Survival Analysis and Machine Learning

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14-17 July 2025
Eka Hotel Conference Center
AMPATH
Eldoret, Kenya
Funding: Fogarty Institute of the NIH, U Hasselt

Basics of event-time data (survival data)

What kinds of endpoints are event time data?

- Studies of mortality – time to death
- Studies of disease process – time to progression, time to recovery
- Studies with combined outcomes – time to MI or heart failure

Sometimes called **survival data** or **failure time data**

Overview

- Description of a study of HIV-related mortality
- What are event-time data and what makes them different?
- Representing and summarizing event-time data
- Regression models for event-time data

Bloomfield *et al. BMC Infectious Diseases* 2014, **14**:284
http://www.biomedcentral.com/1471-2334/14/284

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Blood pressure level impacts risk of death among HIV seropositive adults in Kenya: a retrospective analysis of electronic health records

Gerald S Bloomfield[1,2,3*], Joseph W Hogan[4,5], Alfred Keter[5,6], Thomas L Holland[7], Edwin Sang[5,6], Sylvester Kimaiyo[5,6] and Eric J Velazquez[1,2,3]

Study of risk factors for HIV-related mortality

Longitudinal study of 50,000 people living with HIV (PLWH) in Kenya between 2005 and 2010

Key objective: Assess the effect of blood pressure on mortality

Secondary objectives:

- Assess impact of other markers of co-morbidities (diabetes risk, liver disease)
- Estimate short- and long-term survival rates

Study of risk factors for HIV-related mortality

Primary endpoint: Time from enrollment to death

Covariates (predictors, features):

- SBP, DBP
- Gender
- BMI
- Hemoglobin (marker of CVD risk, stroke etc.)
- Creatinine (kidney function marker)
- CD4 count at enrollment (immune function marker)
- ART status at enrollment
- WHO disease stage at enrollment (1 to 4)
- Marital status (yes/no)
- Urban/rural
- Advanced HIV (yes/no)

Table 1 Summary of characteristics by gender

Variable	Women (n = 36616)	Men (n = 12859)	Overall (n = 49475)
Age, median (IQR), years	32 (26-39)	38 (31-46)	33 (27-41)
Age category, No. (%), years			
<25	7473 (20.4)	812 (6.3)	8285 (16.8)
25-34	15227 (41.6)	4183 (32.5)	19410 (39.2)
35-44	9049 (24.7)	4362 (33.9)	13411 (27.1)
45-54	3739 (10.2)	2447 (19.0)	6186 (12.5)
55-64	948 (2.6)	803 (6.2)	1751 (3.5)
≥65	180 (0.5)	252 (2.0)	432 (0.9)
SBP, median (IQR), mmHg	110 (100-120)	110 (100-120)	110 (100-120)
DBP, median (IQR), mmHg	70 (60-72)	70 (60-79)	70 (60-74)
SBP category, No. (%), mmHg			
<100	3822 (10.4)	1083 (8.4)	4905 (9.9)
100-119	21145 (57.8)	6444 (50.1)	27589 (55.8)
120-139	10145 (27.7)	4488 (34.9)	14633 (29.6)
≥140	1504 (4.1)	844 (6.6)	2348 (4.8)
DBP category, No. (%), mmHg			
<60	1748 (4.8)	571 (4.4)	2319 (4.7)
60-79	27702 (75.7)	9107 (70.8)	36809 (74.4)
80-89	5905 (16.1)	2620 (20.4)	8525 (17.2)
≥90	1261 (3.4)	561 (4.4)	1822 (3.7)

BMI, median (IQR), kg/m^{2a}	21.5 (19.3-24.0)	20.1 (18.4-21.9)	21.0 (19.0-23.5)
BMI category, No. (%), kg/m^{2a}			
<18.5	5348 (16.8)	2855 (25.9)	8203 (19.1)
18.5 - <25	20645 (64.8)	7495 (67.9)	28140 (65.6)
25 - <30	4716 (14.8)	595 (5.4)	5311 (12.4)
≥30	1173 (3.7)	97 (0.9)	1270 (3.0)
Hemoglobin, median (IQR), g/dL[b]	11.8 (10.2-13.1)	13.8 (11.9-15.3)	12.2 (10.5-13.7)
Creatinine, median (IQR), µmol/L[c]	60 (51-71.4)	76 (64.5-89)	63.8 (53-77)
CD4 count, median (IQR), cells/mm^{3d}	413 (296-581)	363 (271-502)	399 (288-561)
CD4 category, no. (%), cells/mm^{3d}			
200-350	9705 (37.4)	4019 (46.8)	13,724 (39.8)
>350	16224 (62.6)	4566 (53.2)	20790 (60.2)
ART naïve at enrollment, No. (%)	33345 (91.1)	11645 (90.6)	44990 (90.9)
WHO stage at enrollment, No. (%)[e]			
Stage 1	17304 (60.5)	4803 (48.0)	22107 (57.2)
Stage 2	6647 (23.2)	2658 (26.6)	9305 (24.1)
Stage 3	4666 (16.3)	2547 (25.5)	7213 (18.7)
Urban	16970 (46.4)	6165 (47.9)	23135 (46.8)
Married/living with partner[f]	19045 (54.0)	9127 (73.1)	28172 (59.0)

Data used for this workshop

We created a *synthetic dataset* having 5000 individual records

- Distribution of variables mimics that in the actual study
- None of the individual records is identical to an actual patient record
- Missing data patterns have been preserved

R code for importing and summarizing data

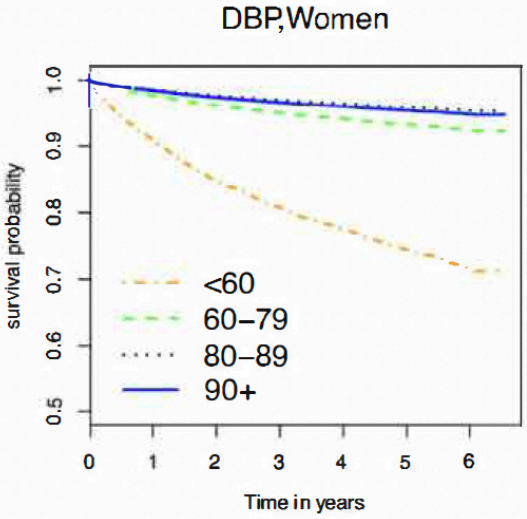
```
# Import the data
# load the data into your working directory
load("Workshop2025.Rdata")


# Explore the data structure using str()
str(htndat)
View(htndat)
```

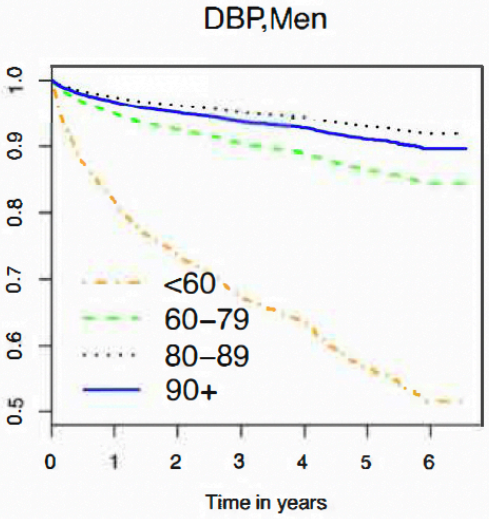
Refer to R code for ways to prepare summaries of the data using `gtsummary`

