MACHINE LEARNING METHOD IN COMPETING RISK SURVIVAL MODEL

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Abstract

Survival analysis has been developed and used in many areas, including health care, economics, finance, manufacturing, and others. It needs the same rigor as other areas of machine learning, like regression and classification. This study considers random forests for modelling survival data with competing risks. This nonparametric method (NP) can be used to identify cause-specific variables and calculate the cumulative incidence function (CIF). Random survival forest is a collection of tree based prediction method that estimates the likelihood of success for competing risks. Two competing risk criteria (splitting log-rank and Gray's test) and cause-specific Cox regression models were fitted to the data using a cross-validation procedure. The Integrated Brier Score (IBS) and the Concordance Index (CI) were used in the study to validate the model and also study explains the above described models for a real time medical data and the results of which are discussed in details.

Keywords: Survival Models, Competing risk, CoxPH model, Cumulative Incidence Function, Random Survival Forest.

1. INTRODUCTION

Survival analysis using competing risk data (CR) is widely used in medical research and is gaining increasing attention and interest in a variety of research fields. The most common classical methods for assessing survival data are the Cox proportional hazard (CoxPH), CIF and the Fine and Gray method. By treating the CIF curve as a sub distribution function, Fine and Gray provided a methodology for computing the CIF with variables.

Recently, Machine Learning (ML) methods have been rapidly practical in various fields to automatically analyze large volumes of data. The main concept of ML is to learn the algorithm from repeated input data, and to recognize hidden patterns and relationships from huge, noisy and complex data. An important feature of the ML

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approach is the construction of a prediction model with the presence of nonlinear effects and complex interactions, among several variables. Therefore, ML is widely used in medicine to identify important risk factors and predict diseases. In addition, ML techniques have been adapted to statistical learning concepts and principles (Hastie.T et al.2001).

Random survival forests, a well-known collective tree method for right-censored survival data analysis. Findings of application of this method show that making ensembles by the average base learners, like trees, can significantly increase the performance of prediction. The Random Forest Survival (RSF) method is a generalized Breiman's Random Forest (RF) method for the analysis of time to event data. In RF, randomization is done in two ways. First, for the growth of each tree, a random sampling with replacement (bootstrap method) is taken from the data set. Second, in each tree node, some explanatory variables are chosen at randomly.

The implementation of RSF is similar to the RF method and follows its general principles, the steps of which are: (i) Survival trees grow using bootstrapped data, (ii) When splitting tree nodes, several explanatory variables are randomly decided on from the list of variables, (iii) Trees usually grow deep until the cessation condition is met, and (iv) the survival forest ensemble is estimated by the predicted mean survival measures of the trees.

After fitting a model, it is very important to check the performance of the model. C-index and Brier statistics are commonly calculated and presented in RSF survival analysis. To compare the Cox prediction model obtained in this fashion to other prediction models, we used a random forest.

Razaei.M et al (2020) identified the way of analysing right-censored survival data using survival random forests. Using a randomized CR RSF model under conditions of competing risk Hamidi. O et al (2017) determined the influencing factors for AIDS progression in HIV-positive patients in Iran's Hamadan province.

CIF represents the cumulative probability of an event due to a particular type of cause over time, is a valuable quantity for CR data (Pintilie, 2006). Fine and Gray (1999) established a way to directly model the CIF by modeling a subdistribution hazard function. R. J. Gray (2014) created user manual for the R package "cmprsk," which gives user-friendly instructions on how to utilise sub distribution functions for competing risks. Ping Wang et al (2019) provides a better understanding of latest improvements in survival analysis, as well as guidance on using ML approaches to address emerging challenges in censored data applications.

By changing a piecewise-linear criterion function, Diagonal survival tree guidance ideas can be extended to competing hazards (Malgorzata Kretowska, 2018). In addition, tree-based ensembles are proposed for analysing competing

events. Halina Frydman & Anna Matuszyk (2022) were used CR Random Survival Forest for financial datasets that contain two competing credit risks, default and prepaid. [8], [10] and [12] are provided the R package deal vignetee with appropriate heritage on RSF models. These sources for machine learning analysis of time to event data that is concise and easy to understand.

This paper is prepared as the following structure. The CIF and the KM survival function for the time to event data with competing risks are discussed in Section 2. Section 3 reviewed the CR RSF, its splitting criteria, variable selection methods, and performance evaluation. These techniques are implemented to the PBC (Primary Biliary Liver Disease) data in Section 4. The summary and finding of this work are given in Section 5.

