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Research paper

Prognostic Factors of Long-term Survival among Rheumatic Heart Disease using Standard versus Cox Proportional Hazard Mixture Cure Model

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Abstract

The mixture cure model brings a great interest among researchers to the analyses survival data in the presence of cured. This study highlighted the importance of cured to be considered when the study population consists of two different type of groups. In such situations, the appropriate model is warranted. In this work, the standard Cox Proportional Hazard (PH) model and Cox PH mixture cure model were employed in order to highlight the difference and the usefulness of the mixture cure model over standard model. The Rheumatic Heart Disease (RHD) dataset could be applied for this purpose. Results—The cured fraction was estimated to be 93.7%. The cure analysis shows the effect of Coronary Pulmonary Bypass (*P*-value=0.015), Mitral procedure (*P*-value=0.067) and Age (P-value=0.035) were significantly associated with cured among the RHD patients. Meanwhile, the length of hospital stay (*P*-value=0.055) and older age (*P*-value=0.063) were significantly associated with uncured patients. However, the standard Cox PH model do not allow to discriminate the effects of prognostic factors between these two different patients. The results reveled that HPT (*P*-value<0.030), emergency Intra Operative status (*P*-value=0.001), Mitral valve procedures (*P*-value=0.031), CPB (*P*-value=0.000), HOSP (<6 days groups) (*P*-value=0.020) and Redo Post-Operative status (*P*-value=0.002) were identified as factors associated with the time to death among patients. Conclusion— The results exhibited the advantages of mixture cure model over standard survival model when the cured present in the data.

Keywords: *Cox Proportional Hazard Cure Model; Long-Term Survival; Prognostic Factors; Rheumatic Heart Disease; Standard Cox Proportional Hazard Model*

1. Introduction

Standard survival models (i.e., Cox Proportional Hazard (PH) model) is one of the most widely use among researchers to study the effects of several factors associated with the time to the occurrences of an event interest [1]. These models only consist of one population with assume that all subjects are at risk of experience the event interest over sufficiently long follow-up. This is true since many clinical studies focusing on mortality of persons affected by a particular disease [2]. However, with a rapid improvement in medical treatment and health care nowadays, there has been a great interest to see some patients are free from any signs or symptoms of the disease. These surviving patients are known as long-term survivors or cured in the sense that the event of interest (i.e., death) do not be seen even after an extended the follow-up. And meanwhile, the remaining patients eventually experience an event of interest (i.e., death) known as uncured patients. Therefore, such data postulate the mixture of two group of populations.

Due to these different types of group patients, led to a spate of statistical models that can handle the mixed two type of different group of patients. The mixture cure model is also known as a long-term survival model. The mixture cure model is an extension of the standard survival model with the additional element of cured. The advantage of this mixture cure models is the ability to discriminant the effect of prognostics factors between cured and uncured patients [3-13]. Moreover, different type of patients are believed that come from different type of populations. Therefore, the use of standard survival models that assume single populations is not appropriate. Therefore, the standard survival models are not useful to discriminate the effects of prognostic factors between cured and uncured patients. This study demonstrates the application of mixture cure model using Rheumatic Heart Disease (RHD) dataset.

Although the standard Cox PH model has been widely established in Rheumatology studies [14-18], this mixture cure model is not widely used to identify the prognostic factors that significantly associated with survival among RHD patients. In this study, the standard Cox PH model and Cox PH mixture cure model were employed in order to highlight the difference and the usefulness of the mixture cure model over standard survival models.

2. Methodology

2.1 Patient's information

A cohort-retrospective study was conducted among 721 RHD patients. These secondary data were obtained from patients at University Kebangsaan Malaysia (UKM) Heart and Lung Centre and National Heart Institute (Institut Jantung Negara, IJN), Malaysia who underwent mitral valve repair between 1 January 1992 until 31 December 2011.
The following seven factors were assessed: Hypertension (HPT) (1=yes, 0=No), Coronary Pulmonary Bypass (CPB) in minutes, Mitral valve repair procedures (1=Combination repair with other procedures, 0=repair alone), Length of hospital stay (HOSP) (1=< 6 days, 2= 6-14 days versus 3=>14 days), Intra-Operative status (Intra Operative) (1=elective, 2=emergency, 3=urgent), Post-Operative status (Post Operative)(1=first operation, 0=redo), and Age (years).
The survival time was measured in days starting from the date of first surgery until death or end of study. The patient's status was recorded as either death or censor. Censored cases are assumed to be non-informative. Deaths after undergoing rheumatic surgery were regarded as a failure and an event interest. Survival time was measured in days starting from the date of first surgery until the experience of death or study endpoint.

2.2 Research Framework

The research framework for this study can be represented throughout Figure 1.