Summaries of mortality data

- Survival curves
- Hazard functions
- Event rates per person-time follow up
- Medians, percentiles

Survival curves





Event rates

Table 2 Unadjusted mortality rates per 100 person years by blood pressure groups for men and women with and without advanced HIV

Characteristic	Person years	Women events	Mortality rate (95% CI)	Person years	Men events	Mortality rate (95% CI)
Advanced HIV[a]						
Systolic blood pressure						
SBP <100 mmHg	3447	113	3.3 (2.7-3.9)	816	57	7.0 (5.4-9.1)
SBP 100-119 mmHg	18648	364	2.0 (1.8-2.2)	5966	219	3.7 (3.2-4.2)
SBP 120-139 mmHg	7954	116	1.5 (1.2-1.7)	4001	96	2.4 (2.0-2.9)
SBP ≥140 mmHg	1095	23	2.1 (1.4-3.2)	590	21	3.6 (2.3-5.5)
Diastolic blood pressure						
DBP <60 mmHg	1164	73	6.3 (5.0-8.0)	356	56	15.8 (12.1-20.5)
DBP 60-79 mmHg	23988	467	1.9 (1.8-2.1)	8142	283	3.5 (3.1-3.9)
DBP 80-89 mmHg	4913	58	1.2 (0.9-1.5)	2372	45	1.9 (1.4-2.5)
DBP ≥90 mmHg	1079	18	1.7 (1.1-2.6)	504	9	1.8 (0.9-3.4)

Important features of event time data

- All values are **positive** – cannot have negative time
- Some people have **partial information** due to **censoring**

Partial information and censoring

Notation

$$\begin{aligned} T &= \text{actual time to an event} \\ T^* &= \text{observed follow-up time} \\ \Delta &= \mathbb{I}(T = T^*) \end{aligned}$$

Types of observed information about T

- Full observed; e.g., $T = 45$
- Right censored; e.g., $T > 30$
- Interval censored; e.g., $26 < T < 40$

Our examples: T is either *observed* or *right-censored*

Representations of event history data

Follow up time and observation indicator

T^*	Δ	Interpretation
5	1	$T = 5$
8	1	$T = 8$
10	0	$T > 10$
12	1	$T = 12$
15	0	$T > 15$

Those with $\Delta = 0$ are **right-censored**

Information about T is not fully missing; it's **partially observed**

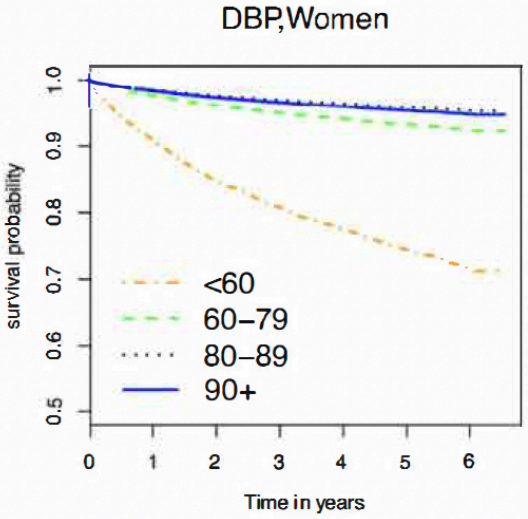
Summaries of event history data: Survivor function

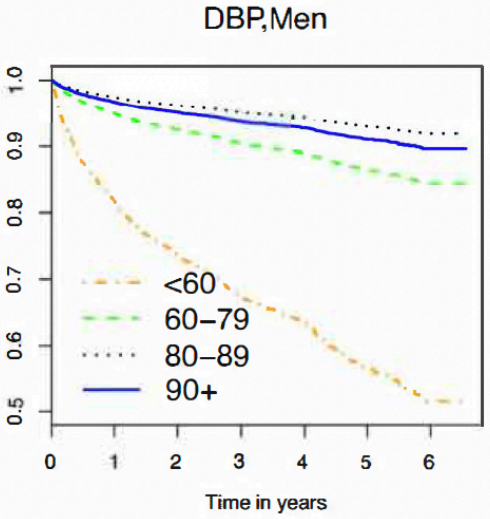
Survivor function:

- proportion event-free as a function of time
- decreases over time as more events occur

$$S(t) = P(T \leq t)$$

Survival curves



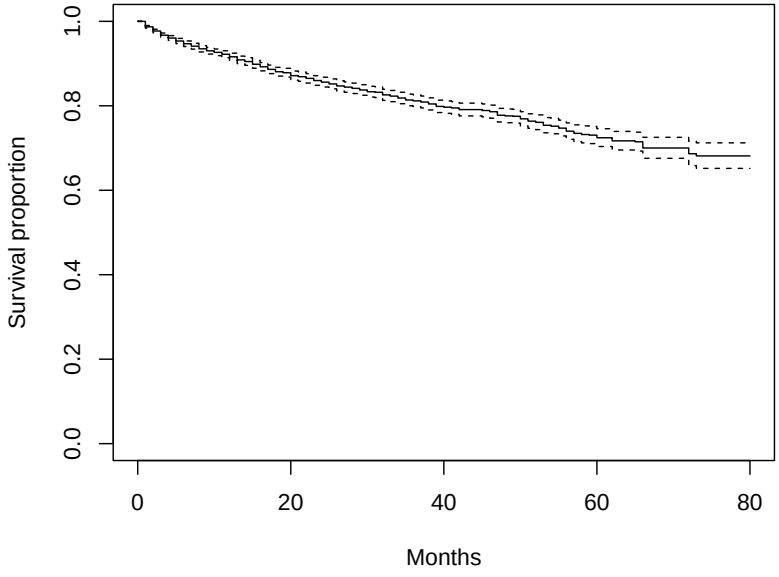


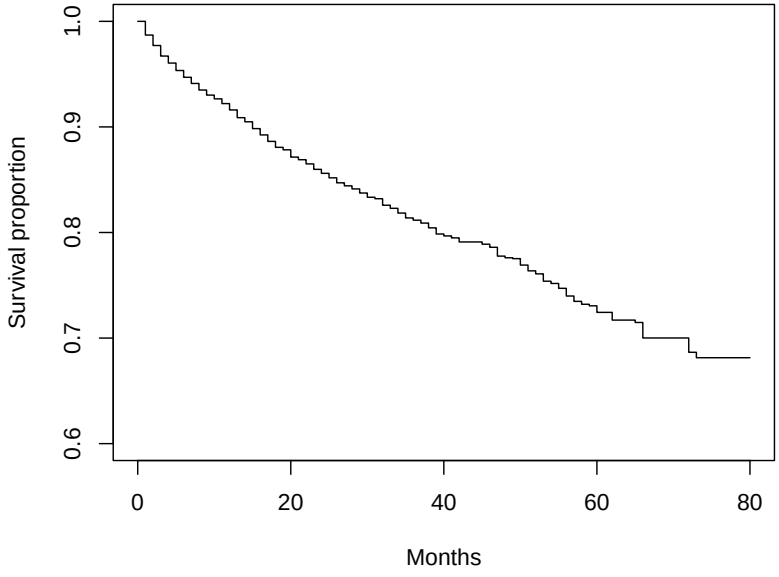
Calculating $\hat{S}(t)$: Kaplan-Meier Estimator

