Survival analysis

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Introduction

Survival analysis is a general term describing the analytic techniques for data in which the endpoint is the time measured from a defined beginning to the occurrence of a specified event. The endpoint is the *event time*.

- In a cancer clinical trial, the outcome of interest is the survival time of patients from the start of treatment until death.
- In a study of married couples, the outcome of interest is the time from the wedding until the birth of the first child.
- In a study of the carcinogenicity of a chemical, rats are exposed to the chemical and the outcome of interest is the time until a tumor develops.

Censoring

Event-time data are subject to *censoring*. Censoring occurs when the event of interest is not observed for some of the subjects in the study. The most common causes of censoring are

- The subject has not yet had the event when the study is terminated.
- The subject is lost to follow-up or withdrawn from the study.
- The subject dies from causes not relevant to the study.

In general, we assume that censoring is *non-informative*. That is to say, censoring should not convey information about the patient's outcome (event versus non-event).

Types of censoring

- Right-censoring
  - Event occurs *after* a given time point
  - E.g. In a clinical trial with overall survival as the primary endpoint, the subject has not had the event when the study is terminated. For this subject the event is assumed to occur *after* the study's termination.
- Left-censoring
  - Event occurs *before* a given time point
  - E.g. Three months following surgical removal of the primary tumor, patients are examined to see if cancer has recurred. Events for these patients are assumed to have occurred prior to three months post surgery.

Types of censoring (cont.)

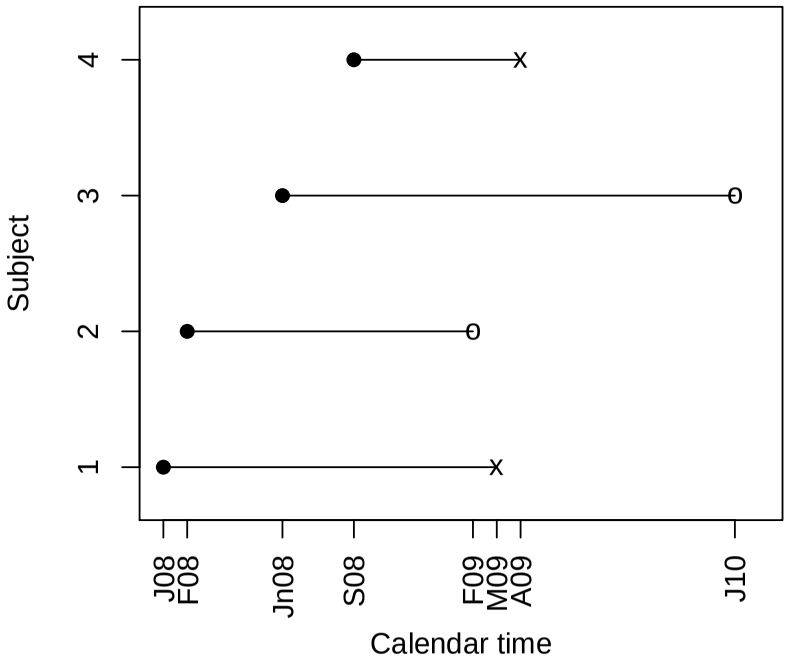
- Interval-censoring
  - Event occurs *between* two time points
  - E.g. In a clinical trial with progression-free survival as the primary endpoint, subjects are examined every three months to determine if cancer has progressed from baseline. At a six-month follow-up visit, a patient has not progressed, but at the nine-month follow-up visit, progression has occurred. The event for this subject is assumed to have occurred between six and nine months.

