Survival Analysis
Module III: Deep Dive

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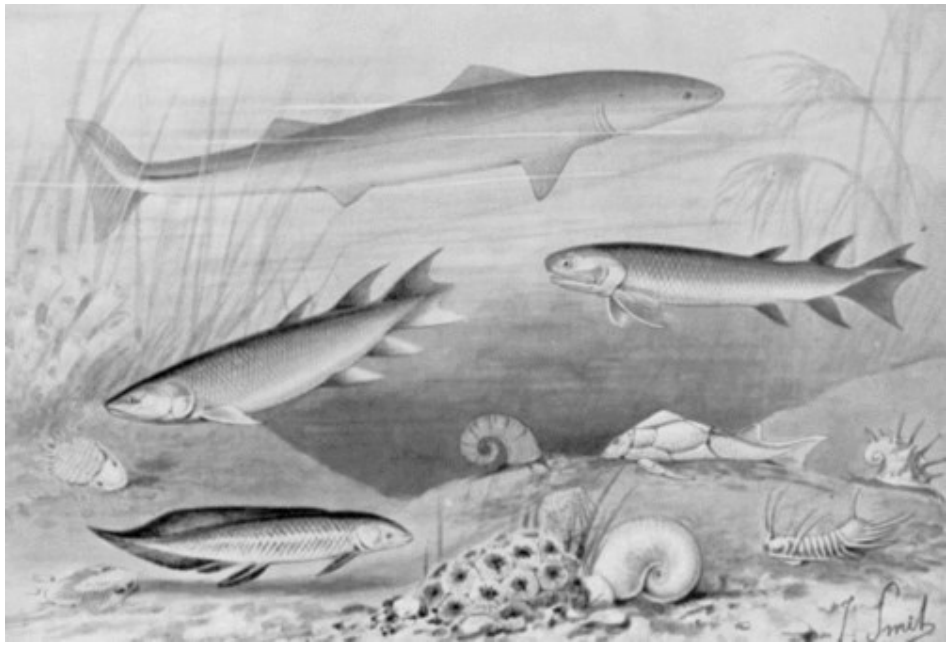
Introduction

- Last time, we wandered in the trees of survival analysis and examined how to determine survival times of a group or across groups

- Today, we'll swim over to examine the effects of factors on survival times via tree and regression models
- We will also look at detailed examples in R and SAS



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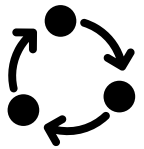
Reviewing the Basics



- Survival analysis uses time-to-event data (correct format needed)
- Almost always involves censoring
- Common calculations are survival and hazard function
- Kaplan-Meier curves are non-parametric
- Parametric curves also available with more math
- The curves of two groups can be compared with log-rank test
- Extending beyond two groups or involving co-variates requires tree-based methods or Cox regression

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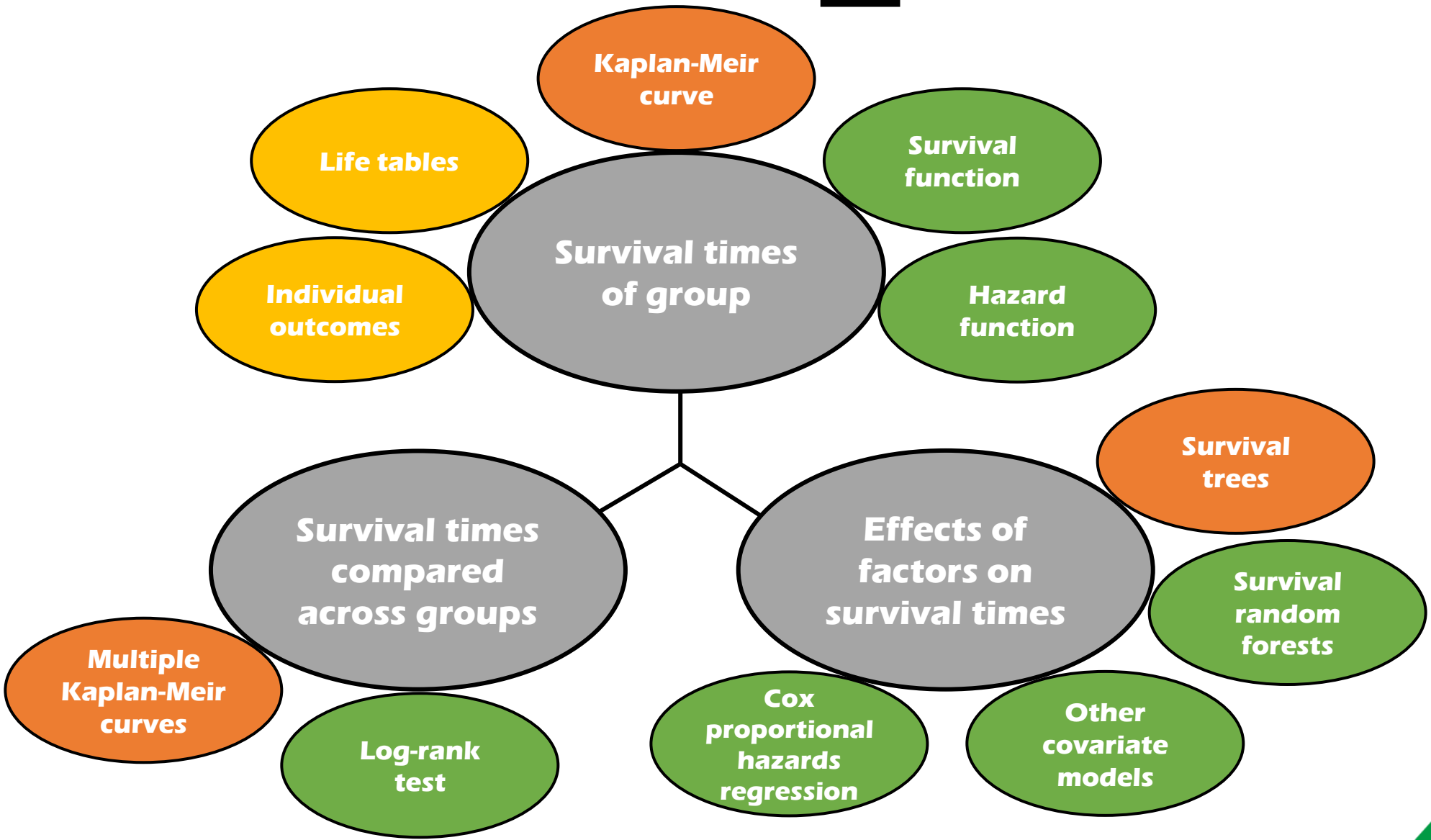

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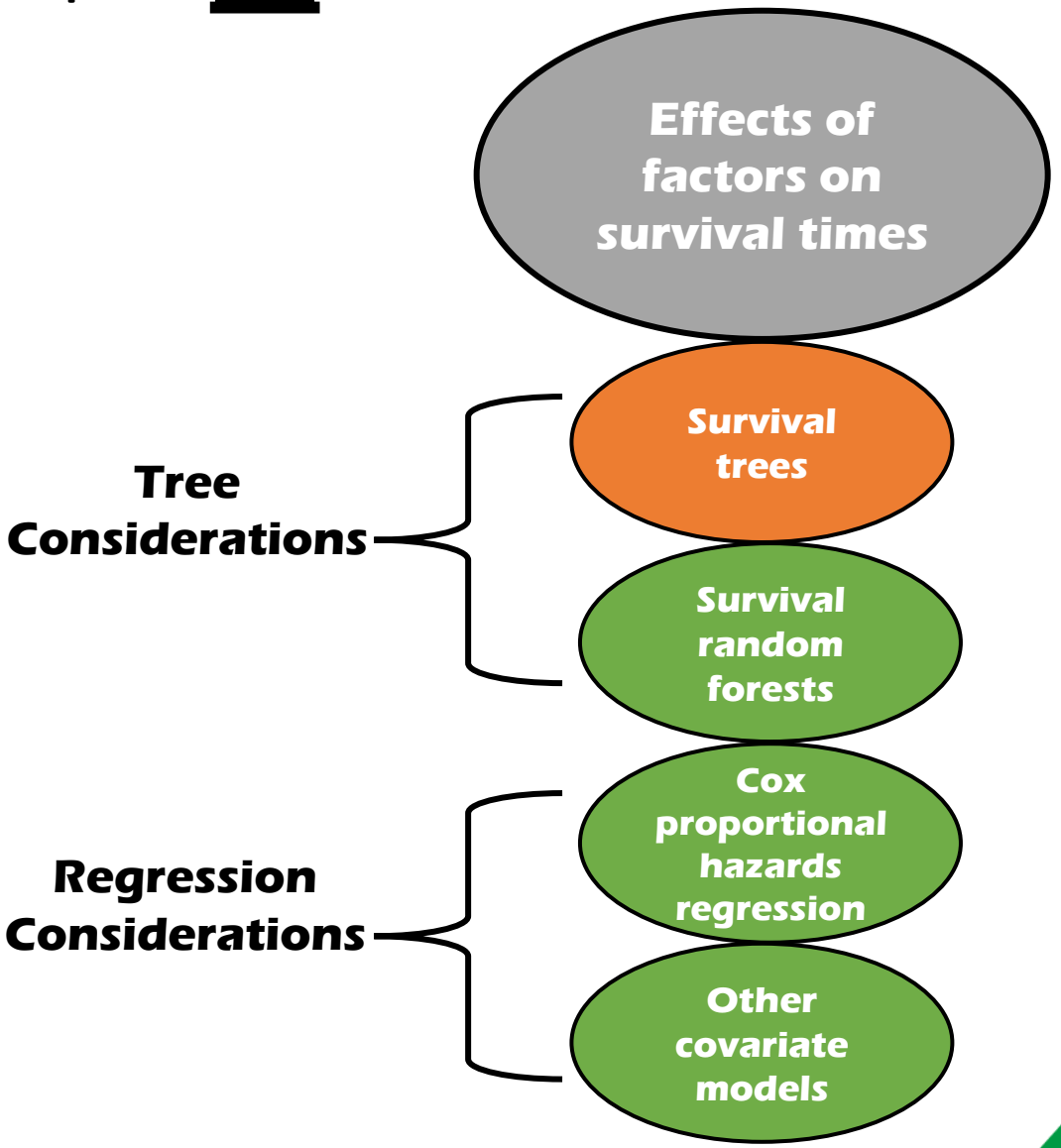

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Regression Considerations

- Cox Proportional Hazards regression, aka Cox regression, is used to predicted the probability of an event (death/otherwise) across time for given values of predictor variables [1]
- Extension of basic survival analysis; analogous of going from simple to multiple regression [2]
- Better yet, think of logistic regression and odds ratios
- Relating several risk factors to survival time by measuring hazard rate [2]
- Cox model is semi-parametric
- Parametric regression models are also available

Risk Factor [2]	Parameter Estimate	P-value
Age (years)	0.11149	0.0001
Male sex	0.67958	0.0001

Risk Factor	Parameter Estimate	P-value	Hazard Radio (CI)
Age (years)	0.11691	0.0001	1.124 (1.111-1.138)
Male sex	0.40359	0.0002	1.497 (1.215-1.845)
Systolic Blood Pressure	0.01645	0.0001	1.017 (1.012-1.021)
Current Smoker	0.76798	0.0001	2.155 (1.758-2.643)
Total Serum Cholesterol	-0.00209	0.0963	0.998 (0.995-2.643)
Diabetes	-0.02366	0.1585	0.816 (0.615-1.083)