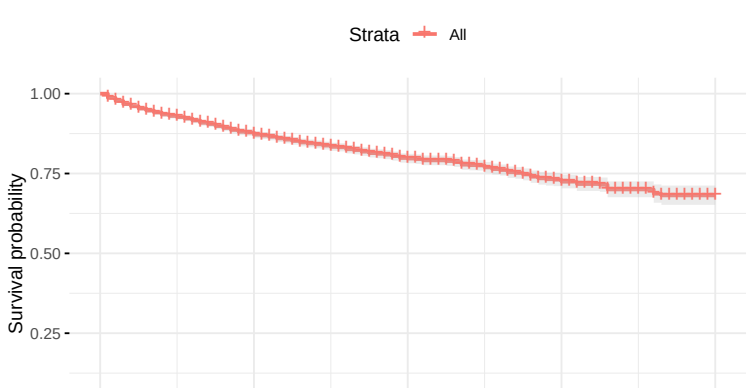
T^*	Δ	at risk	events	$\hat{S}(t)$
0		8	0	1.0
5	1	8	1	$(1 - 1/8) = .83$
8	1	7	1	$.83 \times (1 - 1/7) = .71$
10	0	6	0	.71
12	1	5	1	$.71 \times (1 - 1/5) = .57$
15	0	4	0	.57
16	0	3	0	.57
22	1	2	1	$.57 \times (1 - 1/2) = .29$
26	0	1	0	.29

Survival curves for HTN data

```
view(htndat)
view(htndat[c("survmonth", "event")])

# Create the survival object

surv_obj <- with(htndat, Surv(time = survmonth, event = event))

# Explanation:
#  - 'time'  = months from baseline to death or censoring
#  - 'event' = 1 if death occurred, 0 if censored

# Fit overall KM curve
km_overall <- survfit(surv_obj ~ 1, data = htndat)
print(km_overall)

# basic plot
plot(km_overall, xlab="Months", ylab="Survival proportion")
```


Survival proportion
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
Months


Survival proportion
1.0
0.9
0.8
0.7
0.6
0
20
40
60
80
Months


Strata
All
1.00
0.75
0.50
0.25
0.00
Survival probability
0
20
40
60
80
Time (months)
Number at risk
Strata
All
4998
2547
1321
471
10
0
20
40
60
80
Time (months)

Properties of the Kaplan-Meier estimator

- It's *nonparametric* – does not depend on a model
- It accounts for censoring, but under some assumptions
  - 'non-informative' censoring
  - event rate after censoring is equal that for those who remain in follow-up

'Non-informative censoring' is the assumption underlying all of our analyses today. It may not always hold in practice.

Summaries of event history data

Because of censoring, summaries like mean, SD, median, etc. cannot be calculated directly from the data

Typical approach

1. Calculate an estimate of $S(t)$
2. Use that estimate to derive various summaries

Example: Calculating the median

$$\text{median}(T) \quad = \quad \text{value of } t \text{ such that } S(t) = .5$$

Check understanding

What fraction survived to 20 months?

What fraction survived to 5 years?

What is the 75th percentile of the survival times?

What is the median survival time?

R code for basic summaries from KM curve

```
# summarize KM probs at each time
summary(km_overall)

summary(km_overall, times = 12)

quantile(km_overall, probs=c(.05, .10, .25, .5))

tbl_survfit(km_overall, probs=c(.05, .10, .25, .5))
```

R code for basic summaries from KM curve

```
> summary(km_overall)
```

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
1	4998	65	0.987	0.00160	0.984	0.990
2	4394	44	0.977	0.00217	0.973	0.981
3	4210	43	0.967	0.00263	0.962	0.972
4	4066	28	0.960	0.00290	0.955	0.966
5	3955	29	0.953	0.00316	0.947	0.960
6	3849	26	0.947	0.00338	0.940	0.954
15	2947	21	0.898	0.00482	0.889	0.908
16	2852	19	0.892	0.00498	0.883	0.902
17	2764	19	0.886	0.00514	0.876	0.896
18	2680	17	0.881	0.00528	0.870	0.891
65	318	1	0.715	0.01142	0.693	0.738
66	292	6	0.700	0.01266	0.676	0.725
72	155	3	0.687	0.01464	0.658	0.716
73	133	1	0.681	0.01541	0.652	0.712

Quantiles output

Output from

```
tbl_survfit(km_overall, probs=c(.05, .10, .25, .5))
```

Characteristic	5.0% Percentile	10% Percentile	25% Percentile	50% Percentile
Overall	6.0 (5.0, 7.0)	15 (13, 17)	55 (51, 60)	— (—, —)

Summaries of event history data: Hazard function

Hazard function:

- event *rate* as a function of time
- rate of event at t among those who have not yet had the event

$$h(t) \approx P(T = t \mid T \geq t)$$

Relationship between hazard function and survival function

$$\begin{aligned} h(t) &= -\frac{dS(t)/dt}{S(t)} \\ &\approx \frac{\text{slope of survival curve at } t}{\text{proportion survived up to } t} \end{aligned}$$

Calculating $\hat{h}(t)$

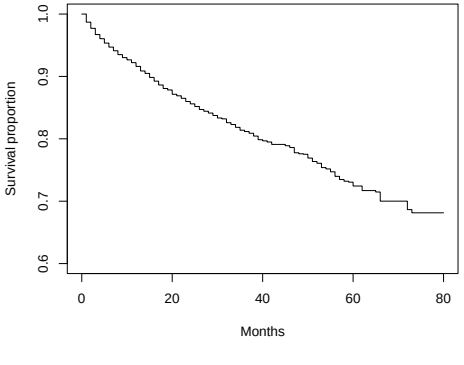
T^*	Δ	at risk	events	$\hat{h}(t)$
0		8	0	—
5	1	8	1	$1/8 = .13$
8	1	7	1	$1/7 = .14$
10	0	6	0	0
12	1	5	1	$1/5 = .20$
15	0	4	0	0
16	0	3	0	0
22	1	2	1	$1/2 = .50$
26	0	1	0	0

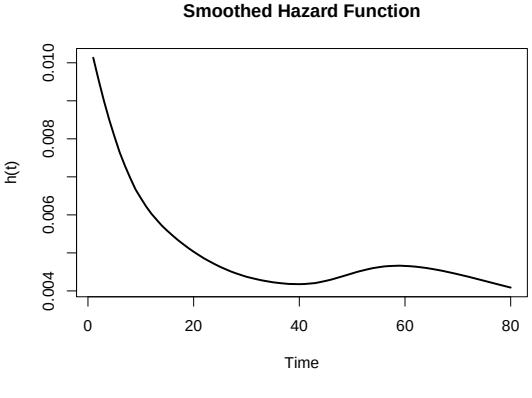
In real data, there can be more than one event at some time points – hence the hazard is not always increasing over time.

