)	0.5474 (0.0214)	0.0008	-0.0190	84.8	0.5336 (0.0188)	0.5340 (0.0169)
4	0.5476 (0.0256)	0.5394 (0.0219)	0.0005	-0.0082	94.8	0.5007 (0.0796)	0.5606 (0.0681)	0.5354 (0.0223)	0.0006	-0.0122	94.4	0.4950 (0.0777)	0.5604 (0.0682)

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 1.5$													
1	0.5695 (0.0224)	0.5544 (0.0233)	0.0008	-0.0151	90.8	0.5388 (0.0168)	0.5384 (0.0167)	0.5444 (0.0225)	0.0011	-0.0251	77.6	0.5316 (0.0161)	0.5314 (0.0161)
2	0.5686 (0.0219)	0.5547 (0.0230)	0.0007	-0.0139	91.0	0.5389 (0.0170)	0.5390 (0.0168)	0.5441 (0.0222)	0.0011	-0.0245	76.8	0.5313 (0.0162)	0.5313 (0.0161)
3	0.5663 (0.0219)	0.5525 (0.0219)	0.0007	-0.0139	90.0	0.5371 (0.0186)	0.5379 (0.0182)	0.5427 (0.0213)	0.0010	-0.0237	77.4	0.5304 (0.0184)	0.5306 (0.0169)
4	0.5476 (0.0256)	0.5378 (0.0217)	0.0006	-0.0098	94.0	0.4987 (0.0796)	0.5601 (0.0681)	0.5320 (0.0215)	0.0007	-0.0155	91.2	0.4904 (0.0774)	0.5595 (0.0679)
Measurement error $\sigma_e^2 = 2.0$													
1	0.5700 (0.0246)	0.5518 (0.0246)	0.0009	-0.0182	87.0	0.0014	-0.0296	0.0014	0.0014	-0.0296	70.8	0.5286 (0.0162)	0.5286 (0.0161)
2	0.5688 (0.0237)	0.5528 (0.0246)	0.0009	-0.0160	87.6	0.0013	-0.0287	0.0013	0.0013	-0.0287	71.2	0.5284 (0.0162)	0.5285 (0.0163)
3	0.5656 (0.0223)	0.5504 (0.0235)	0.0008	-0.0152	88.6	0.0012	-0.0266	0.0012	0.0012	-0.0266	73.2	0.5276 (0.0182)	0.5280 (0.0177)
4	0.5479 (0.0254)	0.5362 (0.0226)	0.0006	-0.0117	94.0	0.0008	-0.0187	0.0008	0.0008	-0.0187	84.8	0.4869 (0.0759)	0.5585 (0.0666)

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 2.5$													
1	0.5694 (0.0224)	0.5499 (0.0237)	0.0009	-0.0195	86.8	0.5366 (0.0172)	0.5353 (0.0168)	0.5381 (0.0218)	0.0015	-0.0313	65.8	0.5270 (0.0156)	0.5270 (0.0156)
2	0.5685 (0.0219)	0.5512 (0.0239)	0.0009	-0.0173	88.8	0.5364 (0.0180)	0.5365 (0.0170)	0.5379 (0.0215)	0.0014	-0.0307	66.4	0.5270 (0.0158)	0.5268 (0.0155)
3	0.5663 (0.0219)	0.5494 (0.0228)	0.0008	-0.0169	88.2	0.5349 (0.0193)	0.5358 (0.0191)	0.5367 (0.0206)	0.0013	-0.0296	65.4	0.5259 (0.0180)	0.5266 (0.0166)
4	0.5475 (0.0257)	0.5357 (0.0214)	0.0006	-0.0118	92.8	0.4955 (0.0796)	0.5599 (0.0681)	0.5276 (0.0201)	0.0008	-0.0200	81.0	0.4836 (0.0758)	0.5593 (0.0680)

Table C. 12: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0.5 and 70% censoring

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.6362 (0.0239)	0.6247 (0.0247)	0.0007	-0.0116	92.2	0.5892 (0.0181)	0.5891 (0.0183)	0.6196 (0.0238)	0.0008	-0.0166	89.6	0.5856 (0.0177)	0.5853 (0.0179)
2	0.6315 (0.0224)	0.6202 (0.0225)	0.0006	-0.0113	91.6	0.5869 (0.0174)	0.5851 (0.0174)	0.6164 (0.0227)	0.0007	-0.0150	89.2	0.5833 (0.0172)	0.5832 (0.0178)

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
3	0.6199 (0.0223)	0.6091 (0.0215)	0.0006	-0.0107	93.8	0.5805 (0.0203)	0.5764 (0.0192)	0.6076 (0.0223)	0.0006	-0.0122	91.2	0.5796 (0.0210)	0.5752 (0.0198)
4	0.5912 (0.0342)	0.5829 (0.0325)	0.0011	-0.0083	94.8	0.5600 (0.0726)	0.5683 (0.0604)	0.5832 (0.0339)	0.0012	-0.0080	94.4	0.5596 (0.0749)	0.5690 (0.0609)
Measurement error $\sigma_e^2 = 0.5$													
1	0.6362 (0.0239)	0.6190 (0.0251)	0.0009	-0.0172	89.2	0.5851 (0.0186)	0.5850 (0.0188)	0.6079 (0.0239)	0.0014	-0.0283	78.0	0.5770 (0.0176)	0.5769 (0.0177)
2	0.6315 (0.0224)	0.6147 (0.0232)	0.0008	-0.0168	88.8	0.5825 (0.0178)	0.5815 (0.0178)	0.6055 (0.0231)	0.0012	-0.0259	79.4	0.5758 (0.0172)	0.5749 (0.0178)
3	0.6199 (0.0223)	0.6036 (0.0215)	0.0007	-0.0163	89.0	0.5764 (0.0206)	0.5724 (0.0187)	0.5985 (0.0223)	0.0010	-0.0214	84.8	0.5720 (0.0209)	0.5695 (0.0192)
4	0.5912 (0.0342)	0.5784 (0.0317)	0.0012	-0.0128	93.2	0.5534 (0.0716)	0.5676 (0.0603)	0.5772 (0.0326)	0.0013	-0.0140	92.6	0.5542 (0.0751)	0.5649 (0.0595)
Measurement error $\sigma_e^2 = 1.0$													
1	0.6362 (0.0239)	0.6113 (0.0262)	0.0013	-0.0250	83.4	0.5798 (0.0194)	0.5791 (0.0193)	0.5922 (0.0241)	0.0025	-0.0440	57.2	0.5656 (0.0177)	0.5657 (0.0176)
2	0.6315 (0.0224)	0.6082 (0.0245)	0.0011	-0.0233	84.2	0.5777 (0.0185)	0.5768 (0.0185)	0.5906 (0.0235)	0.0022	-0.0409	61.0	0.5646 (0.0169)	0.5645 (0.0183)

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
3	0.6199 (0.0223)	0.5974 (0.0222)	0.0010	-0.0224	84.2	0.5722 (0.0210)	0.5676 (0.0188)	0.5855 (0.0225)	0.0017	-0.0343	66.4	0.5628 (0.0196)	0.5598 (0.0195)
4	0.5912 (0.0342)	0.5736 (0.0306)	0.0012	-0.0176	92.4	0.5500 (0.0715)	0.5628 (0.0578)	0.5682 (0.0305)	0.0015	-0.0229	87.0	0.5438 (0.0732)	0.5611 (0.0578)
Measurement error $\sigma_e^2 = 1.5$													
1	0.6361 (0.0239)	0.6094 (0.0267)	0.0014	-0.0267	83.0	0.5784 (0.0197)	0.5778 (0.0197)	0.5889 (0.0249)	0.0029	-0.0473	52.6	0.5633 (0.0181)	0.5632 (0.0181)
2	0.6315 (0.0224)	0.6069 (0.0250)	0.0012	-0.0246	84.2	0.5768 (0.0189)	0.5758 (0.0190)	0.5874 (0.0242)	0.0025	-0.0441	57.2	0.5624 (0.0178)	0.5622 (0.0183)
3	0.6199 (0.0223)	0.5964 (0.0228)	0.0011	-0.0235	83.6	0.5715 (0.0217)	0.5669 (0.0192)	0.5827 (0.0231)	0.0019	-0.0372	64.8	0.5604 (0.0203)	0.5580 (0.0202)
4	0.5913 (0.0342)	0.5726 (0.0305)	0.0013	-0.0186	91.8	0.5488 (0.0713)	0.5625 (0.0579)	0.5660 (0.0301)	0.0015	-0.0252	86.2	0.5415 (0.0730)	0.5599 (0.0573)
Measurement error $\sigma_e^2 = 2.0$													
1	0.6348 (0.0218)	0.6005 (0.0263)	0.0019	-0.0343	74.8	0.5722 (0.0195)	0.5712 (0.0190)	0.5748 (0.0240)	0.0042	-0.0599	28.0	0.5533 (0.0175)	0.5531 (0.0173)
2	0.6304 (0.0211)	0.5999 (0.0253)	0.0016	-0.0305	77.0	0.5721 (0.0197)	0.5706 (0.0184)	0.5739 (0.0237)	0.0038	-0.0565	33.6	0.5529 (0.0177)	0.5523 (0.0174)

Predicted Time	True AUC	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
3	0.6209 (0.0213)	0.5917 (0.0232)	0.0014	-0.0292	75.0	0.5670 (0.0211)	0.5648 (0.0196)	0.5703 (0.0226)	0.0030	-0.0503	39.2	0.5508 (0.0199)	0.5504 (0.0190)
4	0.5877 (0.0359)	0.5665 (0.0286)	0.0013	-0.0212	86.6	0.5452 (0.0690)	0.5570 (0.0584)	0.5567 (0.0272)	0.0017	-0.0310	76.4	0.5319 (0.0693)	0.5548 (0.0574)
Measurement error $\sigma_e^2 = 2.5$													
1	0.6360 (0.0241)	0.5967 (0.0280)	0.0023	-0.0393	69.4	0.5694 (0.0206)	0.5685 (0.0202)	0.5684 (0.0244)	0.0052	-0.0676	20.4	0.5486 (0.0176)	0.5485 (0.0176)
2	0.6312 (0.0225)	0.5974 (0.0269)	0.0019	-0.0339	74.6	0.5701 (0.0202)	0.5688 (0.0201)	0.5676 (0.0239)	0.0046	-0.0636	22.8	0.5478 (0.0172)	0.5483 (0.0180)
3	0.6196 (0.0223)	0.5889 (0.0244)	0.0015	-0.0308	75.0	0.5644 (0.0216)	0.5629 (0.0200)	0.5647 (0.0228)	0.0035	-0.0549	30.8	0.5461 (0.0194)	0.5463 (0.0189)
4	0.5911 (0.0344)	0.5679 (0.0299)	0.0014	-0.0232	86.0	0.5419 (0.0708)	0.5620 (0.0583)	0.5529 (0.0270)	0.0022	-0.0382	66.8	0.5227 (0.0695)	0.5583 (0.0569)

Table C. 13: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=0.75 and 70% censoring

