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Research Article

A Semiparametric Mixture Cure Rate Model for Tuberculosis Data

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A B S T R A C T

Introduction: One of the essential questions in health research is a patient's survival. The two primary families of the cure models are the mixture cure model and the promotion time cure model. A mixture cure model is a type of survival theory that considers that there are both susceptible and non-susceptible people in the population under study, but they will never be exposed to the relevant event.

Methods: A total of 1236 patients with pulmonary tuberculosis were included in this work, and time to sputum culture conversion was the event of interest. A major comparison was done between the failure time distribution and cure probability models for treatment, gender, weight, drug susceptibility test, and age between adjusted and unadjusted versions. The R studio version 1.1.447 statistical software was used for all kinds of statistical analyses.

Results: Models with two different aspects were compared. The outcomes of Mixture Cure Models (MCM) and Promotion Time Cure Models (PTCM) were significant, as expected. Estimates for the cure probability model perform better under MCM than those for the failure time distribution model. The MCM's performance has a significant impact on how well the cure fraction is estimated. It additionally supports determining the variables that influence the time to sputum conversion.

Conclusions: Only the MCM model can distinguish between a treatment's impact on an event's timing and occurrence. It was seen that firstly, the results of the cure probability model appeared differently in relation to those of the pure MCM's failure time distribution model; secondly, the results of the comparison between MCMs and PTCMs are more favourable.

Keywords: Cox Proportional Hazards Model, Semiparametric Mixture Cure Model, Promotion Time Cure Model, R Package

Introduction

Unquestionably, the semiparametric Cox proportional hazards model (CPHM) and the non-parametric log-rank test are the statistical methods that are employed most frequently to analyse clinical trials with time-to-event outcomes.[1,2] The latter, although popular, also makes use of the proportional hazards assumption, according to which, even though the absolute underlying risk may change over time, the hazard ratio[3] (HR) between the two groups remains the same. The emergence of treatments with various mechanisms of action on the occurrence of events of interest, particularly recurrence, has challenged these "classical" survival methods, even though they are typically appropriate in clinical settings where we expect a few patients to be cured and where the primary goal is to identify the treatment that prolongs the duration of the event of interest. Testing treatments that have a rebounded impact or a delayed treatment effect will undoubtedly result in non-proportional consequences. The proportion of patients who are cured, with or without modifying the timing of the event for the other patients, can change as a result of new therapies having a curative impact. In this situation, a combination of "cured" and "uncured" patients will make up the study samples.[4] It should be noted that if overall survival or disease-free survival is the primary endpoint, it is obvious that no patient can be saved from dying. Instead, one must speak of long-term survivors, who can be conveniently thought of as having been (statistically) cured. The Proportional Hazard (PH) assumption of the Cox model might be compromised in a population of short- and long-term survivors that is so varied. While time-varying covariate effects have been added in the classic CPHM to address non-proportionality, these methodologies do not adequately allow one to distinguish between the curative and life-prolonging benefits of the treatment. When the PH assumption is violated, cure rate models might be seen as a valuable alternative to the traditional CPHM for directly describing the heterogeneity within the patient's group.[5]

The two types of cure regression models put forth are mixture cure models (MCM)[6] and promotion time cure models (PTCM). They explicitly model the population's ability to survive using a combination of two patient types: those who are cured and those who are not. The capacity to separate the effects of covariates and a key benefit of these models is their ability to predict treatment outcomes, in particular, the likelihood of cure and the time until uncured patients fail, which leads to a more accurate assessment of the clinical benefit than with a standard Cox analysis.

We have used the data from medical studies related to tuberculosis from the National Institute for Research in Tuberculosis (NIRT) - Indian Council of Medical Research (ICMR), Chennai, India to assess the model and the data related to sputum culture conversion of tuberculosis patients enrolled in the Randomized Controlled Clinical Trial (RCT).[7] We studied all patients diagnosed with tuberculosis as well as those whose sputum smear results changed from positive to negative. Patients who had an event of interest but hadn't actually experienced it or were still alive, and those who hadn't turned up for their scheduled course of treatment, were all referred to as censored. When not everyone is expected to experience the relevant event or when the survival of the individuals under consideration is higher than that of the general population, cure rate models are used in time-to-event research. A semiparametric model is a type of parametric survival model in which it is believed that a certain proportion of research participants or patients would not experience the specified event. In MCM, the 'cured' and 'uncured' subjects are represented separately, with the 'cured' people exposed to no additional risk and the 'uncured' individuals sensitive to more risk, and this is simulated using a semiparametric survival distribution. Several important considerations must be made while using semiparametric cure models: the functional form of "uncured" survival must be specified, and sufficient survival functions must be provided to detect excess risks at the time of first diagnosis.[8] For convergence, skewed estimations must be avoided when the cure ratio is 80% or above; particularly while utilising the Gamma distribution, computational challenges must be taken into consideration, making less distributional assumptions.[6]

