CLINICALLY USEFUL MEASURES IN SURVIVAL ANALYSIS: THE RESTRICTED MEAN SURVIVAL TIME AS AN ALTERNATIVE TO THE HAZARD RATIO

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ABSTRACT: Hazard ratios are ubiquitously used in time to event applications to quantify treatment effects. Although hazard ratios are invaluable for hypothesis testing, other adjusted measures of association, both relative and absolute, may be used to fully appreciate studies results, especially when the assumption of proportional hazards does not hold. In the following we will show the use of restricted mean survival time, a measure of association that received a lot of attention in the last years, estimated through the follow-up time. Direct regression models on RMST and Machine Learning approaches are available. Examples will be used to illustrate the different approaches.

KEYWORDS: restricted mean survival time, machine learning, direct regression.

1 Introduction

Restricted mean survival time (RMST) differences between groups have been advocated as useful measures of association in time to event studies. In fact, while the ubiquitously used hazard ratios are invaluable for hypothesis testing, measures of association based on RMST, both relative and absolute, may have a more plain clinical interpretation and help to fully elucidate study results.

Many recent contributions focused on estimates of the difference in RMST through follow-up times, instead of using a single time horizon. The resulting curve can be used to quantify the association in time units. Moreover regression models have been developed to directly regress RMST on covariate patterns. These methods are based either of IPCW or on pseudo-values (PV). In particular, the method based on PV is easily implementable with available software and makes possible to adopt Machine Learning methods, such as the Deep Neural Network (DNN) proposed by Zhao, 2021.

We investigated the ability of DNN to account for complex covariate patterns, such as interactions, using literature data as done in Ambrogi *et al.*, 2022.

2 Methods

In survival analysis the time T elapsed from an initial event to the possible occurrence of a terminating event is analysed. Generally, only a right-censored version of the random variable T is observe. Therefore, instead of the mean value of T the τ-restricted mean survival time (RMST) is used:

$$RMST(\tau) = \int_0^\tau S(t)dt \tag{1}$$

where $S(t) = P(T > t) = \exp(-\int_0^t \lambda(u)du)$ is the survival function and $\lambda(t)$ is the hazard function. The $RMST(\tau)$ represents the expected lifetime over a time horizon equal to τ. The $RMST(\tau)$ can be estimated non-parametrically based on the Kaplan-Meier estimator or model-based.

Direct regression of RMST as a function of covariate values was studied by Tian *et al.*, 2014, based on inverse probability of censoring weighting, and by Andersen *et al.*, 2004 based on pseudo-values.

A joint model for several τ-values, $\tau_1, \ldots, \tau_j, \ldots, \tau_M$, including an interaction term between the treatment and a function, $f(\cdot)$, of time, to model a time-varying treatment effect is

$$g(RMST(\tau|Z)) = h(\tau) + \beta Z + \gamma Z f(\tau). \tag{2}$$

Commonly used link functions are the **log**, the **logit** or the identity function. Estimation based on pseudo-values is discussed in Ambrogi *et al.*, 2022, while estimation based on IPCW is presented in Zhong & Schaubel, 2022.

Recently a deep neural network (DNN) model was presented for RMST prediction by Zhao, 2021 called DnnRMST. The DNN is based on pseudo-values estimated at multiple times during the follow-up and optimized using MSE. The DNN consists of an input layer, some hidden layers and a multiple output layer with M nodes, for the pseudo-values at the different times. The DNN can be implemented using the Keras library in R (Allaire & Chollet, 2022). Hyper-parameters can be selected using a random grid search over the number of nodes, dropout regularization, ridge regularization and learning rate.

3 Results

Data of a double blind randomised clinical trial studying the effect of prednisone versus placebo on survival in patients with liver cirrhosis, already used for RMST estimation in Andersen *et al.*, 2004, were used to illustrate the methods. The CSL1 trial showed an interaction effect between treatment and presence of ascites, as illustrated in figure 1. Top panels show patients without ascites, while bottom panels show patients with ascites. Left panels show the KM survival curves for treated and control groups. The central figure panels show the non parametric estimate of RMST for treated and control groups. Right panels show the difference between RMST curves for treated vs control groups estimated non-parametrically (solid line), with the direct model with pseudo-values (dotted) and with DnnRMST (red). It is possible to see that, even if the interaction is captured by the DNN, the estimates are not in lines with those of the non-parametric estimators.

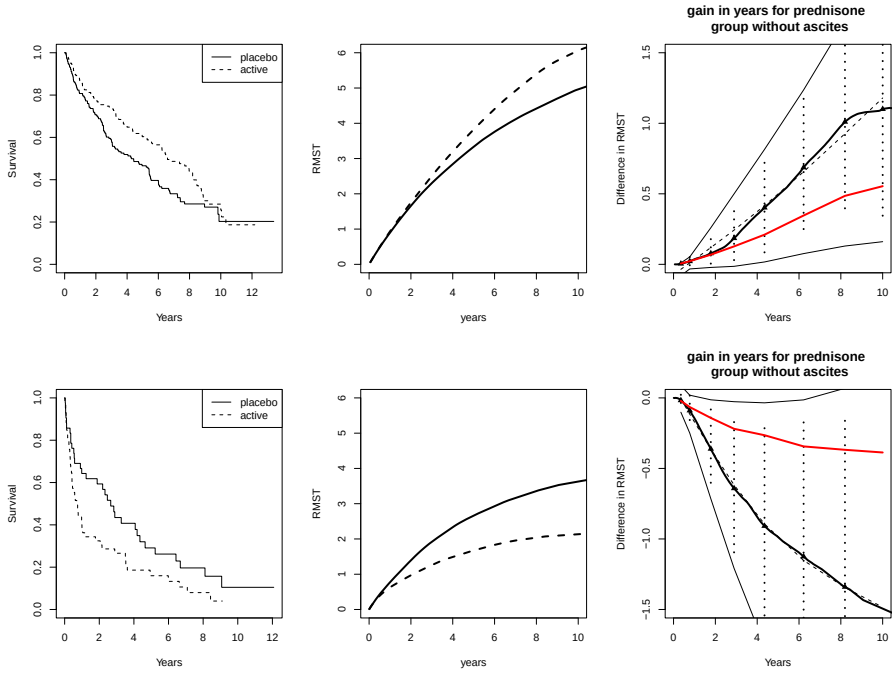

Figure 1. *Comparison of the nonparametric estimate of RMST with the one obtained using direct regression models and DnnRMST.*

4 Discussion

RMST has received a lot of attention in recent years. A possibility introduced for the first time by Royston & Parmar, 2011, is to estimate the difference of RMST curve through the time, to appreciate how the treatment comparison is evolving through time. Different regression methods have been proposed to estimate RMST as a function of time and Machine Learning techniques are also available. One interesting aspect is that of sample size. In fact, ML is in principle able to learn directly from data at the cost of hyper-parameters optimization. However, learning is data expensive and evaluating at which sample size the ML models are able to correctly reproduce complex data pattern is an open research question.

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