**Title:** Graphical Time-to-event (TTE) model diagnostics and evaluation techniques: A tutorial

**Authors (final order TBD):** Giselle Brown (1), Jonathan French (2), Nidal Al-Huniti (3), Justin Wilkins(5), Benjamin Weber(1), Matthew M. Hutmacher (4), and the Model Evaluation Group of the International Society of Pharmacometrics (ISoP) Standards and Best Practices Committee.

**Affiliations:**

(1) Boehringer Ingelheim Pharmaceuticals, Inc., Connecticut, USA

(2) Metrum Research Group, LLC, Connecticut, USA

(3) Quantitative Clinical Pharmacology, AstraZeneca, Waltham, Massachusetts, USA

(4) Ann Arbor Pharmacometrics Group Inc, Michigan, USA

(5)

**Running title:** A Tutorial on Graphical Evaluation of Time-to-Event Models

**Corresponding author:**

**Giselle Brown,** 900 Ridgebury Road, Ridgefield, CT, giselle.brown@boehringer-ingelheim.com

**Key words:** Time to event analysis, Visual predictive check, Hazard, Survival analysis

**Word count:** --

**Figure count:** --

**Table count:** --

**Reference count:** --

## Introduction



Time-to-event (TTE) models are statistical models to describe the distribution of … Examples include time to hospitalization, time to first seizure, time to transplant rejection, time to tumor progression. Early methodological development of time-to-event models investigated time-to-death; hence TTE modeling is also frequently called survival analysis.

Differentiating features from other, continuous data endpoints, include: censoring, … Discuss parametric vs. semi-parametric models. We will focus on parametric models.

Many applications in the pharmacometrics literature. Cite some examples. Mention what makes these unique/different.

This tutorial is intended to provide an overview of graphical methods for evaluating the fit of parametric TTE models. The primary audience for this tutorial is individuals with limited experience in parametric time-to-event modeling. As such, our focus is on models for the time to *first* event. In addition, we consider models that include only time invariant predictors. We assume the reader has some basic familiarity with the terminology and concepts of time-to-event modeling. We refer the reader to other sources to provide the concepts and mathematical details of model fitting (cite: Holford paper; Collett book; Harrell book; others?). We will touch on common features of diagnostics for models for repeated time-to-event data or time varying predictors in the Discussion.

To demonstrate the application of model diagnostics, we use two case studies. The first is based on simulated data. Using simulated data allows for a comparison of model diagnostics for a set of mis-specified models to those from the ‘correct’ model. The second is based on a set of data from a real clinical trial. This example allows us to explore the performance of the diagnostics in ‘real-world’ conditions. The two case studies are described in more detail in the following section.

Overall, this tutorial attempts to provide a realistic application of time-to-event analyses in clinical drug development. However, some simplifications were made to allow focusing on the key aspects of visual diagnostics for TTE analyses (e.g., restricting the number of mis-specified hazard functions and covariates influencing the hazard).

## Case study 1: Simulated data

* + *Describe design of the case study* 
    - *Two goals/tasks in this section:*
* *First, describe the design of the trial as you would do it for a real trial*

*Second, describe how assumptions/procedures for the clinical trial simulation*

* + - *Goal: Tell the reader how the data was simulated (include distribution used, how censoring was simulated) while keeping the technical language to a minimum; move technical take and notation to the appendix*
  + *Describe the data. Use KM plots, exposure response box plots, demographic plots (table or box plots by dose)*

For this case study the desired effects of an investigational new drug on the incidence of hospitalization (i.e., the event of interest) were tested in a phase II dose finding study.

A total of 800 patients suffering from a cardiovascular disease were randomized into four parallel treatment groups (n = 200 per treatment group). The patients received ether a 0 (placebo) 1, 3 or 10 mg tablet once per day for 24 weeks. Hospitalizations were recorded on a weekly basis. During week five, sparse blood sampling was conducted once per patients so that individual level pharmacokinetic parameters could be obtained.

From previous studies, the investigational new drug is known to achieve pharmacokinetic steady state within 72h. Also, the drug’s apparent clearance (CL/F) was shown to be 1 L/h, distributed log-normally across subjects, with an approximate 30% coefficient of variation.

### Data Simulation and Assumptions

* The drug effect on the hazard was assumed to be driven by plasma exposure, explicitly AUC,0-tau,ss and gender.
* The higher the exposure the lower the risk of hospitalization. Males were assumed to be XXX.
* The placebo doses subjects are the reference group for this analysis (dose / AUC = 0 and gender = male). The onset half-life of the exposure effect is such that 90% of the effect is achieved by 5 months (20 weeks). Finally, we assume the censoring process will happen closer to 24 weeks then the start of the study.

Events were simulated according to the 2-parameter Weibull distribution, which describes event rates proportional to the power of time. The Weibull hazard function (Equation 1) depends on two parameters, scale (λ) and shape (α). Five weeks was selected as the median time () to event for the reference group and the value for α = 3. The scale parameter (λ), calculated as , is 0.177. Emax model and linear models were selected describe the drug and covariate effects, respectively (Equation 2).

Censoring times were simulated using a Beta distribution scaled to 24 weeks with parameters 4 and 2. Given this censoring mechanism, about 1% of the censoring happens before the median of the survival distribution (5 weeks) and 10% happens after 21 weeks (illustrated in Figure 1A) and the resulting time to hospitalization is illustrated in Figure 1B.

The final case study data set consists of 800 subjects with a total of 734 events. Area under the curve at steady state (AUCss) was calculated as for each subject. The distributions of subject exposure, gender, and time to the first event are illustrated in Figure 1C. Table 2 summarizes the simulated patient characteristics.

Visualization of time-to-event data is usually done by creating a survival plot, which graphs the distribution of survival times in a study. Survival plots can be stratified by factors of interest (i.e., dose group, gender, age group, etc.) in order to investigate the differences between groups. A nonparametric maximum likelihood estimator for survival, , developed by Kaplan and Meier (KM) was used to generate survival for the plot in Figure 1D. The KM estimator works as a left continuous decreasing step function where jumps occur at events Figure 1E shows the estimate survival probabilities versus days on treatment. From this plot we can see the time to hospitalization increases with increasing dose.

### Data Analysis

First, parameters were estimated for the true model and then systematically for each of seven mis-specified models (Table 1). Models were fitted to the data using the Laplacian method in NONMEM version 3.0. Post processing and graphical evaluation were performed using R Version 3.2.2, Perl-speaks-NONMEM (PsN) Version 4.6.0, Ggplot2 Version 2.1.0 and Xpose4 version 4.5.3.

Table 1: Models fit to the simulated time-to-hospitalization data. The data-generating model is Model 1. The other seven models exemplify different mis-specified models.

|  |  |  |  |
| --- | --- | --- | --- |
| *Model* | *Hazard function* | *Drug effect* | *Covariate effect* |
| *1* | *Weibull* | *Emax* | *Included* |
| *2* | *Weibull* | *Emax* | *Excluded♠* |
| *3* | *Weibull* | *Linear♠* | *Included* |
| *4* | *Weibull* | *Linear♠* | *Excluded♠* |
| *5* | *Exponential♠* | *Emax* | *Included* |
| *6* | *Exponential♠* | *Emax* | *Excluded♠* |
| *7* | *Exponential♠* | *Linear♠* | *Included* |
| *8* | *Exponential♠* | *Linear♠* | *Excluded♠* |
| *♠=Misspecified* | | | |

## Case Study 2: Progression-free survival in metastatic colorectal cancer

The real-world example uses data from the control arm of a randomized, double-blind, multi-center Phase II/III study in patients with previously untreated metastatic colorectal cancer (ClinicalTrials.gov ID: NCT00384176). The control arm was Bevacizumab in combination with 5-fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX). Data were obtained from Project Datasphere (citation?; www.projectdatasphere.org).

The primary endpoint for this study was progression-free survival (PFS) (citation of primary results?). For this example, we will focus on overall survival (OS).

The goal is to demonstrate model diagnostics, not to find the ‘best’ model.

Imagine we are constructing a model to investigate predictors of OS in patients treated with Bevacizumab in combination with FOLFOX.

Describe the sample size and number of events. Show overall K-M plot (and also stratified by some key covariates?) Summary table of potential covariates.

### Data Analysis

Weibull and log-logistic models. Covariate effects of … Code is included as supplementary material.

## Model Diagnostics

Graphical comparisons of observed and predicted distributions have long been a standard method of model evaluation of pharmacometric models (Martin Bergstrand, 2009). This section provides a practical overview of simulation-based and residual-based diagnostics for the evaluation of TTE models**.**

### Simulation-based diagnostics

Simulation-based assessment of model quality has become an integral part of pharmacometric model evaluation. Yano *et. al,* was the first to bring this concept (originated by Gelman *et. al.)* into pharmacometrics (Yano, Beal, & Sheiner, 2001) (Gelman, Meng, & Stern, 1996). The general algorithm for constructing a predictive check is to construct a summary statistic from the observed data and, then, to compare the observed data summary to the predictive distribution of the summary statistic implied by the model. Because the predictive distribution typically cannot be derived analytically, we use simulation to approximate it.