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.6949 (0.0213)	0.6789 (0.0229)	0.0008	-0.0161	90.0	0.6305 (0.0178)	0.6277 (0.0179)	0.6700 (0.0222)	0.0011	-0.0249	78.0	0.6231 (0.0169)	0.6221 (0.0174)
2	0.6825 (0.0208)	0.6665 (0.0211)	0.0007	-0.0160	87.0	0.6227 (0.0177)	0.6178 (0.0169)	0.6617 (0.0214)	0.0009	-0.0208	82.8	0.6180 (0.0175)	0.6153 (0.0172)
3	0.6640 (0.0228)	0.6478 (0.0219)	0.0007	-0.0162	89.4	0.6113 (0.0223)	0.6031 (0.0217)	0.6476 (0.0221)	0.0008	-0.0164	88.8	0.6089 (0.0216)	0.6047 (0.0219)
4	0.6266 (0.0408)	0.6143 (0.0385)	0.0016	-0.0122	93.4	0.5932 (0.0652)	0.5802 (0.0582)	0.6198 (0.0401)	0.0017	-0.0068	94.0	0.5965 (0.0663)	0.5854 (0.0594)
Measurement error $\sigma_e^2 = 0.5$													
1	0.6949 (0.0213)	0.6710 (0.0242)	0.0012	-0.0239	82.6	0.6243 (0.0187)	0.6224 (0.0186)	0.6528 (0.0227)	0.0023	-0.0421	52.8	0.6103 (0.0169)	0.6093 (0.0176)
2	0.6825 (0.0208)	0.6588 (0.0218)	0.0010	-0.0237	82.0	0.6168 (0.0182)	0.6124 (0.0174)	0.6467 (0.0219)	0.0018	-0.0358	64.0	0.6065 (0.0175)	0.6043 (0.0174)
3	0.6640 (0.0228)	0.6401 (0.0219)	0.0010	-0.0238	80.4	0.6057 (0.0211)	0.5976 (0.0213)	0.6355 (0.0220)	0.0013	-0.0285	74.8	0.5991 (0.0208)	0.5966 (0.0217)
4	0.6266 (0.0408)	0.6076 (0.0362)	0.0017	-0.0190	90.4	0.5891 (0.0631)	0.5739 (0.0577)	0.6124 (0.0373)	0.0016	-0.0142	92.4	0.5887 (0.0633)	0.5822 (0.0598)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 1.0$													
1	0.6949 (0.0213)	0.6605 (0.0261)	0.0019	-0.0344	72.2	0.6166 (0.0200)	0.6146 (0.0198)	0.6299 (0.0231)	0.0048	-0.0650	21.4	0.5934 (0.0173)	0.5926 (0.0173)
2	0.6825 (0.0208)	0.6501 (0.0231)	0.0016	-0.0324	71.2	0.6103 (0.0191)	0.6059 (0.0178)	0.6260 (0.0224)	0.0037	-0.0565	29.0	0.5909 (0.0177)	0.5897 (0.0174)
3	0.6640 (0.0228)	0.6319 (0.0224)	0.0015	-0.0320	68.0	0.5988 (0.0218)	0.5925 (0.0210)	0.6181 (0.0220)	0.0026	-0.0459	43.8	0.5863 (0.0207)	0.5839 (0.0209)
4	0.6266 (0.0408)	0.6000 (0.0338)	0.0018	-0.0265	88.0	0.5810 (0.0621)	0.5704 (0.0558)	0.6000 (0.0337)	0.0018	-0.0266	86.8	0.5768 (0.0603)	0.5747 (0.0577)
Measurement error $\sigma_e^2 = 1.5$													
1	0.6946 (0.0217)	0.6520 (0.0284)	0.0026	-0.0426	67.0	0.6102 (0.0216)	0.6085 (0.0213)	0.6148 (0.0242)	0.0070	-0.0798	9.6	0.5822 (0.0178)	0.5819 (0.0180)
2	0.6827 (0.0206)	0.6440 (0.0255)	0.0021	-0.0387	67.4	0.6052 (0.0203)	0.6021 (0.0197)	0.6118 (0.0232)	0.0056	-0.0708	14.0	0.5803 (0.0176)	0.5797 (0.0180)
3	0.6631 (0.0229)	0.6259 (0.0239)	0.0020	-0.0372	64.8	0.5941 (0.0218)	0.5878 (0.0217)	0.6052 (0.0226)	0.0039	-0.0579	27.4	0.5758 (0.0200)	0.5754 (0.0206)
4	0.6260 (0.0392)	0.5962 (0.0326)	0.0019	-0.0297	84.6	0.5803 (0.0605)	0.5654 (0.0553)	0.5894 (0.0320)	0.0024	-0.0365	78.4	0.5718 (0.0610)	0.5638 (0.0560)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 2.0$													
1	0.6961 (0.0211)	0.6477 (0.0282)	0.0031	-0.0484	55.6	0.6072 (0.0215)	0.6050 (0.0213)	0.6050 (0.0234)	0.0088	-0.0911	2.6	0.5753 (0.0174)	0.5747 (0.0172)
2	0.6831 (0.0204)	0.6410 (0.0248)	0.0024	-0.0421	56.0	0.6033 (0.0205)	0.5994 (0.0184)	0.6028 (0.0228)	0.0070	-0.0803	5.4	0.5736 (0.0176)	0.5732 (0.0173)
3	0.6640 (0.0225)	0.6249 (0.0239)	0.0021	-0.0391	60.2	0.5933 (0.0230)	0.5874 (0.0216)	0.5975 (0.0223)	0.0049	-0.0665	15.6	0.5704 (0.0203)	0.5697 (0.0202)
4	0.6269 (0.0410)	0.5941 (0.0319)	0.0021	-0.0328	83.0	0.5758 (0.0639)	0.5665 (0.0551)	0.5834 (0.0301)	0.0028	-0.0435	68.4	0.5637 (0.0592)	0.5621 (0.0549)
Measurement error $\sigma_e^2 = 2.5$													
1	0.6952 (0.0233)	0.6399 (0.0307)	0.0040	-0.0553	56.8	0.6016 (0.0233)	0.5993 (0.0226)	0.5953 (0.0246)	0.0106	-0.0999	1.4	0.5679 (0.0179)	0.5678 (0.0180)
2	0.6825 (0.0214)	0.6361 (0.0280)	0.0029	-0.0464	62.4	0.5994 (0.0219)	0.5961 (0.0212)	0.5933 (0.0236)	0.0085	-0.0893	2.8	0.5666 (0.0174)	0.5664 (0.0182)
3	0.6622 (0.0236)	0.6205 (0.0260)	0.0024	-0.0417	60.8	0.5903 (0.0239)	0.5832 (0.0219)	0.5891 (0.0223)	0.0058	-0.0731	8.8	0.5647 (0.0202)	0.5630 (0.0198)
4	0.6252 (0.0383)	0.5929 (0.0338)	0.0022	-0.0323	83.6	0.5774 (0.0620)	0.5631 (0.0539)	0.5752 (0.0301)	0.0034	-0.0500	61.8	0.5570 (0.0600)	0.5567 (0.0511)

Table C. 14: Time-dependent AUC, sensitivity, specificity for adjusted and observed biomarkers when γ=1.0 and 70% censoring

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 0.25$													
1	0.7431 (0.0214)	0.7228 (0.0236)	0.0010	-0.0203	86.4	0.6650 (0.0194)	0.6608 (0.0192)	0.7100 (0.0227)	0.0016	-0.0330	69.8	0.6544 (0.0184)	0.6513 (0.0184)
2	0.7209 (0.0204)	0.7004 (0.0207)	0.0009	-0.0206	83.8	0.6507 (0.0182)	0.6413 (0.0176)	0.6950 (0.0206)	0.0011	-0.0260	76.4	0.6444 (0.0173)	0.6389 (0.0178)
3	0.6942 (0.0240)	0.6739 (0.0228)	0.0009	-0.0203	85.6	0.6337 (0.0226)	0.6198 (0.0232)	0.6757 (0.0234)	0.0009	-0.0185	88.2	0.6324 (0.0230)	0.6235 (0.0235)
4	0.6581 (0.0394)	0.6412 (0.0371)	0.0017	-0.0169	93.4	0.6180 (0.0573)	0.5951 (0.0509)	0.6486 (0.0404)	0.0017	-0.0095	94.6	0.6202 (0.0591)	0.6042 (0.0558)
Measurement error $\sigma_e^2 = 0.5$													
1	0.7431 (0.0214)	0.7133 (0.0254)	0.0015	-0.0298	79.0	0.6577 (0.0207)	0.6536 (0.0204)	0.6877 (0.0233)	0.0036	-0.0554	31.2	0.6366 (0.0182)	0.6349 (0.0185)
2	0.7209 (0.0204)	0.6914 (0.0218)	0.0013	-0.0295	73.6	0.6437 (0.0188)	0.6346 (0.0180)	0.6765 (0.0209)	0.0024	-0.0445	43.2	0.6292 (0.0176)	0.6259 (0.0171)
3	0.6942 (0.0240)	0.6650 (0.0227)	0.0014	-0.0292	75.0	0.6257 (0.0225)	0.6141 (0.0225)	0.6619 (0.0227)	0.0016	-0.0324	70.0	0.6204 (0.0222)	0.6145 (0.0219)
4	0.6581 (0.0394)	0.6329 (0.0354)	0.0019	-0.0252	90.0	0.6095 (0.0560)	0.5903 (0.0493)	0.6391 (0.0389)	0.0019	-0.0190	93.0	0.6104 (0.0582)	0.5992 (0.0529)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 1.0$													
1	0.7424 (0.0206)	0.7002 (0.0265)	0.0025	-0.0422	86.4	0.6478 (0.0214)	0.6435 (0.0207)	0.6590 (0.0227)	0.0075	-0.0834	69.8	0.6151 (0.0173)	0.6137 (0.0175)
2	0.7211 (0.0200)	0.6817 (0.0231)	0.0021	-0.0395	83.8	0.6363 (0.0199)	0.6274 (0.0188)	0.6524 (0.0218)	0.0052	-0.0687	76.4	0.6105 (0.0175)	0.6089 (0.0179)
3	0.6961 (0.0246)	0.6569 (0.0231)	0.0021	-0.0392	85.6	0.6200 (0.0237)	0.6085 (0.0214)	0.6424 (0.0225)	0.0034	-0.0537	88.2	0.6036 (0.0211)	0.6023 (0.0216)
4	0.6562 (0.0427)	0.6224 (0.0334)	0.0023	-0.0338	93.4	0.6007 (0.0549)	0.5829 (0.0519)	0.6244 (0.0353)	0.0023	-0.0318	94.6	0.6001 (0.0526)	0.5874 (0.0505)
Measurement error $\sigma_e^2 = 1.5$													
1	0.7430 (0.0210)	0.6914 (0.0293)	0.0035	-0.0516	58.8	0.6414 (0.0236)	0.6364 (0.0225)	0.6410 (0.0238)	0.0110	-0.1020	1.0	0.6012 (0.0177)	0.6009 (0.0182)
2	0.7212 (0.0203)	0.6750 (0.0257)	0.0028	-0.0461	57.6	0.6311 (0.0217)	0.6223 (0.0200)	0.6353 (0.0222)	0.0079	-0.0859	1.8	0.5975 (0.0178)	0.5963 (0.0172)
3	0.6964 (0.0246)	0.6533 (0.0242)	0.0024	-0.0431	56.4	0.6169 (0.0236)	0.6054 (0.0225)	0.6291 (0.0228)	0.0050	-0.0673	15.0	0.5947 (0.0215)	0.5912 (0.0215)
4	0.6563 (0.0407)	0.6190 (0.0329)	0.0025	-0.0373	81.6	0.5954 (0.0539)	0.5829 (0.0505)	0.6102 (0.0328)	0.0032	-0.0461	71.8	0.5860 (0.0525)	0.5794 (0.0506)

Predicted Time	True AUC (SE)	Adjusted						Observed					
		AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)	AUC (SE)	MSE	Bias	Cov	Sensitivity (SE)	Specificity (SE)
Measurement error $\sigma_e^2 = 2.0$													
1	0.7425 (0.0216)	0.6829 (0.0320)	0.0046	-0.0596	51.6	0.6348 (0.0256)	0.6307 (0.0242)	0.6278 (0.0244)	0.0137	-0.1147	0.4	0.5917 (0.0182)	0.5913 (0.0182)
2	0.7206 (0.0207)	0.6690 (0.0273)	0.0034	-0.0516	50.0	0.6260 (0.0227)	0.6186 (0.0213)	0.6233 (0.0226)	0.0100	-0.0973	0.8	0.5886 (0.0173)	0.5878 (0.0173)
3	0.6943 (0.0248)	0.6468 (0.0263)	0.0029	-0.0475	53.8	0.6117 (0.0252)	0.6014 (0.0233)	0.6173 (0.0234)	0.0065	-0.0771	8.2	0.5855 (0.0220)	0.5833 (0.0214)
4	0.6573 (0.0421)	0.6154 (0.0325)	0.0028	-0.0419	73.0	0.5946 (0.0503)	0.5779 (0.0482)	0.6044 (0.0321)	0.0038	-0.0529	58.8	0.5808 (0.0479)	0.5763 (0.0483)
Measurement error $\sigma_e^2 = 2.5$													
1	0.7418 (0.0209)	0.6769 (0.0335)	0.0053	-0.0649	48.2	0.6302 (0.0269)	0.6262 (0.0254)	0.6169 (0.0240)	0.0162	-0.1249	0.0	0.5838 (0.0179)	0.5832 (0.0177)
2	0.7196 (0.0194)	0.6647 (0.0276)	0.0038	-0.0549	49.2	0.6229 (0.0238)	0.6151 (0.0217)	0.6131 (0.0225)	0.0119	-0.1065	0.4	0.5815 (0.0171)	0.5804 (0.0175)
3	0.6959 (0.0237)	0.6457 (0.0276)	0.0033	-0.0502	51.8	0.6101 (0.0259)	0.6009 (0.0241)	0.6087 (0.0232)	0.0081	-0.0872	3.0	0.5796 (0.0202)	0.5771 (0.0212)
4	0.6580 (0.0388)	0.6123 (0.0352)	0.0033	-0.0458	73.8	0.5893 (0.0553)	0.5785 (0.0486)	0.5965 (0.0308)	0.0047	-0.0615	46.6	0.5716 (0.0481)	0.5733 (0.0476)

Table C. 15: Time-dependent AUC(SE) for current methods when γ=0 and 50% censoring

