The hazards of survival

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HCC Biostatistics Shared Resource

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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)

Definition

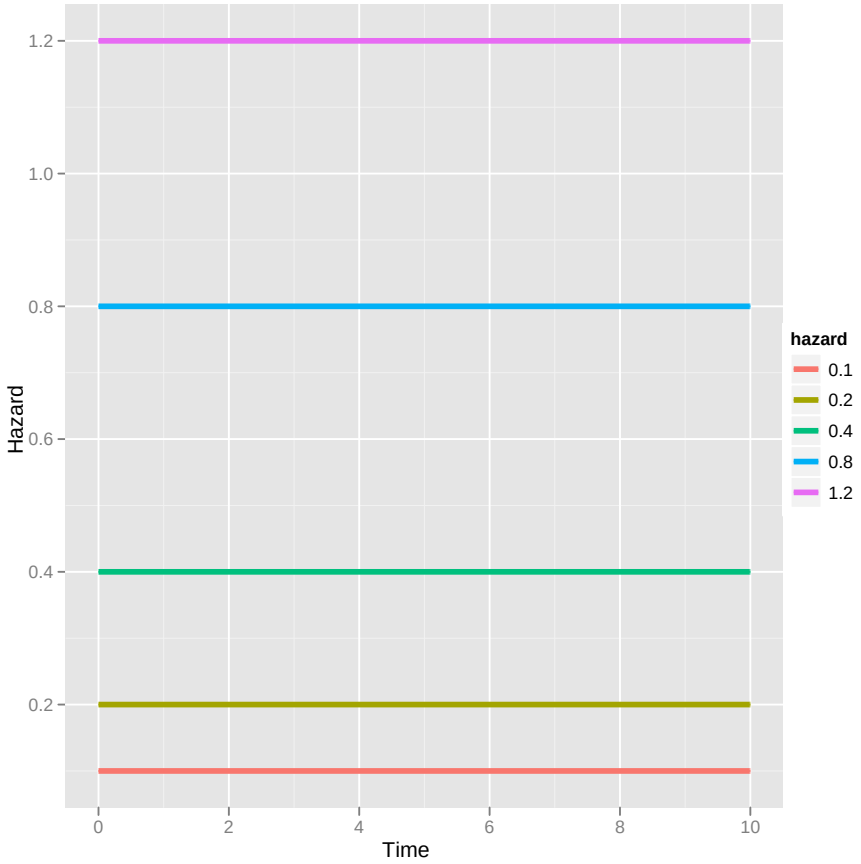
The hazard function

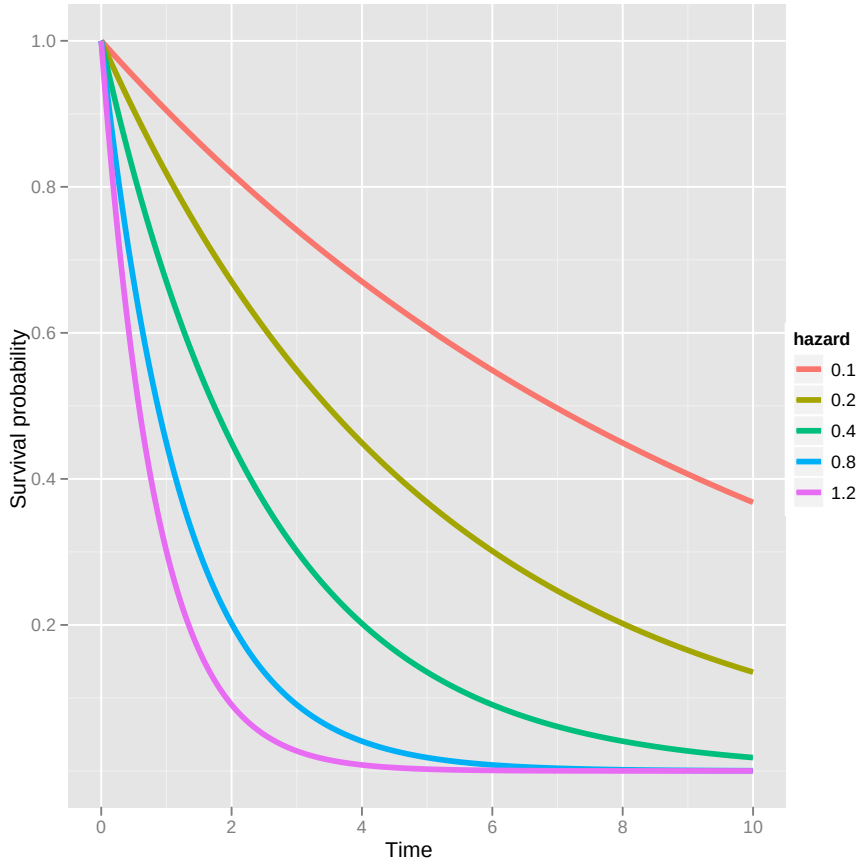
... is the instantaneous mortality rate.