2. COMPETING RISKS FOR SURVIVAL DATA

Competing Risk for time to event data, patients are at risk for different types of failures at p $(p > 1)$. Assuming that the ith failure occurs at T_i , we are only interested in failures with the shortest time $T = min(T_1, T_2, \ldots, T_n)$. The training sample L for CR data is described as $(X_i, t_i, \delta_i),\ i = 1, 2, \ldots, n$, where X_i is the N-dimensional covariate vector, t_i is the time until the first observed event, and $\delta_i = \{0, 1, \ldots, p\}$ indicates a failed case. δ_i Equals to zero denotes censored observation, this means that for a given patient has not happened any failure.

For the distribution of the random variable T (time) for an event of type i (i = 1, 2,...,p) several functions are introduced. Mostly used method for competing risk data is CIF, which is defined as the chance that an event of type i occurs at or before time t, (Putter.H et al 2007):

$$F_i(t) = P(T \le t, \delta = i)$$

CIF function is calculated as

$$\hat{F}_i(t) = \sum_{j|t_j \le t} \frac{d_{ij}}{n_j} \hat{S}(t_{j-1}).$$

where $t_{(1)} < t_{(2)} < \ldots < t_{(D)}$ is an ordered, uncensored time point that is different from training sample L, d_{ij} represents the number of events of type i at time $t_{(j)}$, n_j and d_j represents the number of patients at risk and number of events at time $t_{(j)}$ respectively. $\hat{S}(t)$ is the KM estimator calculated as follows:

$$\hat{S}(t) = \prod_{j|t_{(j)} \le t} \left(\frac{n_j - d_j}{n_j} \right).$$

The "patients specific" CIF for the event of type i is given by

$$F_i(t|X) = P(T \le t, \delta = i | X = (x)).$$

$\hat{F}_i(t|X_{new})$ is the conditional CIF for the new patient with covariate vector X_{new}.

3. RANDOM SURVIVAL FOREST FOR COMPETING RISKS

RSF is one of the ML methods that uses a set of decision trees and provides the most efficient predictor variables related to lifetime. RSF is a ensemble survival trees. Each tree develops with a separate bootstrap sample of training data and random feature selection on each node. Trees in competing risk forests grow as well.

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In each survival tree, the split rule is used to grow the tree and the estimates calculated within the terminal node used to define the ensemble. For CR RSF, the researcher is like to predicting events and detecting risk factors that affect the timing of events.

The RSF model suggested in (Ishwaran et al., 2008) and based on the idea of constructing an ensemble of survival trees (LeBlanc and Crowley, 1993) and aggregating their predictions.

The following are the steps in the RSF algorithm for CR (Ishwaran et al 2014):

1. B times randomly select 63% of samples from the original data using bootstrap sample and keep remaining samples in out-of-bag.
2. Randomly select square root of the number of total variables at each node of the tree. Using the splitting rule, select the variable and use it for split each node.
3. For stopping criteria, terminal node should contain not less than $n_0 > 0$ unique cases
4. Calculate CIF and cumulative cause specific hazards for all P events for each tree
5. For the value of each estimator, choose mean value of the estimates obtained all over the B trees.

In this paper, different splitting rules for CR RSF were fitted, each containing 1000 survival trees. Each tree grows based on an average of about 63% of the data, and each patient's cross-validated out-of-bag survival using the remaining unavailable out-of-bag data (37%). Also, the importance of the variables (VIMP) and the minimum depth for each independent variable are calculated. Independent RSF competing risk forests used for two different survival splitting rules. Generalized logrank splitting rule is used to select variables that affect event-specific hazards and Gray's test splitting rule, which is best suited for significant variables that directly affect the CIF are also used for splitting the observations. The survival and RSF models were compared using the IBS criterion (Mogensen UB et al.2012).

3.1 Splitting Rules

Splitting rules are used in tree growth to determine if a particular node should be properly split into left (l) and right (r) child nodes. For competing risks, we will discuss two risk-specific hypothesis tests and associated splitting rules:

1. Generalized log-rank test, specified by splitrule = "logrank". This examines event-specific hazard equality and is more appropriate when analysis focuses on identifying event-specific risk factors. General logrank test based on weighted difference of Nelson Aalen's event-specific cumulative hazard estimates in child nodes.

