

Diabetic Retinopathy Survival Analysis

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Introduction

Data source

The data set selected for this project is the “Diabetic Retinopathy” dataset residing in the survival library. This dataset includes 394 patients, where 50% of them are diagnosed with “high-risk” diabetic retinopathy. Each patient had one eye randomized to laser treatment and the other eye received no treatment. For each eye, the event of interest was the time from initiation of treatment to the time when visual acuity dropped below 5/200 two visits in a row. The survival time for this data set measures the actual time to blindness in months with censoring caused by dropout, death, or end of the study. The information of this study comes from “Huster, Brookmeyer and Self, Biometrics” (1989) and “American Journal of Ophthalmology” (1976).

Covariates

id: A unique id number assigned to identify each subject

laser: Lists whether xenon or argon laser treatment was given to a subject

age: Lists the age at which the subject was diagnosed with diabetic retinopathy

eye: Lists which of the patient’s eye, left or right, data was taken from. The dataset includes separate observations for data taken from the left and right eyes.

trt: Lists whether the eye was given laser treatment where: 0 = no treatment, 1 = laser.

risk: Lists the risk group assigned to a subject ranging from 6-12

time: Lists either the actual time to blindness in months or the last follow-up in months

Research Question

We are interested to see whether treatment extends the patient’s survival time to blindness after surgery. Additionally, we want to explore whether there is a joint effect between laser, age, eye, and risk with treatment.

Description

```
diabetic_surv <- Surv(diabetic$time, diabetic$status)
diabeticfit <- survfit(diabetic_surv~1)
ggsurvplot(diabeticfit, data = diabetic,
            ggtheme = theme_bw(),
            palette = c("#8DD3C7", "#FF0000"))+ggtitle("KM Curve for all covariates")
```

	id	laser	age	eye	trt	risk	time	status
5	:	2	xenon:228	10	: 26	left :197	0:197	6 : 20
14	:	2	argon:166	12	: 24	right:197	1:197	8 : 37
16	:	2		13	: 20			9 :139
25	:	2		5	: 18			10: 79
29	:	2			15	: 14		11: 64
46	:	2				8	: 12	12: 55
(Other):382							(Other):280	

Figure 1: summary of the diabetic retinopathy data set

Above is the summary to the diabetic dataset. We will construct the survival function for the diabetic dataset using the *Surv* and *survfit* function and plot the Kaplan Meier curve and survival time distribution.

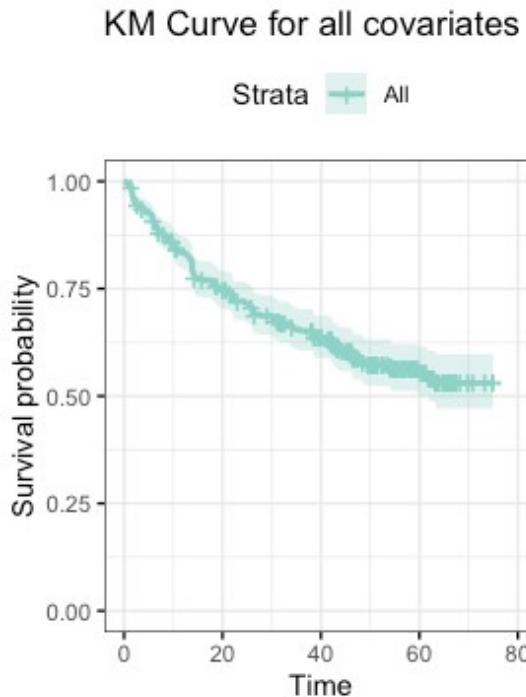


Figure 2: Kaplan Meier Curve for diabetic retinopathy data set

Model fitting

We will now build a Cox PH model with our covariates: id, age, trt, eye, laser, and risk. For each covariate we will plot the Kaplan Meier curve and perform a log rank test.

Treatment fit (0 = no trt, 1 = trt)

```
trtfit <- survfit(Surv(time, status) ~ trt, data = diabetic)
ggsurvplot(trtfit, data = diabetic)
summary(coxph(diabetic_surv ~ trt, data = diabetic))
```

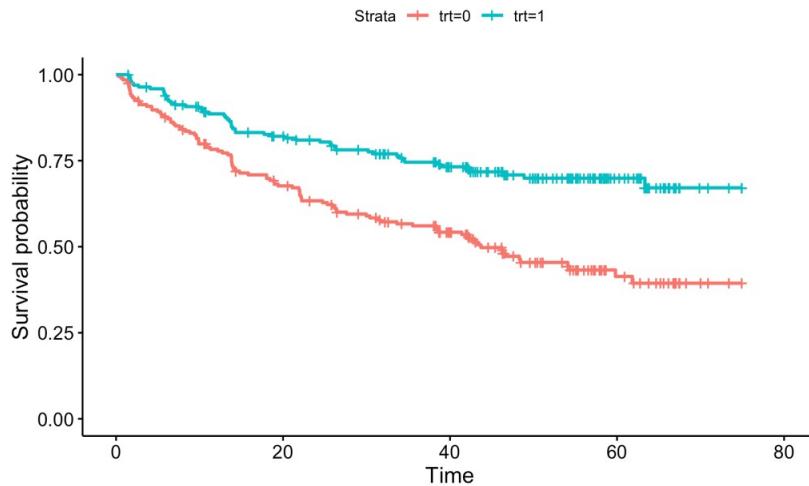


Figure 3: KM curve for treatment fit

```
Call:
coxph(formula = diabetic_surv ~ trt, data = diabetic)

n= 394, number of events= 155

      coef exp(coef) se(coef)      z Pr(>|z|)
trt1 -0.7766    0.4600   0.1688 -4.602 4.19e-06 ***
---
Signif. codes:  0 '****' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
trt1     0.46        2.174    0.3304    0.6403

Concordance= 0.59  (se = 0.02 )
Likelihood ratio test= 22.37  on 1 df,  p=2e-06
Wald test             = 21.17  on 1 df,  p=4e-06
Score (logrank) test = 22.25  on 1 df,  p=2e-06
```

Figure 4: covariate: trt summary

From the output, it is reported that there is a significant difference in survival probability from those who have received treatment versus those who have not.