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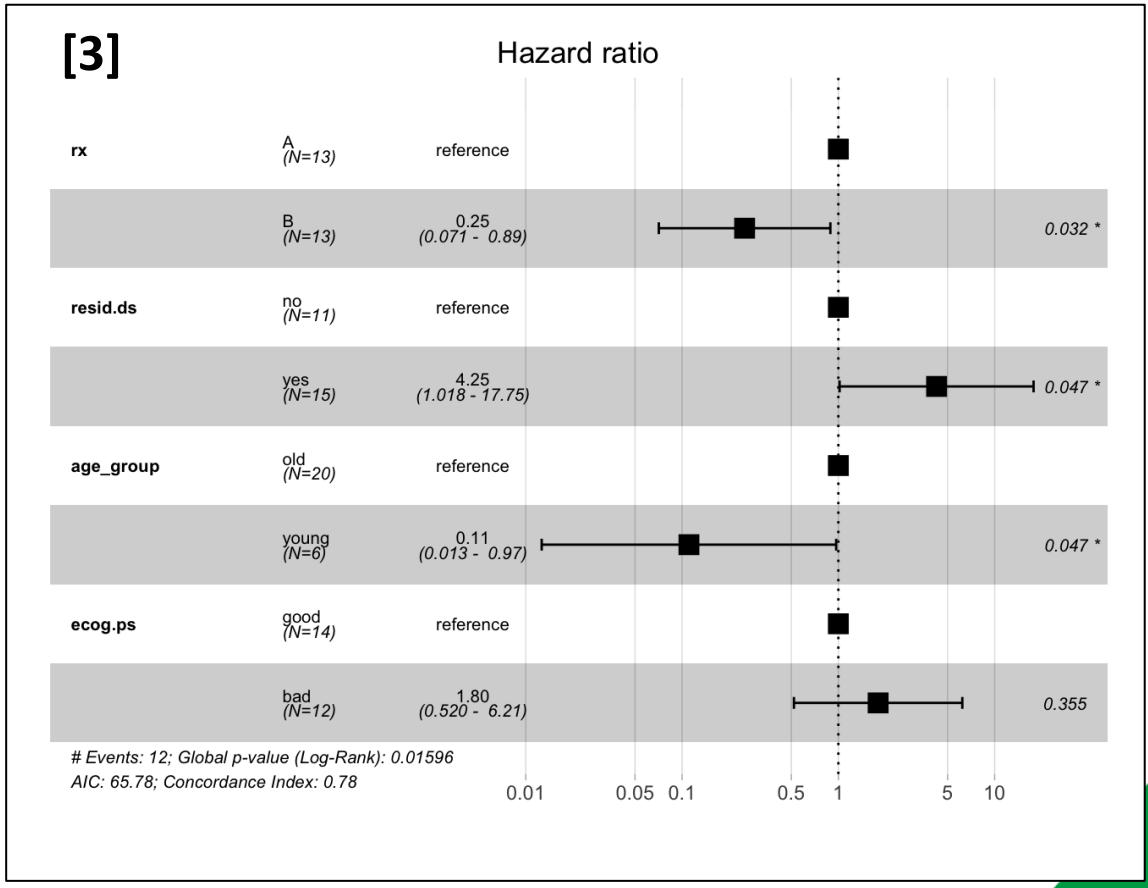
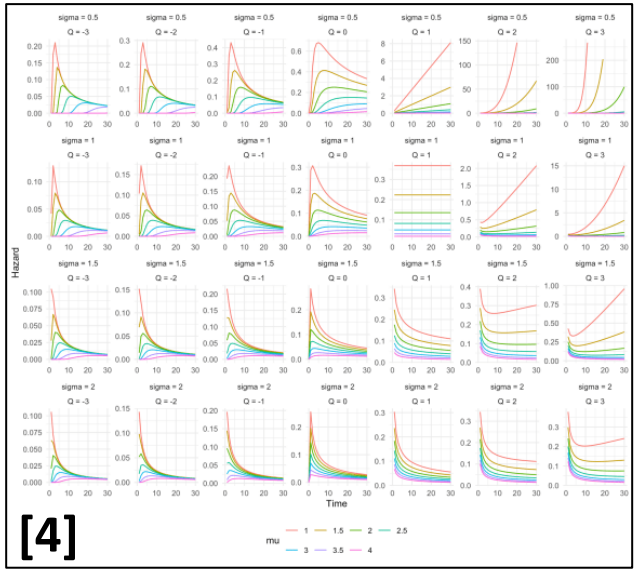
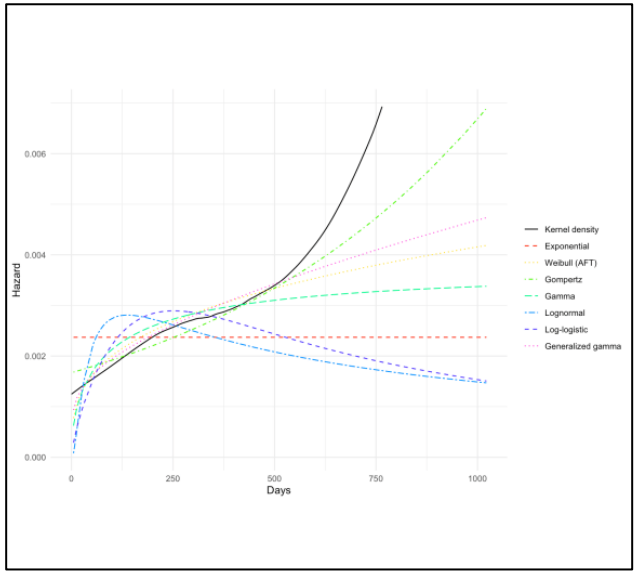


Regression Considerations 2

- Cox models do not assume any particular baseline survival distribution [4]
- Useful but have limitations (ex. poor extrapolation)
- Parametric survival models can do the trick
- Models the data in more detail by using maximum likelihood with an appropriate distribution [5]
- Links survival time or hazard of an individual to covariates using a specified probability distribution [6]
- Distributions include Weibull, exponential, log-normal, etc. [7, 8]
- Different distributions fit different hazards data
- Used for survival, hazard, and proportional hazards



[4]



Regression Considerations 3

[9] Type of Model	Baseline Hazard (Time + event)	Covariates
Non-parametric	No distribution assumed	No distribution assumed
Semi-parametric	No distribution assumed	Some distribution assumed
Parametric	Some distribution assumed	Some distribution assumed

Exponential

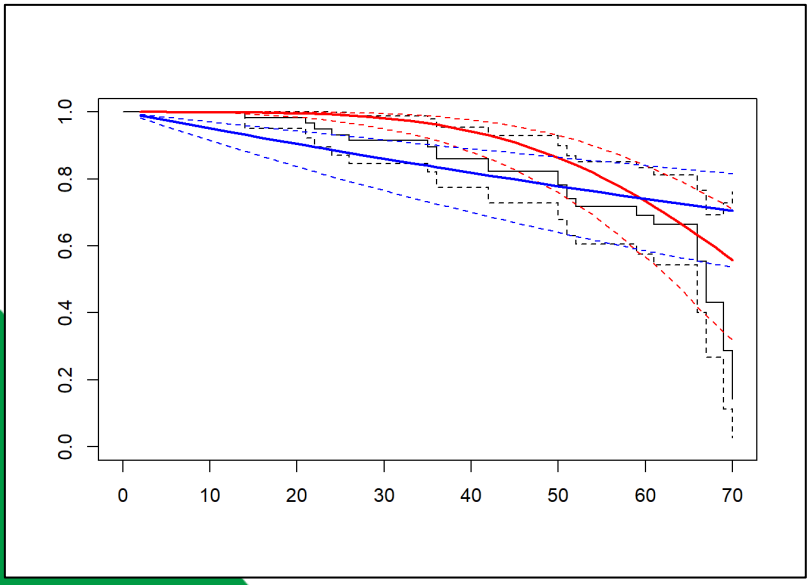
Analysis of Maximum Likelihood Parameter Estimates

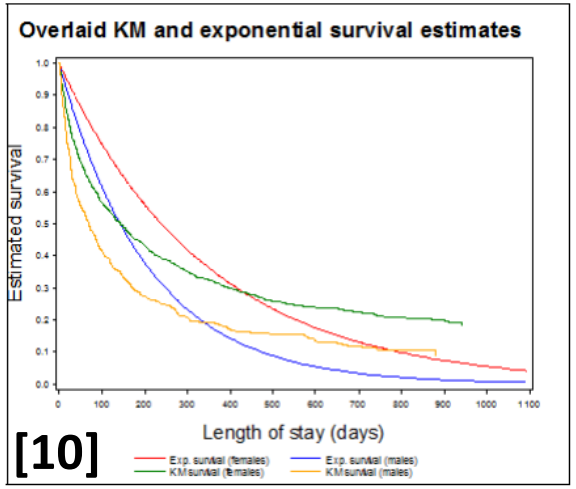
Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	5.8421	0.0333	5.7769	5.9074	30785.8	<.0001
gender	1	-0.5162	0.0619	-0.6375	-0.3948	69.51	<.0001
Scale	0	1.0000	0.0000	1.0000	1.0000		
Weibull Shape	0	1.0000	0.0000	1.0000	1.0000		

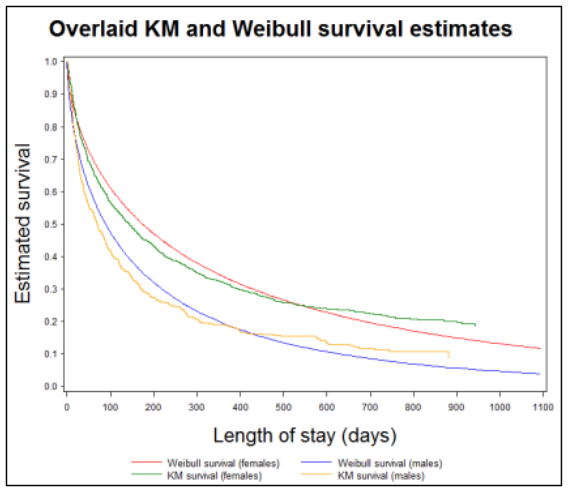
Weibull

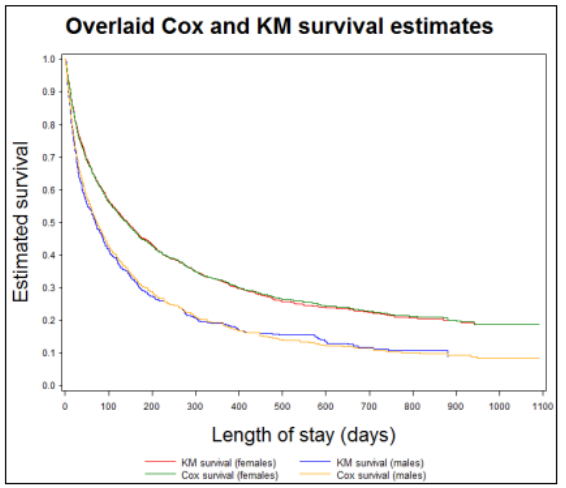
Analysis of Maximum Likelihood Parameter Estimates

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	5.7564	0.0542	5.6502	5.8627	11280.0	<.0001
gender	1	-0.6735	0.1011	-0.8716	-0.4754	44.40	<.0001
Scale	1	1.6275	0.0378	1.5551	1.7032		
Weibull Shape	1	0.6144	0.0143	0.5871	0.6430		









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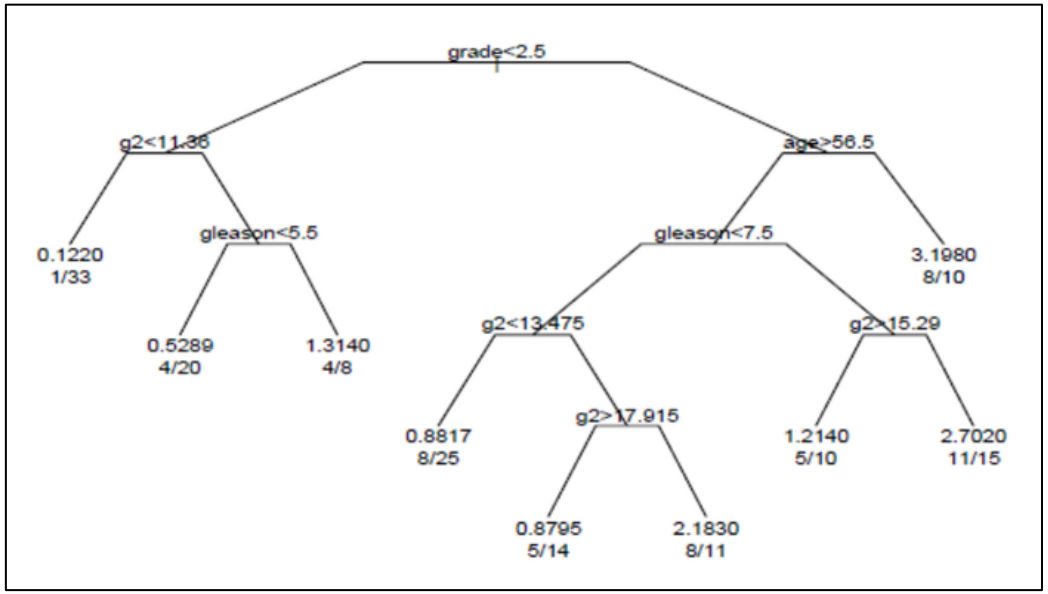
Tree Considerations

- Survival Tree Analysis
  - Alternative method to Cox regression, which tries to separate events (0/1) via partitioning [11]
  - Each branch indicates a split via a value of the variable
  - Ends are called terminal nodes, and they indicate the number of subjects with an event
- Survival Random Forest
  - Extension of survival tree analysis [12]
  - Instead of building one tree, many trees are built and then averaged
  - Prediction errors are estimated by resampling (bootstrap)
  - Survival and hazard curves can be generated



Other Considerations

What if you have multiple events?

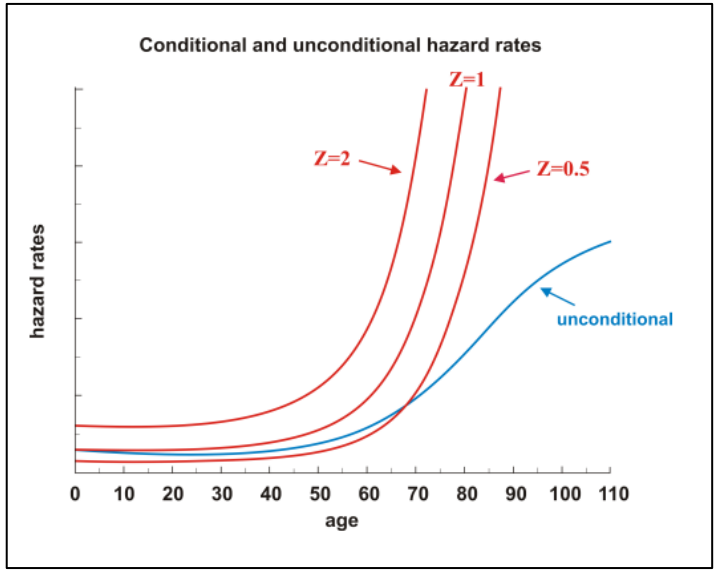
- Ex. Multiple tumor sites or heterogenous populations
- **Frailty models**
- Account for correlation within a group by introducing 'frailty term' as random effect [13, 14]
- Idea is to consider event (ex. tumor) as locus and the person/family/liter as the random effect [15]
- More broadly for accounting for the fact that individuals do not have the same underlying risk [16]

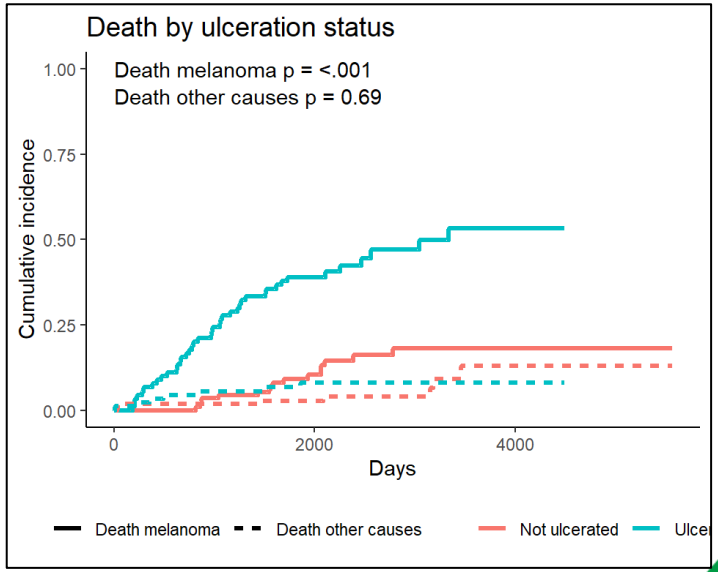
What if there are multiple ways to die?

