Understanding the impact laser eye treatments have on delaying diabetic retinopathy

Introduction

Diabetic people tend to struggle from various illnesses caused by the disease including complications of the heart, nerve damage, and eye damage - also known as diabetic retinopathy. Diabetic retinopathy can worsen if left untreated, potentially leading to complete blindness. For this reason, a medical study conducted by Michigan Medicine attempted to examine how two different laser eye treatments could delay loss of vision among 197 diabetic patients who were at risk of loss of visual acuity. This report aims to analyze the results of this study in order to better understand how the laser treatments affected visual acuity, and to understand how a patient's age of diagnosis and risk of retinopathy impact visual acuity. Given the data is censored, we performed a survival analysis that includes modeling the probability of losing eyesight by estimating a survival function and fitting our data to a frailty model. From the results of the analysis, we conclude that laser eye treatment helps to delay diabetic retinopathy, although both laser treatments work about the same, and risk of eyesight loss has an impact on visual acuity, but not age of diagnosis.

Method

When developing our statistical approach to analyze the results of this study, we must take into account two complications about the data: our data is censored and each patient's treated eye is possibly correlated with the same patient's untreated eye. First, in the span of time the study took place, patients either lost their eyesight on one eye (or both), or patients were lost to follow-up either because of death, dropout, or the study came to an end. Among those patients who dropped out of the study (or their time in the study ended) we no longer have information about whether they lost (or didn't lose) their eyesight after the study. Given the data is censored in this manner and we don't have complete information on the outcome for each patient's eye, we'll conduct a survival analysis by attempting to model the probability of losing sight in one's eye after a particular time. The second complication is that each patient had one eye be given the laser treatment and the other eye was given no treatment (the control eye), which could possibly lead to correlated observations. For this reason, we will use a frailty model on our data, which is designed to take into account possible correlation among observations.

Now that we understand these two complications in our data, we'll structure the analysis into three parts: we'll estimate the Keibler-Meier Survival function/curve (overall and by different variables), perform a Log-Rank Test on each possible curve we generate, and fit a frailty model on our data. The Keibler-Meier (KM) Survival curve estimates the probability of something not happening past some time. In our particular case, the KM survival curve will estimate the probability of an eye not losing their eyesight past some time. We will stratify the curve based on different characteristics of a patient including age of diabetes diagnosis, risk score, and most importantly, treatment type. The survival curve stratified by treatment type will allow us to understand if the proportion of eyes that will not lose their eyesight is different among the treatment and control group, and thus, this will help us understand the efficacy of the laser treatment on visual acuity. In order to test whether the differences are meaningful, we will perform a log-rank test on all the survival functions we create.

While the survival curve takes into account one predictor (or variable) at a time, we also want to understand the probability of losing eyesight by using the information from multiple predictors. For this reason, we'll also fit a frailty model, which is an extension of the cox-proportional hazards model, onto our data to model the probability of losing eyesight. The frailty model will not only show if there's a difference in outcomes among the treatment groups, but the model will also help us quantify the effect a particular variable has on the survival rate (e.g. on the risk of losing eyesight). In deciding which predictors to go in the model, we decided to include treatment type, position of the eye, age of diagnosis, and risk score since these characteristics came out to be statistically significant in the log-rank tests.

Data

The data for this analysis was collected from an experiment performed by Michigan Medicine in which two different laser eye treatments were administered to patients with risk of diabetic retinopathy. A total of 197 clinical participants were recruited to partake in the experiment, where each participant had one eye be given one of the two laser treatments, and the other eye was given no laser treatment (this eye served as the "control" group). The treated eye was given either the argon laser treatment or the xenon laser treatment. The eye in which the treatment was administered was selected at random. After being given the laser treatment, participants were followed up every three months, each time being assessed on the clarity of their eyesight vision (visual acuity) and whether that had worsened since the start of the experiment. In addition to recording information about their eyesight, Michigan Medicine also recorded data on a patient's age in which they were diagnosed with diabetes and the clinical risk of losing visual acuity (only participants with a risk score of at least 6 in one eye were allowed to participate in study).

