

Stratification in the Cox model

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Introduction

- Today's topic is the use of stratification in Cox regression
- There are two main purposes of stratification:
 - It is useful as a diagnostic for checking the proportional hazards assumption
 - It offers a way of extending the Cox model to allow for non-proportionality with respect to some covariates

VA Lung Cancer data

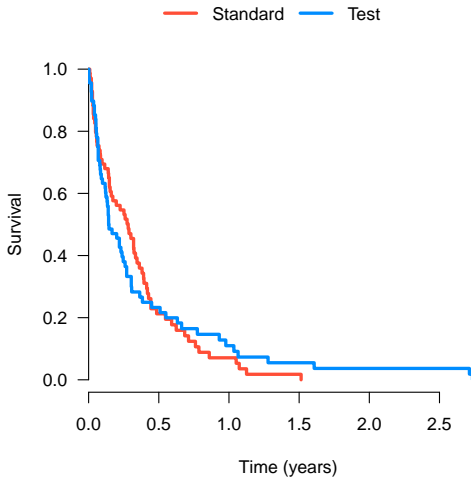
- To illustrate these concepts, we will look at a classic survival data set, the VA lung cancer data (`veteran` in the `survival` package)
- The data comes from a clinical trial carried out by the Veterans' Administration on male veterans with advanced, inoperable lung cancer
- In the trial, patients were randomized to receive either a standard chemotherapy or an experimental chemotherapy, and the primary endpoint was the time until death

Covariates

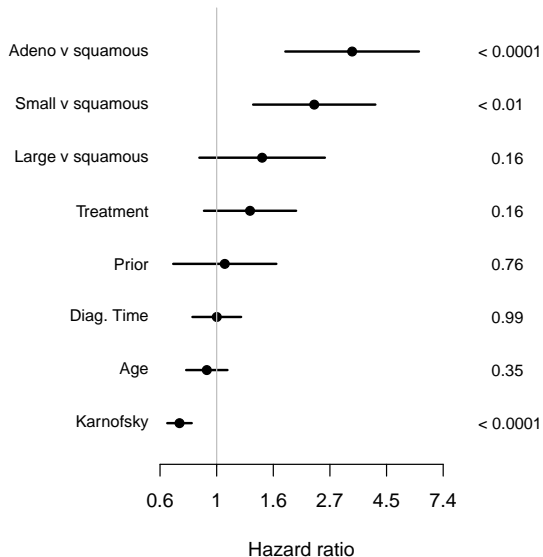
A number of covariates which potentially affect survival were also recorded:

- **karno**: The Karnofsky score, a way of quantifying the patient's overall baseline status, with ≥ 70 denoting that the patient is able to care for themselves, 40 – 60 meaning that the patient requires assistance and regular medical care, and 10 – 30 meaning that the patient is hospitalized
- **diagtime**: Time in months from diagnosis to randomization
- **age**: Age in years at randomization
- **prior**: Indicator for whether the patient had received prior therapy
- **celltype**: Type of tumor (small cell, large cell, squamous, adenocarcinoma)

Kaplan-Meier



Cox results



Diagnostics for proportional hazards

- Consider the following as a way to assess the proportional hazards assumption: rather than including a term in the model as a covariate, we will estimate separate baseline hazards $\hat{\Lambda}_{01}, \hat{\Lambda}_{02}, \dots$, for each level of the covariate
- If the baseline hazards appear proportional, then it is reasonable to model the term in the regular manner

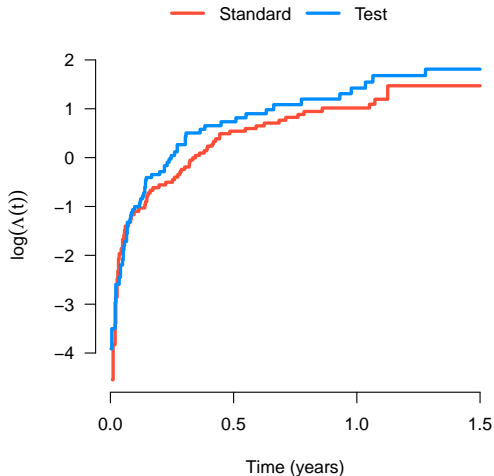
Diagnostic plot types

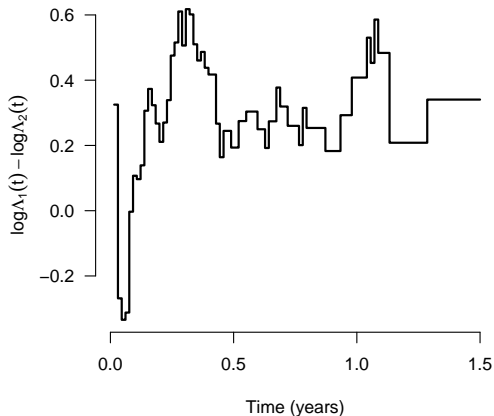
- Because proportionality is difficult to assess by visual inspection, it is common to plot $\log \hat{\Lambda}_0$:

$$\begin{aligned}\Lambda_i(t) &= \Lambda_0(t) \exp(\eta_i) \\ \implies \log \Lambda_i(t) &= \log \Lambda_0(t) + \eta_i\end{aligned}$$

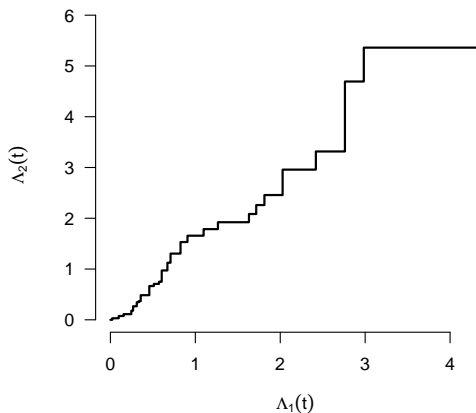
- An alternative, known as the *Andersen plot*, is to plot $\hat{\Lambda}_{01}$ versus $\hat{\Lambda}_{02}$; under proportional hazards this should be a straight line with slope $\exp(\eta)$

