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Methodology

Bias in Mean Survival From Fitting Cure Models With Limited Follow-Up

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ABSTRACT

Objectives: When populations contain mixtures of cured and uncured patients, the use of traditional parametric approaches to estimate overall survival (OS) can be biased. Mixture cure models may reduce bias compared with traditional parametric models, but their accuracy is subject to certain conditions. Importantly, mixture cure models assume that that there is enough follow-up to identify individuals censored at the end of the follow-up period as cured. The purpose of this article is to describe biases that can occur when mixture cure models are used to estimate mean survival from data with limited follow-up.

Methods: We analyzed 6 trials conducted by the SWOG Cancer Research Network Leukemia Committee. For each trial, we analyzed 2 data sets: the data released to the committee when the results of the trial were unblinded and a second data set with additional follow-up. We estimated mean OS using parametric survival models with and without a cure fraction.

Results: When using mixture cure models, in 4 trials, estimates of mean OS were higher with the first analysis (with limited follow-up) compared with estimates from data with longer follow-up. In 1 trial, the reverse pattern was observed. In 1 trial, the cure estimate changed little with additional follow-up.

Conclusions: Caution should be taken when using mixture cure models in scenarios with limited follow-up. The biases resulting from fitting these models may be exacerbated when the models are being used to extrapolate OS and estimate mean OS.

Keywords: cure models, oncology, overall survival, survival analysis.

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Introduction

In recent years, several trials evaluating novel treatments have suggested that a fraction of patients will survive long-term, potentially exhibiting a risk of death similar to persons without cancer.[1] When populations contain mixtures of cured and uncured patients, the use of traditional parametric approaches to estimate overall survival (OS) has been shown to produce biased estimates.[2] In these situations, mixture cure models are attractive alternatives. Mixture cure models explicitly characterize heterogeneity by estimating the probability a patient is cured (potentially conditional on patient-level covariates), while modeling survival separately for the cured and not cured subpopulations.[3–5]

Although mixture cure models can reduce bias in survival estimation compared with traditional parametric models, their accuracy is subject to certain conditions. Importantly, mixture cure models implicitly assume that that there is enough follow-up to identify "failures" (ie, deaths), such that individuals censored at the end of the follow-up period are in fact cured. Survival curves that represent mixtures of cured and uncured patients will exhibit a plateau at the tail of the Kaplan-Meier curve, indicating that there are no failures after a particular time point.[6] Trials with limited follow-up, however, may also exhibit an apparent plateau in the Kaplan-Meier curve because of heavy censoring and small numbers of patients represented in the plateau. We urge caution in these situations. Accordingly, the purpose of this article is to describe biases that can occur when mixture cure models are used to estimate mean survival from data with limited follow-up. In particular, we will show that such models can result in both conservative and anticonservative bias in a manner that is unpredictable. To illustrate our concern, we take advantage of archived data for 6 trials from the SWOG Cancer Research Network Leukemia Committee. Using parametric models that do and do not incorporate a cure fraction, we estimate mean survival using the data initially provided to the study team (exhibiting some plateau in survival) and then reestimate these values using additional years of follow-up.

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Approaches to Cure Models

Cure models have been an active area of research for more than 50 years. The most popular framework is to assume that the study population is a mixture of patients who are cured and patients who are not cured and to explicitly model this mixture.[3-5] In this framework, regression models can be used to estimate the probability that a patient is cured and to predict the survival of patients who are not cured.

There are no diagnostic tests that can assess whether an individual patient is cured of their cancer. Long-term follow-up is the ultimate way to identify a cured subpopulation. Accordingly, mixture cure models do not identify individual patients as cured but rather estimate a probability that a patient is cured. What is considered adequate follow-up to be confident that a cured fraction exists varies across cancers? "Long" follow-up may be less than 5 years for a cancer with high mortality, whereas 20 years may not provide adequate follow-up for low-mortality cancers.