    $H_0: h_{p,l}(t) = h_{p,r}(t), for\ all\ t \leq \tau.$

2. Gray's test, specified by splitrule = "logrankCR" which is the default used by the package. This is a modified version of Gray's test (RJ Gray 1988) which looks for equality in the cumulative incidence of causes. This is

most suitable when the goal is long term probability prediction.

$$H_0: F_{p,l}(t) = F_{p,r}(t), for\ all\ t \le \tau.$$

3.2 Performance Evaluation Metrics

The C-index and the prediction error identified by the IBS are used to evaluate prediction performance of the models. The C-Index is mapped to the area under the Receiver Operating Characteristic Curve (ROC) and assesses the probability that the expected outcome of the first failed case will deteriorate in a randomly selected pair of cases. BS is the square of the difference between the actual and predicted result.

C-index

When an RSF model is fitted, model performance evaluation indicators such as C index are required. C-index obtained using following rules:

1. Obtain all feasible pairs of cases.
2. Remove those pairs whose lower survival time is censored. Remove pairs i and j if $T_i = T_j$ unless at least one is a death (Occurrence of event). Permissible is the total number of permissible pairs.
3. For every permitted pair where $T_i \ne T_j$, count 1 if the lower survival time has worse predicted measure; count 0.5 if predicted measures are tied. For every permitted pair, where $T_i = T_j$ and both are deaths, count 1 if predicted measures are tied; if not, count 0.5. For each permissible pair where $T_i = T_j$, but not both are deaths, count 1 if the death has worse predicted measure; if not, count 0.5. Concordance is sum over all permissible pairs.

4. C-index = No.of Concordant pair/(No.of Concordant pair +No. of disconcordant pair).

The prediction error rate of an RSF model can be determined using the C-index to indicate its prediction accuracy. The 1-C index with a value between 0 and 1 corresponds to the predicted error rate. RSF models with better prediction accuracy have a low prediction error rate. [Ishwaran et al (2008), Harrell(1982)].

Brier Score

When evaluating predictions over a period $(0, t')$ instead of for a time t, the prediction error can be averaged over the period using IBS (Graf et al. 1999), as shown in the equation below:

$$IBS = \frac{1}{N}\sum_{i=1}^{N}\int_{0}^{t'} w_i(t)[\hat{y}_i(t) - y_i(t)]^2\ dW(t),$$

where $W(t)$ denotes weight function, for which the usual selections are $W(t) = t/t'$ or $W(t) = (1 - \hat{S}(t))/(1 - \hat{S}(t'))$, The estimated survivor function is denoted by $\hat{S}(t)$. BS, as defined above, quantifies the mean squared difference between the predictions made and the

actual outcome; hence, the smaller the BS, the better the predictive model.

3.3 Variable Selection in CR RSF

Variable Importance

Filtering on the basis of the relevance of variables makes it possible to select (VIMP) variables. For a variable x, VIMP is calculated as follows. When we generate an alternative bootstrap sample from the training dataset, we ignore about 37% of the observations, consistent with conventional bootstrap theory. Out of bag (OOB) observations are those that have been excluded from the bootstrap sample, while in-bag observations are those that have been included. Compute the VIMP for the variable x by putting each OOB observation into the in-bag competing risk tree. Randomly assign child nodes when x split occurs. Each event-specific CIF is calculated and averaged. The VIMP for x is the j-specific prediction error CIF of j for the original ensemble event, subtracted from the prediction error for the new ensemble obtained using a random x assignment (Breiman (2001), Ishwaran (2007)). The IBS is used to calculate the prediction errors. Large importance levels suggest factors that are predictive, On the other hand, zero or negative values indicate unpredictable variables.

Minimal Depth

The Minimal depth algorithm evaluates the predictive power of a variable by the depth of the first split of the variable from the root node of the tree (Ishwaran, Kogalur, Gorodeski et al., 2010). The smaller this value, the more predictive it is of the other value. There are benefits to using a simplified approach when evaluating competing risks. First, the minimal depth approach is easier to use than using a VIMP model, which can determine an appropriate minimal depth level for a given set of variables. Second, can be use a single forest to identify all the variables that affect the probability of a long-term event, but it is also significant to identify the variables that are specific to the event. Demonstrates an easy way to combine minimal depth with cause-specific VIMPs.