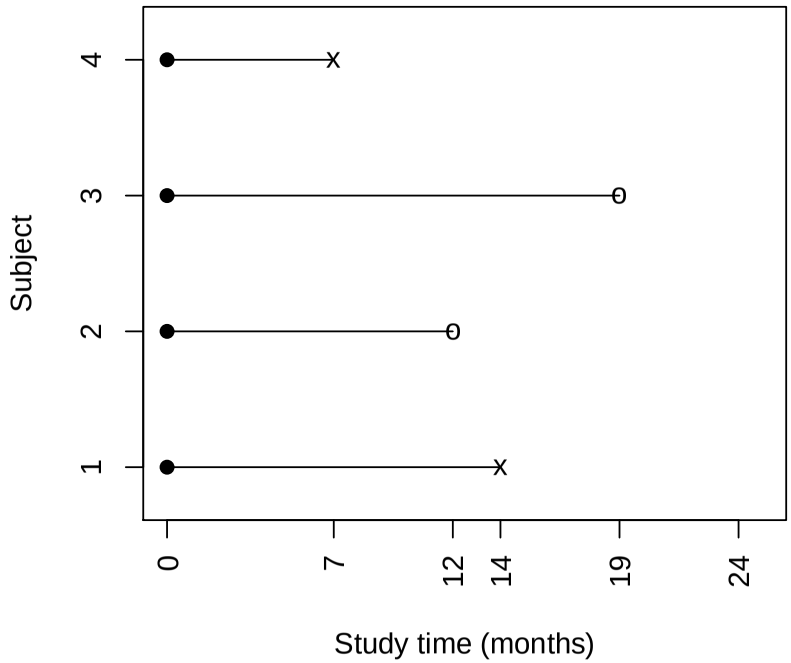
In this presentation, we will focus on right-censored data.

Event-time data

ID	Entry	End	Time (mos)	Event
1	01/01/08	03/01/09	14	Death
2	02/01/08	02/01/09	12	Lost to FU
3	06/01/08	01/01/10	19	Study ended
4	09/01/08	04/01/09	7	Death

Event-time data depiction





Data issues

- Distribution of event times tends to be positively skewed
  - Some observations have much longer event times than others
  - Non-normal distribution
- Censoring
  - Event times only partially observed
  - Comparison of mean event time between groups not appropriate

Statistical answers to clinical questions

Q *"What is my chance of living beyond 5 years with this disease?"*

A Survival function, $S(t)$

Q *"What is my risk of dying today from this disease?"*

A Hazard function, $h(t)$

Both the survival and the hazard are functions of t (here, t = time to death)

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The survival function

Let T represent the time to a specified event with the observed time for a given subject denoted by t.

The survival function

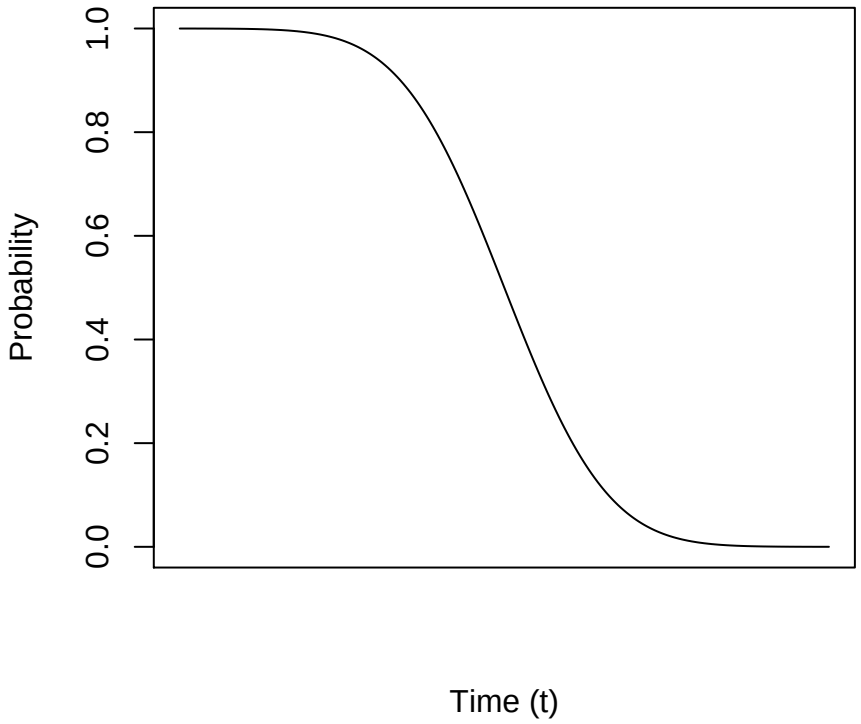
... is the probability of surviving at least t time units. We write

