Research paper

Estimation of the censoring distribution in clinical trials

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Abstract

Clinical studies with time to event endpoints typically report the median follow-up (i.e., censoring) time for the subjects in the trial, alongside the median time to event. The reason for this is to provide information about the opportunity for subjects in the study to experience the event of interest (Betensky, 2015 [1]). The median follow-up time is often calculated from the Kaplan–Meier estimate for time to censoring. In most clinical studies, the censoring time is a composite measure, defined as the minimum of time to drop-out from the study and time to administrative end of study. The time to drop-out component may or may not be observed; it is observed only if drop-out occurs before the event and the end of the study. However, the time to end of study is observed for each subject, as it is the time from entry to the study to the calendar date that is administratively set as the end of the study. It is known even for subjects who have the event prior to the end of the study. This decomposition of the censoring time into a time that is itself potentially censored and a time that is fully observed raises the interesting question of whether estimation of the censoring distribution could be improved through a decoupling of these times. We demonstrate in simulations that consideration of censoring in this way yields reduced variability under some circumstances and should be used in practice. We illustrate these concepts through application to a meningioma study.

1. Introduction

There is broad agreement that information regarding the follow-up time in a clinical study is informative and should be reported alongside the primary results about the event time of interest. Korn [2] and Schenper and Smith [3] noted that length of follow-up is important because the findings of a study should be restricted to the time frame in which most of the subjects have been observed. These papers noted that some definitions of follow-up time are entangled with the time to event of interest, and they both stated that a good measure of follow-up is one that is independent of the distribution of the time to event of interest. To satisfy this criterion, both papers recommended the definition of follow-up time to be the time to censoring, i.e., the time to drop-out from the study or the time of administrative completion of the study.

In the common setting of random censoring, each subject is assumed to have a latent drop-out time, which is observed only if it occurs before the event time and before the end of the study. Each subject also has a fully observed time to end of the study. This is determined by the administrative end of the study, which is a calendar date that is the same for all subjects. With respect to the event time of interest, the minimum of the drop-out time and the time to end of the study operates as the censoring mechanism. Thus, for estimation of the censoring distribution, all that is required is this composite measure, which for estimation, must be treated as being right-censored by the time to event. This is easily accomplished through use of the Kaplan–Meier estimator, with censoring treated as the event. However, given that the censoring time has a component that is fully observed for all subjects, an alternative, augmented estimator of the censoring distribution is available [2]. As it makes more use of subjects’ data, this estimator has the potential to be more efficient than the estimator that uses the composite time to censoring.

Korn [2] first introduced the augmented estimator and provided an application of it, but did not undertake a simulation study to evaluate its properties. Schenper and Smith [3] compared the estimates

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of the median times to censoring for the two estimators of follow-up in simulations that examined three censoring scenarios. In two of these scenarios, the time to drop-out and the time to end of study had a simple dependence structure. They found the medians to be comparable, and therefore recommended use of the standard Kaplan–Meier estimator of censoring, rather than the augmented estimator. However, Schemper and Smith [3] did not investigate the variability associated with the two estimators in their simulation study. In this note, we sought to investigate the relative efficiency of the two estimators under a wide range of scenarios for the distributions of time to event, time to drop-out and time to end of study.

This paper is organized as follows. In Section 2 we define notation and present the estimators. In Section 3, we report the results of extensive simulation studies. We estimate the censoring distributions and associated confidence intervals for a meningioma study in Section 4. Lastly, we conclude in Section 5.