- Ex. death from breast cancer or stroke
- **Competing risks**
- Partitions events that occur in model into discrete competing events [14]
- Cumulative Index function most used [17]

What if time is discrete rather than continuous?

- Ex. time until graduation measured in semesters
- **Logistic regression**
- Tricky bit is setting up data so that censoring is incorporated [14]
- Helpful introduction here [18]





Other Considerations 2

What if you are interested in a covariate measure **after** follow-up?

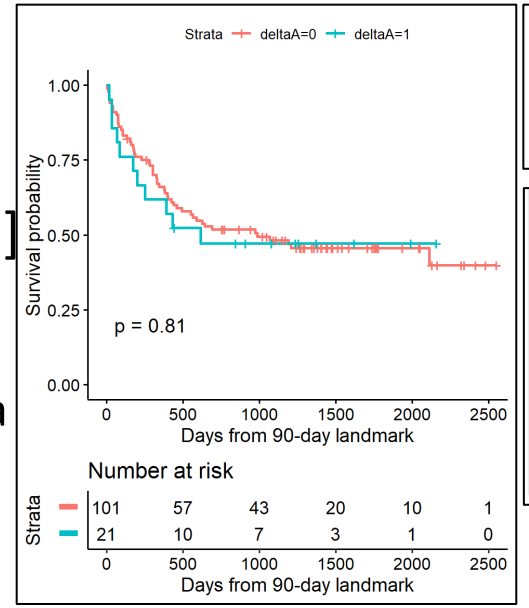
- Ex. tumor response to treatment
- **Landmark** or **time-dependent covariate** analysis [19]
  - **Landmark** -> select fixed time after baseline, subset population, Cox regression as normal
  - **Time-dependent** -> more work involved setting up data with multiple time intervals for each patient to account for different levels of covariate across time [20]

What about survival estimates for those who have already survived a given time or event?

- **Conditional survival**
- Different curves for different conditions [19]

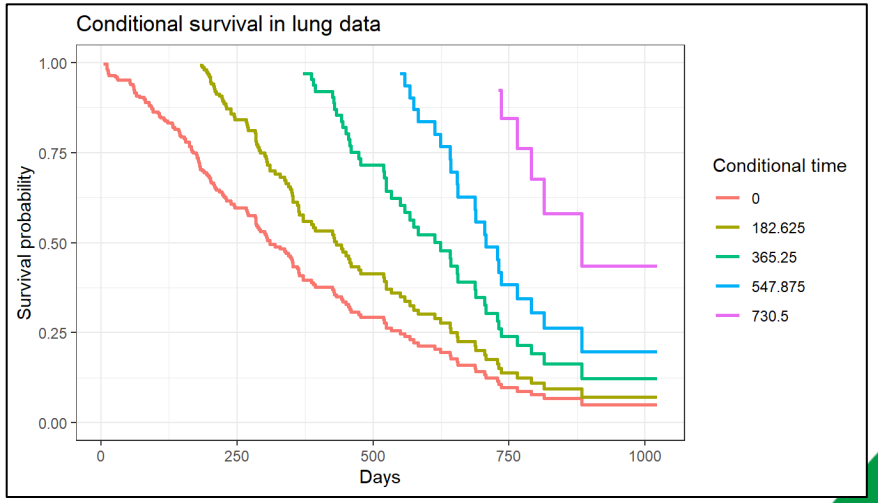
What if you're an obligate Bayesian?

- **Bayesian** methods available too [21]



	subject	time1	time2	death	creatinine
1	5	0	90	0	0.9
2	5	90	120	0	1.5
3	5	120	185	1	1.2

##	my_id	T1	delta1	id	tstart	tstop	death	agvhd
## 1	1	2081	0	1	0	67	0	0
## 2	1	2081	0	1	67	2081	0	1
## 3	2	1602	0	2	0	1602	0	0
## 4	3	1496	0	3	0	1496	0	0
## 5	4	1462	0	4	0	70	0	0
## 6	4	1462	0	4	70	1462	0	1
## 7	5	1433	0	5	0	1433	0	0



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Assessment 1

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Step-by-step Example 1.1

Survival Analysis in R

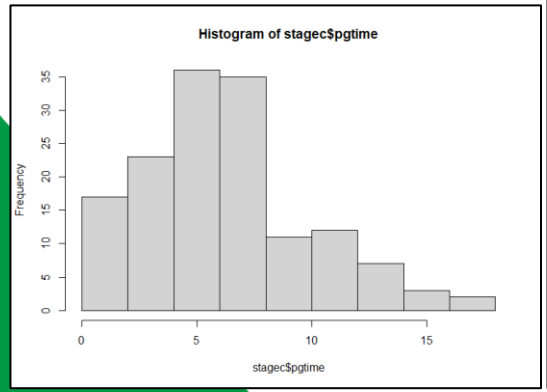
Prostate Cancer: Cox regression with single variable

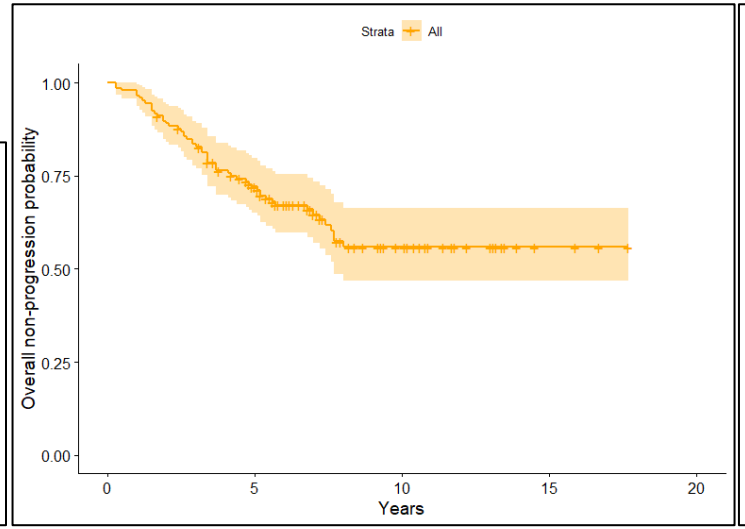
```
library(ggplot2)
library(survival)
library(survminer)
library(broom)
library(knitr)
library(gtsummary)
library(muhaz)
library(flexsurv)
library(data.table)
library(rpart)
library(randomForestSRC)
library(MASS)
```

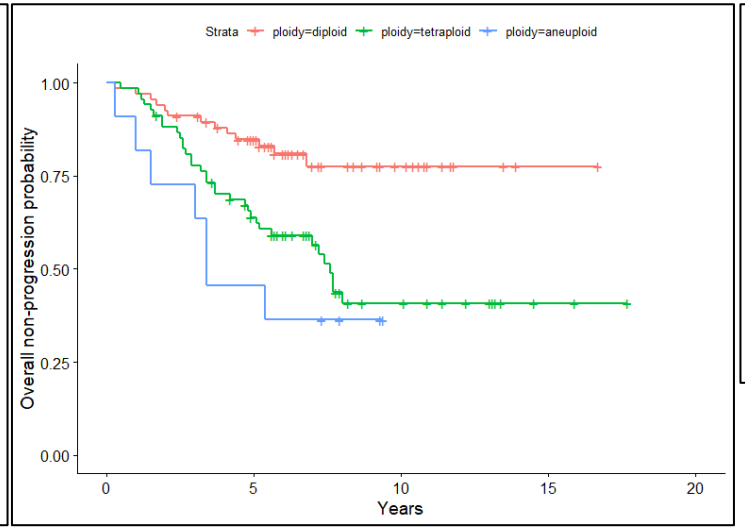
```
head(stagec)
hist(stagec$pgtime) #years
table(stagec$pgstat)
fit1 <- ggsurvplot(
  fit = survfit(Surv(pgtime, pgstat)~1, data=stagec),
  xlab="Years",
  ylab="Overall non-progression probability",
  palette = "orange")
fit1
```

0	1
92	54

```
mod1 <-coxph(Surv(pgtime,pgstat)~ploidy, data=stagec)
mod1 %>%
  gtsummary::tbl_regression(exp=TRUE)
fit2 <- ggsurvplot(
  fit = survfit(Surv(pgtime, pgstat)~ploidy, data=stagec),
  xlab="Years",
  ylab="Overall non-progression probability")
fit2
```







Characteristic	HR[1]	95% CI[1]	p-value
ploidy			
diploid	—	—	
tetraploid	2.84	1.50, 5.39	0.001
aneuploid	4.34	1.73, 10.9	0.002

[1] HR = Hazard Ratio, CI = Confidence Interval

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Step-by-step Example 1.2

Prostate Cancer: Cox regression with multiple variables

```
mod2.1 <-coxph(Surv(pgtime, pgstat)~ploidy
               + age + factor(eet)
               + g2 + factor(grade) + factor(gleason),
               data=stagec)
mod2.1 %>%
 gtsummary::tbl_regression(exp=TRUE)

mod2.2 <-coxph(Surv(pgtime, pgstat)~ploidy
               + age + factor(eet)
               + g2 + grade + gleason,
               data=stagec)
mod2.2 %>%
 gtsummary::tbl_regression(exp=TRUE)

mod2.3 <-coxph(Surv(pgtime, pgstat)~ploidy
               + g2,
               data=stagec)
mod2.3 %>%
 gtsummary::tbl_regression(exp=TRUE)
```

Characteristic	HR[1]	95% CI[1]	p-value
ploidy			
diploid	—	—	
tetraploid	3.23	1.78, 5.88	<0.001
aneuploid	5.39	1.93, 15.0	0.001
age	0.99	0.94, 1.05	0.8
factor(eet)			
1	—	—	
2	1.22	0.64, 2.33	0.5
g2	0.95	0.92, 0.99	0.006
factor(grade)			
1	—	—	
2	5,491,404	2,561,074, 11,774,560	<0.001
3	10,958,263	5,688,299, 21,110,621	<0.001
4	59,372,886	20,437,407, 172,484,680	<0.001
factor(gleason)			
3	—	—	
4	0.08	0.02, 0.31	<0.001
5	0.02	0.01, 0.06	<0.001
6	0.05	0.02, 0.09	<0.001
7	0.07	0.04, 0.13	<0.001
8	0.06	0.03, 0.13	<0.001
9	0.08	0.02, 0.25	<0.001
10	1.00	0.16, 6.20	>0.9

[1] HR = Hazard Ratio, CI = Confidence Interval

Characteristic	HR[1]	95% CI[1]	p-value
ploidy			
diploid	—	—	
tetraploid	2.69	1.17, 6.20	0.020
aneuploid	3.39	0.92, 12.5	0.067
age	0.98	0.93, 1.04	0.5
factor(eet)			
1	—	—	
2	1.09	0.53, 2.28	0.8
g2	0.95	0.90, 1.00	0.037
grade	3.96	1.69, 9.32	0.002
gleason	1.23	0.88, 1.73	0.2

[1] HR = Hazard Ratio, CI = Confidence Interval

Characteristic	HR[1]	95% CI[1]	p-value
ploidy			
diploid	—	—	
tetraploid	4.20	1.90, 9.31	<0.001
aneuploid	7.17	2.31, 22.2	<0.001
g2	0.97	0.92, 1.01	0.2

[1] HR = Hazard Ratio, CI = Confidence Interval

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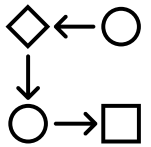
Step-by-step Example 1.3



Prostate Cancer: Parametric models [4]

```
k_haz_est <-muhaz(stagec$pgtime, stagec$pgstat)

k_haz <-data.table(time=k_haz_est$est.grid,
                   est= k_haz_est$haz.est,
                   method="Kernel density")

dists <- c("exp", "weibull", "gompertz", "gamma",
           "lognormal", "llogis", "gengamma")

dists_long <- c("Exponential", "Weibull (AFT)",
                "Gompertz", "Gamma", "Lognormal", "Log-logistic",
                "Generalized gamma")

parametric_haz <- vector(mode = "list", length = length(dists))
```

```
for (i in 1:length(dists)){
  fit <- flexsurvreg(Surv(pgtime, pgstat) ~ 1, data = stagec, dist = dists[i])
  parametric_haz[[i]] <- summary(fit, type = "hazard",
                                 ci = FALSE, tidy = TRUE)
  parametric_haz[[i]]$method <- dists_long[i]
}

parametric_haz <- rbindlist(parametric_haz)

haz <- rbind(k_haz, parametric_haz)

haz[, method := factor(method,
                       levels = c("Kernel density",
                                  dists_long))]

n_dists <- length(dists)
```

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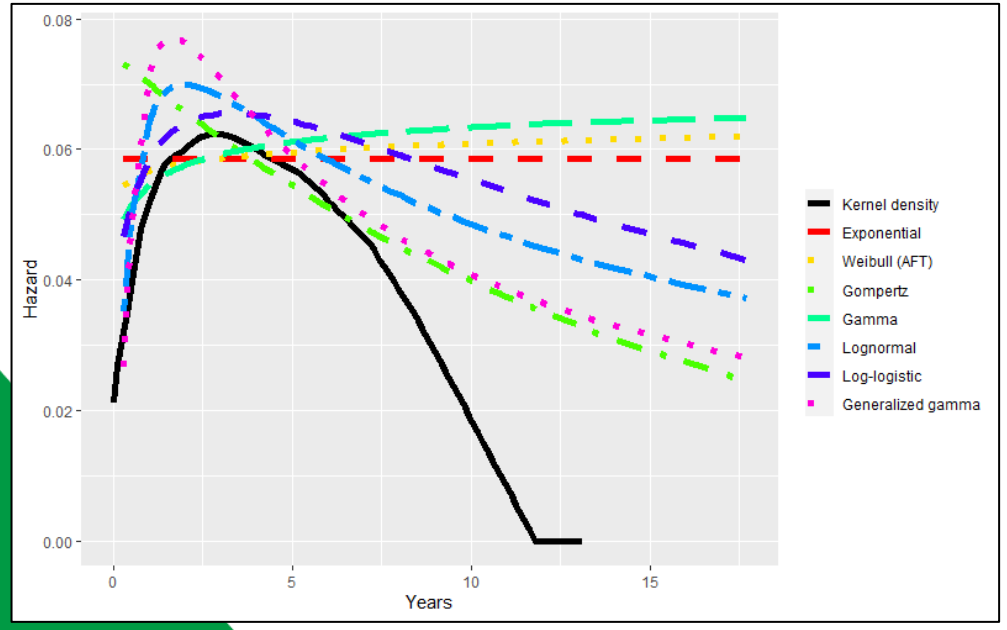
Step-by-step Example 1.3