$$S(t) = \text{Prob}(T > t).$$

For example, a five-year survival rate is an estimate of the probability that death will occur *after* five years. Dying after five years is equivalent to surviving at least five years. The five-year survival rate is $S(5) = \text{Prob}(T > 5)$.

Properties of $S(t) = \text{Prob}(T > t)$

- Non-increasing function of t
- $S(0) = 1$. In words, at the beginning of observation, no subject has had the event of interest.
- $S(\infty) = 0$. In words, if subjects were observed forever, everyone would eventually experience the event.



Estimation of $S(t)$

The most common estimator of the survival function is the *Kaplan-Meier estimator*, also known as the *Product-limit estimator*. It is a non-parametric estimator of survival, which means that it requires no distributional assumptions about the event times.

segue to Douillard et al., Figure 2

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The hazard function

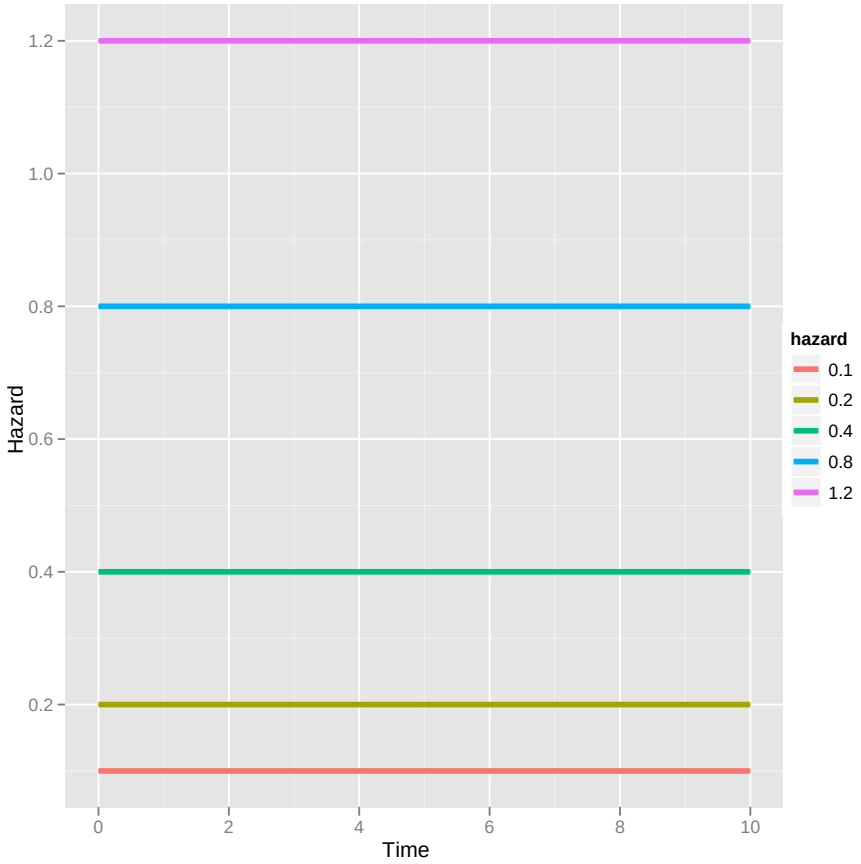
The hazard function

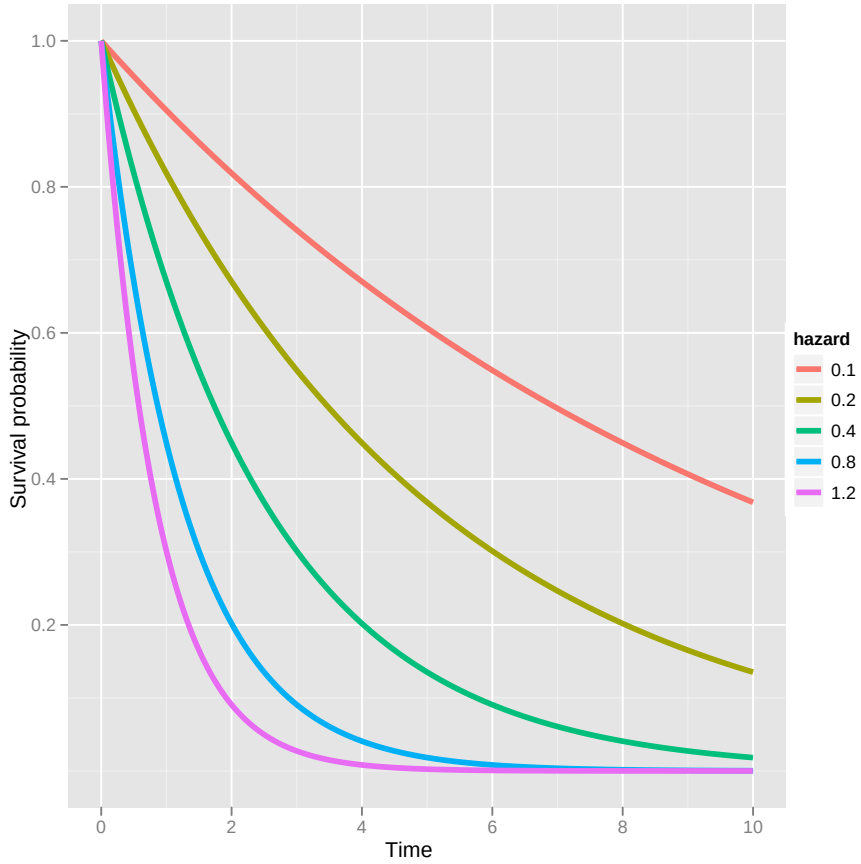
... is the instantaneous mortality rate.

What is the rate at which people are dying ...

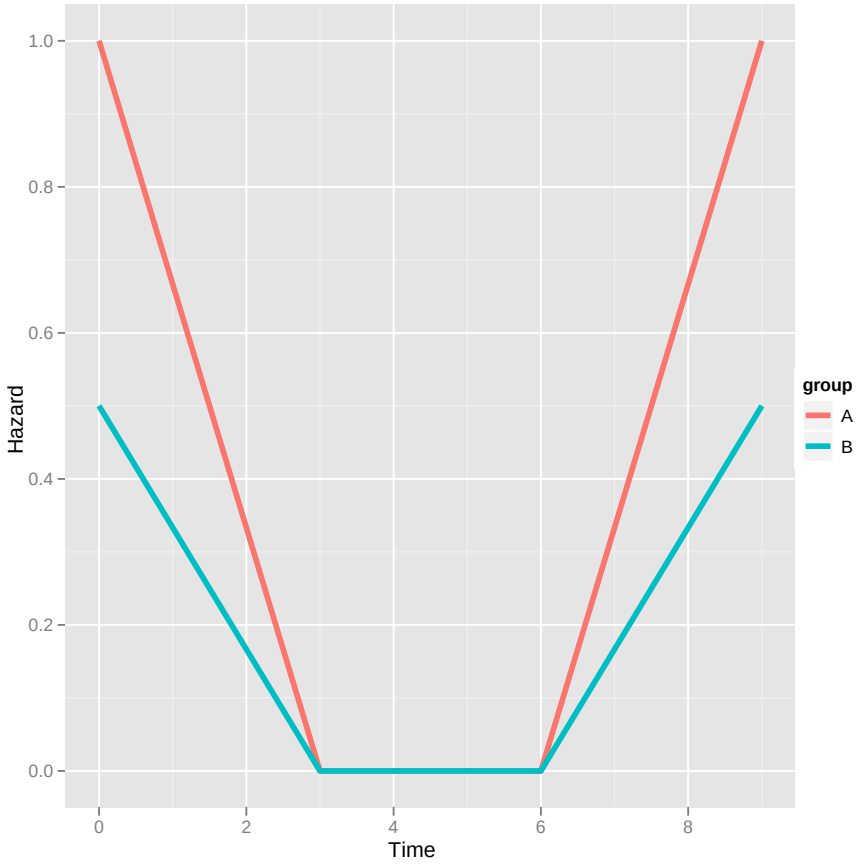
- today?
- this month?
- this year?