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.4977 (0.0342)	0.4996 (0.0346)	0.4984 (0.0542)	0.4980 (0.0535)	0.4987 (0.0532)	0.4984 (0.0531)	0.4987 (0.0531)	0.4983 (0.0531)	0.4975 (0.0437)	0.4973 (0.0405)
2	0.4987 (0.0221)	0.4998 (0.0209)	0.5004 (0.0371)	0.4999 (0.0344)	0.5002 (0.0357)	0.4996 (0.0327)	0.5001 (0.0356)	0.4995 (0.0326)	0.5013 (0.0325)	0.5004 (0.0298)
3	0.4979 (0.0279)	0.4969 (0.0251)	0.4997 (0.0506)	0.4981 (0.0460)	0.5002 (0.0452)	0.4983 (0.0402)	0.5003 (0.0447)	0.4984 (0.0396)	0.4996 (0.0334)	0.4994 (0.0304)
4	0.4860 (0.0587)	0.4854 (0.0541)	0.5017 (0.2517)	0.5002 (0.2513)	0.5013 (0.0902)	0.4996 (0.0836)	0.5010 (0.0902)	0.4993 (0.0831)	0.5045 (0.1119)	0.5001 (0.1189)
Measurement error $\sigma_e^2 = 0.5$										
1	0.4972 (0.0341)	0.4994 (0.0340)	0.4988 (0.0544)	0.4984 (0.0521)	0.4989 (0.0534)	0.4986 (0.0489)	0.4988 (0.0532)	0.4983 (0.0517)	0.4973 (0.0450)	0.4973 (0.0407)
2	0.4990 (0.0240)	0.4995 (0.0214)	0.5002 (0.0404)	0.4997 (0.0345)	0.5003 (0.0390)	0.5001 (0.0340)	0.5003 (0.0388)	0.4997 (0.0331)	0.5012 (0.0326)	0.5003 (0.0300)
3	0.4979 (0.0294)	0.4968 (0.0251)	0.4996 (0.0531)	0.4980 (0.0464)	0.5003 (0.0479)	0.5000 (0.0406)	0.5001 (0.0473)	0.4987 (0.0400)	0.5005 (0.0338)	0.5003 (0.0297)
4	0.4888 (0.0635)	0.4867 (0.0560)	0.5026 (0.2479)	0.4983 (0.2457)	0.5043 (0.0994)	0.5039 (0.0902)	0.5039 (0.0993)	0.5024 (0.0870)	0.5077 (0.1160)	0.5008 (0.1112)
Measurement error $\sigma_e^2 = 1.0$										
1	0.4961 (0.0336)	0.4998 (0.0346)	0.4994 (0.0540)	0.4993 (0.0527)	0.4996 (0.0526)	0.4995 (0.0472)	0.4997 (0.0526)	0.4995 (0.0525)	0.4974 (0.0437)	0.4996 (0.0402)
2	0.4982 (0.0235)	0.4992 (0.0213)	0.5008 (0.0399)	0.4998 (0.0345)	0.5005 (0.0388)	0.5004 (0.0324)	0.5006 (0.0385)	0.4998 (0.0329)	0.5014 (0.0330)	0.5005 (0.0301)
3	0.4973 (0.0291)	0.4955 (0.0243)	0.4996 (0.0537)	0.4968 (0.0461)	0.4990 (0.0489)	0.4989 (0.0397)	0.4991 (0.0481)	0.4968 (0.0394)	0.5002 (0.0356)	0.4995 (0.0309)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**
4	0.4910 (0.0628)	0.4859 (0.0550)	0.5123 (0.2533)	0.5023 (0.2498)	0.5043 (0.0993)	0.5041 (0.0877)	0.5042 (0.0995)	0.4996 (0.0844)	0.5047 (0.1108)	0.5009 (0.0191)
Measurement error $\sigma_e^2 = 1.5$										
1	0.4968 (0.0334)	0.5008 (0.0338)	0.5013 (0.0546)	0.5009 (0.0514)	0.5013 (0.0524)	0.5010 (0.0512)	0.5013 (0.0524)	0.5009 (0.0512)	0.5004 (0.0458)	0.4995 (0.0403)
2	0.4982 (0.0250)	0.4988 (0.0217)	0.5013 (0.0434)	0.4996 (0.0345)	0.5012 (0.0411)	0.4995 (0.0332)	0.5012 (0.0409)	0.4994 (0.0327)	0.5017 (0.0348)	0.4996 (0.0291)
3	0.4987 (0.0308)	0.4964 (0.0246)	0.5018 (0.0584)	0.4981 (0.0470)	0.5025 (0.0521)	0.4991 (0.0400)	0.5024 (0.0517)	0.4992 (0.0396)	0.5019 (0.0370)	0.4998 (0.0316)
4	0.4911 (0.0666)	0.4850 (0.0572)	0.4977 (0.2541)	0.4907 (0.2478)	0.5056 (0.1055)	0.5007 (0.0865)	0.5053 (0.1056)	0.5005 (0.0860)	0.4986 (0.1127)	0.4979 (0.1148)
Measurement error $\sigma_e^2 = 2.0$										
1	0.4993 (0.0329)	0.4986 (0.0334)	0.4984 (0.0558)	0.4973 (0.0512)	0.4994 (0.0535)	0.4981 (0.0513)	0.4992 (0.0533)	0.4981 (0.0511)	0.5001 (0.0481)	0.4982 (0.0435)
2	0.4964 (0.0279)	0.4991 (0.0229)	0.4998 (0.0482)	0.4987 (0.0364)	0.5006 (0.0460)	0.4995 (0.0361)	0.5004 (0.0457)	0.4993 (0.0357)	0.5010 (0.0353)	0.5008 (0.0296)
3	0.4964 (0.0307)	0.4975 (0.0243)	0.4976 (0.0578)	0.4964 (0.0453)	0.4994 (0.0518)	0.4978 (0.0388)	0.4990 (0.0512)	0.4977 (0.0384)	0.5003 (0.0370)	0.4994 (0.0317)
4	0.4876 (0.0678)	0.4869 (0.0577)	0.4962 (0.2321)	0.4920 (0.2267)	0.5028 (0.1113)	0.4993 (0.0893)	0.5028 (0.1107)	0.4989 (0.0889)	0.5120 (0.1098)	0.5013 (0.1143)
Measurement error $\sigma_e^2 = 2.5$										
1	0.4971 (0.0345)	0.5014 (0.0342)	0.5010 (0.0576)	0.5012 (0.0525)	0.5013 (0.0545)	0.5017 (0.0524)	0.5013 (0.0546)	0.5016 (0.0523)	0.5006 (0.0474)	0.5017 (0.0406)
2	0.4969 (0.0275)	0.4997 (0.0223)	0.4994 (0.0496)	0.4997 (0.0345)	0.5002 (0.0467)	0.5006 (0.0339)	0.5001 (0.0465)	0.5004 (0.0338)	0.5002 (0.0364)	0.5004 (0.0270)
3	0.4975 (0.0314)	0.4997 (0.0228)	0.5008 (0.0619)	0.5013 (0.0441)	0.5014 (0.0533)	0.5031 (0.0361)	0.5014 (0.0535)	0.5030 (0.0359)	0.5011 (0.0378)	0.5020 (0.0314)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
4	0.4888 (0.0720)	0.4868 (0.0587)	0.4998 (0.2472)	0.4946 (0.2335)	0.5013 (0.1160)	0.4994 (0.0898)	0.5013 (0.1165)	0.4996 (0.0898)	0.5005 (0.1114)	0.4971 (0.1137)

Table C. 16: Time-dependent AUC(SE) for current methods when γ=0.25 and 50% censoring

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.5489 (0.0350)	0.5407 (0.0338)	0.5785 (0.0494)	0.5638 (0.0487)	0.5784 (0.0492)	0.5641 (0.0488)	0.5784 (0.0491)	0.5641 (0.0487)	0.5742 (0.0401)	0.5616 (0.0398)
2	0.5524 (0.0239)	0.5434 (0.0222)	0.5877 (0.0370)	0.5722 (0.0350)	0.5871 (0.0365)	0.5721 (0.0346)	0.5871 (0.0361)	0.5721 (0.0342)	0.5746 (0.0301)	0.5618 (0.0288)
3	0.5651 (0.0268)	0.5531 (0.0249)	0.6146 (0.0487)	0.5937 (0.0463)	0.6140 (0.0413)	0.5941 (0.0385)	0.6142 (0.0412)	0.5943 (0.0384)	0.5732 (0.0320)	0.5599 (0.0305)
4	0.5969 (0.0476)	0.5783 (0.0478)	0.6966 (0.1968)	0.6605 (0.1956)	0.6923 (0.0749)	0.6600 (0.0757)	0.6924 (0.0748)	0.6697 (0.0739)	0.5705 (0.0977)	0.5593 (0.1020)
Measurement error $\sigma_e^2 = 0.5$										
1	0.5513 (0.0355)	0.5374 (0.0336)	0.5845 (0.0499)	0.5587 (0.0488)	0.5836 (0.0492)	0.5588 (0.0487)	0.5837 (0.0492)	0.5588 (0.0486)	0.5785 (0.0413)	0.5563 (0.0397)
2	0.5549 (0.0253)	0.5394 (0.0225)	0.5928 (0.0388)	0.5659 (0.0349)	0.5912 (0.0378)	0.5657 (0.0345)	0.5915 (0.0375)	0.5657 (0.0341)	0.5776 (0.0315)	0.5558 (0.0288)
3	0.5684 (0.0283)	0.5484 (0.0247)	0.6209 (0.0515)	0.5851 (0.0467)	0.6195 (0.0439)	0.5856 (0.0388)	0.6196 (0.0438)	0.5857 (0.0387)	0.5763 (0.0332)	0.5552 (0.0305)
4	0.6026 (0.489)	0.5702 (0.479)	0.7059 (0.2015)	0.6441 (0.1983)	0.7003 (0.0768)	0.6452 (0.0770)	0.7003 (0.0767)	0.6453 (0.0771)	0.5755 (0.1009)	0.5487 (0.1030)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 1.0$										
1	0.5550 (0.0365)	0.5325 (0.0339)	0.5933 (0.0461)	0.5514 (0.0492)	0.5913 (0.0498)	0.5516 (0.0490)	0.5913 (0.0498)	0.5515 (0.0490)	0.5843 (0.0419)	0.5489 (0.0396)
2	0.5580 (0.0272)	0.5338 (0.0228)	0.5990 (0.0397)	0.5572 (0.0351)	0.5974 (0.0403)	0.5570 (0.0344)	0.5976 (0.0401)	0.5570 (0.0340)	0.5815 (0.0336)	0.5484 (0.0296)
3	0.5718 (0.0304)	0.5413 (0.0249)	0.6312 (0.0482)	0.5732 (0.0471)	0.6264 (0.0480)	0.5738 (0.0392)	0.6266 (0.0480)	0.5738 (0.0391)	0.5807 (0.0353)	0.5464 (0.0308)
4	0.6091 (0.0516)	0.5583 (0.0493)	0.7223 (0.0807)	0.6217 (0.2010)	0.7108 (0.0807)	0.6246 (0.0788)	0.7107 (0.0807)	0.6246 (0.0789)	0.5756 (0.1001)	0.5447 (0.1028)
Measurement error $\sigma_e^2 = 1.5$										
1	0.5582 (0.0375)	0.5292 (0.0343)	0.6009 (0.0529)	0.5463 (0.0494)	0.5971 (0.0508)	0.5464 (0.0492)	0.5971 (0.0509)	0.5464 (0.0492)	0.5892 (0.0431)	0.5444 (0.0400)
2	0.5598 (0.0286)	0.5301 (0.0230)	0.6062 (0.0447)	0.5512 (0.0351)	0.6017 (0.0426)	0.5510 (0.0344)	0.6017 (0.0424)	0.5510 (0.0339)	0.5839 (0.0353)	0.5428 (0.0298)
3	0.5737 (0.0320)	0.5366 (0.0250)	0.6365 (0.0588)	0.5653 (0.0472)	0.6310 (0.0514)	0.5659 (0.0393)	0.6310 (0.0513)	0.5659 (0.0392)	0.5833 (0.0357)	0.5414 (0.0295)
4	0.6125 (0.0535)	0.5508 (0.0492)	0.7319 (0.2078)	0.6071 (0.2025)	0.7170 (0.0844)	0.6108 (0.0801)	0.7170 (0.0846)	0.6108 (0.0802)	0.5756 (0.0979)	0.5383 (0.1038)
Measurement error $\sigma_e^2 = 2.0$										
1	0.5615 (0.0386)	0.5268 (0.0279)	0.6069 (0.0544)	0.5426 (0.0496)	0.6016 (0.0518)	0.5426 (0.0494)	0.6017 (0.0519)	0.5426 (0.0493)	0.5936 (0.0445)	0.5410 (0.0405)
2	0.5615 (0.0300)	0.5276 (0.0208)	0.6112 (0.0473)	0.5468 (0.0351)	0.6052 (0.0446)	0.5467 (0.0344)	0.6054 (0.0444)	0.5466 (0.0339)	0.5856 (0.0372)	0.5388 (0.0294)
3	0.5749 (0.0336)	0.5333 (0.0236)	0.6419 (0.0620)	0.5596 (0.0472)	0.6345 (0.0543)	0.5601 (0.0393)	0.6347 (0.0542)	0.5602 (0.0392)	0.5851 (0.0377)	0.5381 (0.0303)
4	0.6147 (0.0565)	0.5451 (0.0457)	0.7416 (0.2100)	0.5964 (0.2031)	0.7215 (0.0880)	0.6008 (0.0810)	0.7214 (0.0882)	0.6006 (0.0811)	0.5792 (0.0992)	0.5323 (0.1024)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 2.5$										
1	0.5644 (0.0394)	0.5252 (0.0346)	0.6119 (0.0559)	0.5397 (0.0498)	0.6053 (0.0526)	0.5397 (0.0495)	0.6053 (0.0528)	0.5397 (0.0494)	0.5960 (0.0463)	0.5378 (0.0404)
2	0.5628 (0.0312)	0.5257 (0.0231)	0.6153 (0.0497)	0.5435 (0.0351)	0.6080 (0.0465)	0.5433 (0.0343)	0.6081 (0.0463)	0.5433 (0.0339)	0.5873 (0.0382)	0.5362 (0.0292)
3	0.5757 (0.0350)	0.5307 (0.0250)	0.6463 (0.0647)	0.5552 (0.0471)	0.6371 (0.0568)	0.5558 (0.0394)	0.6372 (0.0567)	0.5558 (0.0393)	0.5867 (0.0390)	0.5345 (0.0310)
4	0.6160 (0.0595)	0.5405 (0.0497)	0.7489 (0.2118)	0.5882 (0.2034)	0.7244 (0.0913)	0.5931 (0.0815)	0.7243 (0.0916)	0.5929 (0.0816)	0.5748 (0.0975)	0.5335 (0.1024)

