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An Integrated Model for Overall and Conditional Survival Analysis in Epidemiologic Studies

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Abstract

Survival analysis is a well-known statistical technique which evaluates the elapsed time from "Time 0" to an outcome of interest. Time 0 might be the date of diagnosis or when an intervention is begun, while the outcome might be death, relapse or cure. Although this informs overall survival (OS), there is also interest in conditional survival (CS). That is, conditional on surviving to an intermediate milestone of specific interest, what is the survival experience thereafter? A common CS analytic approach is to apply standard survival techniques restricted to individuals event-free and uncensored at the milestone. However, the characteristics of subjects at risk at the milestone may be different than those at Time 0 leaving the inferences vulnerable to confounding. Moreover, survival to the milestone is a stochastic quantity and this needs to be reflected in the inferences.

In this paper, we present an integrated statistical model for performing OS and CS survival analysis. We indicate how to formulate the model, derive the OS and CS probabilities together with their confidence limits, and perform tests of significance.

It is shown that the estimators enjoy optimal asymptotic properties, and hypotheses can be readily tested using Wald χ^2 procedures. Point estimates are similar to those from a proportional hazards model. The standard errors, however, are larger correctly reflecting the variability associated with surviving to the milestone. The advantage of this approach is that all OS and CS inferences are performed in a single integrated model leading to a coherent inferential strategy.

Keywords: Asymptotic properties; Conditional survival probabilities; Maximum likelihood estimation; Piecewise exponential model; Survival analysis; Wald χ^2 test

Abbreviations: AFT: Accelerated Failure Time; CS: Conditional Survival; KM: Kaplan-Meier; OS: Overall Survival; PE: Piecewise Exponential; PH: Proportional Hazards; SE: Standard Error

Introduction

Survival analysis is a well-known statistical methodology in biomedical research. An origin or "Time 0" is identified and the elapsed time to an event of specific interest is derived. Individuals who do not experience the event are censored by the end of their respective follow-up.

Let T signify the elapsed time. Let $F(t)=Pr(T\leq t)$, and $S(t)=1-F(t)$ be the survival function. A variety of statistical methods [1] are available including the Kaplan-Meier (KM) method to estimate S(t) and the log-rank test to compare it across prognostic factors or interventions. Regression techniques, including the proportional hazards (PH) model as well as the accelerated failure time (AFT) models, can be applied to adjust for covariates. These methods evaluate the overall survival (OS) from Time 0. This is important from a public health perspective in that it informs long-term clinical prognosis.

Clinical investigators are also interested in conditional survival (CS) [2-4]. That is, for any $t_k>t_j$, $S(t_k>t_j)=Pr(T>t_k/T>t_j)$, where t_j is a meaningful intermediate milestone. For example, if there is a high probability of rejection in the first year following transplantation, the overall 5-year prognosis may be poor. However, if a subject remains rejection-free by the first-year milestone, the conditional probability of remaining rejection-free until the fifth year might be good. This provides insight into how prognosis evolves over time, and may be helpful for counseling patients [5,6]. CS is widely applied in oncology [2-11], cardiology [12,13], transplantation [14,15], and other medical conditions [16-19].

Following the laws of probability,

$$S(t_k>t_j)=S(t_k)/S(t_j) \quad (1)$$

KM estimates or those from the PH and AFT models can be substituted into this expression to generate point estimates. It is unclear, however, how to derive the corresponding standard errors (SEs) and perform statistical inference. A common CS approach [3] is to ignore $S(t_j)$ and apply OS techniques restricted to the subset of individuals who remained event-free and uncensored at t_j. The SEs are then derived [20] using Greenwood's formula. However, there are problems with this approach. The characteristics of subjects at risk at the milestone may be different than those at Time 0. If age is prognostic, for example, then the CS analysis will be based on a different age population. Even if age is included as a covariate in their respective PH models, other unknown factors may be selecting the CS analysis population leaving the inferences vulnerable to confounding. This will lead to a fragmented inferential strategy especially if it is repeated at a number of different milestones. Analytically, it fails to account for $S(t_j)$ in the denominator of eqn. (1). $S(t_j)$ is a stochastic quantity with an associated sampling distribution, and this needs to be reflected properly in the estimates. As a consequence, the derived confidence intervals will be incorrect.