R code for calculating and plotting hazard function

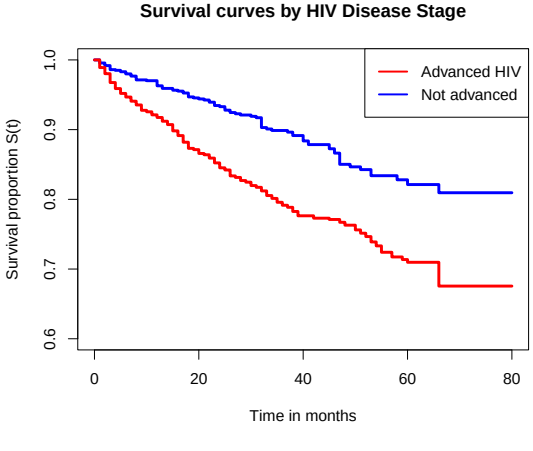
```
# Hazard functions
fit.hazard <- bshazard(surv_obj ~ 1, data = htndat)

# Extract smoothed hazard and log-hazard
time_vals  <- fit.hazard$time
hazard     <- fit.hazard$hazard
log_hazard <- log(hazard)

# Plot hazard with confidence bands
plot(time_vals, hazard, type = "l", lwd = 2,
     xlab = "Time", ylab = "h(t)", main = "Smoothed Hazard Function")

polygon(c(fit.hazard$time, rev(fit.hazard$time)),
        c(fit.hazard$upper, rev(fit.hazard$lower)),
        col = rgb(0, 0, 1, 0.2), border = NA)

# Plot log-hazard
plot(time_vals, log_hazard, type = "l", lwd = 2,
     xlab = "Time", ylab = "log h(t)", main = "Smoothed Log-Hazard Function")
```

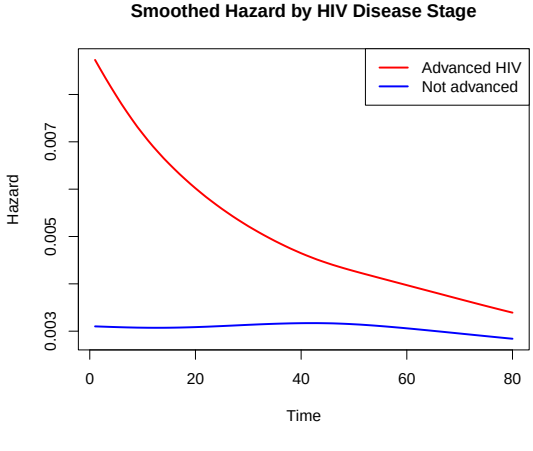
Hazard function vs survival function





Hazard function vs survival function





R code for calculating stratified survival curves

```
# Overall KM survival plot by advanced HIV status
km_adv <- survfit(surv_obj ~ factor(adv_HIV), data = htndat)

plot(km_adv, lwd=3, col=c("blue","red"), ylim=c(.6,1) ,
     xlab="Time in months", ylab="Survival proportion S(t)",
     main="Survival curves by HIV Disease Stage")

legend("topright",
       legend = c("Advanced HIV", "Not advanced"),
       col    = c("red", "blue"),
       lwd    = 2)
```

R code for calculating stratified hazard curves

```
## Fit smoothed hazard models for each level
fit_adv    <- bshazard(Surv(time = survmonth, event = event) ~ 1,
                       data = htndat[htndat$adv_HIV == 1, ])
fit_notadv <- bshazard(Surv(time = survmonth, event = event) ~ 1,
                       data = htndat[htndat$adv_HIV == 0, ])

## Common y-limits so the curves share the same scale
ylim_vals <- range(c(fit_adv$hazard, fit_notadv$hazard))

## Plot the hazard functions
plot(fit_adv$time, fit_adv$hazard, type = "l", lwd = 2, col = "red",
     xlab = "Time", ylab = "Hazard",
     main = "Smoothed Hazard by HIV Disease Stage",
     ylim = ylim_vals)

lines(fit_notadv$time, fit_notadv$hazard, lwd = 2, col = "blue")

legend("topright",
       legend = c("Advanced HIV", "Not advanced"),
       col    = c("red", "blue"), lwd    = 2)
```

Regression model for survival data

Accelerated failure time model (AFT)

$$\log T = \mu + \alpha X + \sigma\epsilon$$

where X is a covariate and ϵ is an error term

- Models the survival time directly
- α is the effect of X on **survival time**
- Works well for parametric models (e.g., log-normal)
- Harder to fit without parametric assumptions

Regression model for survival data

Proportional hazards model (PH)

$$\begin{aligned} \log h(t) &= \log h_0(t) + \beta X \\ &\text{or} \\ h(t) &= h_0(t) \exp(\beta X) \end{aligned}$$

where X is a covariate and $h_0(t)$ is a 'baseline hazard' function

- Models the hazard function, not survival time
- Very flexible – do not have to model $h_0(t)$ in many cases
- β is the effect of X on **event rate**

Proportional hazards model with binary covariate

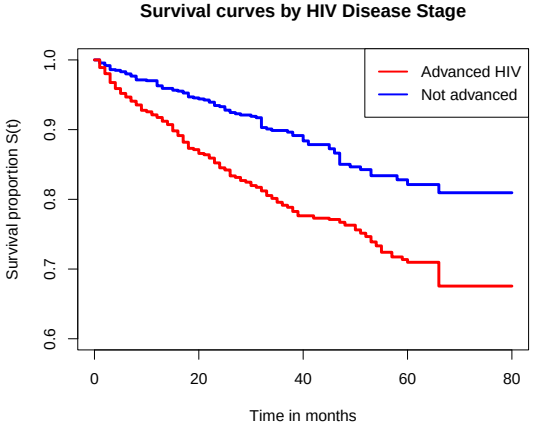
Model specification

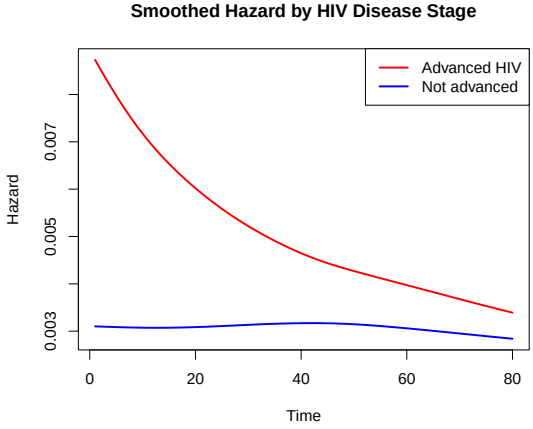
$$\begin{aligned} \log h(t) &= \log h_0(t) + \beta X \\ X &= 1 \text{ advanced HIV, } 0 \text{ if not} \end{aligned}$$

Interpretation

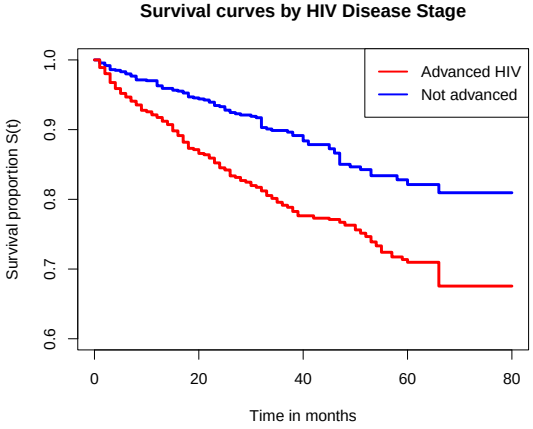
$$\begin{aligned} \log h_0(t) &= \text{log hazard function when } X = 0 \\ \log h_0(t) + \beta &= \text{log hazard function when } X = 1 \\ \beta &= \text{difference in log hazard functions,} \\ &\quad \textit{assumed constant over time} \end{aligned}$$