Logistic regression is a common choice for modeling the probability that a patient is cured.[7] Both patients who are cured and patients who are not cured are subject to "background" mortality not related to cancer. Patients who are not cured are subject to additional mortality from their cancer, and parametric survival models are often used to estimate this excess mortality. Mathematically, the survival for a population with a cure fraction described by a mixture model can be written as:

$$S(t,\ x) = S_B(t,\ x)[p(x) + (1 - p(x))S_E(t,\ x)], \quad (1)$$

where $S(t, x)$ denotes the (average) survival function of the whole population (cured and uncured) at time t conditional on covariates x, $S_B(t, x)$ denotes the survival function for a population without the disease of interest at time t conditional on covariates x, $p(x)$ denotes the probability of being cured conditional on covariates x, and $S_E(t, x)$ denotes the disease-specific (eg, cancer) survival function at time t conditional on covariates x.[8,9] We note that S_B, p, and S_E can be written more generally to depend on different covariates, but we focus on the scenario with shared covariates without loss of generality. S_B can be calculated from external data; for our application, we used age- and gender-matched mortality data from US Social Security life tables. We modeled $p(x)$ with logistic regression, and we considered several parametric models for S_E.

Cure Models in Economic Evaluation

Economic evaluations of competing interventions often estimate mean OS to calculate other statistics such as quality-adjusted life-years and the incremental cost-effectiveness ratio. If observed survival is not zero at the end of the observation period, the mean value cannot be estimated without constructing a model for extrapolation. Parametric models such as the Weibull and log-normal can be used. If a population contains a mixture of cured and not cured patients, the mean survival of the population can be calculated as the weighted average of the mean survival times of the cured and not cured subpopulations, weighted by the relative proportions. In the model in Equation 1, the mean OS of the cured proportion is the mean of the background survival (S_B), whereas the mean OS for patients who are not cured is a function of both the background survival (S_B) and the disease-related survival (S_E). The mean of a random variable with survival function $S(t)$ is equal to $\int_0^\infty S(t)dt$, so the mean OS for cured patients is equal to $\int_0^\infty S_B(t)dt$and the mean OS for patients who are not cured is equal to $\int_0^\infty S_B(t)S_E(t)dt$.

Study Design

Patient Populations

We analyzed 3 phase II, 1 phase II/III, and 2 phase III trials that were conducted by the SWOG Cancer Research Network (SWOG.org) that had primary results released to the SWOG Leukemia Committee between 2009 and 2016.[10-16] We selected 2016 as the latest release time to allow for additional follow-up between the original primary results and our follow-up survival analysis (in 2019). We note that for some leukemias, the label *long-term survival model* may be more appropriate than *cure model*. For clarity, in the following we use the term *cure model*, but the term *long-term survival model* could be used interchangeably as appropriate for the application. Institutional review boards of participating institutions approved all protocols, and patients were treated according to the Declaration of Helsinki.

Statistical Methods

Survival was estimated using the Kaplan-Meier method. There were no significant treatment effects on survival endpoints in any of the randomized trials analyzed, and analyses are presented for all arms analyzed together to increase precision in estimates. We fit both models with and without a cure fraction to estimate mean survival for each trial based on the archived outcome data from when the primary results of the trial were released and then again from survival data from January 2019. Parameters for $p(x)$ and $S_E(t, x)$ from Equation 1 were estimated using the score equations from the log-likelihood in Lambert.[9] Mean survival for patients who were not cured (equal to $\int_0^\infty S_B(t)S_E(t)dt$) was calculated by evaluating the numerical integral. Background mortality for each patient was taken from the age- and gender-matched US Social Security area population based on the year the first patient was enrolled on the study. Although background rates from most population-based sources also contain mortality associated with leukemia, in practice this has little effect on the parameter estimates.[17] Akaike information criterion (AIC) was estimated for each model. We considered Weibull, log-normal, and log-logistic parametric survival models and used AIC to evaluate model fit. Weibull models fit all the trials best (by AIC) for both cure and noncure models and so are presented here.

