CBB Workshop: Introduction to Survival Analysis

with Practical Applications in R

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Center for Bioinformatics and Biostatistics
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Agenda

- 1st Session 13:00–14:00
  - → The basics of survival analysis
- Coffee Break 14:00–14:30
- 2nd Session 14:30–16:00
  - → Practical application in R
  - → examples, graphics, and exercises

Introduction to Survival Analysis

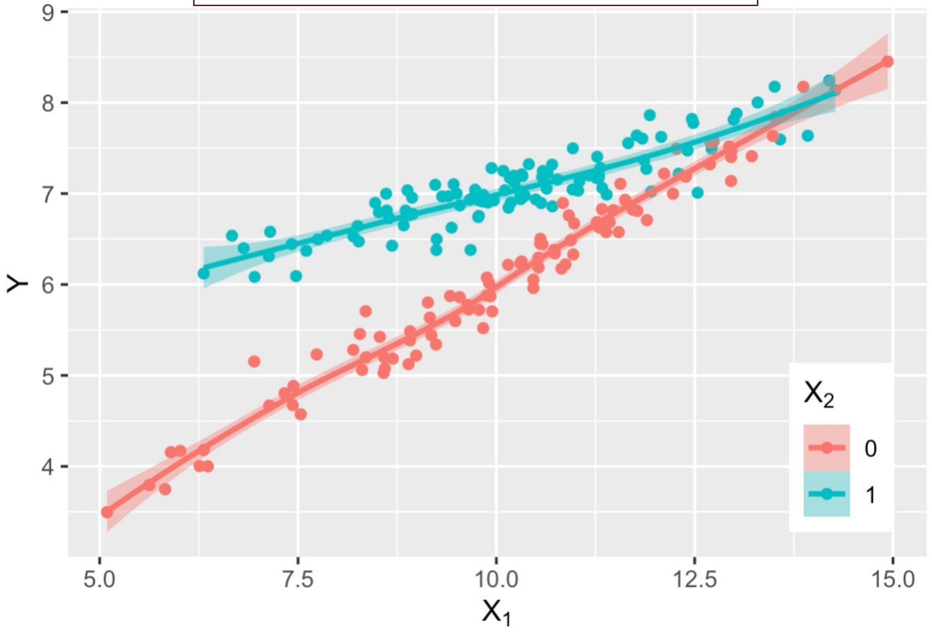
Outline

- The most important concepts of survival analysis
    1. The type of data we use
    2. The survival function & the cumulative incidence function
    3. The hazard rate function
    4. The Cox proportional hazards regression model

Our Typical Statistical Analysis

- Typical data & research question relationship:
  - → We measure some **Outcome variable (Y)**
  - → We measure a set of **Covariates (X_1, X_2, …)**
    - Exposure/risk factor variables potentially associated with the outcome
  - → We perform some statistical analysis—**Regression Model**

$$\hat{Y} = 1 + 0.5X_1 + 4X_2 - 0.3X_1X_2$$

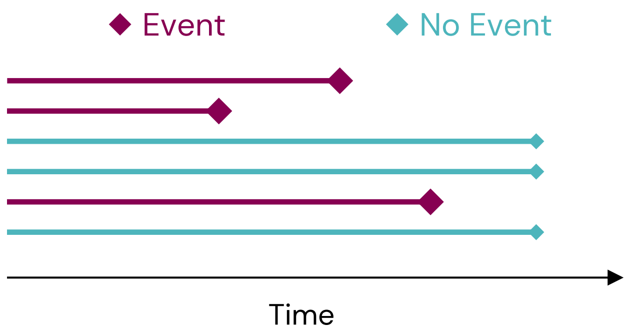


What is Survival Analysis?

- Survival Analysis is a special family of statistical analysis
- **The outcome is time**
- We measure the time until a particular event
  - → Death (Mortality)
  - → Diagnosis of a particular disease (Incidence)
  - → Progression to a stage of disease
  - → etc.

Time-to-Event Data

- Time-to-event outcome:
  1. The time duration we followed each subject
  2. Whether or not they experienced the event



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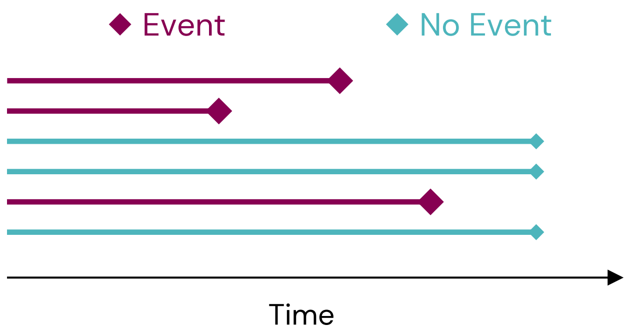
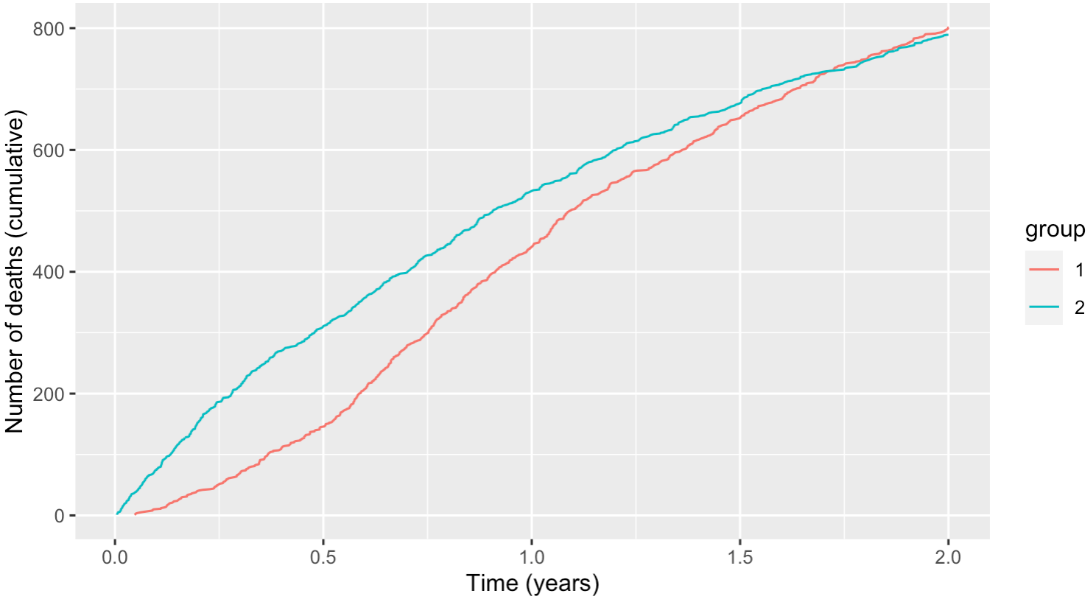


