Survival Analysis on Pediatric Kidney Transplants

Niels van der Drift - Severin Holtmann - Mikdad Kanbar

Introduction

- Data inspection, overall survival, and mortality ratio based on donor type
- Hazard Ratio’s and Univariate Cox Models
- Multivariate Cox Model and Proportional Hazard Assumptions

Data Inspection

Research background:

- A cohort of 9775 children who have undergone kidney transplantation from United Network for Organ Sharing (UNOS)

Variables of interest:

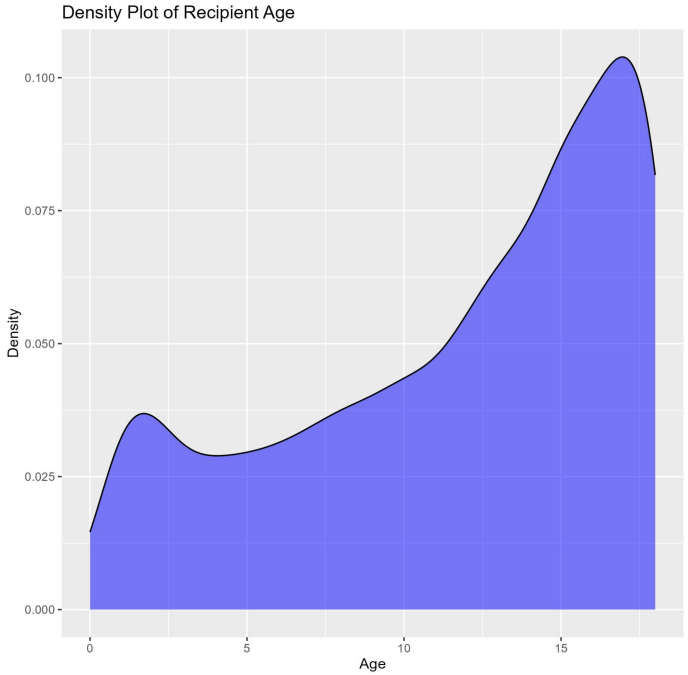
- **Age.1**: Age of the recipient
- **Age**: Age of the donor
- **txtype**: Deceased vs Alive Donor (0/1)
- **hlamat**: HLA Match Level (0-6): immune system match between donor and recipient
- **Cold_isc:** Hours a kidney spends out of the donor body before transplant

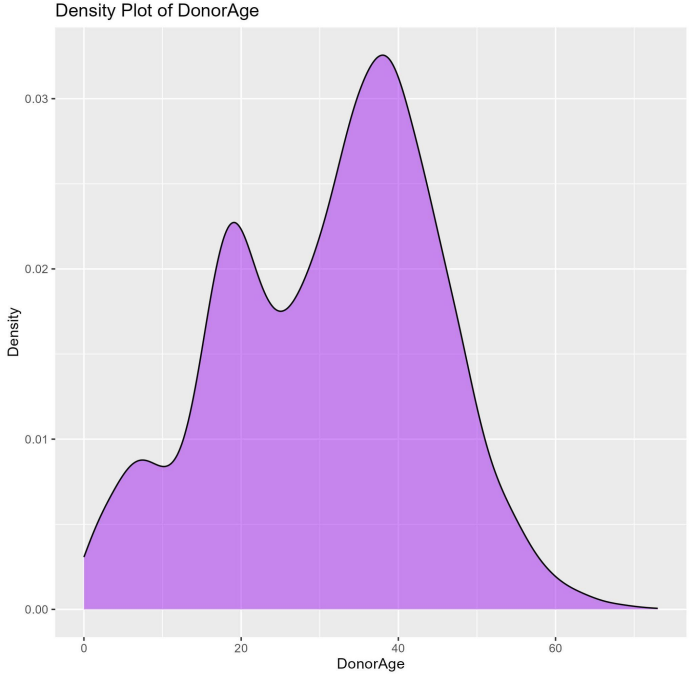
Survival variables:

- **fu**: Follow-up time (years)
- **death**: Alive vs Post Transplant Mortality (0/1)

