Time-dependent covariates and survival curves

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Ideas

- Time-dependent covariates are very useful
- Absolute risk and hazard ratios are complimentary
- In multistate models, both are essential
- But you can't compute Pr(future outcome) with a time-dependent variable

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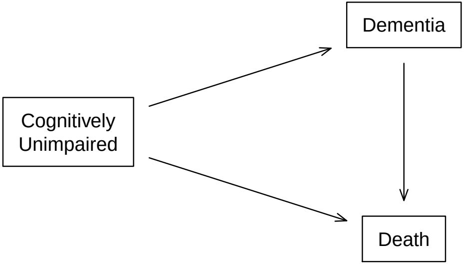
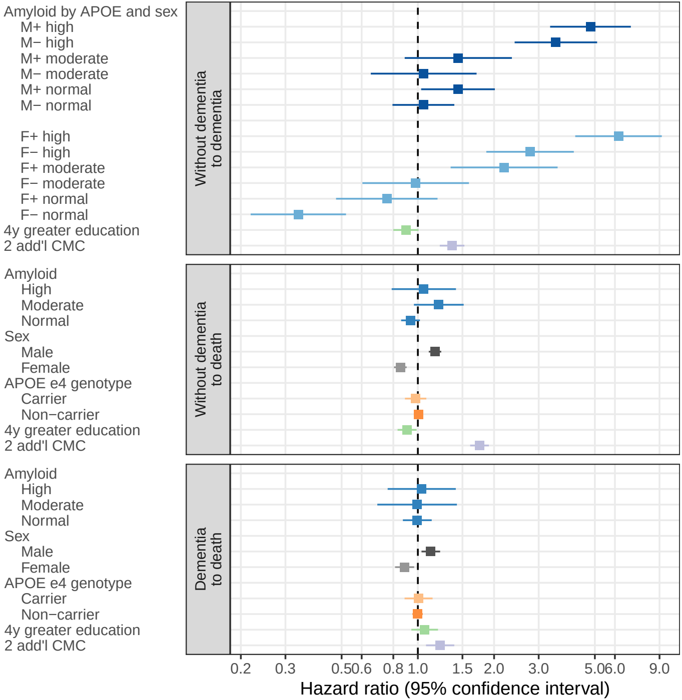
- Time-dependent covariates are very useful
- Absolute risk and hazard ratios are complimentary
- In multistate models, both are essential
- But you can't compute Pr(future outcome) with a time-dependent variable
- But I need it . . .

Mayo Clinic Study of Aging

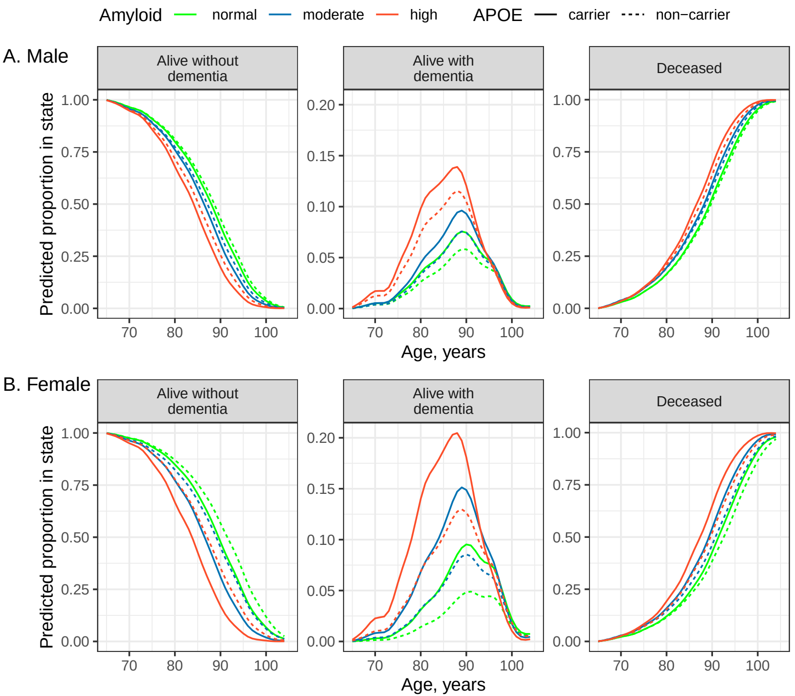


Data

- 4984 subjects, up to 16 years follow-up (median 4)
- 712 dementia events, 1852 deaths
- 51% male
- 27% APOE carrier
- initial amyloid: 24, 7, 5, 64% normal, moderate, high, NA
- initial CMC 0: 753, 1: 1005, 2: 1087, 3: 1088, 4-5: 897 6-7: 114