In terms of characteristics of the people who participated in the study, the average age of diabetic diagnosis was 20 years old, where most participants were diagnosed when they were juveniles (ages 1 - 19) then when they were adults (ages 20 and up). The average risk score of losing visual acuity among participants was a score of 10. 155 patient eyes were reported to have lost vision, where the remaining 239 were lost to follow up. Among those eyes that lost vision, the median time that it took to lose vision was 14 months since the start of the study.

Results

Given that we are working with censored data, and thus are unaware of the outcome of certain eyes, we will start by modeling the probability of not losing eyesight past a particular moment in time by estimating the Kaplan-Meier Survival curve. Doing so will allow us to address whether the laser treatment had an impact on delaying diabetic retinopathy. For easier interpretation, we will equivalently interpret this probability as the proportion of eyes that did not lose eyesight past a certain time.

Figure 1 visualizes the Kaplan-Meier Survival curve, both overall and by stratifying the curve among different variables such as diagnosis age, risk score, and treatment type. The plot on the top right corner shows the survival curve (e.g. the proportion of eyes that did not lose their eyesight past a certain time) by treatment type. The graph shows that the proportion of eyes who have not lost their eyesight remains higher among the treated eyes than among the control eyes. This is evidence that these laser eye treatments do help in delaying diabetic retinopathy. However, across the two laser treatments, the proportion of eyes that have not lost their sight remains about the same. Therefore, there's evidence that both laser eye treatments perform just as well in treating retinopathy. We also see evidence that risk score does impact visual acuity. For example, eyes with a risk score of 10 tended to have a lower proportion of eyes that lost their eyesight (in other words, eyes with this risk score had the highest proportion of eyes that did lose their eyesight) than any of the other risk scores. Generally, higher risk scores implied that the probability of losing your eyesight was higher than those eyes with lower risk scores. Age of diabetic diagnosis shows no evidence of their being a difference between these two groups, so therefore we suspect that diagnosis age will not have an impact on visual acuity (as we later show with the log-rank test and frailty model).