Now looking at the output to the summary, the p-value is 4.19e-06, which is less than the 0.05 significance level, thus concluding that the laser treatment has a significant effect on the survival time.

Eye fit

```
eyefit <- survfit(Surv(time, status)~eye, data = diabetic)
ggsurvplot(eyefit, data = diabetic)
summary(coxph(diabetic_surv~eye, data = diabetic))
```

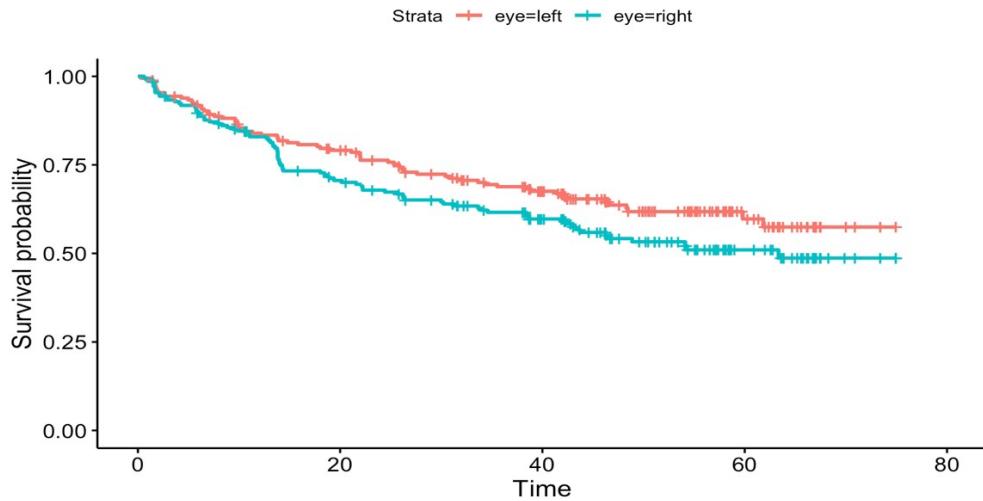


Figure 5: KM curve for eye fit

```
Call:
coxph(formula = diabetic_surv ~ eye, data = diabetic)

n= 394, number of events= 155

            coef exp(coef)  se(coef)      z Pr(>|z|)
eyeright 0.2807    1.3241   0.1617 1.736   0.0825 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

            exp(coef) exp(-coef) lower .95 upper .95
eyeright     1.324      0.7552   0.9645    1.818

Concordance= 0.535  (se = 0.021 )
Likelihood ratio test= 3.04  on 1 df,   p=0.08
Wald test          = 3.02  on 1 df,   p=0.08
Score (logrank) test = 3.03  on 1 df,   p=0.08
```

Figure 6: covariate: eye summary

Looking at the output, we can see that there is a very slight difference in survival probability from those who have received treatment in the left eye versus the right.

Now viewing the output to the summary, the p-value is 0.0825, which is greater than the 0.05 significance level, thus we will refuse to reject the null hypothesis and conclude that the covariate eye is not statistically significant to affect the survival time.

Laser fit

```

laserfit <- survfit(Surv(time,status) ~ laser, data = diabetic)
ggsurvplot(laserfit, data = diabetic)
summary(coxph(diabetic_surv~laser, data = diabetic))

```

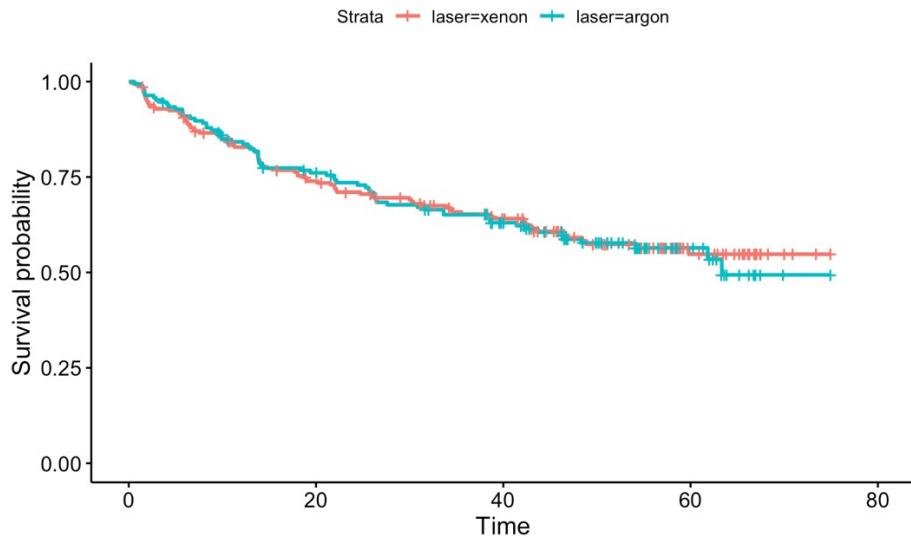


Figure 7: KM curve for laser fit

```

Call:
coxph(formula = diabetic_surv ~ laser, data = diabetic)

n= 394, number of events= 155

      coef exp(coef)  se(coef)      z Pr(>|z|)
laserargon 0.02166   1.02189  0.16195 0.134    0.894

      exp(coef) exp(-coef) lower .95 upper .95
laserargon     1.022      0.9786    0.744    1.404

Concordance= 0.499  (se = 0.021 )
Likelihood ratio test= 0.02  on 1 df,   p=0.9
Wald test          = 0.02  on 1 df,   p=0.9
Score (logrank) test = 0.02  on 1 df,   p=0.9

```

Figure 8: covariate: laser summary

Looking at the plot, there is no difference in survival probability from those who have received the argon laser versus the xenon laser.

