A Novel Tool for Visualizing Composite Endpoint Associations

Lutz P. Breitling, MD, MSc

Composite end points play a major role in cardiovascular clinical epidemiology, with many studies examining, for example, the time to the first major adverse cardiac event. Beyond the cardiovascular field, progression-free survival is an important outcome in oncology, and even general mortality can be considered a composite of cause-specific mortalities. Although the common application of composite end points supports their popularity and usefulness, disadvantages and caveats also have been pointed out.[1] One difficulty in composite end point studies is the transparent reporting of results in an accessible way, most authors suggesting the side-to-side reporting of results pertaining to separate analyses of the composite end point and its individual components.

Composite end point associations depend on the individual component associations in a complex way. Study duration may further complicate this through 2 main mechanisms. First, the association with any of the component outcomes may be time-varying. Second, the relative importance of the component outcomes may change with time.[2] Such study duration–dependent issues are likely to affect a substantial proportion of composite end point studies, but current analysis and reporting practices might often fail to reveal this. Thus, a straight-forward graphical summary of composite end point associations was sought, which would readily disclose such time-varying aspects of composite and underlying component associations. The longitudinal β plot here suggested might be used to this end, providing a simple tool for exploration and communication.

EXAMPLE APPLICATION

The longitudinal β plot is motivated by the so-called time-dependent coefficient plot, which is commonly used to assess the proportional hazards assumption (ie, that the hazard ratio of some predictors is constant throughout follow-up).[3] In brief, a time-dependent coefficient plot shows the development of the predictor outcome association over time, giving a straight horizontal line if the association is perfectly constant. By combining the time-dependent association estimate of a composite end point analysis with time-dependent estimates of the underlying component outcomes, the longitudinal β plot reveals how the composite end point association evolves and changes as a result of the underlying component outcome associations. Generally speaking, changes in the composite end point association may be caused by changes in the strength of either or both component associations or by changes in the relative frequency of the component end points, as demonstrated in the toy example provided in the Data Supplement alongside some more technical comments.

To provide an instructive real-life example for the application of the longitudinal β plot, freely available data of the International Stroke Trial were examined (see Data Supplement for further information and funding).[4] In brief, and not to be over-

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interpreted with respect to the subject matter, the age-adjusted association of impaired consciousness (24% prevalence) with all-cause mortality after ischemic stroke was analyzed (analysis data set featuring 13 780 subjects with median follow-up 185 days; 1651 and 1655 cerebrovascular and noncerebrovascular deaths, respectively). Figure (A) shows a standard time-dependent coefficient plot for this model, suggesting a somewhat larger association during the first weeks of follow-up. Figure (B) shows the longitudinal β plot for the same association, treating all-cause mortality as a composite of cerebrovascular and noncerebrovascular mortality. This plot reveals that the stronger association of impaired consciousness with all-cause mortality (shown by the black solid line) during early follow-up was almost exclusively because of a stronger association with cerebrovascular mortality (represented by the red dashed line) during this time period. The association with noncerebrovascular mortality (blue dotted line) was rather constant throughout the study, hardly explaining the stronger association with the composite end point during early follow-up.

Conventional hazard ratio estimates (95% CIs) for these associations would have been 3.8 (3.6–4.1; all-cause mortality), 5.2 (4.7–5.7; cerebrovascular mortality), and 2.8 (2.6–3.1; noncerebrovascular mortality). A significant violation of the proportional hazards assumption was detected for all 3 models using standard testing procedures.[3] Often, this would only be briefly mentioned in the methods, results, or limitations section, with an ultimate statement that the reported hazard ratios present some kind of averaged estimates and thus may be interpreted as suggesting an overall much stronger association of impaired consciousness with cerebrovascular than noncerebrovascular or all-cause mortality. The longitudinal β plot, however, suggested that this stronger association was limited to early follow-up, whereas the associations converge later on. Standard reporting practices in such a situation may be insufficient and misleading. They could insightfully be complemented by the graphical approach proposed.