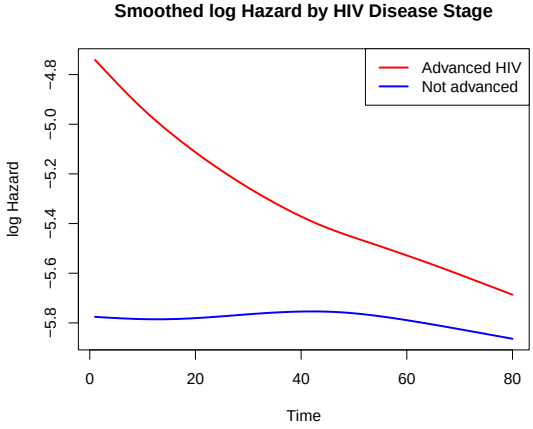
Hazard function vs survival function





Log hazard function vs survival function





Fitted model

Model specification

$$\begin{aligned} \log h(t) &= \log h_0(t) + \beta X \\ X &= \text{1 advanced HIV, 0 if not} \end{aligned}$$

```
> univ_cox <- coxph( Surv(survmonth, event) ~ adv_HIV,
                              data = htndat, ties = "efron")
> summary(univ_cox)

  n= 3038, number of events= 398
   (1960 observations deleted due to missingness)

         coef exp(coef) se(coef)    z Pr(>|z|)
adv_HIV 0.697     2.008    0.116 6.01 1.86e-09 ***
```

log hazard ratio $\hat{\beta} = .697$

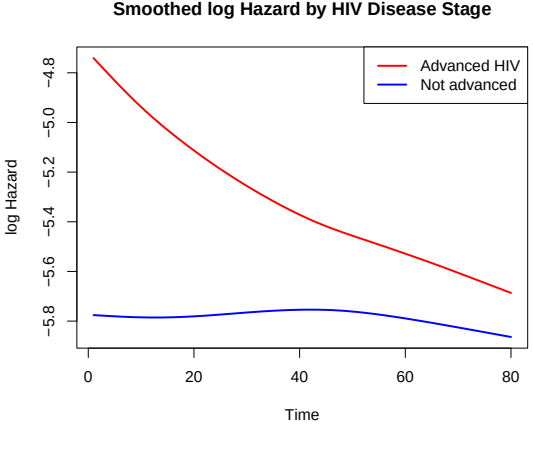
hazard ratio $\exp(.697) = 2.008$

Visualizing the model

$$\begin{aligned} \log h(t) &= \log h_0(t) + \beta X \\ X &= 1 \text{ advanced HIV, } 0 \text{ if not} \end{aligned}$$

log hazard ratio $\hat{\beta} = .697$

- How to interpret $\hat{\beta}$?
- Is this an appropriate model?



Examining proportional hazards assumption

Proportional hazards assumption can be assessed using **Schoenfeld residual plots**

These use a special type of residual to get an estimate of the HR as a function of time

$$\hat{\beta}(t) \quad = \quad \text{HR as a function of time}$$

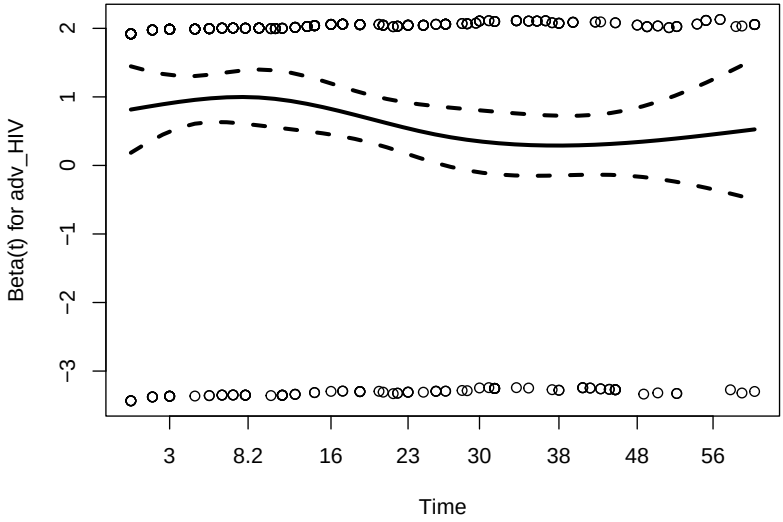
If PH assumption is met, $\hat{\beta}(t)$ will be a constant function of time (flat line)

R code for assessing PH assumption

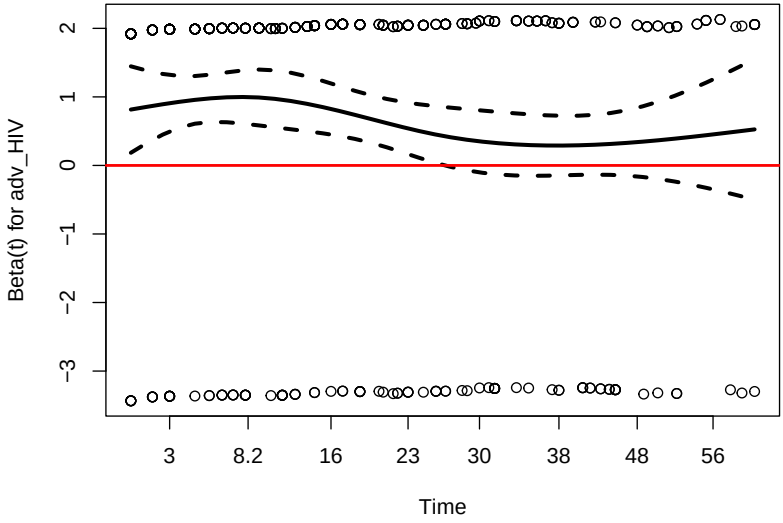
This code tests the PH assumption for advanced HIV effect using the fitted model `univ_cox`

```
## Using Schoenfeld residuals
> plot(cox.zph(univ_cox), lwd=3)

## Using a test of hypothesis (H0: proportional hazards holds)
> cox.zph(univ_cox)

        chisq df     p
adv_HIV  3.65  1 0.056
GLOBAL   3.65  1 0.056
```

Schoenfeld residual plot of $\hat{\beta}(t)$



Schoenfeld residual plot of $\hat{\beta}(t)$



Elaborate to allow hazard ratio to change over time

Add time-by-covariate interaction

$$\log h(t) \quad = \quad \log h_0(t) + \beta X + \delta(X \cdot t)$$

Interpretation

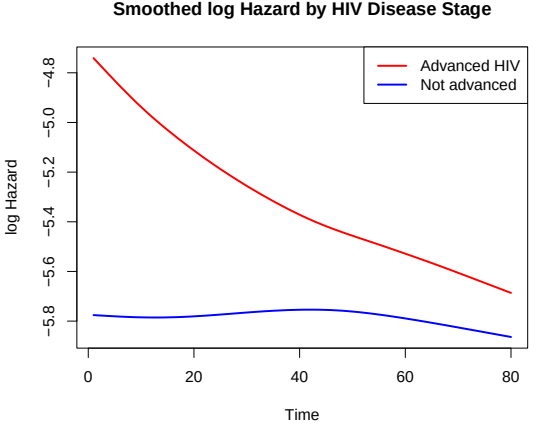
- $\beta + \delta t =$ log HR at time t
- $\beta =$ log HR near $t = 0$

Time-varying hazard ratio: fitted model

$$\log h(t) = \log h_0(t) + \beta X + \delta(X \cdot t)$$

$$\hat{\beta} = .973$$
$$\hat{\delta} = -.013$$

- How to interpret $\hat{\beta}$?
- How to calculate HR at different times?