The standard simulation-based diagnostic in the pharmacometrics literature is the visual predictive check (VPC) (Holford N. , 2005) (Karlsson & Holford, 2008).

The predictive check most commonly used for time-to-event data is a VPC based on the survival function. This predictive check compares an estimate of the observed survival function to the model-based predictive distribution for the observed survival function. Typically, the survival function is estimated with a non-parametric estimator of , such as the Kaplan-Meier estimator <insert reference for K-M>.

The hazard-based VPC is similar in concept to the survival-based VPC, except that the focus of the VPC is at the level of the hazard function, not the survival function <insert reference to Huh and Hutmacher>. The estimated hazard function,, based on the original data is then graphically compared to the predictive distribution for . For the purposes of this tutorial, we will focus on the binned hazard estimator, although there are several other possible estimators of the hazard function <Huh and Hutmacher>.

Finally, we can compare other observed summary statistics to their corresponding model-based predictive distribution. One common summary statistic for time-to-event data is the hazard ratio. In the following examples, the 90% prediction intervals of the simulated data were calculated across 1000 simulations from the model and overlaid with the corresponding observed data. In all VPCs, the observed data is expected to fall within the 90% prediction interval of the simulated data, if the model is (approximately) correct.

### Residual-based diagnostics

In addition to simulation-based diagnostics such as predictive checks, residual-based diagnostics can be useful. While not frequently utilized in pharmacometric modeling of TTE data, residual-based diagnostics have a long history in the field of statistics. The primary difference between these residuals and the classical residuals from regression models is that residuals from TTE models are not always of the “Observed minus Expected” form. In this evaluation, we focus on two types of residuals: Deviance residuals and Cox-Snell residuals.

Deviance residuals are transformations of the difference between the observed number of events and the expected cumulative number of events predicted by the model. The transformation is intended to make the residual distribution symmetric around zero, to aid in interpretation. Deviance residuals are most useful for identifying outliers and assessing whether drug and covariate effects have been modeled using the (approximately) correct functional form.

Cox-Snell residuals are defined as the value of the predicted cumulative hazard at the event or censoring time., Under the assumption the model is correct, the Cox-Snell residuals are expected to follow a standard exponential distribution () [4]. Modifications to the Cox-Snell residual have been proposed to adjust for censoring and been used in pharmacometric literature [5]. These modifications account for the fact that the cumulative hazard for censored observations is smaller than it would be had the actual event time been observed. Cox-Snell residuals are primarily used to assess overall adequacy of the model.

The statistical details for simulating data for and constructing VPCs and for generating residual-based diagnostics are provided in the Supplementary Material.

## Results: Case Study 1 (simulated data) [GB]

Models 1-8 were fitted to the simulated data. For each model, Table 3 lists the objective function value (OFV) and AIC. Table 4 presents the parameter estimates. Based on the numeric summaries of AIC and OFV, we can see that Model 1 is clearly preferred over the other seven models. While we have designed this simple example to have clear differences between models, in general, numerical model comparisons will not always be able to clearly identify better fitting models.

To demonstrate the pros and cons of each of the types of model diagnostic, we will consider model evaluation in three areas: overall fit, covariate effects, and whether a summary statistic of interest is modeled correctly. To keep the focus on relevant aspects of the models, we will focus on comparisons of Model 1 (Weibull; Emax dose-response, including effect of sex; the true model) with Model 2 (exclusion of sex effect), Model 3 (linear dose response) and Model 5 (Exponential).

### Diagnostic plots from Model 1

Panel of plots: Modified Cox-Snell; Deviance residuals vs. AUC and gender; overall survival VPC; overall hazard VPCs

For each figure, describe what is plotted; what is expected for a good model.

### Assessment of overall-fit: Cox-Snell residuals, VPCs

The primary graphical diagnostics for assessing overall fit of the model are plots of the Cox-Snell residuals and both the survival- and hazard-based VPCs. Plots of the Cox-Snell residuals for Models 1, 2, 3, and 5 are shown in Figure 2. If the model fits well, the distribution of Cox-Snell residuals should be approximately exponential. As these plots are constructed, that equates to following close to the (red) line of identity. Based on the Cox-Snell residuals, Models 1, 2 and 3 appear to provide a good, overall fit to the data; however, Model 5 does not.

Figure 3 shows the unstratified survival-based VPCs and Figure 4 shows the unstratified hazard-based VPCs. In the survival-based VPCs, the black line is the estimated (unstratified Kaplan-Meier) survival function. The green envelope is the 90% prediction interval for the survival function. In the hazard-based VPCs, the blue line is the estimated (unstratified, binned) hazard function, and the pink envelope is the model-based 90% prediction interval. For both types of VPC, if the model fits well, the observed survival or hazard function should largely fall within the prediction interval. Based on the survival-based VPCs, Models 1, 2 and 3 appear to provide a good, overall fit to the data; however Model 5 does not. The hazard-based VPCs indicated that neither Model 3 nor Model 5 fits the data well.

Overall, the Cox-Snell residuals and survival-based VPCs are effective at distinguishing between baseline hazard models (Model 5 vs. Model 1) but not as effective at differentiating between models with the correct baseline hazard but incorrect covariate forms (e.g., Model 3 vs. Model 1). The hazard-based VPC shows small but noticeable differences between Model 3 and Model 1.

In our experience, the use of AIC can be a good guide for comparing models based on overall fit, including choice of baseline hazard model. While Cox-Snell plots are intended for this purpose, they typically do not provide substantially more information than AIC. Between the simulation-based diagnostics, the hazard-based VPC provides more discrimination than the survival-based VPC for assessing overall fit.

Overall fit is a fairly low bar. More often, we are interested in evaluating the fit of a model in specific subgroups of patients defined by covariates and/or whether or not we have adequately captured the functional relationship between continuous covariates and the time-to-event distribution.

### Assessment of covariate effects: deviance residuals, VPCs

Typically, we are interested in understanding if the models the correct functional relationship between covariates and outcome and whether the model can accurately recapitulate data in key subgroups of patients. IN this example, we are primarily focused on capturing the exposure-response relationship correctly and whether we accurately capture the survival distributions in each dose group.

The primary model evaluation tools we examine are plots of the deviance residuals and both survival- and hazard-based VPCs.

#### Deviance residuals

#### Survival-based VPCs

#### Hazard-based VPCs

Panel of plots comparing Models 1, 2, 3 and 5. Describe how they compare to Model 1 and how to interpret.

### Assessment of other summary statistic: VPCs for HR comparing each dose to placebo

Panel of plots comparing Models 1, 3 and 5. Describe how they compare to Model 1 and how to interpret.

## Results: Case Study 2 (real-world data)

## Discussion [GB]

* + *Task: Outline some bullet points*
  + Hazard misspecification
    - Easily detectable using any of these methods
    - Note: it may be difficult to graphically determine the difference between the Weibull and Gompertz models, which both can be used to describe time varying hazards
    - The hazard based VPC might be very useful during early model development. Unstratified plots of the Weibull distribution (Figure 5, scenario 3 & 4) give a clear indication that these models do not describe the data at later time points. This could eliminate further investigation of models with a linear drug effect. The corresponding survival based VPC plots were not as clear.
  + Drug effect misspecification
    - Best detected my simulation based methods
    - Survival based VPCs
      * Easy to implement in R, xpose package
      * Stratifying by dose is crucial for detection
        + Unstratified plots of scenarios 1 – 4 indicate that the model adequately describes the data
        + Stratified plots of scenarios 1 – 4 show with a linear model the survival probability for the placebo and 10 mg dose groups is under predicted and the 3 mg dose group over predicted over the time course.
    - Hazard based VPCs
      * Not currently automated; code will need to be manually updated depending on the user’s needs
      * Stratifying by dose is helpful for detection.
      * If automated could be a nice complement to survival based VPC plots
  + Gender effect misspecification
    - One could argue for a time invariant covariate, such as gender, a graphical analysis stratified by covariate using any of the methods described is equally as informative as modeling with or without the covariate.
  + Diagnostic tools
    - Cox-Snell residuals are simple to make, these diagnostics are only sensitive to large departures from the correct model.
    - Work confirms omitting covariates or including incorrect functional form for a covariate effects are not well-detected by these diagnostics [4].
    - It is difficult to select between the models based upon these residuals.
    - KMMC – Figures 12 and 13
      * Probably not appropriate here because we don’t have continuous or time varying covariates
      * *Notes: that for continuous and time-varying covariates, in contrast to the baseline categorical covariate discussed in this example, a more sophisticated approach to model evaluation is needed. One straightforward tool is the KMMC VPC [PAGE poster Hooker & Karlsson 2012].*
      * *For assessing the appropriateness of including continuous and time-varying covariates, simple stratification is not sufficient. A modified KM VPC, dubbed the Kaplan-Meier Mean Covariate (KMMC) plot, has been proposed to overcome this problem [cite]: at every inflection point in a KM survival curve, the mean of a given covariate across all the subjects remaining in the study is calculated. This “running mean” may be expected to increase or decrease over the course of the study if it is influential. Simulating numerous times from a given model and comparing the observed running mean with its predicted distribution provides a useful assessment of the covariate’s value in the model. Cite [Hooker A & Karlsson MO (2012). The Kaplan-Meier Mean Covariate plot (KMMC): a new diagnostic for covariates in time-to-event models. PAGE 21 (2012) Abstr 2564 [www.page-meeting.org/?abstract=2564]*
    - Deviance residuals
      * Because Deviance residuals are transformations of the “observed minus expected” number of cumulative events, observations with large Deviance residuals are not well fitted by the model, similar to residuals from traditional regression models. Consequently, Deviance residuals can be used to identify outlier observations. Similarly, plotting the deviance residuals against covariates, can be used to assess whether there is evidence for misspecification of the functional form of a covariate model but not the underlying hazard or drug effect model.

