An Optimized Survival Prediction Method for Kidney Transplant Recipients

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***Abstract*—Human organ transplantation is a lifesaving process for many of the patients suffering from end stage diseases. Transplantation surgeons are often confronted with the question of the expected survival prognosis for this expensive and perilous process.The aim of the work is to identify an optimal model for predicting the survival of the recipient based on the available organ. This study identifies important features of the recipient and donor parameters for training the model. The study compares the performance of the Random Survival Forest (RSF), which is a machine learning method, and the Cox Proportional Hazard (CPH) model, which is a statistical model, to identify the more accurate model for survival prediction. Variations of the C-index, Brier score, and cumulative Area Under Curve evaluate the survival models considered. This study suggests that CPH which is a statistical method is a better option for forecasting graft and patient survival for an improved clinical outcome.**

Keywords—Cox proportional hazard model; random survival forest; C-index; brier score; area under curve; organ transplantation; survival prognosis

I. INTRODUCTION

Kidney transplantation is the only option for those patients identified that the dialysis is no longer a viable solution. According to Organ Procurement and Transplantation Network (OPTN), while there were 88,901 patients waiting for kidney transplantation in US, only 25,499 transplantations were performed in year 2022 [1]. In India, there are around 2 lakhs kidney patients waiting for transplantation per year. However only 10,000 transplantations are performed in a year [2]. Kidney from deceased donor has proven to be a better source to reduce the waiting time for the transplant recipients. There was a huge leap in the number of transplantations in United States due to increase in deceased organ donation. But the Delayed Graft Function (DGF) continues in an upward trend and occurred in 24% of adult kidney transplants in 2021 [3]. Increased DGF is a concern, as it increases the risk of acute rejection and death [4]. To reduce the risk of DGF by taking precaution in the selection of donor kidneys, minimizing cold ischemia time, and monitoring of the recipient after transplantation [5]. In this post pandemic era, especially as it is very difficult to procure an organ, transplant surgeon has to select an ideal recipient for the available organ. Despite having a variety of technologies and infrastructure, relatively little of it is used in such crucial life-saving procedures. The reason and motivation for selecting this topic for research work is mainly as a result of the lack of transplantable organs. As the availability of organs is very less, we have to make sure that each organ is allocated to the right recipient who can ensure maximize life expectancy. Computer algorithms which suggest the best match for a better survival prognosis helps to increase the success rate of post-transplantation.

Exploiting the new-age technologies to identify the correct recipient for the available organ helps to achieve a better survival prognosis. Sophisticated method helps to find a correct patient in less amount of time promoting interinstitutional organ transplantation without affecting the preservation time of the deceased organ [6]. Implementation of an organ harvesting and transplantation network using IoT and Blockchain improve the efficacy of the organ allocation system. It also monitors the pathophysiological changes in donors and recipients which help in improving the overall quality of organ transplantation [7].

There are numerous survival prediction algorithms that use statistical or machine learning algorithms which are suitable for respective field of study. Random Survival Forest is a machine learning algorithm which predicts by leveraging an ensemble of multiple decision tree. RSF is the machine learning method used for survival prediction particularly while handling complex, high-dimensional data and when making predictions is the key objective. Cox proportional hazard is the statistical method used for survival prediction particularly when there is censored data and when understanding the impact of covariates is the primary goal. The Cox Proportional Hazards (CPH) model and the Random Survival Forest (RSF) algorithm are both significant in the field of survival analysis and have distinct advantages and applications. Selection between them is usually based on the specific characteristics of the data and research objectives. The objective of this paper is to compare the accuracy of survival prediction done by CPH which is a statistical method with RSF which is a machine learning method.