Prostate Cancer: Parametric models

```
ggplot(haz, aes(x = time, y = est, col = method, linetype = method)) +
  geom_line(size=2) +
  xlab("Years") + ylab("Hazard") +
  scale_colour_manual(name = "",
                      values = c("black", rainbow(n_dists))) +
  scale_linetype_manual(name = "",
                        values = c(1, rep_len(2:6, n_dists)))
```




```
mod3 <-flexsurvreg(Surv(pgtime, pgstat)~ploidy,
                   data=stagec, dist='gengamma')
mod3 %>%
  gtsummary::tbl_regression(exp=TRUE)
```

Characteristic	exp(Beta)	95% CI[1]	p-value
mu	3.05	2.32, 3.78	
sigma	1.42	1.01, 2.00	
Q	-0.05	-1.02, 0.93	
ploidytetraploid	-0.85	-1.48, -0.21	0.004
ploidyaneuploid	-1.56	-2.57, -0.55	0.001

[1] CI = Confidence Interval

```
mod4 <-flexsurvreg(Surv(pgtime, pgstat)~ploidy + g2 + factor(grade),
                   data=stagec, dist='gengamma')
mod4 %>%
  gtsummary::tbl_regression(exp=TRUE)
```

Characteristic	exp(Beta)	95% CI[1]	p-value
mu	6.12	-133, 146	
sigma	1.18	1.02, 1.37	
Q	-0.56	-1.48, 0.37	
ploidytetraploid	-1.17	-1.81, -0.54	<0.001
ploidyaneuploid	-1.62	-2.75, -0.49	0.002
g2	0.07	0.03, 0.11	<0.001
factor(grade)2	-3.51	-143, 136	0.5
factor(grade)3	-4.62	-144, 135	0.5
factor(grade)4	-6.76	-146, 133	0.5

[1] CI = Confidence Interval

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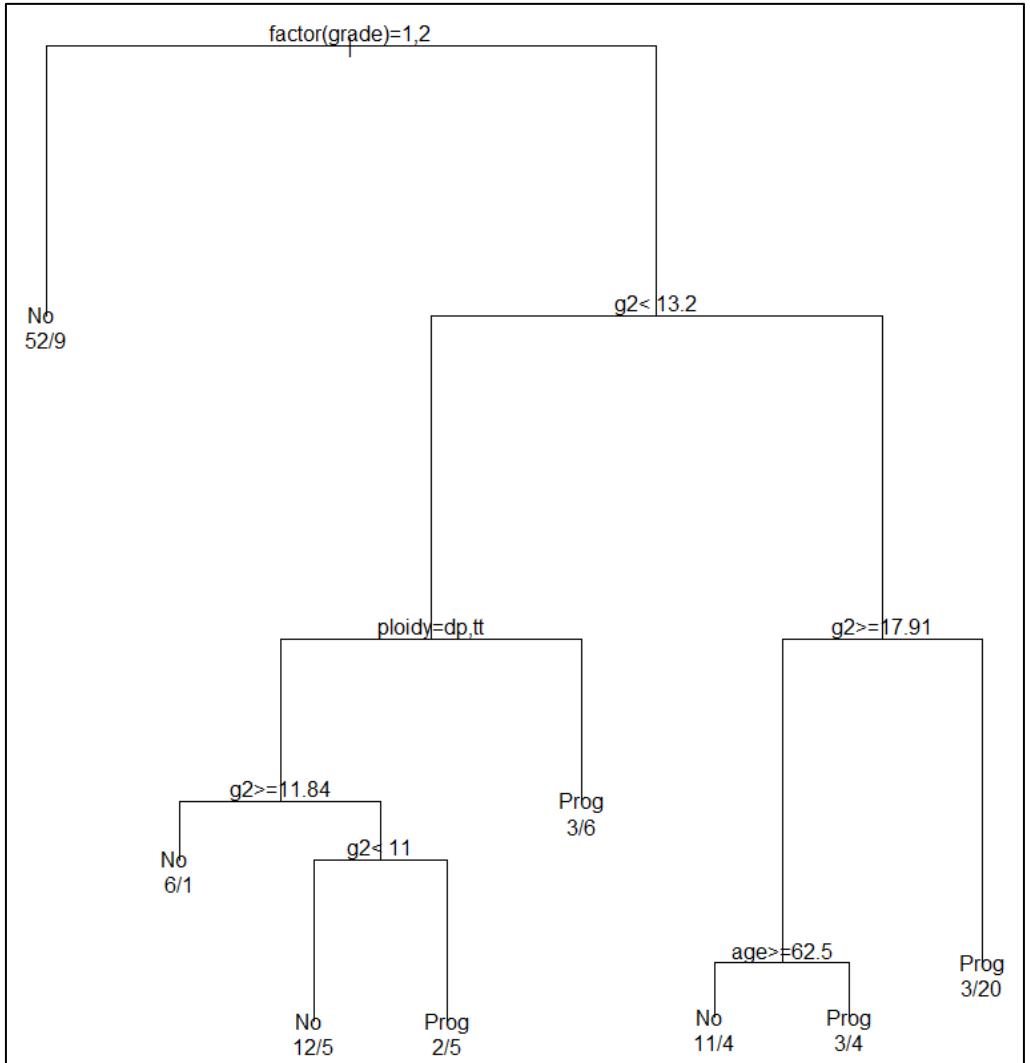
Step-by-step Example 1.4

Prostate Cancer: Survival Tree

```
stagec$progstat <- factor(stagec$pgstat, levels = 0:1,
                          labels = c("No", "Prog"))
tree1 <- rpart(progstat ~ age + factor(eet)
               + g2 + factor(grade) + factor(gleason) + ploidy,
               data = stagec, method = 'class')
par(mar=rep(0.1, 4))
plot(tree1)
text(tree1, use.n=TRUE, min=2)
par(mar=c(5.1, 4.1, 4.1, 2.1))
```



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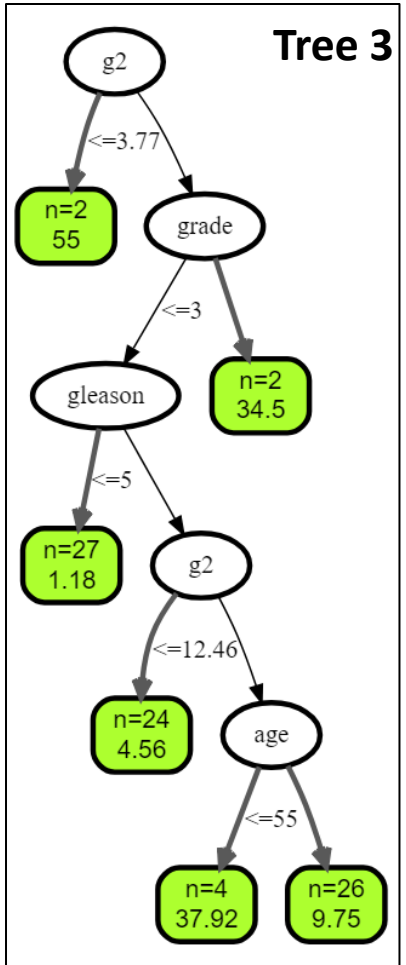
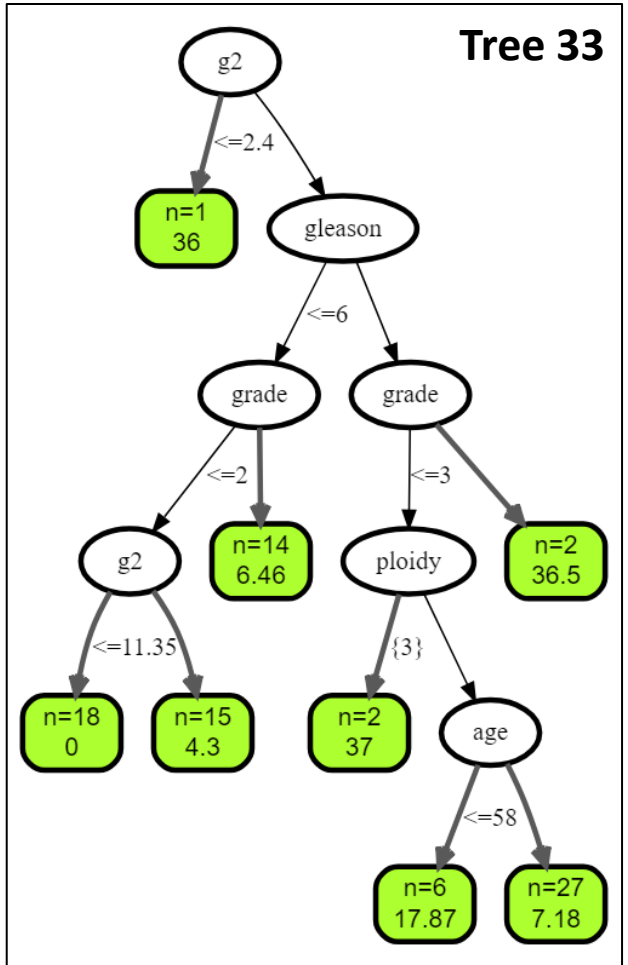
Step-by-step Example 1.5

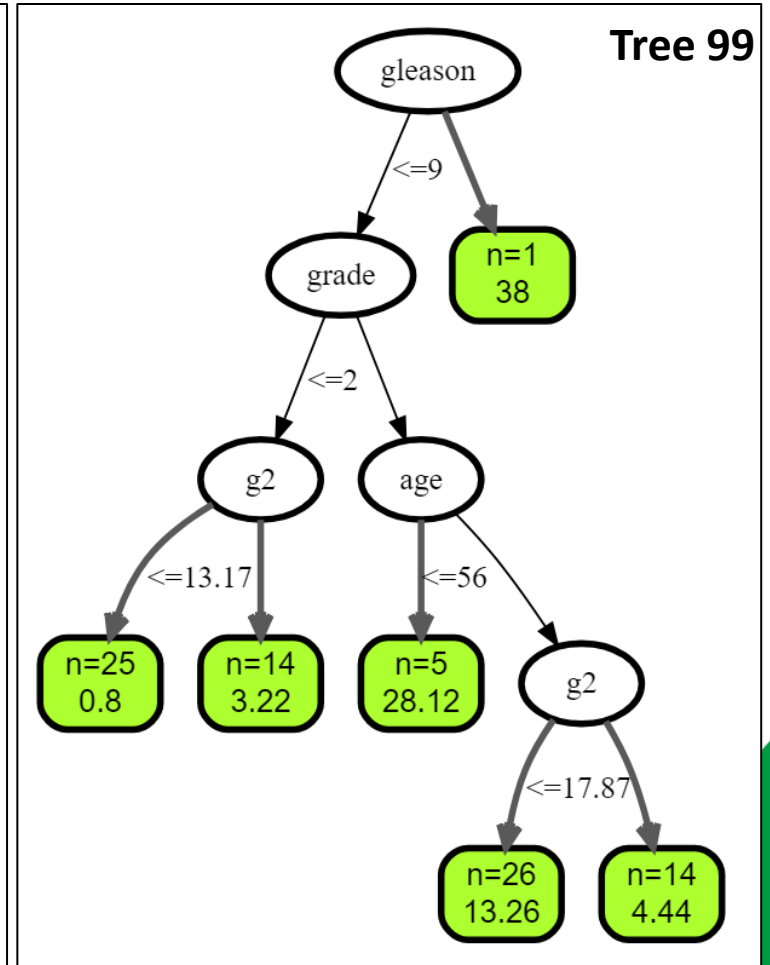
Prostate Cancer: Survival Random Forest

```
v.obj <-rfsrc(Surv(pgtime, pgstat) ~ age
        + factor(eet) + g2 + factor(grade)
        + factor(gleason) + ploidy,
        data=stagec,
        ntree=100, block.size=1)

plot(get.tree.rfsrc(v.obj, 3))
plot(get.tree.rfsrc(v.obj, 33))
plot(get.tree.rfsrc(v.obj, 99))
```







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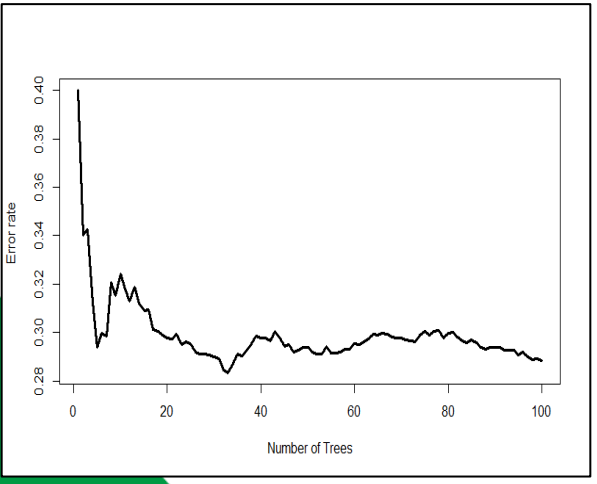
Step-by-step Example 1.5