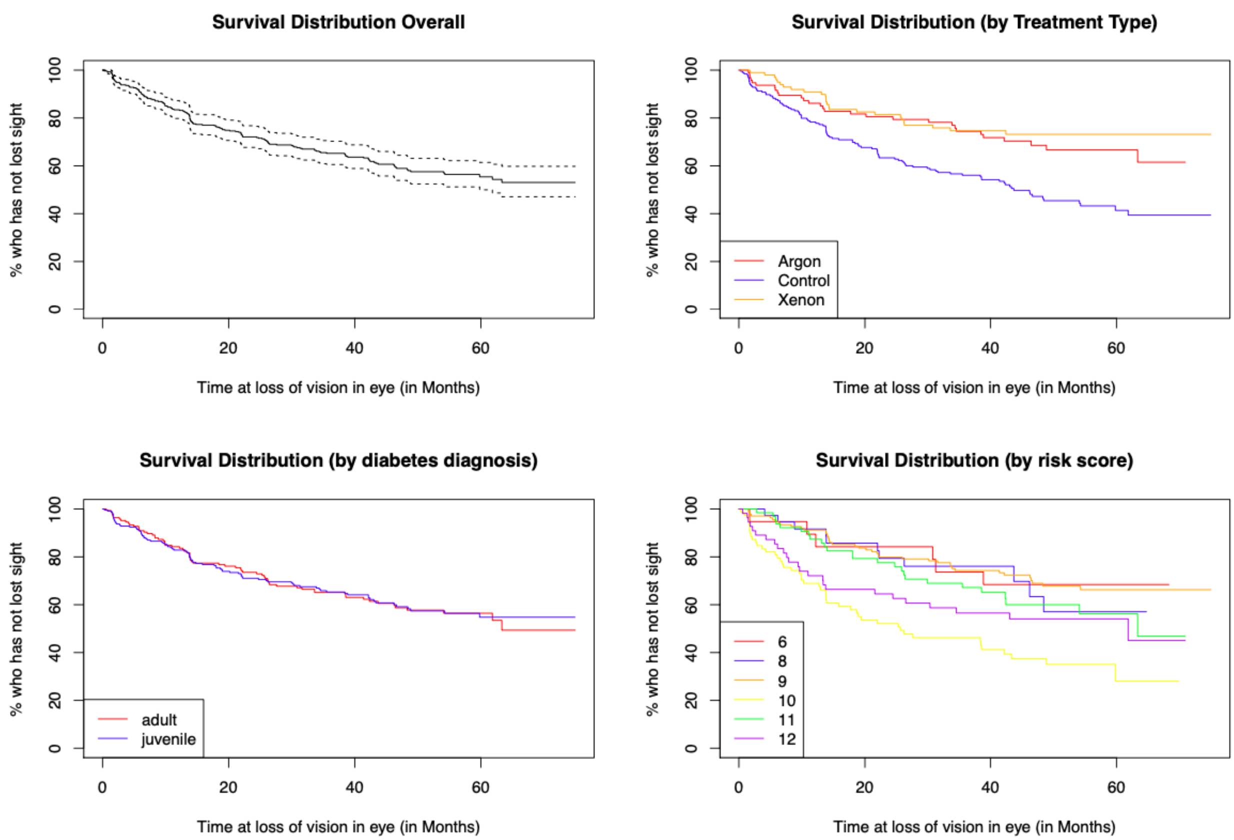
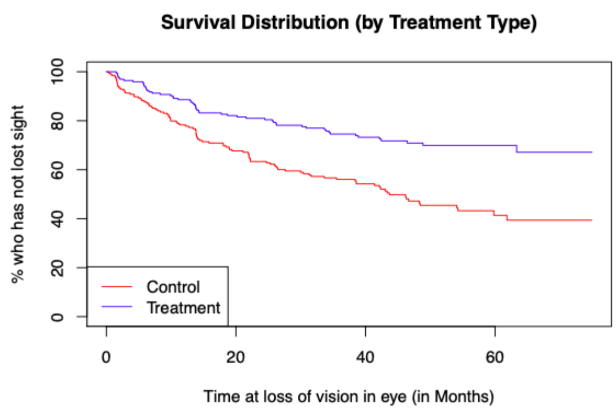


Figure 1: Kaplan-Meier Survival curves. Overall, by treatment type, risk score, and age of diabetic diagnosis (clockwise, starting from top left).

Additionally, in Figure 2, we see that there are some differences in the survival curve across the treatment type and eye. Specifically, by looking at the plot on the right, we see that the treated right eye has a higher proportion of eyes not losing sight than the treated left eye (as well as the other groups). This indicates that the eye you get treated does have an impact on visual acuity, so we'll include this information in our frailty model.



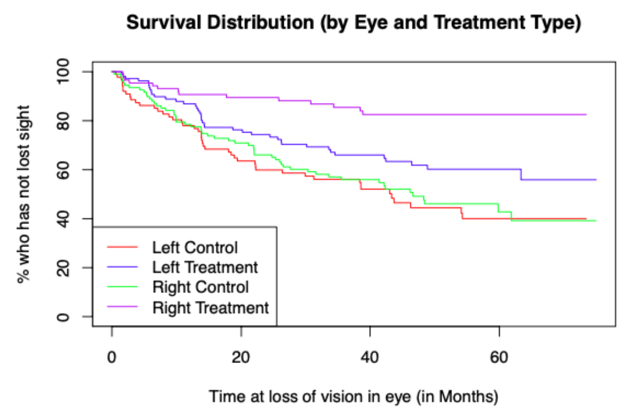


Figure 2: Kaplan-Meier Survival curves. By treatment type (control vs. treatment), and position of eye and treatment type.