For example:

id	time	event	age	sex	bmi	masld
23	6.08	0	32	female	35.2	no
24	6.79	0	43	female	24.5	no
25	3.65	0	39	male	24.3	no
27	0.59	1	62	female	30.2	no
32	11.67	0	45	male	22.1	no
33	2.03	1	58	male	26.7	no
36	1.13	0	53	female	24.8	no
37	7.59	0	47	male	21.9	no
38	9.11	0	54	female	22.1	no
40	4.67	1	61	female	28.4	no
41	6.10	1	45	female	26.3	no

Why two-part outcome?

- Can't we just look at the final outcome?



- <u>Example:</u>
  Mortality over 2 years
  comparing 2 groups

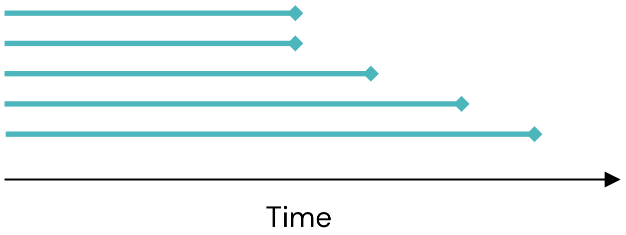
- Not just **what** happens,
  but also **when**

- Who experiences more
- events and/or events sooner?

Censoring

- We don't observe events for everyone
  - → We end the follow-up at some point
  - → (Given enough time, would everyone have the event?)

- **"Censored at time *t*"** = event occurs sometime after *t*
  - → *i.e. we didn't observe it yet*
  - → *a.k.a. "lost to follow-up"*

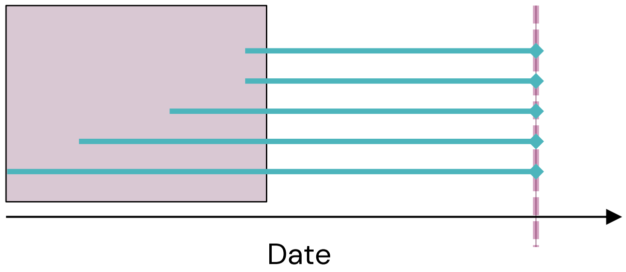


Censoring

- We don’t observe events for everyone
  - → We end the follow-up at some point
  - → (Given enough time, would everyone have the event?)

- **“Censored at time *t*”** = event occurs sometime after *t*
  - → *i.e. we didn’t observe it <u>yet</u>*
  - → *a.k.a. “lost to follow-up”*

- Often due to inclusion/recruitment over time and with a fixed end date



Now What?

- **What do we want to know?**

- In a typical non-survival analysis:

a) Summary statistics (mean/median, proportions) including
   - → standard errors (confidence intervals)
   - → comparisons between groups (graphically or with statistical tests)

b) Proper regression model
   a) Mulitvariate model
   b) Effect sizes (mean differences, odds ratios, etc.) and confidence intervals
   c) Statistical tests for association with the outcome