Amyloid by APOE and sex
M+ high
M− high
M+ moderate
M− moderate
M+ normal
M− normal
F+ high
F− high
F+ moderate
F− moderate
F+ normal
F− normal
4y greater education
2 add'l CMC
Without dementia to dementia
Amyloid
High
Moderate
Normal
Sex
Male
Female
APOE e4 genotype
Carrier
Non−carrier
4y greater education
2 add'l CMC
Without dementia to death
Amyloid
High
Moderate
Normal
Sex
Male
Female
APOE e4 genotype
Carrier
Non−carrier
4y greater education
2 add'l CMC
Dementia to death
0.2
0.3
0.5
0.6
0.8
1.0
1.5
2.0
3.0
5.0
6.0
9.0
Hazard ratio (95% confidence interval)



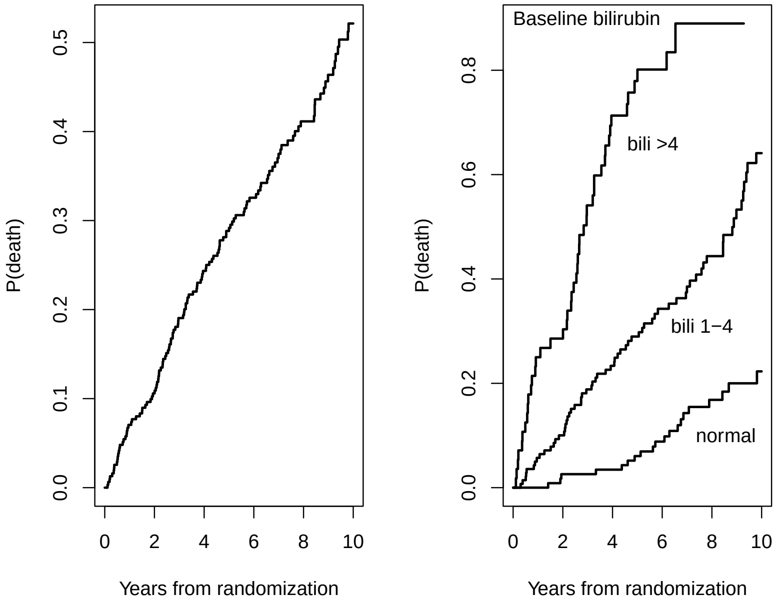
Amyloid
normal
moderate
high
APOE
carrier
non−carrier
A. Male
Alive without dementia
Alive with dementia
Deceased
Predicted proportion in state
Age, years
B. Female
Alive without dementia
Alive with dementia
Deceased
Predicted proportion in state
Age, years

Primary Biliary Cirrhosis

- Two clinical trials of D-penicillamine for treamtment of PBC
- No treatment effect
- Data merged, and used as a model for natural history of PBC (n=418)
- Covariates of bilirubin (10.4), age (5.1), albumin (3.8), edema (3.3), prothrombin time (3.1)
- Concordance = .835
- `pbc` and `pbcseq` data sets