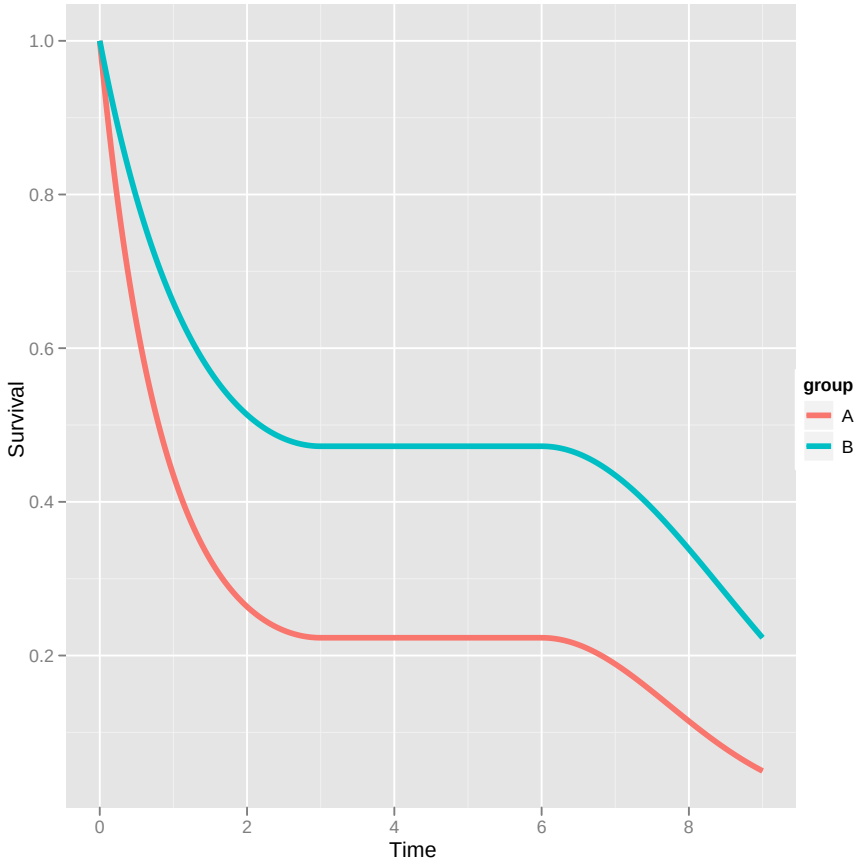
Constant hazard and related survival





Non-constant hazard and related survival





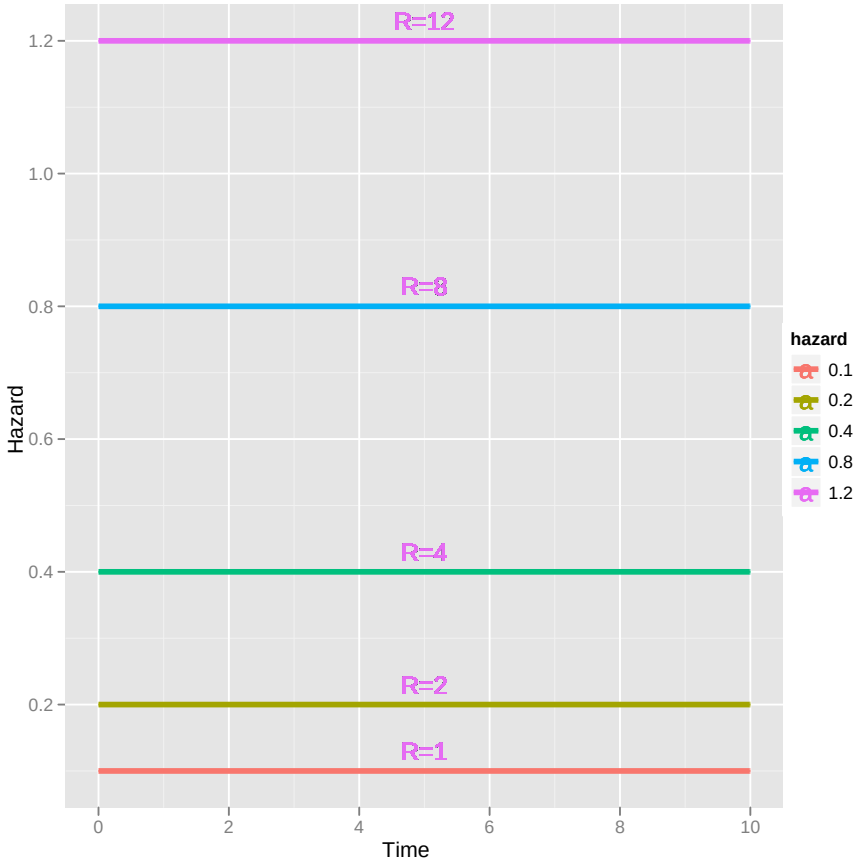
Hazard functions in practice

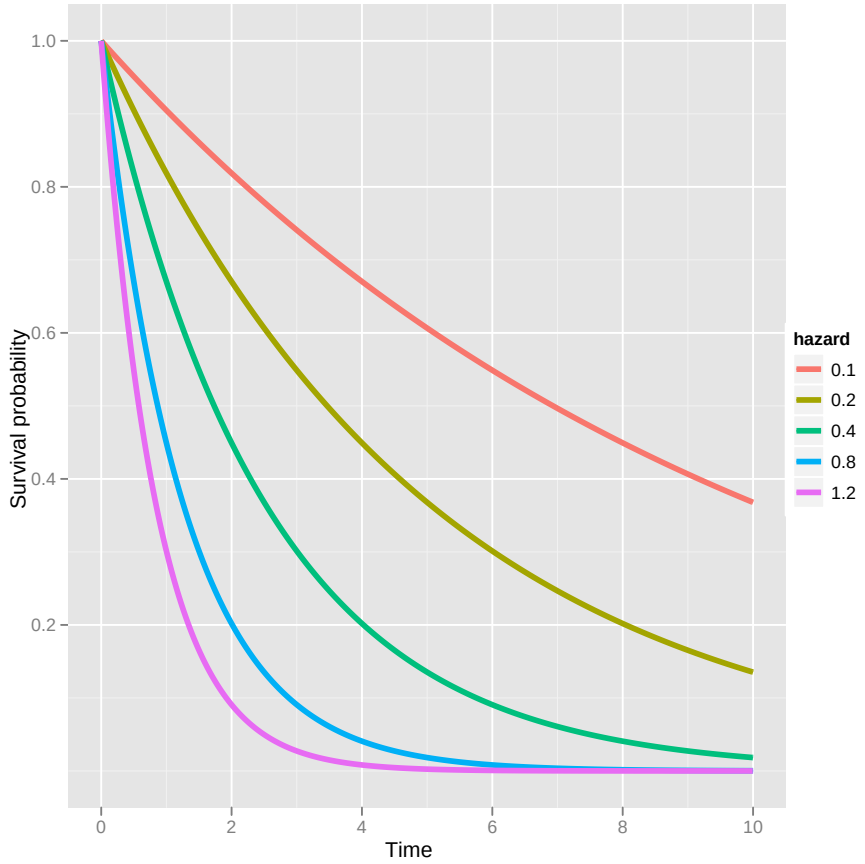
- Limited use of hazard function alone
- Most often interested in *ratio* of hazard functions
- Ratio provides estimate of "my risk relative to yours" where ...
  - I’m randomized to protocol A and you’re randomized to protocol B.
  - I’m old and you’re young.
  - My ECOG performance status is 2 and your performance status is 0.
  - I’m WT KRAS randomized to panitumumab+FOLFOX4 and you’re WT KRAS randomized to FOLFOX4 only.