CONCLUSIONS

As demonstrated in the above example, the longitudinal β plot has the potential to convey much more infor-

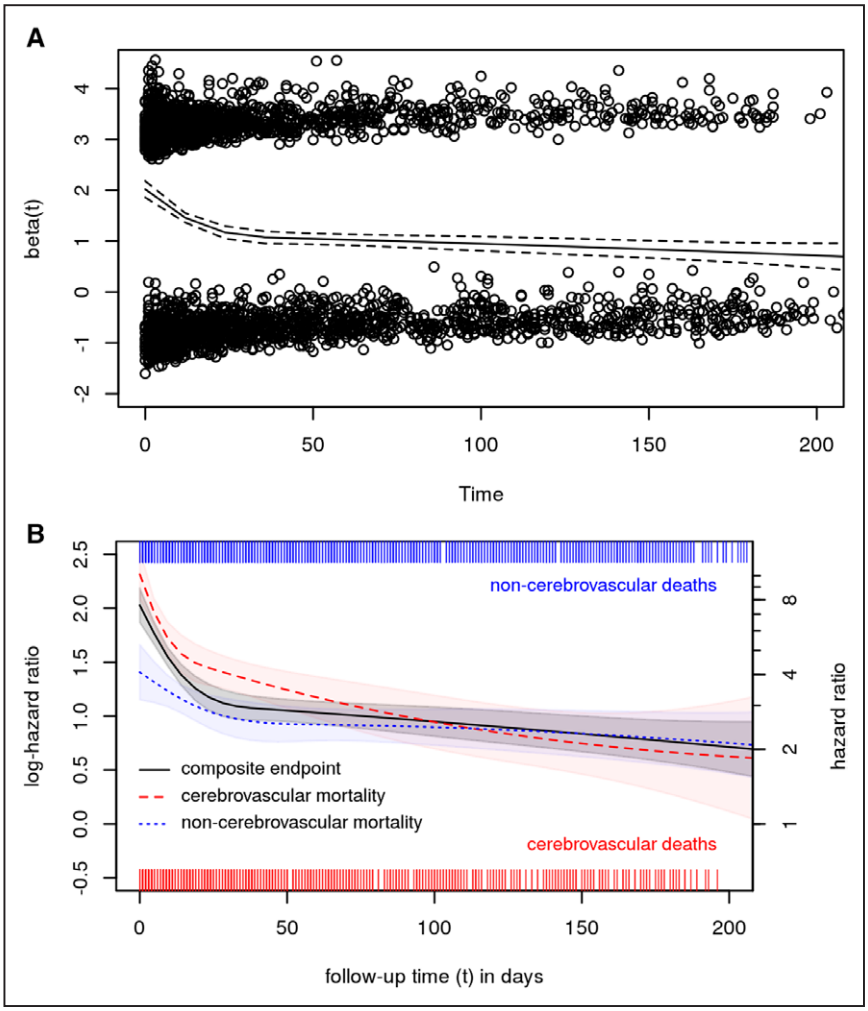

Figure. Example plots based on the International Stroke Trial (IST). **A,** The Schoenfeld residuals in a time-dependent coefficient plot of the association of impaired consciousness with mortality in IST, as conventionally used for proportional hazards assessments and produced with a standard function call in R. **B**, The corresponding longitudinal β plot, depicting the time-dependent association with the composite end point, cerebrovascular and noncerebrovascular deaths in black (solid line), red (dashed line), and blue (dotted line), respectively, with rugs marking the respective event times. Shaded areas show corresponding 95% CIs.

mation than conventional summaries or tabulations at a glance. It seems rather intuitive even without statistical background and hopefully provides a useful tool for exploratory composite end point analyses and accessible communication of complex longitudinal composite end point patterns. Some open issues remain, for example, alternative choices for estimating the smoothing lines or limited clarity if more than 2 components are to be visualized.

CODING

All analyses presented here were done using R 3.3.2 (R Foundation for Statistical Computing 2016, Vienna, Austria) and the extension package survival.[3] Figure (A) shows standard output of a function for testing the Cox proportional hazards assumption, whereas Figure (B) was drawn using a simple custom function. Example code for a 2-component composite end point is available as a Data Supplement.

DISCLOSURES

None.

AFFILIATION

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FOOTNOTES

The Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.117.004226/-/DC1.

Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org.