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

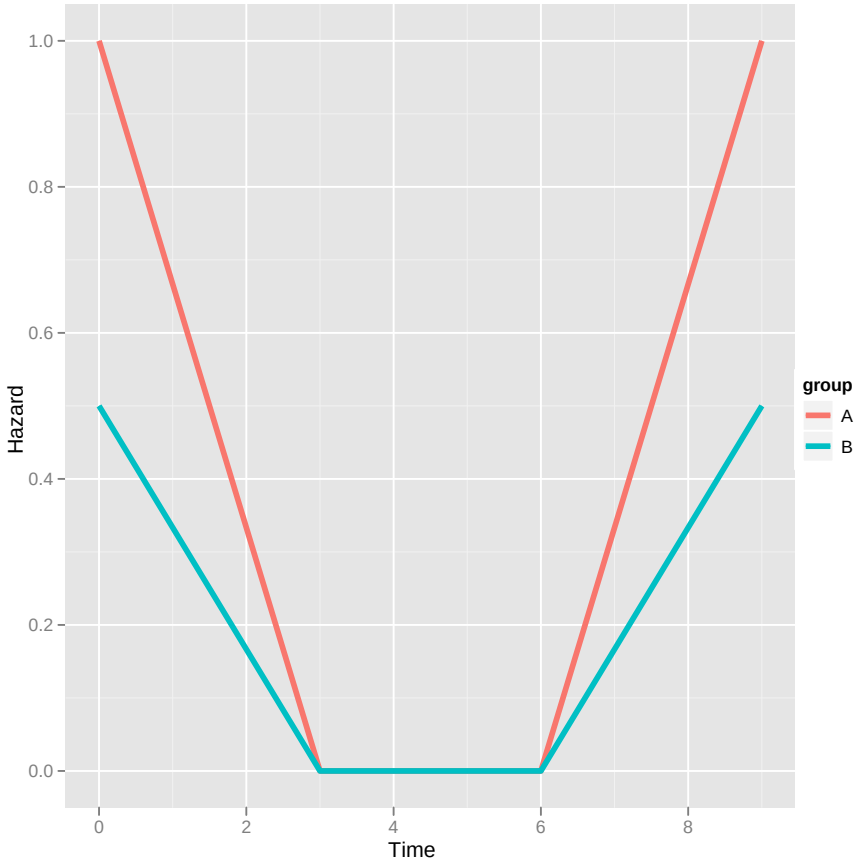
- today?
- this month?
- this year?