From the summary, the p-value for the covariate laser is 0.894, which is above the 0.05 significance level, thus we will refuse to reject the null hypothesis and conclude that the covariate laser is not statistically significant to affect the survival time.

Risk fit

```
riskfit <- survfit(Surv(time, status) ~ risk, data = diabetic)
ggsurvplot(riskfit, data = diabetic)
summary(coxph(diabetic_surv ~ risk, data = diabetic))
```

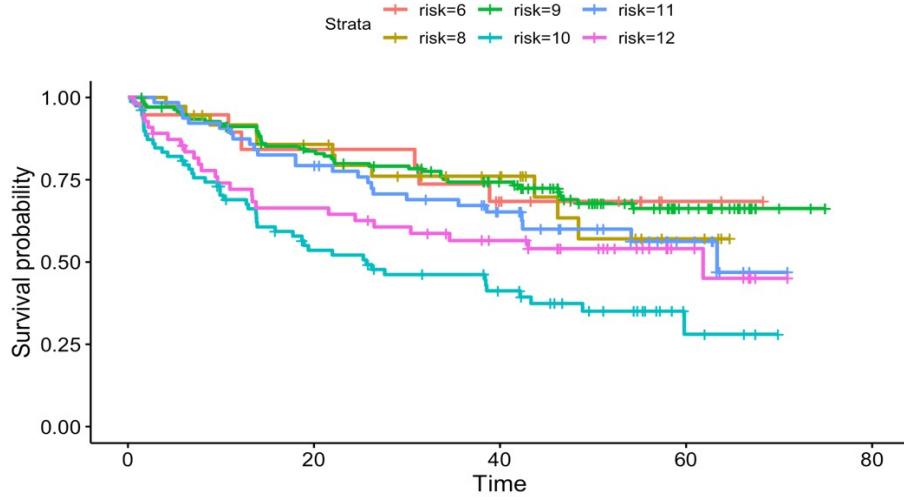


Figure 9: KM curve for risk fit

```
Call:
coxph(formula = diabetic_surv ~ risk, data = diabetic)

n= 394, number of events= 155

      coef exp(coef) se(coef)     z Pr(>|z|)
risk8   0.08168  1.08511  0.50771  0.161  0.8722
risk9  -0.03937  0.96139  0.43720 -0.090  0.9282
risk10  1.05868  2.88257  0.43400  2.439  0.0147 *
risk11  0.32097  1.37847  0.45474  0.706  0.4803
risk12  0.60708  1.83507  0.45472  1.335  0.1819
---
Signif. codes:  0 '****' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
risk8    1.0851      0.9216   0.4012    2.935
risk9    0.9614      1.0402   0.4081    2.265
risk10   2.8826      0.3469   1.2313    6.748
risk11   1.3785      0.7254   0.5654    3.361
risk12   1.8351      0.5449   0.7526    4.474

Concordance= 0.623  (se = 0.023 )
Likelihood ratio test= 28.95  on 5 df,  p=2e-05
Wald test             = 30.67  on 5 df,  p=1e-05
Score (logrank) test = 32.98  on 5 df,  p=4e-06
```

Figure 10: covariate: risk summary

From the output, it can be reported that there are differences in survival probability between different risk groups. We will conclude significance in this covariate since the p-value of 2e-05 is less than our 0.05 significance level, thus we will reject the null hypothesis and conclude that the covariate risk has a significant effect to our survival time.

Age fit

We have clustered the age data into two groups, juvenile and adult. Juvenile contains all the subjects who are less than 20 years old, and Adult contains subjects whose age are above 20.

```
juvenile <- 1*(as.numeric(diabetic$age) < 20)
adult <- 1*(as.numeric(diabetic$age) > 20)
agefit <- survfit(Surv(time, status) ~juvenile, data = diabetic)
ggsurvplot(agefit, data = diabetic, legend.labs = c("Adult", "Juvenile"))
summary(coxph(diabetic_surv~juvenile, data = diabetic))
summary(coxph(diabetic_surv~age, data = diabetic))
```