In this paper, we apply the piecewise exponential (PE) survival

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model. Like the PH model, It avoids making arbitrary assumptions on the shape of the hazard function and provides for covariates. The advantage is that it provides a single integrated platform for performing inference on both OS and CS probabilities. We describe how to formulate the model for this analysis. We demonstrate how to manipulate the resulting parameter estimates and associated covariance structure to derive the OS and CS probabilities taking $S(t_j)$ into account. Then, we discuss how to perform statistical inference on these quantities for drawing substantive conclusions. We conclude with an example from the oncology literature evaluating the survival of patients treated for colon cancer.

Statistical Methodology

Piecewise exponential model

Let f(t)=-d[S(t)/dt be the density function. The instantaneous hazard is $\lambda(t)=f(t)/S(t)$. It can be shown that $d\{\ln S(t)\}/dt=-f(t)/S(t)=-\lambda(t)$. Integrating with respect to t, it follows that,

$$S(t) = \exp\left\{-\int_0^t \lambda(s)ds\right\} = \exp\{-\Lambda(t)\}, \quad (2)$$

Where $\Lambda(t)$ is the cumulative hazard over (0,t) For the exponential distribution, $S(t)=e^{-\lambda t}$, with density $f(t)=\lambda e^{-\lambda t}$ and hazard, $\lambda(t)=\lambda e^{-\lambda t}/e^{-\lambda t}=\lambda$. It therefore prescribes a constant instantaneous hazard function, and the cumulative hazard over an interval of size Δ is $\lambda\Delta$.

The PE model partitions time into J disjoint intervals, indexed by j, with constant hazard λ_j, within any interval but different hazards across the intervals. The partition is generally suggested by the study design or the wider clinical context. In a cohort study, it might refer to yearly (or monthly) intervals of clinical interest; in a randomized clinical trial (RCT), it would generally coincide with the schedule of evaluations. If the intervals are too wide, they may not capture adequately how the hazard is changing over time. If they are too narrow, there may not be enough events in any interval leading to problems in estimating the parameters. Sensitivity analyses are frequently performed to assess robustness of the inferences to the choice of the partition, and we return to this point in the example.

Let $0=\tau_0<\tau_1<\tau_2<\ldots<\tau_J<\infty$ represent the cutpoints where τ_J is the maximum amount of follow-up time observed. If $\Delta k=\tau_k-\tau_{k-1}$ then the cumulative hazard up to the end of the j-th interval (j=1, …, J) is,

$$\ddot{E}_j = \sum_{k=1}^{j} \lambda_k \Delta_k \quad (3)$$

and eqn. (2) becomes $S_j = S(t_j) = \exp\left\{-\sum_{k=1}^{j} \lambda_k \Delta_k\right\}$.

Regression model

Without loss of generality, assume that there are two groups under consideration, indexed by a, and there is interest in comparing them. Let T_{ai} represent the survival time for the i-th subject in the a-th group, and x_{ai} be a set of covariates of interest. Then, the PE regression model is written as,

$$\ln(T_{ai}) = \mu_j + \alpha_a + (\mathbf{x}'_{ai} - \mathbf{x}'_{ref})\boldsymbol{\beta},$$

plus an error term, where x_{ref} are reference values for the covariates, generally the overall means. Under the exponential distribution, the hazard is the reciprocal of the expected event time, so an equivalent representation is,

$$\ln[\lambda_{ai}(t)] = -\mu_j - \alpha_a - (\mathbf{x}'_{ai} - \mathbf{x}'_{ref})\boldsymbol{\beta}.$$

The $\{\mu_j\}$ provide flexibility in characterizing the ln hazard over the intervals. α_a is the group effect, and this model prescribes a constant group difference on the ln hazard scale, i.e., proportional hazards, over time. However, to provide greater flexibility to characterize and compare the different groups, the model is generalized to,

$$\ln(T_{ai}) = -\ln[\lambda_{ai}(t)] = \mu_{aj} + (\mathbf{x}'_{ai} - \mathbf{x}'_{ref})\boldsymbol{\beta}. \quad (4)$$

Conceptually, this is equivalent to a group × time interaction model. Because the covariates are centered at their reference values, the $\{\mu_{aj}\}$ are "adjusted" for the covariates and they can effectively be ignored in the derivation below.