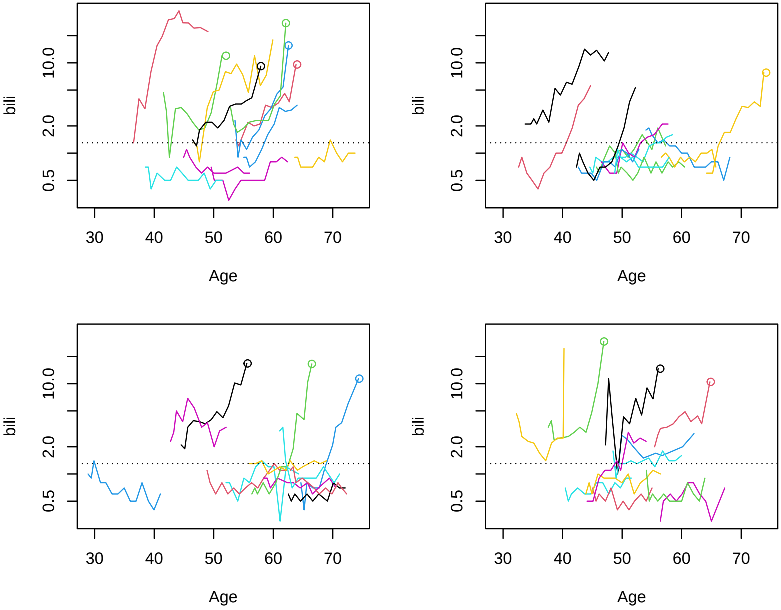
Model

- Use only bilirubin and age, categorical bilirubin
- Use `pbcseq` subset (n=312)
- Planned visits at 6m, 1yr, yearly thereafter
- Time-dependent bilirubin



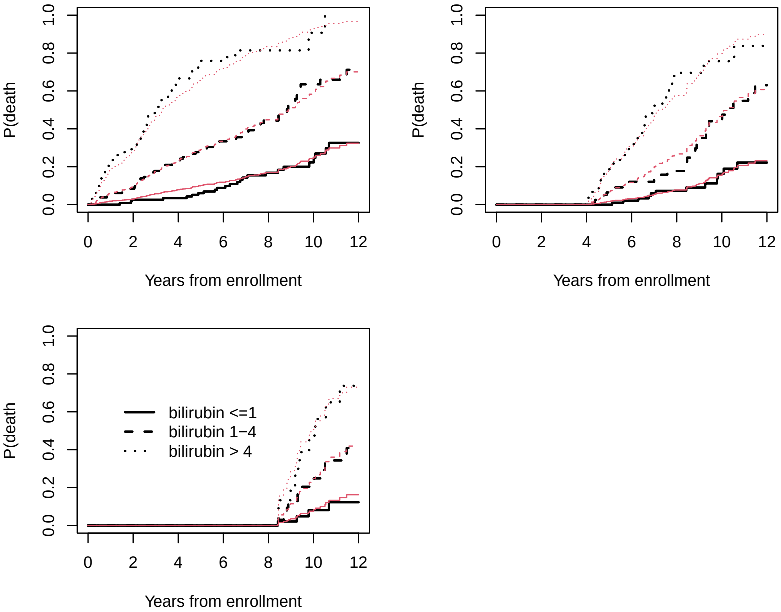
P(death)
0.0
0.1
0.2
0.3
0.4
0.5
0
2
4
6
8
10
Years from randomization
Baseline bilirubin
bili >4
bili 1−4
normal
P(death)
0.0
0.2
0.4
0.6
0.8
0
2
4
6
8
10
Years from randomization

	Hazard Ratio			
	Age10	bili 1–4	bili > 4	C
Time-fixed	1.5	3.5	14.0	0.79
Time-dependent	1.6	2.9	27.1	0.86



bili
10.0
2.0
0.5
30
40
50
60
70
Age
bili
10.0
2.0
0.5
30
40
50
60
70
Age
bili
10.0
2.0
0.5
30
40
50
60
70
Age
bili
10.0
2.0
0.5
30
40
50
60
70
Age