hlamat	age	age.1	cold_isc	death	year	sex	txtype	fu
Min. :0.000	Min. : 0.0	Min. : 0.00	Min. : 0.00	Min. :0.00000	Min. :1990	Min. :0.0000	Min. :0.0000	Min. : 0.000
1st Qu.:2.000	1st Qu.:21.0	1st Qu.: 8.00	1st Qu.: 1.00	1st Qu.:0.00000	1st Qu.:1993	1st Qu.:0.0000	1st Qu.:0.0000	1st Qu.: 1.096
Median :3.000	Median :33.0	Median :13.00	Median : 7.00	Median :0.00000	Median :1996	Median :1.0000	Median :0.0000	Median : 3.115
Mean :2.574	Mean :31.3	Mean :11.65	Mean :10.86	Mean :0.04757	Mean :1996	Mean :0.5894	Mean :0.4734	Mean : 3.888
3rd Qu.:3.000	3rd Qu.:41.0	3rd Qu.:16.00	3rd Qu.:19.00	3rd Qu.:0.00000	3rd Qu.:1999	3rd Qu.:1.0000	3rd Qu.:1.0000	3rd Qu.: 5.978
Max. :6.000	Max. :73.0	Max. :18.00	Max. :72.00	Max. :1.00000	Max. :2002	Max. :1.0000	Max. :1.0000	Max. :12.532
NA's :234	NA's :113	NA's :9	NA's :2250	NA	NA	NA	NA	NA

Data Inspection





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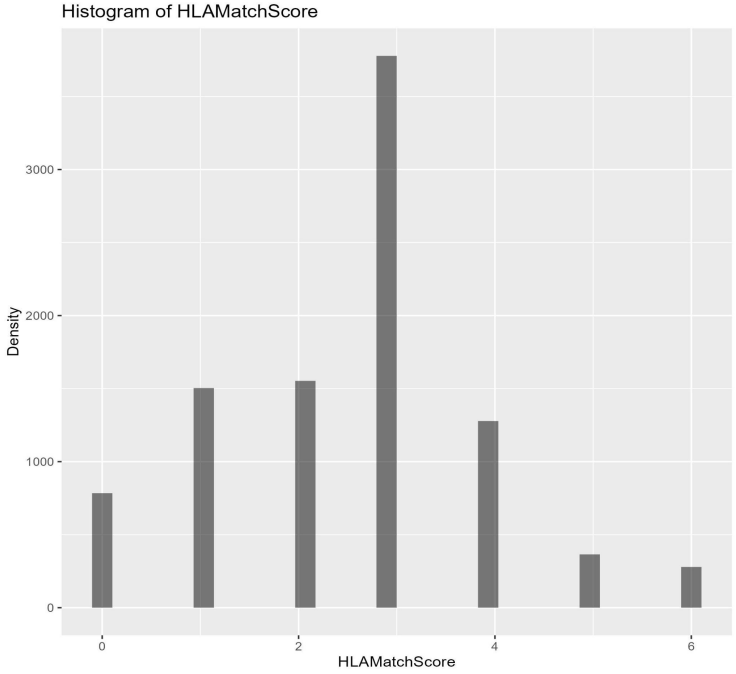