The following section summarizes the review and key findings of related works. The following section after the literature review explains the details regarding the dataset and the methods used. In the material and method section selects the two most significant algorithms based on the review of papers involving survival prediction. The following sub-sections of evaluate the performance of the statistical and machine learning models. The discrimination assessment of the models is done by the calculation of Concordance-index. Time-dependent Brier score is as an alternative method to assess the calibration, of both the methods. Even though, Random

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Survival Forest and Cox's proportional hazards model were performing equally well in terms of discrimination (c-index) and in terms of calibration (IBS), there is notable difference in terms of time dependent Receiver Operating Characteristic (ROC) curve or the cumulative Area Under Curve obtained. This paper suggests CPH as an optimized survival prediction method for kidney transplant recipients.

II. Literature Review

Lentine, Krista L et al., [3] reflected in their paper that amid COVID-19 pandemic, the field of kidney transplantation faced both successes and challenges in broader geographic organ distribution. The United States witnessed a record number of kidney transplants, mainly due to the increase in deceased donor kidney donation. However, disparities in access to living donor kidney transplant persist, especially for non-White and publicly insured patients. Delayed graft function (DGF) continues an upward trend and occurred in 24% of adult kidney transplants in 2021. Five-year graft survival for deceased donor transplant was 88.6% versus 80.7% for recipients aged 18-34 years, and 82.1% versus 68.0% for recipients aged 65 years or older. The rate of deceased donor transplants among pediatric candidates recovered in 2021 from a low in 2020.

In this paper, the authors Grant, Shannon et al. evaluate various goodness-of-fit tests for the Cox proportional hazards model with time-varying covariates [8]. The Cox proportional hazards model is used in survival analysis to assess the relationship between covariates and the hazard rate. However, when the covariates are time-varying, traditional goodness-of-fit tests may not perform well. The authors propose and compare several alternative tests to assess the model's fit to the data. The key findings of the paper may include insights into the accuracy and reliability of different goodness-of-fit tests when applied to this particular scenario. This research is valuable for improving the assessment of how well the Cox model fits the data when dealing with covariate changes over time, which is a common occurrence in survival analysis studies.

Spooner, A., Chen, E., Sowmya, A. et al. did a comparative study of, ten machine learning algorithms that can perform survival analysis [9]. In this study performance and stability of high dimensional and heterogeneous clinical data was carried out. The researchers developed new prediction models that incorporated immunological factors, recipient, and donor variables, and compared their performance with conventional models. They analyzed data from 3,117 kidney transplant recipients in a multicenter cohort. The results showed that using a survival decision tree model significantly increased the accuracy of graft survival prediction compared to a conventional decision tree model. The occurrence of acute rejection within the first-year post-transplant found to be associated with a 4.27-fold increase in the risk of graft failure.

Yoo, K.D., Noh, J., Lee, H. et al. in their work discusses the challenges in analyzing data from clinical trials and cohort studies, particularly those related to dementia [10]. Such data is often high-dimensional, censored, and heterogeneous, making traditional statistical methods insufficient. Machine learning models that can predict the time until a patient develops dementia have become essential in understanding dementia risks. They offer more accurate results when dealing with complex clinical data. The study compares ten machine learning algorithms combined with eight feature selection methods to analyze high-dimensional and heterogeneous clinical data. The models predict survival to dementia using baseline data from two different studies: the Sydney Memory and Ageing Study (MAS) and the Alzheimer's Disease Neuroimaging Initiative (ADNI). The models achieved promising performance values, with a maximum concordance index of 0.82 for MAS and 0.93 for ADNI.

The authors K. Suresh, C. Severn, and D. Ghosh [11] discuss various types of discrete-time survival models, such as the Cox proportional hazards model, the logistic regression model, and parametric models like the Weibull and exponential models. The authors emphasize the potential benefits of using machine learning algorithms for more accurate and robust predictions, while also acknowledging the challenges and complexities involved in these approaches.