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SUPPLEMENTAL MATERIAL

Novel tool for visualizing composite endpoint associations

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Contents

The longitudinal beta plot for composite endpoint associations : description and simulated data example

The longitudinal beta plot is based on the time-dependent coefficient plot, in which the covariate-specific so-called Schoenfeld residuals of a Cox regression model are plotted against the follow-up observation time. As developed in detail elsewhere (Therneau TM, Grambsch PM. Modeling survival data : extending the Cox model. Springer, New York 2007), a smoother fitted to such a plot reflects the regression coefficient beta (i.e., the log-hazard ratio) of the association of the respective covariate with the outcome in an observation time-dependent manner. The main use of this time-dependent coefficient plot is to test the proportional hazards assumption, i.e., the constancy of the association of the exposure with the outcome.

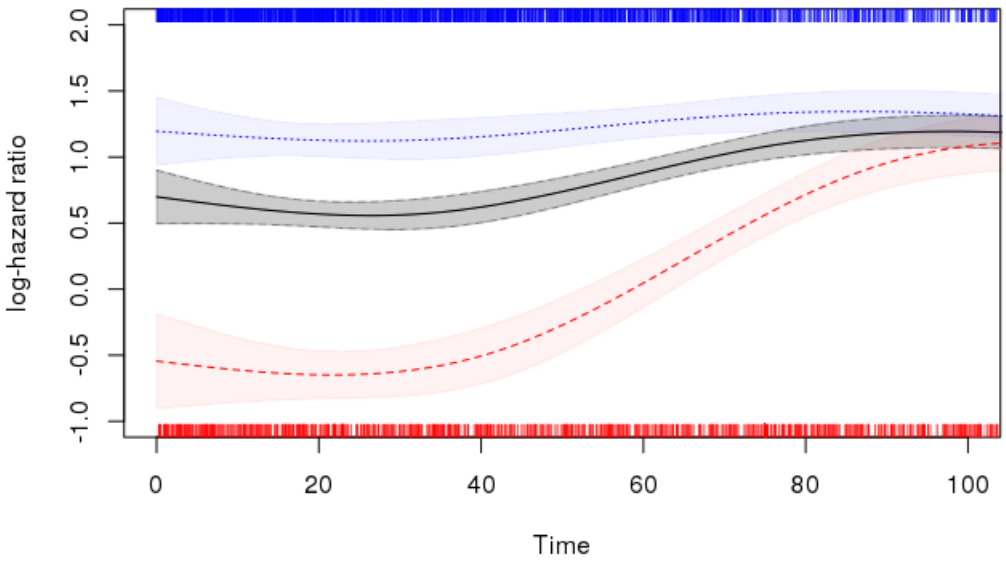
The longitudinal beta plot combines smoothers of multiple time-dependent coefficient plots, namely those originating from standard Cox regression models of an exposure's associations with some composite endpoint and its components, into one plot. Additional features that may be added to such a plot include the individual times at which either event was observed, and confidence intervals around the time-varying association estimates. Both features may help to get an idea how the overall association in the composite endpoint analysis evolves. Consider, for example, **Supplemental Figure 1**,

for which a composite endpoint made up of two outcomes (“blue” and “red”) was simulated using two different scenarios. In both cases, the composite endpoint association was simulated in such a way that it was weaker during early follow-up and stronger during later follow-up, but this pattern results from very different underlying component associations. In **Supplemental Figure 1A**, the black line shows the estimate of the composite endpoint association over follow-up time, starting with a beta value (log-hazard ratio) of just above 0.5 (equaling a hazard ratio of 1.6) at the beginning of the study and reaching a stronger association with a beta value of 1 (hazard ratio of 2.7) during later follow-up. The blue line shows that the underlying association with the “blue” component outcome is essentially constant throughout follow-up. The time-variability of the association with the composite endpoint results solely from the “red” component association, which itself is not at all constant and draws the composite endpoint association downward during early (but not during later) follow-up. In **Supplemental Figure 1B**, the overall association with the composite endpoint is very similar to the previous simulation, weaker during early and stronger during later follow-up. In this case, however, the longitudinal beta plot reveals at first glance that the association with either component outcome does not change with time. Instead, during early follow-up, the weak “red” component outcome dominates the composite endpoint, whereas the “blue” component with its stronger association is rare during early follow-up and becomes more frequent and dominating only during later follow-up. Taken together, time-constant component associations in the second scenario produce a time-varying composite endpoint association because of changing relative contributions to the composite endpoint.