Model estimation

For computer applications, the model is fit by creating a dataset with one observation for each interval during which the individual is at risk of the event [21]. The last interval is the one in which s/he either has the event or is censored by the end of his/her follow-up. The time variable is the elapsed time from the beginning of the interval until the event or censoring occurs; the censoring indicator is defined accordingly. Baseline covariates are repeated across the multiple observations per subject; time-dependent covariates (if any) are set their values at the beginning of each interval.

Standard maximum likelihood estimation procedures are applied to perform inference. Starting with initial estimates of the parameters, a Newton-Raphson or Fisher scoring algorithm is applied to iterate to a solution [22]. Upon convergence, the ensuing $\hat{\mu}' = [\hat{\mu}'_1 \quad \hat{\mu}'_2]$, where $\hat{\mu}'_a = [\hat{\mu}_{a1} \quad \ldots \quad \hat{\mu}_{aJ}]$, is asymptotically normal and unbiased. Its asymptotic covariance matrix is consistently estimated by the inverse of the Fisher information matrix and is denoted by $\Sigma_{\hat{\mu}}$.

Four Steps to Generate the ln OS Probabilities

Let $\hat{S}' = [\hat{S}'_1 \quad \hat{S}'_2]$, where $\hat{S}'_a = [\hat{S}_a(\tau_1) \quad \ldots \quad \hat{S}_a(\tau_J)]$ and define $\hat{\boldsymbol{\lambda}}$ and $\hat{\Lambda}$ analogously. First from eqn. (4), $\widehat{\ln(\lambda)} = -\hat{\mu}$ with covariance matrix, $\Sigma_{\widehat{\ln(\lambda)}} = \Sigma_{\hat{\mu}}$. Next, $\widehat{\ln(\lambda)}$ is exponentiated to derive $\hat{\lambda}$. Applying the delta method [23], $\Sigma_{\hat{\lambda}} = BD\Sigma_{\widehat{\ln(\lambda)}}D'$, where D is a matrix of first-order partial derivatives. In this case, it is a diagonal matrix consisting of the elements of $\hat{\lambda}$. Next, from eqn. (3), $\hat{\Lambda}_{aj} = \sum_{k=1}^{j} \hat{\lambda}_{ak}\Delta_k$. Define the lower triangular matrix,

$$\mathbf{A} = \begin{bmatrix} \Delta_1 & & & \\ \Delta_1 & \Delta_2 & & \\ \vdots & \vdots & & \\ \Delta_1 & \Delta_2 & \ldots & \Delta_J \end{bmatrix}. \quad (5)$$

Then, $\hat{\ddot{E}} = (I_2 \ddot{\otimes} A)\hat{\lambda}$ where $\otimes$ signifies the Kronecker product. The corresponding covariance structure is $\Sigma_{\hat{\Lambda}} = (I_2 \ddot{\otimes} A)\Sigma_{\hat{\lambda}}(I_2 \ddot{\otimes} A)'$, i.e., a block diagonal structure with $A\Sigma_{\hat{\lambda}_a}A'$ on the diagonal blocks. Finally, from eqn. (2), $\widehat{\ln(S)} = -\hat{\Lambda}$ and $\Sigma_{\widehat{\ln(S)}} = \Sigma_{\hat{\ddot{E}}}$. Note that A ensures that a covariance structure is reflected among the elements of $\widehat{\ln(S)}$.