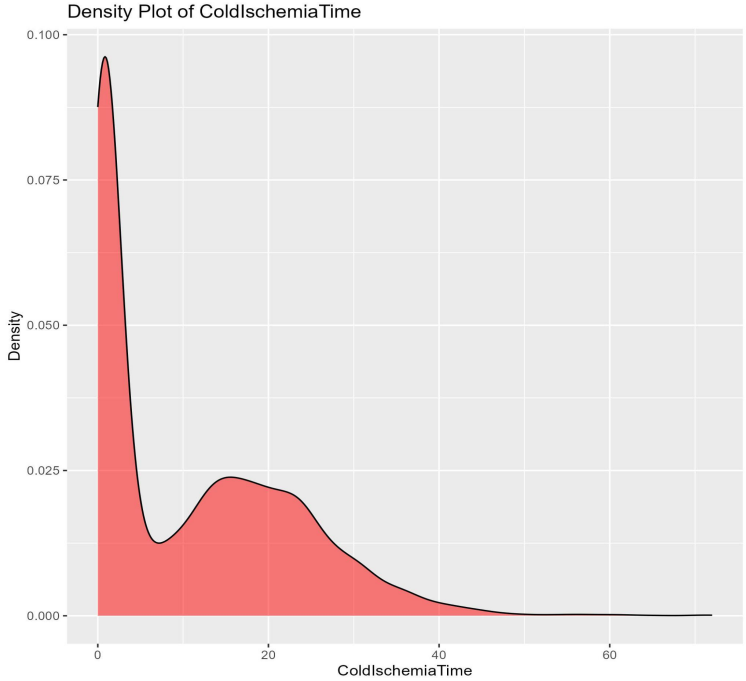

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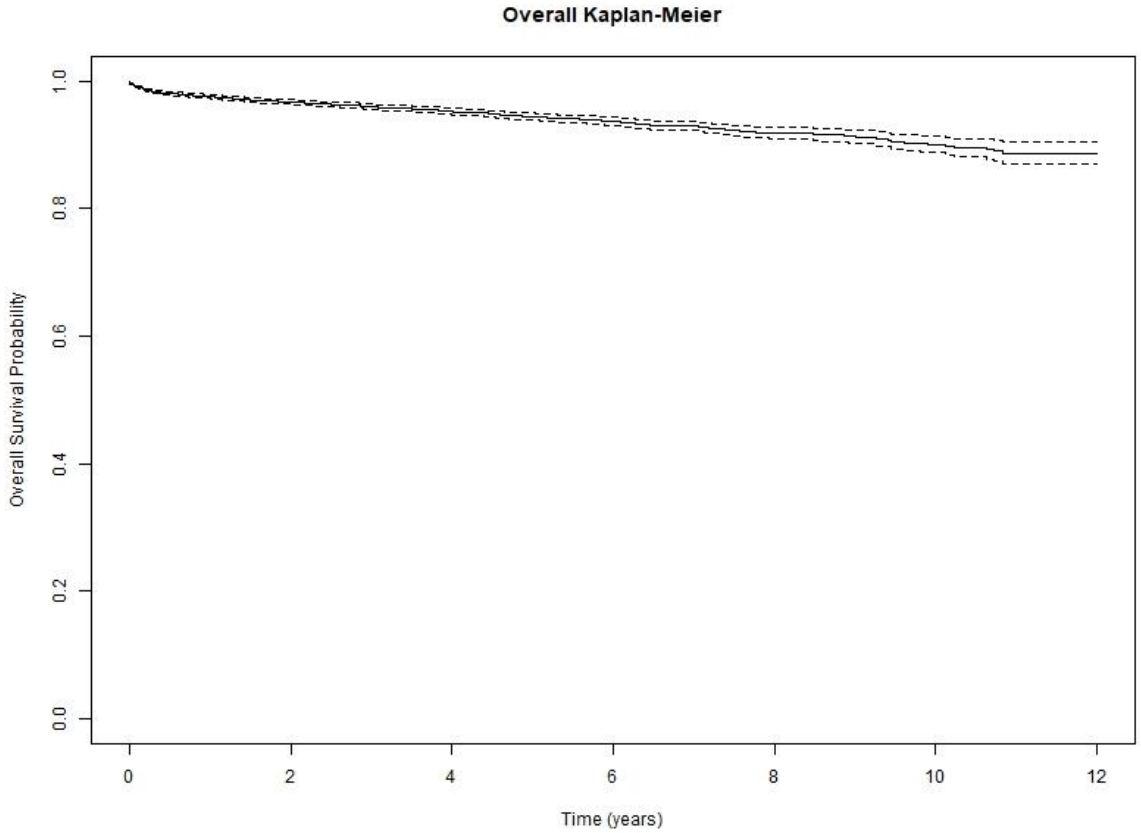
NA's :234	NA's :113	NA's :9	NA's :2250	NA	NA	NA	NA	NA

Overall survival probability 12 years after transplant



Comparing Mortality Rates

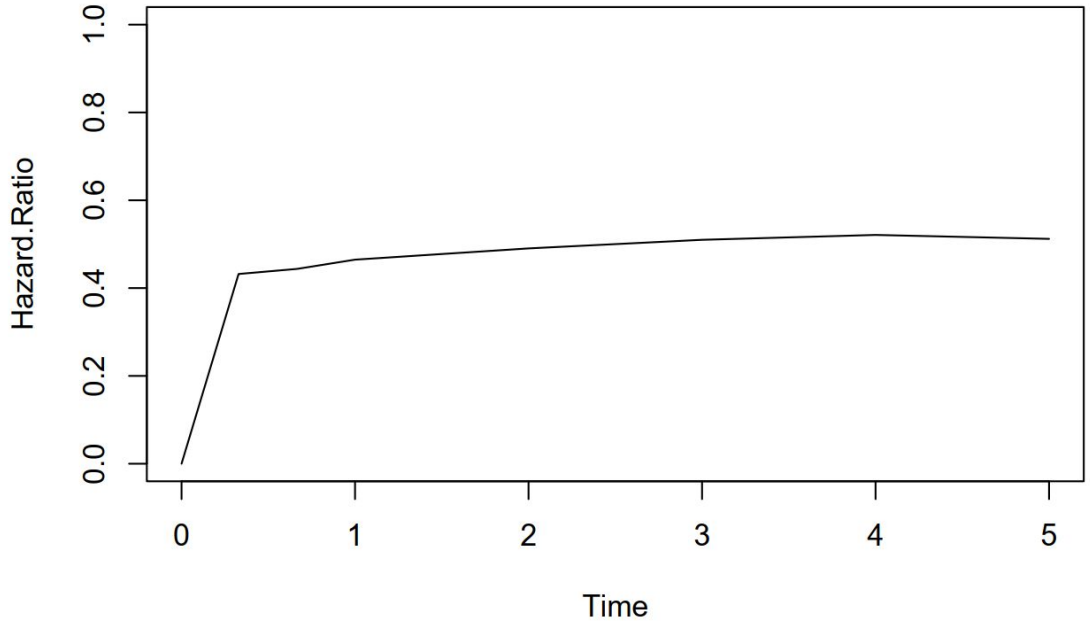
Deceased donor:

	Time	Occurrences	People at Risk	Hazard	1 - Hazard	Survival	Mortality	cumHaz
1	0.0000000	0	5148	0	1	1.0000000	0.0000000	0.0000000
99	0.3287671	0	4637	0	1	0.9898905	0.0101095	0.0101592
190	0.6657534	0	4374	0	1	0.9870652	0.0129348	0.0130170
286	1.0000000	0	4056	0	1	0.9845543	0.0154457	0.0155638
515	2.0000000	0	3428	0	1	0.9782992	0.0217008	0.0219362
745	3.0000000	0	2829	0	1	0.9730770	0.0269230	0.0272876
973	4.0000000	0	2297	0	1	0.9669280	0.0330720	0.0336255
1206	5.0000000	0	1789	0	1	0.9616331	0.0383669	0.0391150

Living donor:

	Time	Occurrences	People at Risk	Hazard	1 - Hazard	Survival	Mortality	cumHaz
1	0.0000000	4	4627	0.0008645	0.9991355	0.9991355	0.0008645	0.0008645
106	0.3287671	0	4158	0.0000000	1.0000000	0.9766033	0.0233967	0.0236692
203	0.6657534	0	3897	0.0000000	1.0000000	0.9708459	0.0291541	0.0295813
305	1.0000000	2	3630	0.0005510	0.9994490	0.9667654	0.0332346	0.0337926
562	2.0000000	0	3023	0.0000000	1.0000000	0.9557460	0.0442540	0.0452542
829	3.0000000	0	2419	0.0000000	1.0000000	0.9472001	0.0527999	0.0542342
1094	4.0000000	0	1853	0.0000000	1.0000000	0.9365245	0.0634755	0.0655662
1343	5.0000000	0	1408	0.0000000	1.0000000	0.9250764	0.0749236	0.0778614