|  |  |  |
| --- | --- | --- |
| **Diagnostic** | **Pros** | **Usefulness demonstrated in** |
| Survival based VPC1 | Easy to interpret, implemented in software, straightforward | TTE analysis **P**  RTTE analysis |
| Kaplan Meier Mean Covariate VPC1 | Easy to interpret, implemented in software, straightforward | TTE analysis **P**  RTTE analysis |
| Hazard based VPC2 | Sensitive | TTE analysis **P** |
| Deviance residuals3 | More sensitive than other residual-based diagnostics | TTE analysis **P** |
| Cox-Snell residuals4 | Easy to interpret, robust | TTE analysis **P** |
| **P** = present publication *Plan to add other publications*  How to implement: 1 PsN documentation, VPC section 5 & Xpose documentation *kaplan.plot()* ; 2 Supplementary material, section BH1 & Huh and Hutmacher, 2016 (doi: 10.1007/s10928-015-9454-9); 3 Supplementary material, section DEVRES; 4 Supplementary material, section CSRES | | |

* + Recommendations table. The idea here to give pros and a list of references (your thoughts? would it be useful or is it overkill?)
  + Describe a detailed Data simulation (Maybe for the appendix) – still working out this idea

## Tables

### Table 1: True Values

|  |  |
| --- | --- |
| **Parameter** | **True value** |
|  |  |
| Shape | 3 |
| Scale | 0. 177 |
| E max | 0.063 |
| E50 | 7.39 |
| θGENDER | 2 |
| 1 , where weeks is the median survival time for the reference hazard of the Weibull distribution | | |

### Table 2: Simulated patient characteristics

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Simulated patient characteristics | | | | | |
| Treatment arm | Placebo | 1 mg | 3 mg | 10 mg | **Total** |
| n | 200 | 200 | 200 | 200 | 800 |
| Gender: Male | 106 | 101 | 91 | 108 | 406 |
| Gender: Female | 94 | 99 | 109 | 92 | 394 |
| n, adverse events | 197 | 194 | 180 | 163 | 734 |
| AUCss, mean  (range) | 0 mg⋅hr/L  (NA) | 1.01 mg⋅hr/L  (0.47 – 2.20) | 3.20 mg⋅hr/L  (1.45 – 8.35) | 10.62 mg⋅hr/L  (4.50 – 25.67) | 3.71 mg⋅hr/L  (0 – 25.67) |

|  |
| --- |
|  |

### Table 3: Key scenarios

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Model | Hazard function | Drug effect | Covariate effect | OFV | Δ OFV | n, parameters | AIC | Δ AIC♣ |
| 1 | Weibull | Emax | Included | 3461.39 | ---- | 5 | 3471.39 | --- |
| 2 | Weibull | Emax | Excluded♠ | 3536.46 | + 75.07♦ | 4 | 3544.46 | + 73.07 |
| 3 | Weibull | Linear♠ | Included | 3591.21 | ---- | 4 | 3599.21 | + 127.82 |
| 4 | Weibull | Linear♠ | Excluded♠ | 3641.4 | + 50.19♦ | 3 | 3647.40 | + 176.01 |
| 5 | Exponential♠ | Emax | Included | 4360.74 | ---- | 4 | 4368.74 | + 897.35 |
| 6 | Exponential♠ | Emax | Excluded♠ | 4375.12 | + 14.38♦ | 3 | 4381.12 | + 909.73 |
| 7 | Exponential♠ | Linear♠ | Included | 4377.24 | ---- | 3 | 4383.24 | + 911.85 |
| 8 | Exponential♠ | Linear♠ | Excluded♠ | 4389.45 | + 12.21♦ | 2 | 4393.45 | + 922.06 |
| ♠=Misspecified ; ♦= change in OFV as compared to the preceding scenario; ♣ = change in AIC as compared to scenario 1 | | | | | | | | |

### Table 4: Final parameter estimates

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Model | Lambda (%RSE) | Gamma (%RSE) | Emax (%RSE) | θgender (%RSE) | EC50 (%RSE) |
| 1 | 0.172526 (2.49) | 3.0792 (2.86) | -2.62873 (5.64) | 0.659553 (10.9) | 1.71503 (17.7) |
| 2 | 0.188286 (2.48) | 2.92451 (2.91) | -2.53238 (6.38) | NA | 1.95034 (20.6) |
|  | | | | |  |
| Model | Lambda (%RSE) | Gamma (%RSE) | θAUC (%RSE) | θgender (%RSE) |
| 3 | 0.141607 (2.31) | 2.77476 (2.78) | -0.15368 (7.33) | 0.53017 (14.3) |
| 4 | 0.155109 (1.93) | 2.69197 (2.84) | -0.15072 (7.41) | NA |
|  | | | | |
| Model | Lambda (%RSE) | Emax (%RSE) | θgender (%RSE) | EC50 (%RSE) |
| 5 | 0.183195 (3.14) | -1.08699 (8.43) | 0.280871 (12) | 2.51839 (24.7) |
| 6 | 0.206994 (2.84) | -1.11486 (9.55) | NA | 2.8877 (27.7) |
|  | | | |  | |
| Model | Lambda (%RSE) | θAUC (%RSE) | θgender (%RSE) |
| 7 | 0.151581 (3.04) | -0.06807 (8.36) | 0.257723 (13.7) |
| 8 | 0.171995 (2.31) | -0.06885 (8.38) | NA |

