Applied Survival Analysis Using R Chapter 9: Multiple Survival Outcomes and Competing Risks

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Outline

1. Clustered Survival Times
2. Marginal Survival Models
3. Frailty Survival Models
4. Cause-Specific Hazards

Problem

- The type of survival data commonly we have considered has, as *an endpoint*, *a single cause of death*, and the survival times of each case have been assumed to be *independent*.
- Problem:
  - How about the independence assumption no longer holds in clustered data?
  - How about the event may repeat indefinitely, and then we would have multiple times per person?
  - How about only the first of several outcomes is observable?

Example

mutation carrier in female relatives among families

Determine if a female was a mutation carrier, and find the relationship between mutation and breast cancer, this subset consists of 1,960 families with two or more female relatives; for those with three or more female relatives, two were selected at random.

```
> ashkenazi[ashkenazi$famID %in% c(1, 9, 94), ]
     famID     brcancer     age     mutant
1        1            0      73          0
2        1            0      40          0
7        9            0      89          0
8        9            1      60          0
87      94            1      44          1
88      94            0      45          1
```

- And we know the covariate is “`mutant`” ,the censoring variable is “`brcancer`”.

Model

- Suppose that there is only one covariate, and its estimate is $\hat{\beta}$,*ignoring* the cluster structure first.
- Denote the estimate of its variance (from the Cox model) by $\hat{V}$, and the standard error of the estimate is then $\hat{V}^{1/2} = \sqrt{\hat{V}}$. and assume all subjects are independent.
- To obtain a correction due to the clustering structure, define a *score residual* for subject j in cluster i:

$$s_{ij} = \delta_{ij}[z_{ij} - \bar{z}(t_{ij})] - \sum_{t_u \le t_{ij}} [z_i - \bar{z}(t_{ij})] e^{z_i \beta} \left[\hat{H}_0(t_u) - \hat{H}_0(t_{u-1}) \right] \quad (1)$$

Model

- The first part of this residual is the *Schoenfeld residual* in Chapter 7
- Formulate a quantity C defined by:

$$C = \sum_{i=1}^{G} \sum_{j=1}^{n_i} \sum_{m=1}^{n_i} s_{ij} s_{im} \tag{2}$$

- We can define a cluster-adjusted variance by $V^* = \hat{V}^2 \cdot C$, and a standard error for $\hat{\beta}$ by $\sqrt{V^*}$.
- If there are q covariates, $se(\beta) = [diag(V^*)]^{1/2}$, and the score residuals s_{ij} are $1 \times q$ matrices, $C = \sum_{i=1}^{G} \sum_{j=1}^{n_i} \sum_{m=1}^{n_i} \underset{\sim}{s'_{ij}} \underset{\sim}{s_{im}}$, and the cluster-adjusted covariance matrix is given by $V^* = \hat{V} C \hat{V}$.

Generalize to clustered survival data

- The independent survival data, with the *i*th observation given by (t_i, δ_i, z_i), the likelihood function:

$$L(\beta; z_i) = \prod_{i=1}^{n} f(t_i, \beta)^{\delta_i} S(t_i, \beta)^{1-\delta_i} = \prod_{i=1}^{n} h(t_i, \beta)^{\delta_i} S(t_i, \beta) \qquad (3)$$

  or in baseline cumulative hazard:

$$L(\beta; z_i) = \prod_{i=1}^{n} [h_0(t_i) e^{z_i\beta}]^{\delta_i} \cdot e^{-H_0(t_i)} e^{z_i\beta} \qquad (4)$$

  where $H_0(t_i) = -\int_0^{t_i} h_0(v)dv$ is the baseline cumulative hazard.
- Now suppose that the survival times are organized into clusters