R code for time-varying HR

```
> tv_cox <- coxph(surv_obj ~ adv_HIV + tt(adv_HIV),
                  data = htndat,
                  tt = function(x, t, ...) x * t)

> summary(tv_cox)

Call:
coxph(formula = surv_obj ~ adv_HIV + tt(adv_HIV), data = htndat,
    tt = function(x, t, ...) x * t)

  n= 3038, number of events= 398
   (1960 observations deleted due to missingness)

                 coef exp(coef)  se(coef)      z Pr(>|z|)
adv_HIV      0.972570  2.644733  0.188536  5.159 2.49e-07 ***
tt(adv_HIV) -0.013329  0.986759  0.006883 -1.937   0.0528 .
---
```

Regression with continuous covariate

Example: model effect of SBP on mortality hazard

$$log h(t) \quad = \quad \log h_0(t) + \beta \, \text{SBP}$$

Important questions

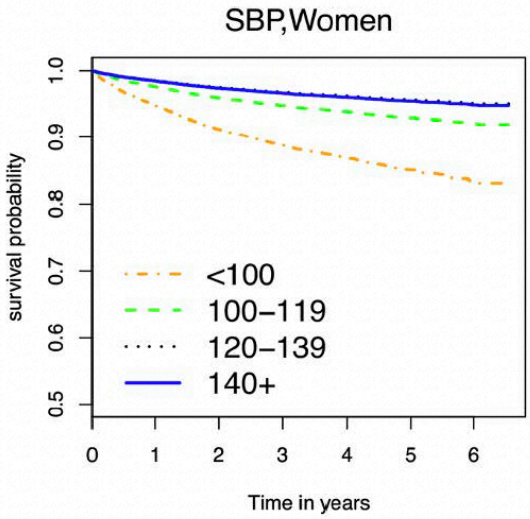
- How to interpret β
- Is the true effect of SBP linear?
- How to make the model more flexible

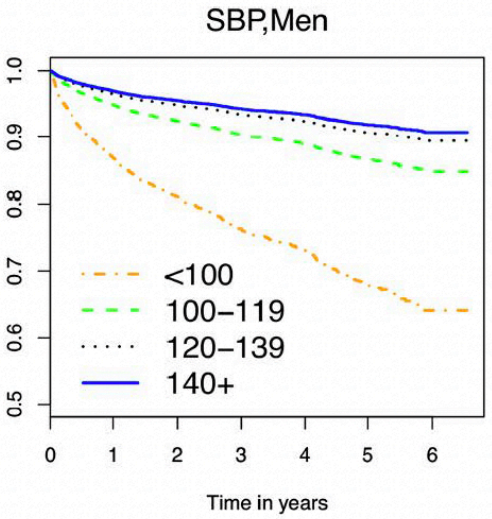
Summaries of SBP effect

Table 2 Unadjusted mortality rates per 100 person years by blood pressure groups for men and women with and without advanced HIV

Characteristic	Person years	Women events	Mortality rate (95% CI)	Person years	Men events	Mortality rate (95% CI)
Advanced HIV[a]						
Systolic blood pressure						
SBP <100 mmHg	3447	113	3.3 (2.7-3.9)	816	57	7.0 (5.4-9.1)
SBP 100-119 mmHg	18648	364	2.0 (1.8-2.2)	5966	219	3.7 (3.2-4.2)
SBP 120-139 mmHg	7954	116	1.5 (1.2-1.7)	4001	96	2.4 (2.0-2.9)
SBP ≥140 mmHg	1095	23	2.1 (1.4-3.2)	590	21	3.6 (2.3-5.5)

Summaries of SBP effect





Model building process

1. Fit model with linear effect

$$\log h(t) \quad = \quad \log h_0(t) + \beta \text{ SBP}$$

2. Examine residual plot to see if linearity is reasonable

3. Fit new model with nonlinear effect, using splines

$$\log h(t) \quad = \quad \log h_0(t) + f(\text{SBP})$$

where f is a function that is estimated from the data

Model with linear effect: R code

```
## ----model1-------------------------------------------------------------
# Center SBP at 120 for interpretability and save data in dat
dat <- htndat %>%
  dplyr::mutate(sbp_c120 = SBP - 120)

# Fit Cox model with SBP only
model1 <- coxph(
  Surv(survmonth, event) ~ sbp_c120,
  data    = dat,
  ties    = "efron"
)
summary(model1)
# There is evidence of effect of SBP on time to death
```

Model with linear effect: Output

```
> summary(model1)
Call:
coxph(formula = Surv(survmonth, event) ~ sbp_c120, data = dat,
    ties = "efron")

  n= 4998, number of events= 749

             coef exp(coef) se(coef)      z Pr(>|z|)
sbp_c120 -0.02246   0.97779  0.00286 -7.853 4.05e-15 ***
---
         exp(coef) exp(-coef) lower .95 upper .95
sbp_c120    0.9778      1.023    0.9723    0.9833
```

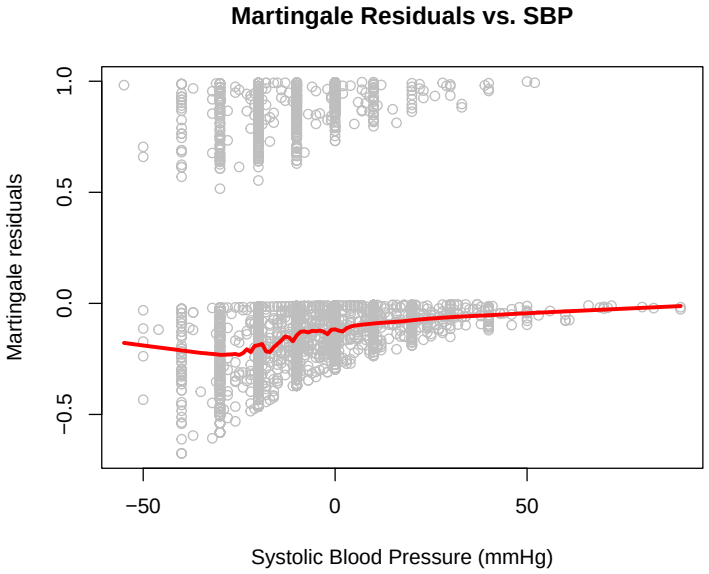
Parameter estimates

$$\begin{array}{ll} \text{log hazard ratio} & \hat{\beta} = -.022 \\ \text{hazard ratio} & \exp(-.022) = .98 \end{array}$$