III. Methods and Materials

Random Survival Forest is a well-known Machine learning algorithms to explore the time to event, in order to study the survival prognosis. Cox Proportional Hazard is a classic statistical approach used on deidentified medical data which may have a high proportion of censored data. While handling censored observations, it can parallelly predict hazard ratio to investigate the association between covariates and survival time of a patient [12]. The aim of the study is to compare the accuracy of survival prediction of the two methods. Training using same dataset gives a better comparison of performance for both Random Survival Forest (RSF) model and Cox Proportional Hazard (CPH) model.

A. Dataset

The proposed study, use the dataset from United Network for Organ Sharing (UNOS). Standard Transplant Analysis and Research (STAR) files consist of de-identified patient-level information of the transplant recipients and waiting list applicants. The dataset covers patient information starting from January 10, 1987. For the purpose of research, a request sent to UNOS for the STAR dataset. UNOS allowed downloading of STAR dataset from file server on signing a non-disclosure agreement. The data for each type of transplantation covers various attributes of both recipient and donor including survival timeline information. A subset of about 2000 patient data, were used for the comparison study. Attributes selected for training the model includes five features of the transplantation data, along with one event indicator and another attribute indicating the time to event. The event indicator, PX_STATUS is labelled in four classes, to represent DEAD, ALIVE, RETX or LOST. Mapping to binary representation, the value 'False' assigned to ALIVE status and value 'True' assigned to remaining three status. The five features selected are age of the recipient (AGE), age of the donor (AGE_DON), BMI of the recipient (BMI_CALC), HLA mismatch number between recipient and donor (HLAMIS) and cold ischemia time (COLD_ISCH_KI) for the organ. The attribute time to event PTIME is the time interval between the transplantation date and the date at which the event happened, indicated in number of days.

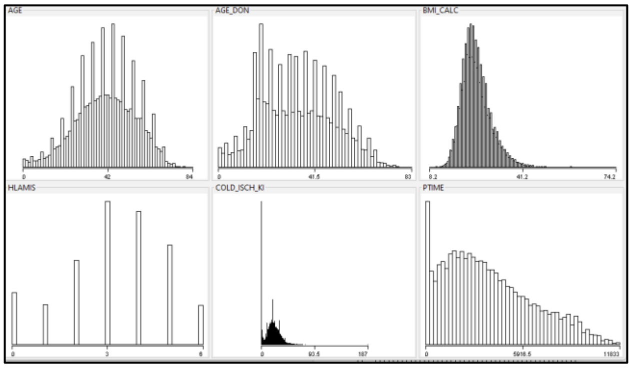

Fig. 1. Feature distribution against time.

Fig. 1 depicts the distribution of selected features against the time span event of patient survival time in days (PTIME).

B. Staistical Method based Analysis

Cox proportional-hazards (CPH) model is the statistical method to analyze the risk of several features towards the time to event. This method measures the hazard ratio of covariates on the survival of an individual. Hazard function h(t) or instantaneous failure rate shows the risk of an event occurring for an individual at any point of time [13]. In case of an individual who has undergone transplantation, the event can be death or re-transplantation at time t. Calculation of Hazard function h(t) is as follows [12]:

$$H(t) = H_0(t) \times \exp(b_1x_1 + b_2x_2 + b_3x_3 + \cdots + b_kx_k)$$

where $H_0(t)$ is the cumulative baseline hazard function and $x_1, x_2, \ldots x_k$ are the subset of predictor variables considered.

The calculation of survival function S(t), using CPH model is as follows [12]:

$$S(t) = \exp(-H_0(t) \times PI)$$

where PI, the Prognostic Index. Calculation of PI is as follows:

$$PI = x_1b_1 + x_2b_2 + x_3b_3 + \cdots + x_kb_k$$

Survival times are subject to right-censoring. Therefore, we need to consider an individual's event indicator (PX_STAT) in addition to survival time (PTIME) [14]. CoxPHSurvivalAnalysis is the python library which is fully compatible to do the required statistical analysis on the dataset and hence used in current analysis of data. PX_STATUS and PTIME are stored as a structured array. The first field is an indication of observed survival status. Occurrence of event indicated as, 'True' value, and 'False' value to indicate the remaining status. The second field denoting the observed survival time (PTIME), which corresponds to the number days between the transplantation date and the time of death (if PX_STATUS == 'True') or person contacted last time (if PX_STATUS == 'False').