Generalize to clustered survival data

- Assign each individual in a cluster a common factor known as a *frailty* or, alternatively, as a *random effect*, and denote the frailty for all individuals in the *i*th cluster by ω_i, then the hazard function for the *j*th subject in the *i*th cluster as follows:

$$h_{ij}(t_{ij}) = h_0(t_{ij}) \cdot \omega_i e^{z_{ij}\beta} \tag{5}$$

  and ω_i is vary from one cluster to another, and a common model that governs this variability is a *gamma distribution*

$$g(\omega_i, \theta) = \frac{\omega^{\frac{1}{\theta}-1} e^{-\frac{\omega}{\theta}}}{\Gamma(\frac{1}{\theta})\theta^{\frac{1}{\theta}}} \tag{6}$$

Generalize to clustered survival data

- When we take frailties ω_i into consideration, the the joint likelihood for the jth subject in the ith cluster would be:

$$L_{ij}(\beta, \theta; \omega_i, t_{ij}, \delta_{ij}, z_{ij}) = g(\omega_i, \theta) \cdot [h_0(t_{ij})\omega_i e^{z_{ij}\beta}]^{\delta_{ij}} \cdot e^{-H_0(t_{ij})\omega_i e^{z_{ij}\beta}} \quad (7)$$

  and the full likelihood would be:

$$L(\beta, \theta) = \prod_{i=1}^{G} \prod_{j=1}^{n_i} L_{ij}(\beta, \theta; \omega_i, t_{ij}, \delta_{ij}, z_{ij}) \quad (8)$$

- The frailties are *latent* variables, we cannot directly observe. Thus, to obtain estimates of β and θ we need to use a multistage procedure called the *EM (expectation-maximization) algorithm*.

Example

- Using standard Cox proportional hazards model to predict the age of onset of breast cancer depending on mutant.

```
> result.coxph <- coxph(Surv(age, brcancer) ~ mutant,
data=ashkenazi)
> summary(result.coxph)
 n= 3920, number of events= 473
            coef    exp(coef)    se(coef)    z       Pr(>|z|)
mutant    1.1907    3.2895       0.1984    6.002    1.95e-09 ***
```

- The log partial likelihood from this model is obtained as follows:

```
result.coxph$loglik
[1] -3579.707   -3566.745
```

- -3579.707 is no covarites and the -3566.745 is model with "`mutant`" included as a predictor, the likelihood ratio test statistic is twice the difference, $G^2 = 2(3579.707 - 3566.745)$ $= 25.924$,compared to a chi-square distribution with 1 df.

Model with cluster

```
> result.coxph.cluster <- coxph(Surv(age, brcancer) ~ mutant +
cluster(famID), data=ashkenazi)
> summary(result.coxph.cluster)
n= 3920, number of events= 473
         coef   exp(coef)  se(coef)  robust.se   z    Pr(>|z|)
mutant  1.1907   3.2895     0.1984     0.2023  5.886  3.96e-09 ***
```

- The “`robust se`”, this estimate is only slightly higher than the one from the standard Cox model, indicating that the effect of clustering within first-degree relatives is small.

```
> result.coxph.frail <- coxph(Surv(age, brcancer) ~ mutant +
frailty(famID), data=ashkenazi)
> summary(result.coxph.frail)
      n= 3920, number of events= 473
               coef  se(coef)    se2    Chisq    DF     p
mutant        1.272   0.2317   0.2004   30.13   1.0  4.0e-08
frailty(famID)                         221.50 211.6  3.1e-01
```

New facility in R

- The “frailty” option, is the “coxme” package,must be separately downloaded and installed.

```
> library(coxme)
> result.coxme <- coxme(Surv(age, brcancer) ~ mutant + (1|famID),
data=ashkenazi)
> summary(result.coxme)
Cox mixed-effects model fit by maximum likelihood
  Data: ashkenazi events,
  n = 473, 3920
  Iterations= 10 63
                    NULL     Integrated     Fitted
Log-likelihood  -3579.707    -3564.622   -3411.522
                  Chisq    df        p          AIC       BIC
Integrated loglik 30.17   2.0   2.8100e-07   26.17    17.85
Penalized loglik 336.37  150.1  2.2204e-16   36.16   -588.13
Model:  Surv(age, brcancer) ~ mutant + (1 | famID)
Fixed coefficients
           coef      exp(coef)     se(coef)     z       p
mutant   1.236609    3.443914    0.2205358   5.61   2.1e-08
Random effects
 Group Variable   Std Dev    Variance
 famID Intercept 0.5912135  0.3495334
```