Table C. 17: Time-dependent AUC(SE) for current methods when γ=0.5 and 50% censoring

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.6046 (0.0363)	0.5852 (0.0338)	0.6567 (0.0456)	0.6286 (0.0454)	0.6561 (0.0453)	0.6289 (0.0453)	0.6562 (0.0453)	0.6289 (0.0453)	0.6455 (0.0377)	0.6198 (0.0367)
2	0.6070 (0.0262)	0.5869 (0.0237)	0.6700 (0.0360)	0.6397 (0.0348)	0.6689 (0.0352)	0.6397 (0.0341)	0.6690 (0.0348)	0.6398 (0.0337)	0.6409 (0.0293)	0.6167 (0.0281)
3	0.6250 (0.0269)	0.6022 (0.0245)	0.7155 (0.0444)	0.6762 (0.0428)	0.7142 (0.0369)	0.6769 (0.0353)	0.7144 (0.0367)	0.6771 (0.0350)	0.6366 (0.0314)	0.6108 (0.0311)
4	0.6669 (0.0396)	0.6349 (0.0387)	0.8120 (0.1413)	0.7570 (0.1430)	0.8032 (0.0519)	0.7530 (0.0576)	0.8032 (0.0520)	0.7530 (0.0575)	0.6242 (0.0809)	0.5930 (0.0868)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.5$										
1	0.6108 (0.0380)	0.5777 (0.0337)	0.6670 (0.0466)	0.6179 (0.0460)	0.6651 (0.0459)	0.6181 (0.0458)	0.6652 (0.0459)	0.6181 (0.0459)	0.6533 (0.0382)	0.6104 (0.0375)
2	0.6128 (0.0279)	0.5788 (0.0233)	0.6793 (0.0380)	0.6272 (0.0353)	0.6768 (0.0368)	0.6272 (0.0345)	0.6770 (0.0365)	0.6272 (0.0341)	0.6463 (0.0297)	0.6052 (0.0283)
3	0.6316 (0.0282)	0.5931 (0.0241)	0.7268 (0.0465)	0.6600 (0.0431)	0.7237 (0.0393)	0.6607 (0.0360)	0.7239 (0.0390)	0.6609 (0.0357)	0.6426 (0.0316)	0.5997 (0.0313)
4	0.6763 (0.0411)	0.6216 (0.0385)	0.8261 (0.1423)	0.7318 (0.1445)	0.8142 (0.0525)	0.7295 (0.0611)	0.8141 (0.0527)	0.7294 (0.0612)	0.6312 (0.0837)	0.5842 (0.0860)
Measurement error $\sigma_e^2 = 1.0$										
1	0.6204 (0.0405)	0.5670 (0.0342)	0.6833 (0.0486)	0.6028 (0.0472)	0.6788 (0.0473)	0.6029 (0.0469)	0.6789 (0.0473)	0.6029 (0.0470)	0.6637 (0.0403)	0.5959 (0.0387)
2	0.6200 (0.0303)	0.5672 (0.0235)	0.6933 (0.0417)	0.6098 (0.0358)	0.6878 (0.0400)	0.6098 (0.0349)	0.6880 (0.0397)	0.6098 (0.0344)	0.6540 (0.0326)	0.5908 (0.0286)
3	0.6387 (0.0301)	0.5799 (0.0242)	0.7429 (0.0502)	0.6375 (0.0435)	0.7355 (0.0429)	0.6383 (0.0370)	0.7358 (0.0426)	0.6384 (0.0366)	0.6488 (0.0330)	0.5847 (0.0315)
4	0.6873 (0.0444)	0.6027 (0.0394)	0.8471 (0.1443)	0.6974 (0.1468)	0.8278 (0.0546)	0.6969 (0.0651)	0.8277 (0.0549)	0.6967 (0.0652)	0.6400 (0.0813)	0.5701 (0.0874)
Measurement error $\sigma_e^2 = 1.5$										
1	0.6285 (0.0428)	0.5600 (0.0348)	0.6960 (0.0506)	0.5923 (0.0479)	0.6890 (0.0487)	0.5924 (0.0476)	0.6891 (0.0487)	0.5923 (0.0477)	0.6719 (0.0421)	0.5863 (0.0390)
2	0.6249 (0.0328)	0.5597 (0.0235)	0.7041 (0.0451)	0.5979 (0.0359)	0.6958 (0.0428)	0.5979 (0.0350)	0.6960 (0.0425)	0.5978 (0.0346)	0.6589 (0.0344)	0.5804 (0.0288)
3	0.6429 (0.0324)	0.5712 (0.0243)	0.7543 (0.0537)	0.6225 (0.0438)	0.7431 (0.0464)	0.6233 (0.0375)	0.7433 (0.0461)	0.6234 (0.0370)	0.6526 (0.0360)	0.5754 (0.0323)
4	0.6936 (0.0482)	0.5906 (0.0400)	0.8621 (0.1458)	0.6745 (0.1485)	0.8353 (0.0571)	0.6750 (0.0676)	0.8352 (0.0574)	0.6747 (0.0678)	0.6460 (0.0780)	0.5591 (0.0915)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 2.0$										
1	0.6352 (0.0448)	0.5549 (0.0352)	0.7059 (0.0522)	0.5846 (0.0485)	0.6966 (0.0499)	0.5846 (0.0481)	0.6966 (0.0499)	0.5846 (0.0482)	0.6788 (0.0429)	0.5789 (0.0392)
2	0.6287 (0.0350)	0.5542 (0.0236)	0.7126 (0.0482)	0.5892 (0.0360)	0.7016 (0.0454)	0.5892 (0.0351)	0.7017 (0.0451)	0.5892 (0.0346)	0.6617 (0.0373)	0.5734 (0.0287)
3	0.6453 (0.0346)	0.5648 (0.0243)	0.7630 (0.0572)	0.6116 (0.0440)	0.7479 (0.0496)	0.6125 (0.0378)	0.7481 (0.0493)	0.6125 (0.0373)	0.6551 (0.0379)	0.5679 (0.0313)
4	0.6970 (0.0517)	0.5818 (0.0401)	0.8742 (0.1476)	0.6577 (0.1495)	0.8394 (0.0601)	0.6592 (0.0692)	0.8393 (0.0605)	0.6588 (0.0693)	0.6512 (0.0807)	0.5562 (0.0894)
Measurement error $\sigma_e^2 = 2.5$										
1	0.6407 (0.0463)	0.5511 (0.0354)	0.7138 (0.0536)	0.5786 (0.0488)	0.7023 (0.0510)	0.5786 (0.0485)	0.7023 (0.0511)	0.5786 (0.0485)	0.6835 (0.0453)	0.5735 (0.0396)
2	0.6317 (0.0372)	0.5501 (0.0235)	0.7196 (0.0512)	0.5825 (0.0360)	0.7060 (0.0479)	0.5826 (0.0351)	0.7060 (0.0477)	0.5825 (0.0347)	0.6645 (0.0395)	0.5677 (0.0285)
3	0.6471 (0.0367)	0.5598 (0.0245)	0.7701 (0.0608)	0.6032 (0.0440)	0.7513 (0.0529)	0.6041 (0.0380)	0.7515 (0.0526)	0.6042 (0.0375)	0.6563 (0.0402)	0.5627 (0.0318)
4	0.6991 (0.0556)	0.5748 (0.0411)	0.8847 (0.1498)	0.6448 (0.1502)	0.8413 (0.0642)	0.6469 (0.0702)	0.8412 (0.0645)	0.6464 (0.0704)	0.6473 (0.0801)	0.5508 (0.0906)

Table C. 18: Time-dependent AUC(SE) for current methods when γ=0.75 and 50% censoring