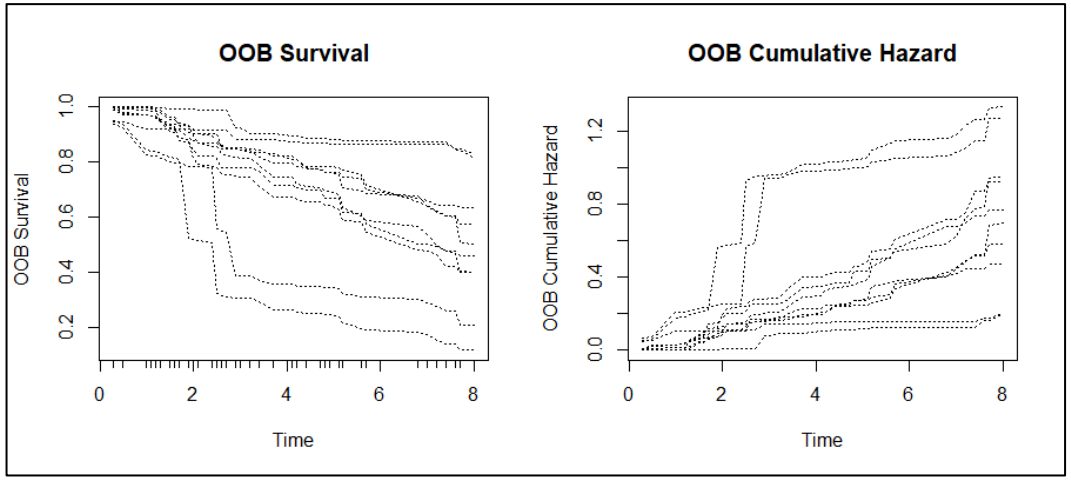
Prostate Cancer: Survival Random Forest

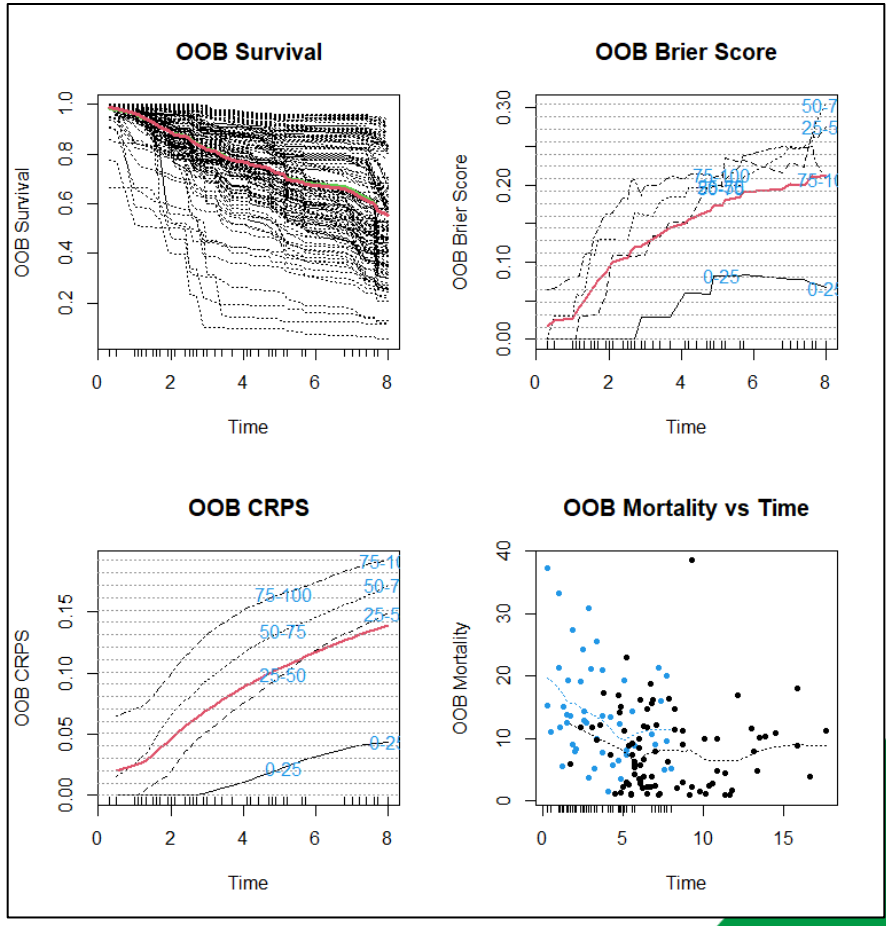
print(v.obj)
plot(v.obj)

plot.survival(v.obj, subset=1:10)
plot.survival(v.obj)

```
                         Sample size: 134
                      Number of deaths: 49
                      Number of trees: 100
            Forest terminal node size: 15
        Average no. of terminal nodes: 7.41
No. of variables tried at each split: 3
              Total no. of variables: 6
      Resampling used to grow trees: swor
   Resample size used to grow trees: 85
                           Analysis: RSF
                             Family: surv
                   Splitting rule: logrank *random*
   Number of random split points: 10
                 (OOB) Error rate: 29.20688208%
```







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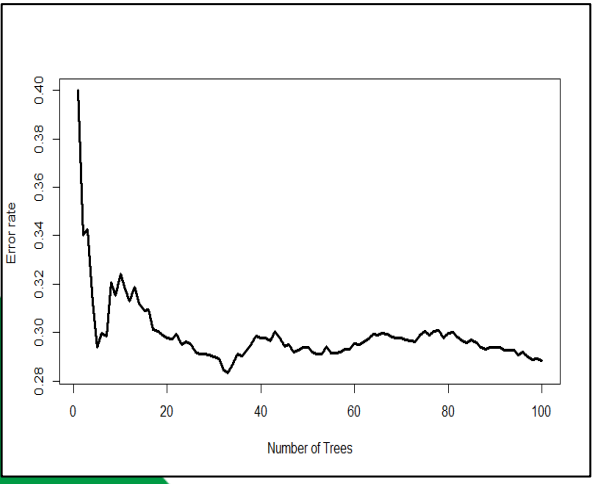
Step-by-step Example 1.5

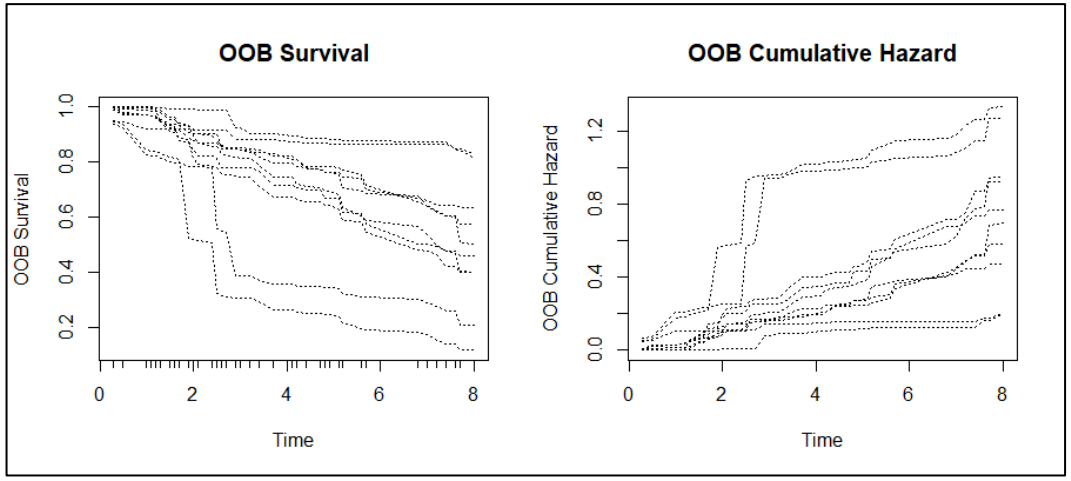
Prostate Cancer: Survival Random Forest

print(v.obj)
plot(v.obj)

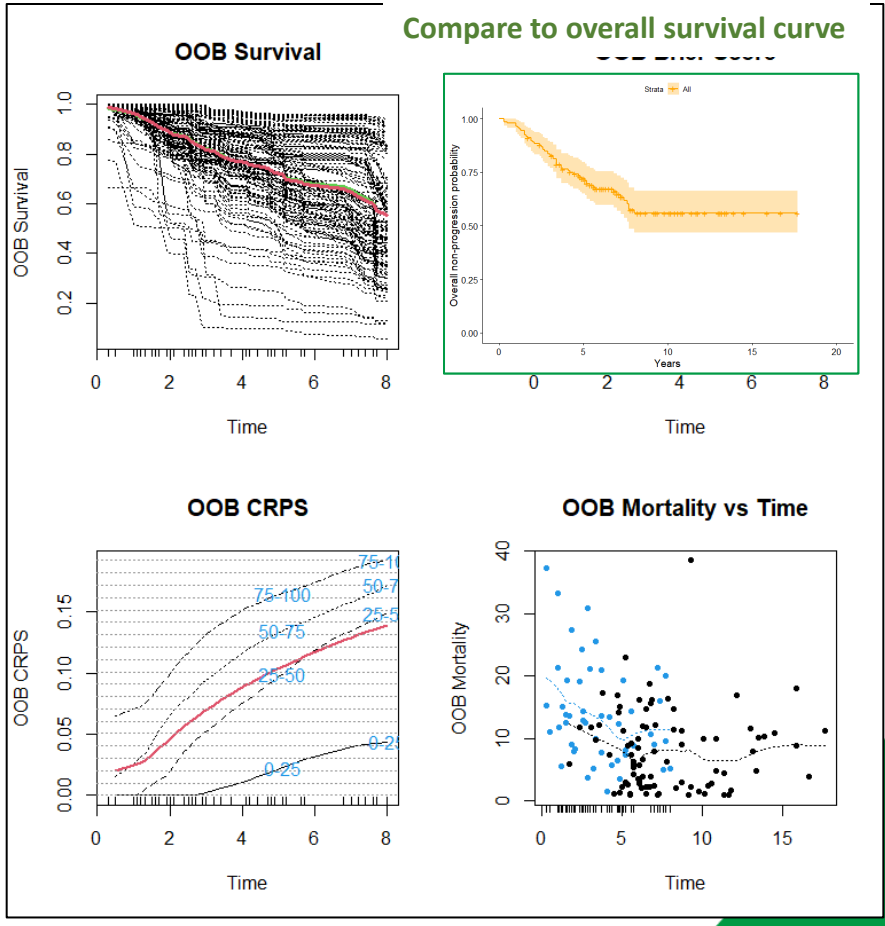
plot.survival(v.obj, subset=1:10)
plot.survival(v.obj)

```
                         Sample size: 134
                 Number of deaths: 49
                  Number of trees: 100
       Forest terminal node size: 15
   Average no. of terminal nodes: 7.41
No. of variables tried at each split: 3
         Total no. of variables: 6
   Resampling used to grow trees: swor
Resample size used to grow trees: 85
                        Analysis: RSF
                          Family: surv
                Splitting rule: logrank *random*
Number of random split points: 10
                (OOB) Error rate: 29.20688208%
```





Compare to overall survival curve



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Step-by-step Example 1.6

Lung Cancer: Frailty Model [22]

```
head(lung)

 #no random effect
mod5.1 <-coxph(Surv(time, status) ~ age,
          data=lung)
mod5.1 %>%
 gtsummary::tbl_regression(exp=TRUE)

 #random institutional effect
mod5.2 <-coxph(Surv(time, status) ~ age
          + frailty(inst, df=4),
          data=lung)
mod5.2 %>%
 gtsummary::tbl_regression(exp=TRUE)
```

Characteristic	HR[1]	95% CI[1]	p-value
age	1.02	1.00, 1.04	0.042

[1] HR = Hazard Ratio, CI = Confidence Interval

Characteristic	HR[1]	95% CI[1]	p-value
age	1.02	1.00, 1.04	0.038
frailty(inst, df = 4)			0.5

[1] HR = Hazard Ratio, CI = Confidence Interval

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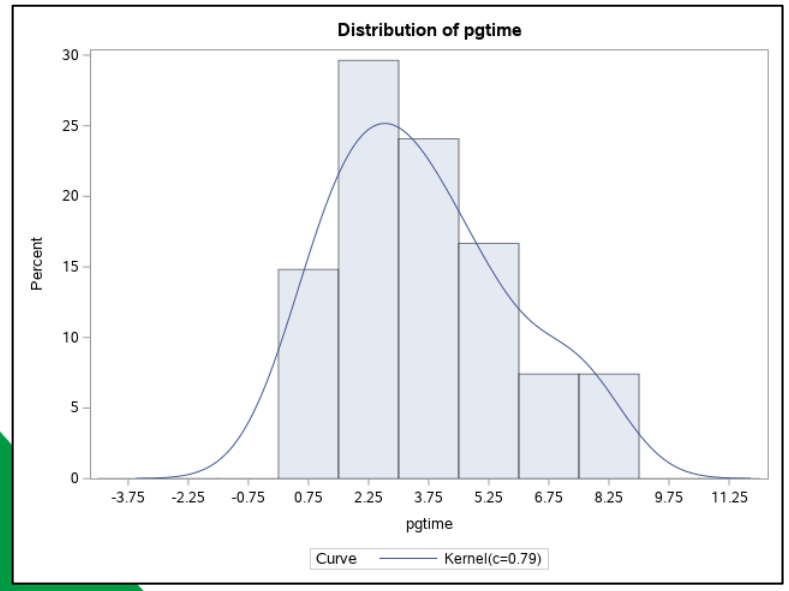
Step-by-step Example 2.1