Results

The characteristics of each trial are summarized in Table 1. In the interest of space, we provide detailed analysis of 2 of the trials, S1117 and S1203. Outcomes of the other 4 trials are summarized briefly below.

For S1117, when the data were released to the study team in 2014, there was a small plateau at the tail of the Kapan-Meier curve (Fig. 1A). S1117 was closed soon after the phase II accrual goal was met, so there was heavy censoring along the survival curve. With additional follow-up in 2019 (Fig. 1B), there was no apparent plateau in survival. Fitting a standard Weibull model (without a cure fraction) to each of these curves, the 2019 data Weibull results estimated longer survival compared with the 2014 estimate (Figs. 1C and D). Fitting mixture cure models to both data sets, the 2014 data led to a more optimistic estimate of long-term OS than the 2019 data (Supplementary Fig. 1E and F, found at https://doi.org/10.1016/j.jval.2020.02.015). Table 2 summarizes the mean OS for each of these models. For the standard Weibull model, the mean OS was estimated to be 1.9 years with the 2014 data compared with 2.8 years with the 2019 data; with the

Table 1. Characteristics of trials analyzed.

	S0106	S0325	S0703	S0805	S1117	S1203
Disease	AML	CML	AML	ALL	MDS	AML
Phase	III	II	II	II	II/III	III
Number of arms	2	3	1	1	3	3
Treatments evaluated	7 + 3, 7 + 3 + GO	Imatinib, dasatinib	Aza + GO	Hyper-CVAD + dasatinib	Aza, Aza + Len, Aza + Vor	7 + 3, IA, IA + Vor
n	598	392	139	95	277	738
Age, median (range), y	47 (18-60)	50 (18-90)	73 (60-88)	44 (20-60)	70 (28-93)	49 (18-60)
Percentage female	47	39	40	55	31	49
Years enrolled	2004 to 2009	2004 to 2009	2009 to 2012	2010 to 2013	2012 to 2014	2013 to 2016
Year primary results released	2009	2012	2013	2016	2014	2016
Protocol maximum follow-up	5 years	5 years	5 years	5 years	5 years	5 years
Percentage censored when results released vs 2019	58 vs 49	95 vs 93	27 vs 7	71 vs 60	71 vs 26	69 vs 49

7 + 3 indicates standard of care AML therapy with cytarabine + daunorubicin; Aza, azacytidine; ALL, acute lymphoblastic leukemia; AML indicates acute myeloid leukemia; CML, chronic myeloid leukemia; GO, gemtuzumab ozogamicin (Mylotarg); Hyper-CVAD, standard-of-care ALL therapy regimen including the drugs cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine; IA, high-dose cytarabine and idarubicin; Len, lenalidomide; MDS, myelodysplastic syndrome; Vor, vorinostat.

mixture cure Weibull model, the mean OS was 7.7 years versus 4.9 years for 2014 and 2019, respectively.

When the S1203 data were released to the study team in 2016, there was a small plateau at the tail of the Kaplan-Meier curve, with heavy censoring before the plateau (Supplementary Fig. 2A). S1203 was a randomized phase III trials that stopped at an interim analysis because of futility; the interim analysis occurred soon after accrual to the trial completed, leading to heavy censoring over the survival curve. With additional follow-up in 2019 (Supplementary Fig. 2B), there was no evidence of a plateau in survival, as patients continued to die during the ongoing follow-up. Fitting a standard Weibull model to each of these curves, the 2019 data Weibull fit estimated longer survival compared with the 2016 estimates (Supplementary Figs. 2C and D). Fitting mixture cure models to both data sets, the 2016 data lead to a less optimistic estimate of OS (Supplementary Figs. 2E and F). Table 2 summarizes the mean OS for each of these models. For the standard Weibull model, the mean OS was estimated to be 3.7 years with the 2016 data compared with 6.9 years with the 2019 data; with the mixture cure Weibull model, the mean OS was 12.4 years versus 16.4 years for 2014 and 2019, respectively.