Martingale residual plots: R code

```
## ----Martingale------------------------------------------------------
# Martingale residuals using model 1
htndat$mart_resid <- residuals(model1, type = "martingale")

## ----MartingalePlot--------------------------------------------------
# Plot Martingale vs. linear predictor, SBP
plot(
  htndat$SBP-120,
  htndat$mart_resid,
  xlab = "Systolic Blood Pressure (mmHg)",
  ylab = "Martingale residuals",
  main = "Martingale Residuals vs. SBP",
  col="gray"
)

lines(
  lowess(htndat$SBP-120, htndat$mart_resid, f = 0.20),
  col = "red",
  lwd = 3
)
```

Martingale residual plot



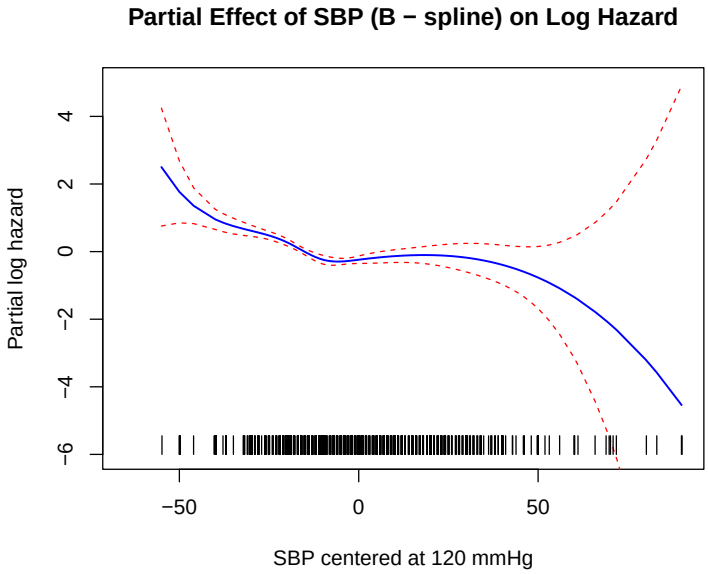
Regression spline for SBP: R code

```
## ----splineReg-------------------------------------------------------
# choose interior knots at the .05, .35, .65, .95 quantiles of sbp_c120

###
knots <- quantile(dat$sbp_c120, probs = c(0.20, 0.50, 0.80))

# fit Cox model with a 3-df B-spline for sbp_c120 plus adv_HIV as a covariate
model_spline <- coxph(
  Surv(survmonth, event) ~ bs(sbp_c120, knots = knots, degree = 3),
  data    = dat,
  ties    = "efron"
)
summary(model_spline)
```

Plotting regression spline: R code

```
## ------------------------------------------------------------------------
# Visualize the partial effects of B-spline terms
termplot(
  model_spline,
  terms          = 1,            # first term is the bs(sbp_c150, ...) spline
  se             = TRUE,
  rug            = TRUE,
  col.term       = "blue",
  col.se         = "red",
  col.res        = "darkgray",
  main           = "Partial Effect of SBP (B - spline) on Log Hazard",
  xlab           = "SBP centered at 120 mmHg",
  ylab           = "Partial log hazard",
  ylim=c(-6,5)
)
```

Effect of SBP using cubic b-spline regression spline



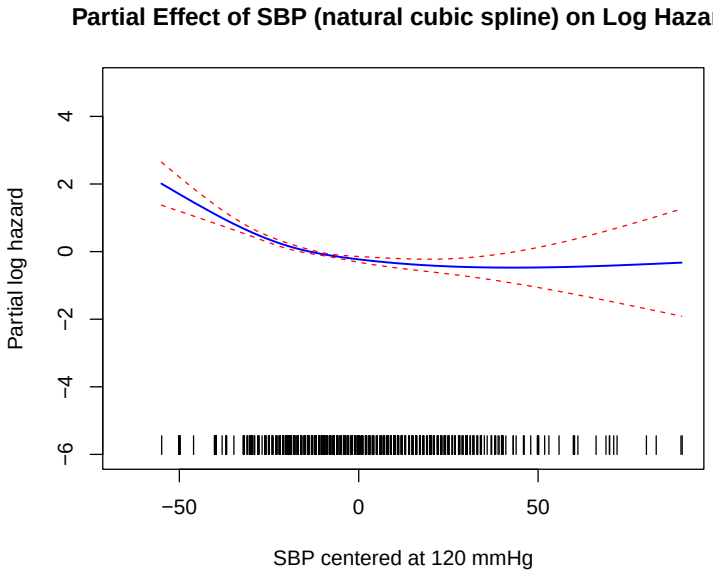
Another smoothing approach - natural spline

```
# fit Cox model with a 3-df natural spline for sbp_c120 plus adv_HIV as a covariate
model_spline <- coxph(
  Surv(survmonth, event) ~ ns(sbp_c120, df=3),
  data    = dat,
  ties    = "efron"
)
summary(model_spline)
```

Comparison

- `bs()` fits cubic smoothing spline - may have erratic tail behavior
- `ns()` fits natural cubic spline - constrains tail behavior

Effect of SBP using regression spline



Fitting models with other predictors

SBP and advanced HIV status

$$\log h(t) = \log h_0(t) + \beta_1 \text{SBP} + \beta_2 \text{Adv}$$

Add interaction to see if SBP effect differs by Adv HIV

$$\log h(t) = \log h_0(t) + \beta_1 \text{SBP} + \beta_2 \text{Adv} + \beta_3 (\text{SBP} \times \text{Adv})$$

Complex model to combine ideas we have discussed

- Add age and gender to the model
- Use spline term for SBP and age
- Allow hazard for advanced HIV to vary with time

$$\log h(t) = \log h_0(t) + f_1(\text{SBP}) + f_2(\text{age})\beta_1 \text{male.gender} \beta_2 \text{Adv}$$

Fitting models with other predictors

SBP and advanced HIV status

$$\log h(t) = \log h_0(t) + \beta_1 \text{SBP} + \beta_2 \text{Adv}$$

```
> summary(model3)
Call:
coxph(formula = Surv(survmonth, event) ~ sbp_c120 + as.factor(adv_HIV),
    data = dat, ties = "efron")

  n= 3038, number of events= 398
   (1960 observations deleted due to missingness)

                         coef exp(coef)  se(coef)      z Pr(>|z|)
sbp_c120            -0.016011  0.984117  0.003723 -4.301 1.70e-05 ***
as.factor(adv_HIV)1  0.686845  1.987435  0.116028  5.920 3.23e-09 ***
---

                    exp(coef) exp(-coef) lower .95 upper .95
sbp_c120               0.9841     1.0161     0.977     0.9913
as.factor(adv_HIV)1    1.9874     0.5032     1.583     2.4949
```

Fitting models with other predictors

Add interaction to see if SBP effect differs by Adv HIV

$$\log h(t) = \log h_0(t) + \beta_1 \text{SBP} + \beta_2 \text{Adv} + \beta_3 (\text{SBP} \times \text{Adv})$$