Cox proportional-hazards model estimates the hazard ratio of a covariate and the effect on the survival of the patient. The extracted hazard ratio and specific distribution generates the survival time of a patient. Features are used to predict the survival time of an individual. The method overcomes the disadvantage of directly estimating survival time from censored data.

C. Machine Learning Method based Survival Analysis

Random survival forests, is an ensemble tree method for analysis of right-censored survival data. Predictions using Random Survival Forest predictions are an aggregation of the predictions of individual trees in the ensemble. Aggregation of the tree-based Nelson-Aalen estimators leads to the construction of the ensemble in Random Survival Forest [15]. The ensemble survival function from random survival forest is as follows:

$$\hat{S}^{rsf}(t|x) = \exp(-\frac{1}{B}\sum_{b=1}^{B} \hat{H}_b(t|x))$$

Corresponding to covariate value x, $\tilde{N}_b^*(s, x)$ is the count of the uncensored events until time s and $\tilde{Y}_b^*(s, x)$ is the number of risks at time s. The estimated conditional cumulative hazard function in each terminal node of a tree using the Nelson-Aalen estimator is as follows:

$$\hat{H}_b(t|x) = \int_0^t \frac{\tilde{N}_b^*(\mathrm{d}s, x)}{\tilde{y}_b^*(s, x)}$$

RandomSurvivalForest is the python library used for RSF model creation.

D. Performance Evaluation of Stastical and Machine Learning Models

Sample data of six real-world clinical datasets from UNOS evaluates the performance of Cox proportional-hazards model and Random survival forests. Table I shows the clinical dataset used for the analysis. The discriminatory power of five features used to evaluate the predictions done by these predictive models. 20% of training data assess the prediction of the model to predict the survival of a patient after transplantation.

TABLE I. SAMPLE DATA – UNOS DATASET FOR THE FEATURES

	AGE	***AGE_DON***	***BMI_CALC***	***HLAMIS***	***COLD_ISCH_KI***
Sample 1	4	30	21.3	4.0	1.0
Sample 2	10	27	21.3	6.0	9.0
Sample 3	14	5	16.0	5.0	37.0
Sample 4	72	37	22.5	3.0	2.0
Sample 5	72	16	24.1	2.0	17.0
Sample 6	72	62	22.4	5.0	21.0

Graphs generated visualized the evaluation of the results for the given dataset.

a) Survival Probability Graph: The survival probability graph in Fig. 2 shows the probability of survival against the number of days, using Cox Proportional Hazard model.

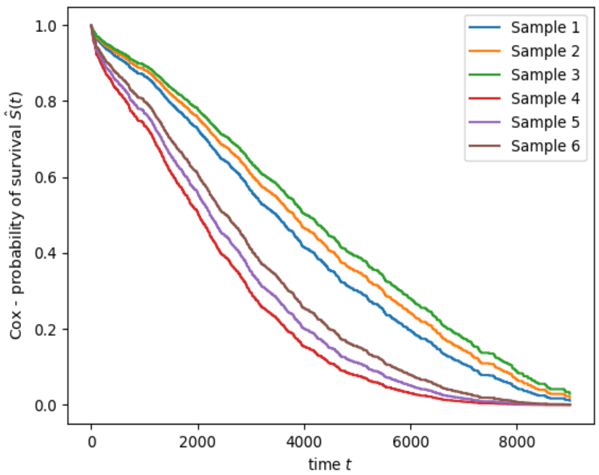

Fig. 2. Probability of survival using Cox PH.

The survival probability graph in Fig. 3 shows the probability of survival against the number of days, using Random Survival Forest model.