Survival curves for the other trials are provided in the supplemental figures, and mean OS estimates are summarized in Table 2. For most of the cohorts, the AIC values were smaller (smaller values indicating better fit) for the standard Weibull models without a cure fraction compared with the mixture cure models (Table 2).

Discussion

We have previously published analyses demonstrating that standard survival modeling techniques may be insufficient to estimate survival for cost-effectiveness studies in situations in which therapies appear to cure a proportion of patients treated.[2] In our example, we found that a cure model approach yielded substantially different estimates of mean survival compared with traditional modeling approaches, such that the estimate of incremental cost-effectiveness was significantly changed using the cure models. Since publication of our finding, mixture cure models have been used in several economic evaluations,[18,19] perhaps in part due to the expectation that mixture cure modeling will uniformly increase estimates of survival, and therefore cost-effectiveness, compared with traditional modeling. In this article, we demonstrate that early, enthusiastic use of mixture cure models may be a problematic choice, particularly for studies with small sample sizes or immature follow-up data for estimating OS.

Although we believe that cure models can be a useful tool, we also are aware of the number of assumptions that are required to use such models. Prior to this report, no study has evaluated the consequences of limited follow-up in the applications of cure models in health economic analyses. Our analysis provides empirical evidence on the potential implications in violations in the assumption of adequate follow-up when using cure models. Under an assumption that cured patients will never experience the event of interest, prior work has found that cure fraction estimates can be quite sensitive to model assumptions.[20] Similarly, applying different parametric models to data with limited follow-up can produce substantially different estimates of long-term outcome.[21]

We found that cure models were sensitive to the plateau of the survival function, even in the presence of limited information. For example, in S1117, there are 12 censored patients in the plateau of the 2014 data, whereas there are 79 patients censored before the plateau, so the plateau estimate is based on data with limited follow-up. Cure models use the plateau as an estimate of the cure fraction,[6] and with additional follow-up, it is clear that the 2014 estimates are an overestimate of survival. We note that evidence for a true plateau is dependent on the length of follow-up; the apparent "plateau" in the 2014 analysis of S1117 disappears when the Kaplan-Meier curve is recalculated using additional years of follow-up.

Figure 1. Overall survival (OS) of S1117. (A) Kaplan-Meier estimate of OS when primary results released in 2014. (B) Kaplan-Meier estimate of OS with data from 2014 and 2019. (C, D) Kaplan-Meier estimates of OS (solid lines) and standard Weibull models (dotted lines).