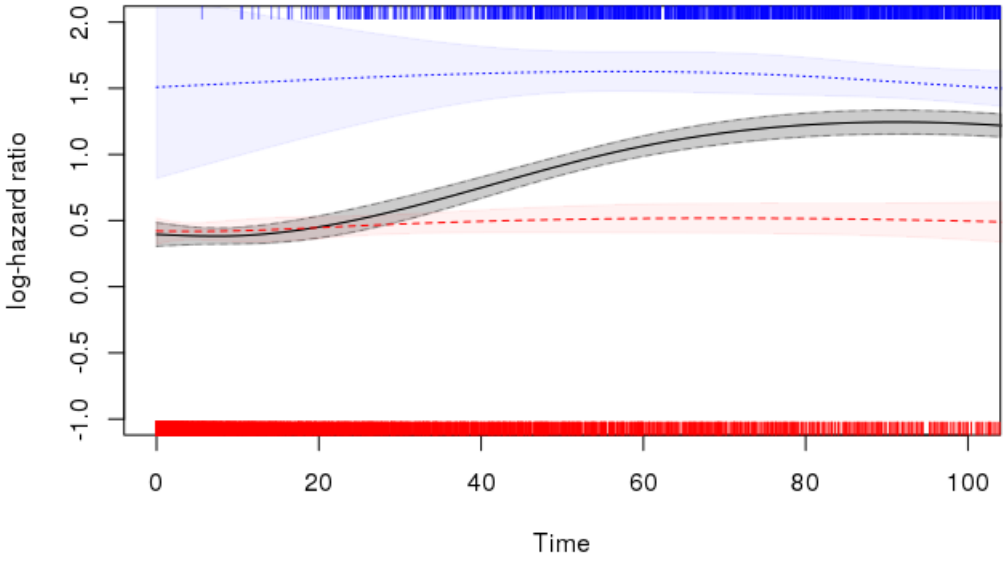
The alert reader may notice that standard Cox regression models are used in the construction of the longitudinal beta plot, even though component outcome analyses of a composite endpoint actually constitute a competing risk problem (if a subject experiences one of the component outcomes, it cannot experience another component outcome later on). However, the so-called cause-specific hazard ratios obtained by applying the standard Cox regression method seem to be the most relevant estimate of the component associations in this context, because they quantify the increase in the instantaneous component hazard rate among subjects who are still in the study at any particular time-point. One should only bear in mind that these cause-specific associations do not translate directly into event frequencies, i.e. a component cause-specific hazard ratio of 2 does not imply that the respective component outcome will be observed twice as often as in the comparison group. Inferences of the latter kind do not hold in the presence of competing risks (because some subjects will be removed from the population at risk by experiencing the competing other component outcome) and indeed would require the application of special methods, such as the subdistributional proportional hazards model (Lau et al.: Competing risk regression models for epidemiologic data. Am J Epidemiol 2009, 170:244).

Supplemental Figure 1. Longitudinal beta plots for two simulated composite endpoint scenarios (black solid line: composite endpoint association; red dashed line and bottom rugs: first component outcome; blue dotted line and top rugs: second component outcome). In both cases, a composite endpoint was simulated from two component outcomes, producing an association increasing in strength during later follow-up. However, in scenario A, this time-varying pattern results solely from the association with the first ("red") component outcome, which strongly increases with increasing follow-up time. In scenario B, the association with the composite endpoint is similar to scenario A, but the associations with both component outcomes are very constant throughout the study time. The association with the composite endpoint increases with study duration because the second ("blue") component outcome with its stronger association becomes relatively more frequent and dominating during later follow-up in this scenario.

A



B



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Further information on IST data used

The corrected version of the publicly available IST database was used (Sandercock et al.: The International Stroke Trial database. Trials 2012, 13:24), and the great work and efforts of the International Stroke Trial Collaborative Group, who collected and made available these data, are gratefully acknowledged.

For the example analyses, the association of impaired consciousness (conscious state at randomization 'drowsy' or 'unconscious', as contrasted with 'fully alert' as the reference category) with all-cause mortality during six months of follow-up was analyzed. All-cause mortality was treated as a composite of cerebrovascular mortality (death from the initial or recurrent stroke) and non-cerebrovascular mortality (any other cause, including unknowns).