PTCMs, often referred to as non-mixed cure models, were primarily used to contrast the outcomes of MCMs. They are based on a completely different methodology. We shall demonstrate that some specific PTCMs could be seen as CPHMs that support a cure fraction. They are also commonly referred to as bounded cumulative hazard models.

Methods

A cure fraction and an uncured fraction are both present in cure rate models, which are survival models. Boag (1949) was the first to design the non-mixture cure rate model.[9] The traditional cure rate model was created by Berkson and Gauge in 1952, and a mixed model was later developed.[10] Survival techniques typically presume that all subjects will ultimately encounter the relevant event within a given time frame. A part of the population may, however, never witness the event of interest under some circumstances. A "cure" fraction must therefore be included in a statistical model. This circumstance motivates the inclusion of a cure fraction[9] in a statistical model to investigate the possibility of treating a particular disease of interest. In this article, the MCMs were evaluated systematically with the *"smcure"*[11] statistical simulation program using R software to assess the model. The use of mixture cure rate models in R software is another feature of this article. The goal of the MCM is to explicitly account

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for the fact that there are both cured and uncured patients in the population. Mixture cure modelling was created as a strategy for dealing with the circumstances in which a subset of individuals receives healing, resulting in the fact that those individuals would never experience the event of interest.[12,13] Boag, Berkson, Gauge, and Haybittle (1949) developed the first combination cure models as a result of a study regarding the calculation of cure rates. In many studies, parametric and semiparametric mixed cure models have been proposed and analysed.[14] However, because it is more challenging to meet the parametric assumptions in parametric models, semiparametric models are often of higher interest. Numerous authors have investigated the parametric method for MCMs. Consequently, modelling and estimation using semi-parametric mixed cure models have been studied in more recent publications.[12] In order to express the MCM, let Y represent an individual's exposure to the event of interest and T represent the event's failure time[15,16] (Y = 1 for exposure and Y = 0 for non-exposure), $1-\pi(z)$ give the probability of being cured when the vector of covariates z is given, and S(t|Y = 1,x) be the probability of survival for susceptible and uncured patients at time t, given a certain covariate vector x.

Covariate vectors x and z can affect the survival and cure[12] functions, respectively. The mixture cure model is expressed as follows:

$$S_{pop}(t|x,z) = \pi(z)S(t|Y=1,x) + (1-\pi(z)) \quad (1)$$

where $S_{pop}(t|x,z)$ provides the unconditional survival function of T for the whole population. In this case, the incidence is denoted by $\pi(z)$, and the latency is specified by $S(t|Y=1,x)$. As part of the modelling technique for the MCM, the cure proportion and survival distribution of patients who are not cured are separately considered.[17] The effects of the covariate vector z on the cure proportion are frequently modelled by starting with the incidence component of the model and using the logit link function, where b is a covariate vector and a vector of unknown parameters.

However, there are alternative link functions, such as the probit link $\phi^{-1}(\pi(z)) = bz$, where ϕ denotes the standard normal cumulative distribution function and the complementary log-loglink, $\log(-\log(1-\pi(z))) = bz$.

The model's latency portion is to be defined as the proportional hazards (PH) model. Let $S_0(t)$ represent the baseline survival function for uncured (susceptible) individuals. The proportional hazards mixture cure[14] (PHMC) model is chosen when $S_0(t)^{e^{\beta x}} = (t|Y=1,x)$.