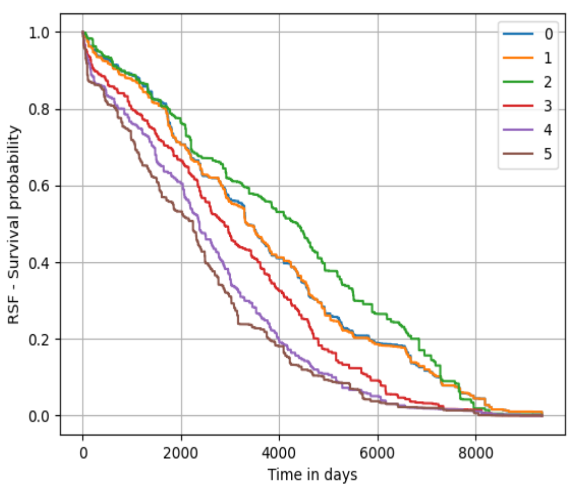

Fig. 3. Probability of survival using RSF.

Fig. 2 and Fig. 3 show that younger recipient is having more survival rate in comparison to older recipient. Both CPH and RSF show similar trends.

b) Hazard Graph: The graph in Fig. 4 shows the Cumulative hazard function against survival time in days, using Cox Proportional Hazard model. The graph in Fig. 5 shows the Cumulative Hazard function using Random Survival Forest [16].

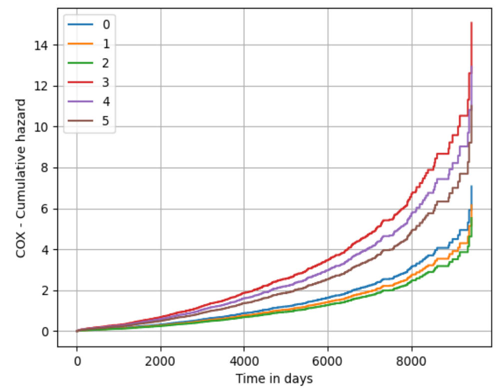

Fig. 4. Cumulative hazard using Cox PH.

Cumulative hazard function reconfirms the finding identified in the survival probability graph.

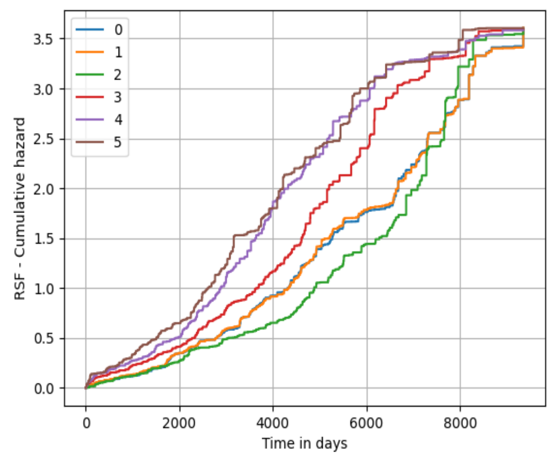

Fig. 5. Cumulative hazard using RSF.

c) Permutation Importance: The feature importance of estimators for a given dataset is determined by the permutation importance function. The permutation feature importance measures the increase in the prediction error of the model as a result of permuting the values of a feature. Computation of the permutation importance [17][18], i_j for the feature f_j, is as follows:

$$i_j = s - \frac{1}{k}\sum_{k=1}^{K} s_{k,j}$$

where, s is the reference score for the data D, on predictive fitted model m, calculated for K repetition for each feature f_j. The results of permutation feature importance for both the model shows that age of the recipient variable is the main driver of prediction. The variation of data in these columns causes the mean square error in both models to increase. Compared to CPH model, RSF model depends mostly on this variable. Table II shows the permutation feature importance of CPH model and Table III shows the same using RSF model.