## Figures

### Figure 1A: Censoring distribution

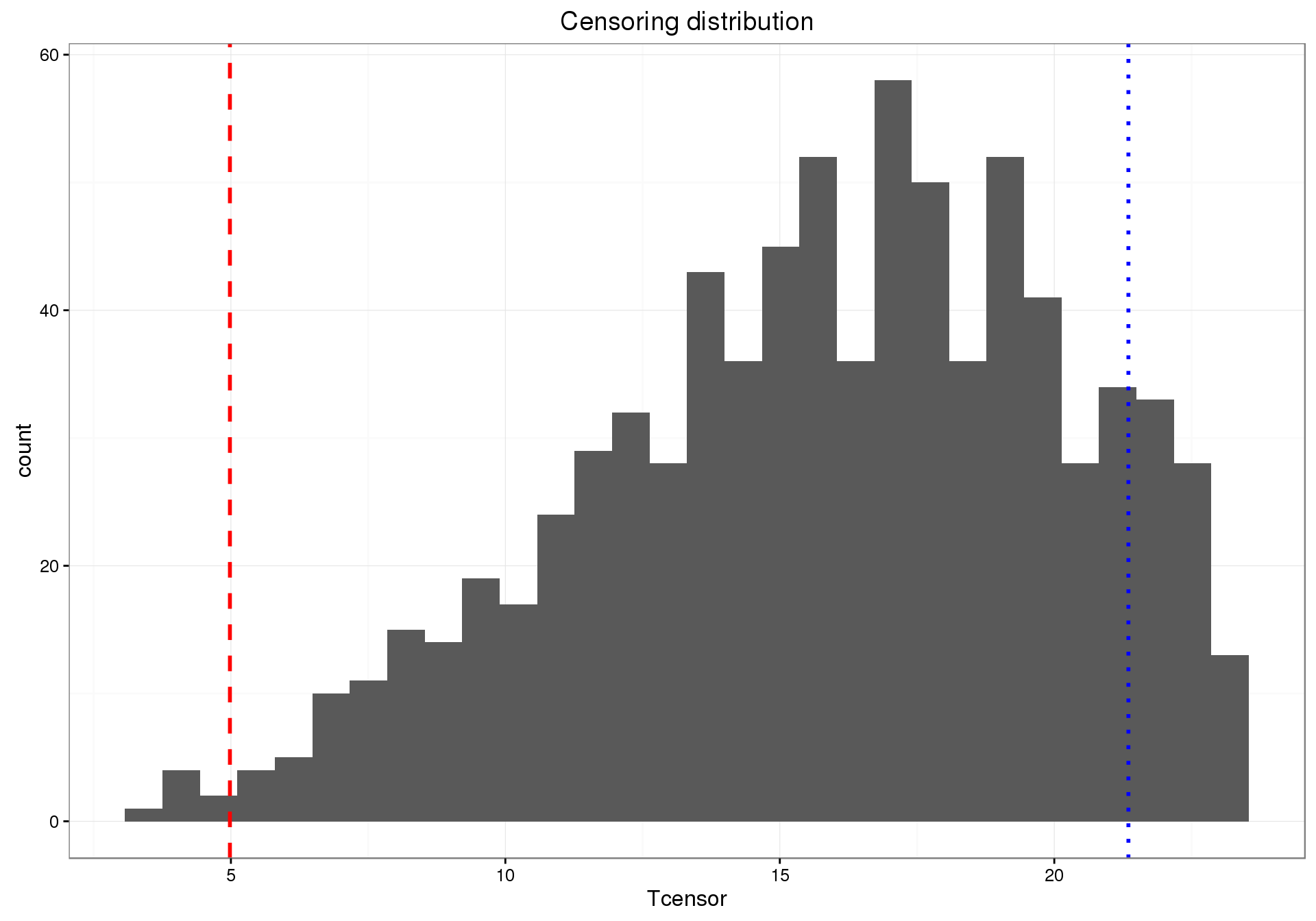
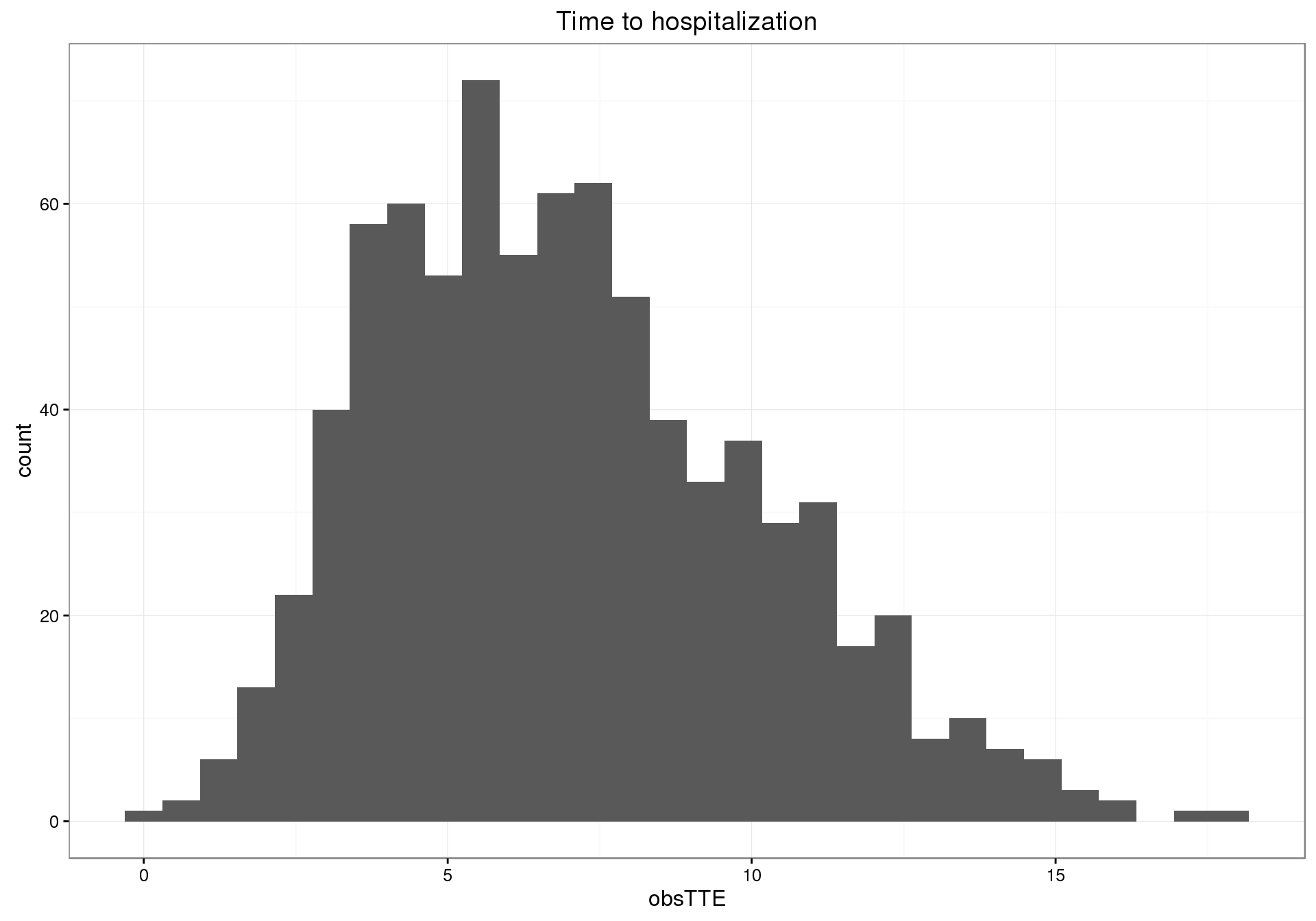


Figure 1A: Time to event distribution. The dashed red line represents the median of the survival distribution. The dotted blue line represents week 21.

