The Kaplan-Meier Mean Covariate (KMMC) plot: a new diagnostic for covariates in time-to-event models.

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Background

When building time-to-event (TTE) models it is often difficult to screen for covariates (or predictors) and it can be especially challenging to understand, and illustrate, how covariates should be included in the model. Additionally, it can be challenging to illustrate the importance of included covariates.

Stratification can work for time-constant categorical predictors but cannot be used for continuous and/or time-varying covariates without loss of information.

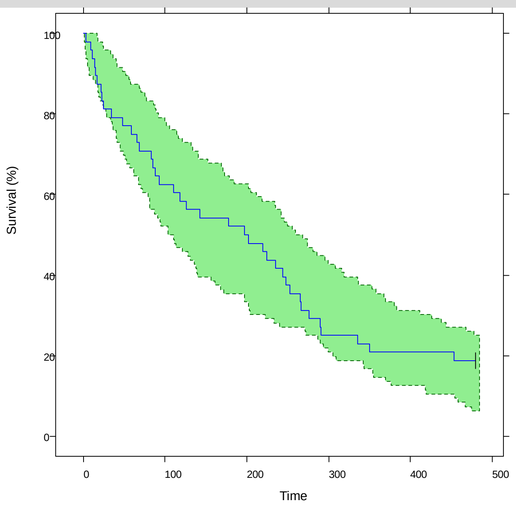

Figure 1. Model with constant hazard. Data is simulated with concentration dependence.

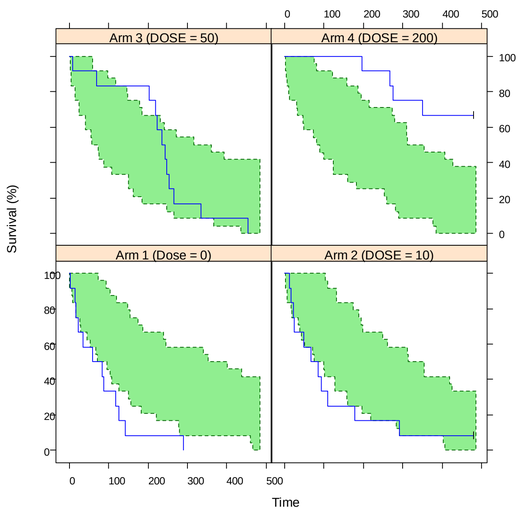

Figure 2. Kaplan-Meier VPC using categorical covariate stratification.

Study design for investigations:

- A (simulated) proof-of-concept clinical trial evaluating a new agent for inhibition/ amelioration of reflux events
- 48 patients with frequent reflux episodes
- Randomized, double-blind, 4 arm, single-dose (placebo, 10 50, 200 mg) parallel trial
- Time to first moderate or severe reflux event recorded.

Objective

In this work we present a new graphical tool that can overcome these problems; the Kaplan-Meier Mean Covariate (KMMC) plot.

Methods

The KMMC plot computes the mean (or any other function) of a covariate for all of the individuals still in a study at every inflection point of a Kaplan-Meier survival curve.

This “running” mean of a covariate that is influential on survival would be expected to increase or decrease as a study progresses.

Simulating from a model numerous times will give numerous simulated KMMC curves, and a VPC of the KMMC can thus be created, allowing for comparison between model predictions and the true data.

The plot is easily created using the latest versions of PsN [1] and Xpose [2].

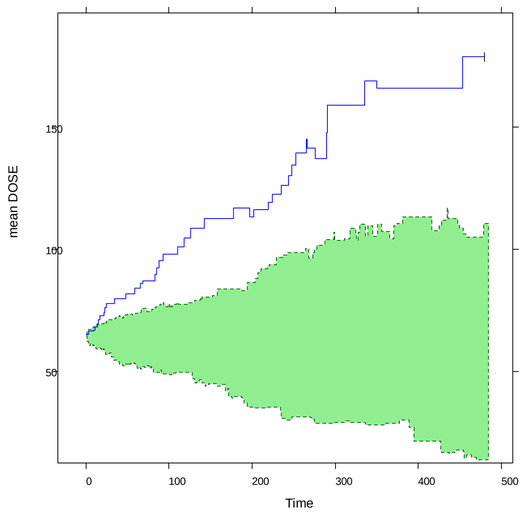

Figure 4. A KMMC plot of mean dose for the model and data shown in figures 1-3. Mean dose increases as no/low dose individuals have events. Indicates that dose or some other correlated covariate should be in TTE model.

PsN command:

vpc run51.mod -tte=RTTE -flip_comments -samples=100 -stratify_on=DOSE

Xpose command:

kaplan.plot(x="TIME", y="DV", object=xpdb,VPC=T, cov="DOSE", cov.fun="mean")

References

[1] Perl Speaks NONMEM (PsN), www.psn.sf.net.

[2] Xpose, www.xpose.sf.net.

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Results

KMMC can be used for continuous or categorical covariates and can easily handle both time-constant and time-varying covariates.