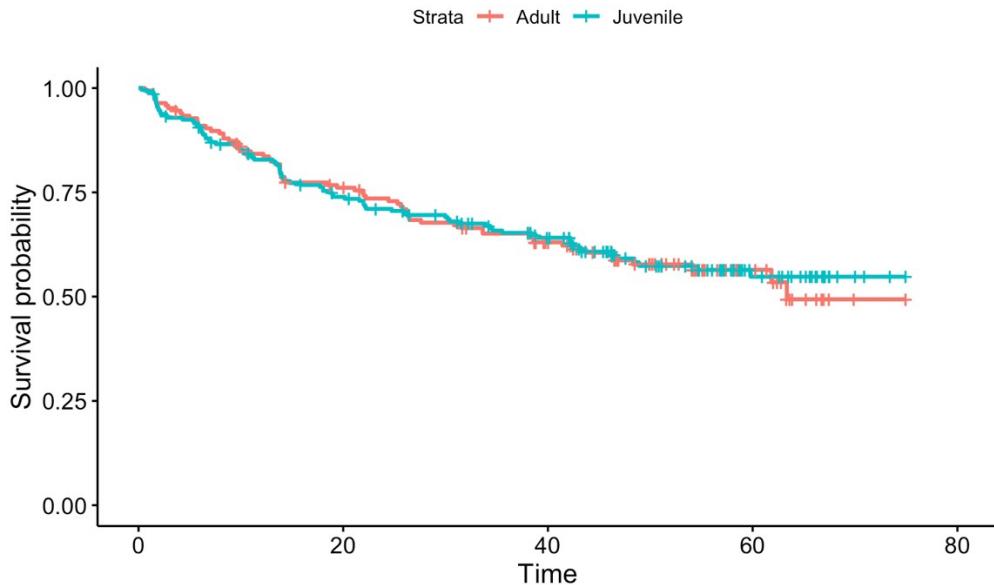


Figure 11: KM curve for age fit

```
Call:
coxph(formula = diabetic_surv ~ juvenile, data = diabetic)

n= 394, number of events= 155

      coef  exp(coef)  se(coef)      z Pr(>|z|)
juvenile -0.02166    0.97858   0.16195 -0.134    0.894

      exp(coef)  exp(-coef) lower .95 upper .95
juvenile    0.9786       1.022    0.7124    1.344

Concordance= 0.499  (se = 0.021 )
Likelihood ratio test= 0.02  on 1 df,   p=0.9
Wald test            = 0.02  on 1 df,   p=0.9
Score (logrank) test = 0.02  on 1 df,   p=0.9
```

Figure 12: covariate: age summary

The output shows that there is no difference in survival probability between juvenile and adult. Now looking at the output to the summary, the p-value is 0.894, which is greater than the 0.05 significance level, concluding that we will refuse to reject the null hypothesis and conclude that the covariate age is not statistically significant to affect the survival time.

We will now conduct the **Log-Rank test** to confirm our Kaplan Meier estimation.

```

Call:
survdiff(formula = diabetic_surv ~ juvenile, data = diabetic)

      N Observed Expected (O-E)^2/E (O-E)^2/V
juvenile=0 166      68      67.2   0.00988   0.0175
juvenile=1 228      87      87.8   0.00756   0.0175

Chisq= 0 on 1 degrees of freedom, p= 0.9
Call:
survdiff(formula = diabetic_surv ~ eye, data = diabetic)

      N Observed Expected (O-E)^2/E (O-E)^2/V
eye=left 197      69      79.8    1.47     3.03
eye=right 197     86      75.2    1.56     3.03

Chisq= 3 on 1 degrees of freedom, p= 0.08
Call:
survdiff(formula = diabetic_surv ~ laser, data = diabetic)

      N Observed Expected (O-E)^2/E (O-E)^2/V
laser=xenon 228     87      87.8   0.00756   0.0175
laser=argon 166     68      67.2   0.00988   0.0175

Chisq= 0 on 1 degrees of freedom, p= 0.9
Call:
survdiff(formula = diabetic_surv ~ trt, data = diabetic)

      N Observed Expected (O-E)^2/E (O-E)^2/V
trt=0 197     101      71.8    11.9     22.2
trt=1 197      54      83.2    10.3     22.2

Chisq= 22.2 on 1 degrees of freedom, p= 2e-06
Call:
survdiff(formula = diabetic_surv ~ risk, data = diabetic)

      N Observed Expected (O-E)^2/E (O-E)^2/V
risk=6   20       6      8.68   0.8285   0.8791
risk=8   37      11     14.73   0.9467   1.0480
risk=9   139     41     61.67   6.9299  11.5767
risk=10  79      47     23.81  22.5717  26.8303
risk=11  64      25     26.33   0.0668   0.0806
risk=12  55      25     19.77   1.3842   1.5887

Chisq= 33 on 5 degrees of freedom, p= 4e-06

```

Figure 13: log rank test for all covariates

It is reported that the p-value of treatment and risk are smaller than the significance level of 0.05, thus concluding that these variables have significant effects on the successfullness of surgery and will be included in our model.

Now, we will examine the log-log plot for all the relevant covariates.