TABLE II. PERMUTATION IMPORTANCE-CPH

Permutation Importance-CPH		
	Importance mean	**Importance std**
AGE	0.024935	0.016718
AGE_DON	0.023710	0.012844
BMI_CALC	0.002368	0.007720
HLAMIS	-0.001456	0.002062
COLD_ISCH_KI	-0.005284	0.007599

TABLE III. PERMUTATION IMPORTANCE-RSF

Permutation Importance-RSF		
	Importance mean	**Importance std**
AGE	0.049249	0.019136
AGE_DON	0.015333	0.006105
BMI_CALC	0.003339	0.003046
HLAMIS	0.001181	0.004930
COLD_ISCH_KI	0.000656	0.004182

d) Concordance Index (C-Index): C-Index or C-statistic is a measure of predictive accuracy of a model particularly used for survival analysis. C-Index value indicates, a higher risk should result in a shorter time to the adverse event. Therefore, if a model predicts a higher risk score for the first patient ($\eta_i > \eta_j$), we also expect a shorter survival time in comparison with the other patient ($T_i < T_j$).

$$c = \frac{\Sigma_{i,j} I(T_i > T_j) \cdot I(\eta_j > \eta_i). \Delta_j}{\Sigma_{i,j} I(T_i > T_j) \cdot \Delta_j}$$

Split the dataset in training and test sets. Fit the models on the training set. Evaluate the model performances (C-index) on the test set. The desirable values range is between 0.5 and 1. Closer the value towards 1, the more the model differentiates between early events (higher risk) and later occurrences (lower risk). The C-index maintains an implicit dependency on time [19]. The C-index becomes more biased when the amount of censoring is more [20]. CPH gave a Concordance Index of 0.5505 while using RSF, the C-index is calculated as 0.5427. As the number shows CPH gives a better performance than RSF in terms of C-Index.

e) Brier Score: Brier Score or Brier Probability score is a measure of the accuracy of the forecast done by a model. The score particularly evaluates the probabilistic prediction. The time-dependent Brier score is an extension of the mean squared error to right censored data. Inverse probability of censoring weights ($1 / \hat{G}(t)$) and the model's predicted probability of upcoming events up to the time t ($\hat{\Pi}(t|x)$), estimates the Brier score as given below [21].

$$BS^{\wedge}(t) = \frac{1}{n}\sum_{i=1}^{n} 1 \frac{\hat{s}^2(t|x_i) I\{T_i \le t\}\delta_i}{\hat{G}(T_i - |x_i)} + \frac{\left(1 - \hat{s}(t|x_i)\right)^2 I\{T_i > t\}}{\hat{G}(t|x_i)}$$

The integrated Brier score at time T is as follows:

$$IBS(T) = \frac{1}{T}\int_0^T BS(t)\,\mathrm{d}t$$

Lower values for the Brier score indicate better prediction performance. Using the Brier score we can calculate the continuous rank probability score (CRPS), defined as the Integrated Brier Score (IBS) divided by time. CPH gave an Integrated Brier score of 0.1958, and 0.1967 while using RSF. In terms of Brier Score, both CPH and RSF are equally performing, however CPH is having slightly better prediction performance.

f) Receiver Operating Characteristic Curve (ROC): Another performance metric to compare the models is time dependent ROC curve [21]. The time-dependent ROC curve is a graphical representation used in survival analysis. This is used to evaluate the performance of predictive models designed to estimate the probability of an event occurring at a specific time in the future. It is also known as the dynamic or cumulative Area Under the Curve (AUC). In the graphical representation of the curve, the x-axis represents time, and the y-axis represents a measure of the model's performance at that specific time. As seen in the Fig. 6, the CPH performance is better than the RSF. The mean value for CPH is 0.602 which is higher than the RSF mean 0.568.

