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Evaluating Additive Interaction Using Survival Percentiles

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Abstract: Evaluation of statistical interaction in time-to-event analysis is usually limited to the study of multiplicative interaction, via inclusion of a product term in a Cox proportional-hazard model. Measures of additive interaction are available but seldom used. All measures of interaction in survival analysis, whether additive or multiplicative, are in the metric of hazard, usually assuming that the interaction between two predictors of interest is constant during the follow-up period. We introduce a measure to evaluate additive interaction in survival analysis in the metric of time. This measure can be calculated by evaluating survival percentiles, defined as the time points by which different subpopulations reach the same incidence proportion. Using this approach, the probability of the outcome is fixed and the time variable is estimated. We also show that by using a regression model for the evaluation of conditional survival percentiles, including a product term between the two exposures in the model, interaction is evaluated as a deviation from additivity of the effects. In the simple case of two binary exposures, the product term is interpreted as excess/decrease in survival time (i.e., years, months, days) due to the presence of both exposures. This measure of interaction is dependent on the fraction of events being considered, thus allowing evaluation of how interaction changes during the observed follow-up. Evaluation of interaction in the context of survival percentiles allows deriving a measure of additive interaction without assuming a constant effect over time, overcoming two main limitations of commonly used approaches.

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Statistical interaction is commonly evaluated by including a product-term between two exposures of interest in the model.[1,2] Whether an additive or multiplicative interaction is evaluated depends on the scale of the chosen statistical model.[3] In survival analysis, the usual choice is the Cox proportional-hazard regression and statistical interaction is generally assessed as a deviation from multiplicativity, often without any mention of the scale issue.[4,5]

Interaction on the additive scale, however, is a more intuitive concept with a particular public health meaning, and investigating and presenting statistical interaction according to both scales has been widely recommended.[1,3,6,7] To evaluate additive interaction in survival analysis, measures derived from multiplicative models, such as the relative risk due to interaction, the synergy index, or the attributable proportion due to interaction have been proposed.[8,9] As a possible alternative, Rod et al.[4] suggested the use of the additive hazard model.

All the available measures, whether additive or multiplicative, calculate interactions on the rate scale, estimating probabilities or hazards of the event within a fixed follow-up time. Another possible approach for the analysis of time-to-event data is the evaluation of survival percentiles, defined as the time by which a certain fraction of the population has experienced the event of interest.[10] When focusing on survival percentiles, a specific probability of the event is fixed and is the time point to be estimated. While common scales for the evaluation of interaction, such as the risk differences scale, the risk ratios scale, and the odds ratio scale, have been studied extensively, measures of interaction on the survival time scale have never been investigated. This approach can be particularly relevant in the analysis of ultimate or inevitable outcomes, such as death. Statistical methods to estimate survival percentiles, and differences in survival percentiles according to exposure level, are available at the univariable and multivariable level.[10] Among these, Laplace regression is a flexible approach to directly estimate the conditional percentiles of the time-to-event variable as a linear combination of the predictors.[11,12]

The aim of this article is to present the evaluation of statistical interaction in the context of survival percentiles, introducing Laplace regression as a possible approach to evaluate and test additive interaction in time-to-event analysis.

DEFINING ADDITIVE INTERACTION IN THE CONTEXT OF SURVIVAL PERCENTILES

The common scenario in time-to-event analysis is represented by a cohort of n individuals, free from a specific disease of interest D at time $t = 0$, who are observed during a follow-up period to evaluate the disease-free survival. Survival percentiles can be defined as the time points by which specific proportions

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of the study population have experienced the event *D*. For example, the time by which the first 50% of the individuals have experienced the event is defined as 50th survival percentile or median survival. The survival curve depicts a complete summary of the entire range of observed survival percentiles, presenting the proportion of events during the follow-up time. A common approach to evaluate the survival function is to fix a specific time *t*—usually the end of follow-up—and to estimate survival probabilities or rates of the event *D* in the time interval [0, *t*], possibly according to levels of specific exposures or risk factors. In a percentile approach, on the other hand, the incidence proportion *p* is fixed to a specific level and the outcome to be evaluated is the corresponding survival percentile, the time *t* by which the study population reaches the specific fraction of events *p*.