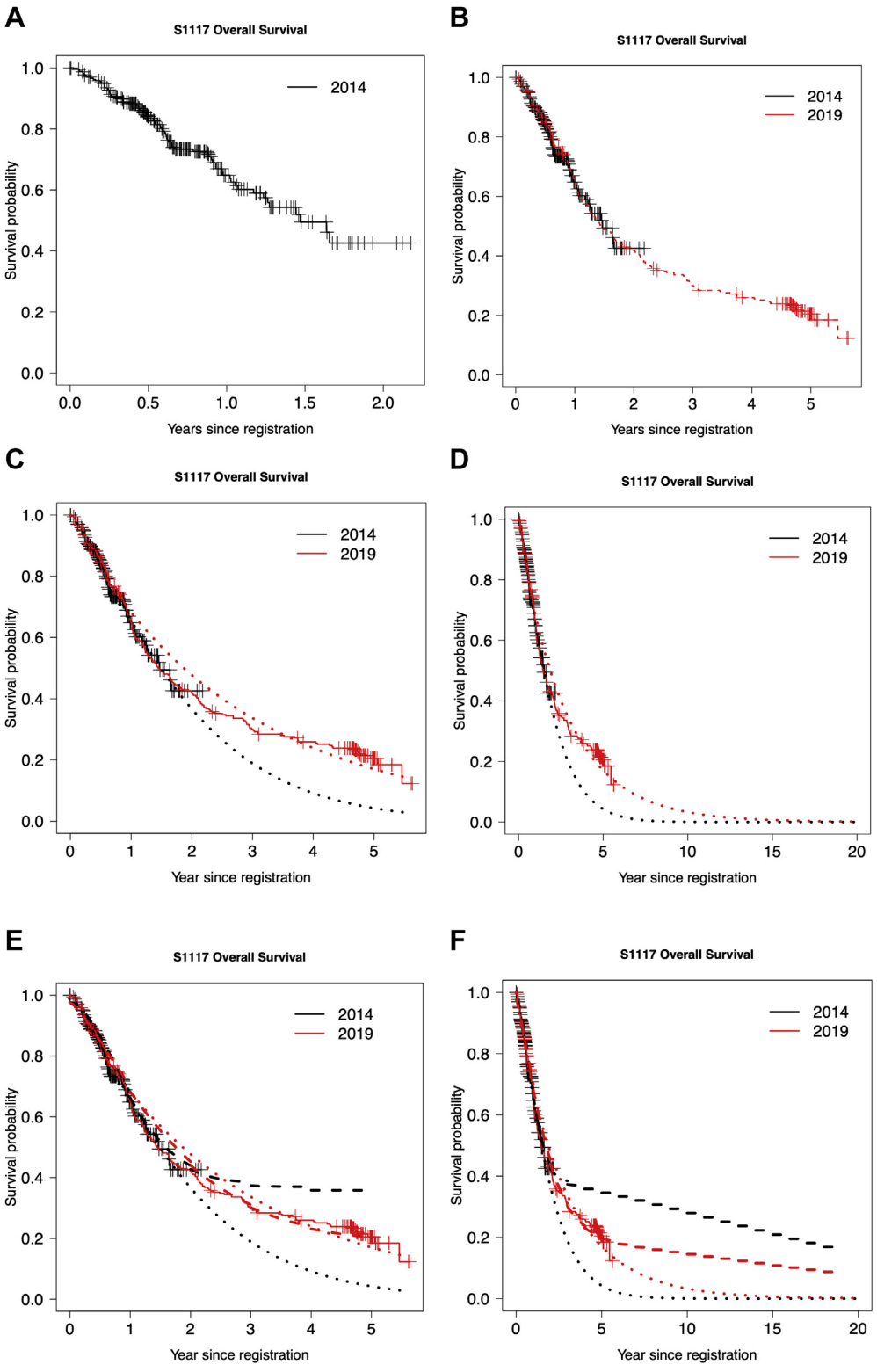

Table 2. Mean OS in years for standard Weibull and mixture cure Weibull models.

Trial	Year	Weibull		Mixture cure Weibull				
		Mean OS	AIC	Mean OS not cured	Mean OS cured	Proportion cured	Overall mean OS	AIC
S0106	2009	4.0	757.4	2.0	36.5	32%	13.2	975.8
	2019	9.8	1611.6	8.2	36.4	<1%	8.4	1725.8
S0325	2012	59.8	183.4	21.2	32.2	40%	25.5	179.3
	2019	67.9	204.8	23.2	32.1	30%	25.9	195.7
S0703	2013	1.6	249.4	1.1	13.7	15%	3.0	475.5
	2019	1.5	334.4	1.3	13.7	5%	1.9	508.1
S0805	2016	12.1	179.8	1.7	39.9	66%	26.9	186.7
	2019	12.3	240.4	10.8	39.9	<1%	10.6	227.1
S0117	2014	1.9	289.4	1.0	17.2	41%	7.7	442.6
	2019	2.8	820.0	1.6	17.2	21%	4.9	823.3
S1203	2016	3.7	929.0	1.9	36.2	31%	12.4	1419.1
	2019	6.9	1813.0	1.7	36.1	43%	16.4	2120.1

AIC indicates Akaike information criterion; OS, overall survival.