Predicted Time	NNE AUC(SE)		KMCD AUC(SE)		IPCW AUC(SE)		CIPCW AUC(SE)		FP AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.6605 (0.0376)	0.6285 (0.0346)	0.7266 (0.0415)	0.6871 (0.0419)	0.7255 (0.0409)	0.6873 (0.0415)	0.7256 (0.0409)	0.6873 (0.0416)	0.7086 (0.0334)	0.6873 (0.0338)
2	0.6589 (0.0268)	0.6285 (0.0239)	0.7448 (0.0329)	0.7017 (0.0321)	0.7430 (0.0315)	0.7016 (0.0308)	0.7432 (0.0312)	0.7017 (0.0306)	0.6968 (0.0278)	0.6608 (0.0262)
3	0.6710 (0.0266)	0.6390 (0.0238)	0.7922 (0.0401)	0.7386 (0.0398)	0.7897 (0.0321)	0.7391 (0.0315)	0.7900 (0.0318)	0.7393 (0.0311)	0.6861 (0.0297)	0.6462 (0.0306)
4	0.7101 (0.0349)	0.6689 (0.0336)	0.8723 (0.1056)	0.8084 (0.1094)	0.8644 (0.0363)	0.8060 (0.0443)	0.8646 (0.0365)	0.8063 (0.0446)	0.6632 (0.0692)	0.6221 (0.0752)
Measurement error $\sigma_e^2 = 0.5$										
1	0.6707 (0.0398)	0.6163 (0.0344)	0.7399 (0.0423)	0.6713 (0.0427)	0.7371 (0.0416)	0.6714 (0.0423)	0.7371 (0.0416)	0.6714 (0.0424)	0.7190 (0.0343)	0.6593 (0.0344)
2	0.6677 (0.0284)	0.6167 (0.0236)	0.7574 (0.0353)	0.6839 (0.0329)	0.7534 (0.0334)	0.6838 (0.0316)	0.7536 (0.0332)	0.6838 (0.0313)	0.7045 (0.0285)	0.6454 (0.0268)
3	0.6801 (0.0279)	0.6265 (0.0235)	0.8071 (0.0419)	0.7165 (0.0406)	0.8015 (0.0339)	0.7170 (0.0326)	0.8018 (0.0336)	0.7172 (0.0322)	0.6934 (0.0300)	0.6289 (0.0304)
4	0.7221 (0.0367)	0.6526 (0.0333)	0.8887 (0.1061)	0.7796 (0.1116)	0.8759 (0.0356)	0.7781 (0.0484)	0.8761 (0.0363)	0.7784 (0.0487)	0.6769 (0.0652)	0.6070 (0.0743)
Measurement error $\sigma_e^2 = 1.0$										
1	0.6863 (0.0433)	0.5995 (0.0345)	0.7606 (0.0442)	0.6490 (0.0439)	0.7544 (0.0431)	0.6491 (0.0436)	0.7545 (0.0430)	0.6491 (0.0436)	0.7328 (0.0366)	0.6380 (0.0356)
2	0.6795 (0.0319)	0.5999 (0.0236)	0.7759 (0.0394)	0.6591 (0.0337)	0.7676 (0.0369)	0.6589 (0.0323)	0.7678 (0.0367)	0.6590 (0.0321)	0.7144 (0.0312)	0.6243 (0.0274)
3	0.6910 (0.0301)	0.6087 (0.0235)	0.8276 (0.0454)	0.6861 (0.0415)	0.8157 (0.0371)	0.6866 (0.0341)	0.8161 (0.0368)	0.6868 (0.0336)	0.7029 (0.0320)	0.6093 (0.0312)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
4	0.7371 (0.0405)	0.6297 (0.0338)	0.9118 (0.1070)	0.7396 (0.1143)	0.8891 (0.0370)	0.7394 (0.0530)	0.8893 (0.0371)	0.7397 (0.0533)	0.6921 (0.0654)	0.5847 (0.0698)
Measurement error $\sigma_e^2 = 1.5$										
1	0.6990 (0.0466)	0.5884 (0.0347)	0.7765 (0.0465)	0.6337 (0.0446)	0.7673 (0.0451)	0.6337 (0.0443)	0.7673 (0.0450)	0.6337 (0.0443)	0.7433 (0.0396)	0.6241 (0.0363)
2	0.6879 (0.0354)	0.5887 (0.0238)	0.7899 (0.0432)	0.6421 (0.0340)	0.7776 (0.0401)	0.6420 (0.0326)	0.7777 (0.0400)	0.6419 (0.0324)	0.7206 (0.0337)	0.6101 (0.0277)
3	0.6976 (0.0326)	0.5968 (0.0234)	0.8420 (0.0489)	0.6657 (0.0421)	0.8243 (0.0401)	0.6662 (0.0349)	0.8246 (0.0399)	0.6664 (0.0344)	0.7077 (0.0347)	0.5958 (0.0313)
4	0.7463 (0.0442)	0.6150 (0.0342)	0.9284 (0.1077)	0.7129 (0.1163)	0.8961 (0.0388)	0.7134 (0.0561)	0.8963 (0.0388)	0.7136 (0.0563)	0.6979 (0.0655)	0.5757 (0.0702)
Measurement error $\sigma_e^2 = 2.0$										
1	0.7104 (0.0515)	0.5829 (0.0345)	0.7911 (0.0502)	0.6241 (0.0453)	0.7791 (0.0491)	0.6244 (0.0455)	0.7791 (0.0491)	0.6244 (0.0455)	0.7528 (0.0422)	0.6151 (0.0352)
2	0.6943 (0.0385)	0.5835 (0.0230)	0.8028 (0.0463)	0.6320 (0.0334)	0.7868 (0.0437)	0.6326 (0.0326)	0.7870 (0.0436)	0.6326 (0.0324)	0.7258 (0.0369)	0.6024 (0.0260)
3	0.6997 (0.0345)	0.5907 (0.0232)	0.8533 (0.0547)	0.6532 (0.0421)	0.8289 (0.0442)	0.6541 (0.0337)	0.8291 (0.0442)	0.6543 (0.0334)	0.7127 (0.0372)	0.5887 (0.0305)
4	0.7525 (0.0502)	0.6075 (0.0340)	0.9487 (0.1143)	0.7004 (0.1152)	0.9014 (0.0443)	0.6981 (0.0577)	0.9017 (0.0440)	0.6986 (0.0572)	0.7043 (0.0640)	0.5714 (0.0726)
Measurement error $\sigma_e^2 = 2.5$										
1	0.7159 (0.0515)	0.5740 (0.0348)	0.7966 (0.0503)	0.6129 (0.0460)	0.7822 (0.0487)	0.7082 (0.0405)	0.7821 (0.0487)	0.6128 (0.0458)	0.7558 (0.0437)	0.6929 (0.0314)
2	0.6981 (0.0415)	0.5742 (0.0236)	0.8081 (0.0499)	0.6197 (0.0341)	0.7887 (0.0458)	0.7253 (0.0287)	0.7886 (0.0458)	0.6195 (0.0326)	0.7274 (0.0393)	0.6821 (0.0256)
3	0.7040 (0.0377)	0.5815 (0.0233)	0.8598 (0.0561)	0.6398 (0.0429)	0.8318 (0.0464)	0.7693 (0.0300)	0.8321 (0.0463)	0.6406 (0.0354)	0.7106 (0.0398)	0.6710 (0.0289)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
4	0.7555 (0.0519)	0.5958 (0.0350)	0.9505 (0.1119)	0.6779 (0.1178)	0.9005 (0.0456)	0.8450 (0.0374)	0.9007 (0.0457)	0.6804 (0.0594)	0.7004 (0.0696)	0.6467 (0.0700)

Table C. 19: Time-dependent AUC(SE) for current methods when γ=1.0 and 50% censoring

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.7134 (0.0361)	0.6702 (0.0339)	0.7880 (0.0366)	0.7398 (0.0377)	0.7865 (0.0361)	0.7399 (0.0374)	0.7866 (0.0360)	0.7400 (0.0374)	0.7611 (0.0288)	0.7173 (0.0294)
2	0.7018 (0.0275)	0.6625 (0.0249)	0.8061 (0.0306)	0.7522 (0.0306)	0.8037 (0.0292)	0.7522 (0.0294)	0.8039 (0.0290)	0.7523 (0.0293)	0.7406 (0.0256)	0.6933 (0.0252)
3	0.7061 (0.0256)	0.6663 (0.0231)	0.8474 (0.0357)	0.7834 (0.0368)	0.8438 (0.0265)	0.7838 (0.0276)	0.8441 (0.0264)	0.7841 (0.0273)	0.7231 (0.0276)	0.6708 (0.0285)
4	0.7363 (0.0317)	0.6879 (0.0303)	0.9058 (0.0795)	0.8356 (0.0845)	0.8983 (0.0275)	0.8346 (0.0367)	0.8985 (0.0276)	0.8350 (0.0369)	0.7025 (0.0557)	0.6471 (0.0586)
Measurement error $\sigma_e^2 = 0.5$										
1	0.7274 (0.0381)	0.6538 (0.0339)	0.8030 (0.0374)	0.7669 (0.0369)	0.7993 (0.0368)	0.7196 (0.0385)	0.7994 (0.0367)	0.7197 (0.0385)	0.7725 (0.0301)	0.6978 (0.0303)
2	0.7135 (0.0291)	0.6471 (0.0246)	0.8209 (0.0326)	0.7833 (0.0276)	0.8155 (0.0310)	0.7296 (0.0306)	0.8157 (0.0308)	0.7296 (0.0305)	0.7500 (0.0273)	0.6739 (0.0264)
3	0.7175 (0.0266)	0.6510 (0.0227)	0.8642 (0.0371)	0.8206 (0.0347)	0.8562 (0.0281)	0.7574 (0.0294)	0.8565 (0.0280)	0.7576 (0.0291)	0.7332 (0.0287)	0.6495 (0.0309)
4	0.7505 (0.0333)	0.6692 (0.0299)	0.9233 (0.0793)	0.8825 (0.0804)	0.9095 (0.0272)	0.8039 (0.0414)	0.9097 (0.0273)	0.8043 (0.0417)	0.7157 (0.0554)	0.6252 (0.0600)

Predicted Time	NNE AUC(SE)		KMCD AUC(SE)		IPCW AUC(SE)		CIPCW AUC(SE)		FP AUC(SE)	
	Adjusted	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**
Measurement error $\sigma_e^2 = 1.0$										
1	0.7488 (0.0413)	0.6306 (0.0336)	0.8256 (0.0395)	0.6908 (0.0402)	0.8182 (0.0386)	0.6909 (0.0400)	0.8183 (0.0384)	0.6909 (0.0400)	0.7874 (0.0328)	0.6717 (0.0320)
2	0.7296 (0.0319)	0.6256 (0.0243)	0.8418 (0.0364)	0.6980 (0.0329)	0.8310 (0.0340)	0.6981 (0.0318)	0.8312 (0.0337)	0.6981 (0.0317)	0.7611 (0.0300)	0.6471 (0.0270)
3	0.7317 (0.0282)	0.6297 (0.0222)	0.8865 (0.0402)	0.7205 (0.0392)	0.8703 (0.0309)	0.7212 (0.0319)	0.8706 (0.0308)	0.7214 (0.0314)	0.7441 (0.0305)	0.6247 (0.0302)
4	0.7686 (0.0355)	0.6440 (0.0302)	0.9469 (0.0798)	0.7599 (0.0896)	0.9216 (0.0272)	0.7613 (0.0471)	0.9218 (0.0272)	0.7616 (0.0473)	0.7303 (0.0520)	0.5995 (0.0601)
Measurement error $\sigma_e^2 = 1.5$										
1	0.7640 (0.0439)	0.6152 (0.0335)	0.8419 (0.0416)	0.6707 (0.0409)	0.8314 (0.0405)	0.6707 (0.0409)	0.8314 (0.0403)	0.6707 (0.0408)	0.7982 (0.0358)	0.6538 (0.0334)
2	0.7407 (0.0345)	0.6112 (0.0245)	0.8570 (0.0397)	0.6764 (0.0334)	0.8412 (0.0365)	0.6766 (0.0323)	0.8413 (0.0364)	0.6766 (0.0321)	0.7687 (0.0326)	0.6291 (0.0275)
3	0.7402 (0.0296)	0.6155 (0.0221)	0.9021 (0.0432)	0.6963 (0.0399)	0.8785 (0.0330)	0.6970 (0.0333)	0.8787 (0.0329)	0.6970 (0.0327)	0.7511 (0.0327)	0.6085 (0.0311)
4	0.7799 (0.0370)	0.6279 (0.0305)	0.9642 (0.0805)	0.7310 (0.0915)	0.9281 (0.0280)	0.7330 (0.0502)	0.9283 (0.0280)	0.7330 (0.0503)	0.7397 (0.0517)	0.5912 (0.0619)
Measurement error $\sigma_e^2 = 2.0$										
1	0.7754 (0.0490)	0.6071 (0.0337)	0.8565 (0.0448)	0.6578 (0.0417)	0.8432 (0.0441)	0.6581 (0.0418)	0.8433 (0.0441)	0.6581 (0.0418)	0.8090 (0.0387)	0.6412 (0.0324)
2	0.7474 (0.0380)	0.6031 (0.0231)	0.8703 (0.0431)	0.6627 (0.0327)	0.8499 (0.0394)	0.6632 (0.0316)	0.8501 (0.0394)	0.6633 (0.0314)	0.7736 (0.0349)	0.6197 (0.0262)
3	0.7424 (0.0328)	0.6072 (0.0232)	0.9147 (0.0494)	0.6808 (0.0411)	0.8826 (0.0360)	0.6813 (0.0321)	0.8828 (0.0360)	0.6816 (0.0319)	0.7551 (0.0358)	0.6008 (0.0307)
4	0.7871 (0.0422)	0.6205 (0.0313)	0.9868 (0.0883)	0.7202 (0.0932)	0.9329 (0.0325)	0.7172 (0.0512)	0.9331 (0.0324)	0.7175 (0.0504)	0.7500 (0.0547)	0.5830 (0.0592)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 2.5$										
1	0.7841 (0.0502)	0.5967 (0.0338)	0.8629 (0.0461)	0.6454 (0.0429)	0.8476 (0.0454)	0.6455 (0.0429)	0.8475 (0.0453)	0.6454 (0.0429)	0.8123 (0.0407)	0.6303 (0.0339)
2	0.7547 (0.0403)	0.5933 (0.0244)	0.8769 (0.0455)	0.6493 (0.0343)	0.8530 (0.0418)	0.6497 (0.0331)	0.8530 (0.0417)	0.6495 (0.0330)	0.7772 (0.0391)	0.6087 (0.0284)
3	0.7488 (0.0334)	0.5975 (0.0220)	0.9217 (0.0492)	0.6653 (0.0406)	0.8857 (0.0383)	0.6669 (0.0349)	0.8859 (0.0383)	0.6668 (0.0341)	0.7553 (0.0389)	0.5895 (0.0330)
4	0.7915 (0.0415)	0.6075 (0.0313)	0.9878 (0.0832)	0.6923 (0.0936)	0.9326 (0.0329)	0.6969 (0.0541)	0.9328 (0.0329)	0.6968 (0.0541)	0.7398 (0.0562)	0.5720 (0.0598)

Table C. 20: Time-dependent AUC(SE) for current methods when γ=0 and 70% censoring

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.4981 (0.0347)	0.4993 (0.0341)	0.4975 (0.0564)	0.4978 (0.0545)	0.4987 (0.0559)	0.4990 (0.0544)	0.4984 (0.0556)	0.4986 (0.0542)	0.4966 (0.0500)	0.4974 (0.0483)
2	0.4980 (0.0292)	0.4984 (0.0277)	0.4970 (0.0478)	0.4974 (0.0441)	0.4982 (0.0468)	0.4987 (0.0440)	0.4976 (0.0462)	0.4981 (0.0433)	0.5009 (0.0431)	0.5013 (0.0416)
3	0.4979 (0.0352)	0.4984 (0.0328)	0.4995 (0.0725)	0.4991 (0.0689)	0.5022 (0.0573)	0.5029 (0.0539)	0.5019 (0.0576)	0.5026 (0.0541)	0.4978 (0.0501)	0.4986 (0.0503)
4	0.4641 (0.0927)	0.4628 (0.0902)	0.4840 (0.4077)	0.4792 (0.3960)	0.4938 (0.1501)	0.4913 (0.1477)	0.4940 (0.1526)	0.4913 (0.1493)	0.4893 (0.2146)	0.4931 (0.2249)
Measurement error $\sigma_e^2 = 0.5$										