### Figure1B. Time to hospitalization distribution



### Figure 1C: Simulated patient distributions: Exposure & gender

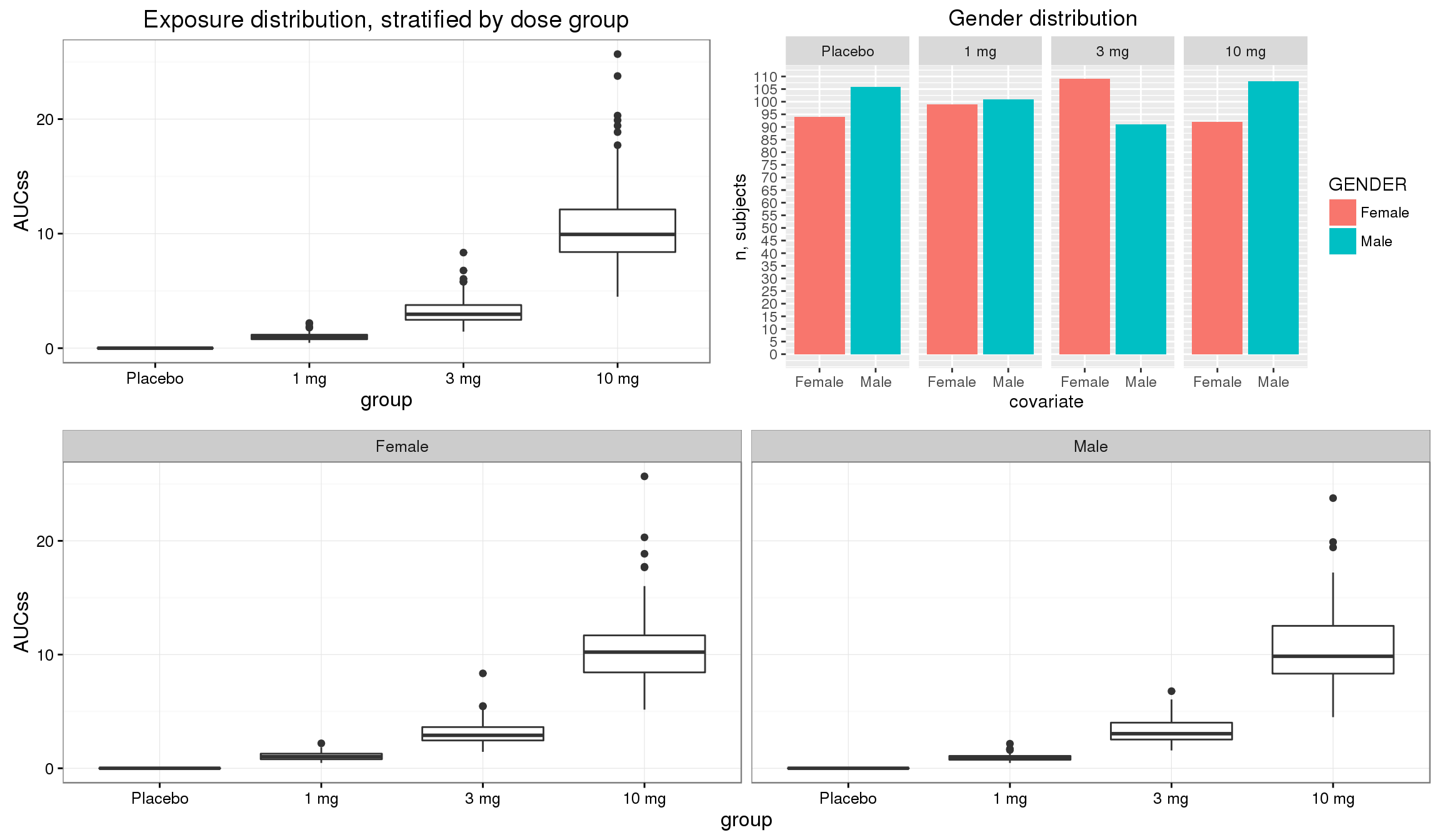
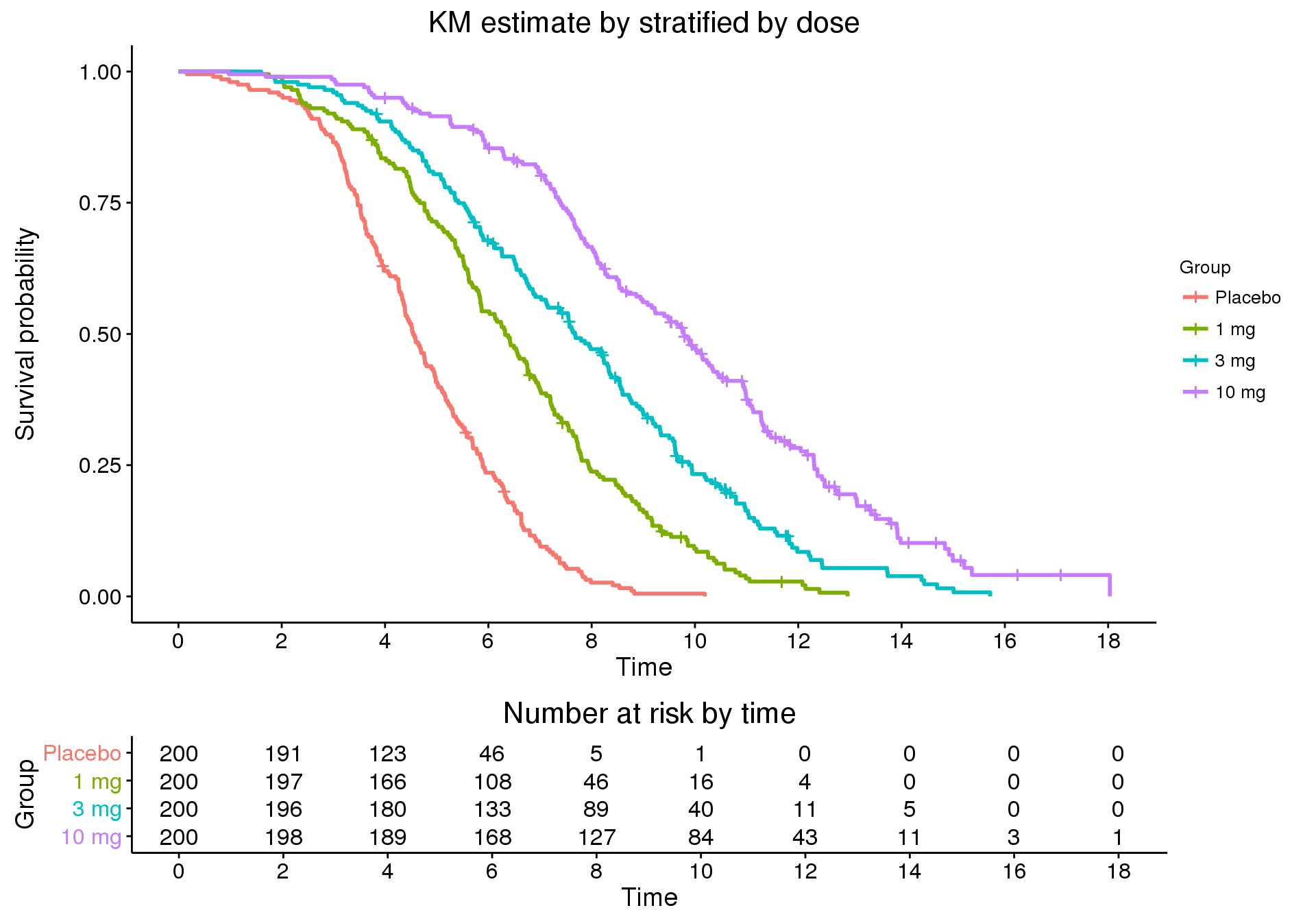
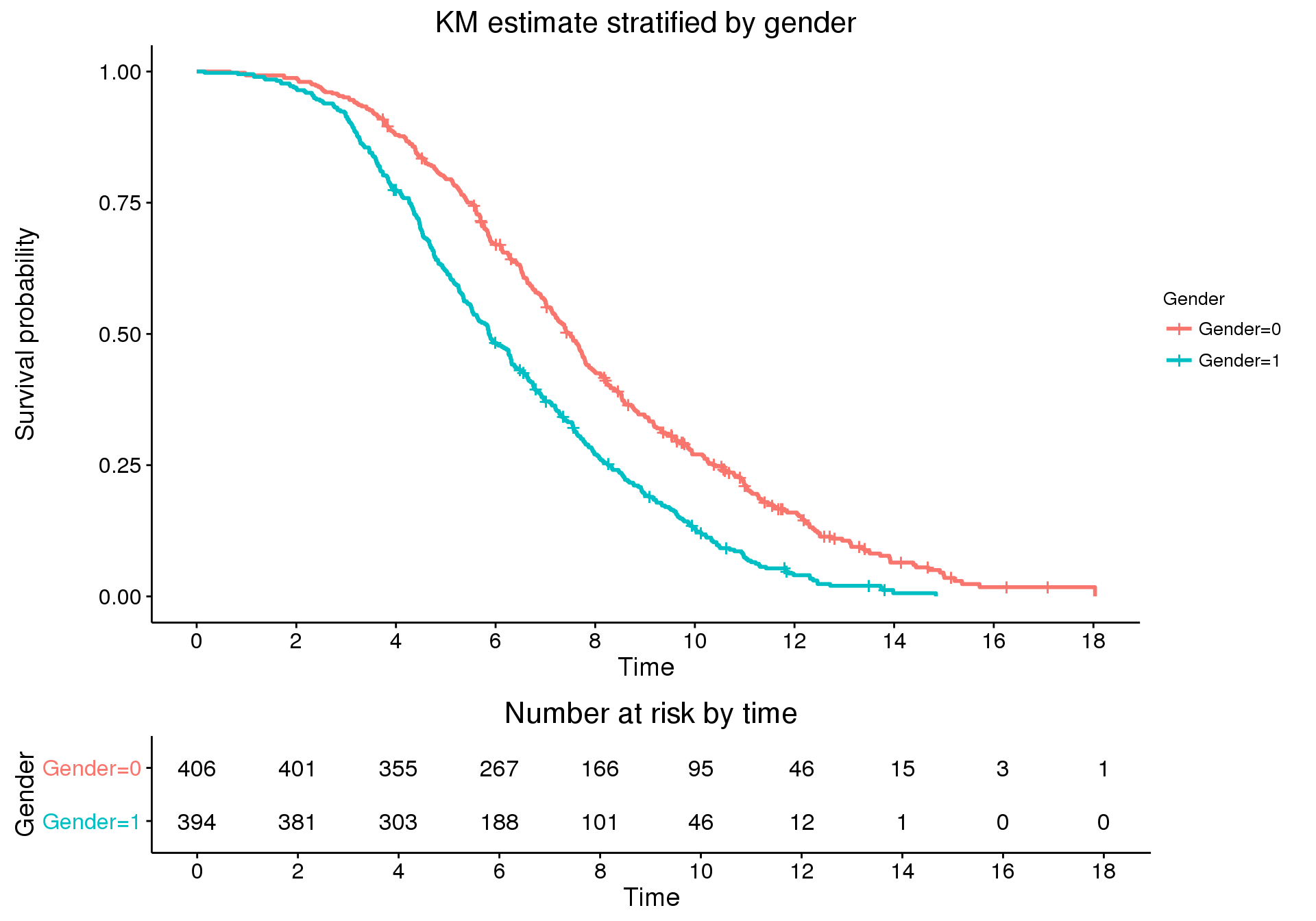


Figure 1C: Exposure and gender distributions. In each boxplot, the horizontal line represents the median, the box represents the interquartile range (IQR), the whiskers illustrate the data falling within 1.5 x IQR, and the dots represent outliers falling outside of 1.5 x IQR.

### Figure 1D: Survival curves (stratified by dose)



### Figure 1E: Survival Curves (stratified by gender)

Figure 2: Modified Cox Snell residuals (unstratified)

|  |  |
| --- | --- |
| Model 1 | Model 2 |
| Model 3 | Model 5 |



































































Figure 3: Survival-based Visual Predictive Check (unstratified). Black line is observed Kaplan-Meier estimator. Green envelope is point-wise model-based 90% prediction interval.

|  |  |
| --- | --- |
| Model 1 | Model 2 |
| Model 3 | Model 5 |

Figure 4: Hazard-based Visual Predictive Check (unstratified). Blue line is estimated hazard function. Pink envelope is model-based 90% prediction interval.