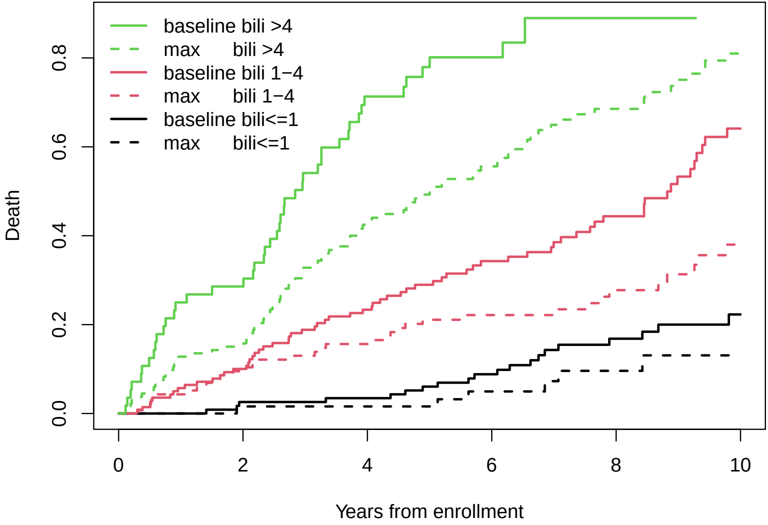
Conservative approach



- No explicit use of time-dependent data
- Curves are correct, but meh
- Aside: these are marginal over age. This matters.

Worst approach

- Cateorize each subject by their max bilirubin achieved
- A variant of immortal time bias
  - Covariate that depends on the future
  - Endpoint that depends on the future
  - Selection that depends on the future

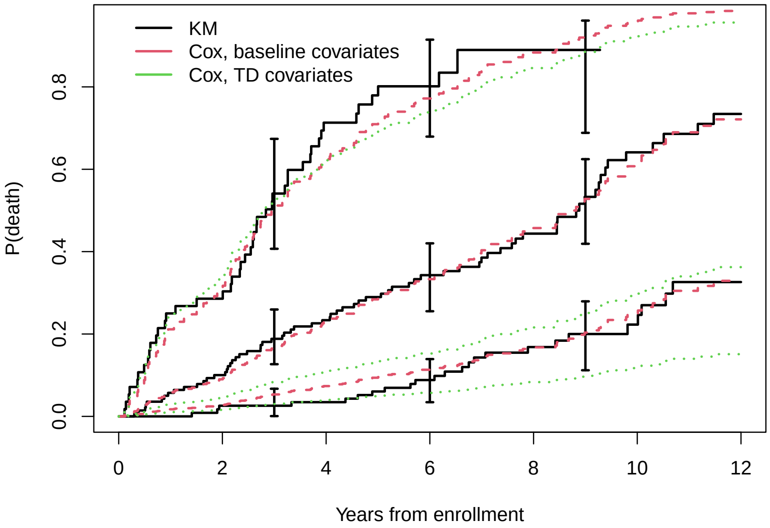


baseline bili >4
max bili >4
baseline bili 1−4
max bili 1−4
baseline bili<=1
max bili<=1
Death
0.0
0.2
0.4
0.6
0.8
0
2
4
6
8
10
Years from enrollment

Useless: static referrent

- Fit the time-dependent Cox model
- Predict the survival for a fixed covariate set
- Example in Therneau and Grambsch

```
fit <- coxph(Surv(year1, year2, death) ~ age10 + bili3,
               pdata, id=id)
dummy1 <- data.frame(age10= mean(pdat0$age10),
                      bili3= "1-4")
surv1 <- survfit(fit, dummy1)

dummy2 <- data.frame(age10= pdat0$age10,
               bili3="1-4")
surv2 <- survfit(dummy2)
```


KM
Cox, baseline covariates
Cox, TD covariates
P(death)
0.0
0.2
0.4
0.6
0.8
0
2
4
6
8
10
12
Years from enrollment

What went wrong?

- Baseline covariates
  - Cox model based on baseline bilirubin
  - Prediction for someone with a specified baseline bilirubin
- TD covariates
  - Cox model based in TD bilirubin
  - Middle curve is the prediction for a cohort of subjects who start with bilirubin 1-4, and then *never change*
- Baseline bili: 116 normal, 140 1-4, 56 > 4
- Almost all of the 140 progress