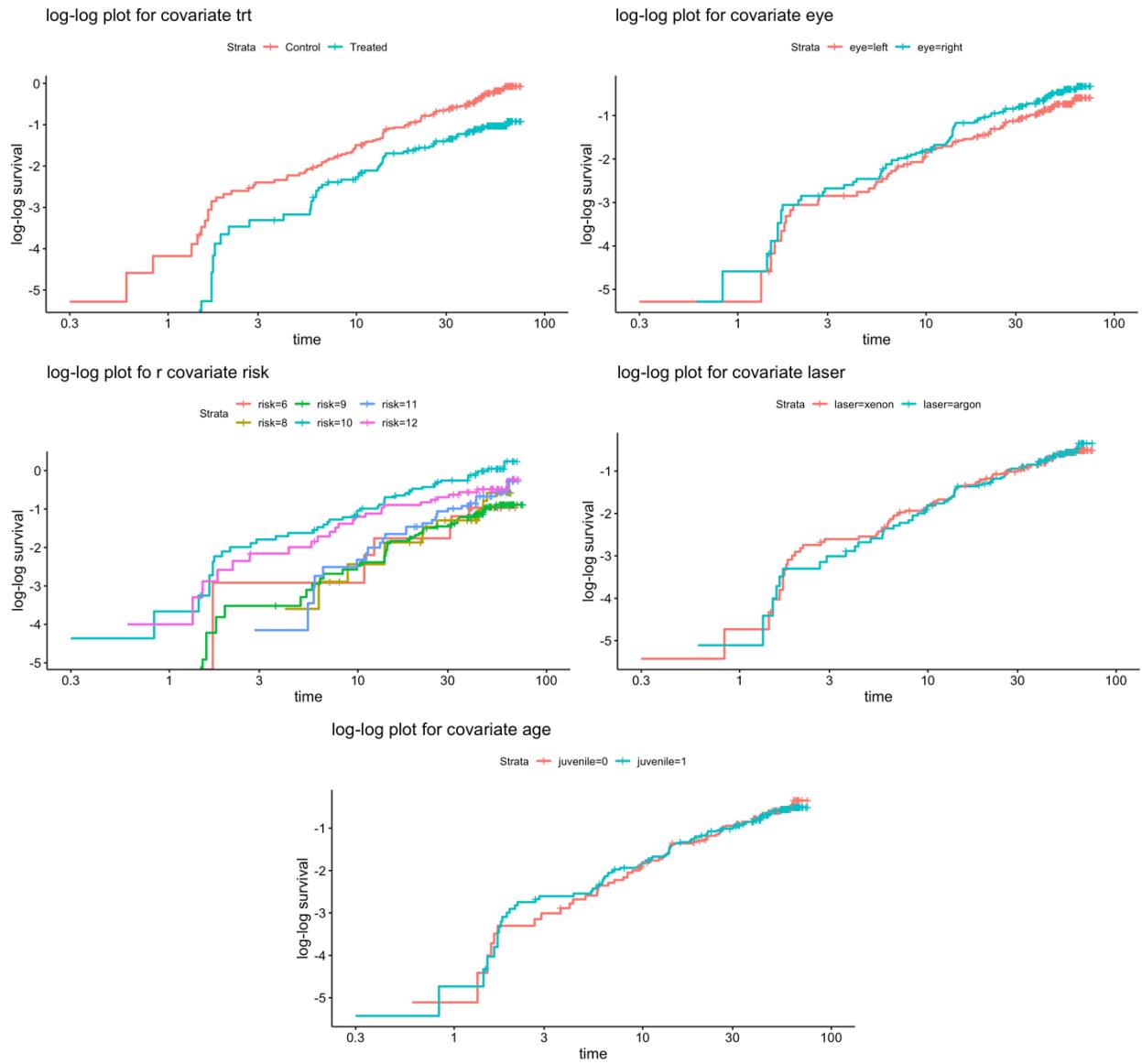


Figure 14: log-log plot for all relevant covariates

Looking at the plot, we can assume that the log-log plot for only the covariate, treatment, is parallel. This indicates that the relationship between your covariate and the outcome variable is a constant proportional relationship. Thus, no matter what the value of the covariate is, the rate of change of the outcome variable is always the same. However, covariates: eye, risk, laser, and age are not parallel. This means that the relationship between these covariates and the outcome is not linear, this meaning that there are effects of these covariates may be different for different levels or that there may be other factors contributing to the outcomes.

After looking at the covariates independently to see their impact on the survival time, we will now look at the full model with all the covariates to check the likelihood, Wald, and score.

```
summary(fit1)
anova(fit1)
```

```
Likelihood ratio test= 152.7  on 60 df,  p=5e-10
Wald test             = 122.8  on 60 df,  p=3e-06
Score (logrank) test = 159.5  on 60 df,  p=6e-11
```

Figure 14: summary for full model

```
Analysis of Deviance Table
Cox model: response is diabetic_surv
Terms added sequentially (first to last)

      loglik  Chisq Df Pr(>|Chi|)
NULL    -867.99
eye     -866.47  3.0362  1   0.08142 .
laser   -866.46  0.0220  1   0.88218
risk    -852.73 27.4476  5  4.666e-05 ***
trt     -839.53 26.4051  1  2.768e-07 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Figure 15: analysis of variance table for full model

The full model for the diabetic data set passes the Likelihood ratio test, Wald test, and Score (log rank) test, however there are some covariates that do not prove to be significant in the model. In order to make our mode better we will proceed to conduct forward elimination and analyze the AIC value.

```

fit1 <- coxph(diabetic_surv ~ eye + laser + risk + trt , data = diabetic)
fit2 <- coxph(diabetic_surv ~ 1, diabetic)
stepAIC(fit2, direction = "forward", scope = list(upper = fit1, lower = fit2))

Start: AIC=1735.97
diabetic_surv ~ 1

      Df   AIC
+ trt   1 1715.6
+ risk   5 1717.0
+ eye    1 1734.9
<none> 1736.0
+ laser  1 1738.0

Step: AIC=1715.6
diabetic_surv ~ trt

      Df   AIC
+ risk   5 1694.0
+ eye    1 1712.7
<none> 1715.6
+ laser  1 1717.5

Step: AIC=1693.97
diabetic_surv ~ trt + risk

      Df   AIC
+ eye    1 1693.1
<none> 1694.0
+ laser  1 1695.8

Step: AIC=1693.14
diabetic_surv ~ trt + risk + eye

      Df   AIC
<none> 1693.1
+ laser  1 1695.1
Call:
coxph(formula = diabetic_surv ~ trt + risk + eye, data = diabetic)

      coef exp(coef) se(coef)      z      P
trt1   -0.84836  0.42811  0.17003 -4.990 6.05e-07
risk8   -0.03554  0.96508  0.50821 -0.070  0.9442
risk9   -0.08068  0.92249  0.43771 -0.184  0.8538
risk10   1.03779  2.82299  0.43402  2.391  0.0168
risk11   0.29171  1.33872  0.45509  0.641  0.5215
risk12   0.53298  1.70400  0.45483  1.172  0.2413
eyeright 0.27406  1.31529  0.16348  1.676  0.0937