2. Measures and estimators of follow-up

Let $X$ denote the time to the event, such as death or disease progression, $L$ denote the time to drop-out from the study and $E$ denote the time to end of study. All of the times are measured relative to the time origin of study entry. Let $C = \min(L, E)$ denote the time to censoring, $Y = \min(X, C)$ denote the observed portion of the time to event, and $\delta$ denote the indicator function for $X \leq C$. Under the assumption of independence of $X$ and $C$, the distribution of $X$ can be estimated nonparametrically by applying the Kaplan–Meier estimator to $\{Y, 1 - \delta\}$. The distribution of $C$ can be estimated by applying the Kaplan–Meier estimator to $\{Y, 1 - \delta\}$. We correct an assertion by Schmep and Smith [3] and note that this Kaplan–Meier is a valid estimator of the distribution of $C$ regardless of whether $L$ and $E$ are independent; i.e., regardless of whether time to drop-out is associated with time from study entry to the end of study date, or equivalently, with the time of accrual to the trial. It is only for estimation of the survival distribution of $L$ that independence between $L$ and $E$ is necessary as, in that case, $E$ is part of the censoring variable for $L$. In practice, $L$ and $E$ would not be independent if drop-out from the trial were associated with calendar date, which might occur if the administration of the trial improved markedly over time, which in turn, reduce the drop-out rate from the trial in patients recruited later.

Korn [2] and Schmep and Smith [3] considered an alternative estimator for the distribution of time to censoring that exploits the availability of the time to end of study for every subject regardless of their times to event or drop-out. This estimator is based on the expression of $C$ as the minimum of $L$ and $E$:

$$P(C > \tau) = P(\min(L, E) > \tau) = P(L > \tau, E > \tau) = P(E > \tau)P(\min(L, E) > \tau),$$

which is equal to $P(E > \tau)P(L > \tau) = S_L(\tau)S_E(\tau)$ when $L$ and $E$ are independent. The censoring distribution in (1) can thus be estimated by $\hat{S}_C(\tau)\hat{S}_E(\tau)$, where $\hat{S}_E(\tau) = \hat{P}(E > \tau)$ is the empirical survival function estimator for $E$ and $\hat{S}_L(\tau) = \hat{P}(L > \tau)$ is the Kaplan–Meier estimator for $L$. The empirical survival function for $E$ is estimated using the observed values of $E$ for all subjects; $\hat{S}_E(\tau)$ is the proportion of subjects with $E \geq \tau$. Estimation of $\hat{S}_E(\tau)$ involves applying the Kaplan–Meier estimator to $\{Y, \epsilon\}$, where $\epsilon$ is the indicator function for $L \leq \min(X, E)$.

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### Table 1

| Sample size | Death Hazard Rate | Drop-out Hazard Rates | Measures of Follow-up (Median) |
|-------------|------------------|-----------------------|-------------------------------|
|             |                  | Early Entry | Late Entry | C: KM | 95% CI | CP(%) | C:Augmented | 95% CI | CP(%) | Uncensored | 95% CI |
| 100         | 0.04             | 0.02        | 0.02       | 22.8  | (17.7, 29.5) | 94.0 | 22.7       | (17.9, 28.0) | 94.7 | 22.7       | (18.7, 27.1) |
| 0.04        | 0.02             | 0.02        | 1          | 34.4  | (21.5, 45.2) | 94.2 | 34.5       | (22.8, 40.9) | 93.7 | 34.5       | (24.1, 40.8) |
| 0.04        | 0.04             | 0           | 0          | 22.1  | (17.8, 26.8) | 94.3 | 22.1       | (18.1, 26.1) | 95.0 | 22.0       | (18.8, 25.4) |
| 0.04        | 0.04             | 0           | 0          | 22.5  | (18.8, 27.1) | 95.1 | 22.5       | (19.1, 26.4) | 94.6 | 22.5       | (19.7, 25.7) |
| 0.04        | 0.04             | 0           | 0          | 22.0  | (19.0, 25.5) | 95.6 | 22.0       | (19.2, 25.0) | 95.7 | 22.0       | (19.7, 24.5) |

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![Figure 1](a) Sample size of 100 per simulations ![Figure 1](b) Sample size of 200 per simulation
and is valid as long as \( L \) is independent of \( E \) and \( X \), though \( E \) and \( X \) need not be independent. We note that the standard Kaplan–Meier estimator for \( C \), which we denote by \( \hat{S}_C(t) \), is equivalent to \( \hat{S}_E(t)\hat{S}_L(t) \), where \( \hat{S}_E(t) \) denotes the Kaplan–Meier estimator of \( \{Y, \gamma\} \), with \( \gamma \) being the indicator function for \( E \leq \min(L, X) \). Thus, the alternative estimator augments the standard estimator with observed values of \( E \) for all subjects, including those with \( \min(L, X) \leq E \).