3.4 Computational details

All the analyses were obtained by R (Version:4.2.1) statistical programming language and its packages. The packages are "survival", "riskRegression", "cmprsk", "randomforestSRC", "pec" and "prodlim". The software is immensely useful to generate suitable graphical plots that ease the comparison and makes inferences more lucid.

3. ILLUSTRATION FOR PBC DATA

PBC data were taken from "survival" package in R statistical software. This knowledge is derived from the clinical trial of primary Biliary Liver Disease (PBC) of the liver carried out among 1974 and 1984. A total of 424 patients with PBC, referred to prevention dressing Clinic during this ten-year period, met the eligibility criteria for the randomized, placebo-controlled trial of D-penicillamine. The analysis was based on 418 patients with 20 predictors in the data. Data description is given in Table 1.

Table 1: Description of Variable in Primary Biliary Cirrhosis (PBC) Data

VARIABLES	Description	CODE (Num, percentage)
age	Age in years	Min 26 years Max 78 years
albumin	serum albumin (g/dl)	
alk.phos	alkaline phosphotase (U/liter)	
ascites	presence of ascites	0 (288, 69) 1 (24, 6) NA (106,25)
ast	aspartate aminotransferase, once called SGOT (U/ml)	
bili	serum bilirunbin (mg/dl)	
chol	serum cholesterol (mg/dl)	
copper	urine copper (ug/day)	
edema	0 no edema, 0.5 untreated or successfully treated 1 edema despite diuretic therapy	0 (354, 85) 0.5 (44,10) 1 (20, 5)
hepato	presence of hepatomegaly or enlarged liver	0 (152,36) 1 (160,38) NA(106,25)
id	case number	1-418
platelet	platelet count	
protime	standardised blood clotting time	
sex	male/female	Male(44, 11) Female(374,89)
spiders	blood vessel malformations in the skin	
stage	histologic stage of disease (needs biopsy)(1,2,3,4)	1(21,5) 2(92,22) 3(155,37) 4(144,35) NA(6,1)
status	status at endpoint, 0/1/2 for censored, transplant, dead	0(232,55) 1(25,6) 2(161,39)

VARIABLES	Description	CODE (Num, percentage)
time	number of days between registration and the earlier of death, transplantion, or study analysis in July, 1986	41-4795
trt	1/2/NA for D-penicillmain, placebo, not randomised	1(158,38) 2(154,37) NA(106,25)
trig	triglycerides (mg/dl)	

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Results and discussion

First, To impute missing data, a random forest is grown and used. Create a forest and use it to retrieve data. External calculations such as ensemble calculations and error rates are disabled. Import PBC data with different levels of missing values. (When different quantities of missing values are present, PBC data are imputed.)
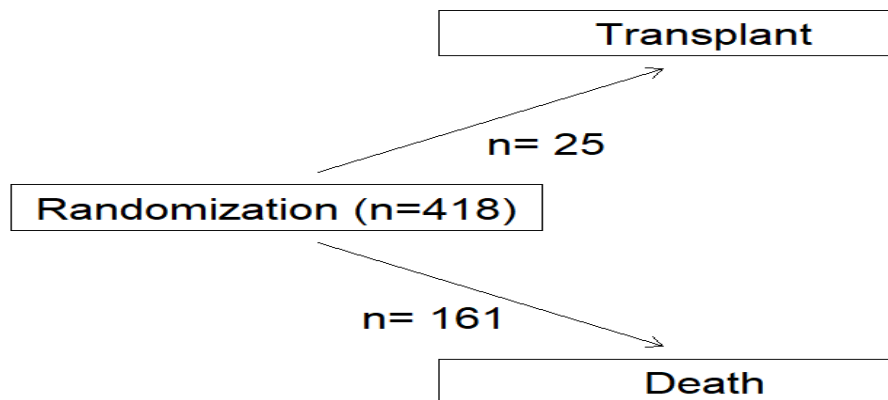

Figure 1. PBC Data: Competing *Risks Outcome*

In a competing risk study, 418 patients were followed using PBC data. Patients were treated with D-penicillmain, placebo, and non-randomized. The two types of events are Transplant and Death and the data is subject to right censoring. From the PBC data, it is observed that 25 patients are Transplant cause, 161 patients are death cause and remaining 232 patients are censored which is plotted in Figure1.