Kaplan-Meier Estimation with Competing Risks

- A patient may potentially experience *multiple events*, only the first-occurring of which can be observed, eg: diagnosis with prostate cancer until death from that Cause 1 to Cause 2, but for a particular patient we can only observe the time to the first event.
- One way:Select each as the primary event, and to treat the other as a censoring event.
- However,Obtain unbiased estimates of survival curves, this simplistic method would require the usually *false assumption* that the two causes of death are independent.

Kaplan-Meier Estimation with Competing Risks

Fig. 9.1 Kaplan-Meier estimates of the probabilities of death from prostate cancer and from other causes

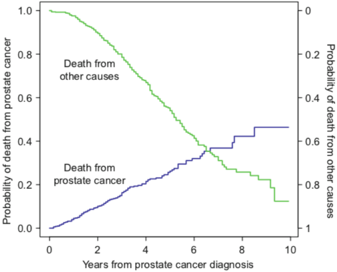
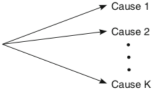


Fig. 9.2 Subject can die of only one of K causes



- Skip the R codes, and the result shows above, but such an exercise would require the assumption that the causes be independent. This assumption cannot be tested from the data,

Cause-Specific Hazards and Cumulative Incidence Functions

- Suppose that there are K distinct causes of death, and each subject can experience at most one of the K causes of death
- With competing risks, it is helpful to define, for each cause of interest, a function known as the *cumulative risk function*

$$F_j(t) = Pr(T \leq t, C = j) = \int_0^t h_j(u)S(u)du \tag{9}$$

- And the hazards is:

$$h_j(t) = \lim_{\delta \to 0} \left(\frac{Pr(t < T < t + \delta, C = j | T > t)}{\Delta} \right) \tag{10}$$

- It's easy to get:

$$h(t) = \sum_{j=1}^{K} h_j(t) \tag{11}$$

Formula

- Suppose now that we have D distinct ordered failure times t_1 ,t_2,..., t_D, estimate the hazard at the ith time ti using $\hat{h}(t_i) = d_i/n_i$
- The cause-specific hazard for the kth hazard may be written in a similar form as $\hat{h}_k(t_i) = d_{ik}/n_i$
- The probability of failure from any cause at time t_i is the product of $\hat{S}(t_{i-1})$, the probability of being alive just before t_i, and $\hat{h}(t_i)$, the risk of dying at t_i. Similarly, the probability of failure due to cause k at that time is $\hat{S}(t_{i-1})\hat{h}(t_i)$
- So the *cumulative incidence function* is:

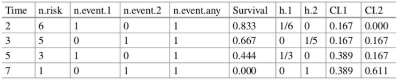
$$\hat{F}_k(t) = \sum_{t_i \leq t} \hat{S}(t_{i-1})\hat{h}(t_i) \tag{12}$$

Example

- First compute the overall survival distribution.

```
> tt <- c(2,7,5,3,4,6)
> status <- c(1,2,1,2,0,0)
> status.any <- as.numeric(status >= 1)
> result.any <- survfit(Surv(tt, status.any) ~ 1)
> result.any$surv
[1] 0.8333333 0.6666667 0.6666667 0.4444444 0.4444444 0.0000000
```

- Compute the cumulative incidence functions as in the following table:



Time	n.risk	n.event.1	n.event.2	n.event.any	Survival	h.1	h.2	CI.1	CI.2
2	6	1	0	1	0.833	1/6	0	0.167	0.000
3	5	0	1	1	0.667	0	1/5	0.167	0.167
5	3	1	0	1	0.444	1/3	0	0.389	0.167
7	1	0	1	1	0.000	0	1	0.389	0.611

Example

- Returning to the prostate cancer example of Fig. 9.1,now estimate the competing risks cumulative incidence functions as follows:

```
> sf <- survfit(Surv(survTime, status, type="mstate") ~ 1,
data=prostateSurvival.highrisk)
> tt <- sf$time
> CIs <- sf$pstate
> ci1 <- CIs[,1]
> ci2 <- CIs[,2]
> times <- tt/12
> Rci2 <- 1 - ci2
```

- Plot

```
> plot(Rci2 ~ times, type="s", ylim=c(0,1),lwd=2, color="green",
xlab="Time in years". ylab="Survival probability")
> lines(ci1~times, type="s", lwd=2, col="blue")
> lines(surv.other.km ~ time.km, type="s",
col="lightgreen", lwd=1)
> lines(cumDist.prost.km ~ time.km, type="s",
col="lightblue", lwd=1)
```

Example

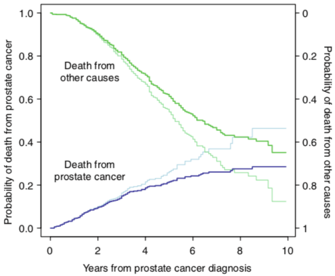


Fig. 9.4 Cumulative incidence of death from prostate cancer and from other causes, compared to the Kaplan-Meier estimates

- These curves represent estimates of the actual probabilities that a patient will die of a *particular cause*, rather than hypothetical probabilities that he would die of one cause in the absence of the other.

Regression Methods for Cause-Specific Hazards

- Modeling covariate information for competing risks too difficult to define precisely the hazard function on which the covariates should operate.
- Study the effects of the, *remaining covariates (grade and age)* on prostate cancer death, treating other causes of death as censoring indicator.

```
> prostateSurvival.T2 <- prostateSurvival[prostateSurvival$stage
=="T2",]
> attach(prostateSurvival.T2)
> result.prostate <- coxph(Surv(survTime, status.prost) ~ grade +
ageGroup)
> summary(result.prostate)
                  coef    exp(coef)    se(coef)     z      Pr(>|z|)
gradepoor        1.2199    3.3867       0.1004   12.154   < 2e-16 ***
ageGroup70-74   -0.2860    0.7513       0.2595   -1.102   0.2704
ageGroup75-79    0.4027    1.4958       0.2257    1.784   0.0744
ageGroup80+      0.9728    2.6454       0.2148    4.529   5.92e-06 ***
```

Regression Methods for Cause-Specific Hazards

- Conclusion:Patients having poorly differentiated disease (grade = poor) have much worse prognosis than do patients with moderately differentiated disease (the reference group here), with a log-hazard ratio of 1.2199.
- Define a "sub-distribution hazard"

$$\bar{h}_k(t) = \lim_{\delta \to 0} \frac{pr(t < T_k < t + \delta | E)}{\delta} \tag{13}$$

where the conditional event is given by:

$$E = \{\{T_k > t\} or \{T_{k'} \leq t \; and \; k' \neq k\}\} \tag{14}$$

Example

- When computing these sub-distribution hazards, the risk set includes not only those currently alive and at risk for the *k*th event type, but also those who *died earlier of other causes*.
- This method is implemented in the “`crr`” function in the R package “`cmprsk`”.

```
> cov.matrix <- model.matrix(~ grade + ageGroup)
> head(cov.matrix)
(Intercept)  gradepoor  ageGroup70-74  ageGroup75-79  ageGroup80+
1      1         0           1               0             0
2      1         1           0               1             0
3      1         1           0               1             0
4      1         1           0               0             1
5      1         0           0               1             0
6      1         0           0               1             0
> cov.matrix.use <- cov.matrix[,-1] # drop the first column
```