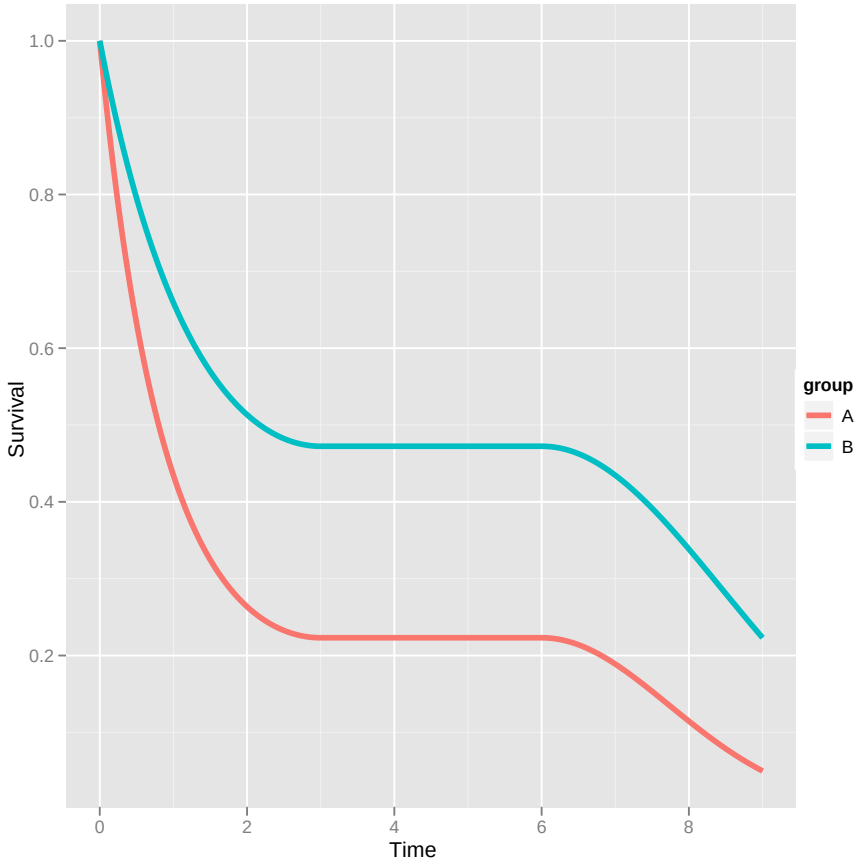
Constant hazard and related survival





Non-constant hazard and related survival





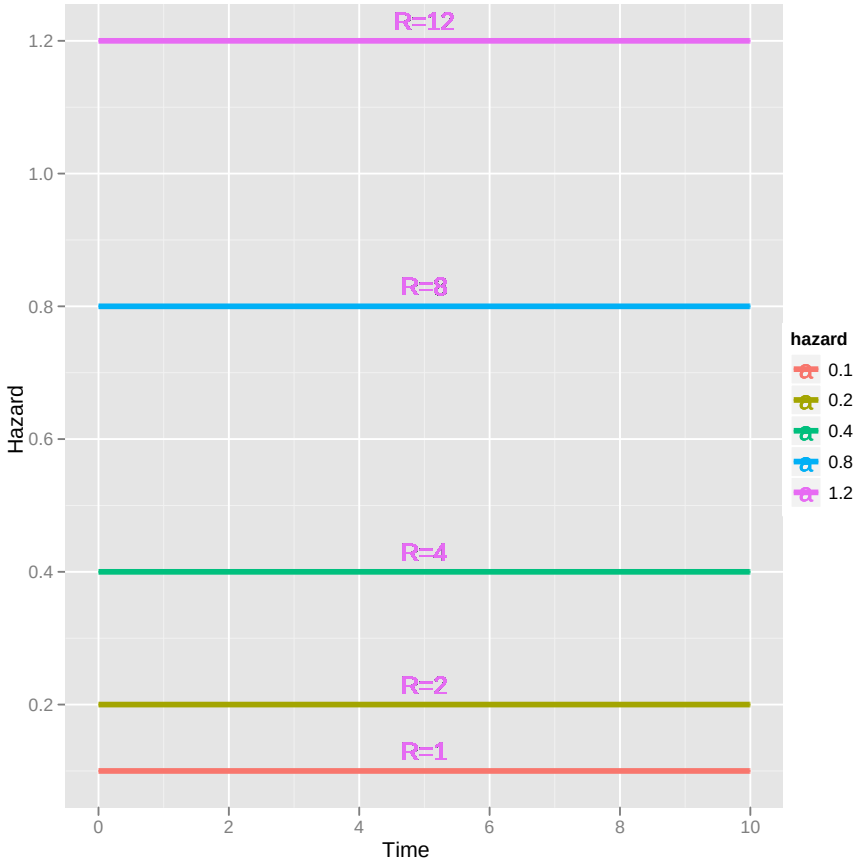
Hazard functions in practice

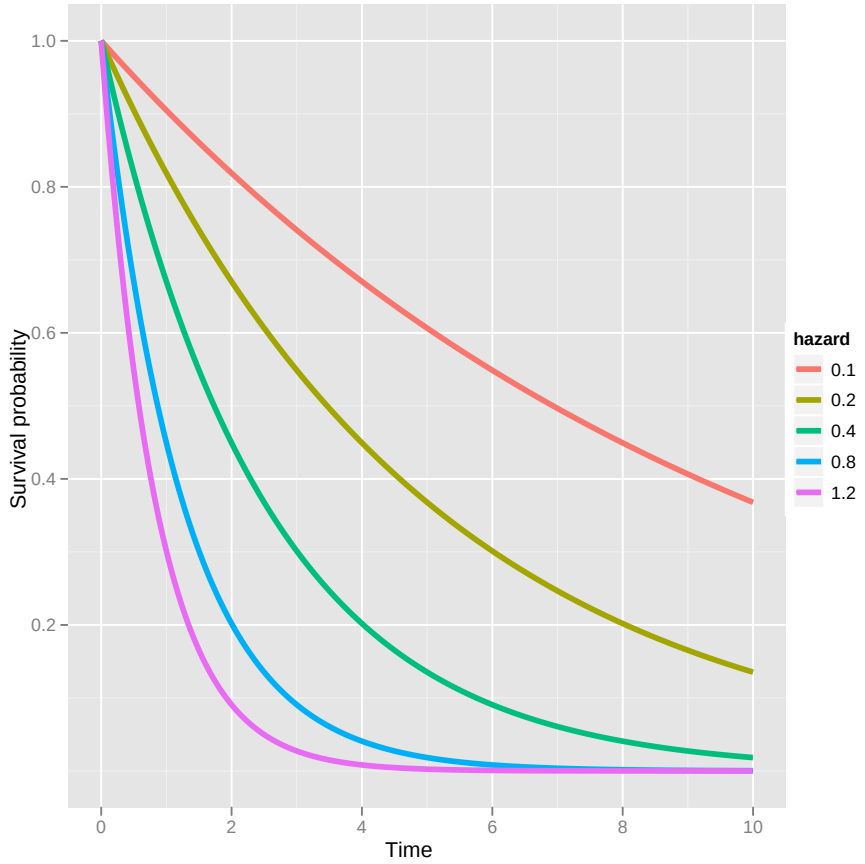
- Limited use of hazard function alone
- Most often interested in *ratio* of hazard functions
- Ratio provides estimate of "my risk relative to yours" where ...
  - I’m randomized to protocol A and you’re randomized to protocol B.
  - I’m old and you’re young.
  - My performance status is 2 and your performance status is 0.