At this point, we could exponentiate again to derive the OS probabilities directly. However, as we show below, remaining on the ln scale allows for a direct derivation of the CS probabilities. Moreover, note that we are not restricted to the specific $\{\tau_j\}$ defining the cutpoints. Let $0<t<\Delta_j$ represent a duration of interest from τ_{j-1}. Then, from eqn.

(3), $\hat{\Lambda}_{aj}(t) = \sum_{k=1}^{j-1} \hat{\lambda}_{ak}\Delta_k + \hat{\lambda}_{aj}t$, and this could be used to estimate the OS curve in fine steps between the cutpoints.

Finally, all the transformations in the steps above are one-to-one, continuous, twice-differentiable functions of their arguments. Three of the four are linear transformations preserving their asymptotic properties. Further, Agresti [23] demonstrated that the application of the delta method in the second step results in an estimator that is asymptotically normal and unbiased; the estimator of its covariance structure is consistent. As a consequence, $\widehat{\ln(S)}$ is asymptotically normal and unbiased with covariance structure consistently estimated by $\Sigma_{\widehat{\ln(S)}}$.

Inferences on the OS and CS Probabilities

Confidence intervals for the OS probabilities

Starting with the $\widehat{\ln(S)}$ and $\boldsymbol{\Sigma}_{\widehat{\ln(S)}}$ derived on the last step, the SEs are the square roots of the diagonal elements of $\Sigma_{\widehat{\ln(S)}}$. Using the appropriate percentile of the standard normal distribution, asymptotic confidence intervals are created on the ln scale in the usual manner, and then exponentiated to derive their counterparts on the S(t) scale.

Wald tests for hypotheses on the OS probabilities

Let C represent a (c×2J) full-rank set of linear contrasts among the elements of ln (S), and consider an hypothesis of the form, H_o:C ln(S)=0, versus H_A:C ln(S)≠0. In light of the asymptotic properties of $\widehat{\ln(S)}$, the quadratic form,

$$Q = \left(\mathbf{C}\widehat{\ln(\mathbf{S})} - 0\right)' \left\{\mathbf{C}\boldsymbol{\Sigma}_{\widehat{\ln(\mathbf{S})}}\mathbf{C}'\right\}^{-1} \left(\mathbf{C}\widehat{\ln(\mathbf{S})} - 0\right), \quad (6)$$

is asymptotically distributed as a $\div^2_{(c)}$ distribution, and Q can be referred to the percentiles of this distribution.

An important consideration is testing for differences at specific cut points. Consider $H_0: S_1(\tau_j) = S_2(\tau_j)$, or equivalently, $H_0: \ln S_1(\tau_j) = \ln S_2(\tau_j)$. Then, eqn. (6) can be applied using $C = [c' \quad -c']$, where $\mathbf{c}'$ is a (1×J) vector of 0s with +1 in the j-th position. This is quite general, and can be applied for any set of one (or more) cutpoints of specific interest. The overall difference in the survival probabilities is evaluated by taking, $C = [I_J \quad -I_J]$, where I_J is the (J×J) identity matrix, and Q will have J degrees of freedom. This is different than the 1 degree of freedom test in the PH model. The PE model (4) is equivalent to a group × time interaction model, whereas the PH model is equivalent to a main effects model under a proportional hazards assumption.

Inference on the CS Probabilities

CS probabilities are defined as ratios; however, they correspond to differences on the ln scale, i.e., from eqn. (1), ln S(τk/τj)=lnS(τk)-lnS(τj). To derive the CS probabilities at $\tau'_{j+1} = [\tau_{j+1} \quad \tau_{j+2} \quad \dots \quad \tau_J]$, conditional on surviving until τ_j, define the(J-j)×J linear transformation matrix,

$$L = \begin{bmatrix} 0 & -1 & 1 & & \\ 0 & -1 & & 1 & \\ M & M & & & O \\ 0 & -1 & & & 1 \end{bmatrix}. \quad (7)$$

The first columns of 0s correspond to $\{\tau_1,\dots\tau_{j-1}\}$, the -1 column corresponds to τj, while the last columns corresponds to$\{\tau_{j+1},\dots\tau_J\}$. The estimator of ln $S(\tau_{j+1}/\tau_j)$ in the two groups is $(I_2 \ddot{A} L)\widehat{\ln(S)}$; its covariance structure is the block diagonal structure, $(I_2 \ddot{A} L)\Sigma_{\widehat{\ln(S)}}(I_2 \ddot{A} L)'$. Because this is a linear transformation of the lnOS probabilities, the ln CS probabilities inherit the favorable large-sample properties.