Comparing Mortality Rates

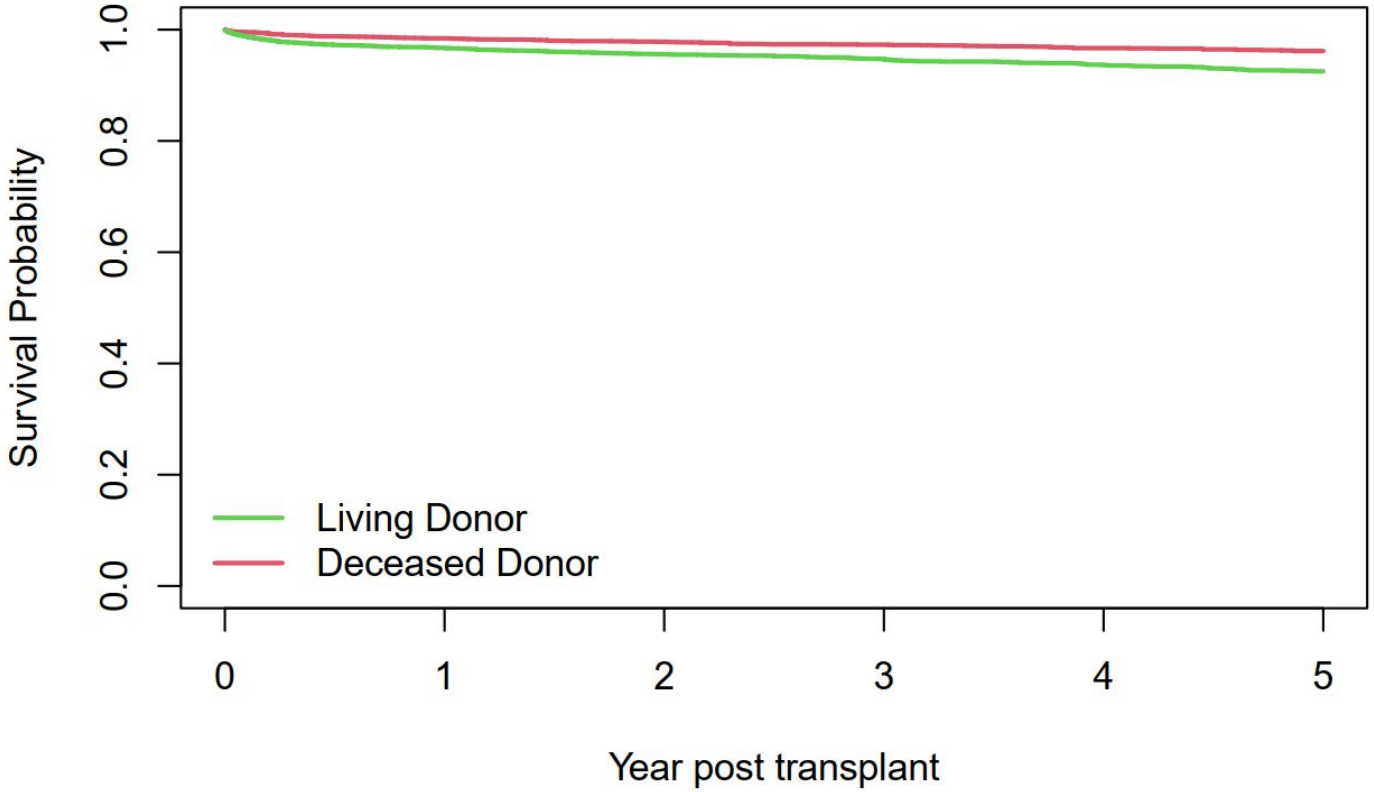


When dividing deceased donor mortality by living donor mortality, we find a ratio of roughly 0.5.

This suggests that the risk of death is about twice as high if the donor is still alive.

Counter-intuitive? One would assume that a kidney from a living donor would lead to higher survival

Comparing Kaplan-Meier Curves between Donor Types



Cox model with donor type as predictor

```
## Call:
## coxph(formula = Surv(fu, death) ~ txtype, data = unos_data)
##
##   n= 9775, number of events= 465
##
##           coef exp(coef) se(coef)     z Pr(>|z|)
## txtype 0.64469   1.90539  0.09558 6.745 1.53e-11 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##        exp(coef) exp(-coef) lower .95 upper .95
## txtype     1.905     0.5248      1.58     2.298
##
## Concordance= 0.586  (se = 0.012 )
## Likelihood ratio test= 47.1  on 1 df,   p=7e-12
## Wald test            = 45.5  on 1 df,   p=2e-11
## Score (logrank) test = 47.09  on 1 df,   p=7e-12
```

The exp(coef) value of 1.90539 represents the hazard ratio for living donor kidney recipients compared to deceased donor kidney recipients.

This means that the hazard of mortality is **1.91 times** higher for living donor kidney recipients compared to deceased donor kidney recipients. (wrong coding ?)

Cox Model with Recipient Age (Continuous) as Predictor

```
Call:
coxph(formula = Surv(fu, death) ~ age.1, data = unos_data)

  n= 9766, number of events= 464
   (9 observations deleted due to missingness)

           coef exp(coef)  se(coef)      z Pr(>|z|)
age.1 -0.042550  0.958342  0.008434 -5.045 4.53e-07 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

      exp(coef) exp(-coef) lower .95 upper .95
age.1    0.9583      1.043    0.9426    0.9743

Concordance= 0.586  (se = 0.016 )
Likelihood ratio test= 24.81  on 1 df,   p=6e-07
Wald test            = 25.45  on 1 df,   p=5e-07
Score (logrank) test = 25.75  on 1 df,   p=4e-07
```

Cox Model with Recipient Age (Categorical) as Predictor

```
## Call:
## coxph(formula = Surv(fu, death) ~ age_cat, data = unos_data)
##
##   n= 7303, number of events= 348
##    (44 observations deleted due to missingness)
##
##                    coef exp(coef) se(coef)      z Pr(>|z|)
## age_cat(10,15]  -0.1336    0.8750   0.1294 -1.032    0.302
## age_cat(15,Inf] -0.1093    0.8964   0.1303 -0.839    0.401
##
##                 exp(coef) exp(-coef) lower .95 upper .95
## age_cat(10,15]     0.8750      1.143    0.6789     1.128
## age_cat(15,Inf]    0.8964      1.116    0.6944     1.157
##
## Concordance= 0.53  (se = 0.016 )
## Likelihood ratio test= 1.25  on 2 df,   p=0.5
## Wald test            = 1.26  on 2 df,   p=0.5
## Score (logrank) test = 1.26  on 2 df,   p=0.5
```

Multivariate Cox Model with All Variables as Predictors

```
Call:
coxph(formula = Surv(fu, death) ~ cold_isc + sex + txtype + hlamat +
    age.1 * age, data = unos_data, method = "breslow")

  n= 7347, number of events= 351
   (2428 observations deleted due to missingness)

               coef  exp(coef)   se(coef)      z Pr(>|z|)
cold_isc   0.0047135  1.0047247  0.0067681  0.696  0.48616
sex       -0.0806924  0.9224774  0.1086716 -0.743  0.45776
txtype     0.3471755  1.4150650  0.1891947  1.835  0.06650 .
hlamat    -0.0612583  0.9405802  0.0443540 -1.381  0.16724
age.1     -0.0666207  0.9355500  0.0222801 -2.990  0.00279 **
age       -0.0224923  0.9777588  0.0096357 -2.334  0.01958 *
age.1:age  0.0016306  1.0016319  0.0007316  2.229  0.02583 *
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

Backward Selection Method

