Survival Analysis of TCGA Liver cancer expressed gene transcript

Sailendra Pradhananga (sailendra.pradhanaga@scilifelab.se)

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1 Introduction

Survival analysis are statistical toolkits that are used to analyzing the outcome of variables based on time period of event occurrence. The event could be either be death, outbreak of disease or failure of automobile parts which are then followed specified time period in days, weeks or years. The major part of the these type of data involves two kinds of variables: first is the time to event and second whether the event have occurred or not. Based on different methods such as non parametric model such Kaplan Meier method or regression model such as cox proportional hazards two function, survival function and hazard function. The survival function gives the probability for each time-points of surviving up to that events while hazard function whether the event has occurred or not given the individual has survived or not. The main aim of these type of analysis is find the relationship between the survival time and variables under study such as drugs, gene expression, treatment either with different covariates such as age, gender, race.

In the current project, we are provided a liver cancer patients of different races dataset survival time and gene expression dataset of various grades. The main aim was to model the data with survival model in order find the potential prognostic marker for survival of patients using Cox Proportional Hazard models. Additionally, using the multiple hypothesis correction we predicted 4698 gene transcripts at 0.05 FDR.

2 Method

2.1 TCGA Dataset

The TCGA dataset for the analysis was download from the (http://kaell.org/files/survivalLIHC.txt) site. As already stated in the project guidelines, these are the cancer patient expression data from the sequenced liver tumor. Additionally there are few other features implication each cancer patient ethnicity, sex and cancer types. These data were first read into python notebook as pandas data frame as done in jupyter notebook. Additional exploratory analysis was done in the notebook itself. The dataset consists of both categorical features and numerical data of gene expression dataset.

2.2 Preprocessing of Dataset

In the survival analysis, the different categorical features were provided of liver cancer patients. These categorical features includes Gender, Race, Stage , Status, Age and LivingDays of different cancer patients. These categorical features were then coded into different numerical codes . Originally, the dataset consists of gene expression profile os $19,571$. Furthermore, only those gene expression data were taken which had at least an expression in one of the patients.

2.3 Cox proportional Hazard model

Cox proportional hazards regression, used to relate several risk factors or exposures, considered simultaneously, to survival time. In the current project we used the implementation of Cox regression hazard model implemented on lifelines packages. Although I had tried including other covariates such as age and temperature to be used in the model, at this phase we have used individual expression of each gene transcript iteratively in order to get hazard function and survival rates of each gene transcripts. Based on proportional hazard model we get an p-value estimates of gene transcript. However not all the gene transcripts fitted into the Cox survival model thus we excluded to get final list of pvalues for each transcripts.

2.4 Multiple testing correction

As discussed in earlier exercises we have implemented multiple testing correction for all the p.value estimates of gene expression for liver cancer to occur. However since we are testing multiple features, the pvalue < 0.05 might be too lenient estimates. Hence based on storey and tribasni papser [] an q value estimates were made of all the pvalues calculated. We fitted the cubic spline in the π_0 estimates in the given λ values.

3 Result

3.1 TCGA Liver Cancer cohort characterstics

The cancer cohort consists of different phenotypic features such liver cancer types, age, gender, which are further summarized in table 1 . Importantly, the important dependent variable is the status of an patient cohort and the living days which is the measure of the time of survival.. The average living days for alive patient cohort is 896.80 while for dead sample cohort is 655.21 with pvalues < 0.001 as figure 1

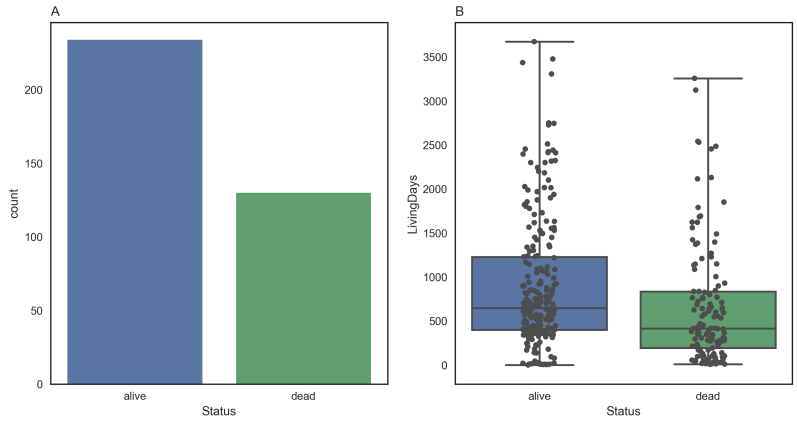

Figure 1: A) Number of alive and dead patients in the liver cancer cohort, the number of alive patients are nearly twice as many as dead patients. B) Distribution of living days in two status group , alive and dead.