As with the OS probabilities above, the SEs are derived as the square roots of the diagonal elements of the covariance structure; asymptotic confidence intervals on the ln scale are formed in the usual manner and exponentiated to derive their counterparts on the CS scale. Wald tests similar to those described above can be applied to derived CS probabilities to compare them overall or at one or more time points.

An Example

Background

Moertel et al. [24,25] reported the results of an RCT evaluating adjuvant therapy following resection for colon cancer. From 1984 to 1987, patients with stage III colon cancer who had fully recovered from surgery were assigned to one of three groups including levamisole only, combination therapy with levamisole and fluorouracil, or an observational control group. In the active interventions, treatment was administered over a period of 1 year, and this will be taken as the milestone in our CS analysis. The full details of the eligibility criteria, interventions and study procedures are provided in the original publications.

The dataset was downloaded from the GitHub public data-sharing website [26]. The analysis population consisted of 304, 310 and 315 patients assigned to the combination, levamisole and observational groups, respectively. Follow-up ranged to slightly beyond 9 years with a median of 5.4 years. Figure 1 presents the survival curves estimated by the KM method. OS probabilities at 5 years were 63%, 54% and 53% in the combination, levamisole, and observational groups, respectively. A log-rank test indicated that while there was an overall treatment difference, there was no significant difference between levamisole and the observational group (p=0.79). Because of this, and for ease of presentation, they were pooled together in our analysis.

Cutpoints

The number of cutpoints must strike a balance between fully characterizing the survival curves and estimating all the resulting $\{\mu_{aj}\}$ reliably. Figure 2 presents a histogram of the number of deaths

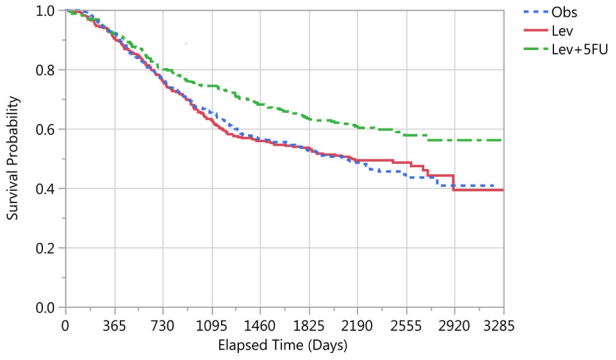

Figure 1: OS survival curves, by treatment assignment, from a Kaplan-Meier analysis.

occurring in 12-month intervals. Among the 452 deaths, 30 occurred during the 6th year but there were only 18 thereafter. One interval was therefore formed starting at month 72 and extending through the end of follow-up. There were considerable numbers of deaths during the first two years of follow-up. Given that our milestone was at 12 months, it seemed prudent to use two 6-month intervals to characterize OS up to the milestone and two 6-month intervals for CS thereafter. In the middle, 12- and 24-month intervals seemed adequate, and we adopted cutpoints at 36 and 48 months. Thus, 7 cutpoints were used including 6, 12, 18, 24, 36, 48, and 72 with the final interval extending to the end of follow-up.

Inference on the OS probabilities

Although the published analysis did not adjust for covariates, we adjusted for age and sex. Age ranged from 18 to 85 years with a mean of 60 years; 52% were male. Age was centered at its mean while sex was coded as a (-1, +1) variable. The data were analyzed using SAS (Cary, NC).