The Survival Function

The Survival Function

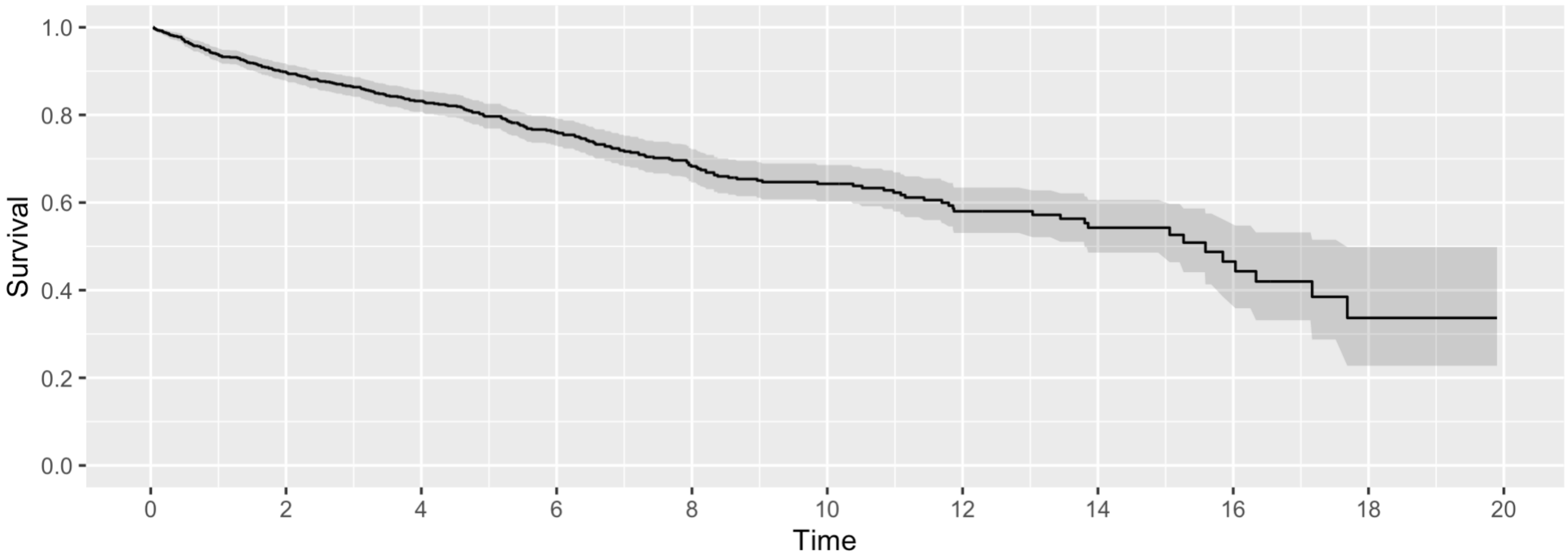
- If we measure the time to event, a reasonable question might be:
- *"What is the probability of not having the event by time t?"*
  or
  "What proportion of the population will not have the event by time t?"

- The survival function S(t): The probability of being event-free by time *t*
- It's a probability which decreases over time

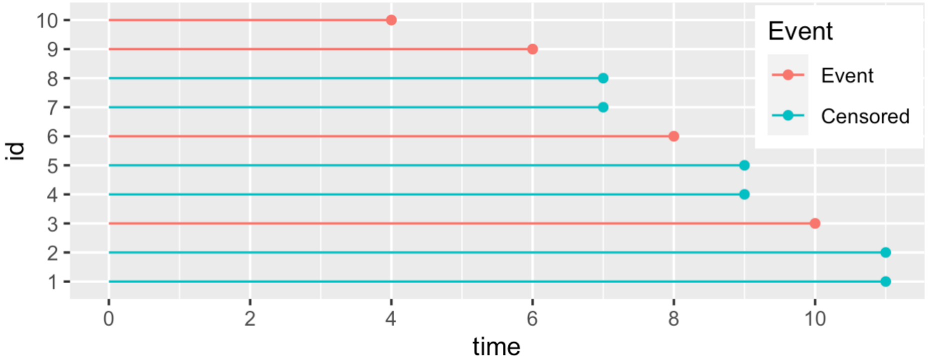
- $S(0) = 1 \qquad\qquad if \quad t_1 < t_2 \quad then \quad S(t_1) \geq S(t_2)$

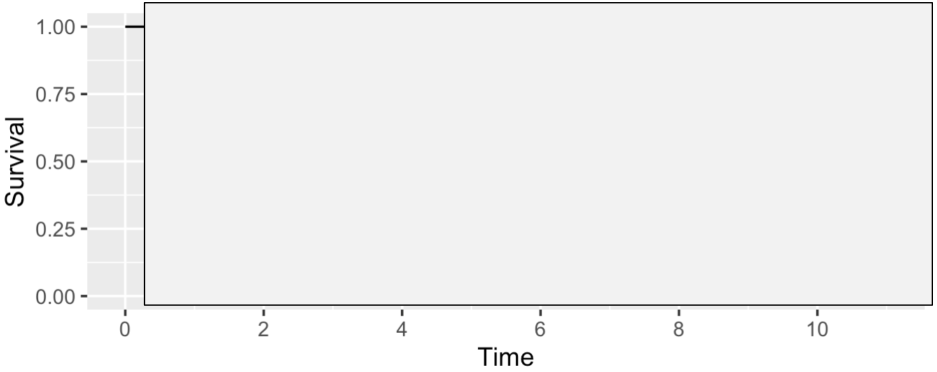
Kaplan-Meier Estimate

- Kaplan-Meier estimate of the survival function (with 95% confidence int.)