Data Source and Description

The National Institute for Research in Tuberculosis (NIRT), Indian Council of Medical Research (ICMR), Chennai, India was the site of the study. A total of 1236 patients with pulmonary tuberculosis (TB) were included in one of the disease's RCTs. Patients received three different treatments, including a control treatment. Each treatment period occurred for a total of six months. Time to sputum culture conversion (from positive to negative) throughout the therapy period was the event of interest, and sputum was tested every month during the treatment period. The R software was used for all types of statistical analyses. Ethics approval for this study was obtained from ICMR.

Results

The results of modelling the time to sputum culture conversion using the TB data have been shown in this section. Among the 1236 patients, 74.7% were men and 23.3% were women. Semi-parametric MCMs were used to estimate the relative survival and survival of the non-converted population for various age groups and genders. The unadjusted cure probability was estimated by a semi-parametric model. The estimate for the cure probability model produced better results than the estimate for the failure time distribution model when treatment, gender, weight, drug susceptibility test, and age group were taken into account. Despite the fact that there are currently multiple disease types for which we can expect a portion of the population to be cured, cure models are still hardly employed in clinical trials. The CPHM offers accurate estimates of the treatment effect as long as the PH assumption is met, which is one argument against the use of cure models. In fact, it demonstrates that in situations where we have PH, the treatment coefficient is entirely recovered in size and significance if the cure fraction is disregarded and a CPHM is fitted. Given the mathematical connection between the CPHM and the semiparametric PTCM, this is, in fact, correct and not at all surprising.

The treatment regimen's cure probability was estimated using a semiparametric cure model in the form of an unadjusted method, with its HR (1.0439) being higher than the HR (1.0266) of the failure time distribution model. Additionally, for gender, the cure probability model HR (0.9163), as well as the failure time distribution model HR (0.8087), were quite similar.

The weight at baseline, the estimate for the cure probability model HR (1.1913), was more than the estimate for the failure time distribution model HR (1.0608) but both crossed one. In the drug susceptibility test, an estimate for the cure probability model HR (1.9348) had a higher conversion cure rate than the failure time distribution model HR (1.84389) and the same factor was influencing the event of interest. Regarding age, it is significant to mention that this factor had a significant impact, as evidenced by the fact that the HR was higher than 1 compared to the HR predicted by the failure time distribution model. Table 1 shows the baseline characteristics of TB regimens including control.

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Table 1.Baseline Characteristics of TB Regimens Including Control

Characteristics	Control (N = 407) n (%)	Regimen-I (N = 414) n (%)	Regimen-II (N = 415) n (%)	p Value
Sputum culture conversion	355 (87.2)	368 (88.9)	338 (81.4)	0.017
Gender				
Female	97 (23.8)	113 (27.3)	103 (24.8)	NS
Male	310 (76.2)	301 (72.7)	312 (75.2)	
Resistant to any one drug	77 (18.9)	71 (17.1)	82 (19.8)	NS
Sensitivity to all drugs	330 (81.1)	343 (82.9)	333 (80.2)	
Mean age (years), SD	33.05, 11.39	32.46, 11.41	33.29, 11.58	-
Mean weight[#] (kg), SD	41.35, 6.54	40.49, 6.46	41.06, 6.52	-
Age group (years)				
≤ 20	44 (10.8)	43 (10.3)	41 (9.8)	-
21–25	84 (20.6)	99 (23.9)	93 (22.4)	-
26–30	71 (17.4)	77 (18.5)	68 (16.3)	-
31–35	59 (14.4)	53 (12.8)	59 (14.2)	-
36–40	48 (11.7)	47 (11.3)	50 (12.0)	-
41–45	39 (9.5)	34 (8.2)	39 (9.3)	-
≥ 46	62 (15.2)	61 (14.7)	65 (15.6)	-

NS: Not significant, [#]: Weight at baseline

The parameters for time to event sputum culture conversion and estimate for failure time distribution have been reported in Table 2 with the unadjusted cure probability estimation using the semiparametric model.

The parameters for time to event sputum culture conversion and estimate for failure time distribution have been reported in Table 3 with the adjusted cure probability estimation using the semiparametric model.