```
Call:
coxph(formula = Surv(fu, death) ~ sex + txtype + hlamat + age.1 *
    age, data = unos_data, method = "breslow")

  n= 9433, number of events= 449
   (342 observations deleted due to missingness)

               coef  exp(coef)   se(coef)      z Pr(>|z|)
sex       -0.0999397  0.9048920  0.0959073 -1.042  0.29739
txtype     0.3773892  1.4584718  0.1222194  3.088  0.00202 **
hlamat    -0.0915721  0.9124955  0.0402870 -2.273  0.02303 *
age.1     -0.1313814  0.8768832  0.0178443 -7.363 1.80e-13 ***
age       -0.0453338  0.9556784  0.0077646 -5.838 5.27e-09 ***
age.1:age  0.0033324  1.0033380  0.0005994  5.560 2.70e-08 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

Sex is the least significant predictor so we dropped it

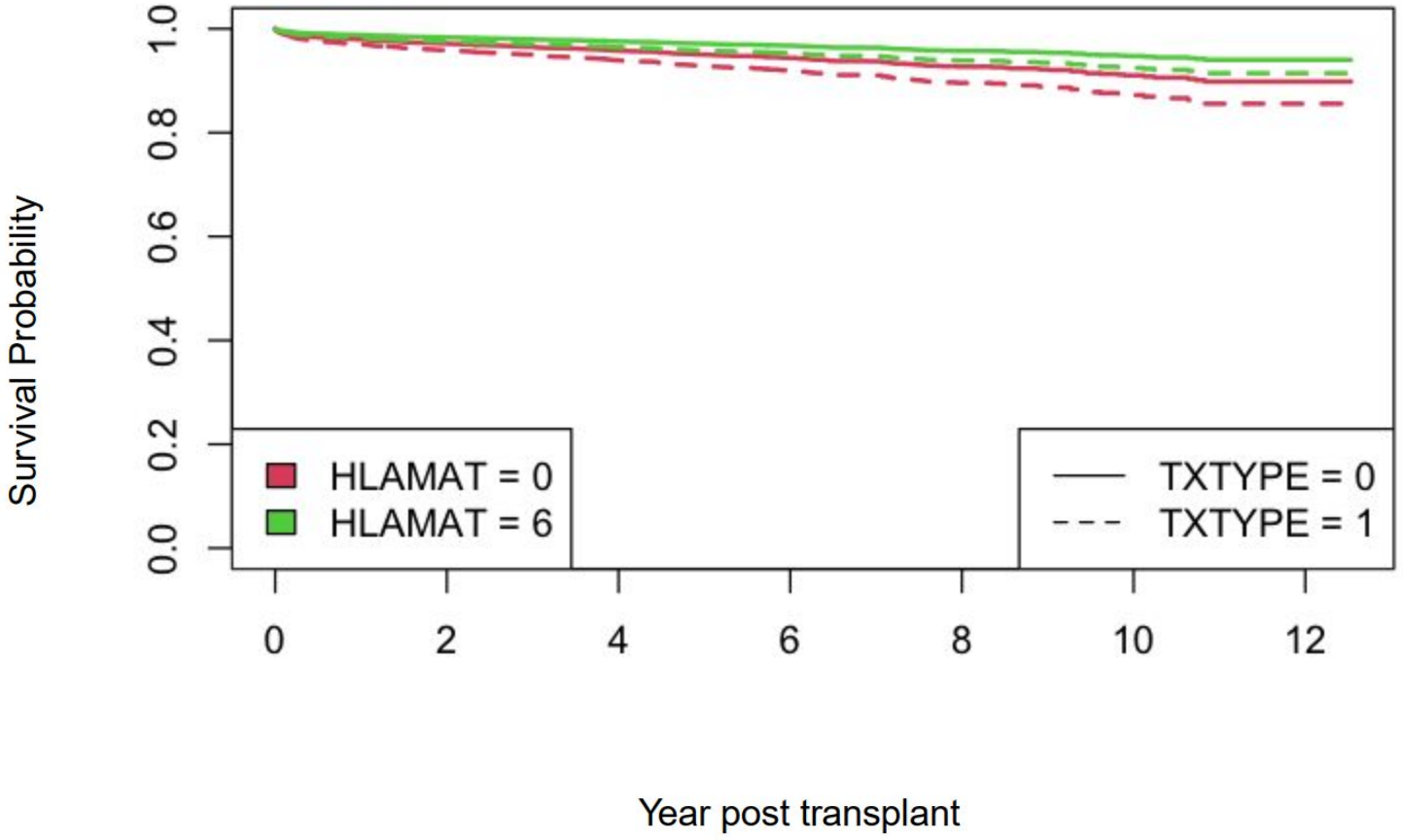
Final model

```
Call:
coxph(formula = Surv(fu, death) ~ txtype + hlamat + age.1 * age,
    data = unos_data, method = "breslow")

  n= 9433, number of events= 449
   (342 observations deleted due to missingness)

               coef  exp(coef)   se(coef)      z Pr(>|z|)
txtype     0.3735962  1.4529503  0.1221736  3.058  0.00223 **
hlamat    -0.0924870  0.9116611  0.0402858 -2.296  0.02169 *
age.1     -0.1303368  0.8777997  0.0178149 -7.316 2.55e-13 ***
age       -0.0453928  0.9556221  0.0077665 -5.845 5.08e-09 ***
age.1:age  0.0033232  1.0033287  0.0005993  5.545 2.94e-08 ***
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1
```