Predicted Time	NNE AUC(SE)		KMCD AUC(SE)		IPCW AUC(SE)		CIPCW AUC(SE)		FP AUC(SE)	
	Adjusted	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Adjusted**	**Adjusted**	**Observed**	**Adjusted**	**Observed**
1	0.4986 (0.0360)	0.5009 (0.0348)	0.5003 (0.0586)	0.5007 (0.0553)	0.5011 (0.0575)	0.5016 (0.0553)	0.5009 (0.0573)	0.5013 (0.0552)	0.4979 (0.0512)	0.4992 (0.0485)
2	0.4983 (0.0300)	0.4992 (0.0275)	0.4982 (0.0503)	0.4988 (0.0443)	0.4987 (0.0481)	0.4996 (0.0434)	0.4983 (0.0478)	0.4991 (0.0429)	0.5006 (0.0424)	0.5004 (0.0389)
3	0.4990 (0.0358)	0.4991 (0.0319)	0.5027 (0.0756)	0.5018 (0.0688)	0.5039 (0.0584)	0.5041 (0.0526)	0.5039 (0.0590)	0.5041 (0.0527)	0.5030 (0.0533)	0.5021 (0.0494)
4	0.4681 (0.0950)	0.4648 (0.0917)	0.4987 (0.4201)	0.4908 (0.3993)	0.4977 (0.1545)	0.4946 (0.1502)	0.4983 (0.1570)	0.4949 (0.1516)	0.4917 (0.2111)	0.5022 (0.2197)
Measurement error $\sigma_e^2 = 1.0$										
1	0.4984 (0.0385)	0.5019 (0.0368)	0.5014 (0.0643)	0.5016 (0.0578)	0.5018 (0.0612)	0.5022 (0.0571)	0.5018 (0.0612)	0.5022 (0.0571)	0.5009 (0.0557)	0.5002 (0.0496)
2	0.4980 (0.0309)	0.4994 (0.0276)	0.4989 (0.0546)	0.4996 (0.0432)	0.4999 (0.0521)	0.5005 (0.0433)	0.4999 (0.0516)	0.5005 (0.0426)	0.5012 (0.0453)	0.5025 (0.0391)
3	0.4988 (0.0384)	0.4988 (0.0333)	0.5025 (0.0813)	0.5029 (0.0674)	0.5039 (0.0650)	0.5044 (0.0544)	0.5039 (0.0650)	0.5045 (0.0543)	0.5009 (0.0557)	0.5014 (0.0497)
4	0.4652 (0.1018)	0.4629 (0.0931)	0.4808 (0.4358)	0.4915 (0.4142)	0.4899 (0.1620)	0.4927 (0.1493)	0.4899 (0.1639)	0.4923 (0.1502)	0.5109 (0.2084)	0.4992 (0.2138)
Measurement error $\sigma_e^2 = 1.5$										
1	0.4975 (0.0401)	0.5017 (0.0380)	0.5014 (0.0683)	0.5023 (0.0590)	0.5011 (0.0636)	0.5023 (0.0584)	0.5012 (0.0637)	0.5022 (0.0584)	0.4994 (0.0588)	0.4995 (0.0501)
2	0.4977 (0.0333)	0.4993 (0.0277)	0.4994 (0.0610)	0.5004 (0.0434)	0.4998 (0.0571)	0.5008 (0.0433)	0.4998 (0.0567)	0.5006 (0.0426)	0.5006 (0.0482)	0.5026 (0.0397)
3	0.4979 (0.0400)	0.4984 (0.0344)	0.5033 (0.0864)	0.5029 (0.0720)	0.5030 (0.0684)	0.5039 (0.0566)	0.5031 (0.0684)	0.5041 (0.0565)	0.5025 (0.0546)	0.5014 (0.0528)
4	0.4705 (0.1056)	0.4656 (0.0916)	0.4930 (0.4345)	0.4924 (0.4191)	0.4907 (0.1691)	0.4955 (0.1469)	0.4898 (0.1707)	0.4950 (0.1479)	0.4987 (0.2019)	0.4916 (0.2205)
Measurement error $\sigma_e^2 = 2.0$										

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Adjusted	Adjusted	Observed	Adjusted	Observed
1	0.4980 (0.0403)	0.5018 (0.0374)	0.5025 (0.0705)	0.5027 (0.0579)	0.5019 (0.0645)	0.5026 (0.0573)	0.5020 (0.0646)	0.5026 (0.0572)	0.5011 (0.0609)	0.5012 (0.0505)
2	0.4981 (0.0341)	0.4997 (0.0275)	0.5008 (0.0644)	0.5013 (0.0432)	0.5012 (0.0596)	0.5018 (0.0436)	0.5012 (0.0593)	0.5015 (0.0429)	0.5015 (0.0497)	0.5029 (0.0394)
3	0.4983 (0.0407)	0.4979 (0.0349)	0.5036 (0.0893)	0.5020 (0.0700)	0.5043 (0.0713)	0.5045 (0.0573)	0.5042 (0.0712)	0.5044 (0.0575)	0.5028 (0.0553)	0.5007 (0.0496)
4	0.4756 (0.1056)	0.4668 (0.0919)	0.4905 (0.4452)	0.4942 (0.4159)	0.4933 (0.1731)	0.4967 (0.1503)	0.4925 (0.1741)	0.4959 (0.1513)	0.5010 (0.2076)	0.4998 (0.2174)
Measurement error $\sigma_e^2 = 2.5$										
1	0.4977 (0.0433)	0.5028 (0.0387)	0.5021 (0.0757)	0.5027 (0.0591)	0.5024 (0.0687)	0.5032 (0.0582)	0.5024 (0.0690)	0.5030 (0.0583)	0.5004 (0.0624)	0.5012 (0.0492)
2	0.4965 (0.0348)	0.4992 (0.0274)	0.4985 (0.0669)	0.5001 (0.0433)	0.4994 (0.0612)	0.5010 (0.0436)	0.4993 (0.0608)	0.5008 (0.0429)	0.4995 (0.0522)	0.5024 (0.0385)
3	0.4979 (0.0433)	0.4985 (0.0332)	0.5024 (0.0946)	0.5036 (0.0670)	0.5030 (0.0769)	0.5047 (0.0557)	0.5031 (0.0768)	0.5050 (0.0553)	0.5023 (0.0598)	0.5014 (0.0517)
4	0.4697 (0.1119)	0.4639 (0.0937)	0.4870 (0.4484)	0.5002 (0.4194)	0.4915 (0.1778)	0.4947 (0.1495)	0.4910 (0.1794)	0.4942 (0.1505)	0.5106 (0.2022)	0.4946 (0.2152)

Table C. 21: Time-dependent AUC(SE) for current methods when γ=0.25 and 70% censoring

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.5486 (0.0332)	0.5408 (0.0323)	0.5790 (0.0470)	0.5646 (0.0469)	0.5790 (0.0469)	0.5649 (0.0469)	0.5789 (0.0468)	0.5648 (0.0468)	0.5760 (0.0365)	0.5630 (0.0352)

Predicted Time	NNE AUC(SE)		KMCD AUC(SE)		IPCW AUC(SE)		CIPCW AUC(SE)		FP AUC(SE)	
	Adjusted	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**
2	0.5536 (0.0227)	0.5451 (0.0214)	0.5880 (0.0326)	0.5733 (0.0310)	0.5884 (0.0320)	0.5739 (0.0305)	0.5883 (0.0318)	0.5738 (0.0304)	0.5749 (0.0240)	0.5628 (0.0232)
3	0.5674 (0.0206)	0.5568 (0.0189)	0.6150 (0.0360)	0.5959 (0.0337)	0.6153 (0.0310)	0.5966 (0.0283)	0.6152 (0.0310)	0.5965 (0.0283)	0.5745 (0.0247)	0.5623 (0.0244)
4	0.6069 (0.0349)	0.5891 (0.0336)	0.6956 (0.1228)	0.6641 (0.1234)	0.6975 (0.0576)	0.6662 (0.0561)	0.6976 (0.0578)	0.6664 (0.0563)	0.5726 (0.0703)	0.5588 (0.0703)
Measurement error $\sigma_e^2 = 0.5$										
1	0.5522 (0.0399)	0.5379 (0.0368)	0.5854 (0.0582)	0.5590 (0.0545)	0.5841 (0.0571)	0.5597 (0.0547)	0.5839 (0.0568)	0.5595 (0.0544)	0.5799 (0.0541)	0.5582 (0.0501)
2	0.5546 (0.0330)	0.5404 (0.0284)	0.5934 (0.0509)	0.5669 (0.0446)	0.5914 (0.0496)	0.5674 (0.0437)	0.5909 (0.0493)	0.5669 (0.0434)	0.5771 (0.0418)	0.5573 (0.0395)
3	0.5669 (0.0354)	0.5493 (0.0317)	0.6230 (0.0736)	0.5884 (0.0666)	0.6217 (0.0573)	0.5905 (0.0510)	0.6220 (0.0575)	0.5905 (0.0511)	0.5791 (0.0502)	0.5571 (0.0493)
4	0.5904 (0.0834)	0.5589 (0.0784)	0.7104 (0.3775)	0.6521 (0.3582)	0.6988 (0.1325)	0.6458 (0.1353)	0.7000 (0.1340)	0.6462 (0.1375)	0.5703 (0.2024)	0.5447 (0.2071)
Measurement error $\sigma_e^2 = 1.0$										
1	0.5560 (0.0430)	0.5336 (0.0379)	0.5951 (0.0624)	0.5516 (0.0553)	0.5913 (0.0599)	0.5522 (0.0555)	0.5912 (0.0596)	0.5520 (0.0552)	0.5858 (0.0556)	0.5516 (0.0497)
2	0.5571 (0.0353)	0.5353 (0.0284)	0.6013 (0.0559)	0.5584 (0.0444)	0.5967 (0.0535)	0.5588 (0.0438)	0.5964 (0.0531)	0.5584 (0.0434)	0.5800 (0.0439)	0.5491 (0.0384)
3	0.5696 (0.0379)	0.5428 (0.0315)	0.6326 (0.0787)	0.5777 (0.0666)	0.6277 (0.0622)	0.5794 (0.0512)	0.6281 (0.0625)	0.5794 (0.0511)	0.5818 (0.0524)	0.5499 (0.0502)
4	0.5965 (0.0871)	0.5461 (0.0801)	0.7261 (0.3836)	0.6355 (0.3586)	0.7065 (0.1355)	0.6263 (0.1380)	0.7079 (0.1363)	0.6264 (0.1402)	0.5845 (0.1961)	0.5428 (0.2071)
Measurement error $\sigma_e^2 = 1.5$										
1	0.5591 (0.0452)	0.5307 (0.0383)	0.6029 (0.0661)	0.5465 (0.0558)	0.5964 (0.0622)	0.5471 (0.0558)	0.5964 (0.0620)	0.5469 (0.0555)	0.5892 (0.0594)	0.5462 (0.0490)