Let *G* and *E* be two binary exposures, which can take values 0 or 1, and are both risk factors for the event *D*. Figure 1 presents a possible survival experience for the four combinations of the two exposures (i.e., $G = 0$, $E = 0$; $G = 1$, $E = 0$; $G = 0$, $E = 1$; $G = 1$, $E = 1$). Given a fixed proportion of events *p*, the *p*th survival percentiles for each of the four groups (t_{00}, t_{10}, t_{01}, t_{11}) are displayed in the figure. The difference ($t_{11} - t_{00}$) represents the difference in the *p*th survival percentile between participants with both exposures and participants with neither. The quantities ($t_{10} - t_{00}$) and ($t_{01} - t_{00}$) are the differences between participants with only exposure *G* or *E*, respectively, and participants with neither exposure. Following the conventional notation introduced in terms of risk,[1,7] the following difference represents an intuitive measure of interaction at the *p*th percentile (I_p):

$$I_p = (t_{11} - t_{00}) - [(t_{10} - t_{00}) + (t_{01} - t_{00})] \quad (1)$$

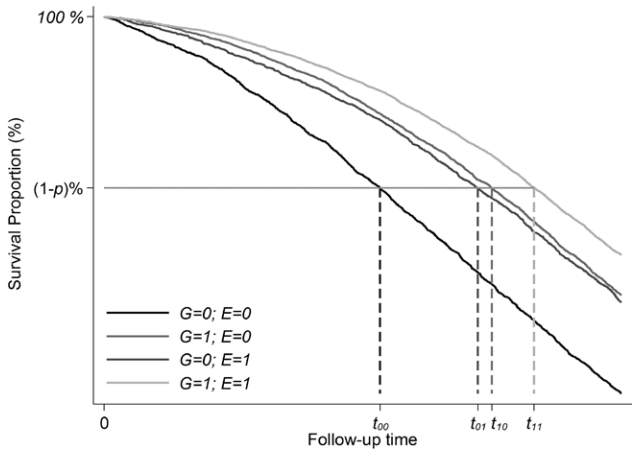

FIGURE 1. Survival percentiles. Given a fixed fraction of cases, survival percentiles are defined as the time points by which different subpopulations reach the same proportion of events. The *horizontal line* indicates a specific survival proportion. The time points t_{00}, t_{10}, t_{01}, and t_{11} are the *p*th percentiles in each of the four possible combinations of two binary exposures *G* and *E*.

This difference, calculated as an additive measure, can be rewritten as $t_{11} - t_{10} - t_{01} + t_{00}$ and represents a measure of interaction on the metric of survival time. It expresses to what extent the difference in survival due to the presence of both exposures exceeds the sum of survival differences due to each specific exposure. Comparing this measure with 0, we can define the interaction as superadditive, if greater than 0, or subadditive otherwise.

LAPLACE REGRESSION

Unadjusted differences in survival percentiles can be obtained from the Kaplan–Meier method, deriving the confidence intervals of the differences via bootstrap. When adjustment for other covariates is needed, other methods to evaluate survival percentiles are required. Laplace regression was introduced as a method for estimating the conditional percentiles of a potentially censored outcome, and can be used in time-to-event analysis to evaluate adjusted survival percentiles.[10,11] Differently from other survival analysis techniques, Laplace regression directly models the percentiles of the time variable as a linear combination of the predictors. Coefficients estimates can be interpreted as differences in time (i.e., years, months, days) by which different subpopulations reach the same fraction of events. As any regression method, Laplace can model the outcome (i.e., survival time) as a function of multiple covariates, possibly including continuous exposures with flexible transformations. Situations of heteroskedasticity can be accommodated by letting the scale parameter depend on one or more covariates. Multiple percentiles can be estimated simultaneously, testing coefficients within and between survival percentiles. The simultaneous estimation and plotting of different percentiles might require some smoothing, depending on the variability across percentiles, and algorithms such as the *lowess* can be applied.