The times \( L \) and \( E \) may be dependent if dropout from the study is not uniform over the calendar time of the study. For example, if an alternative treatment becomes available near the end of an ongoing study, but only to patients who have had minimal exposure to the drug being tested in the current trial, those with smaller \( E \) (i.e., those who entered the study late) would also have smaller \( L \). In the case in which \( L \) and \( E \) are dependent, Korn [2] proposed use of a self-consistency estimator derived by Korwar and Dahiy [4] for estimation of \( P(L > t | E > t) \), which amounts to separate Kaplan–Meier estimation for \( L \) among subjects with \( E > t \), for every \( t \), with adjustment for independent censoring of \( L \) by \( X \). Estimation of \( P(L > t | E > t) = 1 - P(L \leq t | E > t) \) exploits the fact that among the subset of realizations of \((X, L, E)\) such that \( E > t \) and \( L \leq t \) hold, \( L \) can be censored by \( X \) only, and not by \( E \). Since \( L \) is assumed independent of \( X \), assumptions of the Kaplan–Meier estimator are satisfied so that it can be used to estimate \( P(L > t | E > t) \) without bias. More generally, the Kaplan–Meier estimator can estimate \( P(L > k | E > t) \) for all \( k \leq t \) whenever \( X \) is independent of \( L \), regardless of the association between \( L \) and \( E \).

The variance for the Kaplan–Meier estimator for \( C \) can be estimated using Greenwood’s formula. Based on the law of total variances, and assuming independence of \( \hat{S}_E(t) \) and \( \hat{S}_L(t) \), the variance of the augmented estimator at time \( t \) can be approximated as

\[
\text{Var}[\hat{S}_E(t)\hat{S}_L(t)] = \text{Var}[E[\hat{S}_E(t)\hat{S}_L(t)|\hat{S}_E(t)] + E[\text{Var}[\hat{S}_E(t)\hat{S}_L(t)|\hat{S}_E(t)]] \\
\approx \text{Var}[\hat{S}_E(t)\hat{S}_L(t)^2] + \text{Var}[\hat{S}_E(t)\hat{S}_L(t)]/	ext{Var}(\hat{S}_L(t)),
\]

where \( \text{Var}(\hat{S}_L(t)) \) is calculated using Greenwood’s formula, and \( \text{Var}(\hat{S}_E(t)) = \hat{S}_E(t)(1-\hat{S}_E(t))/n \). The independence assumption is not exactly correct because \( \hat{S}_E(t) \) is a function of the \( E \)’s and \( \hat{S}_L(t) \) is a function of the \( L, E, X \)’s. However, we expect any dependence to be weak given the role of the \( E \)’s in \( \hat{S}_L(t) \) as part of the censoring variable.

Fig. 2. Empirical variances of the \( \hat{S}_E(t)\hat{S}_L(t) \) (black dotted line) as a function of time with the y-axis on the log scale and the approximated variance using the conditional variance formula (red dotted line) for \( E = 5 \), \( X = 4 \), and \( L = 6 \), where \( L \), \( E \), and \( X \) are mutually independent. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
We see empirical evidence of this in the simulation results displayed in Fig. 4. While it would be desirable to use (2) along with Greenwood’s variance formula for \( \hat{S} \) to calculate the relative efficiency of the two estimators, this does not appear to be analytically tractable.