Table 1 reports the adjusted OS probabilities at the different cutpoints together with their asymptotic SEs. The SEs became progressively larger at the later cutpoints due to the diminishing numbers of subjects at risk. They were also consistently smaller in the pooled group due to the larger sample size. The estimated OS probabilities (SEs) in the pooled group included 0.76 (0.02) and 0.64 (0.02) at years 2 and 3 respectively, compared to 0.80 (0.02) and 0.74 (0.03) under combination therapy. Wald χ^2 tests indicated no significant difference at year 2 (p=0.13) but there was a significant difference at year 3 (p=0.001). A test for the overall difference was significant at p=0.008.

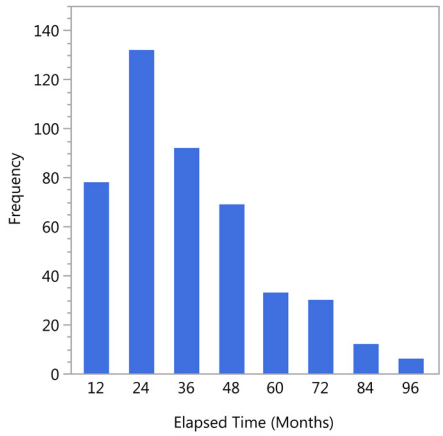

Figure 2: Frequency histogram of the number of deaths by follow-up year.

Table 1 also reports the results from a standard PH analysis. The estimates of the OS probabilities and their SEs from the two models were generally within ±0.01 of each other. The largest discrepancies occurred in the combination arm during the initial two years, e.g., +0.016 at year 1 and +0.017 at year 2, and we return to this point below.

Inference on the CS probabilities

The milestone was the end of the 12-month treatment, and the CS analysis evaluates survival among patients who successfully completed treatment. The linear transformation eqn. (7) was applied using $L=[0_{6\times1}\text{-}1_{6\times1}I_{6\times6}$. Table 2 reports the resulting CS probabilities with their asymptotic SEs. In the pooled group, CS probabilities (SEs) were 0.83 (0.02) and 0.70 (0.02) at years 2 and 3, respectively, compared to 0.87 (0.02) and 0.81 (0.02) in the combination group. There was no significant difference at year 2 (p=0.08), but the difference at year 3 (p=0.0003) reached significance. Table 2 also reports the results from the conventional approach of applying a PH model restricted to those remaining event-free and uncensored at 1 year. There was good agreement in the probability estimates between the two models generally falling within ±0.01 of each other. Importantly, the SEs were all larger under the PE model, e.g., 0.020 vs. 0.014 in the combination group at year 2. This reflects that the PE model is taking into account the additional variability associated with $S(t_j)$ in the denominator.

Sensitivity analysis

The largest discrepancies in the OS probabilities occurred at the beginning of follow-up, suggesting that additional cutpoints may be necessary. In a sensitivity analysis, we adopted 3-month cutpoints during the first 24 months, plus an additional cutpoint at month 30. This resulted in 12 cutpoints including 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48, and 72 months, with the final interval extending through the end of follow-up. The results are reported in an on-line supplement. The additional cutpoints did not improve the estimates nor the SEs of the OS and CS probabilities at the original set of cutpoints. This suggests that the number of cutpoints is not really the critical issue. Rather, identifying cutpoints that capture the dynamics of the changing survival curve is the key consideration (Supplementary file).

Discussion

The piecewise exponential is a general survival model sharing many of the desirable properties of the standard PH model. In particular, it also avoids making arbitrary assumptions on the shape of the hazard function. Instead, it approximates the hazard by partitioning time into disjoint intervals and applying a different exponential hazard in each one. The advantage is that it is straightforward to manipulate the parameter estimates to derive point estimates and associated covariance structure of both the OS and CS probabilities. These estimators enjoy