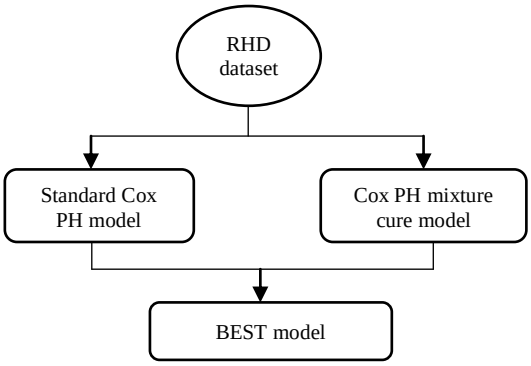

Figure 1: Research framework

2.2.1. Standard Cox Proportional Hazard Model

Let $x_{i1}, x_{i2}, \ldots, x_{ip}$ be the values of p covariate for a particular i^{th} subject. The mathematical form for the standard Cox PH model proposed by [1] is modelled as:

$$h(t|\, x_i) = h_0(t) \sum_{k=1}^{p} \exp(\beta_k x_{ik}),\ k = 1, 2, \ldots\ldots, p \quad (1)$$

where,
$h(t|\, x_i)$ is hazard function at time t for a subject with covariate x
$h_0(t)$ is the so-called baseline hazard function of the underlying survival distribution
β_k is the vector of k^{th} unknown regression coefficients
p is the number of covariates.

2.2.2. Cox Proportional Hazard Mixture Cure Model

This Cox PH mixture cure model was first introduced by [7]. The model is formulated by assumes the study population is a mixture of uncured and cured by employing the logistic regression in the incidence part whereas the standard PH model [1] in the latency part. In this model, the PH assumption is employed to describe the effect of x_i on the distribution of the survival time distribution for uncured part.
Let U be the unobserved indicator denoting whether a subject is uncured ($U = 1$) or cured ($U = 0$)to the event of interest. T denote the random variable of a non-negative value for the survival time, z and x as the covariate vectors for the incidence and latency part respectively (may same covariates). The marginal survival probability $S(t \mid x, z)$ for the entire population of subjects can be written as:

$$S(t \mid x, z) = \pi(z) \times S_{u0}(U = 1, t|x)^{\exp(\beta x)} + (1 - \pi(z)) \quad (2)$$

where,
$\pi(z))$ is the probability of eventually experiencing the event of interest
$\big(1 - \pi(z)\big)$ is the probability of eventually cured from the disease or never experiencing the event of interest
$S_{u0}(U = 1, t|x)$ is arbitrary baseline survival function of uncured subject may depend on a covariate vector x
The Cox PH mixture cure model can potentially distinguish between prognostic factors of cured and factors associated with the time to death by providing the two estimated values of Hazard Ratios (HR) and Odds Ratios (OR) for the factors associated with time to death and cured among patients [3-4,13-14]. For interpretation, those with OR greater than 1 indicates an increase in the proportion of long-

term survivors that can be obtained in the cured part whereas HR less than 1 indicates an increase in survival rate among patients who are uncured that can be obtained in the uncured part. A 2-tailed *P*-value< 0.05 was considered to be statistically significant. All analyses were performed using R software.

3. Results and Discussions

Figure 2 shows the probability of death among RHD patients with 1, 6, and 7 years of survival probability were 96.9%, 94.7%, and 93.7% respectively. These survival probabilities show a minimal change before the curves level-off to the survival probability of 93.7% after 2000 days (~7 years). This indicates that the Kaplan-Meier survival curve level-off at non-zero proportion after approximately 7 years, showing that a long and stable plateau tail with no further event of interest has been observed thereafter. In this scenario, the majority of patients survive and only a small portion of patients die within the study period. Therefore, it is natural to consider this cure model. With significant progress in medical and health sciences, there has a great interest to see the patients are expected to be cured. Once the cured proportion has been identifies in the data, the cure provides more informative information than the standard approaches.
Table 1 shows the results of the Cox PH mixture cure model and standard Cox PH model using stepwise variable selection. Three of these variables—CBP (*P*-value=0.015), Mitral procedures (*P*-value=0.067) and Age (*P*-value=0.035) —were identified as factors associated with cured. While HOSP between 6 -14 days (*P*-value=0.055) and Age (*P*-value=0.063) were associated with the time to death.
In multivariate analysis of standard Cox PH model, six of these variables— HPT (P-value<0.030), emergency Intra Operative status (P-value=0.001), Mitral valve procedures (P-value=0.031), CPB (P-value=0.000), HOSP (<6 days groups) (P-value=0.020) and Redo Post-Operative status (P-value=0.002) were identified as factors associated with the time to death.

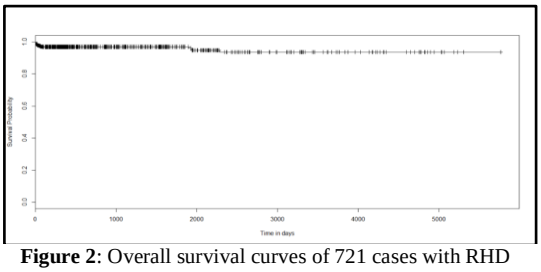

Figure 2: Overall survival curves of 721 cases with RHD

The Cox PH mixture cure model further delineated separately each factor that contributions to the incidence and latency part. The standard Cox PH model indicated patients with mitral valve repair alone have a higher risk of death, compared to patients in the combination surgery (*P*-value=0.031). This model only reports the effects of factors on the risk of death, which aggregates the results between the effect on the incidence and latency, or in other words, there is no direct way to separate from these two effects on survival time.
The mixture cure model analysis, however, answers two separate questions: (1) Are patients with combination mitral valve repair procedure more likely to die? (incidence); and (2) Among those who are cured, are these patients with combination mitral valve repair procedure more likely to die sooner? (latency). The column on the left side in Table 1 indicate that those patients with combination procedures, have a higher risk of death compared to mitral valve repair alone patients (OR= 0.735, *P*-value= 0.067), but among uncured patients, mitral procedures do not have an impact on the latency of cure (HR= 0.6, *P*-value= 0.732).