|  |  |
| --- | --- |
| Model 1 | Model 2 |
| Model 3 | Model 5 |

# Bibliography

|  |  |
| --- | --- |
| [1] | E. L. Kaplan and P. Meier, "Nonparametric estimation from incomplete observations," *Journal of the American statistical association,* vol. 53, pp. 457-481, 1958. |
| [2] | J. T. Rich, J. G. Neely, R. C. Paniello, C. C. J. Voelker, B. Nussenbaum and E. W. Wang, "A practical guide to understanding Kaplan-Meier curves," *Otolaryngology-Head and Neck Surgery,* vol. 143, pp. 331-336, 2010. |
| [3] | M. A. T. S. O. Karlsson and N. I. C. K. Holford, "A tutorial on visual predictive checks," in *Annual Meeting of the Population Approach Group in Europe*, 2008. |
| [4] | D. Collett, Modelling survival data in medical research, CRC press, 2015. |
| [5] | C. Hu and M. E. Sale, "A joint model for nonlinear longitudinal data with informative dropout," *Journal of Pharmacokinetics and Pharmacodynamics,* vol. 30, pp. 83-103, 2003. |
| [6] | A. C. H. M. O. K. Martin Bergstrand, "Visual Predictive Checks for Censored and Categorical data," in *Methodology- Model evaluation*, 2009. |
| [7] | E. L. Plan, G. Ma, M. Någård, J. Jensen and M. O. Karlsson, "Transient lower esophageal sphincter relaxation pharmacokinetic-pharmacodynamic modeling: count model and repeated time-to-event model," *Journal of Pharmacology and Experimental Therapeutics,* vol. 339, pp. 878-885, 2011. |
| [8] | N. Holford, "The visual predictive check—superiority to standard diagnostic (Rorschach) Plots. 2005," in *Abstract*, 2005. |
| [9] | P. K. Andersen, O. Borgan, R. D. Gill and N. Keiding, Statistical models based on counting processes, Springer Science & Business Media, 2012. |
| [10] | R. V. Juul, S. Rasmussen, M. Kreilgaard, L. L. Christrup, U. S. H. Simonsson and T. M. Lund, "Repeated time-to-event analysis of consecutive analgesic events in postoperative pain," *The Journal of the American Society of Anesthesiologists,* vol. 123, pp. 1411-1419, 2015. |
| [11] | F. Harrell, Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis, Springer, 2015. |
| [12] | W. B. Nelson, Recurrent events data analysis for product repairs, disease recurrences, and other applications, SIAM, 2003. |
| [13] | A. Gelman, X.-L. Meng and H. Stern, "Posterior predictive assessment of model fitness via realized discrepancies," *Statistica sinica,* pp. 733-760, 1996. |
| [14] | K. E. Karlsson, E. L. Plan and M. O. Karlsson, "Performance of three estimation methods in repeated time-to-event modeling," *The AAPS journal,* vol. 13, pp. 83-91, 2011. |
| [15] | K. E. Karlsson, E. L. Plan and M. O. Karlsson, "Performance of three estimation methods in repeated time-to-event modeling," *The AAPS journal,* vol. 13, pp. 83-91, 2011. |
| [16] | S. L. Beal, L. B. Sheiner, A. J. Boeckmann and R. J. Bauer, "NONMEM 7.3. 0 Users Guides," *ICON Development Solutions, Hanover,* 1989. |
| [17] | T.-H.-T. Nguyen, M.-S. Mouksassi, N. Holford, N. Al-Huniti, I. Freedman, A. C. Hooker, J. John, M. O. Karlsson, D. R. Mould, J. J. Pérez Ruixo and others, "Model evaluation of continuous data pharmacometric models: Metrics and graphics," *CPT: Pharmacometrics \& Systems Pharmacology,* 2016. |
| [18] | T. M. Therneau, P. M. Grambsch and T. R. Fleming, "Martingale-based residuals for survival models," *Biometrika,* pp. 147-160, 1990. |
| [19] | M. I. D. EFPIA, S. F. Marshall, R. Burghaus, V. Cosson, S. Y. Cheung, M. Chenel, O. Dellapasqua, N. Frey, B. Hamrén, L. Harnisch and others, "Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation.," *CPT: pharmacometrics \& systems pharmacology,* vol. 5, p. 93, 2016. |
| [20] | Y. Yano, S. L. Beal and L. B. Sheiner, "Evaluating pharmacokinetic/pharmacodynamic models using the posterior predictive check," *Journal of pharmacokinetics and pharmacodynamics,* vol. 28, pp. 171-192, 2001. |
| [21] | J. Crowley and M. Hu, "Covariance analysis of heart transplant survival data," *Journal of the American Statistical Association,* vol. 72, pp. 27-36, 1977. |
| [22] | D. R. Mould and R. N. Upton, "Basic concepts in population modeling, simulation, and model-based drug development," *CPT: pharmacometrics \& systems pharmacology,* vol. 1, pp. 1-14, 2012. |
| [23] | N. Holford, "A time to event tutorial for pharmacometricians," *CPT: pharmacometrics \& systems pharmacology,* vol. 2, pp. 1-8, 2013. |
| [24] | R. C. Team, "R A Language and Environment for Statistical Computing," 2015. |
| [25] | J. Nyberg, "Simulating large time-to-event trials in NONMEM," in *Page 23*, 2014. |
| [26] | O. Aalen, "Nonparametric inference in connection with multiple decrement models," *Scandinavian Journal of Statistics,* pp. 15-27, 1976. |
| [27] | W. Nelson, "Theory and applications of hazard plotting for censored failure data," *Technometrics,* vol. 14, pp. 945-966, 1972. |
| [28] | J. D. Kalbfleisch and R. L. Prentice, The statistical analysis of failure time data, vol. 360, John Wiley & Sons, 2011. |
| [29] | J. P. Klein and M. L. Moeschberger, Survival analysis: techniques for censored and truncated data, Springer Science & Business Media, 2005. |
| [30] | B. W. Turnbull, "The empirical distribution function with arbitrarily grouped, censored and truncated data," *Journal of the Royal Statistical Society. Series B (Methodological),* pp. 290-295, 1976. |
| [31] | M. Hutmacher, "Visual Predictive Checks for the Evaluation of the Hazard Function in Time-to-Event Analyses," in *Page 22*, 2013. |
| [32] | Y. Huh and M. M. Hutmacher, "Application of a hazard-based visual predictive check to evaluate parametric hazard models," *Journal of pharmacokinetics and pharmacodynamics,* vol. 43, pp. 57-71, 2016. |
| [33] | L. Lindbom, P. Pihlgren and N. Jonsson, "PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM," *Computer methods and programs in biomedicine,* vol. 79, pp. 241-257, 2005. |
| [34] | L. Lindbom, J. Ribbing and E. N. Jonsson, "Perl-speaks-NONMEM (PsN)—a Perl module for NONMEM related programming," *Computer methods and programs in biomedicine,* vol. 75, pp. 85-94, 2004. |
| [35] | E. N. Jonsson and M. O. Karlsson, "Xpose--an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM," *Computer Methods and Programs in Biomedicine,* vol. 58, pp. 51-64, 1999. |
| [36] | R. Y. C. Liu and J. Van Ryzin, "A histogram estimator of the hazard rate with censored data," *The Annals of Statistics,* pp. 592-605, 1985. |
| [37] | S. M. Snapinn, Q. I. Jiang and B. Iglewicz, "Illustrating the impact of a time-varying covariate with an extended Kaplan-Meier estimator," *The American Statistician,* vol. 59, pp. 301-307, 2005. |
| [38] | J. Stare, M. Pohar and R. Henderson, "Goodness of fit of relative survival models," *Statistics in medicine,* vol. 24, pp. 3911-3925, 2005. |

Supplemental material

## Code

### A1. Data set generation:

library(survival)

library(survminer)

library(ggplot2)

library(dplyr)

## Set seed:

set.seed(4321)

set.seed(160516)

doses = c(0,1,3,10)

nPerGroup = 200

nGroups = length(doses)

nTotal = nPerGroup \* nGroups

# Define parameters for Weibull distribution

med0 = 10

alpha = 3

lambda = 1/med0 \* log(2)^(1/alpha)

gamma = 2 # E50

hrAt10 = 4 # hazard ratio

theta3 = log(hrAt10)\*(gamma+10)/10 # Effect at 10 mg dose is a HR of 4 (at steady-state)

theta4 = log(2)

theta = c(theta3,theta4)

params=list(lambda=lambda, alpha=alpha,theta=theta, gamma=gamma)

# Define parameters for CL distribution and binar covariate

TVCL = 1

CVCL = 0.3

probX = 0.5

# Set-up design and simulate exposure, random time-to-event on survival scale,

# and random censoring time.

data = data.frame(ID = rep(1:nTotal),

dose = rep(doses, each=nPerGroup),

CL = TVCL \* exp(rnorm(nTotal,0,CVCL)),

x = rbinom(nTotal,size=1,prob=probX),

Utte = runif(nTotal),

Tcensor = 24 \* rbeta(nTotal,shape1 = 4, shape2 = 2))

data = mutate(data,

AUCss = dose/CL,

group = factor(dose, levels=doses,

labels=c('Placebo', paste(doses[-1],'mg')))

)

# Define Weibull-like hazard function

hazWeib = function(t,AUC,x,params) {

h0 = with(params, alpha \* lambda^alpha \* t^(alpha-1))

h = with(params, h0 \* exp((theta[1]\*AUC/(gamma+AUC)) + theta[2]\*x))

return(h)

}

# Define function for simulating time-to-event data based on inverting

# the survival curve

simFun = function(t, AUC,x,U,params, hazFun) {

cumHaz = integrate(hazFun, lower=0, upper=t, AUC=AUC, x=x, params=params)$value

return(cumHaz + log(U))