Treatment (Version 1)

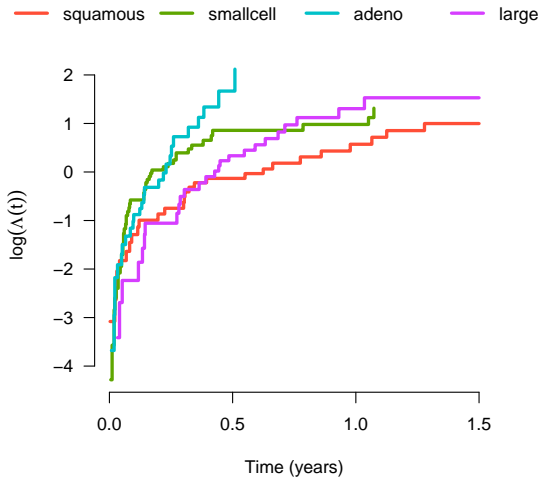


Treatment (Version 2) ($\hat{\beta} = 0.29$)

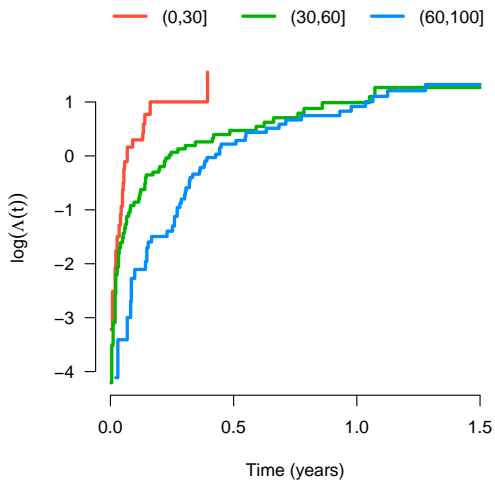
Treatment (Version 3, the Andersen plot)



Cell type



Karnofsky



Remarks

- Treatment appears broadly proportional except for very short-term survival
- Proportional hazards appears questionable with respect to cell type
- Karnofsky status also appears non-proportional, with the variable losing relevance over time (which makes sense)

The stratified Cox model

- What should we do in the presence of variables with non-proportional effects?
- One remedy is to allow for different baseline hazards for each level of the variable:

$$\lambda_{ij}(t) = \lambda_{0j}(t) \exp(\mathbf{x}_i^T \boldsymbol{\beta}),$$

where $\lambda_{ij}(t)$ is the hazard function for the i th subject, who belongs to the j th stratum

- The model may seem complex, but is entirely straightforward in the likelihood framework, as we can simply combine likelihoods across strata:

$$L(\boldsymbol{\beta}) = \prod_j L_j(\boldsymbol{\beta})$$

Stratified Cox model: Details

Furthermore,

$$\ell(\boldsymbol{\beta}) = \sum_j \ell_j(\boldsymbol{\beta})$$

$$\mathbf{u}(\boldsymbol{\beta}) = \sum_j \mathbf{u}_j(\boldsymbol{\beta})$$

$$\mathbf{I}(\boldsymbol{\beta}) = \sum_j \mathbf{I}_j(\boldsymbol{\beta}),$$

so estimation, the Newton-Raphson algorithm, and inference are all straightforward as well: we simply have to sum the contributions from each stratum

R code

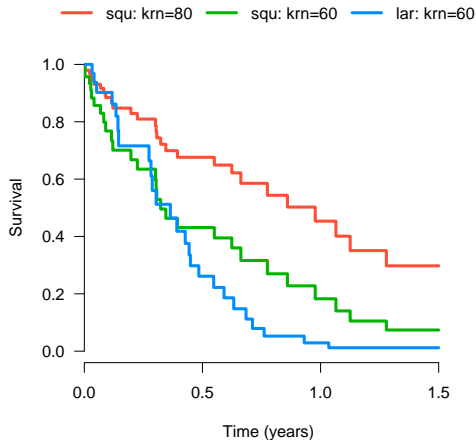
- The `survival` package makes it easy to fit stratified Cox models through the use of the `strata` function:

```
fit <- coxph(S ~ trt + karno + ... + strata(celltype))
```

- `summary(fit)` will then provide a summary for all the parametric terms (`trt`, `karno`, ...), but not `celltype`
- `survfit(fit)` will estimate K different baseline hazard functions, one for each stratum (here, $K = 4$)

Predictions

Standard treatment, wait 12 months, age 40, no prior treatment



Final remarks

- Stratified Cox models are a useful extension of the standard Cox models to allow for covariates with non-proportional hazards
- A minor drawback is that stratifying unnecessarily (i.e., even though the PH assumption is met) reduces estimation efficiency, although the loss is typically very small
- A larger limitation of stratification is that it becomes messy with continuous variables and with multiple stratification variables, as there is no way to impose an additive structure

Final remarks (cont'd)

- The other primary limitation of stratified models is that there is no way to carry out inference for the stratification variables
- For example, stratification is commonly used to aggregate results across multi-center studies, because comparing these sites is typically not of interest
- Stratification is less useful in dealing with non-proportionality with respect to treatment – we are definitely interested in estimating the effect of treatment, and although we can obtain descriptive measures by estimating baseline coefficients, confidence intervals and tests are lacking
- In such cases, a more satisfying approach is to directly model the changing effect of the predictor over time, a topic we will cover in a future lecture