Although the mixture cure model fit for study S1117 using data available in 2014 estimated a higher mean OS than a model fit to more mature data from 2019 (7.7 versus 4.9 years), we observed the opposite pattern in S1203, in which mean OS reported using 2016 data was less than the more mature data in 2019 (12.4 versus 16.4 years).

In S0106, S0703, and S0805, the mean OS from the mixture cure model fit on earlier data sets was greater than the mean with additional follow-up, often by more than 50%. In S0325, the results were fairly similar in the 2 analyses, likely because of the small number of events in the trial and limited changes in event rates with additional follow-up.

In 5 of the 6 trials evaluated, we found that the bias from fitting mixture cure models to data with limited follow-up resulted in both conservative and anticonservative estimates of mean OS compared with estimates with additional follow-up. When bias is predictable, statistical methods can be used to adjust for such bias. The bias from fitting a cure model with limited follow-up does not appear to be predictable and so is unlikely to be able to be remediated through bias-adjustment techniques.

Perhaps the most important lesson from this exercise is the need to reevaluate the potential "cure fractions" after additional years of follow-up. SWOG trials typically continue to collect outcome data on patients after the primary results of the study are released; data are collected for a protocol-specified amount of time regardless of when the primary outcomes are published. In addition, SWOG archives outcomes of each study twice a year until the primary results are released, and then archives all published analyses of each study. The problem of immature survival data is most acute for treatments that the Food and Drug Administration (FDA) has designated with breakthrough status or accelerated approval. In these situations, the FDA requires demonstration of effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit.[22] OS data are typically immature at the time the initial findings are released. Although FDA approval of products with these designations may be sufficient to introduce them into clinical practice, health technology assessments and economic evaluations may be problematic. As we have noted in a previous evaluation of a breakthrough therapy that appears to have a cured fraction, estimates of cost-effectiveness must be considered preliminary until survival data are mature.[18]

When considering health economic analyses using potential surrogate endpoints for a cure fraction such as progression-free survival, relapse-free survival, or event-free survival, the same issues with bias associated with limited follow-up arise. Because the event horizon for surrogate endpoints is often significantly shorter than OS, adequate follow-up for fitting a cure model may be reached sooner. We note that because surrogate endpoints such as progression-free survival include additional events beyond death, if a cure fraction exists, the surrogate endpoint may underestimate the true cure fraction. Before using a surrogate endpoint to estimate a cure fraction in a data set, retrospective analyses validating the surrogate endpoint in this specific treatment and disease setting would be required, and future validation with additional follow-up would be warranted.

There is no formal statistical test to evaluate the adequacy of follow-up to fit cure models. Those that have been proposed can be both conservative and anticonservative.[6] Prior authors have suggested examining likelihood plots and parameter estimates for different parametric choices of the survival function for noncured patients; longer follow-up may be needed if the likelihood function is flat or if the estimates show significant variation. Further research is needed to identify tests for adequacy of follow-up.

When there are limited follow-up data on many patients, even in a setting where there is scientific or clinical expectation of a cure fraction, we do not recommend using cure models in for inference health economic analyses. The bias is potentially too large and unpredictable to allow for reliable inference. In situations in which adequate follow-up is available, we agree with others who recommend fitting multiple parametric models for disease-specific survival function in addition to models without cure fractions as sensitivity analyses.[23,24] In addition to analyzing the graphical fit of each model, model fit criteria such as the AIC and Bayesian information criterion can be used to guide model selection. In some of our examples, the AIC suggested that alternatives to cure fraction modeling may be preferable.

We conclude that caution should be taken when using mixture cure models in scenarios in which assumptions about adequate follow-up are not met. The bias resulting from fitting these models

may be exacerbated when the models are being used to extrapolate OS and calculate mean OS.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.02.015.

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