Table 2.Unadjusted Cure Probability Estimation using Semiparametric Model

Proportional Hazards Model	Estimate for Failure Time Distribution Model		Estimate for a Cure Probability Model	
	Coeff.	HR	Coeff.	HR
Treatment regimen-I	0.03758	1.03830	0.04300	1.0439
Regimen-II	-0.12060	0.88638	-	-
Gender	-0.21233	0.80870	-0.08738	0.9163
Weight at baseline	0.00606	1.00608	0.17507	1.1913
Drug susceptibility test	0.61188	1.84389	0.66000	1.9348
Age group ≤ 20 (years) (ref)	-	-	0.39285	1.4812
21–25	-0.08709	0.91660	-	-
26–30	-0.21105	0.80973	-	-
31–35	-0.23499	0.79058	-	-
36–40	-0.29589	0.74387	-	-
41–45	-0.30602	0.73637	-	-
≥ 46	-0.19663	0.82150	-	-

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Table 3.Adjusted Cure Probability Estimation using Semiparametric Model

Proportional Hazards Model	Estimate for Failure Time Distribution Model		Estimate for Cure Probability Model	
	Coeff.	aHR	Coeff.	aHR
Treatment regimen-I	0.0223	1.0226	-0.8990	0.4070
Regimen-II	-0.1252	0.8823	-	-
Gender	-0.2434	0.7840	0.0006	1.0006
Weight at baseline	0.0108	1.0109	0.0340	1.0346
Drug susceptibility test	0.6333	1.8839	19.7478	2.1124
Age group (years)	-	-	0.0100	1.0101
21–25	-0.1130	0.8931	-	-
26–30	-0.1828	0.8329	-	-
31–35	-0.1656	0.8474	-	-
36–40	-0.2072	0.8129	-	-
41–45	-0.2646	0.7675	-	-
≥ 46	-0.1286	0.8793	-	-

aHR: Adjusted Hazard Rate

Table 3 shows the estimated adjusted cure probability based on a semiparametric model. Utilising an adjusted approach cure probability model for the treatment regimen, the HR (0.4070) and the failure time distribution model HR, estimation was performed using a semiparametric cure model (1.0266). Furthermore, the cure probability model HR (1.0006) outperformed the failure time distribution model HR for gender (0.7840).

Weight at baseline, failure time distribution model HR estimate (1.0109), and cure probability model HR estimate (1.0346) all crossed 1, indicating that this variable affects the event of interest. The failure time distribution model HR (1.8839) in the drug susceptibility test had a greater conversion cure rate than the estimate for the cure probability model HR (2.1124), and the same factor influences the outcome of interest. It is crucial to note that age is another significant factor and it is mentioned that this factor has a significant impact, as evidenced by the fact that the HR was higher than 1 compared to the HR predicted by the failure time distribution model. Table 4 shows the analysis as per the CPHM.

Table 4.Semiparametric Cox PH Model (CPHM)

Semiparametric Cox PH Model	Coeff	Exp(Coef)	seCoeff	Z	Lower 0.95	Upper 0.95
Treatment (ref-control) regimen-I	0.035425	1.036060	0.074553	0.63467	0.8952	1.1991
Regimen-II	-0.161153	0.851162	0.076212	0.03447#	0.7331	0.9883
Gender (ref:female)	-0.316504	0.728692	0.076014	0.00003#	0.6278	0.8458
Weight at baseline (ref: < 40)	0.013582	1.013674	0.004496	0.00252#	1.0048	1.0226
Drug susceptible test (ref)	-0.790216	0.453747	0.090780	0.0000#	0.3798	0.5421
Age group (years) (< 21–25)	0.157372	1.170431	0.114833	0.17055	0.9345	1.4659

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26–30	0.021705	1.021943	0.108057	0.84080	0.8269	1.2630
31–35	-0.058825	0.942871	0.108291	0.58698	0.7626	1.1658
36–40	-0.037093	0.963587	0.113830	0.74453	0.7709	1.2044
41–45	-0.105641	0.899748	0.121223	0.38350	0.7095	1.1411
≥ 46	-0.163521	0.849149	0.130828	0.21134	0.6571	1.0973