Likelihood ratio test=56.84 on 7 df, p=6.443e-10
n= 394, number of events= 155

```

Figure 16: forwards elimination

Despite the model with the three covariates: trt, risk, eye has reported the lowest AIC value of 1693.14, eye has not passed any other test. Instead, we will pick our final model to contain the two covariates trt and risk from the principle of parsimony.

Our final expected model is coxph(diabetic_surv ~ trt + risk, data = diabetic)

```
Call:  
coxph(formula = diabetic_surv ~ trt + risk, data = diabetic)  
  
n= 394, number of events= 155  
  
          coef exp(coef)  se(coef)      z Pr(>|z|)  
trt1    -0.82462   0.43840   0.16946 -4.866 1.14e-06 ***  
risk8   -0.04873   0.95244   0.50823 -0.096  0.9236  
risk9   -0.11240   0.89368   0.43746 -0.257  0.7972  
risk10   1.04355   2.83927   0.43399  2.405  0.0162 *  
risk11   0.26325   1.30115   0.45486  0.579  0.5628  
risk12   0.53227   1.70279   0.45499  1.170  0.2421  
---  
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1  
  
          exp(coef)  exp(-coef) lower .95 upper .95  
trt1     0.4384      2.2810   0.3145   0.6111  
risk8    0.9524      1.0499   0.3518   2.5789  
risk9    0.8937      1.1190   0.3792   2.1064  
risk10   2.8393      0.3522   1.2128   6.6470  
risk11   1.3011      0.7686   0.5335   3.1732  
risk12   1.7028      0.5873   0.6980   4.1538  
  
Concordance= 0.668 (se = 0.022 )  
Likelihood ratio test= 54.01 on 6 df,  p=7e-10  
Wald test            = 54.43 on 6 df,  p=6e-10  
Score (logrank) test = 57.81 on 6 df,  p=1e-10
```

Figure 17: summary of our final model

Model checking

```
diabetic.zph <- cox.zph(coxph(diabetic_surv ~ risk * trt, data = diabetic))
diabetic.zph
ggcoxzph(diabetic.zph)
```

	chisq	df	p
risk	7.593	5	0.18
trt	0.631	1	0.43
risk:trt	2.715	5	0.74
GLOBAL	12.084	11	0.36

Figure 18: comparison of correlation of the Schoenfeld residuals w/time for our final model
Global Schoenfeld Test p: 0.3573

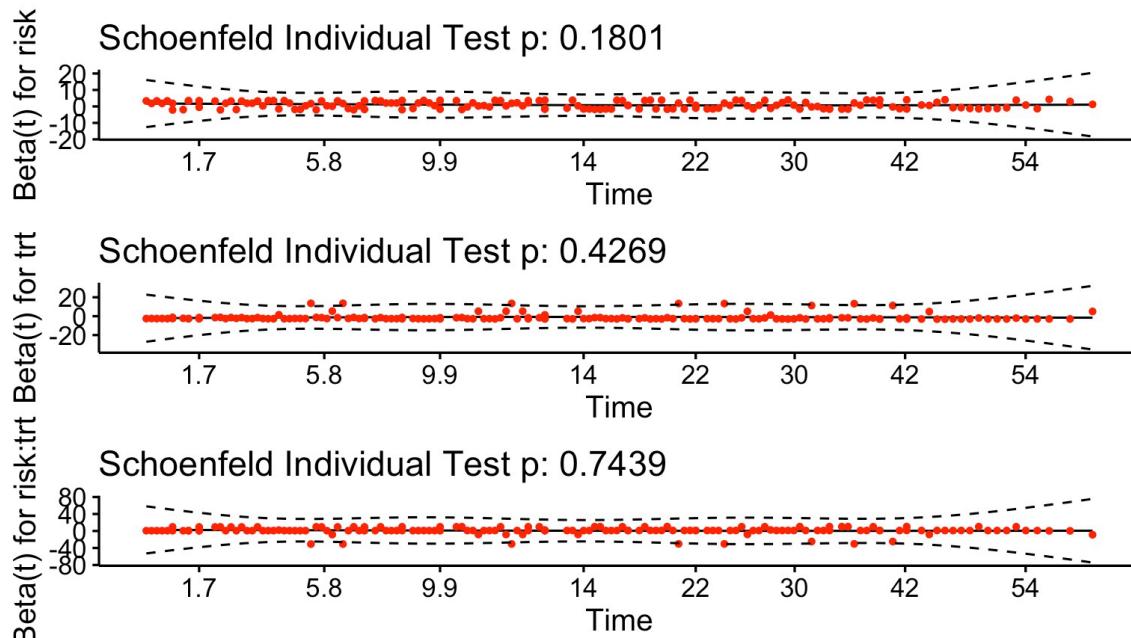


Figure 19: Global Schoenfeld Test of our final model

We will now perform PH assumption test on independence between Schoenfeld residual and time using the `cox.zph()` function. This function compares the correlation of the Schoenfeld residuals with time. Since the p-values are all greater than 0.05, we will fail to reject the null hypothesis and conclude that there is not a case that the relationship is a function of time, and the assumption is satisfied. Looking at the p-value we can also assume that the model is suitable and the interaction term between risk and trt is not significant meaning they are not correlated.