Laplace regression assumes the errors follow an asymmetric Laplace distribution. Nevertheless, this parametric assumption, shared by other methods in quantile regression,[13–16] has been shown not to influence the performances of the model under different data distributions.[11,12,17] Simulations studies from previous articles have documented good performances of the model in terms of computational speed, precision, robustness of standard errors, and coverage of confidence intervals that was close to the nominal value.[11,18] Performance of the model was further improved after the introduction of a gradient search maximization algorithm, currently implemented for the estimation of the model.[18] A flexible user-friendly program for the estimation of Laplace regression, which makes use of this algorithm, is available in Stata.[12]

Recent developments have increased the potential of Laplace regression in the epidemiologic context, presenting how to use the method to derive and draw adjusted survival curves,[19] and to estimate percentile of attained age at the event of interest.[17] This latter study presented the meaning and

estimation of survival percentiles with different time scales, exploring the statistical properties of Laplace in estimating percentiles of attained age, and discussing the advantages that this application may accrue in time-to-event analysis.[17]

EVALUATING ADDITIVE INTERACTION WITH LAPLACE REGRESSION

To evaluate the impact of the two binary exposures G and E and their interaction on the pth survival percentile of the time variable T, we can fit the following model

$$T(p \mid G, E) = \beta_0(p) + \beta_1(p) \cdot G + \beta_2(p) \cdot E + \beta_3(p) \cdot G \cdot E \quad (2)$$

The time variable T is defined as time between entry into the study and experiencing the event D. An implicit assumption to allow interpretability of Equation (2) is that parameters are constrained to keep the right-hand side of the equation positive. This should hold for all the observed, and possibly for all the potentially observable, combinations of covariate patterns. To improve interpretability, we prefer to code G and E so that their effects are in the same direction, that is, $\beta_1(p)$ and $\beta_2(p)$ have the same sign. From Equation (2), it is possible to estimate the pth survival percentiles for the four combinations of the two exposures, corresponding to the time points displayed in Figure 1.

$$t_{00} = T_i(p \mid G = 0, E = 0) = \beta_0(p) + \beta_1(p) \cdot 0 + \beta_2(p) \cdot 0 + \beta_3(p) \cdot 0 = \beta_0(p)$$

$$t_{10} = T_i(p \mid G = 1, E = 0) = \beta_0(p) + \beta_1(p) \cdot 1 + \beta_2(p) \cdot 0 + \beta_3(p) \cdot 0 = \beta_0(p) + \beta_1(p)$$

$$t_{01} = T_i(p \mid G = 0, E = 1) = \beta_0(p) + \beta_1(p) \cdot 0 + \beta_2(p) \cdot 1 + \beta_3(p) \cdot 0 = \beta_0(p) + \beta_2(p)$$

$$t_{11} = T_i(p \mid G = 1, E = 1) = \beta_0(p) + \beta_1(p) \cdot 1 + \beta_2(p) \cdot 1 + \beta_3(p) \cdot 1 = \beta_0(p) + \beta_1(p) + \beta_2(p) + \beta_3(p)$$

It simply follows that the measure of additive interaction (1) is estimated by the parameter $\beta_3(p)$. If $\beta_3(p) > 0$, we are in the presence of superadditive interaction between G and E. If $\beta_3(p) < 0$, the interaction is subadditive. The statistical test associated with the parameter $\beta_3(p)$ can hence be viewed as a test for additive interaction. Model (2) can be extended to include additional covariates. In this situation, the interpretation of the product term coefficient as a measure of additive interaction is still valid when conditioning on the additional covariates.

The fact that in a percentile approach the incidence proportion p is fixed at a specific value, as displayed in Figure 1, implies that the measure of additive interaction depends on p. This allows the study of interaction between two risk factors according to the fraction of events considered.

EMPIRICAL EXAMPLE

We evaluated the interaction between smoking status (0 = current smoker; 1 = never smoker) and educational level (0 = primary education; 1 = high school/university education) in predicting overall mortality. We used data from the Cohort of Swedish Men and the Swedish Mammography Cohort, two large cohorts of ~80,000 men and women from central Sweden, aged 45–83 at baseline, established in 1997 and largely described elsewhere.[20] After exclusions we considered in these analyses 71,238 participants who were followed up for 16 years between January 1, 1998, and December 31, 2013. During this period, an overall 23% of the study participants died (n = 16,346). Because of the different fractions of cases across strata of the exposures, we focused our main analysis on the 10th survival percentile, the time by which the first 10% of subjects have died.