#significant with p < 0.05

Table 5a.Proportion Time Cure Model

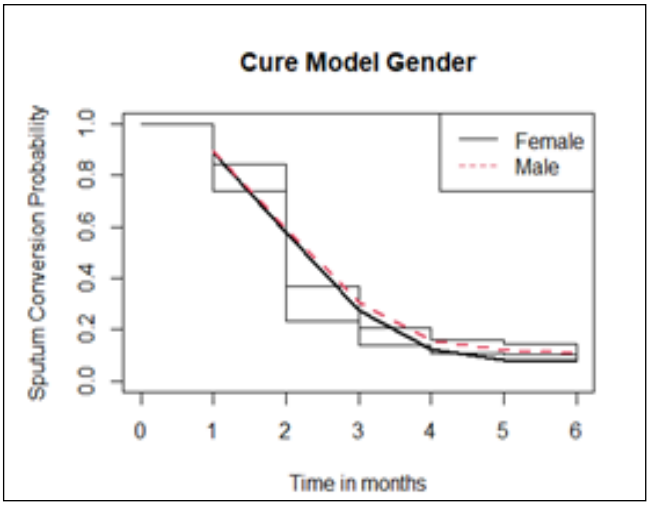
Proportion Time Cure Model	Estimates	Exp(β)	Std Err	p Value
Treatment	-0.1755	0.839037	0.1533	0.2524
Gender	-0.2024	0.816768	0.3287	0.5379
Age	0.0019	1.001902	0.0655	0.9769
Weight at baseline	0.0307	1.031176	0.0201	0.1417
Drug susceptible test	1.7941***	6.01406	0.2327	$1.245e^{-14}$***
Intercept	0.2122	-	-	-

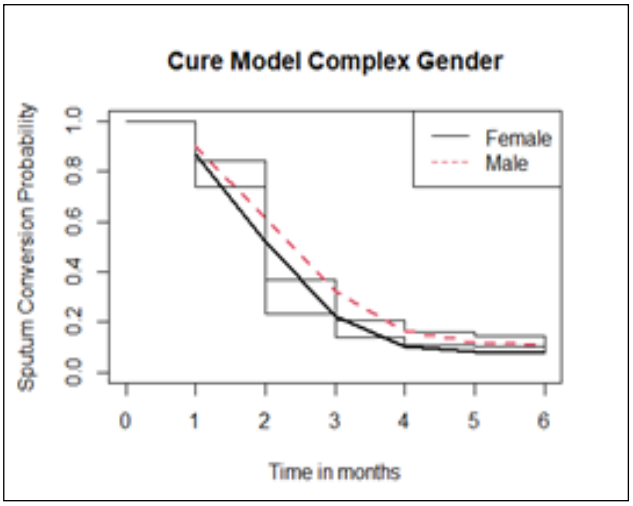
***: p < 0.000

Table 5b.Mixture Cure Models

Mixture Cure Models	Estimates for Cure Probability Model	Exp(β_Cure)	Estimates for Failure Time Distribution Model	Exp (β_Failure)
Treatment	-0.2879 **	0.749837	-0.0189	0.98127
Gender	-0.9760 ***	0.376815	-0.1800 ***	0.83527
Age	0.0057	1.005716	-0.0052 ***	0.99481
Weight at baseline	0.0610 ***	1.062899	0.0052	1.00521
Drug susceptible test	2.4046 ***	11.074	0.0922	1.09658
Intercept	-0.5786	-	-	-

**: p < 0.001, ***: p < 0.000





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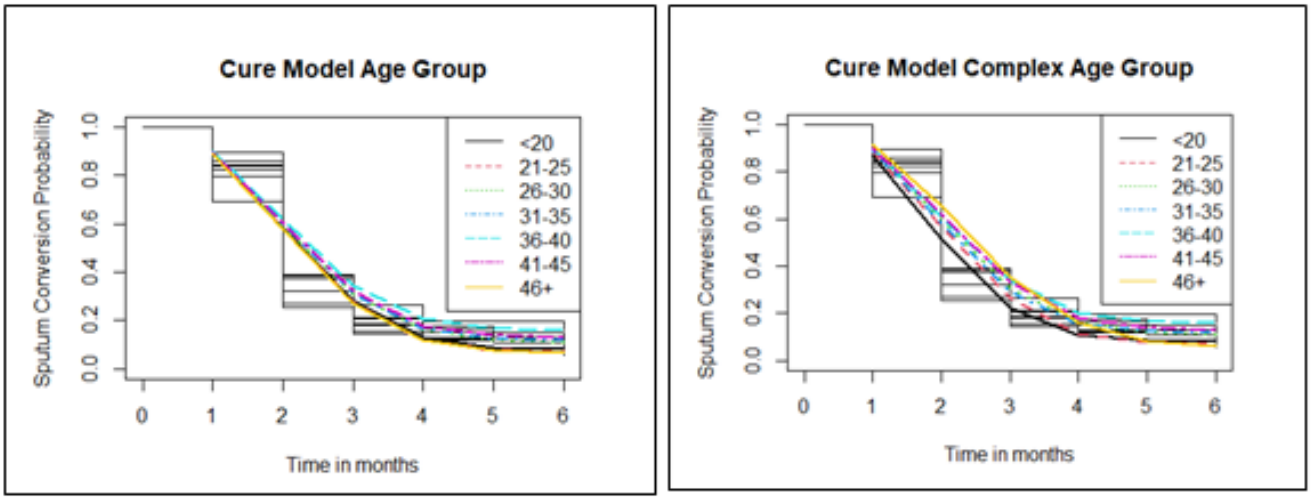