Predicted Time	NNE AUC(SE)		KMCD AUC(SE)		IPCW AUC(SE)		CIPCW AUC(SE)		FP AUC(SE)	
	Adjusted	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**
2	0.5582 (0.0372)	0.5319 (0.0283)	0.6074 (0.0603)	0.5526 (0.0442)	0.6002 (0.0568)	0.5529 (0.0436)	0.5999 (0.0564)	0.5525 (0.0431)	0.5822 (0.0460)	0.5447 (0.0388)
3	0.5700 (0.0399)	0.5386 (0.0313)	0.6394 (0.0834)	0.5703 (0.0666)	0.6309 (0.0667)	0.5717 (0.0514)	0.6314 (0.0670)	0.5717 (0.0513)	0.5835 (0.0536)	0.5430 (0.0494)
4	0.5972 (0.0885)	0.5375 (0.0811)	0.7385 (0.3863)	0.6230 (0.3595)	0.7105 (0.1390)	0.6128 (0.1393)	0.7121 (0.1394)	0.6127 (0.1416)	0.5754 (0.1996)	0.5428 (0.2066)
Measurement error $\sigma_e^2 = 2.0$										
1	0.5613 (0.0461)	0.5271 (0.0366)	0.6091 (0.0679)	0.5426 (0.0535)	0.5996 (0.0622)	0.5424 (0.0536)	0.5995 (0.0623)	0.5422 (0.0535)	0.5925 (0.0588)	0.5413 (0.0473)
2	0.5589 (0.0390)	0.5280 (0.0286)	0.6122 (0.0657)	0.5465 (0.0451)	0.6035 (0.0603)	0.5473 (0.0440)	0.6034 (0.0602)	0.5472 (0.0434)	0.5849 (0.0507)	0.5408 (0.0424)
3	0.5694 (0.0445)	0.5337 (0.0363)	0.6429 (0.0954)	0.5617 (0.0739)	0.6308 (0.0759)	0.5633 (0.0594)	0.6306 (0.0758)	0.5631 (0.0597)	0.5826 (0.0585)	0.5368 (0.0474)
4	0.5929 (0.0965)	0.5275 (0.0832)	0.7350 (0.3880)	0.5920 (0.3895)	0.7004 (0.1467)	0.5930 (0.1412)	0.7001 (0.1479)	0.5925 (0.1431)	0.5719 (0.1950)	0.5367 (0.2092)
Measurement error $\sigma_e^2 = 2.5$										
1	0.5646 (0.0499)	0.5262 (0.0385)	0.6147 (0.0729)	0.5394 (0.0563)	0.6039 (0.0669)	0.5402 (0.0563)	0.6039 (0.0667)	0.5400 (0.0559)	0.5963 (0.0624)	0.5394 (0.0479)
2	0.5601 (0.0411)	0.5269 (0.0283)	0.6167 (0.0678)	0.5446 (0.0439)	0.6051 (0.0624)	0.5448 (0.0435)	0.6049 (0.0619)	0.5446 (0.0430)	0.5840 (0.0506)	0.5372 (0.0383)
3	0.5708 (0.0443)	0.5326 (0.0315)	0.6499 (0.0920)	0.5603 (0.0666)	0.6354 (0.0746)	0.5613 (0.0517)	0.6359 (0.0749)	0.5613 (0.0514)	0.5859 (0.0576)	0.5371 (0.0507)
4	0.5986 (0.0936)	0.5274 (0.0819)	0.7586 (0.3898)	0.6063 (0.3619)	0.7149 (0.1467)	0.5955 (0.1405)	0.7168 (0.1466)	0.5950 (0.1429)	0.5939 (0.1864)	0.5342 (0.2009)

Table C. 22: Time-dependent AUC(SE) for current methods when γ=0.5 and 70% censoring

Predicted Time	NNE AUC(SE)		KMCD AUC(SE)		IPCW AUC(SE)		CIPCW AUC(SE)		FP AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.6052 (0.0403)	0.5851 (0.0370)	0.6577 (0.0519)	0.6288 (0.0501)	0.6561 (0.0509)	0.6287 (0.0498)	0.6562 (0.0508)	0.6287 (0.0496)	0.6470 (0.0456)	0.6218 (0.0451)
2	0.6070 (0.0302)	0.5869 (0.0277)	0.6718 (0.0437)	0.6406 (0.0414)	0.6705 (0.0437)	0.6411 (0.0416)	0.6708 (0.0430)	0.6413 (0.0408)	0.6424 (0.0416)	0.6179 (0.0393)
3	0.6234 (0.0347)	0.6004 (0.0321)	0.7173 (0.0691)	0.6772 (0.0658)	0.7140 (0.0537)	0.6772 (0.0514)	0.7140 (0.0540)	0.6772 (0.0520)	0.6372 (0.0491)	0.6107 (0.0467)
4	0.6551 (0.0632)	0.6209 (0.0640)	0.8217 (0.2932)	0.7613 (0.3003)	0.7948 (0.0956)	0.7470 (0.1030)	0.7946 (0.0970)	0.7465 (0.1058)	0.6067 (0.1875)	0.5795 (0.1943)
Measurement error $\sigma_e^2 = 0.5$										
1	0.6114 (0.0424)	0.5776 (0.0368)	0.6687 (0.0539)	0.6179 (0.0503)	0.6650 (0.0521)	0.6179 (0.0500)	0.6651 (0.0520)	0.6179 (0.0499)	0.6547 (0.0480)	0.6110 (0.0450)
2	0.6122 (0.0324)	0.5786 (0.0278)	0.6817 (0.0470)	0.6277 (0.0422)	0.6779 (0.0461)	0.6283 (0.0424)	0.6782 (0.0455)	0.6284 (0.0416)	0.6468 (0.0421)	0.6076 (0.0407)
3	0.6293 (0.0366)	0.5910 (0.0322)	0.7293 (0.0720)	0.6606 (0.0664)	0.7229 (0.0564)	0.6612 (0.0526)	0.7230 (0.0567)	0.6611 (0.0533)	0.6426 (0.0483)	0.5987 (0.0472)
4	0.6651 (0.0665)	0.6071 (0.0655)	0.8359 (0.2888)	0.7332 (0.2956)	0.8036 (0.0950)	0.7232 (0.1080)	0.8033 (0.0961)	0.7227 (0.1111)	0.6236 (0.1842)	0.5710 (0.1892)
Measurement error $\sigma_e^2 = 1.0$										
1	0.6209 (0.0463)	0.5667 (0.0368)	0.6861 (0.0577)	0.6026 (0.0509)	0.6778 (0.0545)	0.6026 (0.0506)	0.6780 (0.0544)	0.6026 (0.0506)	0.6655 (0.0509)	0.5970 (0.0450)
2	0.6178 (0.0355)	0.5670 (0.0283)	0.6964 (0.0527)	0.6099 (0.0430)	0.6877 (0.0501)	0.6104 (0.0429)	0.6879 (0.0495)	0.6103 (0.0422)	0.6528 (0.0444)	0.5919 (0.0413)
3	0.6339 (0.0392)	0.5776 (0.0336)	0.7455 (0.0767)	0.6377 (0.0671)	0.7327 (0.0605)	0.6388 (0.0543)	0.7329 (0.0605)	0.6387 (0.0548)	0.6479 (0.0499)	0.5846 (0.0472)

Predicted Time	NNE AUC(SE)		KMCD AUC(SE)		IPCW AUC(SE)		CIPCW AUC(SE)		FP AUC(SE)	
	Adjusted	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**
4	0.6731 (0.0719)	0.5874 (0.0688)	0.8569 (0.2861)	0.6957 (0.2933)	0.8133 (0.0978)	0.6906 (0.1140)	0.8132 (0.0985)	0.6899 (0.1171)	0.6355 (0.1749)	0.5620 (0.1975)
Measurement error $\sigma_e^2 = 1.5$										
1	0.6232 (0.0480)	0.5647 (0.0377)	0.6904 (0.0601)	0.5994 (0.0519)	0.6806 (0.0561)	0.5992 (0.0519)	0.6806 (0.0561)	0.5992 (0.0519)	0.6671 (0.0520)	0.5932 (0.0455)
2	0.6186 (0.0367)	0.5645 (0.0286)	0.6997 (0.0546)	0.6060 (0.0438)	0.6896 (0.0516)	0.6066 (0.0437)	0.6896 (0.0516)	0.6066 (0.0437)	0.6536 (0.0460)	0.5888 (0.0421)
3	0.6344 (0.0396)	0.5752 (0.0341)	0.7491 (0.0778)	0.6330 (0.0673)	0.7344 (0.0618)	0.6347 (0.0555)	0.7344 (0.0618)	0.6347 (0.0555)	0.6499 (0.0521)	0.5830 (0.0486)
4	0.6744 (0.0731)	0.5842 (0.0699)	0.8629 (0.2888)	0.6874 (0.2936)	0.8155 (0.0994)	0.6847 (0.1160)	0.8155 (0.0994)	0.6847 (0.1160)	0.6308 (0.1765)	0.5634 (0.1970)
Measurement error $\sigma_e^2 = 2.0$										
1	0.6324 (0.0549)	0.5544 (0.0375)	0.7086 (0.0665)	0.5828 (0.0528)	0.6929 (0.0619)	0.5835 (0.0520)	0.6930 (0.0619)	0.5834 (0.0520)	0.6785 (0.0568)	0.5803 (0.0455)
2	0.6240 (0.0425)	0.5571 (0.0283)	0.7178 (0.0612)	0.5932 (0.0428)	0.6992 (0.0575)	0.5937 (0.0429)	0.6992 (0.0569)	0.5934 (0.0420)	0.6578 (0.0479)	0.5751 (0.0393)
3	0.6349 (0.0426)	0.5649 (0.0320)	0.7666 (0.0833)	0.6143 (0.0646)	0.7392 (0.0664)	0.6148 (0.0535)	0.7399 (0.0668)	0.6149 (0.0531)	0.6531 (0.0555)	0.5708 (0.0495)
4	0.6832 (0.0783)	0.5750 (0.0686)	0.9059 (0.3081)	0.6862 (0.3005)	0.8310 (0.0967)	0.6674 (0.1217)	0.8321 (0.0969)	0.6679 (0.1230)	0.6444 (0.1695)	0.5519 (0.1914)
Measurement error $\sigma_e^2 = 2.5$										
1	0.6392 (0.0559)	0.5503 (0.0381)	0.7188 (0.0683)	0.5776 (0.0525)	0.6989 (0.0619)	0.5776 (0.0523)	0.6989 (0.0620)	0.5774 (0.0522)	0.6830 (0.0583)	0.5725 (0.0465)
2	0.6259 (0.0442)	0.5497 (0.0280)	0.7243 (0.0669)	0.5819 (0.0436)	0.7023 (0.0598)	0.5829 (0.0434)	0.7022 (0.0593)	0.5826 (0.0427)	0.6606 (0.0530)	0.5701 (0.0422)
3	0.6370 (0.0464)	0.5582 (0.0348)	0.7754 (0.0907)	0.6030 (0.0677)	0.7442 (0.0719)	0.6056 (0.0567)	0.7443 (0.0717)	0.6053 (0.0567)	0.6546 (0.0585)	0.5653 (0.0487)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
4	0.6792 (0.0853)	0.5617 (0.0716)	0.9064 (0.2930)	0.6400 (0.2936)	0.8212 (0.1124)	0.6426 (0.1221)	0.8216 (0.1125)	0.6415 (0.1244)	0.6426 (0.1757)	0.5312 (0.1930)

Table C. 23: Time-dependent AUC(SE) for current methods when γ=0.75 and 70% censoring

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 0.25$										
1	0.6587 (0.0429)	0.6281 (0.0393)	0.7277 (0.0478)	0.6874 (0.0469)	0.7261 (0.0472)	0.6880 (0.0466)	0.7261 (0.0472)	0.6879 (0.0466)	0.7099 (0.0424)	0.6751 (0.0414)
2	0.6573 (0.0322)	0.6293 (0.0290)	0.7472 (0.0406)	0.7035 (0.0385)	0.7447 (0.0391)	0.7041 (0.0367)	0.7445 (0.0388)	0.7038 (0.0363)	0.6978 (0.0381)	0.6630 (0.0371)
3	0.6683 (0.0332)	0.6385 (0.0312)	0.7958 (0.0644)	0.7416 (0.0628)	0.7897 (0.0449)	0.7407 (0.0462)	0.7900 (0.0450)	0.7408 (0.0461)	0.6894 (0.0484)	0.6487 (0.0483)
4	0.7050 (0.0520)	0.6640 (0.0534)	0.8915 (0.2235)	0.8272 (0.2191)	0.8622 (0.0642)	0.8058 (0.0798)	0.8628 (0.0651)	0.8069 (0.0801)	0.6551 (0.1681)	0.6087 (0.1737)
Measurement error $\sigma_e^2 = 0.5$										
1	0.6687 (0.0465)	0.6163 (0.0388)	0.7421 (0.0504)	0.6717 (0.0480)	0.7376 (0.0494)	0.6724 (0.0478)	0.7376 (0.0495)	0.6724 (0.0478)	0.7200 (0.0444)	0.6609 (0.0423)
2	0.6649 (0.0344)	0.6178 (0.0287)	0.7607 (0.0437)	0.6861 (0.0395)	0.7546 (0.0419)	0.6866 (0.0381)	0.7545 (0.0416)	0.6863 (0.0375)	0.7041 (0.0386)	0.6472 (0.0382)
3	0.6755 (0.0341)	0.6257 (0.0310)	0.8116 (0.0666)	0.7197 (0.0635)	0.8003 (0.0462)	0.7190 (0.0475)	0.8007 (0.0463)	0.7190 (0.0475)	0.6961 (0.0460)	0.6323 (0.0472)
4	0.7161 (0.0545)	0.6473 (0.0546)	0.9108 (0.2265)	0.8000 (0.2213)	0.8736 (0.0627)	0.7805 (0.0874)	0.8742 (0.0634)	0.7818 (0.0873)	0.6752 (0.1654)	0.6055 (0.1786)