First, we evaluated the following Laplace regression model on the 10th percentile, with the two binary exposures and their interaction:

$$T(p = 10) = \beta_0 + \beta_1 \cdot \text{smoking} + \beta_2 \cdot \text{education} + \beta_3 \cdot \text{smoking} \cdot \text{education} \quad (3)$$

Predicted values of the 10th survival percentile for each of the four subpopulations, calculated by combining the obtained coefficients estimates, are presented in the Table. The product term β_3, which estimates the additive interaction presented in Equation (1), has a simple and intuitive interpretation, as it represents the excess in survival when both predictors are equal to 1. In our example, the presence of both predictors (nonsmokers and highly educated) was associated with 2.1 additional years of survival (β_3 = 2.1 years, 95% CI: 1.2, 2.9). This excess is larger than 0, suggesting the presence of super additive interaction in predicting mortality between being nonsmoker and highly educated.

We next adjusted for age at baseline as a 5-year categorical variable to evaluate the age-adjusted additive interaction between smoking and education in predicting overall mortality. This adjustment, which can be done simply by including the additional covariate in model (3), strongly changed the estimate of the product-term coefficient to −0.8 years (95% CI: −1.4, −0.1). This suggests that the crude interaction was probably explained by the different distribution of age across strata of the two exposures. In particular, the median age at

TABLE. Tenth Survival Percentiles, in Years, by Levels of Smoking and Education

	Current Smokers	Never Smokers
Low education	t_{00} = 7.5 years (95% CI: 7.2, 7.7)	t_{10} = 9.2 years (95% CI: 9.0, 9.4)
High education	t_{01} = 11.2 years (95% CI: 10.6, 12.0)	t_{11} = 15.0 years (95% CI: 14.3, 15.5)

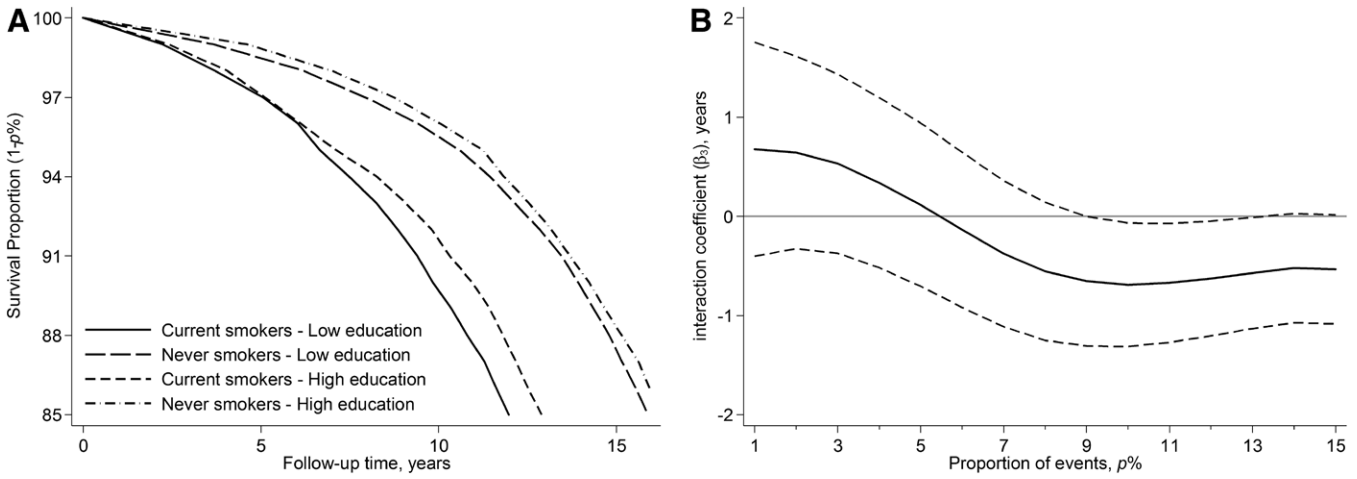

FIGURE 2. A, Age-adjusted survival curves by levels of smoking (current, never) and education (high, low). Curves are calculated from age-adjusted Laplace regression models, with fraction of events between 1 and 15. An interaction term between smoking and education is included in the models. B, The estimates of the interaction term, with confidence interval, smoothed by applying the *lowess* algorithm with a bandwidth of 0.6.

baseline ranged from 53 years for current smokers with high education to 66 years for never smokers with low education.