}

# Simulate true time-to-event data

data$TTE = sapply(1:nTotal, function(i) {

uniroot(simFun, interval=c(0,100),

AUC=data$AUCss[i], x=data$x[i], U=data$Utte[i],

params=params, hazFun=hazWeib)$root

})

# Generate censoring indicator and observed time-to-event variable

data$censored = data$TTE > data$Tcensor

data$obsTTE = ifelse(data$censored==TRUE, data$Tcensor, data$TTE)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ID | dose | CL | x | Utte | Tcensor | AUCss | group | TTE | censored | obsTTE |
| 1 | 0 | 0.87269 | 1 | 0.999953 | 21.81751 | 0 | Placebo | 0.323065 | FALSE | 0.323065 |
| 2 | 0 | 0.91376 | 0 | 0.477246 | 10.55336 | 0 | Placebo | 10.21914 | FALSE | 10.21914 |
| 3 | 0 | 0.935994 | 0 | 0.838839 | 11.03604 | 0 | Placebo | 6.329148 | FALSE | 6.329148 |
| 4 | 0 | 0.859372 | 1 | 0.299589 | 16.55062 | 0 | Placebo | 9.544467 | FALSE | 9.544467 |
| 5 | 0 | 1.057393 | 0 | 0.321969 | 11.09386 | 0 | Placebo | 11.78075 | TRUE | 11.09386 |
| 6 | 0 | 1.039022 | 0 | 0.28498 | 18.88289 | 0 | Placebo | 12.18929 | FALSE | 12.18929 |
| 7 | 0 | 1.028737 | 1 | 0.369168 | 20.02185 | 0 | Placebo | 8.957937 | FALSE | 8.957937 |
| 8 | 0 | 1.28899 | 1 | 0.179124 | 3.953886 | 0 | Placebo | 10.74477 | TRUE | 3.953886 |
| 9 | 0 | 0.839258 | 0 | 0.87933 | 22.33247 | 0 | Placebo | 5.703371 | FALSE | 5.703371 |
| 10 | 0 | 0.986373 | 0 | 0.422987 | 6.504723 | 0 | Placebo | 10.74717 | TRUE | 6.504723 |

### A2. Example NM code for final model

;Sim\_start : add to simulation model

;$SIZES NO=500 LIM6=500

;Sim\_end

$PROB 1 Weibull + Emax + with covariate

$INPUT ID DOSE CLI X1 TIME DV MDV

; DV event = 1, DV censored = 0

$DATA ../../data/derived/SimulatedData\_weibull\_nm.csv IGNORE=@

$SUBROUTINE ADVAN13 TOL=6

$MODEL

COMP=(CHAZ)

$PK

; exposure

AUCSS = 0

IF (DOSE.GT.0) AUCSS = DOSE / CLI

; parameters

DLTA = EXP(THETA(1))

LAMBDA = EXP(THETA(2) + ETA(1))

XEFF = THETA(3)

EMAX = THETA(4)

E50 = EXP(THETA(5))

;BETA = EXP(THETA(6))

; initial conditions

A\_0(1) = 0

$DES

HAZ0 = DLTA \* LAMBDA \* (LAMBDA\*T)\*\*(DLTA-1)

EXPOSURE = AUCSS ; \* (1 - EXP(-BETA\*T))

DEFF = EMAX \* EXPOSURE / (E50 + EXPOSURE)

HAZ = HAZ0 \* EXP(DEFF + XEFF \* X1)

DADT(1) = HAZ

$ERROR

CUMHAZ = A(1)

SURV = EXP(-CUMHAZ)

HAZ0NOW = DLTA \* LAMBDA \* (LAMBDA\*TIME)\*\*(DLTA-1)

EXPOSNOW = AUCSS ; \* (1 - EXP(-BETA\*TIME))

DEFFNOW = EMAX \* EXPOSNOW / (E50 + EXPOSNOW)

LNHAZNOW = LOG(HAZ0NOW) + DEFFNOW + XEFF\*X1

HAZNOW = EXP(LNHAZNOW)

; likelihood = SURV (if censored)

; likelihood = SURV\*HAZNOW (if event)

IF (DV.EQ.1) THEN

LIKE = SURV \* HAZNOW

ELSE

LIKE = SURV

ENDIF

Y = -2 \* LOG(LIKE)

; Martingale residual: rM = (1-CENSOR) + log(SURV)

MARTRES = (DV) - CUMHAZ

; deviance residual = sign(rM) \* SQRT(-2\*(rM + (1-CENS)\*log(-log(SURV))))

SIGNRM = 1

IF (MARTRES < 0) SIGNRM = -1

IF (MDV.EQ.1) THEN

DEVRES = 0

ELSE

DEVRES = SIGNRM \* SQRT(-2 \* (MARTRES + (DV)\*LOG(CUMHAZ)))

ENDIF

; Simulation for model evaluation

IF (ICALL.EQ.4) THEN

CALL RANDOM (2,R)

DV=0

RTTE = 0

IF(TIME.EQ.24.0) RTTE=1

IF(R.GE.SUR) THEN

DV=1

RTTE = 1

ENDIF

ENDIF

$THETA

(1.1) ; LOG(DELTA)

(-2.42) ; log(lambda)

(0.7) ; additive effect of x1 on log hazard

(1.7) ; emax

(0.7 ) ; log(e50)

;(-0.7) ; log(beta)

$OMEGA 0 FIX

;Sim\_start : add/remove for simulation

$ESTIMATION MAXEVAL=9999 -2LL PRINT=5 NOABORT METHOD=1 MSFO=./1.msf

$COV PRINT=E

;$SIMULATION (5988566) (39978 UNIFORM) ONLYSIM NOPREDICTION SUB=1000

;Sim\_end

$TABLE FILE=./1.tab ONEHEADER

ID DOSE AUCSS X1 TIME DV MDV PRED CUMHAZ SURV HAZNOW MARTRES DEVRES

NOAPPEND NOPRINT

$TABLE ID TIME SUR HAZNOW DOSE EVID NOAPPEND NOPRINT ONEHEADER FILE=sdtab1

$TABLE ID AUCSS NOAPPEND NOPRINT ONEHEADER FILE=patab1

$TABLE ID X1 NOAPPEND NOPRINT ONEHEADER FILE=catab1

### A3. R code for Cox Snell and modified Cox Snell residuals

library(survival)

tab <- read.table(file=1.tab, header=TRUE, skip=1,as.is=TRUE)

NMtable <- tab[tab$EVID==0,] # only events, note for events DV=1, for censored DV = 0

NMtable$CSRES <- -log(NMtable$SUR) # Cox Snell residual

NMtable$MCSRES <- -log(NMtable$SUR) + 1-NMtable$DV # or + log(2)-NMtable$DV # modified Cox Snell residual

fit = survfit(Surv(RES,DV)~1,data=NMtable) # RES = CSRES or MCSRES

cs.plot = ggplot(data=NULL,

aes(x=cs.fit$time, y=-log(cs.fit$surv))) + geom\_abline(intercept=0,slope=1,col='red') +

geom\_point() + theme\_bw() + ggtitle(run.prob) + # facet\_wrap(~label, scales="fixed", ncol=2)

labs(x = 'Cox-Snell residual', y='-S(residual)') + lims(x=c(0,ceiling(max(cs.fit$time))),

y=c(0,ceiling(max(cs.fit$time))))

print(cs.plot)

# Other Examples

The time grid method for simulating events using the same model as that used for estimation is illustrated in Figure HAZARD BASED VPC. This shows the Kaplan-Meier survivor function obtained from the original data set and the 95% confidence interval for curves simulated using the time grid method.

### **Supplementary Table X**.

A time grid is shown for simulation of bleeding events associated with warfarin treatment. The time grid covers 1 year period. Events are generated at 1 day intervals. The DVID variable is used to simulate observations of drug concentration (DVID=1, biomarker influencing the hazard (DVID=2) and whether or not an event occurred in the 1 day interval (DVID=3).

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| #ID | TIME | TRT | AMT | RATE | ADDL | II | WT | DVID | DV | MDV |
| 1 | 0 | 1 | 5 | -2 | 364 | 1 | 70 | 0 | . | 1 |
| 1 | 0 | 1 | . | . | . | . | 70 | 1 | . | 1 |
| 1 | 0 | 1 | . | . | . | . | 70 | 2 | . | 1 |
| 1 | 0 | 1 | . | . | . | . | 70 | 3 | . | 1 |
| 1 | 1 | 1 | . | . | . | . | 70 | 1 | . | 1 |
| 1 | 1 | 1 | . | . | . | . | 70 | 2 | . | 1 |
| 1 | 1 | 1 | . | . | . | . | 70 | 3 | . | 1 |

$SIZES NO=1200 LIM6=1200 ; NO AND LIM6 MUST BE >=MAX NUMBER OF OBSERVATIONS RECS/SUBJECT

$PROB SIMULATE TIME TO EVENT

$DATA ..\data.csv

$INPUT ID TIME TRT AMT RATE ADDL II WT DVID DV MDV REP

$SIM (20091202) (20091203 UNIFORM) (20091204 UNIFORM)

(20091218 UNIFORM) (20091220 UNIFORM) ONLYSIM NSUB=1

;O'REILLY RA, AGGELER PM. STUDIES ON COUMARIN ANTICOAGULANT DRUGS.