3. Simulation studies

3.1. Simulations of Schemper and Smith (1996)

We first replicated the simulation study reported in Table 2 of [3] with sample sizes of 100 and 200 and with 5000 repetitions. In particular, we generated \( E \) from an uniform distribution on \([12,60]\), with larger values of \( E \) corresponding to earlier entry to the trial, and we generated \( L \) from an exponential distribution with rate potentially dependent on whether \( E > 24 \) (‘early entry’) versus \( E \leq 24 \) (‘late entry’). For each simulated clinical trial, we estimated the median of the distribution of \( C \) using the Kaplan–Meier estimator, the augmented estimator, and the empirical estimator. We obtained the latter using the simulated values of \( C \) without any censoring; we provide this as a benchmark for the estimation. In addition, we provided the empirical 95% confidence intervals and the coverage probabilities (CP) for the median \( C \) under the Kaplan–Meier and the augmented estimators. Given the approximated confidence interval for the survival distribution of time to censoring, the confidence interval for the median time can be approximated as (largest time with lower limit of survival distribution > 0.5, smallest time with upper limit of survival distribution < 0.5). The average number of times that the true median time falls in between the approximated confidence interval is recorded as the CP. The results are displayed in Table 1.

When the drop-out (\( L \)) hazard rate does not depend on the time of entry (or equivalently on the time to end of study), and for \( n = 100 \), the confidence interval is 1.7 units, or 14.5%, narrower for the augmented estimate of the median of \( C \) as compared to the Kaplan–Meier estimate. When the hazard for drop-out is higher for those who enter the trial later, the confidence interval for the augmented estimate is 5.6 units, or 23.6%, narrower than for the Kaplan–Meier estimate. Alternatively, when the hazard for drop-out is higher for those who enter the trial earlier, the confidence interval for the augmented estimate is 1 unit, or 11.1%, narrower than that for the Kaplan–Meier estimate. In the first of these latter two cases, a wider range of values of \( E \) are observed than in the second case, which serves to increase the precision of the augmented estimator. In all cases the estimates of the median of \( C \) are unbiased. Similar results hold for \( n = 200 \). Fig. 1 displays the estimated survival curves averaged over 5000 replications and the empirical pointwise 95% confidence intervals for the Kaplan–Meier and augmented estimators for \( n = 100 \) and \( n = 200 \). While the estimates all coincide, it is apparent that there is a marked reduction in variability for the augmented estimator, especially for \( n = 100 \).

In summary, when \( L \) and \( E \) are independent, the augmented estimator should have lower variance than the \( \hat{S}_L(t) \) due to its usage of \( E \) from all subjects. When \( L \) and \( E \) are dependent, the augmented estimator uses more information about \( E \) than the Kaplan–Meier estimator and thereby has reduced variability, but also may introduce variability through its stratified estimation of the distribution of \( L \) given \( E \). Our simulations exhibit overall reductions in variability in the case of dependence of \( L \) and \( E \), though there may be other scenarios in which this is not the case.

3.2. \((L,E,X)\) Independent

We first generated \( L \), \( E \), and \( X \) independently from gamma distributions, with probability density function given by \( \Gamma(\alpha)^{-1} x^{\alpha-1} e^{-x/\beta} \). We set the shape parameter, \( \alpha \), equal to the scale parameter, \( \beta \), which we selected from \((4,5,6)\), yielding expected values of 16, 25 and 36. This resulted in a total of 27 simulation scenarios, which include all possible stochastic orderings of \((L, E, X)\). This is of interest because we expect the estimators to exhibit different relative performances depending on these orderings (e.g., \( E \) will contribute more information when it is less than \( L \) compared to when it is greater than \( L \)). For each of 1000 repetitions of each simulation scenario we generated a sample of 100 draws of \((L, E, X)\). We calculated empirical variances, and approximated the theoretical variance using (2), of the estimated distribution functions for time to censoring at time points corresponding to realizations of \( E \) and \( L \), giving fine coverage of the space of realizations. We show one of these scenarios in Figs. 2 and 3; the remaining are presented in Supplementary Section 1. These figures display the densities of \( L \), \( E \) and \( X \) (top panel), \( Q \) (second panel), and the survival function estimates and associated 95% pointwise confidence intervals (bottom panel). We refer to \( Q \) as ‘relative efficiency’. This quotient is less than one at all time points, for all 27 scenarios, indicating lower estimated variance for the augmented estimator, reflecting the added information that it utilizes.