To verify that the survival rates plotted in the curves above are truly different when stratified by different variables, we will perform a hypothesis test called the Log-Rank Test to test for these differences. Generally, the results of the log-rank test verify many of the observations we made in the curves above. In particular, the survival rates across the different treatment groups is statistically significant, meaning that treatment type does have an effect on visual acuity (as we saw above, the curves showed that the two laser treatments performed better than the control). When just looking at eyes that were treated, we do not see a statistically significant difference among the two treatment laser types. Additionally, we also see statistically significant differences in the curves when stratified by risk score and eye (including when position of eye includes information about the treatment type).

The Log-Rank Test	
Variable	**P-value**
Treatment Type (Treatment vs. Control)	< 0.001
Treatment Type	< 0.001

(Argon vs. Xenon Vs. Control)	
Treatment Type (Argon vs. Xenon)	0.40
Diagnosis Age	< 0.001
Diagnosis Age (Juvenile vs. Adult)	0.90
Risk Score	< 0.001
Eye (Left vs. Right)	0.08
Eye by Treatment Type (Left vs. Right and Treatment vs. Control)	< 0.001

Table 1: Log-Rank Test for multiple variables.

Relying on the observations we made above, we now fit a frailty model (which is an extension of the typical cox proportional hazards model) which takes into account the possible correlation between eyes for each patient. Fitting a frailty model will now allow us to estimate the probability of loss in eye vision by accounting for information from multiple predictors. Additionally, the results of the model (e.g. the estimate of the coefficients) will allow us to quantify the extent to which a particular variable (like the treatment type) affects visual acuity.

From Table 2 below, we report the estimated (exponentiated) coefficients of the frailty model for each predictor in the model. All the predictors of the model turned out to be statistically significant. In answering the question of whether the treatment has an effect on visual acuity, the results of the model further confirms that the laser treatments do impact visual acuity. Specifically, with all other features held fixed, the argon laser treatment has a 0.3656 less chance of losing eyesight than the control group, at any point in time. A similar interpretation is given to the coefficient for the Xenon treatment, as both Argon and Xenon have very similar estimates. This also verifies that the effect of the two laser treatments on visual acuity is essentially the same. We also see that for every increase in risk score, there's a 1.18 increased chance of losing eyesight. In other words, the higher your risk score, the more likely you'll lose your eyesight. However, even though diagnosis age is statistically significant, there's practically no impact on visual acuity given the coefficient estimate is 1. In other words, for every increase in diagnosis age, there's no change in the chance of losing eyesight.

Variable	Estimate (95% CI)	P-value
Treatment (Argon)	0.37 (0.23, 0.58)	< 0.01
Treatment (Xenon)	0.36 (0.22, 0.57)	< 0.01
Eye (Right)	0.62 (0.44, 0.88)	< 0.01
Diagnosis Age	1.01 (0.99, 1.02)	< 0.01
Risk Score	1.18 (1.02, 1.36)	< 0.01

Table 2: Coefficient estimates for all variables in the frailty model, as well as their corresponding 95% confidence intervals and p-values.

<u>Conclusion</u>

This report aimed to analyze the results of an experiment conducted by Michigan Medicine in order to determine whether laser eye treatment can help delay loss in vision among diabetic people, and to verify if diagnosis age and risk score impact visual acuity. Given that some patients that took part of the study either dropped out or no longer had data recorded because the study ended, we addressed this in our analysis by conducting a survival analysis. Specifically, our outcome of interest here was not simply information about whether a patient's eye lost it's vision, but more so looking at the probability that a patient's eye would lose eyesight. By estimating the survival function and using a frailty model, we found evidence to show that the two laser treatments were able to delay loss in vision, and both laser treatments were equally as effective in doing so. Additionally, we found an eye's risk score does impact visual acuity, but the age in which a patient was diagnosed with diabetes did not have much impact. Some limitations to the study was that we were not able to study other attributes that could impact loss in vision, including things like race, gender, and other general health of the patient. Nonetheless, the analysis shows promising insight that laser eye treatments can potentially aid diabetic people in managing eye damage or delaying the possibility of loss in eyesight.