Proportional hazards

- When the hazard function for one group is a constant multiple of the hazard function for a second group, we say those groups have *proportional hazards*
- $h_1(t) = h_2(t) \times R$
- R is called the *hazard ratio*
- R quantifies the risk of the event in group one relative to group two

Pictures of proportional hazards





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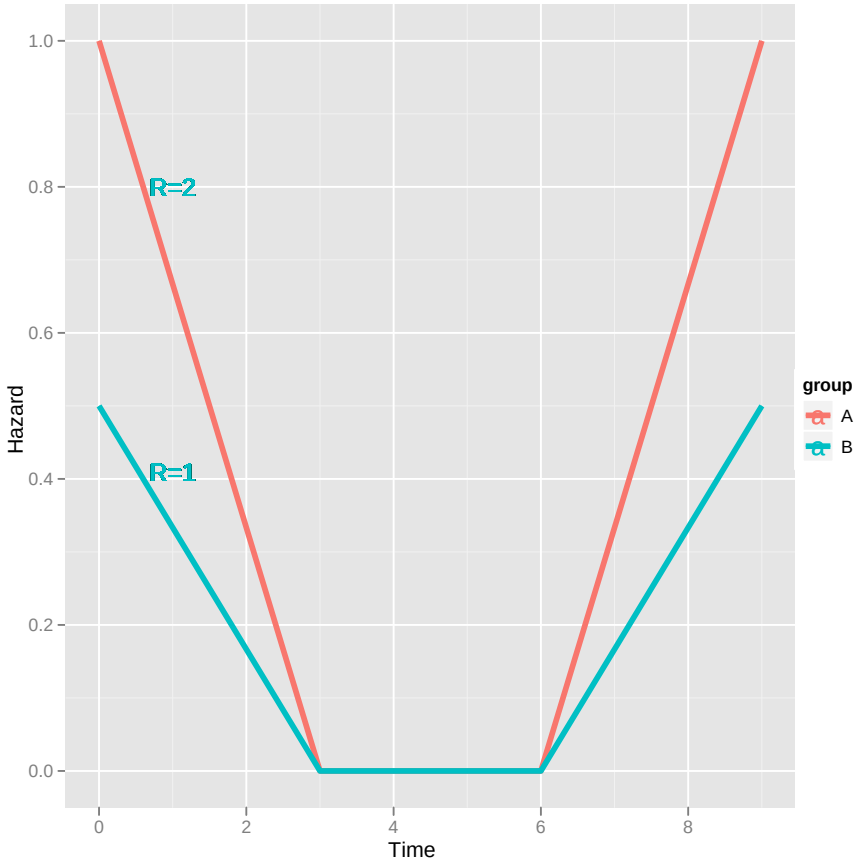