Code example

The following code produces a longitudinal beta plot for the association of age with transplant-free survival in primary biliary cirrhosis (**Supplemental Figure 2**) based on an example dataset distributed with the statistical package R. The code can easily be adopted to accommodate more than two component endpoints or other specific needs of the analyst.

```
########## code example for CircCQO ####

require(survival);
require(splines);

lbplot<-function(cep,ep1,ep2,...){
# function to plot the longitudinal beta plot for the FIRST predictor
# of a multiple Cox regression CEP model...

  rgb123<-c();
  rgb123[1]<-rgb(red  =col2rgb("black")["red"  ,]/255,
                 green=col2rgb("black")["green",]/255,
                 blue =col2rgb("black")["blue" ,]/255, alpha=0.15);
  rgb123[2]<-rgb(red  =col2rgb("red")["red"  ,]/255,
                 green=col2rgb("red")["green",]/255,
                 blue =col2rgb("red")["blue" ,]/255, alpha=0.05);
  rgb123[3]<-rgb(red  =col2rgb("blue")["red"  ,]/255,
                 green=col2rgb("blue")["green",]/255,
                 blue =col2rgb("blue")["blue" ,]/255, alpha=0.05);
```

```
  survival:::plot.cox.zph(cox.zph(cep, transform="identity")[1],
                          col="white", df=4, resid=FALSE, ...);

        # residuals
        rs.cep<-residuals(cep, type="scaledsch");
        rs.ep1<-residuals(ep1, type="scaledsch");
        rs.ep2<-residuals(ep2, type="scaledsch");


        # get event times
        times.cep <- as.numeric(dimnames(rs.cep)[[1]]);
        times.ep1 <- as.numeric(dimnames(rs.ep1)[[1]]);
        times.ep2 <- as.numeric(dimnames(rs.ep2)[[1]]);

       # fit splines
        ns.cep<-lm(rs.cep[,1]~ns(times.cep, df=3));
        ns.ep1<-lm(rs.ep1[,1]~ns(times.ep1, df=3));
        ns.ep2<-lm(rs.ep2[,1]~ns(times.ep2, df=3));

        # predict splines
        xx<-seq(min(times.cep), max(times.cep),length=100);
        p1.cep<-predict(ns.cep, newdata=data.frame(times.cep=xx), se.fit=TRUE);
        p1.ep1<-predict(ns.ep1, newdata=data.frame(times.ep1=xx), se.fit=TRUE);
        p1.ep2<-predict(ns.ep2, newdata=data.frame(times.ep2=xx), se.fit=TRUE);

        # plot event times as rugs
        rug(times.ep1, side=ifelse(median(p1.ep1$fit)<=median(p1.ep2$fit),1,3), col="red");
        rug(times.ep2, side=ifelse(median(p1.ep1$fit)<=median(p1.ep2$fit),3,1), col="blue");


        # plot confidence polygons
        polygon(c(xx, rev(xx)), c(p1.cep$fit+2*p1.cep$se.fit,
               rev(p1.cep$fit-2*p1.cep$se.fit)),
               col=rgb123[1],  border=rgb123[1]);

        polygon(c(xx, rev(xx)), c(    p1.ep1$fit+2*p1.ep1$se.fit,
               rev(p1.ep1$fit-2*p1.ep1$se.fit)),
               col=rgb123[2],  border=rgb123[2]);
        polygon(c(xx, rev(xx)), c(    p1.ep2$fit+2*p1.ep2$se.fit,
               rev(p1.ep2$fit-2*p1.ep2$se.fit)),
               col=rgb123[3],  border=rgb123[3]);

        # plot splines
        lines(y=p1.cep$fit, x=xx, type="l", col="black");
        lines(y=p1.ep1$fit, x=xx, type="l", col="red");
        lines(y=p1.ep2$fit, x=xx, type="l", col="blue");


}

# mC = model for transplant-free survival;
# m1 = model for time to transplant;
# m2 = model for time to death;
mC<-coxph(Surv(time=time, event=status!=0) ~ age+sex, data=pbc);
m1<-coxph(Surv(time=time, event=status==1) ~ age+sex, data=pbc);
m2<-coxph(Surv(time=time, event=status==2) ~ age+sex, data=pbc);

lbplot(mC,m1,m2, ylim=c(-0.3, 0.3));
```

Supplemental Figure 2. Longitudinal beta plot for the association of age with transplant-free survival as produced by the example code (see text for details).