```
fit4 <- coxph(diabetic_surv ~ risk + trt , data = diabetic)
ggforest(fit4,data=diabetic)
```

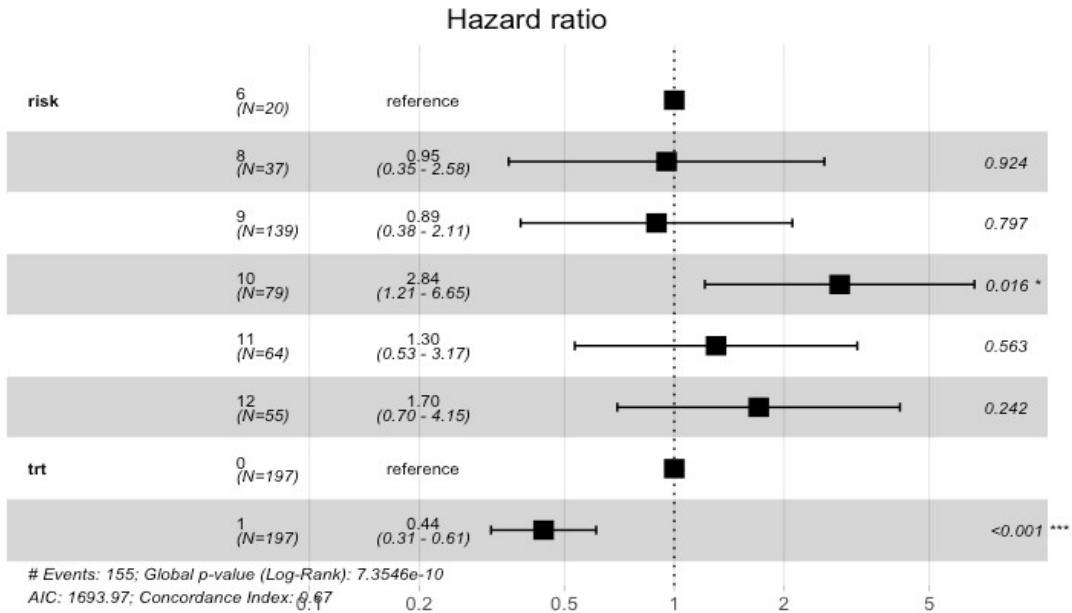


Figure 20: Hazard Ratios of covariates in our final model

The hazard ratio of the covariate treatment is centered at 0.44 with 95% confidence interval 0.31 to 0.61 concluding that receiving the treatment is associated for better survival.

Risk group of 8 is centered around 0.95 with a 95% confidence interval of 0.35 to 2.68, and risk group of 9 is centered around 0.89 with a 95% confidence interval of 0.38 to 2.11. Compared to risk group of 6, risk group of 8 and 9 are associated for better survival. On the other hand, risk group of 10 is centered at 2.84 with a 95% confidence interval of 1.21 to 6.65, risk group of 11 is centered at 1.30 with a 95% confidence interval of 0.53 to 3.17, and risk group of 12 is centered at 1.70 with a 95% confidence interval 0.70 to 4.15. All three risk groups are centered above risk group of 6, thus compared to risk group 6, they are associated with a worse survival rate.

Risk group 10 seems to be so much worse than the others. This could be due to other factors, such as underlying health conditions or environmental factors, that are not accounted for in the data set.

We will now set our risk covariate as a numeric covariate instead of categorical. Looking at risk as a numeric covariate allows for more precise analysis of the relationship between risk and diabetic retinopathy. By looking at risk as a numeric covariate, it is possible to measure the exact magnitude of the association between risk and diabetic retinopathy, which is not possible when looking at risk as a categorical covariate.

```
ggforest(coxph(diabetic_surv ~ as.numeric(risk) + trt, data = diabetic))
```

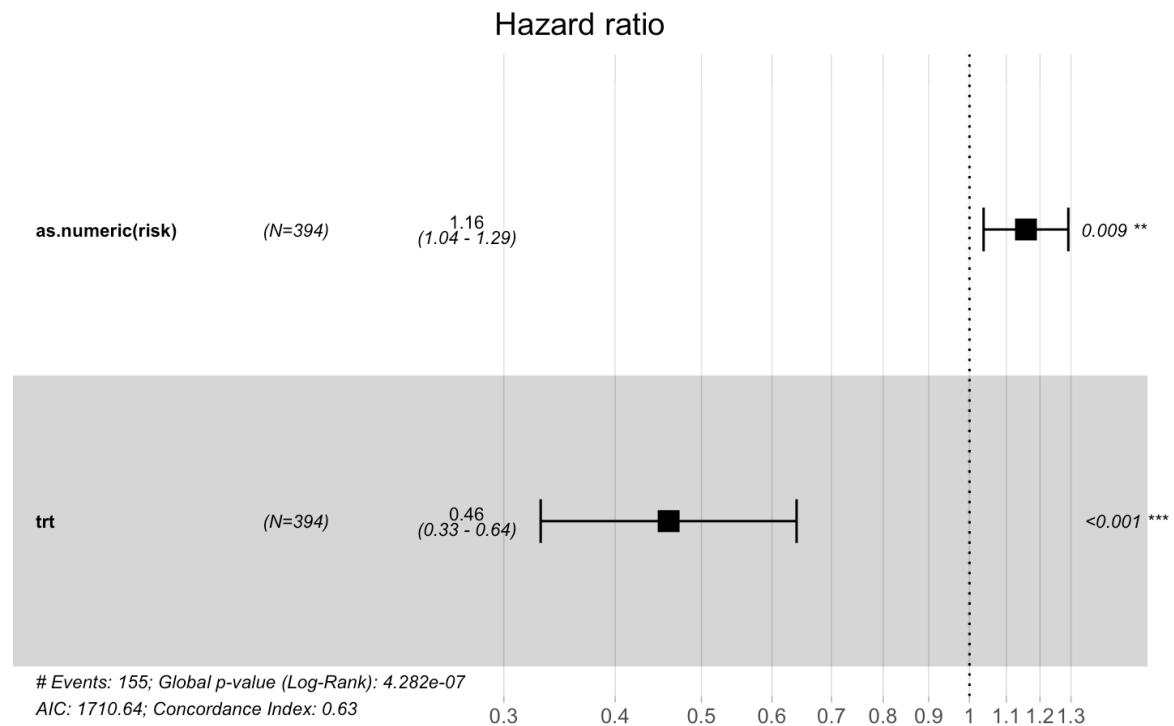


Figure 21: Hazard Ratios of covariates in our final model with risk as a numeric covariate

The hazard ratio of the covariate treatment is centered at 0.46 with 95% confidence interval 0.31 to 0.61. We can assume that the treatment may be associated with a slightly lower risk of diabetic retinopathy compared to the control group.

The hazard ratio of the covariate risk (as a numeric factor) was centered around 1.15 with a 95% confidence interval ranging from 1.03 to 1.29. This suggests that risk as a numeric covariate is associated with a 16% increase in the hazard ratio for diabetic retinopathy. It can be concluded that individuals with higher risk scores are more likely to experience diabetic retinopathy than those with lower risk scores.

Advanced Models

Cluster Frailty Model