;INITIATION OF WARFARIN THERAPY WITHOUT A LOADING DOSE.

;CIRCULATION. 1968;38:169-77.

;O'REILLY RA, AGGELER PM, LEONG LS. STUDIES OF THE COUMARIN ANTICOAGULANT DRUGS:

;THE PHARMACODYNAMICS OF WARFARIN IN MAN.

;J CLIN INVEST. 1963;42(10):1542-51.

;HOLFORD NHG. THE VISUAL PREDICTIVE CHECK – SUPERIORITY TO STANDARD DIAGNOSTIC

;(RORSCHACH) PLOTS

;[WWW.PAGE-MEETING.ORG/?ABSTRACT=738]. PAGE. 2005;14

;EVENT HAZARD

$THETA

0.1 ; POP\_HBASE 1/Y BASELINE HAZARD (MAJOR HAEMORRHAGE)

0.2 ; POP\_HDROP 1/Y BASELINE HAZARD (DROPOUT)

0 FIX ; POP\_BTATRT HAZARD RATIO INCREASE PER 1 MG/D WARFARIN (0.4)

0 FIX ; POP\_BTAPCA HAZARD RATIO INCREASE WITH 100% DECREASE IN PCA (2.0)

0.5 ; POP\_BTAINR HAZARD RATIO INCREASE WITH INR (0.5)

;WARFARIN PKPD

$THETA

(0.01,0.128,1) ; POP\_CL L/H/70KG

(0.01,8.11,20) ; POP\_V L/70KG

(0.01,1.46,24) ; POP\_TABS H

(0.,0.998,24) ; POP\_LAG H

(0.01,96.3,200) ; POP\_PCA0

-1. FIX ; POP\_EMAX

(0.01,1.24,10) ; POP\_C50 MG/L

(0.01,12.9,100) ; POP\_TEQ H

$OMEGA

0.0645 ; PPV\_CL

0.0183 ; PPV\_V

0.619 ; PPV\_TABS

0.278 ; PPV\_LAG

0.001 ; PPV\_PCA0

0 FIX ; PPV\_EMAX

0.191 ; PPV\_C50

0.0116 ; PPV\_TEQ

0.01 ; PPV\_HBASE

$SIGMA

0.00693 ; RUV\_CV

0.0818 ; RUV\_SD MG/L

16. ; RUV\_PCA

$THETA

70 ; TBWKG\_STD KG

$OMEGA

0.01 ; PPV\_TBWKG

$SUBR ADVAN6 TOL=3

$MODEL

COMP=CENTRAL

COMP=PCA

COMP=HAZEVT

COMP=HAZDRP

$PK

IF (NEWIND.LE.1) THEN

LN2=LOG(2)

HASEVT=0 ; NOT HAD EVENT

HASDRP=0 ; NOT DROPPED OUT

SEVTZ=1 ; SURVIVOR FUNCTION AT TIME=0

DOSE=0

ENDIF

IF (ICALL.EQ.4) THEN

IF (NEWIND.LE.1) THEN ; FIRST RECORD

CALL RANDOM(2,R)

UEVT=R ; UNIFORM RANDOM NUMBER FOR EVENT

CALL RANDOM(3,R)

UTRT=R ; UNIFORM RANDOM NUMBER FOR TREATMENT

CALL RANDOM(4,R)

UDRP=R ; UNIFORM RANDOM NUMBER FOR DROPOUT

IF (UTRT.LT.0.25) THEN ; PLACEBO

RATE=0

ADDL=0

II=0

SF1=0

STRT=0

ELSE

IF (UTRT.LT.0.5) THEN ; DOSE 1

SF1=2.5

STRT=1

ELSE

IF (UTRT.LT.0.75) THEN ; DOSE 2

SF1=5

STRT=2

ELSE

SF1=10

STRT=4

ENDIF

ENDIF

ENDIF

STBWKG=TBWKG\_STD\*EXP(PPV\_TBWKG) ; SIMULATED WEIGHT

ENDIF

DOSE=1\*SF1 ; MG

TBWKG=STBWKG

TRT=STRT

ENDIF

F1=DOSE

FSZV=TBWKG/TBWKG\_STD

FSZCL=FSZV\*\*0.75

CL=FSZCL\*POP\_CL\*EXP(PPV\_CL)\*24 ; L/H -> L/D

V=FSZV\*POP\_V\*EXP(PPV\_V)

TABS=POP\_TABS\*EXP(PPV\_TABS)/24 ; H -> D

TLAG=POP\_LAG\*EXP(PPV\_LAG)/24 ; H -> D

PCA0=POP\_PCA0\*EXP(PPV\_PCA0)

EMAX=POP\_EMAX\*EXP(PPV\_EMAX)

C50=POP\_C50\*EXP(PPV\_C50)

TEQ=POP\_TEQ\*EXP(PPV\_TEQ)/24 ; H -> D

HBASE=POP\_HBASE\*EXP(PPV\_HBASE)/365 ; 1/Y -> 1/D

HDROP=POP\_HDROP/365 ; 1/Y -> 1/D

BTATRT=POP\_BTATRT

BTAPCA=POP\_BTAPCA

BTAINR=POP\_BTAINR

D1=TABS

ALAG1=TLAG

S1=V

A\_0(2)=PCA0

KPCA=LN2/TEQ

RPCA=PCA0\*KPCA

$DES

DCP=A(1)/V

DPCA=A(2)

DINR=PCA0/DPCA

PD=1+EMAX\*DCP/(C50+DCP)

DADT(1)=- CL\*DCP ; WARFARIN CONC

DADT(2)=RPCA\*PD - KPCA\*DPCA ; TURNOVER FOR PCA

DADT(3)=HBASE \* EXP(BTATRT\*TRT + BTAINR\*DINR + BTAPCA\*(1-DPCA/PCA0))

DADT(4)=HDROP

$ERROR

CP=A(1)/V

PCA=A(2)

CUMEVT=A(3)

CUMDRP=A(4)

; PROB OF NOT HAVING EVENT UP TO THIS TIME

SEVTT=EXP(-CUMEVT) ; SURVIVOR FUNCTION (T)

; PROB OF NOT HAVING DROPPED OUT TO THIS TIME

SDRPT=EXP(-CUMDRP) ; SURVIVOR FUNCTION (T)

IF (DVID.LE.1) THEN

F\_FLAG=0

Y=CP\*(1+RUV\_CV) + RUV\_SD

ENDIF

IF (DVID.EQ.2) THEN

F\_FLAG=0

Y=PCA + RUV\_PCA

ENDIF

IF (DVID.EQ.3.AND.DV.EQ.0) THEN ; CENSORED EVENT

F\_FLAG=1

Y=SEVTT ; SURVIVOR FUNCTION

ENDIF

IF (DVID.EQ.3.AND.DV.EQ.1) THEN ; EVENT IN INTERVAL

F\_FLAG=1

Y=SEVTZ - SEVTT ; LIKELIHOOD OF EVENT IN INTERVAL

ENDIF

IF (ICALL.EQ.4) THEN

IF (DVID.EQ.3.AND.HASDRP.EQ.0.AND.SDRPT.LT.UDRP) THEN

HASDRP=1

DVX=0 ; CENSORED EVENT

DVIX=3

MDVX=0

ELSE

IF (HASDRP.EQ.0.AND.HASEVT.EQ.0) THEN

IF (DVID.EQ.3) THEN ; CHECK FOR EVENT

IF (SEVTT.LT.UEVT) THEN ; EVENT

HASEVT=1

DVX=1

DVIX=3

MDVX=0

ELSE ; DUMMY EVENT RECORD

DVX=0

DVIX=3

MDVX=1

ENDIF

ELSE ; LAST RECORD (DEFAULT FOR CENSORING) OR OTHER EVID (DOSE, OBS)

IF (DVID.EQ.4) THEN ; LAST RECORD

DVX=0 ; CENSORED EVENT

DVIX=3

MDVX=0

ELSE ; DOSE OR CONC OR PCA

IF (DVID.EQ.0) THEN ; DOSE

DVX=0

MDVX=1

ELSE ; OBSERVATION

DVX=Y

MDVX=0

ENDIF

DVIX=DVID

ENDIF

ENDIF

ELSE ; AFTER DROPOUT OR AFTER EVENT SO CONVERT TO MISSING

DVX=0

DVIX=DVID

MDVX=1

ENDIF

ENDIF

ENDIF

IF (DVID.EQ.3) THEN ; START NEW EVENT INTERVAL

SEVTZ=SEVTT ; SURVIVOR FUNCTION AT START OF NEW INTERVAL

ELSE ; SAVE RECURSIVE RANDOM VARIABLE (ONLY WORKS WITH NM6 OR LATER)

SEVTZ=SEVTZ

ENDIF

INR=PCA0/PCA

$TABLE ID TIME TRT AMT RATE ADDL II TBWKG DVIX DVX MDVX REP

CP PCA INR CL V TABS TLAG F1 PCA0 EMAX C50 TEQ

NOAPPEND ONEHEADER NOPRINT FILE=warf\_inr\_sim\_org.fit