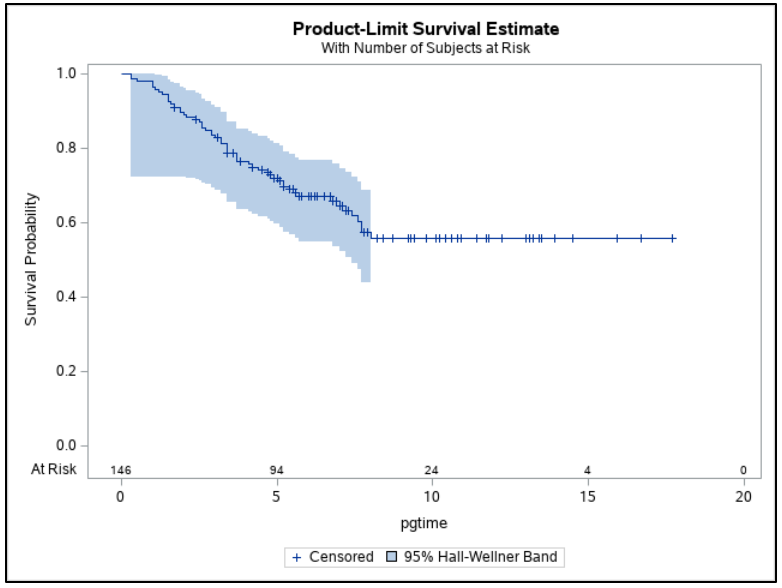
Survival Analysis in SAS

Prostate Cancer Remix: Cox regression with single variable

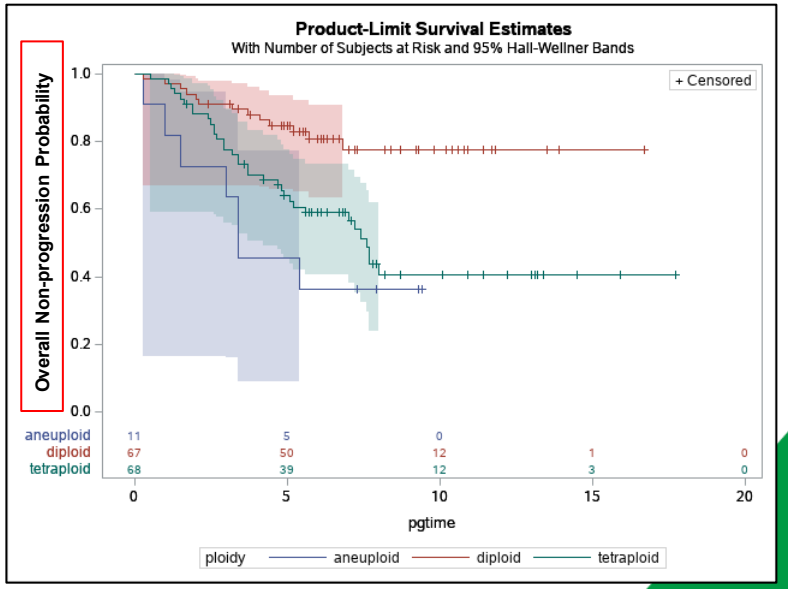
```
PROC UNIVARIATE data =stagec;
        where pgstat=1;
        var pgtime;
        histogram pgtime / kernel;
```




```
PROC LIFETEST data=stagec plots=survival(atrisk cb);
        time pgtime*pgstat(0);
```




```
PROC LIFETEST data=stagec plots=survival(atrisk cb);
        time pgtime*pgstat(0);
        strata ploidy;
```



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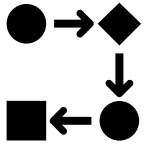
Step-by-step Example 2.1



Prostate Cancer Remix: Cox regression with single variable

```
PROC PHREG data=stagec;
        class ploidy(ref='diploid');
        model pgtime*pgstat(0) = ploidy;
```

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	499.615	484.782
AIC	499.615	488.782
SBC	499.615	492.760

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
ploidy	2	13.1874	0.0014

Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
ploidy	aneuploid	1	1.45706	0.46953	9.6299	0.0019	4.293	ploidy aneuploid
ploidy	tetraploid	1	1.04200	0.32634	10.1951	0.0014	2.835	ploidy tetraploid

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Step-by-step Example 2.2

Prostate Cancer Remix: Cox regression with multiple variables

```
PROC PHREG data=stagec;
        class eet ploidy(ref='diploid');
        model pgtime*pgstat(0)=  eet grade gleason ploidy age g2;
```

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	443.056	395.635
AIC	443.056	409.635
SBC	443.056	422.878

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
eet	1	0.0535	0.8170
grade	1	9.8729	0.0017
gleason	1	1.4413	0.2299
ploidy	2	7.1084	0.0286
age	1	0.3852	0.5348
g2	1	4.3388	0.0373

```
PROC PHREG data=stagec;
        class eet grade gleason ploidy(ref='diploid');
        model pgtime*pgstat(0)=  eet grade gleason ploidy age g2;
```

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	443.056	387.063
AIC	443.056	415.063
SBC	443.056	441.548

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
eet	1	0.2135	0.6440
grade	3	6.8078	0.0783
gleason	6	8.9328	0.1774
ploidy	2	9.2795	0.0097
age	1	0.0547	0.8150
g2	1	3.7837	0.0518

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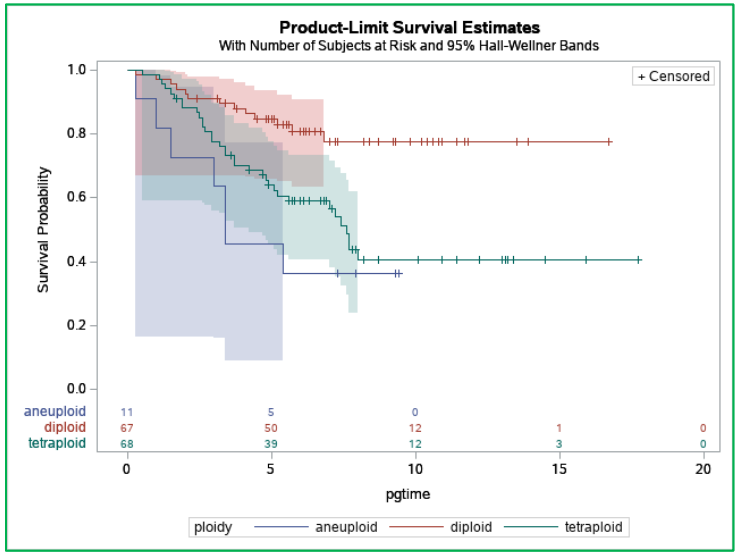
Step-by-step Example 2.2

Prostate Cancer Remix: Cox regression with multiple variables

```
PROC PHREG data=stagec;
        class grade ploidy(ref='ploidy');
        model pgtime*pgstat(0)=grade ploidy g2;
```

Compare to survival curves by ploidy category



Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	465.800	415.848
AIC	465.800	427.848
SBC	465.800	439.439

Type 3 Tests			
Effect	DF	Wald Chi-Square	Pr > ChiSq
grade	3	33.6620	<.0001
ploidy	2	10.0724	0.0065
g2	1	4.8779	0.0272

Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
grade	1	1	-15.99623	787.25505	0.0004	0.9838	0.000	grade 1
grade	2	1	-3.55911	0.61481	33.5124	<.0001	0.028	grade 2
grade	3	1	-2.21068	0.51905	18.1396	<.0001	0.110	grade 3
ploidy	aneuploid	1	1.19649	0.60057	3.9691	0.0463	3.308	ploidy aneuploid
ploidy	tetraploid	1	1.17575	0.40727	8.3342	0.0039	3.241	ploidy tetraploid
g2		1	-0.05662	0.02564	4.8779	0.0272	0.945	

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Step-by-step Example 2.3

Prostate Cancer Remix: Parametric models [23]

```
PROC LIFEREG data=stagec;
        class ploidy;
        model pgtime*pgstat(0)=ploidy/dist=lnormal;
PROC LIFEREG data=stagec;
        class ploidy;
        model pgtime*pgstat(0)=ploidy/dist=logistic;
PROC LIFEREG data=stagec;
        class ploidy;
        model pgtime*pgstat(0)=ploidy/dist=llogistic;
PROC LIFEREG data=stagec;
        class ploidy;
        model pgtime*pgstat(0)=ploidy/dist=gamma;
PROC LIFEREG data=stagec;
        class ploidy;
        model pgtime*pgstat(0)=ploidy/dist=exponential;
PROC LIFEREG data=stagec;
        class ploidy;
        model pgtime*pgstat(0)=ploidy/dist=weibull;
```

Distribution	AICc
lnormal	403.379
logistic	461.343
llogistic	404.043
gamma	405.514
exponential	406.302
weibull	295.114

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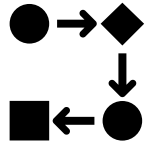
Step-by-step Example 2.3



Prostate Cancer Remix: Parametric models

```
PROC LIFEREG data=stagec;
        class ploidy grade;
        model pgtime*pgstat(0)=ploidy grade g2/dist=weibull;
```

Type III Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
ploidy	2	8.9327	0.0115
grade	3	33.6397	<.0001
g2	1	5.4261	0.0198

Analysis of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	-0.6139	0.5669	-1.7250	0.4972	1.17	0.2789
ploidy	aneuploid	1	-0.0341	0.5344	-1.0816	1.0134	0.00	0.9491
ploidy	diploid	1	0.9880	0.3642	0.2742	1.7019	7.36	0.0067
ploidy	tetraploid	0	0.0000	.	.	.	.	.
grade	1	1	21.0960	61201.47	-119932	119973.8	0.00	0.9997
grade	2	1	2.9549	0.5099	1.9555	3.9542	33.59	<.0001
grade	3	1	1.8259	0.4074	1.0275	2.6244	20.09	<.0001
grade	4	0	0.0000	.	.	.	.	.
g2		1	0.0524	0.0225	0.0083	0.0965	5.43	0.0198
Scale		1	0.8300	0.0978	0.6589	1.0456		
Weibull Shape		1	1.2048	0.1419	0.9564	1.5177		

Compared to semi-parametric Cox regression outcomes

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
grade	1	1	-15.99623	787.25505	0.0004	0.9838	0.000	grade 1
grade	2	1	-3.55911	0.61481	33.5124	<.0001	0.028	grade 2
grade	3	1	-2.21068	0.51905	18.1396	<.0001	0.110	grade 3
ploidy	aneuploid	1	1.19649	0.60057	3.9691	0.0463	3.308	ploidy aneuploid
ploidy	tetraploid	1	1.17575	0.40727	8.3342	0.0039	3.241	ploidy tetraploid
g2		1	-0.05662	0.02564	4.8779	0.0272	0.945	

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Step-by-step Example 2.4

Prostate Cancer: Bayesian Analysis

```
DATA stagec; set stagec;
            if ploidy='diploid' then do; psort=3; end;
            else if ploidy='tetraploid' then do; psort=2; end;
            else do; psort=1; end;
PROC SORT data=stagec;
            by psort;

PROC LIFEREG data=stagec order=data;
            class ploidy;
            model pgtime*pgstat(0)=ploidy/dist=weibull;
```

Type III Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
ploidy	2	11.4246	0.0033

Analysis of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept		1	3.4694	0.3176	2.8469	4.0919	119.32	<.0001
ploidy	aneuploid	1	-1.4734	0.4755	-2.4053	-0.5414	9.60	0.0019
ploidy	tetraploid	1	-0.9535	0.3346	-1.6093	-0.2977	8.12	0.0044
ploidy	diploid	0	0.0000	.	.	.	.	.
Scale		1	0.9616	0.1141	0.7621	1.2135		
Weibull Shape		1	1.0399	0.1234	0.8241	1.3122		

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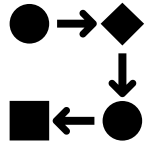
Step-by-step Example 2.4



Prostate Cancer: Bayesian Analysis

```
PROC LIFEREG data=stagec order=data;
        class ploidy;
        model pgtime*pgstat(0)=ploidy/dist=weibull;
        bayes seed=100 outpost=post nbi=2000 nmc=10000 thin=2
                coeffprior=normal(var=1E6)
                scaleprior=gamma(shape=1E-4, iscale=1E-4);
```

Compared to parametric non-Bayesian model outcomes

Analysis of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > Chi Sq
Intercept		1	3.4694	0.3176	2.8469	4.0919	119.32	<.0001
ploidy	aneuploid	1	-1.4734	0.4755	-2.4053	-0.5414	9.60	0.0019
ploidy	tetraploid	1	-0.9535	0.3346	-1.6093	-0.2977	8.12	0.0044
ploidy	diploid	0	0.0000	.	.	.	.	.
Scale		1	0.9616	0.1141	0.7621	1.2135		
Weibull Shape		1	1.0399	0.1234	0.8241	1.3122		

Analysis of Maximum Likelihood Parameter Estimates

Parameter		DF	Estimate	Standard Error	95% Confidence Limits	
Intercept		1	3.4694	0.3176	2.8469	4.0919
ploidy	aneuploid	1	-1.4734	0.4755	-2.4053	-0.5414
ploidy	tetraploid	1	-0.9535	0.3346	-1.6093	-0.2977
ploidy	diploid	0	0.0000	.	.	.
Scale		1	0.9616	0.1141	0.7621	1.2135
Weibull Shape		1	1.0399	0.1234	0.8241	1.3122

Posterior Summaries

Parameter	N	Mean	Standard Deviation	Percentiles		
				25%	50%	75%
Intercept	5000	3.5838	0.3476	3.3432	3.5540	3.7939
ploidyaneuploid	5000	-1.5023	0.5117	-1.8350	-1.4973	-1.1693
ploidytetraploid	5000	-1.0183	0.3626	-1.2521	-0.9964	-0.7586
Scale	5000	1.0166	0.1271	0.9245	1.0063	1.0924

Posterior Intervals

Parameter	Alpha	Equal-Tail Interval		HPD Interval	
Intercept	0.050	2.9829	4.3633	2.9157	4.2751
ploidyaneuploid	0.050	-2.5412	-0.5012	-2.5623	-0.5273
ploidytetraploid	0.050	-1.7861	-0.3781	-1.7520	-0.3575
Scale	0.050	0.8019	1.2989	0.7823	1.2677