```
require(coxme)
fit.cox<-coxph(diabetic_surv~trt + risk, data = diabetic)
fit.frail<-coxme(diabetic_surv~risk + trt +(1|id), data = diabetic)

anova(fit.cox, fit.frail)
AIC(fit.cox)
AIC(fit.frail)
```

Cluster frailty models allow us to account for between-group differences in the risk of an event. This allows us to better assess the effects of covariates and determine if the effects are consistent across groups, or if they vary based on group-level characteristics. It also allows us to assess the effects of clustering on the risk of an event, which can be useful when trying to assess the impact of treatments or interventions.

We will now compare a frailty clustered model with the trt and risk covariates while clustered according to patient ID and a coxph model with the covariates trt and risk.

```
Cox mixed-effects model fit by maximum likelihood
Data: diabetic
events, n = 155, 394
Iterations= 10 44
      NULL Integrated     Fitted
Log-likelihood -867.9858 -848.0618 -768.5804

          Chisq      df      p    AIC      BIC
Integrated loglik 39.85  3.00 1.1476e-08 33.85  24.72
Penalized loglik 198.81 72.07 8.3933e-14 54.68 -164.66

Model: diabetic_surv ~ risk + trt + (1 | id)
Fixed coefficients
      coef exp(coef)      se(coef)      z      p
risk  0.1620192 1.1758828 0.06691706  2.42 1.5e-02
trt  -0.8979756 0.4073935 0.17453962 -5.14 2.7e-07

Random effects
Group Variable Std Dev Variance
id     Intercept 0.8673313 0.7522636
```

Figure 22: summary output of frail model

```
Analysis of Deviance Table
Cox model: response is diabetic_surv
Model 1: ~trt + risk
Model 2: ~risk + trt + (1 | id)
loglik   Chisq Df P(>|Chi|)
1 -853.32
2 -848.06 10.521  1  0.001181 **
---
Signif. codes:  0 '****' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Figure 23: analysis of variance table of cluster frailty model and final model.

The anova table compares the two models. The first value of the table is the likelihood ratio test, which compares the likelihoods of the two models. The results indicate that the frailty cluster model with covariates trt and risk has a higher log likelihood than the coxph model with covariates trt and risk. This suggests that the frailty cluster model is a better fit for the dataset than the coxph model, and that the covariate treatment may be more effective in predicting the time to blindness in the diabetic retinopathy dataset when clustered according to patient ID.

We will compare the two models Akaike Information Criterion score, which is a measure of the goodness of fit of the model. The lower the AIC score, the better the model fit.

```
[1] 1710.644  
[1] 1681.296
```

Figure 24: comparison of AIC values between frail model and expected model

The AICs show a difference to the ordinary Cox model, suggesting that the frailty model may fit better. The model likelihood ratio test also confirms that the frailty model fits better than the ordinary cox model. This suggests that the effect of laser treatment is more pronounced when the data is clustered according to patient ID.

Conclusion

In order to analyze the diabetic retinopathy data and the effects of each variable, we looked at the relationship between each covariate and its effect on the actual time to blindness for each patient. We conducted this analysis through Kaplan Meier curves and log-rank testing. After testing each covariate, we compared the AIC criterion with forward selection to select a well-fitting and suitable model. It was concluded that the two covariates risk and trt were significant for this model. We looked at the interaction term which concluded to have no significance. Additionally, creating two models, a cluster model and a cluster frailty model. After creating those two models, we compared the AIC values and concluded the frailty clustered model is better fit.

Overall, the results of the frailty cluster model and Cox PH model indicate that laser treatment has a statistically significant effect on the risk of blindness in patients with diabetic retinopathy, suggesting that laser treatment may be an effective treatment for diabetic retinopathy. Additionally, from the fit frailty model, we can see that the effect of laser treatment may be more pronounced when the data is clustered according to patient ID.

Citations

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