Sensitivity Analysis

- Investigate extremes of Donor-Patient Match under Living and Deceased Donors
- Median Patient Age, Donor Age used

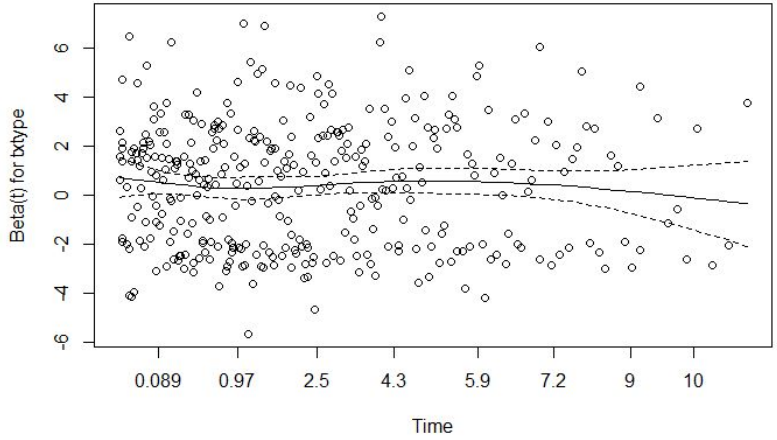
Survival Function for HLAMAT and TXTYPE Groups

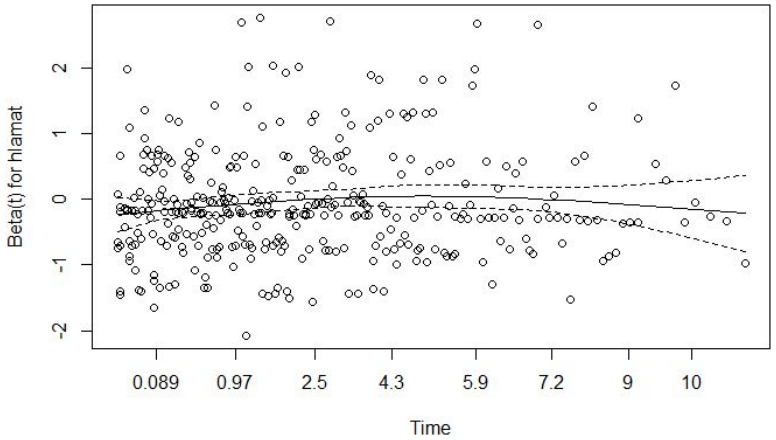


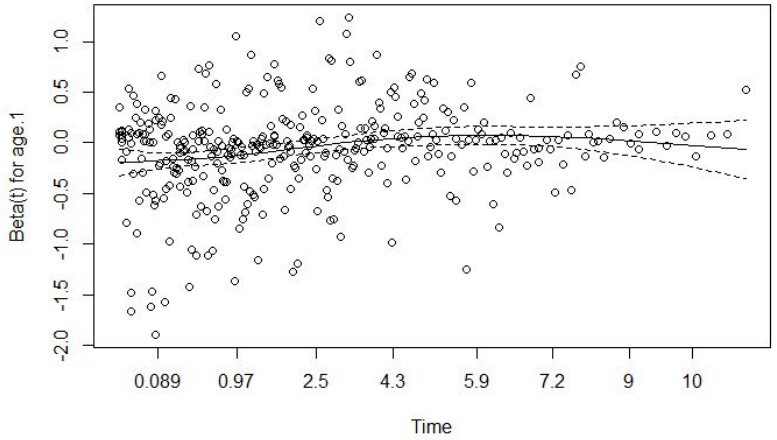
Proportional Hazard Assumptions (cox.zph)