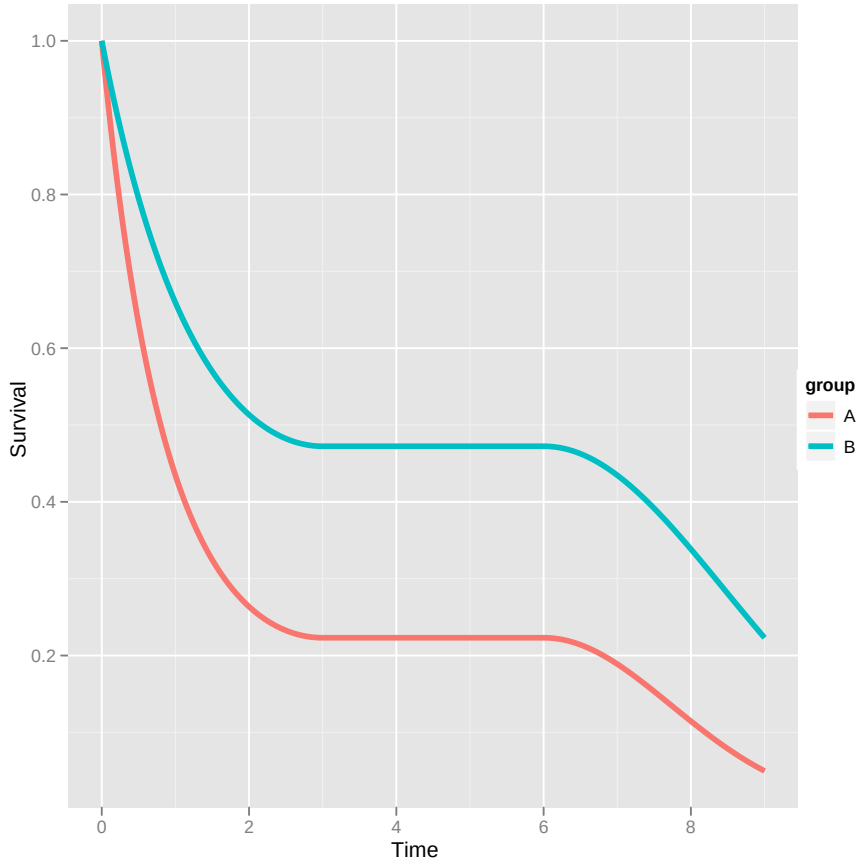

When the hazards are proportional ...

- The corresponding survival curves are non-intersecting.
- The hazard ratio (R) is *constant* over time, but the hazards need not be constant.
- Using a single numerical summary (i.e. the hazard ratio) to quantify risk comparing two groups over time is sensible.

When the hazards are not proportional ...

- The corresponding survival curves will cross.
- The hazard ratio (R) is *not constant* over time.
- Using a single numerical summary (i.e. the hazard ratio) to quantify risk comparing two groups over time is not sensible.

Hazard regression models

- Used to understand how various factors influence the risk of the event
- Provide direct estimates of hazard ratios comparing levels of variables of particular interest
- Most common is the *Cox Proportional Hazards* model

E.g. Suppose we have a trial with two arms, treatment and control. Let $h_i(t)$ be the hazard function for the ith person in the trial, and let $h_C(t)$ be the hazard function for people in the control arm. A model relating these hazards is written

$$h_i(t) = h_C(t) \times e^{b \times X_i}$$

where X_i takes on a value of '1' if the ith person was randomized to treatment and takes on a value of '0' if the ith person was randomized to control.

From hazard regression models to hazard ratios

If person i is in the treatment arm,

$$h_i(t) = h_C(t) \times e^{b \times 1}$$

or

$$h_i(t) = h_C(t) \times \text{some number}$$

or

$$h_i(t) = h_C(t) \times R$$

Because the ith person was in the treatment arm, R is the hazard ratio comparing the risk of death for treated patients relative to control patients.

Multivariable hazard regression models

- Can include many variables in the same model
- In Douillard et al. (p.4699): “Treatment effects on PFS and OS were estimated using stratified Cox proportional hazards models and the Kaplan- Meier method. An exact 95% CI was estimated for a stratified odds ratio for objective RR. The random assignment factors were used for analysis stratification. Descriptive analyses of treatment effects were planned in prospectively identified subsets.”
- The regression model yields an estimated ‘*b*’ for each variable included
- e^b is the hazard ratio corresponding to that variable comparing “level 1 to level 0”
- The multivariable model accommodates ‘adjustment’ of the hazard ratios for confounders