The evaluation of additive interaction can be extended to other fractions of events rather than the first 10%. For example, we fitted age-adjusted Laplace regression models to evaluate the interaction between smoking and education for percentiles 1 to 15. This was done by evaluating model (3), further adjusted for age at baseline, varying p from 1 to 15. Figure 2A presents the survival curves for the four combinations of smoking and education, further adjusted for age at baseline. The estimated coefficients of the interaction term from these models, with confidence interval, are reported in Figure 2B. When looking at the first percentiles, which represent the early cases, the interaction is positive, later decreasing to a subadditivity.

DISCUSSION

In this study, we introduced the topic of interaction in the context of survival percentiles. In a percentile approach to time-to-event outcomes, a specific fraction of events is fixed while the time point is estimated. Interaction can therefore be evaluated in the unit of measurement of time. A measure of additive interaction can be estimated using Laplace regression to model conditional survival percentiles, including a product term between two exposures of interest in the model. The regression coefficient of the product term represents the excess/decrease in survival due to the presence of both the exposures of interest.

Evaluating the possible interaction between two exposures is a common component of epidemiologic studies.[21] A detailed tutorial, summarizing the wide discussion on the topic, has recently been published.[7] It is important to separate the concepts of biological and statistical interaction.[3,22–25] Statistical interaction, which is the focus of this article, arises from a statistical model and should not be used to draw biologic conclusions.[1,24,26,27] Statistical interaction is usually assessed by including in the model a product-term between the two exposures of interest.[2] This implies that the evaluation and interpretation of interaction depend on the scale of the model chosen, which can be either additive or multiplicative.[1]

In the context of time-to-event analysis, the multiplicative nature of the Cox proportional-hazard model implies that interaction analysis is commonly limited to the multiplicative scale.[6] Various studies have underlined the important public health meaning of additive interaction, which can be used to assess which subgroups of individuals are to be treated.[1,6,7,28,29] Presenting both additive and multiplicative measures of interaction has been widely recommended,[7,30–32] but this practice is still very uncommon.[5] Moreover, the absence of interaction on one scale implies the presence of interaction on the other scale.[3,6] In survival analysis, measures of additive interaction such as the relative risk due to interaction, the synergy index, or the attributable proportion due to interaction can be calculated after fitting a Cox model.[8,9] Among these, the relative risk due to interaction is the most frequently utilized approach, even if it can only be used to assess the direction of the additive interaction without any indication on the magnitude.[33] As an alternative approach, the use of the additive hazard regression has been proposed.[4] To the best of our knowledge, however, this method is seldom used in epidemiologic research. When dealing with time-to-event outcomes, the risk of the event of interest often varies across follow-up. All the available measures of interaction, whether additive or multiplicative, are calculated on the risk scale, and commonly assume a time-fixed effect.

Evaluating percentiles of survival represents a possible alternative for the analysis of time-to-event outcomes.[10] Common approaches fix the follow-up time to a specific value and evaluate the risk of the event within that time interval. By

focusing on survival percentiles, on the other hand, a specific survival probability is fixed and the time by which that proportion is achieved is estimated. This change of perspective clarifies the connection between incidence proportion and time, and allows evaluating how the joint effect of two exposures is changing over time.

In this article, we have chosen to use Laplace regression to model survival percentiles because of its stability and computational speed. Other approaches are available and worth mentioning. An option often used in epidemiologic studies is to derive the adjusted survival curves after estimating a Cox model, and calculating the quantiles. This method, however, is computationally demanding and unclear with respect to standard error derivation.[34] Assumptions such as proportionality of hazards strongly influence the shape of the derived survival curve. Other methods to evaluate quantiles of censored outcomes have been proposed and are available in R and SAS.[35–37] These methods make different assumptions and are valid semi-parametric alternatives to Laplace regression.[11]

In this article, we showed how a measure of additive interaction expressed in the metric of time can be derived by evaluating survival percentiles. An advantage of the presented approach is that the additive interaction depends on the specified fraction of events. Within a follow-up time, it is therefore possible to investigate how the interaction between two exposures changes according to the fraction of cases, or equivalently by time. Currently available methods typically provide a single product-term coefficient, implicitly assuming that main effects and their interaction are constant over the entire follow-up time. We limited our presentation to the simplest scenario of two binary covariates. Extension to interaction analysis between categorical or continuous exposures is straightforward.

In conclusion, we introduced the concept of interaction analysis in the metric of time, which can be investigated by switching the focus from survival probabilities to survival percentiles. When Laplace regression is used to model survival percentiles, a measure of additive interaction can be easily estimated without assuming a constant effect over time.

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