Stats 504 Assignment 2: Diabetic Retinopathy

Introduction

Diabetic retinopathy is a diabetes complication that can cause complications with eyes, resulting in loss of vision. This report compares the results of two laser coagulation treatments which attempt to delay the onset of diabetic retinopathy. The findings from this analysis are intended to enable the researchers from Michigan Medicine to quantify the efficacy of both treatments. The report also addresses specific questions of interest such as the influence of age and pre-existing clinical risk of loss of visual acuity on whether a patient loses vision. It is found that both treatments are effective in delaying the onset of diabetic retinopathy, but there is no statistically significant difference between the two treatments.

Methods

The goal of the analysis is to quantify efficacies of the Xenon and Argon laser treatments, as well as provide insights on the effect of other variables on a patient's chance of going blind. Considering that the data was "censored" (meaning that times at which each patient lost vision was not available), a survival analysis model seemed most appropriate in terms of methodology. Survival Analysis modeling attempts to explain the time it takes for an event to occur, which in this case, is the event of losing vision in an eye. More specifically, a Proportional Hazards Survival model is used, as this is able to describe the effect of a unit change in covariates (like treatment group, age, etc) in terms of a multiplicative, which is in line with the requirements of this problem space. However, proportional hazards modeling must be performed with care. In case of paired data such as the one used in this study where each subject provides data for two eyes, a frailty parameter must be added to account for the inter-dependence caused by the paired data. This frailty model is further detailed in the appendix.

As a visual aid (presented in the following section) of trends in patients' vision loss, a Kaplan-Meier curve can be fitted to the data. This depicts the "survival function" of the data, which is the probability of the event in question occurring at any given point in time. For this study, this translates to the probability of a patient losing vision at any given point in time. These curves can be plotted for both the Xenon and Argon treatments, and then contrasted with their respective control groups to get a graphical idea of which treatment works, and if applicable, which one is better. Furthermore, a log-rank test can also be performed to evaluate the statistical differences between the curves in the Kaplan-Meier figure.

Finally, the coefficients resulting from the modeling can be interpreted as multiplicative factors affecting the risk of losing vision, and this is described in the following section.

Results

The data provided by the researchers follows 197 clinic patients, with each patient contributing two rows to the data. Each row provides information about the type of laser treatment received, and the eye it was received on, along with other covariates described in Table 1. The data was clean and no pre-processing or data cleaning was necessary to prepare the data for analysis. The analysis was finally performed on 394 different rows (197 pairs) with each row having 7 different features which are further described below.

Feature	Median (IQR) / Percentage
ID	197 unique subject IDs
Laser	
Xenon	200 (51%)
Argon	194 (49%)
Age	16 (10, 30)
Age Type	
Juvenile	228 (58%)
Adult	166 (42%)
Treatment Group	
Status - Lost to Follow Up	143 (72.5%)
Status - Loss of Vision	54 (27.5%)
Control Group	
Status - Lost to Follow Up	101 (51%)
Status - Loss of Vision	96 (49%)
Follow Up Time	38.8 (13.9, 54.2)
Risk of Loss of Visual Acuity	10 (9, 11)

Table 1: Baseline table indicating summary statistics of data used in the analysis

For the Cox Proportional Hazard model, the response variable i.e the variable we are interested in, is the pair of the Follow Up Time, and the Status. These data points, in conjunction, inform whether a patient reported loss of vision, and if so, after how long in the study. In case the study ended, or the patient became deceased before losing vision, those rows were assigned the “Lost to Follow Up” status, and the Follow Up Time refers to the last follow up the patient had. The Age Type variable remained unused in this analysis, as it provides no new information (mathematically) due to the presence of the Age variable which encapsulates the same information. Finally, the Risk variable indicates the pre-existing risk of a patient losing vision (or visual acuity) in an eye. Owing to no further information about the specifics of this value, it is assumed reasonably that the higher this value, the higher the chance for the patient to lose visual acuity in that eye.

In Figure 1, the Kaplan-Meier curves indicate the probability of retaining vision across time, for each of the groups of interest. It is evident that the two treatment groups, for Xenon and Argon, are distinct from their corresponding control groups, thereby indicative of a positive effect from the laser treatments. This can further be confirmed and quantified by fitting the Cox Proportional Hazard model, and is depicted below.