  - I’m an African American male with a history of smoking randomized to protocol A and you’re an African American male with a history of smoking randomized to protocol B.

Proportional hazards

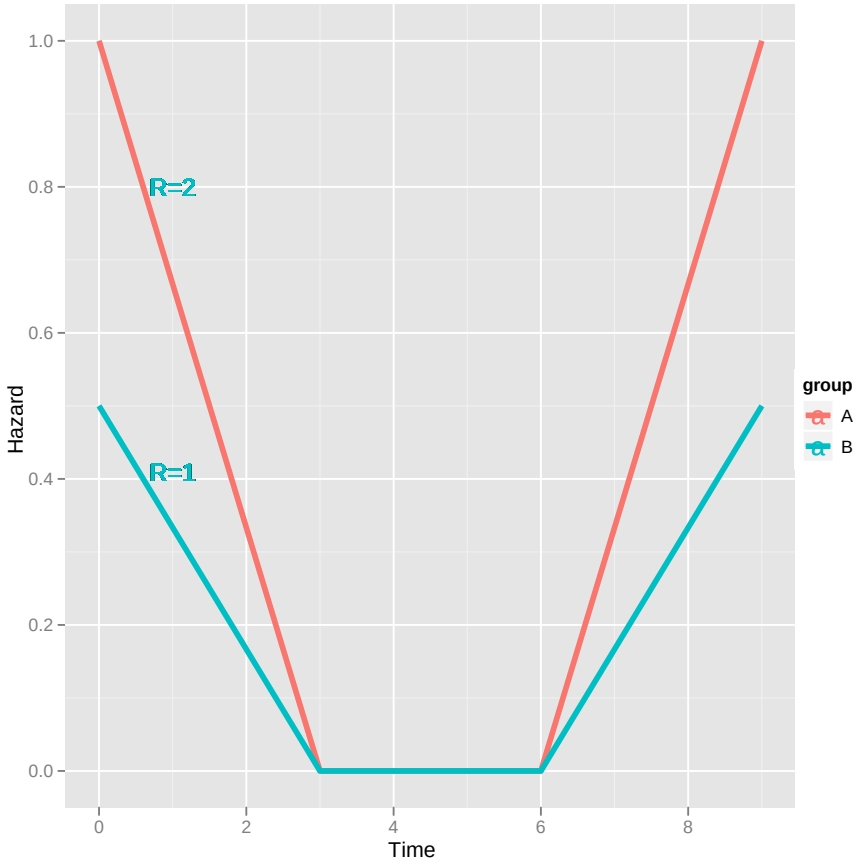
- When the hazard function for one group is a constant multiple of the hazard function for a second group, we say those groups have *proportional hazards*
- $h_1(t) = h_2(t) \times R$
- R is called the *hazard ratio*
- R quantifies the risk of the event in group one relative to group two