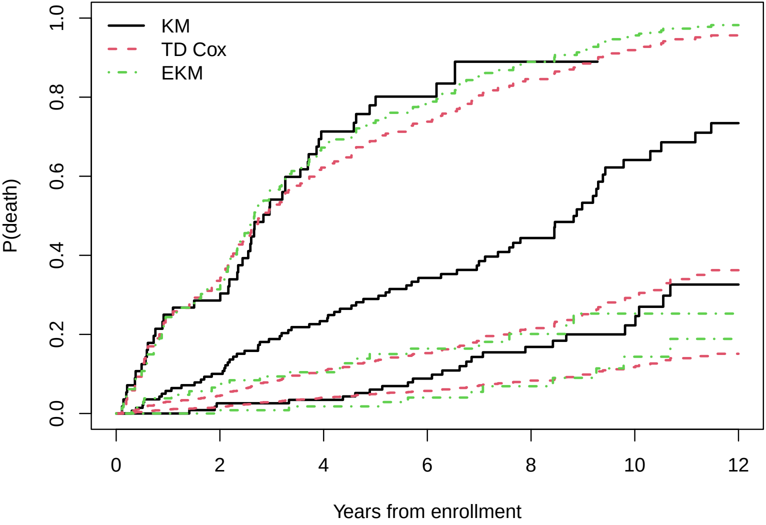
What went wrong?

- Baseline covariates
  - Cox model based on baseline bilirubin
  - Prediction for someone with a specified baseline bilirubin
- TD covariates
  - Cox model based in TD bilirubin
  - Middle curve is the prediction for a cohort of subjects who start with bilirubin 1-4, and then *never change*
- Baseline bili: 116 normal, 140 1-4, 56 > 4
- Almost all of the 140 progress
- Correct estimate for a cohort which doesn't exist

Useless: Extended Kaplan-Meier

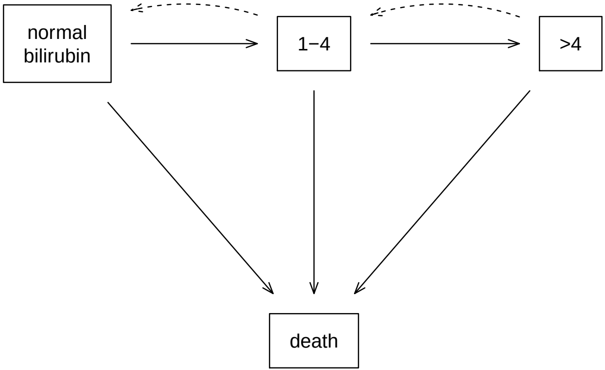
- Snappin et al, American Statistician, 2005
- Use simple survfit on the time-dependent data

```
snappin <- survfit(Surv(year1, year2, death) ~ bili3,
                        data= pdata)
```


KM
TD Cox
EKM
P(death)
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
12
Years from enrollment

Big picture

- To predict future survival with a TD covariate one needs to specify a *covariate path*
- Possible in some cases
- Allowed by the software
- Alternative: use a multistate model


normal
bilirubin
1−4
>4
death

Survival curves

- AJ: specify starting time and/or state (optional)
- Ordinary Cox model: specify the covariates (not optional)
- MSH: specify covariates and optinally the starting time and/or state