Evaluation of Cumulative hazard function at a time interval of 1000 days calculates the time-dependent risk scores. The plot of CPH shows that the model is doing moderately well on average, with an approximate AUC of 0.602. However, there is a clear difference in prediction performance between the AUC curve of RSF and that of CPH. The performance prediction on the test data increases 15 years after the transplantation surgery. It remains high during the initial 4 to 5 years soon after the surgery and also after 15 years of transplantation. Thus, we can conclude that the model is most effective in predicting death both at the low-term and at high-term using the time-dependent AUC curve.

CPH classify and prioritize parameters using multivariate analysis. The model considered the parameters prioritized for the risk of hazard by Cox Proportional Hazard model. These include CIT, Age of the recipient, HLA mismatch, and BMI calculated. Cox proportional hazard prediction model predict survival days. Prediction accuracy of models evaluated by comparing the predicted survival graph against the actual survival days available as part of the UNOS dataset. Including a fitted model-based prediction in the current allocation policy can enhance the outcome of organ transplantation.

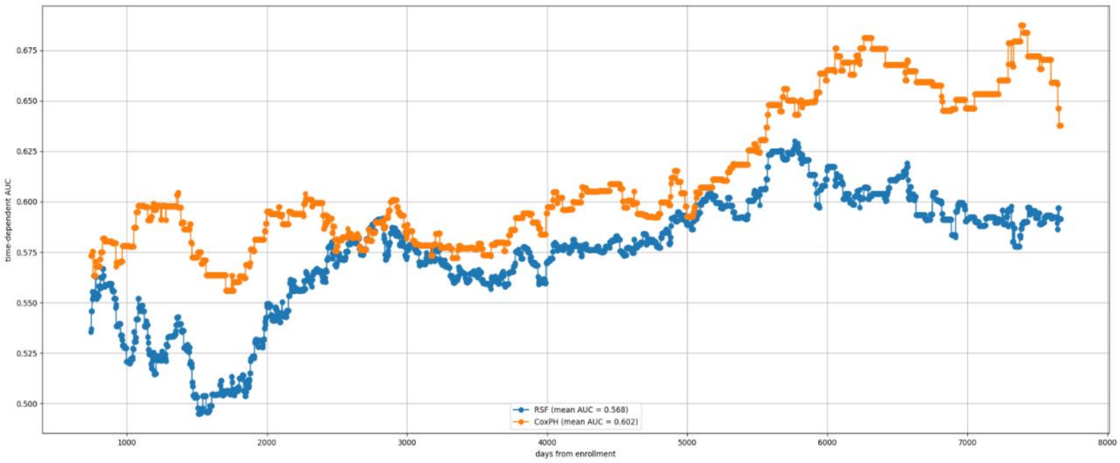

Fig. 6. Comparison of mean AUC -CPH and RSF.

IV. Results

Comparing the result with the predictive performance of the Random Survival Forest model, the Cox proportional hazard model performs impartially better on average, mostly due to the better performance in the intervals 4–5 years, and 15–20 years. Even during the period above 5 years, CPH has equally or better performance than RSF. This shows that even though it is convenient to assess overall performance, using mean AUC, even without considering the mean AUC, CPH is a better method to predict the survival prognosis of transplant recipients.

V. Conclusion

For evaluating survival models considered, variations of the C-index, Permutation Importance, Brier Score, and Cumulative AUC curve proposed over the time are analyzed [21]. The result indicates that both models perform equally well, achieving a concordance index of ~0.55. Evaluation of the prediction of the models is done using alternative methods. Time-dependent Brier score assess the discrimination and calibration, of both the methods. Here again, both the models had the same score of ~0.196. Despite Random Survival Forest and Cox's proportional hazards model performing equally well in terms of discrimination (c-index) and in terms of calibration (IBS), there seems to be a notable difference in terms of time dependent ROC curve or the cumulative AUC. The mean value of AUC with Cox's proportional hazards model outperformed Random Survival Forest. Thus, this paper suggests CPH as an optimized survival prediction method for kidney transplant recipients.

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