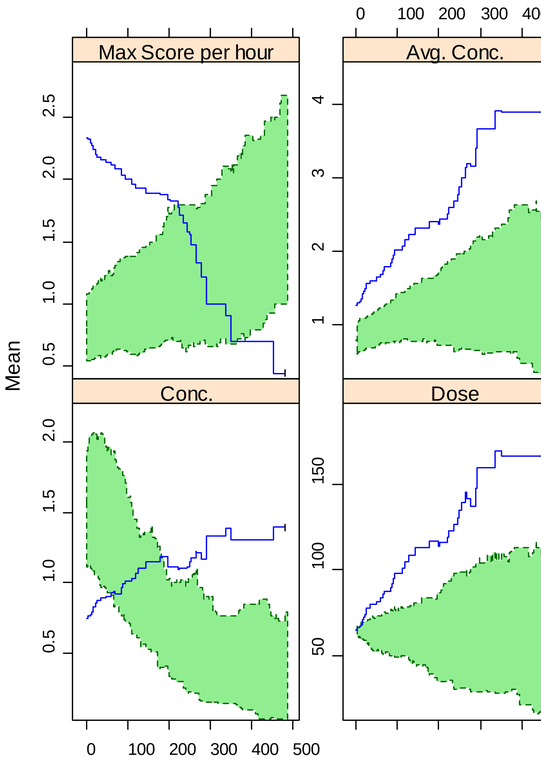

Figure 5. A KMMC plot using concentration (continuous and time-varying).

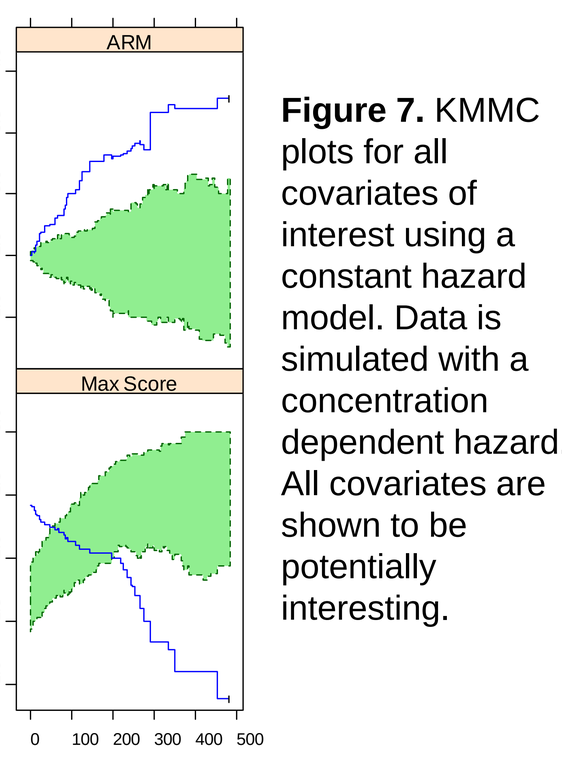

Figure 6. A KMMC plot using dose (categorical – only 4 allowed dose levels in study).

From a base TTE model all covariates can be screened right away using the KMMC plot.

Figure 7. KMMC plots for all covariates of interest using a constant hazard model. Data is simulated with a concentration dependent hazard. All covariates are shown to be potentially interesting.

Below, KMMC plots for both before and after a covariate is included in a TTE model identify the covariate effect and show when a model adequately describes that effect.

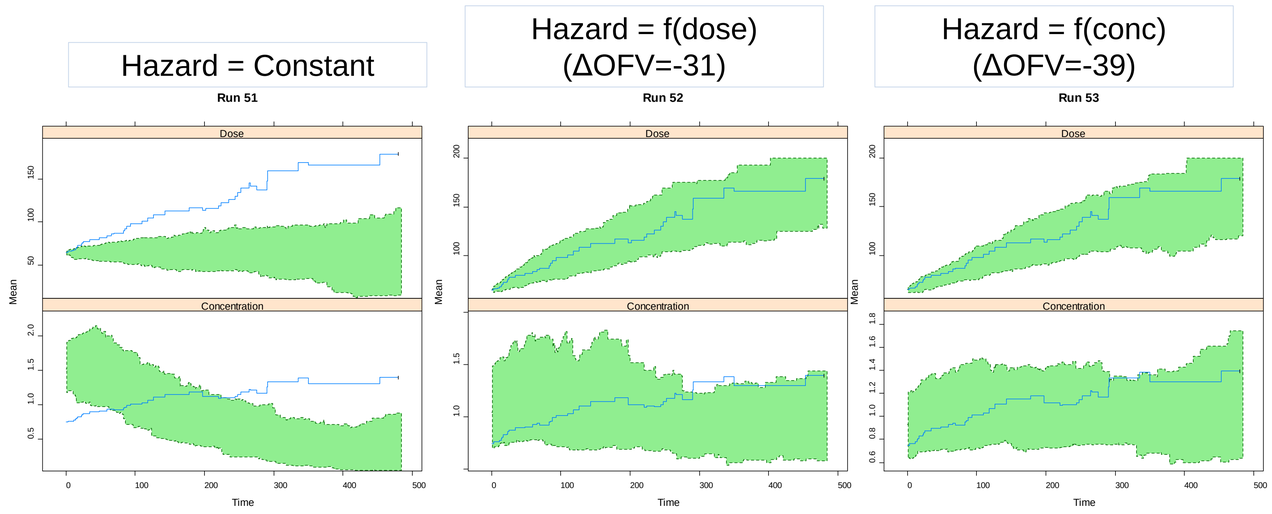

Figure 8. Performance of the KMMC plot. Data is simulated with a concentration dependent hazard.

Conclusions

- KMMC plots can
  - Identify potential covariates that may then be investigated in further model building.
  - Show when a model adequately incorporates covariates into the model.
  - Give hints as to the structure or form the covariate inclusion should take.
  - Handle both continuous and categorical data
  - Handle time-varying covariates
  - Use other functions instead of the mean to summarize covariates
  - Filter out or stratify individuals that are censored in the study so that covariates influencing both censoring and event can be visualized.