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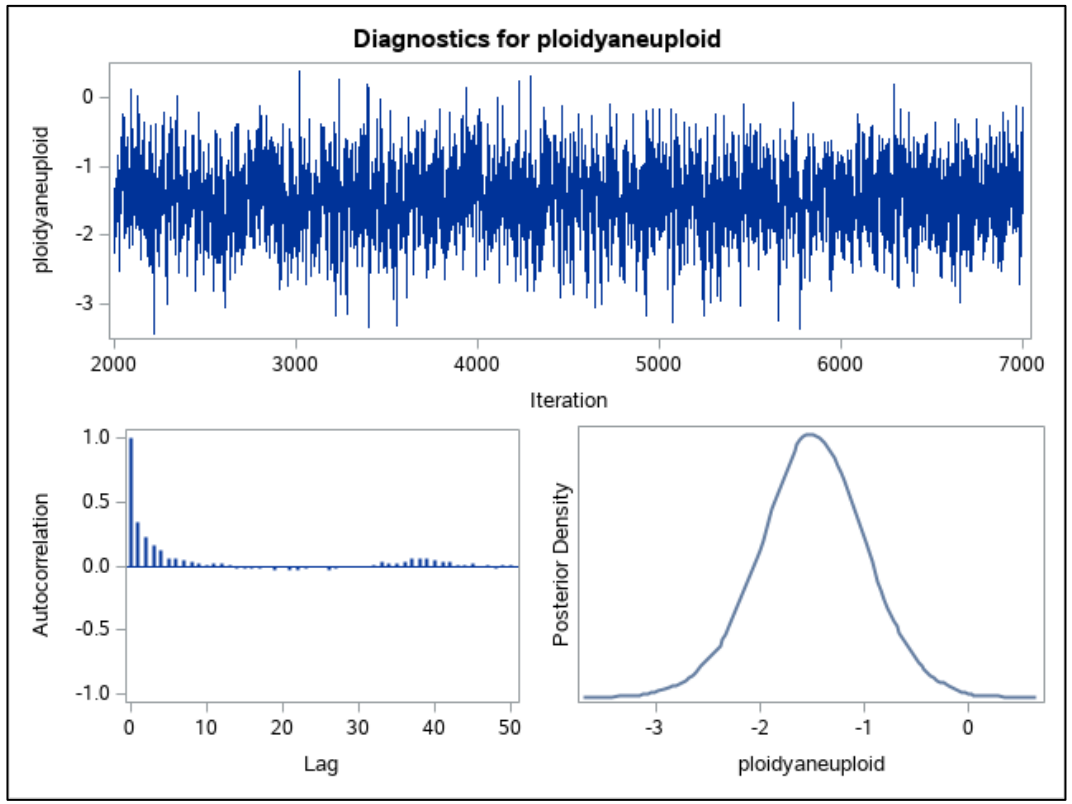
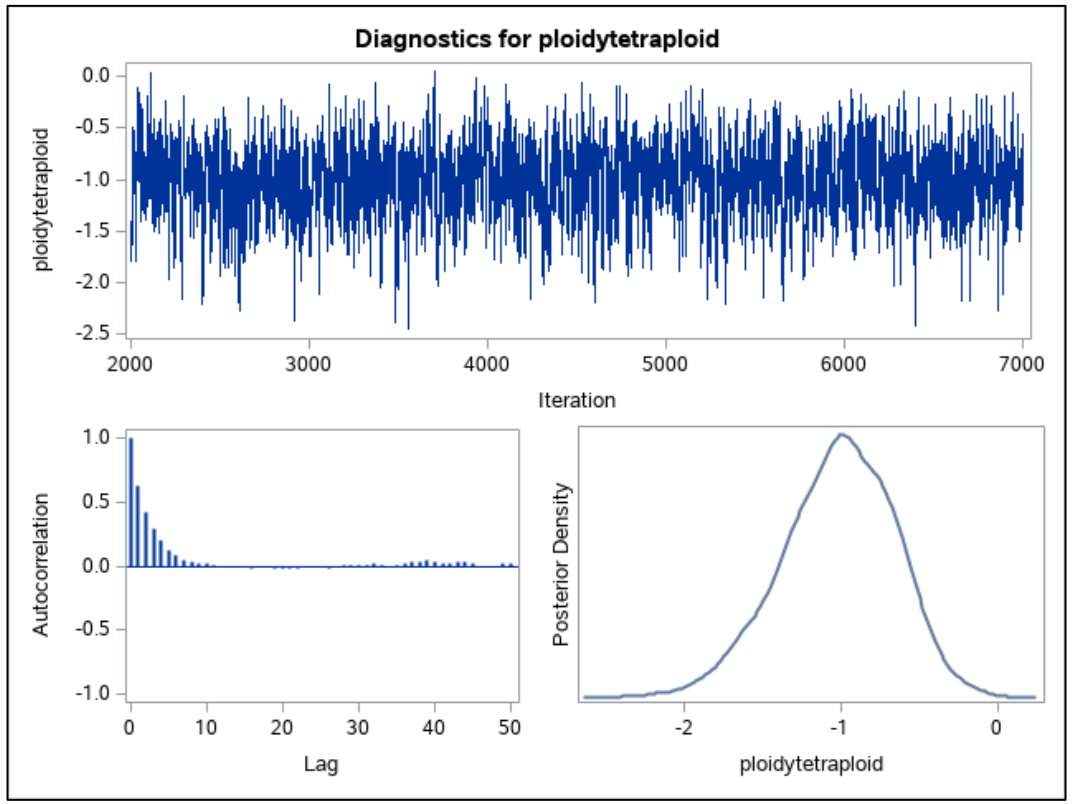
Step-by-step Example 2.4

Prostate Cancer: Bayesian Analysis





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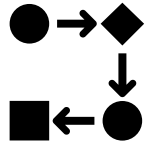
Step-by-step Example 2.5



Heart Transplant: Time-Dependent Variables [24]

```
PROC PHREG data=Heart;
          model Time*Status(0)=XStatus Acc_Age;
          if (WaitTime=. or Time < WaitTime) then XStatus=0.;
          else XStatus=1.0;

PROC PHREG data= Heart;
  model Time*Status(0)= XStatus XAge XScore;
  where NotTyped ^= 'y';
  if (WaitTime = . or Time < WaitTime) then do;
    XStatus=0.;
    XAge=0.;
    XScore= 0.;
  end;
  else do;
    XStatus= 1.0;
    XAge= Xpl_Age;
    XScore= Mismatch;
  end;
```

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	596.651	591.292
AIC	596.651	595.292
SBC	596.651	599.927

Model Fit Statistics		
Criterion	Without Covariates	With Covariates
-2 LOG L	561.680	551.874
AIC	561.680	557.874
SBC	561.680	564.662

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
XStatus	1	-0.06720	0.30594	0.0482	0.8261	0.935
Acc_Age	1	0.03158	0.01446	4.7711	0.0289	1.032

Analysis of Maximum Likelihood Estimates						
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
XStatus	1	-3.19837	1.18746	7.2547	0.0071	0.041
XAge	1	0.05544	0.02263	6.0019	0.0143	1.057
XScore	1	0.44490	0.28001	2.5245	0.1121	1.560

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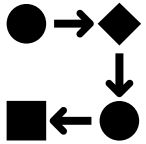
Step-by-step Example 2.6



Leukemia: Competing Risks [25]

```
PROC PHREG data=bmt; *for hazard of relapse;
        class Group / order=internal ref=first param=glm;
        model T*Status(0,2) = Group logWaitTime;
        hazardratio 'Cause-Specific Hazards' Group / diff=pairwise;
  *Cause-specific Hazard (competing events are treated as censored events)
  *Status: 0=Censored, 1=Relapse, 2=Die (w/o relapse)
```

```
DATA risk;
        logWaitTime=5.2;
        Group=1; output;
        Group=2; output;
        Group=3; output;
        format Group DiseaseGroup.;
```

Analysis of Maximum Likelihood Estimates

Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
Group	AML-Low Risk	1	-1.07299	0.46245	5.3836	0.0203	0.342	Group AML-Low Risk
Group	AML-High Risk	1	0.55111	0.36464	2.2842	0.1307	1.735	Group AML-High Risk
Group	ALL	0	0	.	.	.	.	Group ALL
logWaittime		1	-0.23061	0.19440	1.4071	0.2355	0.794	

Cause-Specific Hazards: Hazard Ratios for Group

Description	Point Estimate	95% Wald Confidence Limits	
Group AML-Low Risk vs AML-High Risk	0.197	0.088	0.441
Group AML-High Risk vs AML-Low Risk	5.074	2.268	11.353
Group AML-Low Risk vs ALL	0.342	0.138	0.847
Group ALL vs AML-Low Risk	2.924	1.181	7.238
Group AML-High Risk vs ALL	1.735	0.849	3.546
Group ALL vs AML-High Risk	0.576	0.282	1.178

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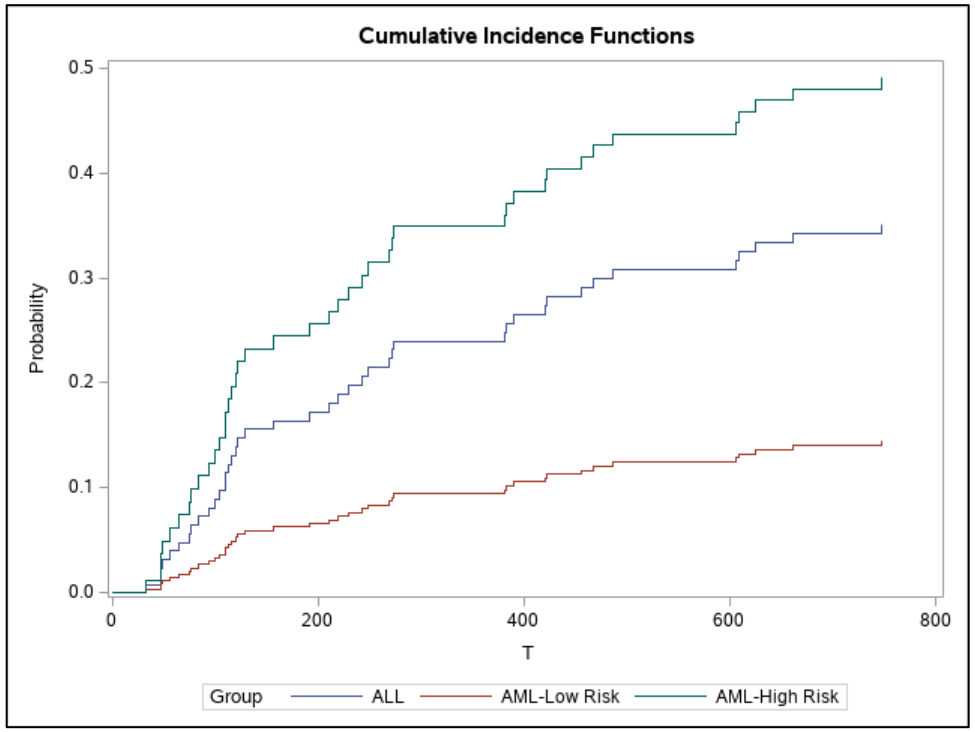
Step-by-step Example 2.6

Leukemia: Competing Risks

```
PROC PHREG data=bmt plots(overlay=stratum)=cif;
        class Group / order=internal ref=first param=glm;
        model T*Status(0) = Group logWaitTime / eventcode=1;
                hazardratio 'Subdistribution Hazards' Group /diff=pairwise;
        baseline covariates=risk out=_null_ /rowid=Group;
```



Subdistribution Hazards: Hazard Ratios for Group			
Description	Point Estimate	95% Wald Confidence Limits	
Group AML-Low Risk vs AML-High Risk	0.231	0.106	0.503
Group AML-High Risk vs AML-Low Risk	4.323	1.990	9.394
Group AML-Low Risk vs ALL	0.362	0.155	0.843
Group ALL vs AML-Low Risk	2.765	1.186	6.445
Group AML-High Risk vs ALL	1.564	0.763	3.203
Group ALL vs AML-High Risk	0.640	0.312	1.310

Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
Group	AML-Low Risk	1	-1.01701	0.43177	5.5481	0.0185	0.362	Group AML-Low Risk
Group	AML-High Risk	1	0.44702	0.36591	1.4925	0.2218	1.564	Group AML-High Risk
Group	ALL	0	0	.	.	.	.	Group ALL
logWaittime		1	-0.28540	0.19563	2.1283	0.1446	0.752	

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Assessment 2

qualtrics XM

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https://und.qualtrics.com/jfe/form/SV_aY2HKfZSPSx8oJ0

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Caveats and Concerns 

- We just scratched the surface on many of the examples
  - Lots of tweaks to exploration, model parameters, and graphing
  - Didn’t cover landmark analysis, conditional survival, or logistic-style regression
- Model fitting and interpretation are important to get right
  - Different procedures will have different outputs
  - Same work that goes into multiple regression or generalized linear models applies
  - Even parametric models with a flexible distribution may be a poor fit
  - Splines or fractional polynomials may be needed [4]
- As always, start simple and build from there

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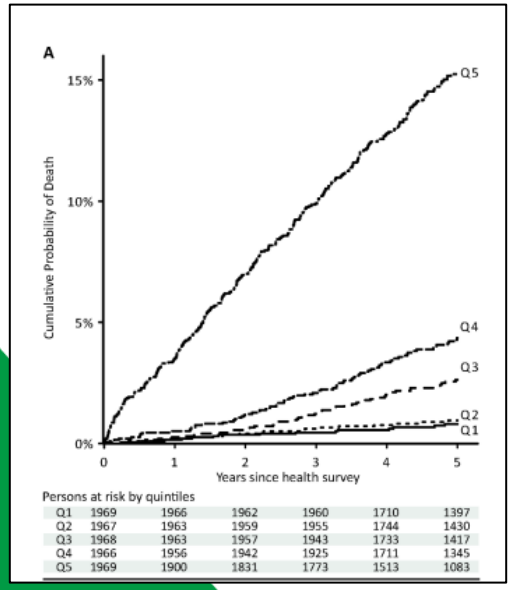
Real World Examples

Fischer K, Kettunen J, Würtz P, Haller T, Havulinna AS, et al. (2014) Biomarker Profiling by Nuclear Magnetic Resonance Spectroscopy for the Prediction of All-Cause Mortality: An Observational Study of 17,345 Persons. PLOS Medicine 11(2): e1001606. https://doi.org/10.1371/journal.pmed.1001606 **[26]**

Early identification of ambulatory persons at high short-term risk of death could benefit targeted prevention. To identify biomarkers for all-cause mortality and enhance risk prediction, we conducted high-throughput profiling of blood specimens in two large population-based cohorts



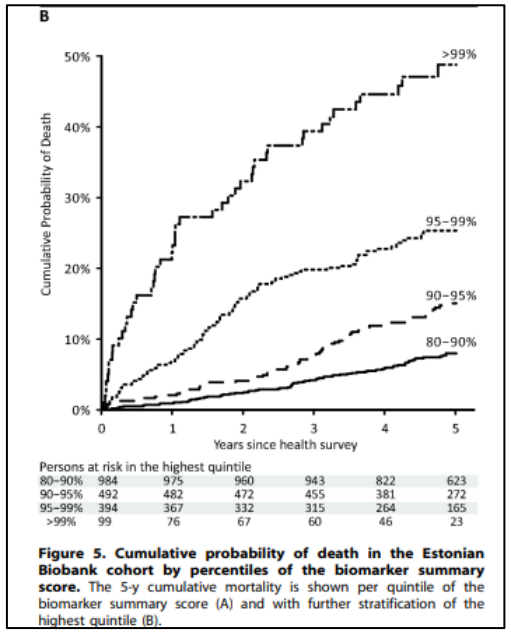


Figure 5. Cumulative probability of death in the Estonian Biobank cohort by percentiles of the biomarker summary score. The 5-y cumulative mortality is shown per quintile of the biomarker summary score (A) and with further stratification of the highest quintile (B).