Example

- Obtain estimates for the prostate cancer as follows, dropping the first (intercept) column of the covariate matrix.

```
> library(cmprsk)
> result.prostate.crr <- crr(survTime, status, cov1=cov.
matrix[,-1], failcode=1)
                    coef    exp(coef)   se(coef)   z       Pr(>|z|)
gradepoor          1.132     3.102       0.101   11.20    0.00000
ageGroup70-74     -0.272     0.762       0.253   -1.08    0.28000
ageGroup75-79      0.367     1.443       0.219    1.67    0.09400
ageGroup80+        0.799     2.224       0.208    3.85    0.00012
```

- The argument "`failcode=1`" refers to death from prostate cancer. For death from other causes, we use "`failcode=2`",

Comparing the Effects of Covariates on Different Causes of Death

- We know the risk of both causes of death increase with age. But does the effect of age differ for these two causes?
- Just split each patient's data into separate rows, one for each cause of death.
- Begin by setting up a "`transition`" matrix using the function "`trans.comprisk`",

```
> tmat <- trans.comprisk(2, names = c("event-free", "prostate",
"other"))
> tmat          to
from          event-free   prostate        other
  event-free      NA           1              2
  prostate        NA          NA             NA
  other           NA          NA             NA
```

- The matrix states that a patient's status can change from "`event-free`" to either "`prostate`" or "`other`", these latter two being causes of death.

Example

- Next, we use the function "`msprep`" to create the new data set, and examine the first few rows, and obtain a summary of the numbers of events of each type as follows:

```
> prostate.long <- msprep(time = cbind(NA, survTime, survTime),
status = cbind(NA, status.prost, status.other),
keep = data.frame(grade, ageGroup), trans = tmat)
> head(prostate.long)
> events(prostate.long)
$Frequencies
            to
from        event-free  prostate  other  no event  total entering
 event-free      0           410   1345      4165              5920
 prostate        0             0      0         0                 0
 other           0             0      0         0                 0
```

- These results indicate that there are 410 deaths due to prostate cancer, 1345 due to other causes,and 4165 censored observations, for 5920 total.

Summary

- Use separate commands, one for “`trans = 1`” (prostate cancer) and the other for “`trans = 2`” (other causes of death), as follows:

```
> summary(coxph(Surv(time, status) ~ grade + ageGroup,
data=prostate.long, subset=trans==1))
> summary(coxph(Surv(time, status) ~ grade + ageGroup,
data=prostate.long, subset=trans==2))
```

- The results are identical to what we obtained before.
- Expect that cancer grade affects prostate cancer death differently than it does death from other causes.

```
> summary(coxph(Surv(time, status) ~ grade*factor(trans) +
 ageGroup + strata(trans), data=prostate.long))
   n= 11840, number of events= 1755
                 coef   exp(coef)  se(coef)     z    Pr(>|z|)
gradepoor       1.239       3.451     0.100  12.391   < 2e-16 ***
factor(trans)2     NA          NA     0.000      NA        NA
ageGroup70-74   0.026       1.027     0.112   0.235   0.81431
ageGroup75-79   0.333       1.395     0.104   3.201   0.00137 **
ageGroup80+     0.833       2.301     0.099   8.394   < 2e-16 ***
gradepoor:
factor(trans)2 -0.963       0.382     0.116  -8.327   < 2e-16 ***
```

Conclusion

- Conclusion: The interaction between a grade of “`poor`” and cause “`2`” (other death). The estimate -0.963 represents the additional effect of *poor grade* on risk of death from *other causes* relative to its effect on prostate cancer death. And the hazard of death from other causes is $exp(0.963) = 0.381$ times the hazard of death from prostate cancer.
- How increasing age affects the risk of dying from prostate cancer and of other causes?

```
> summary(coxph(Surv(time, status) ~ (grade + ageGroup)*trans +
ageGroup + strata(trans), data=prostate.long))
```