Year	Piecewise Exponential Model		Proportional Hazards Model	
	Pooled Levamisole/Observation	Combination Levamisole+5-FU	Pooled Levamisole/Observation	Combination Levamisole+5-FU
0.5	0.976 (0.006)	0.970 (0.010)	0.971 (0.006)	0.980 (0.004)
1.0	0.915 (0.011)	0.918 (0.016)	0.907 (0.010)	0.934 (0.009)
1.5	0.841 (0.015)	0.872 (0.019)	0.836 (0.013)	0.883 (0.013)
2	0.760 (0.017)	0.803 (0.023)	0.752 (0.016)	0.820 (0.017)
3	0.641 (0.019)	0.743 (0.025)	0.645 (0.018)	0.737 (0.022)
4	0.560 (0.020)	0.681 (0.027)	0.566 (0.019)	0.672 (0.025)
6	0.489 (0.020)	0.606 (0.028)	0.489 (0.020)	0.607 (0.028)
9	0.401 (0.028)	0.540 (0.038)	0.413 (0.029)	0.540 (0.035)
Abbreviations: SEs: Standard Errors; PE: Piecewise Exponential; PH: Proportional Hazards; 5-FU: Fluorouracil.				

Table 1: OS probabilities (SEs), adjusted for age and sex, by intervention group at the different cutpoints from the PE and PH models.

Year	Piecewise Exponential Model		Proportional Hazards Model	
	Pooled Levamisole/Observation	Combination Levamisole+5-FU	Pooled Levamisole/Observation	Combination Levamisole+5-FU
0.5	0.919 (0.011)	0.950 (0.013)	0.921 (0.010)	0.948 (0.008)
1.0	0.830 (0.016)	0.874 (0.020)	0.827 (0.014)	0.883 (0.014)
1.5	0.700 (0.019)	0.810 (0.024)	0.708 (0.018)	0.798 (0.020)
2	0.612 (0.020)	0.742 (0.026)	0.619 (0.020)	0.731 (0.024)
3	0.534 (0.021)	0.661 (0.029)	0.534 (0.021)	0.664 (0.028)
4	0.438 (0.030)	0.588 (0.040)	0.450 (0.031)	0.594 (0.036)
6	0.489 (0.020)	0.606 (0.028)	0.489 (0.020)	0.607 (0.028)
9	0.401 (0.028)	0.540 (0.038)	0.413 (0.029)	0.540 (0.035)
Abbreviations: SEs: Standard Errors; PE: Piecewise Exponential; PH: Proportional Hazards; 5-FU: Fluorouracil.				

Table 2: CS probabilities (SEs), adjusted for age and sex, by intervention group at the different cutpoints from the PE and PH models.

optimal asymptotic properties, and hypotheses can be readily tested using Wald χ^2 procedures.

A well-known limitation of the PE model is that care must be taken in identifying the cutpoints in the analysis. Intuitively, there should be a greater number of cutpoints when the survival curve is changing dynamically. This was evident in the first several years of follow-up in our example. Moreover, because of the importance of the milestone, additional cutpoints were applied on either side. It is always important to perform sensitivity analyses; however, our analysis showed that the results are reasonably robust to the choice of the partition.

A major advantage of this approach is that all OS and CS inferences are performed in a single analytic model. The ln OS probabilities are derived using the entire analysis population. The ln CS probabilities are derived as linear combinations thereof, and implicitly therefore they are also based on the entire analysis population. This leads to a coherent set of OS and CS inferences from an integrated model. This contrasts with the common practice of performing separate analyses from Time 0 and the different milestones. The interpretation of the results may be compromised by confounding in the composition of the analysis populations, and simple covariate adjustment provides no guarantee that they can be made equivalent. This leads to a fragmented and uninterpretable inferential strategy.

Finally, in our clinical trial example, the end of the treatment phase was a natural milestone. More generally, investigators frequently distinguish between short-term and long-term clinical effects. The OPERA studies in multiple sclerosis [27], for example, evaluated efficacy over two "epochs" of clinical relevance including weeks 0-24 and 24-96. To be informative, however, inference should be partitioned into two mutually complementary components, i.e., the marginal distribution over the proximal phase and the conditional distribution over the distal one. In our context, these inferential goals can easily be accommodated in a single analytic model. The OS probabilities can be derived over the entire 96 weeks. A Wald χ^2 test can be applied for a difference during the early epoch, while a separate one can be applied to the CS probabilities in the later one.

Conflict of Interest

None declared.

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