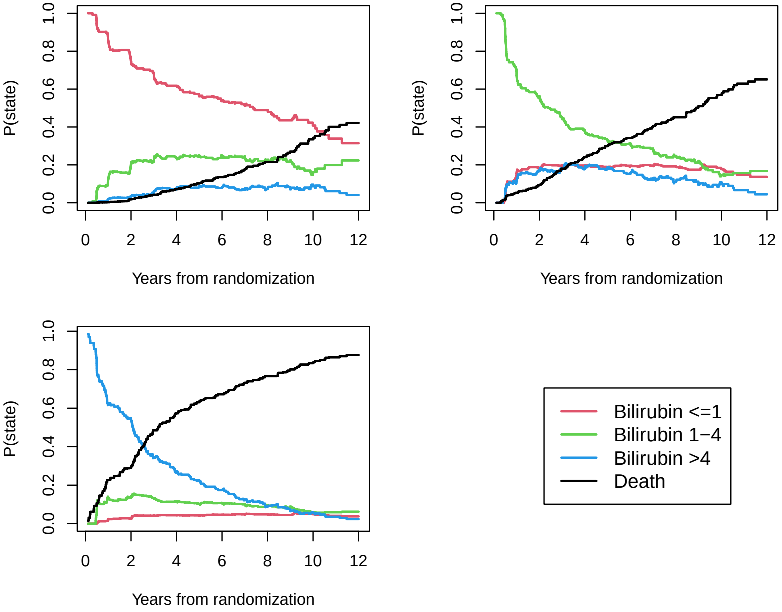
AJ

$$\hat{\lambda}_{jk}(t) = \frac{\sum_i dN_{ijk}(t)}{\sum_i Y_{ij}(t)}$$

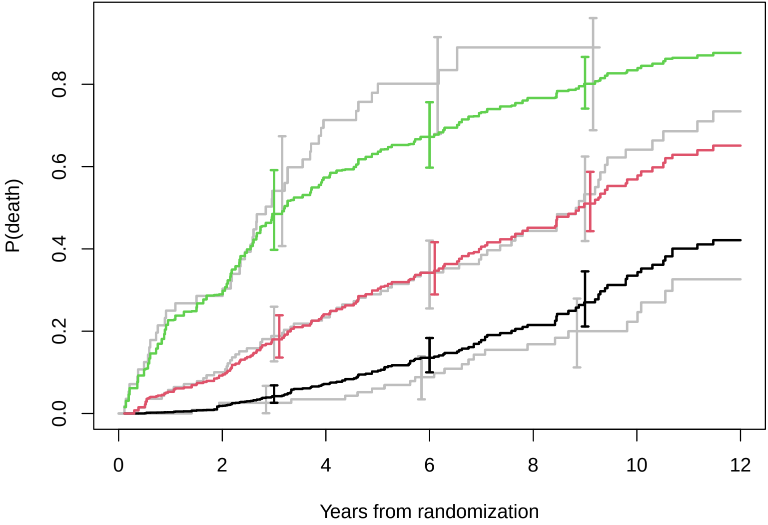
$$H(t) = \begin{pmatrix} \Box & \hat{\lambda}_{12}(t) & \hat{\lambda}_{13}(t) & \hat{\lambda}_{14}(t) \\ \hat{\lambda}_{21}(t) & \Box & \hat{\lambda}_{23}(t) & \hat{\lambda}_{24}(t) \\ \hat{\lambda}_{31}(t) & \hat{\lambda}_{32}(t) & \Box & \hat{\lambda}_{34}(t) \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

$$p(t) = p(t_0) \prod_{t_0 < s \leq t} H(s)$$

- t_0 is the starting time, default = minimum time in the data
- $p(t)$ a vector of length $m=$ number of states.
- t_0 and $p(t_0)$ can be set by the user.


P(state)
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
10
12
Years from randomization
Bilirubin <=1
Bilirubin 1−4
Bilirubin >4
Death

```
aj3a <- survfit(Surv(year1, year2, bstate) ~ 1, pdata,
                istate=bili3, p0=c(1,0,0,0), id=id)
aj3b <- survfit(Surv(year1, year2, bstate) ~ 1, pdata,
                istate=bili3, p0=c(0,1,0,0), id=id)
aj3c <- survfit(Surv(year1, year2, bstate) ~ 1, pdata,
                istate=bili3, p0=c(0,0,1,0), id=id)
```



P(death)
0.0
0.2
0.4
0.6
0.8
0
2
4
6
8
10
12
Years from randomization

Math

The death curve for group “normal at t0” will have an increment at time t of

- KM: KM(t-)* P(death at $t|$ started in 1)
- AJ : $\sum_{j=1}^{3}$ P(currently in $j|$ started in 1) P(death at $t|$ currently in j)
- The AJ uses all the data for all the curves.
  - smaller variance
  - Markov assumption

Hazard models

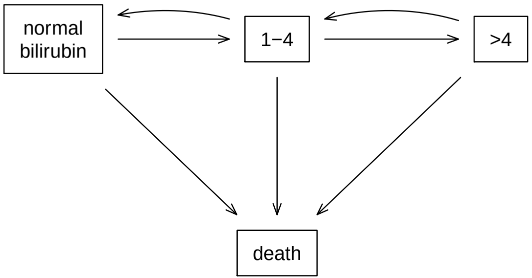
$$\lambda_{ijk}(t) = \lambda_{jk}(t)\exp(X_i\beta)$$
$$\lambda_{j4} = \lambda_d exp(\gamma_j)$$

- A covariate now belongs to the state rather than to the subject.
- Subtle, but with software implications
- Skip covariates for the bili:bili transitions.