1000 trees are used to build a forest; each terminal node must have at least 15 observations; the number of randomly selected variables for splitting is 5, the number of randomly selected split points is 10, the splitting rule is logrankCR and swor bootstrap samples are obtained upon replacement. Finally, the internal error rate 0.1935(Transplant),

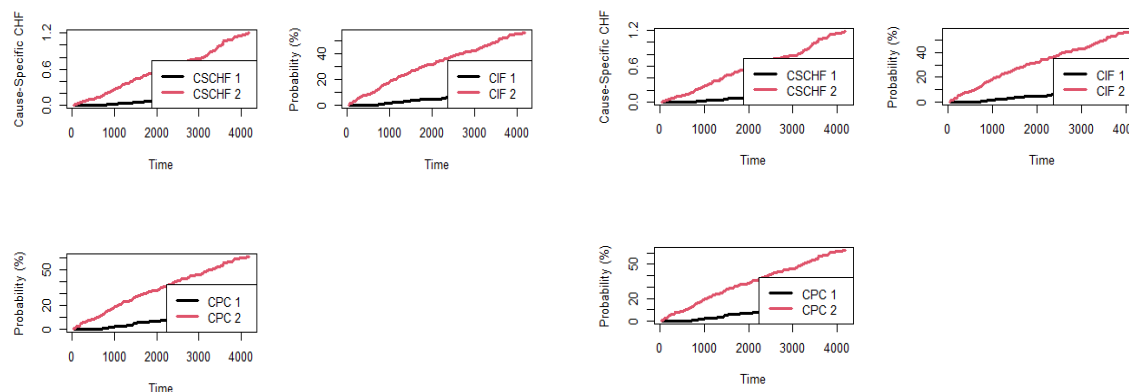Ramakrishnan.M / MACHINE LEARNING METHOD IN COMPETING RISK SURVIVAL MODEL

0.1632(Death) are calculated using OOB ensembles. Similarly, when using logrank splitting rule, error rates 0.2236 (Transplant) and 0.1676 (Death) are obtained respectively.

Gray's test splitrule = "logrankCR".   **Generalized log-rank test splitrule = "logrank".**

Figure 2: Averaged ensemble CSCHF, CIF and CPC from the PBC data using RSF

Figure 2 displays the averaged OOB ensemble CSCHF (cause-specific CHF), CIF and Conditional Probability Curves (CPC) for each event from a forest grown using the Gray and Generalized logrank splitting rule. The CIF for transplant and death is presented in Figure 2. From the above figure, the cumulative incidence probability of Transplant is lower than that of death, which is a competing event.

Table 3: Cause-Specific Cox regression models for PBC data

Variable	Units	Transplant			Death		
		HR	CI	p value	HR	CI	p value
trt	1						
	2	0.63	[0.26;1.48]	0.2871	0.91	[0.63;1.30]	0.5945
age		0.89	[0.85;0.94]	<0.001***	1.04	[1.02;1.06]	<0.001***
sex	male						
	female	0.54	[0.12;2.46]	0.4282	0.94	[0.57;1.56]	0.8199
bili		1.02	[0.90;1.16]	0.7137	1.08	[1.05;1.12]	<0.001***
protime		0.74	[0.42;1.30]	0.2987	1.24	[1.09;1.41]	<0.01**
hepato	0						
	1	3.05	[1.13;8.24]	<0.05*	2.06	[1.39;3.06]	<0.001***
spiders	0						
	1	0.37	[0.11;1.22]	0.1025	1.07	[0.72;1.61]	0.7316
edema	0						
	0.5	2.97	[0.73;12.11]	0.1290	1.21	[0.75;1.95]	0.4340
	1	0.00	[0.00;Inf]	0.9977	2.86	[1.50;5.45]	<0.01**

Variable	Units	Transplant			Death		
chol		1.00	[1.00;1.00]	0.4305	1.00	[1.00;1.00]	0.4161
albumin		0.22	[0.06;0.79]	<0.05*	0.51	[0.33;0.78]	<0.01**
copper		1.00	[1.00;1.01]	0.0564	1.00	[1.00;1.00]	<0.05*
alk.phos		1.00	[1.00;1.00]	0.1041	1.00	[1.00;1.00]	0.7372
ast		1.00	[0.99;1.01]	0.7365	1.00	[1.00;1.01]	0.0556
trig		1.00	[0.99;1.01]	0.8277	1.00	[1.00;1.00]	0.8604
platelet		1.00	[1.00;1.01]	<0.05*	1.00	[1.00;1.00]	0.9290
Note:1)*** has denote highly significant 2) ** has denote significant at 1% level, 3) * has denote significant at 5% level							