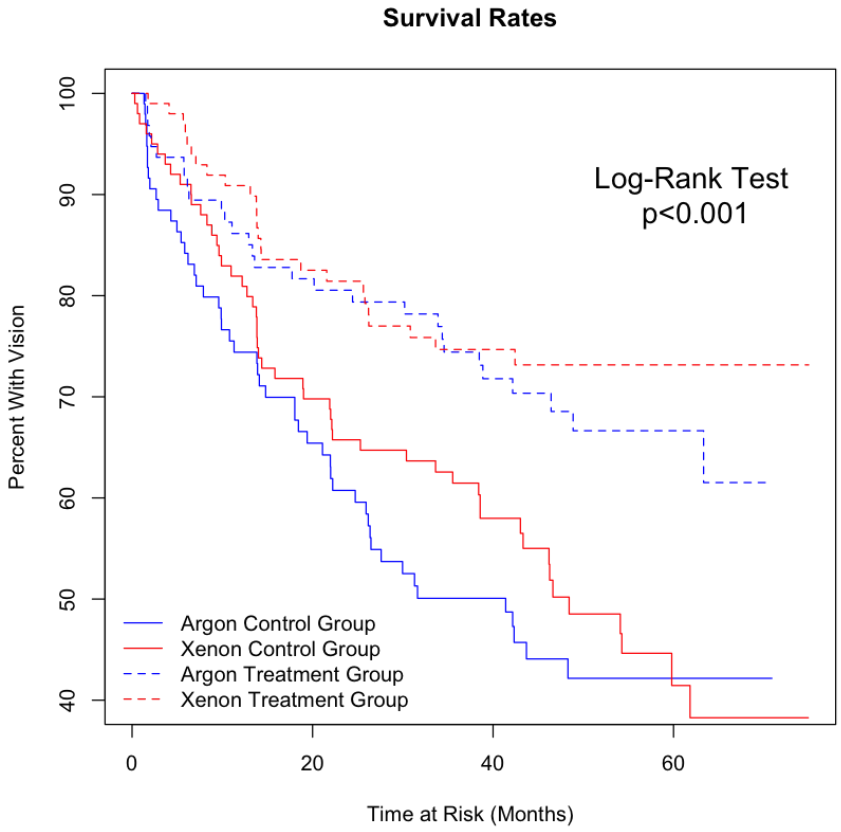

Figure 1: Kaplan-Meier curves indicate that the probability of retaining vision is higher for the two treatments, as compared to the control groups.

The log-rank test is a statistical test to check the validity of the Kaplan-Meier curves. A p-value of less than 0.05 (as observed in Figure 1) indicates that at least one of the curves is significantly different from the others. This could indicate one of two things. Either the significantly different curve is one of the treatment curves, as compared to a control curve, or it could be a statistically significant difference between the two treatment curves, indicating a difference in efficacies of the treatments. To confirm this hypothesis, the Cox Proportional Hazard model is fitted, and results are presented below.

Covariate	Hazard Rate 95% CI	p-value
Treatment (Either Xenon or Argon)	0.38, (0.24 0.62)	<0.001
Treatment Xenon compared to Argon	1.07, (0.54 2.11)	0.85
Risk	1.18, (1.03 1.36)	<0.01
Age	1.007, (0.99 1.02)	0.36

Table 2: Model parameters indicating the Hazard Rate for each covariate.

As the table suggests, Age is a statistically insignificant variable, implying that a change in age does not necessarily affect the time at which a patient loses visual acuity due to diabetic retinopathy. To similarly interpret other parameters, the pre-existing risk of loss of visual acuity is statistically significant, and has a hazard rate of 1.18. In other words, this means if all other covariates were the same between two eyes, an increase of 1 unit in the risk would result in an 18% higher chance of loss of vision. the hazard rates of the treatment effects can be interpreted.

To address the primary research question about the efficacy and quantification of the two treatments, the hazard rates can be interpreted as follows. Receiving either kind of laser treatment, implied a 62% lower chance of loss of vision, whereas the effect of receiving the Argon treatment as opposed to the Xenon treatment was statistically insignificant, and does not seem to affect the risk of losing visual acuity.

In other words, both treatments seem to work in delaying the onset of diabetic retinopathy. However, there is a lack of evidence to statistically claim either treatment performs better than the other.

Conclusion

This report presents the results of an analysis performed on clinic patients' eye treatment data, with the objective of trying to understand the efficacies of both the Argon and Xenon laser treatment. It also addresses the key questions posed by the client regarding specific features of interest like the Age of the patient, and their pre-existing risk of loss of visual acuity. The analysis reveals that Age is not a statistically significant factor, while the pre-existing risk increases chances of losing visual acuity by a multiplicative factor of 1.18. Also, while both the laser treatments show evidence of having the desired effect (reducing risk of losing vision by 62%), there is not enough evidence to suggest one of the laser treatments can be preferred over the other due to a higher efficacy.