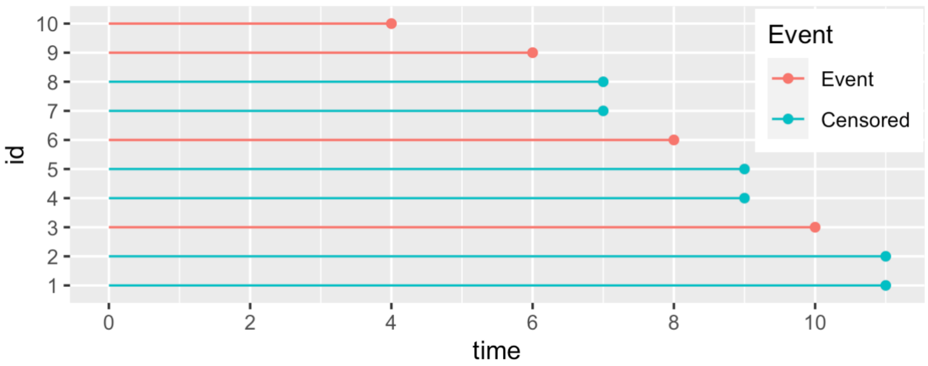
Calculating the Survival Function

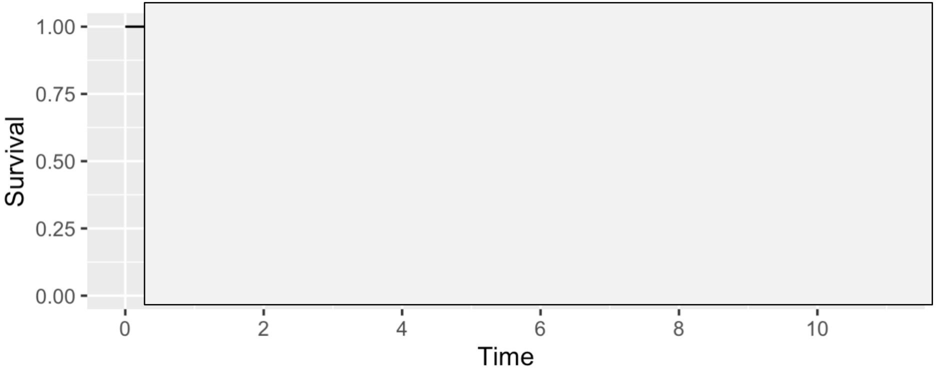




Survival calculation:

Calculating the Survival Function

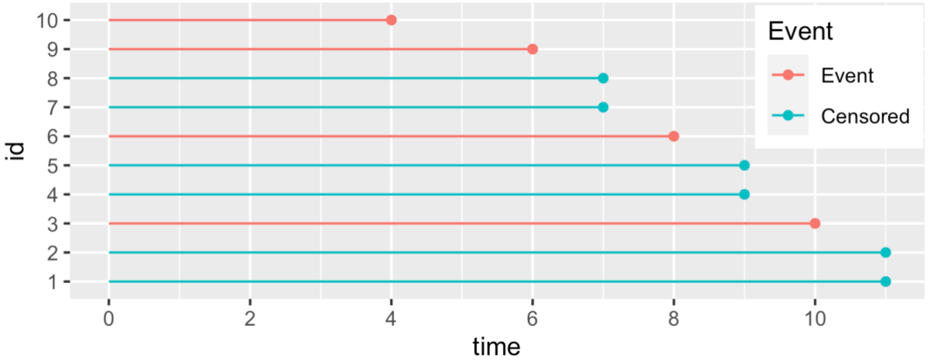


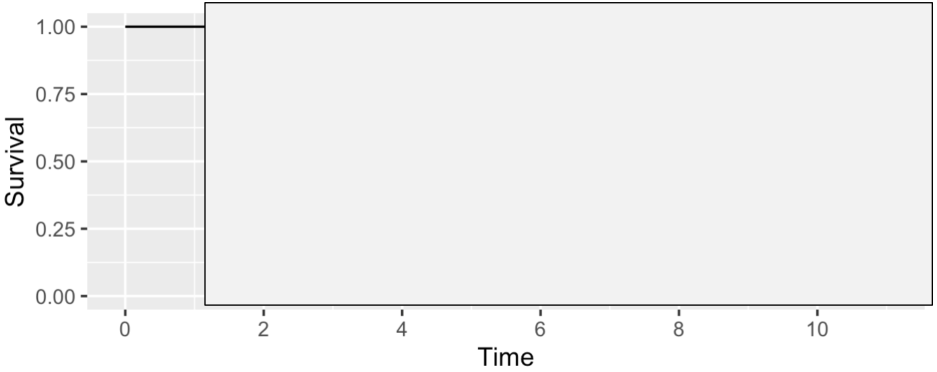


Survival calculation:

- $S(0) = \frac{10}{10} = 1$

Calculating the Survival Function

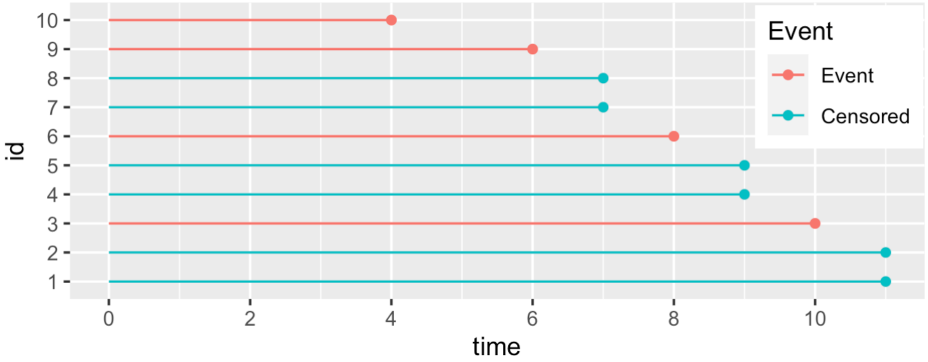


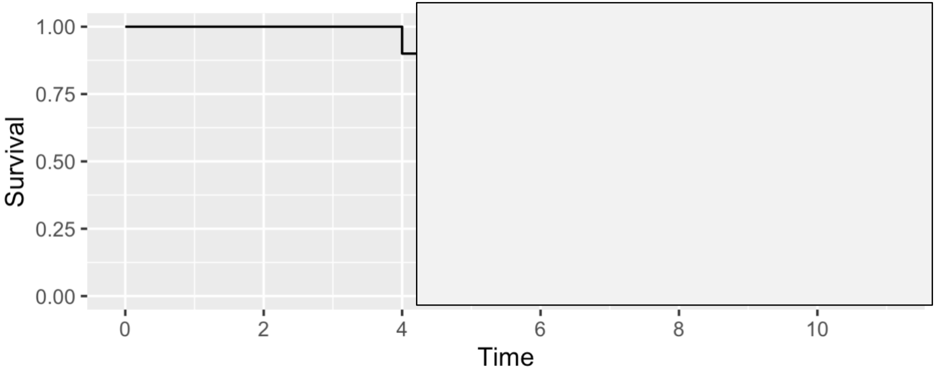


Survival calculation:

- $S(0) = \frac{10}{10} = 1$
- $S(1) = \frac{10}{10} = 1$

Calculating the Survival Function

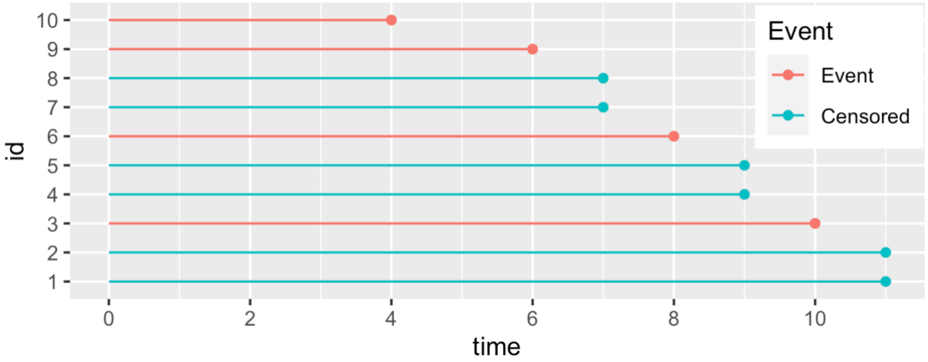


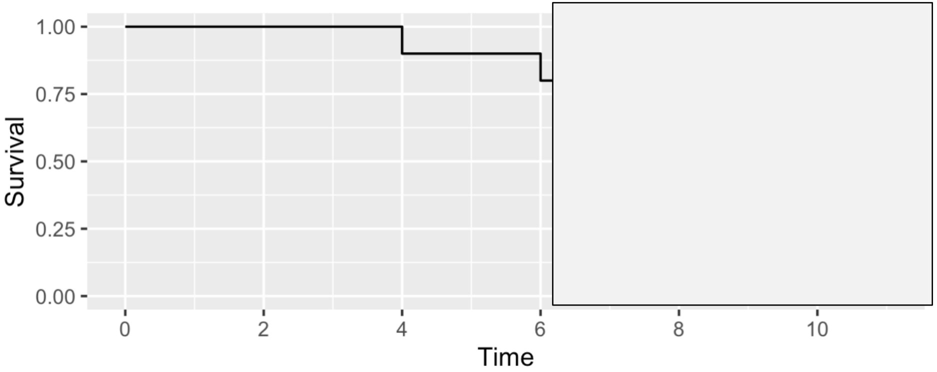


Survival calculation:

- $S(0) = \frac{10}{10} = 1$
- $S(1) = \frac{10}{10} = 1$
- $S(4) = \frac{9}{10} = 0.9$

Calculating the Survival Function

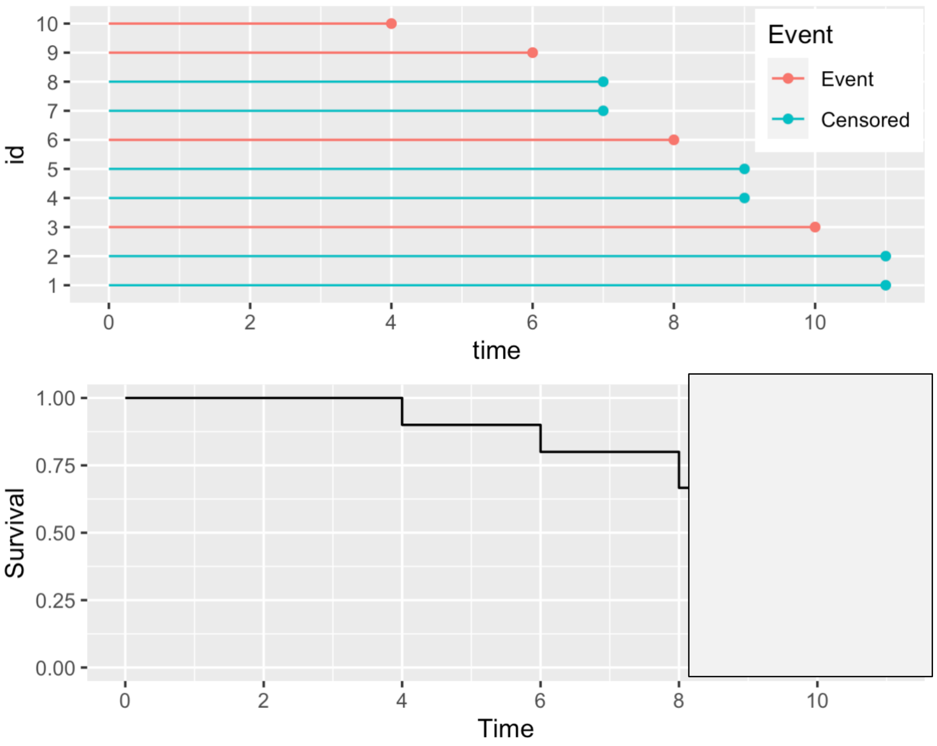




Survival calculation:

- $S(0) = \frac{10}{10} = 1$
- $S(1) = \frac{10}{10} = 1$
- $S(4) = \frac{9}{10} = 0.9$
- $S(6) = S(4) \cdot \frac{8}{9} = 0.9 \cdot 0.89 = 0.8$

Calculating the Survival Function



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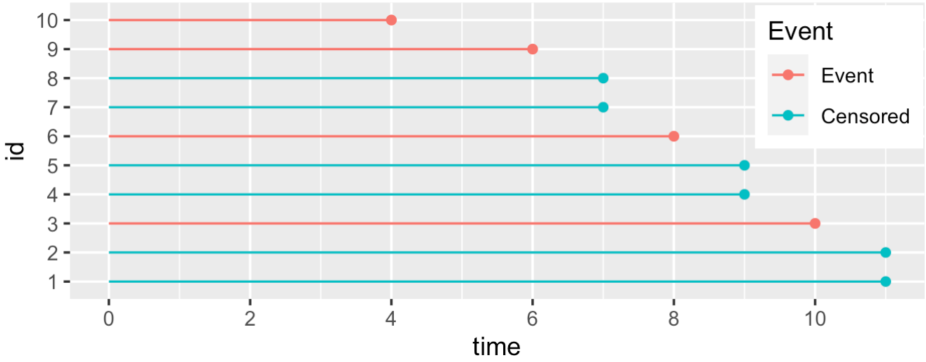
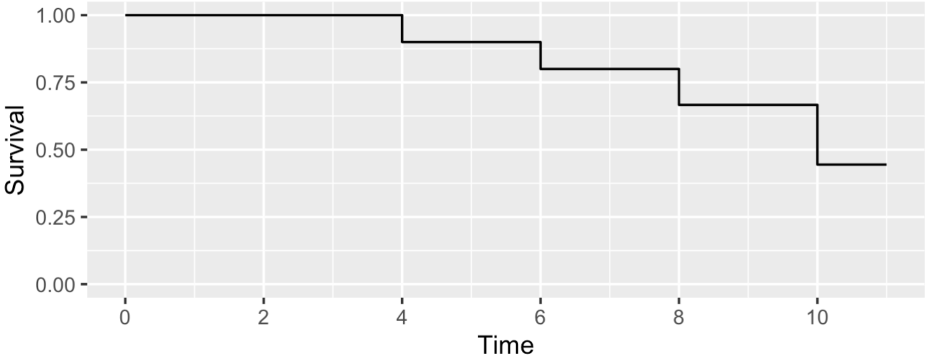
- $S(8) = S(6) \cdot \frac{5}{6} = 0.8 \cdot 0.83 = 0.67$

Calculating the Survival Function





Survival calculation:

- $S(0) = \frac{10}{10} = 1$
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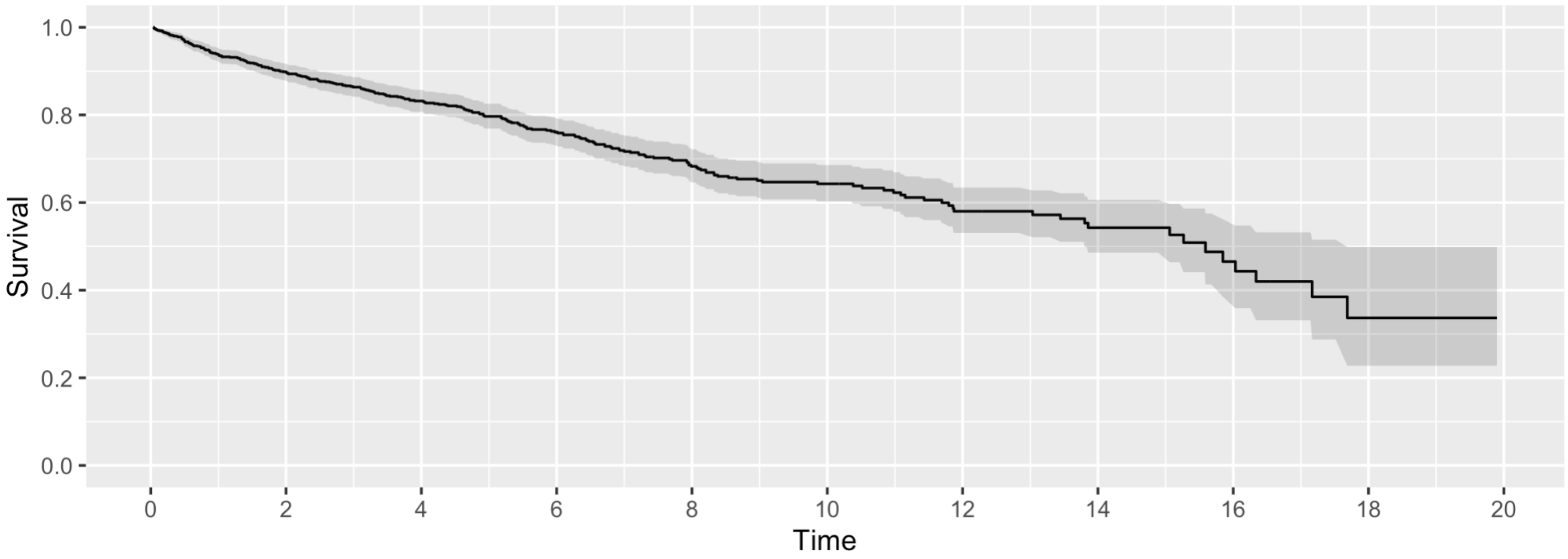
- $S(6) = S(4) \cdot \frac{8}{9} = 0.9 \cdot 0.89 = 0.8$
- $S(8) = S(6) \cdot \frac{5}{6} = 0.8 \cdot 0.83 = 0.67$
- $S(10) = S(8) \cdot \frac{2}{3} = 0.67 \cdot 0.67 = 0.44$