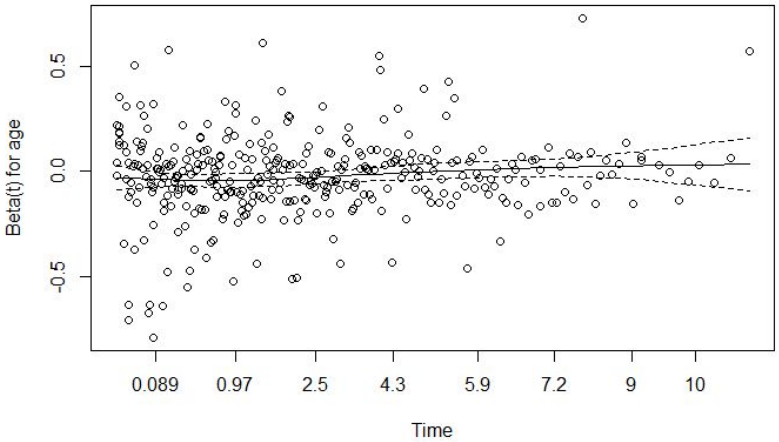
	chisq	df	p
txtype	2.95	1	0.08577
hlamat	8.36	1	0.00384
age.1	34.19	1	5.0e-09
age	11.43	1	0.00072
age.1:age	22.53	1	2.1e-06
GLOBAL	42.68	5	4.3e-08

Proportional Hazard Assumptions (Schoenfeld Residuals)

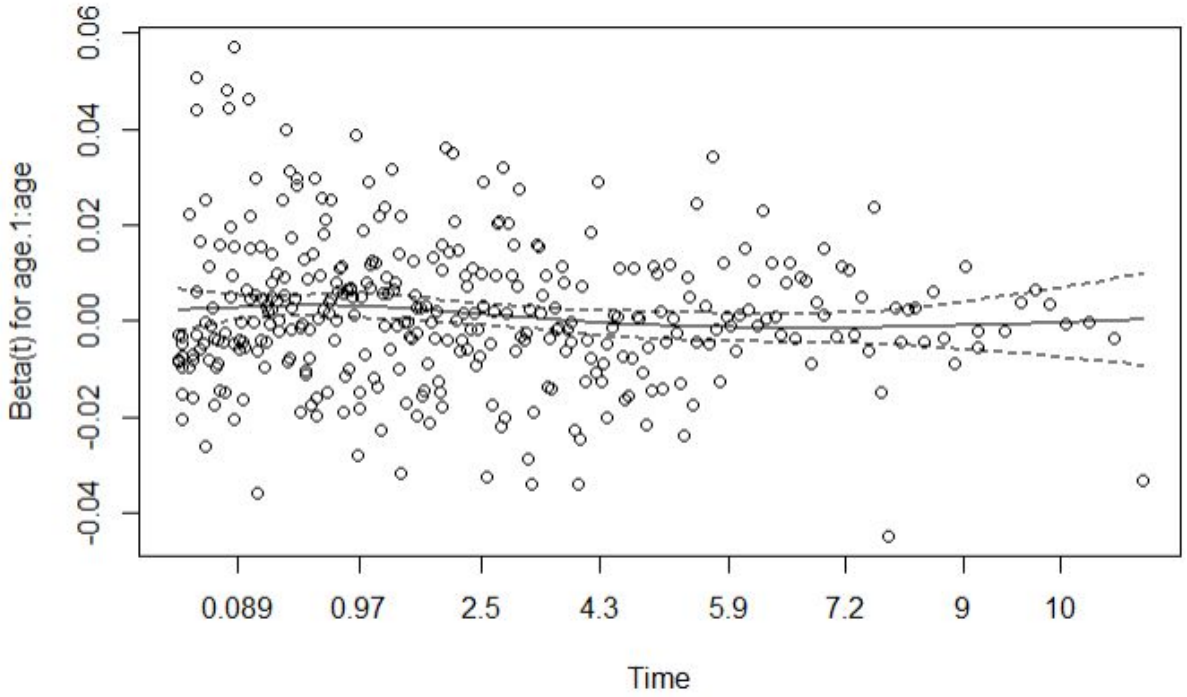








Proportional Hazard Assumptions (Schoenfeld Residuals)



Conclusion

- Donor Status has the greatest impact, Donor Age too
- Interaction between Donor, Patient Age is small, yet significant
- Donor, Patient being Older raises chance of survival
- PH assumptions violated - Predictors not very consistent.

Questions?

Thank you for listening.