Summary statistics of TCGA liver cancer cohorts	
Gender	
male	245
female	119
Race	
white	182
asian	154
black or african american	17
not reported	10
american indian or alaska native	1
Liver cancer stage	
stage i	170
stage ii	83
stage iiia	63
not reported	24
stage iiic	9
stage iiib	8
stage iii	3
stage ivb	2
stage iv	1
stage iva	1
Status	
alive	234
dead	130

Table 1: Summary Statistics of TCGA liver cancer cohort

3.2 Gene expression survival analysis with Cox regression model

The survival analysis requires the time period for the event to occur (in our case death). Thus , in liver cancer cohort variable living days was taken as time variable with status as hazard event. However, other variables had NA available some categorical features so these were not taken into consideration while building Cox regression hazard model implementation in lifeline module in python. Each transcript was taken as dependent variables in the model which gave us survival probabilities and cumulative hazard estimates for each transcript as shown in the figure 2. However not all the gene transcript ran into the model as these gene expression were spares and had missing expression data. These 130 features were excluded from the current analysis. The cox regression model was run in 19219 gene transcripts completely which gave us hazard, survival function. These estimates provided the p-values as the measure of the significance of gene expression

as prognostic marker for liver cancer survival. Out of 19219 gene expression 6032 gene expression was considered significant at p-value < 0.05. However these are raw p-value without taking into account Cox regression model was run for 19219 features.

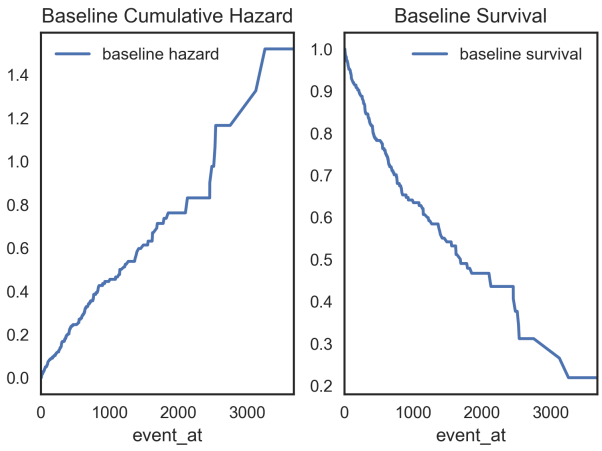

Figure 2: Pictures of animals

3.3 Multiple hypothesis correction

3.3.1 Estimating π_0 estimates on pvalues

Storey and Tibshirani [**?**] provided the mathematical implementation for false positive discovery rate.

3.3.2 Estimation of expression levels based on FDR

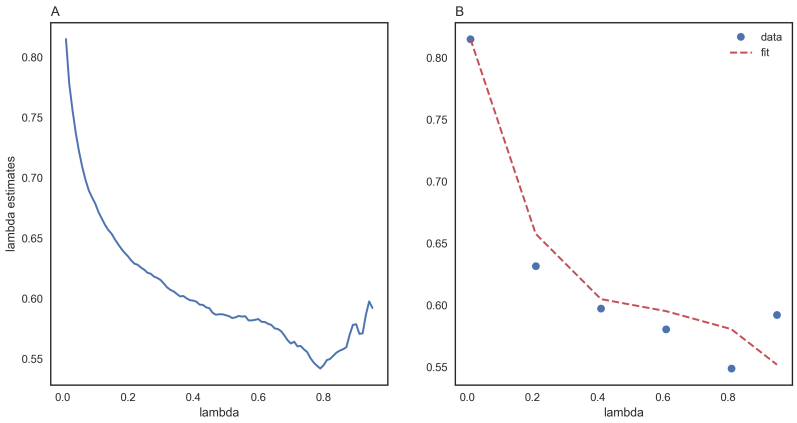

Figure 3: Pictures of animals

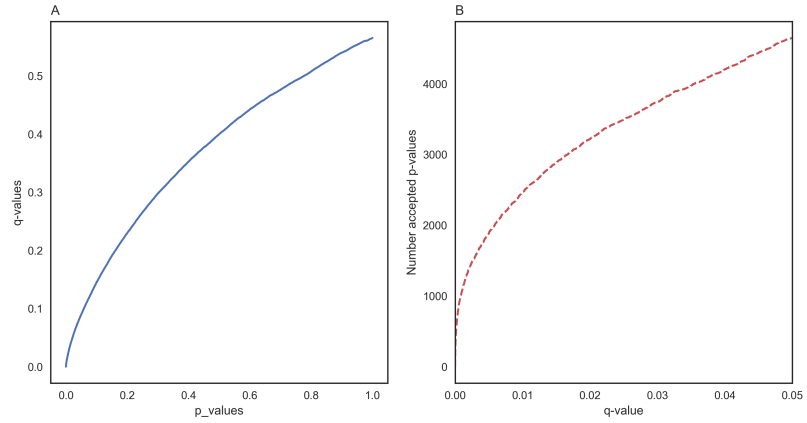

Figure 4: Pictures of animals