From the above table using cause specific COX PH model for all models, it is observed that the covariate hepato 0 have 3.05 times more hazard then the hepato1for Transplant. In Death it is 2.06 times more hazard for hepato1. When age is increased, the chance of transplant is decreased. But cause2 (Death) it is observed that when age increased the chance of death also increased.
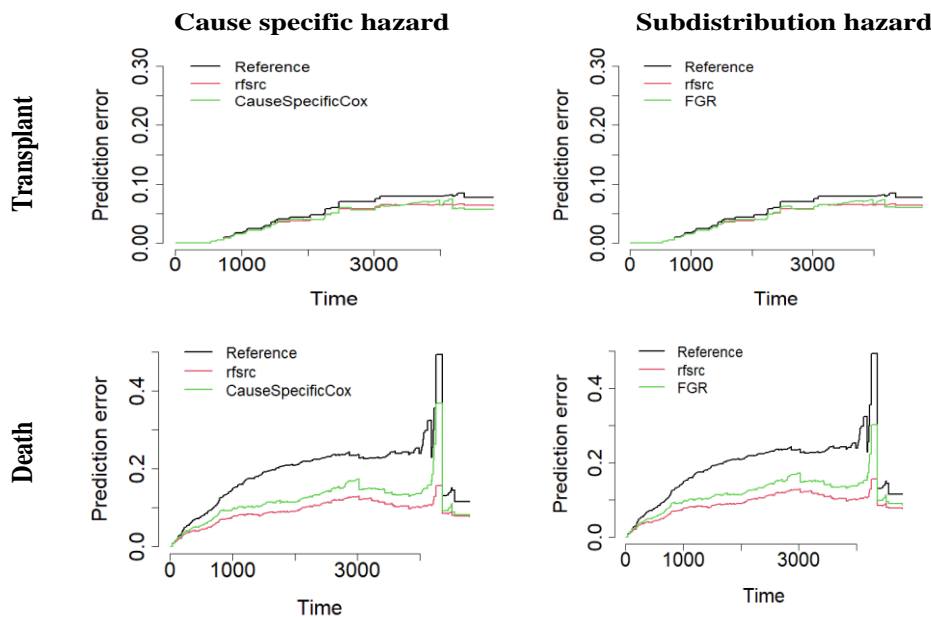

Figure 3: Prediction error curves for PBC data using applied methods.

We utilize the C-index and the prediction error specific through the IBS to assess prediction performance. The prediction error curves presented in the Figure 3 were used to find the performance of the models. Comparing RSF and cause-specific risk based on PBC data, two models use different sets of ideal covariates, making Cox's predictions more rigorous and importantly, determined by IBS. As we can see, the accuracy of Cox's prediction is low. As a

result, RSF appears to be a viable option to CR models. As seen in under all circumstances The RSF model outperformed its conventional predecessor.

Table 4: The IBS value for RSF, Cause specific and Fine-Gray models using PBC data

	CSH		FGH	
	Transplant	Death	Transplant	Death
Reference	0.05	0.189	0.05	0.189
rfsrc	0.042	0.089	0.042	0.089
CauseSpecificCox	0.041	0.118	0.042	0.117

The information for the two modelling methodologies, as well as the Kaplan-Meier model, a null model added by default, is shown in the table above. For the bootstrap, the combined Brier scores were obtained from 0 to 4795 days. In a single graph, for all four models (Figure 3).
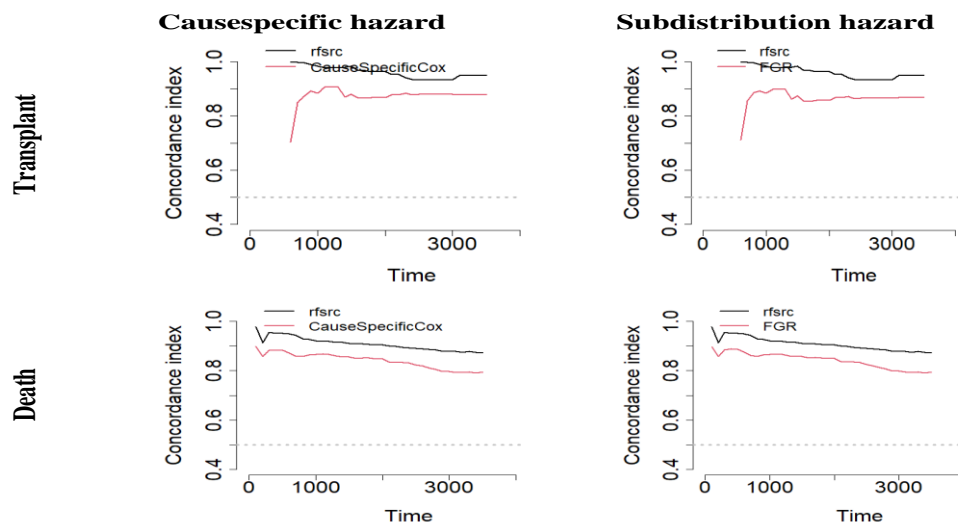