Kaplan-Meier Estimate

- Kaplan-Meier estimate of the survival function (with 95% confidence int.)



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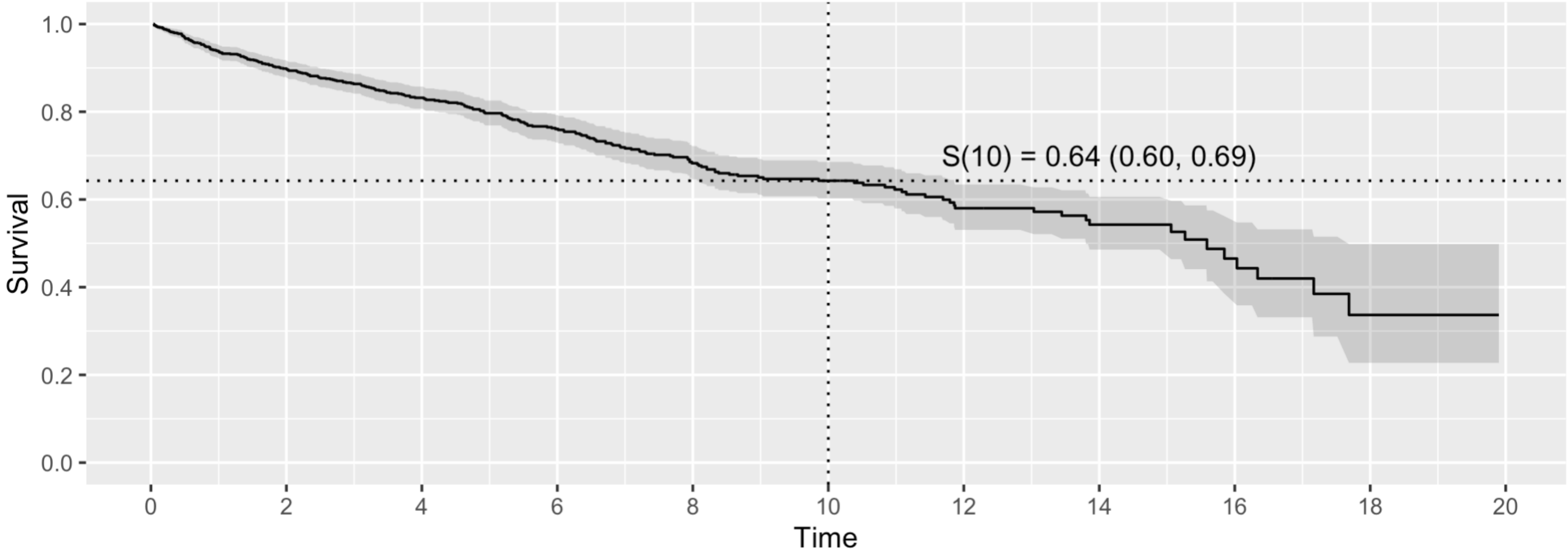