Fig. 2 illustrates the empirical variance of the augmented estimator (black dotted line) compared to the approximated variance estimated using the conditional variance estimator (red dotted line) under the scenario in which \( X \) has shape and scale parameters equal to 4, \( E \) has parameters equal to 5 and \( L \) has parameters equal to 6. We can see that the approximated variance is close to the empirically estimated variance for the augmented estimator. Fig. 3 displays the three panels under the same scenario as Fig. 2. This scenario represents the case in which we expect great benefit from the augmented estimator because \( C = \min(L, E) \) is largely equal to \( E \) and \( E \) is moderatelyensored by \( X \).
Thus, estimation of \( C \) has much to gain from removal of the censoring of \( E \). In fact, the relative efficiency of the augmented estimator is substantial (Fig. 3b), which is also reflected by the narrower confidence intervals for the augmented estimate relative to the Kaplan–Meier in Fig. 3c. Note that the tail of the Kaplan–Meier estimate does not decrease to zero because that there are simulations in which there are still individuals who remain at risk at the largest observed \( C = \min(E, L) \). However, the augmented estimator does decrease to zero because \( E \) is not censored, and so its empirical survival function does decrease to zero.

### 3.3. \( X \) independent of \((L,E)\)

We conducted a similar set of simulations under dependence of \( L \) and \( E \) (but with \( X \) independent of \((L,E)\)). In particular, we first generated \( E \) as a discrete random variable with 46 unique values and with distribution function closely approximating that of a gamma-distributed random variable with equal shape and scale parameters of 4, 5, and 6. We generated \( X \) from a gamma distribution with shape and scale parameters as in the independence case. We constructed dependence between \( L \) and \( E \) by generating \( L \) from a gamma distribution with shape and scale parameters taken to be log transformed and translated functions of \( E \), calibrated such that the expectation of \( L \) would correspond to that of \( L \) in the simulation scenarios under independence. Under such a structure, the correlation coefficient between \( L \) and \( E \) was approximately 0.65 or \( -0.65 \), depending on how \( L \)’s parameters were calculated. We calculated a different (conditional) Kaplan–Meier estimate for \( L \) for each time point, \( t \), after subsetting the data to realizations with \( E \) greater than \( t \), in order to estimate \( P(L > t | E > t) \). As in the independence case, we estimated the empirical survival function \( \hat{S}_L(t) \). Thus, for all \( t \), we estimated the censoring distribution with \( \hat{S}_L(t) \hat{S}_E(t | E > t) \) and compared its variance with that of the Kaplan–Meier estimate at \( t \). Supplementary Sections 2 and 3 display the 27 scenarios for \((L, X)\) in which the correlation between \( L \) and \( E \) is approximately 0.65 and \(-0.65\), respectively.

Fig. 4 illustrates the empirical variance (black dotted line) of the censoring distribution with \( \hat{S}_L(t) \hat{S}_E(t | E > t) \) and compared with the approximated variance estimated with the conditional variance formula (red dotted line) under the scenario in which \( X \) has shape (and scale) parameters equal to 4, \( L \) has shape and scale parameters equal to 6 and \( \text{cor}(E, L) = -0.65 \). Here again, we see great agreement between the two. Fig. 5 displays the three panels for the same scenario in Fig. 4. As in the corresponding independence cases, the results under dependence suggest that there is lower variance for estimating time to censoring with the augmented estimate as compared to the Kaplan–Meier estimate, with considerable gains in efficiency for some scenarios. This observation reflects gains in efficiency due to greater use of available data on \( E \), and potential losses in efficiency in the estimation of \( \hat{S}_L(t | E > t) \) due to the required stratification by \( E \). There is no apparent difference due to positive versus negative correlation between \( E \) and \( L \) as can be seen from the figures in Sections 2 and 3 within the Supplemental material.