Figure 4: C index curve for PBC data using applied methods

Here, to access the match C-index is the frequency with which pairs match between all subject pairs. The discriminative power of a risk prediction model can be used to measure and compare its ability to discriminate between risks. The larger C index value is the better model prediction. It may be visible that the overall performance of RSF is higher than Cox which shown in the above figure.

Table 5: VIMP and minimal depth of the variables for PBC data

VIMP			Minimal Depth		
Variables	**Transplant**	**Death**	**Variables**	**Transplant**	**Death**
trt	0.0008(16)	0.0003(16)	bili	1.492(01)	6.536(01)
age	0.0544 (04)	0.0406(05)	copper	2.958(02)	7.464(05)
sex	0.0071 (13)	0.0018(14)	protime	3.384(03)	7.284(02)
ascites	0.0318(08)	0.0601(03)	edema	3.595(04)	7.678(06)
hepato	0.0286(11)	0.0179(09)	albumin	4.138(05)	7.300(03)
spiders	-0.0026(17)	0.0009(15)	age	4.773(06)	7.460(04)
edema	0.0316(09)	0.1106(02)	stage	4.829(07)	8.232(09)
bili	0.3269(01)	0.2249(01)	hepato	4.928(08)	8.645(14)
chol	0.0477(05)	0.0182(08)	chol	5.065(09)	7.794(07)
albumin	0.0094(12)	0.0314(06)	ast	5.162(10)	7.870(08)
copper	0.1096(03)	0.0449(04)	ascites	5.221(11)	8.437(12)
alk.phos	0.0046(14)	0.0041(12)	platelet	6.171(12)	8.305(10)
ast	0.0461(06)	0.0175(10)	trig	6.304(13)	8.433(11)
trig	0.0022(15)	0.0040(13)	alk.phos	6.391(14)	8.456(13)
platelet	0.0304(10)	0.0075(11)	sex	8.257(15)	8.882(17)
protime	0.1199(02)	0.0449(04)	trt	8.282(16)	8.863(15)
stage	0.0387(07)	0.0213(07)	spiders	8.364(17)	8.881(16)
( ) the number inside the bracket refers the order of important variable					

Larger values for VIMP and Smaller minimum depth values indicates better variable predictability. According to the above table, the maximum VIMP value for the event of interest is for bili (0.3269). Therefore, it is the top-ranking variable in Transplant. In addition, same variable for the competing event (death), the greatest value of VIMP is 0.2249.

However, based on minimal depth values, bili is the first important variable for transplant and death, while copper, protime, edoema, albumin, age, and protime, albumin, age, copper, edoema were the next most important variables for transplant and death, respectively.

4. CONCLUSION

In this paper, Traditional Semi Parametric COX and Machine Learning Technique Random Survival Forest models were applied to PBC real time data. Both models identified the important covariates and its effects on Survival time. Cause-

Specific Cox regression model and CR RSF techniques with two splitting rule i.e. log-rank and Gray's test applied to this study. In the study, the model was verified to predict using the C-index and the IBS. Using Performance indices C-index and IBS, Machine Learning Technique non parametric model performs well than traditional COX. The covariate age, hepato and albumin plays significant variables for both causes (Transplant and Death) while using Cause Specific Hazard Model. VIMP and Minimal Depth identified bili is the first important variable for transplant and death. Copper, protime, edoema, albumin, age are also the important variables for both causes. Finally, it is clearly observed that both models were identified the same covariates as the significant covariate but Machine Learning Technique CR RSF performs better than Semiparametric approach.

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