Table 1: Results of Analyses Using Standard and Cox Proportional Hazard Cure Model with Stepwise Variable Selection

	Standard model Cox PH model		Cox PH mixture cure model			
Variable	HR	*P*-value	OR	*P*-value	HR	*P*-value
CPB	1.009	**0.000**	1.003	**0.015**	1.009	0.259
Length of stay						
<6 days	0.174	**0.002**	0.847	0.190	1.473	0.544
6-14 days	0.579	0.366	0.920	0.423	0.232	**0.055**
>14 days						
Mitral Procedure	4.047	**0.031**	0.735	**0.067**	0.161	0.732
Age		Not selected	1.004	**0.035**	1.028	**0.063**
HPT	4.400	**0.003**			Not selected	
IntraOperation status						
Emergency	7.231	**0.001**			Not selected	
Urgent	0.000	0.987				
Elective						
PostOperation status					Not selected	
Redo	10.950	**0.002**			Not selected	
First surgery					Not selected	

The effects of CPB present a similar case. The standard Cox PH model indicates that increased minutes in CPB more likely increased the risk of death among RHD patients (*P*-value= 0.000). However, cure models show that CPB is associated with incidence, but not with latency. Beyond this effect, age is not associated with time to survive (HR= 0.6, *P*-value= 0.259). Each minute increase in CPB is associated with a 3% higher probability of survival (OR=1.0, *P*-value= 0.015) and not among uncured patients (*P*-value= 0.259). Alternatively, age is not a statistically significant prognosis factor for the incidence of death (OR=1.0, *P*-value= 0.035), but also not prognostic factor for latency of cured (HR=1.0, *P*-value= 0.063). Those who have a length of stay of less than 6 days are strongly associated with increased the risk of death as shown in the standard survival model (*P*-value= 0.002). This result contrast the results of cure models which reflect moderate effect for length of stay between 6 to 14 days on latency of cure (HR= 0.232, *P*-value=0.055) but not prognostic factors for the risk death (OR=0.920, *P*-value= 0.423) among RHD patients.

From this mixture cure model, it can possible to estimate the probability of being cured (incidence) and identify the factors that influence it; while simultaneously estimate the distribution on time to death (latency). In that case, unlike the mixture cure model, the standard model does not allow to distinguish the effects between the events had occurred (incidence) and the timing of an event occurrence (latency). The following are the most important findings between mixture cure models as compared to the standard survival model

Firstly, the standard survival models are the most popular model to study one population that only suitable for serious disease. Meanwhile, the mixture cure models can distinguish the covariate effects between cured and uncured patients which suitable for curable disease. Secondly, for data interpretation. The standard survival models (such as PH model) provide only one estimated value, which is the HR do not postulate the mixture survival data. For example, high (low) HR obtained in the standard PH model represents an increased (reduced) the risk of an event occurrence (i.e., death) [13]. Meanwhile, the mixture cure models are capable to estimate the cured and uncured patients respectively into a single model. From this model formulation, the mixture cure models provide an advantage over the standard models in term of determining the prognostic factor on both cured and uncured subjects simultaneously [12].

Thirdly, with a significantly large number of subjects being cured, the standard survival models are unable to capture the flattening asymptote in the Kaplan-Meier survival plot [5]. For this circumstance, the standard survival models fail to describe adequately the heterogeneity effect among mixture survival data, which contradict the assumption underlying in the standard survival models. Therefore, the mixture cure models were purposely designed to tackle this problem. Furthermore, Cox[1] acknowledges the limitation of his model in long-term study, where the results from cure model may provide better long-term survival information than the standard models since the long-term survival study decouple from the short-term effects [12-13]. Finally, the standard model may be insufficient particularly if the Kaplan-Meier survival curve reaches a plateau tail at a non-zero level over time. This plateau effect is typical for the data set with a significant number of patients to be cured. Therefore, the standard survival model is unable to capture the flattening asymptote of the survival curve as time approaches infinity.

4. Conclusion

This paper has presented the prognostic factors of long-term survival among RHD using standard versus Cox PH mixture cure model. The results revealed that the mixture cure models can be able to characterize the prognostic factors associated with the time to death and cured. However, the standard survival model is useful to determine the prognostic factors associated with the time to death only. The use of standard survival model for such data is not appropriate since the model assumes that all are at risk of experience the event of interest. In this settings, the standard survival model is less appropriate and hence, the cure models can provide more information that is not available in the standard survival model. The cure models have been well fitted to the cured data in which the model developed specifically to address the issue of cured.

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