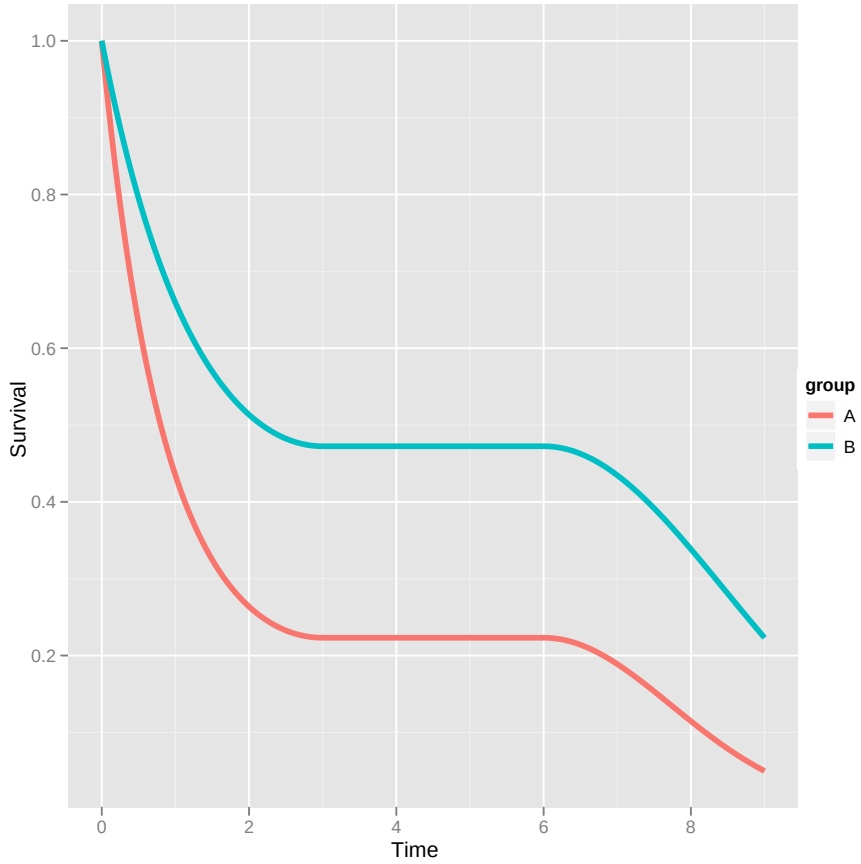
Pictures of proportional hazards





Pictures of proportional hazards





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

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

where T_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 Salama et al. (p.1789): “Cox proportional hazards models of LRC, DC, and OS were conducted ... Variables considered in the models include age, sex, race, PS, tumor stage, nodal stage (>2a), neck dissection, PTV1 dose (Gy), patient cohort, and CR and PR to IndCT.”
- 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

Results from Salama et al. (p. 1792)

"On multivariable analysis for LRC, PS = 2 [hazard ratio (HR) 7.66, 95% CI 1.49 - 39.45, P = 0.0150] and African-American race (HR 3.70, 95% CI 1.36 - 10.09, P = 0.0106) were significantly associated with worse LRC."

Results from Salama et al. (page 1792)

"... higher PTV1 radiation dose (HR 0.95, 95% CI 0.92 - 0.98, P = 0.001) [was] associated with improved OS ... PS of one or two (HR 2.55, 95% CI 1.47 - 4.45, P = 0.0009 and HR 4.46, 95% CI 1.73 - 11.52, P = 0.0020) was associated with worse OS."