Table 2. Hazard ratios for all-cause mortality derived in the Estonian Biobank cohort in the age range 25–74 y.

Variable	Prediction Model without Biomarkers			Prediction Model with Biomarkers		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Female gender	0.67	0.50–0.90	0.009	0.60	0.44–0.81	0.0008
Body mass index[a]	1.05	0.91–1.21	0.52	1.05	0.92–1.20	0.48
Systolic blood pressure[a]	0.96	0.85–1.09	0.51	1.04	0.92–1.18	0.55
Fasting duration (hours)	0.99	0.96–1.02	0.47	1.00	0.97–1.03	0.96
Total cholesterol[a]	1.05	0.91–1.21	0.50	1.15	0.97–1.36	0.11
HDL-cholesterol[a]	0.81	0.69–0.95	0.01	1.07	0.92–1.24	0.37
Triglycerides[a]	0.82	0.70–0.96	0.01	0.93	0.71–1.21	0.60
Creatinine[a]	1.10	1.03–1.18	0.005	1.04	0.96–1.12	0.31
Current smoking	1.86	1.26–2.75	0.002	1.56	1.05–2.33	0.03
Smoking duration (years)[a]	1.21	1.04–1.41	0.01	1.25	1.07–1.46	0.005
Cigarettes per day[a]	0.93	0.80–1.07	0.29	0.89	0.77–1.03	0.11
Alcohol[a]	1.09	0.98–1.21	0.11	1.04	0.94–1.16	0.43
Prevalent diabetes	1.58	1.15–2.15	0.004	1.49	1.09–2.03	0.01
Prevalent cardiovascular disease	1.38	1.05–1.82	0.02	1.42	1.08–1.87	0.01
Prevalent cancer	2.15	1.51–3.05	2×10^{-5}	2.26	1.59–3.20	5×10^{-6}
Alpha-1-acid glycoprotein[a]	—	—	—	1.76	1.57–1.97	9×10^{-23}
Albumin[a]	—	—	—	0.66	0.59–0.73	4×10^{-15}
VLDL particle size[a]	—	—	—	0.74	0.58–0.94	0.01
Citrate[a]	—	—	—	1.47	1.29–1.67	5×10^{-9}

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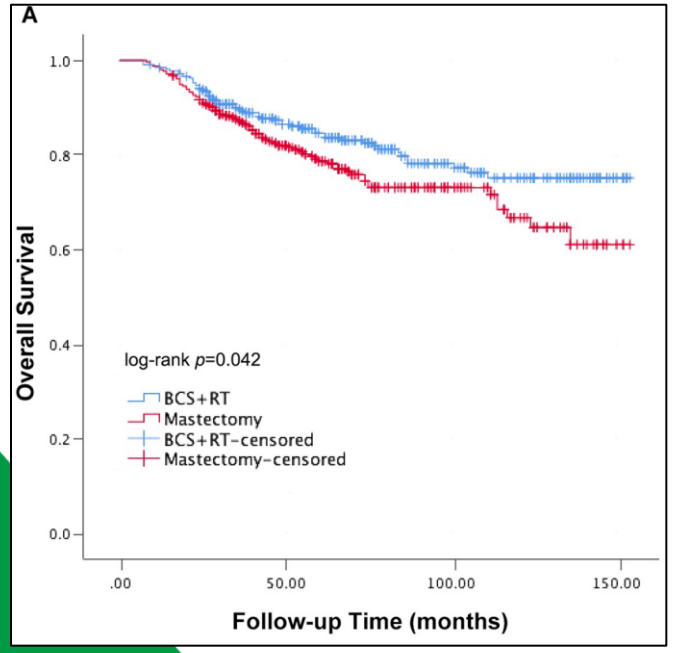
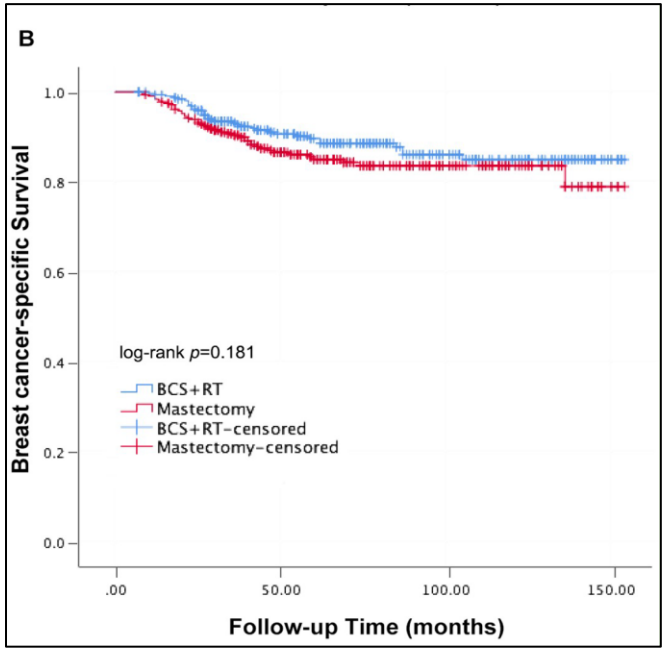
Real World Examples

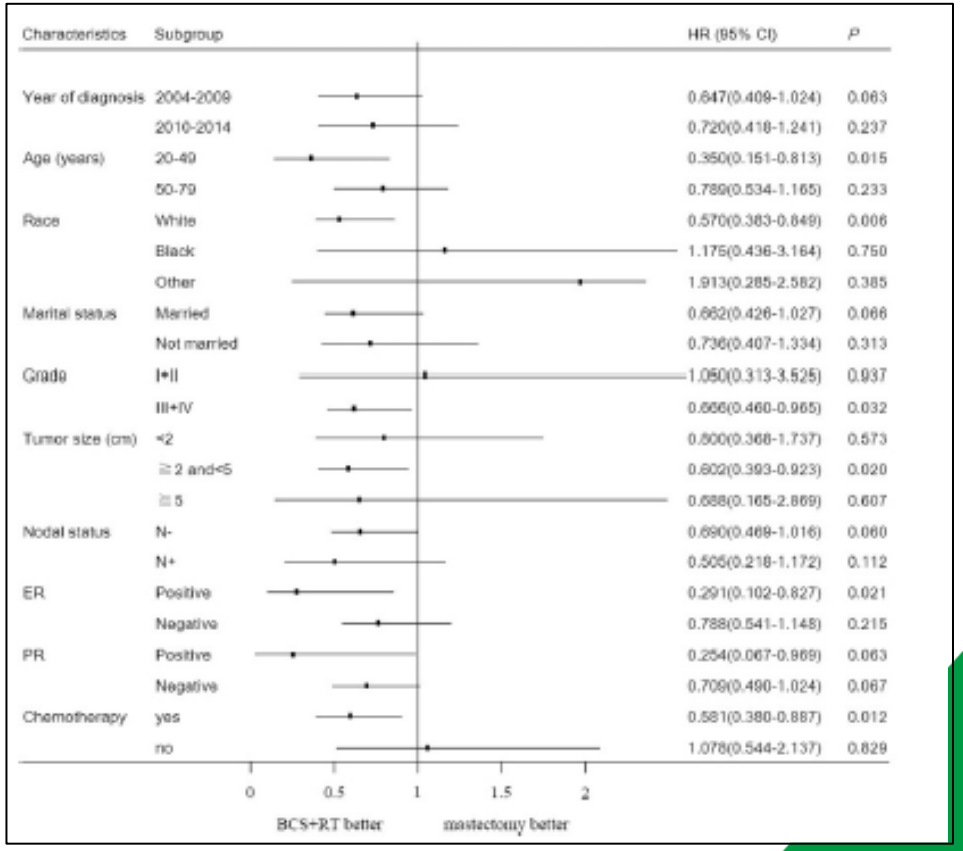
Xia LY, Xu WY, Hu QL (2021) The different outcomes between breast-conserving surgery plus radiotherapy and mastectomy in metaplastic breast cancer: A population-based study. PLOS ONE 16(9): e0256893. https://doi.org/10.1371/journal.pone.0256893 **[27]**

Metaplastic breast cancer (MBC) are rare. The survival outcomes of MBC patients after breast conserving surgery plus radiotherapy (BCS+RT) or mastectomy have not been established. The study aimed to compare survival outcomes of MBC patients subjected to BCS+RT or mastectomy therapeutic options.

The conditional landmark analysis was used to address a lead time bias among the propensity matched cohort. With the landmark, analysis was restricted to the patients who survived to 6 months without death or loss to follow-up.







Real World Examples

Gaspar MJ, Velasco T, Feito I, Alía R, Majada J (2013) Genetic Variation of Drought Tolerance in Pinus pinaster at Three Hierarchical Levels: A Comparison of Induced Osmotic Stress and Field Testing. PLOS ONE 8(11): e79094. https://doi.org/10.1371/journal.pone.0079094 **[28]**

We performed a Polyethylene glycolosmotic induced stress experiment and evaluated two common garden experiments (xeric and mesic sites) to test for survival and growth of a wide range clonal collection of Maritime pine.

To estimate the proportion of plants surviving at a given time, and hence the survival probability at that time for each clone, the Kaplan-Meier method was used as a product-limit estimator . This principle makes it possible to work with conditional and cumulative probabilities.

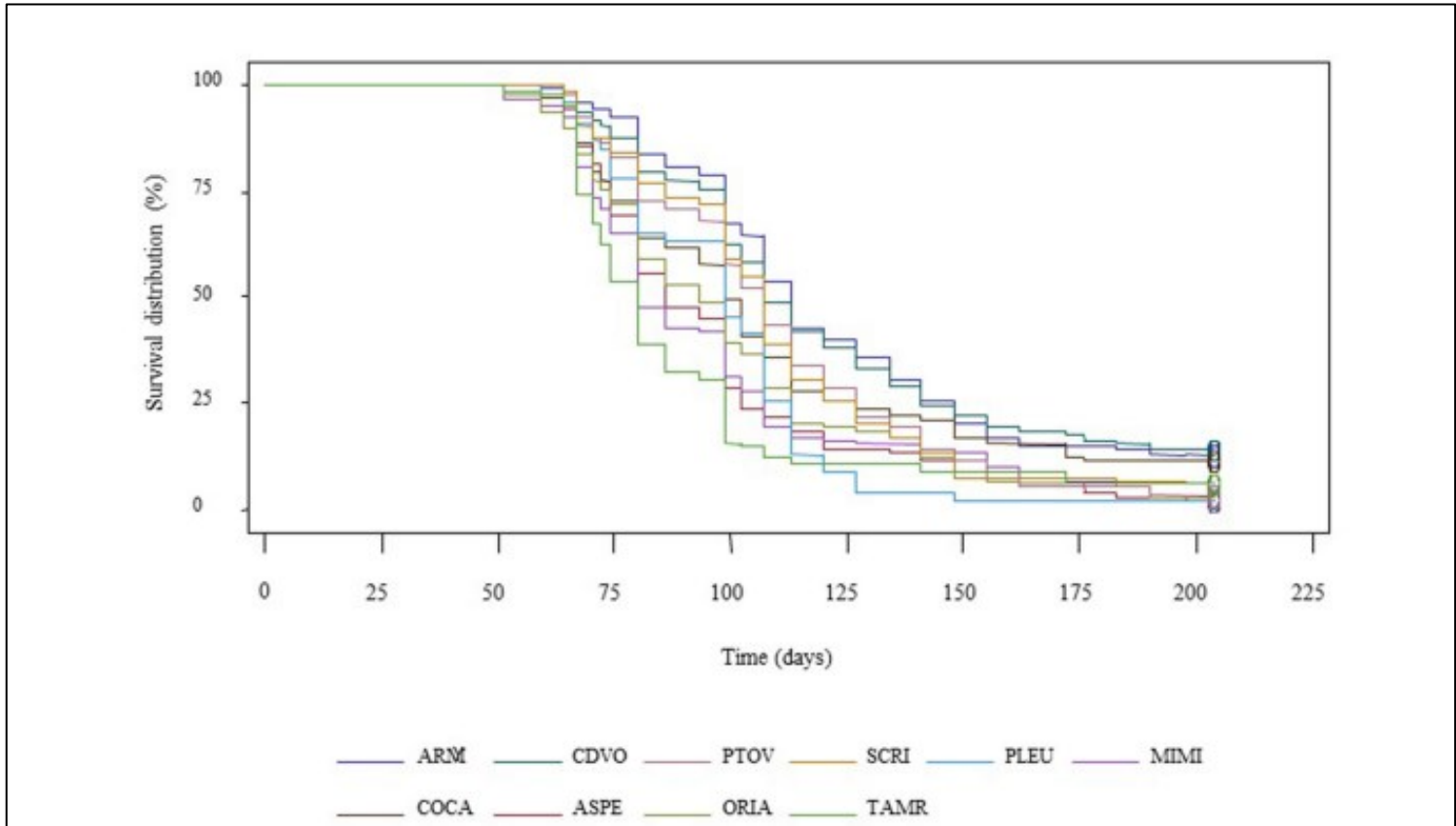


Figure 1. Distribution function of survival by provenance during the PEG-induced osmotic stress experiment, estimated by Kaplan-Meier method.

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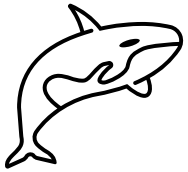
Summary and Conclusion



- Cox regression is the survival analysis equivalent to linear regression
- Parametric models are the survival analysis equivalent to generalized linear models
- Tree based methods are an alternative to Cox regression
- There are a variety of particular methods—such as frailty models, competing risks, and time-dependent variables—that are used under specific circumstances
- At the end of the day, we can determine the effects of factors on survival times

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