Hazard models

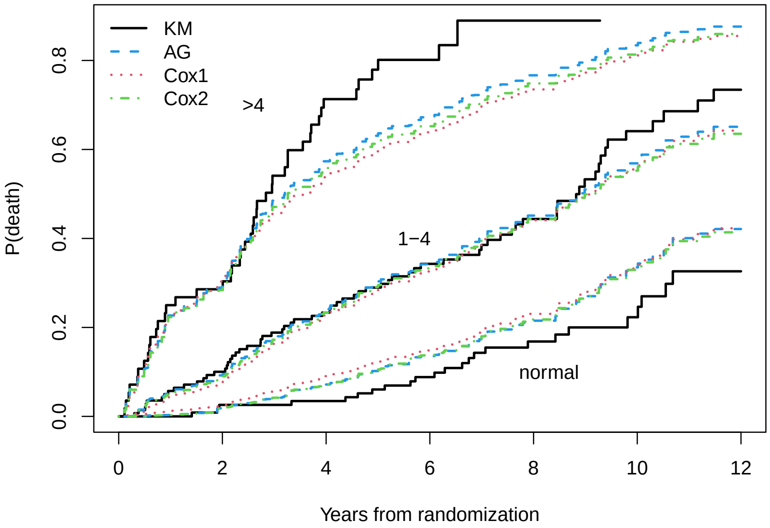
```
mfit0 <- coxph(Surv(year1, year2, death) ~ age10 + bili3,
               ties="breslow", data= pdata)
mfit1 <- coxph(list(Surv(year1, year2, bstate) ~ 1,
                    0:4 ~ age10 / common + shared),
               data= pdata, istate=bili3, id=id)
mfit2 <- coxph(list(Surv(year1, year2, bstate) ~ 1,
                    0:4 ~ age10 +bili3 +1 / common),
               data= pdata, istate=bili3, id=id)

rbind(mfit0= coef(mfit0), mfit1= coef(mfit1),
      mfit2 = coef(mfit2))
          age10 bili31-4  bili3>4
mfit0 0.4780539 1.051721 3.298826
mfit1 0.4780539 1.051721 3.298826
mfit2 0.4780539 1.051721 3.298826
```

```
Call:
coxph(formula = list(Surv(year1, year2, bstate) ~ 1, 0:4 ~
    shared), data = pdata, id = id, istate = bili3)


1:4      coef exp(coef) se(coef) robust se z      p
  age10 0.48      1.61     0.08      0.10 5 3e-06


2:4        coef exp(coef) se(coef) robust se z      p
  age10   0.48      1.61     0.08      0.10 5 3e-06
  ph(1:4) 1.05      2.86     0.38      0.36 3 0.004


3:4         coef exp(coef) se(coef) robust se  z      p
  age10    0.48      1.61     0.08      0.10  5  3e-06
  ph(1:4)  3.30     27.08     0.33      0.31 10 <2e-16

 States:  1= normal, 2= 1-4, 3= >4, 4= death
```


normal
bilirubin
1−4
>4
death

$$\lambda_{14} = \lambda_d \exp(\beta age) \quad (1)$$
$$\lambda_{24} = [\lambda_d \exp(\gamma_{12})] \exp(\beta age) \quad (2)$$
$$\lambda_{34} = [\lambda_d \exp(\gamma_{13})] \exp(\beta age) \quad (3)$$
$$\quad (4)$$

- Same likelihood as the simple TD model, wrt death
- But now we can estimate curves properly
- γ coefficients belong to the hazard/state pair and not the subject


KM
AG
Cox1
Cox2
>4
1−4
normal
P(death)
0.0
0.2
0.4
0.6
0.8
0
2
4
6
8
10
12
Years from randomization

Open questions

- Multistate AJ: honest curves, but no $\hat{\beta}$ for bilirubin
  - How critical is the Markov assumption?
  - Is the reduction in variance bankable?
  - How many sub-states?
  - Multiple variables?
- Multistate hazard model: correct curves AND coefficients
  - How many sub-states?
  - Multiple variables (additivity)
  - Constraints
  - Code
  - Variance (IJ)