Figure 1a.Predicted Survival Probability between Cure Model and Cure Model Complex for Factors influencing Time to TB Conversion

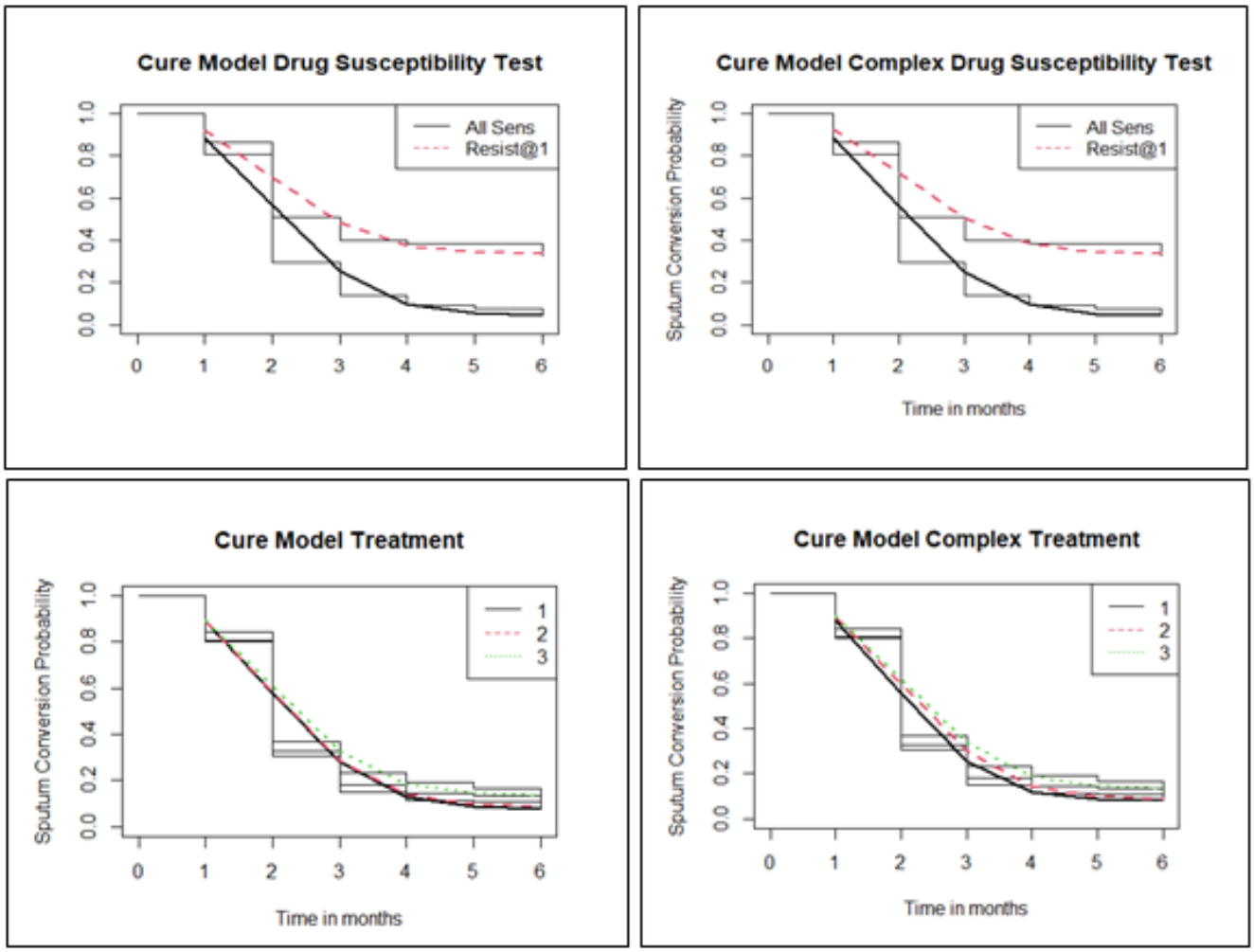

Figure 1b.Predicted Survival Probability between Cure Model and Cure Model Complex for the Drug Susceptibility Test and Treatment Variables that Factors influencing Time to TB Conversion

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Results for the influence of treatment effect adjusted for gender, age, baseline weight, and drug susceptibility test are shown in Tables 5a and 5b. The results of MCMs and PTCMs are significant, as expected. Despite the fact that the PTCM is a non-mixture model category, MCM challenges the outcomes. Tables 5a and 5b show the results (obtained with these models) for the treatment effect after adjusting for age, treatment, drug susceptibility test, and gender. The results from both PTMC and the MCM can be believed, the interpretation of the hazards will be favourable, and the results from both MCM and the PTMC are significant as expected. Estimates for the cure probability model perform better under MCM than those for the failure time distribution model. The primary purpose of PTMC (which is a non-mixed cure model) is to compare it to the pure MCM.

The MCM's performance has a significant impact on how well the cure fraction is estimated. It additionally supports determining the variables that influence the time to sputum conversion. Table 5b shows the covariates and their adjusted estimated cure fractions as follows: treatment (-0.2879), exp(-0.2879) = 0.7498; which is adjusted with age, drug susceptibility test, and gender. Gender (-0.9760), exp(-0.9760) = 2.6538, is the gender-adjusted with age, treatment, drug susceptibility test, and its adjusted predicted cure proportion. The estimated cure fraction under the drug susceptibility test (2.4046); exp(2.4046) was 11.073999. Now, we can distinguish between how these factors influence an event's time and its occurrence according to the MCM. Gender, age (< 20, 21–25, 26–30, 31–35, 36–40, 41–45, and > 45 years), treatments (Reg-I, Reg-II, and Control), and drug susceptibility test (sensitive and resistant) differences between groups have been shown on the predicted survival probability using KM survival curve (Figures 1a and 1b).

Discussion