Software in the form of R code, together with a sample input data set and complete documentation, are available on github repository (https://github.com/jj113/Censoring-Distribution/).

### 4. Meningioma study

Jansen et al. [5] reported on a study of molecular correlates of survival and progression-free survival in patients with atypical meningioma, which is considered to be a more aggressive form of meningioma. There were 86 subjects with completely resected atypical meningiomas from two neurosurgical centers in Ireland that were included in the study. With respect to the endpoint of overall survival, the subjects in the study were censored either due to drop-out from the study or due to the administrative end of the study on May 31, 2010. There were 46 (53.5%) subjects who were censored by \( \min(L, E) \); for 39 (46%) of these, \( E < L \). This means that \( C \) is largely driven by \( E \), rather than by \( L \). This, together with the moderate level of censoring of \( C \) by \( X \) (46.5%), suggests a scenario like that depicted in the simulation of Fig. 3, in which we would expect a relatively greater gain in efficiency with use of the augmented estimator relative to the Kaplan–Meier.

Fig. 6 displays the augmented and Kaplan–Meier estimates of the survival functions for time to censoring, along with 95% bootstrap percentile confidence intervals. We estimated the variances of the two estimates using 2000 bootstrap replications, and confirmed that the augmented estimator does have lower variance than the standard estimator (Fig. 7), with considerably narrower confidence intervals. As expected, the time courses of the variances and the relative efficiency look similar to those in Figs. 3b and c. It is noteworthy also that the two estimates of the distribution of \( C \) are similar, though not identical, with a difference in medians of 9 months, for example. This difference comes from the fact that the augmented estimate relies on the Kaplan–Meier estimate of \( L \), and we do not have much information on \( L \) from these data. In summary, the augmented estimate is preferable for these data given its reduced variability. This reduction in variability is important since inferences from a study should be made only to the time frame of the study, and a better estimate of this time frame provides a stronger inference. Of course, both estimates could be presented to provide the full range of possibility for the distribution of \( C \).

### 5. Conclusions

We have studied two estimators for the distribution of time to censoring when censoring is comprised of both drop-out and administrative end of study. In particular, we present the first results on the added efficiency of the augmented estimator of Korn [2] in certain scenarios.
We observed that when \( L \) and \( E \) are independent, the augmented estimator attained lower variance than the \( \hat{S}_C(t) \) due to its usage of \( E \) from all subjects. Thus, if independence of \( L \) and \( E \) is known from subject matter considerations, we recommend use of the augmented estimator.

When \( L \) and \( E \) are dependent, the augmented estimator uses more information about \( E \) than the Kaplan–Meier estimator, which leads to a reduction in variability, but also may introduce variability through its stratified estimation of the distribution of \( L \) given \( E \). Our simulations exhibit overall reductions in variability in the case of dependence of \( L \) and \( E \), though there may be other scenarios in which this is not the case. Thus, if \( L \) and \( E \) are known to be dependent based on subject matter considerations, and there is a sufficiently large number of observations of \( L \) at different levels of \( E \), we recommend use of the augmented estimator. If, however, they are dependent but there is not much drop-out from the study, there is likely not much advantage from the augmented estimator and we recommend use of the Kaplan–Meier estimator. In cases of uncertainty, we recommend displaying both estimators with their associated bootstrap confidence intervals, as we did for the meningioma study.

**Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**Appendix A. Supplementary data**

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.conctc.2021.100842.

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