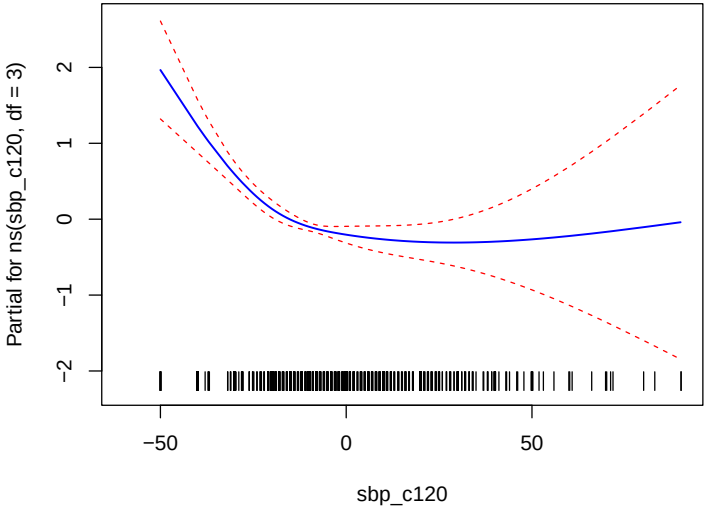
```
Call:
coxph(formula = Surv(survmonth, event) ~ sbp_c120 * as.factor(adv_HIV),
    data = dat, ties = "efron")

  n= 3038, number of events= 398
   (1960 observations deleted due to missingness)

                                    coef exp(coef)  se(coef)      z Pr(>|z|)
sbp_c120                       -0.010847  0.989212  0.007533 -1.440    0.150
as.factor(adv_HIV)1             0.609250  1.839052  0.151291  4.027 5.65e-05 ***
sbp_c120:as.factor(adv_HIV)1 -0.006764  0.993259  0.008665 -0.781    0.435
```

Complex model to combine ideas we have discussed

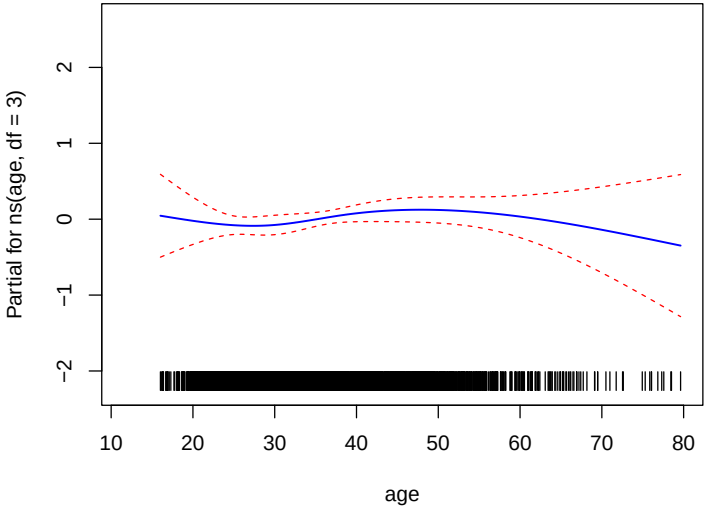
$$\log h(t) = \log h_0(t) + f_1(\text{SBP}) + f_2(\text{age}) + \beta_1 \text{male.gender} + \beta_2 \text{Adv}$$

```
coxph(formula = Surv(survmonth, event) ~ ns(sbp_c120, df = 3) +
    ns(age, df = 3) + as.factor(male.gender) + as.factor(adv_HIV),
    data = dat, ties = "efron")

  n= 3038, number of events= 398
   (1960 observations deleted due to missingness)

                              coef exp(coef)  se(coef)      z Pr(>|z|)
ns(sbp_c120, df = 3)1   -1.921020  0.146457  0.310251 -6.192 5.95e-10 ***
ns(sbp_c120, df = 3)2   -4.609319  0.009959  0.988404 -4.663 3.11e-06 ***
ns(sbp_c120, df = 3)3   -1.296022  0.273618  0.931644 -1.391    0.164
ns(age, df = 3)1         0.368627  1.445748  0.251386  1.466    0.143
ns(age, df = 3)2        -0.270376  0.763092  0.657682 -0.411    0.681
ns(age, df = 3)3        -0.293124  0.745930  0.488120 -0.601    0.548

as.factor(male.gender)1  0.630648  1.878828  0.109065  5.782 7.37e-09 ***
as.factor(adv_HIV)1      0.569175  1.766808  0.118548  4.801 1.58e-06 ***
```

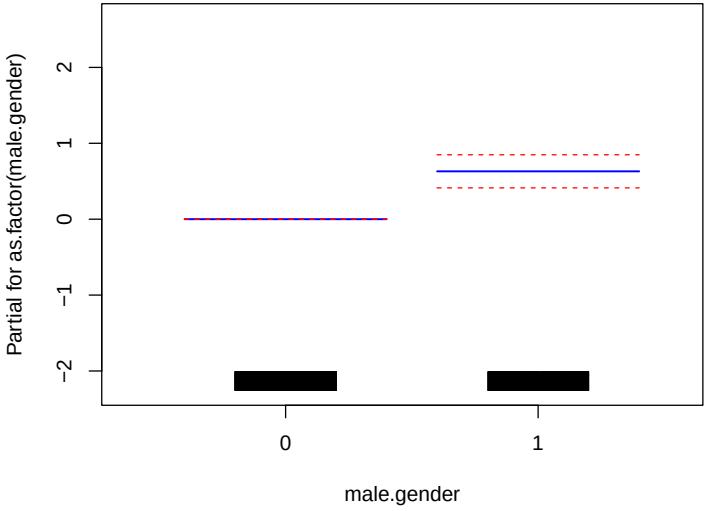
SBP effect



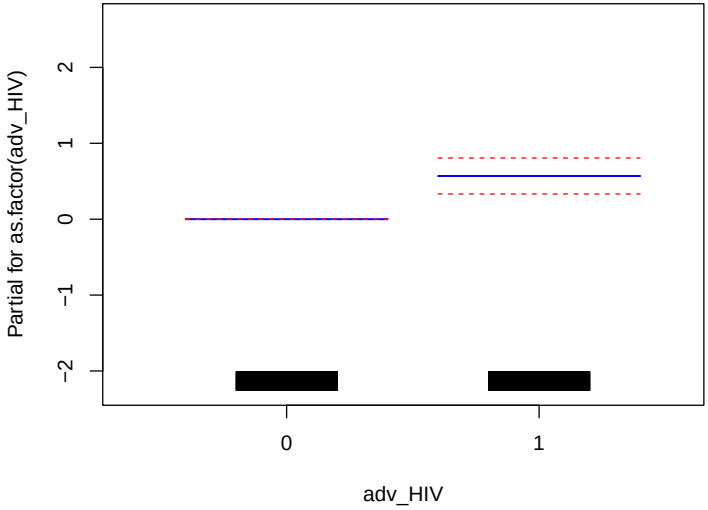
Age effect



Male gender effect



Advanced HIV effect



Exercises for day 1

1. Create stratified survival curves
    1. Stratify by gender
    2. Stratify by marital status
    3. Assess whether hazards look proportional
2. Fit a regression model to assess the effect of hemoglobin on survival
    1. Use a linear trend
    2. Use a natural regression spline
    3. Include gender and advanced HIV status as covariates
    4. Add SBP as a covariate