According to the cure model and the cure complex model, both predicted survival curves are parallel to each other and plateau around the same period. When the cure model and cure complex model are compared, the cure complex model significantly outperforms the cure model, particularly when the time-to-sputum conversion is assessed between groups of these variables. When discussing cure models, two key questions frequently come up. The first question is: When should we utilise a cure rate model to analyse our data and what are the repercussions of doing so?; the second one is: Is a cure rate model indeed necessary and which should we employ—MCM or PTCM? To illustrate this, we have presented a clinical study on tuberculosis that looks at the effects of misspecifying the model to be used for estimation, such as assuming a classic CPHM when the sample actually contains a cure fraction or assuming a mixture cure rate model when the data actually follows a promotion time cure model. The time to event tuberculosis data have greatly benefited from the methodology of adjusted and unadjusted models for the semiparametric cure model. The disease conversion is significantly influenced by almost all factors and covariates. Some variables have changed as a result of the semiparametric cure model's significant improvement in terms of unadjusted and adjusted approaches. The data on the time to event for tuberculosis is properly appreciated by the semiparametric cure model. Tables 4, 5a, and 5b show the results (achieved with the three models) for the treatment effect, adjusted for treatment, age group, drug susceptibility test, and gender.

Conclusion

The findings from CPHM and PTCM are comparable, as would be predicted, with the coefficient's interpretation being related to both short- and long-term impacts. The MCM is the only model that can distinguish between a treatment's impact on an event's timing and occurrence. Models with two different aspects have been compared with two findings; first, the results of the cure probability model have appeared differently in relation to those of the pure mixture cure model's failure time distribution model; second, the results of the comparison between MCMs and PTCMs are more favourable.

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Conflict of Interest: None

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