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
Measurement error $\sigma_e^2 = 1.0$										
1	0.6848 (0.0519)	0.6005 (0.0386)	0.7646 (0.0549)	0.6493 (0.0493)	0.7544 (0.0529)	0.6499 (0.0492)	0.7544 (0.0531)	0.6499 (0.0492)	0.7331 (0.0470)	0.6397 (0.0428)
2	0.6750 (0.0384)	0.6019 (0.0283)	0.7807 (0.0495)	0.6613 (0.0406)	0.7671 (0.0464)	0.6617 (0.0394)	0.7671 (0.0461)	0.6614 (0.0387)	0.7125 (0.0412)	0.6262 (0.0385)
3	0.6837 (0.0368)	0.6083 (0.0316)	0.8338 (0.0709)	0.6895 (0.0640)	0.8124 (0.0493)	0.6889 (0.0492)	0.8126 (0.0496)	0.6889 (0.0490)	0.7045 (0.0487)	0.6125 (0.0488)
4	0.7297 (0.0603)	0.6250 (0.0563)	0.9368 (0.2306)	0.7622 (0.2239)	0.8851 (0.0625)	0.7441 (0.0948)	0.8856 (0.0632)	0.7455 (0.0944)	0.6908 (0.1474)	0.5838 (0.1687)
Measurement error $\sigma_e^2 = 1.5$										
1	0.6979 (0.0556)	0.5894 (0.0372)	0.7812 (0.0591)	0.6340 (0.0489)	0.7657 (0.0560)	0.6342 (0.0484)	0.7660 (0.0561)	0.6342 (0.0484)	0.7441 (0.0510)	0.6262 (0.0430)
2	0.6824 (0.0426)	0.5901 (0.0287)	0.7959 (0.0564)	0.6440 (0.0424)	0.7744 (0.0522)	0.6437 (0.0412)	0.7748 (0.0518)	0.6437 (0.0405)	0.7169 (0.0465)	0.6111 (0.0407)
3	0.6871 (0.0406)	0.5957 (0.0321)	0.8496 (0.0768)	0.6689 (0.0672)	0.8161 (0.0564)	0.6669 (0.0516)	0.8165 (0.0566)	0.6671 (0.0517)	0.7063 (0.0526)	0.5973 (0.0483)
4	0.7321 (0.0670)	0.6064 (0.0566)	0.9612 (0.2263)	0.7316 (0.2181)	0.8853 (0.0674)	0.7150 (0.0998)	0.8856 (0.0681)	0.7162 (0.1006)	0.6891 (0.1570)	0.5849 (0.1790)
Measurement error $\sigma_e^2 = 2.0$										
1	0.7070 (0.0605)	0.5818 (0.0379)	0.7948 (0.0624)	0.6226 (0.0505)	0.7746 (0.0589)	0.6232 (0.0503)	0.7746 (0.0592)	0.6232 (0.0503)	0.7502 (0.0532)	0.6155 (0.0430)
2	0.6861 (0.0463)	0.5828 (0.0283)	0.8076 (0.0601)	0.6317 (0.0417)	0.7804 (0.0547)	0.6322 (0.0405)	0.7804 (0.0545)	0.6320 (0.0397)	0.7196 (0.0482)	0.6006 (0.0386)
3	0.6889 (0.0425)	0.5885 (0.0320)	0.8619 (0.0805)	0.6543 (0.0646)	0.8212 (0.0575)	0.6542 (0.0505)	0.8215 (0.0581)	0.6542 (0.0501)	0.7092 (0.0554)	0.5893 (0.0488)
4	0.7366 (0.0699)	0.5990 (0.0581)	0.9749 (0.2369)	0.7149 (0.2262)	0.8897 (0.0691)	0.7006 (0.1031)	0.8802 (0.0696)	0.7019 (0.1027)	0.6960 (0.1461)	0.5798 (0.1755)

Predicted Time	NNE AUC(SE)		KMCD AUC(SE)		IPCW AUC(SE)		CIPCW AUC(SE)		FP AUC(SE)	
	Adjusted	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**
Measurement error $\sigma_e^2 = 2.5$										
1	0.7153 (0.0625)	0.5738 (0.0372)	0.8040 (0.0645)	0.6128 (0.0496)	0.7792 (0.0598)	0.6127 (0.0492)	0.7792 (0.0599)	0.6125 (0.0491)	0.7557 (0.0548)	0.6048 (0.0445)
2	0.6901 (0.0492)	0.5741 (0.0284)	0.8158 (0.0664)	0.6206 (0.0435)	0.7835 (0.0575)	0.6210 (0.0421)	0.7836 (0.0574)	0.6209 (0.0417)	0.7223 (0.0517)	0.5947 (0.0429)
3	0.6909 (0.0463)	0.5798 (0.0328)	0.8716 (0.0843)	0.6405 (0.0658)	0.8230 (0.0640)	0.6425 (0.0555)	0.8235 (0.0640)	0.6425 (0.0548)	0.7050 (0.0585)	0.5824 (0.0523)
4	0.7358 (0.0761)	0.5826 (0.0626)	0.9844 (0.2323)	0.6721 (0.2379)	0.8824 (0.0823)	0.6741 (0.1071)	0.8826 (0.0826)	0.6739 (0.1095)	0.6854 (0.1545)	0.5502 (0.1804)

Table C. 24: Time-dependent AUC(SE) for current methods when γ=1.0 and 70% censoring

Predicted Time	NNE AUC(SE)		KMCD AUC(SE)		IPCW AUC(SE)		CIPCW AUC(SE)		FP AUC(SE)	
	Adjusted	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**
Measurement error $\sigma_e^2 = 0.25$										
1	0.7130 (0.0399)	0.6697 (0.0366)	0.7892 (0.0415)	0.7397 (0.0412)	0.7862 (0.0403)	0.7395 (0.0405)	0.7864 (0.0402)	0.7396 (0.0405)	0.7620 (0.0358)	0.7167 (0.0372)
2	0.7013 (0.0315)	0.6624 (0.0291)	0.8092 (0.0406)	0.7536 (0.0401)	0.8049 (0.0372)	0.7535 (0.0371)	0.8053 (0.0370)	0.7537 (0.0371)	0.7416 (0.0371)	0.6956 (0.0381)
3	0.7053 (0.0316)	0.6659 (0.0291)	0.8531 (0.0576)	0.7874 (0.0585)	0.8449 (0.0380)	0.7865 (0.0409)	0.8451 (0.0381)	0.7865 (0.0409)	0.7260 (0.0465)	0.6755 (0.0482)
4	0.7304 (0.0469)	0.6804 (0.0478)	0.9168 (0.1622)	0.8406 (0.1684)	0.8913 (0.0487)	0.8284 (0.0655)	0.8915 (0.0489)	0.8288 (0.0663)	0.6917 (0.1474)	0.6262 (0.1641)
Measurement error $\sigma_e^2 = 0.5$										

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted	Observed
1	0.7273 (0.0428)	0.6534 (0.0366)	0.8059 (0.0437)	0.7196 (0.0422)	0.7993 (0.0419)	0.7194 (0.0418)	0.7995 (0.0418)	0.7194 (0.0417)	0.7731 (0.0385)	0.6982 (0.0379)
2	0.7120 (0.0339)	0.6472 (0.0293)	0.8255 (0.0431)	0.7309 (0.0411)	0.8163 (0.0393)	0.7310 (0.0385)	0.8168 (0.0391)	0.7311 (0.0385)	0.7501 (0.0386)	0.6755 (0.0386)
3	0.7152 (0.0329)	0.6503 (0.0290)	0.8712 (0.0590)	0.7603 (0.0593)	0.8565 (0.0393)	0.7601 (0.0437)	0.8567 (0.0393)	0.7601 (0.0436)	0.7368 (0.0458)	0.6523 (0.0478)
4	0.7441 (0.0482)	0.6615 (0.0496)	0.9357 (0.1594)	0.8061 (0.1678)	0.9023 (0.0470)	0.7979 (0.0740)	0.9025 (0.0472)	0.7982 (0.0752)	0.7102 (0.1396)	0.6063 (0.1629)
Measurement error $\sigma_e^2 = 1.0$										
1	0.7447 (0.0499)	0.6324 (0.0367)	0.8305 (0.0484)	0.6915 (0.0439)	0.8183 (0.0466)	0.6922 (0.0440)	0.8183 (0.0467)	0.6921 (0.0439)	0.7885 (0.0411)	0.6729 (0.0378)
2	0.7225 (0.0375)	0.6262 (0.0282)	0.8472 (0.0466)	0.6984 (0.0396)	0.8294 (0.0413)	0.6990 (0.0378)	0.8296 (0.0411)	0.6989 (0.0370)	0.7593 (0.0388)	0.6479 (0.0388)
3	0.7230 (0.0353)	0.6289 (0.0311)	0.8960 (0.0654)	0.7231 (0.0606)	0.8684 (0.0409)	0.7229 (0.0463)	0.8687 (0.0411)	0.7230 (0.0462)	0.7468 (0.0471)	0.6276 (0.0511)
4	0.7611 (0.0525)	0.6432 (0.0500)	0.9698 (0.1600)	0.7759 (0.1634)	0.9194 (0.0452)	0.7682 (0.0796)	0.9198 (0.0454)	0.7691 (0.0789)	0.7252 (0.1346)	0.6034 (0.1606)
Measurement error $\sigma_e^2 = 1.5$										
1	0.7632 (0.0513)	0.6172 (0.0356)	0.8484 (0.0499)	0.6731 (0.0428)	0.8309 (0.0476)	0.6740 (0.0431)	0.8309 (0.0474)	0.6738 (0.0428)	0.7989 (0.0455)	0.6550 (0.0412)
2	0.7340 (0.0422)	0.6124 (0.0285)	0.8632 (0.0530)	0.6777 (0.0401)	0.8376 (0.0473)	0.6797 (0.0391)	0.8376 (0.0468)	0.6795 (0.0383)	0.7640 (0.0461)	0.6315 (0.0394)
3	0.7290 (0.0362)	0.6146 (0.0310)	0.9106 (0.0676)	0.6970 (0.0614)	0.8709 (0.0474)	0.6984 (0.0499)	0.8713 (0.0469)	0.6985 (0.0494)	0.7469 (0.0527)	0.6111 (0.0502)
4	0.7697 (0.0586)	0.6258 (0.0515)	0.9959 (0.1700)	0.7392 (0.1768)	0.9212 (0.0502)	0.7396 (0.0866)	0.9214 (0.0508)	0.7402 (0.0872)	0.7296 (0.1306)	0.5815 (0.1684)
Measurement error $\sigma_e^2 = 2.0$										

Predicted Time	NNE		KMCD		IPCW		CIPCW		FP	
	AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)		AUC(SE)	
	Adjusted	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**	**Adjusted**	**Observed**
1	0.7710 (0.0580)	0.6059 (0.0366)	0.8363 (0.0545)	0.6571 (0.0456)	0.8363 (0.0521)	0.6571 (0.0460)	0.8363 (0.0521)	0.6568 (0.0458)	0.8057 (0.0478)	0.6421 (0.0414)
2	0.7384 (0.0448)	0.6019 (0.0295)	0.8431 (0.0555)	0.6639 (0.0437)	0.8431 (0.0487)	0.6639 (0.0415)	0.8431 (0.0486)	0.6635 (0.0413)	0.7680 (0.0473)	0.6185 (0.0421)
3	0.7290 (0.0389)	0.6037 (0.0309)	0.8731 (0.0701)	0.6818 (0.0626)	0.8731 (0.0491)	0.6818 (0.0513)	0.8733 (0.0490)	0.6817 (0.0509)	0.7473 (0.0557)	0.6005 (0.0529)
4	0.7686 (0.0611)	0.6128 (0.0547)	0.9177 (0.1587)	0.7140 (0.1656)	0.9177 (0.0575)	0.7140 (0.0952)	0.9182 (0.0579)	0.7148 (0.0968)	0.7286 (0.1267)	0.5829 (0.1612)
Measurement error $\sigma_e^2 = 2.5$										
1	0.7815 (0.0588)	0.5955 (0.0358)	0.8698 (0.0556)	0.6452 (0.0451)	0.8439 (0.0529)	0.6449 (0.0451)	0.8439 (0.0529)	0.6449 (0.0451)	0.8116 (0.0486)	0.6288 (0.0401)
2	0.7447 (0.0466)	0.5925 (0.0281)	0.8867 (0.0584)	0.6495 (0.0420)	0.8481 (0.0495)	0.6508 (0.0393)	0.8481 (0.0495)	0.6508 (0.0393)	0.7715 (0.0492)	0.6086 (0.0413)
3	0.7319 (0.0393)	0.5958 (0.0301)	0.9343 (0.0750)	0.6664 (0.0610)	0.8761 (0.0499)	0.6684 (0.0522)	0.8761 (0.0499)	0.6684 (0.0522)	0.7474 (0.0575)	0.5946 (0.0527)
4	0.7722 (0.0602)	0.6006 (0.0560)	1.0182 (0.1667)	0.6969 (0.1707)	0.9206 (0.0567)	0.6954 (0.0934)	0.9206 (0.0567)	0.6954 (0.0934)	0.7253 (0.1296)	0.5698 (0.1666)