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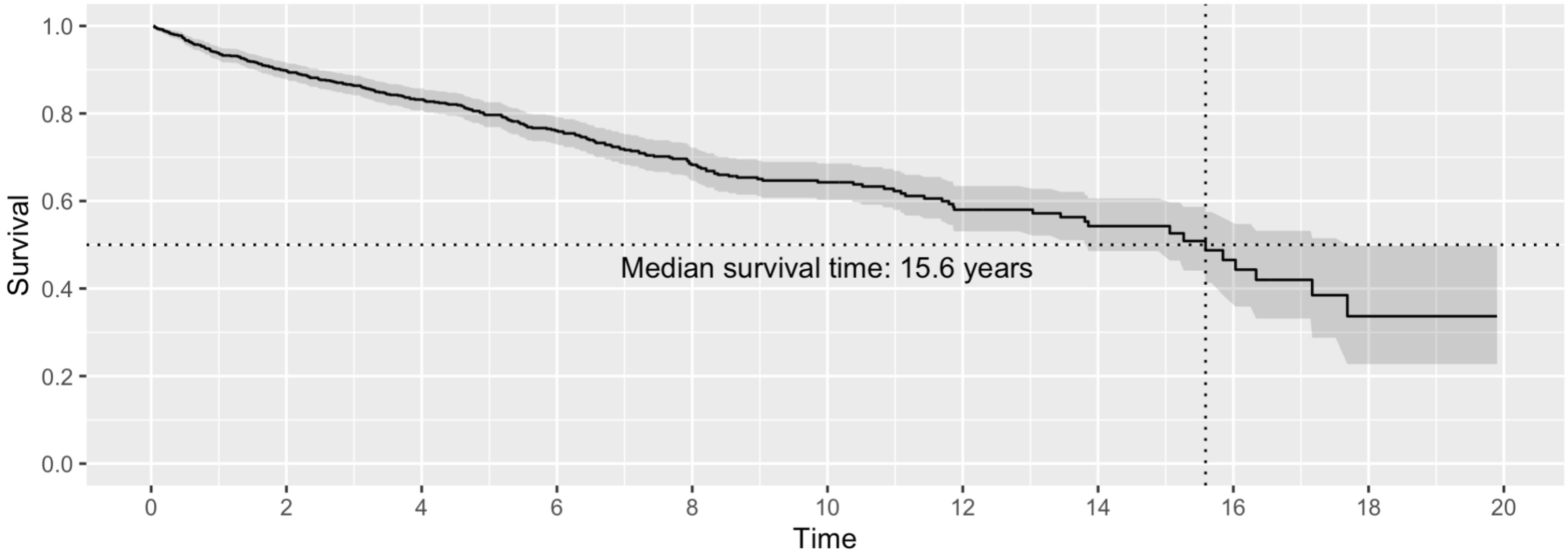
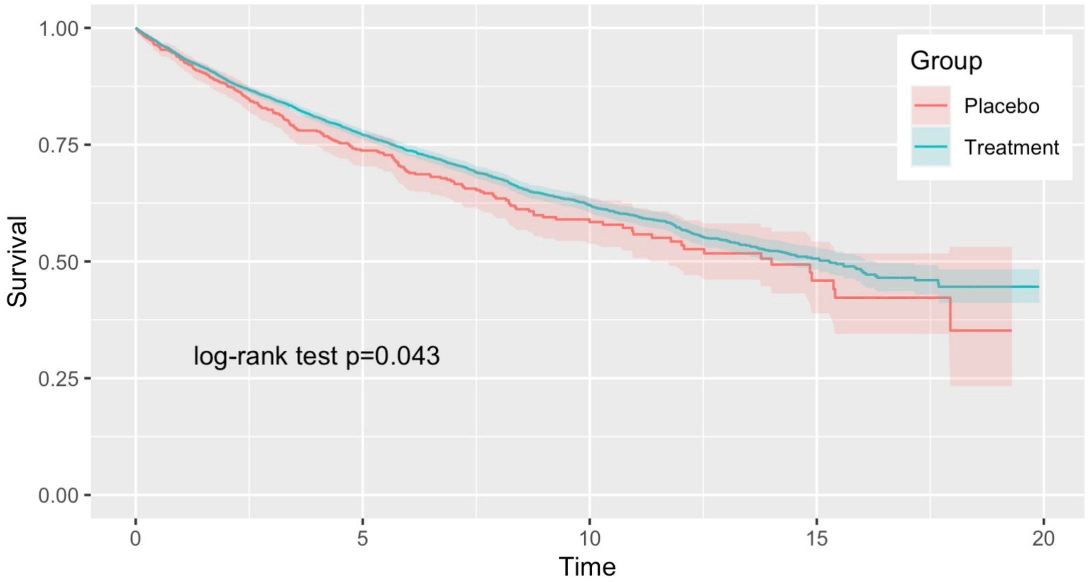
Median survival time

- Another interesting statistic could be the **Median Survival Time**:
  - → The time until 50% have experienced the event.
  - → For which *t* is *S(t)=0.5?*

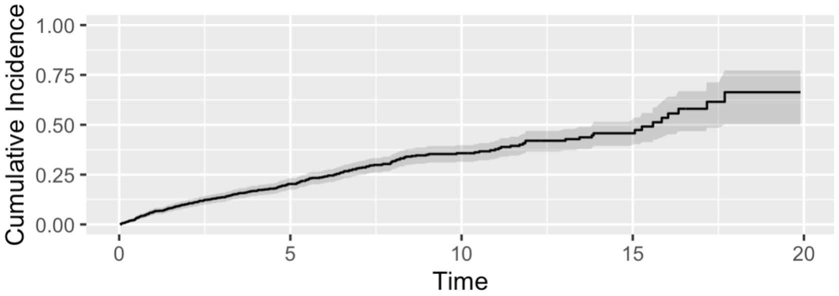


Comparing Survival Curves

- We can compare survival curves between groups
- We can do as statistical test—**the log-rank test**—for difference between the curves



The Cumulative Incidence Function



- *“The risk”*
- $1 - S(t)$

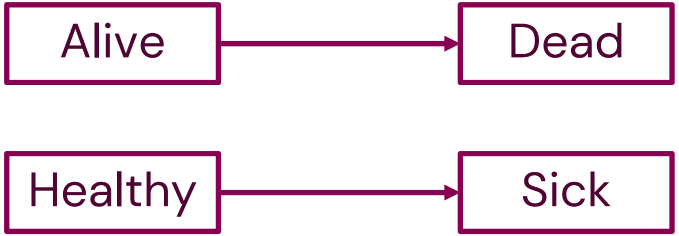
- The proportion who **have had the event** by *t*
- or equivalently the probability of having the event by time *t*

- Study Survival or Cumulative Incidence depending on context
  - → Which more interesting: the event-havers or the event-free?
  - → Cancer researchers favor survival (often survival after cancer dx)
  - → Hepatology favors cumulative incidence (who is at greater risk of dx)

The Hazard Rate

Different View: Transition Between States

- Subject starts in one state and at some timepoint moves to a different state



- We study the transition (the arrow)

- $S(t)$ is the proportion still in the 1st state at time t

The Hazard Rate

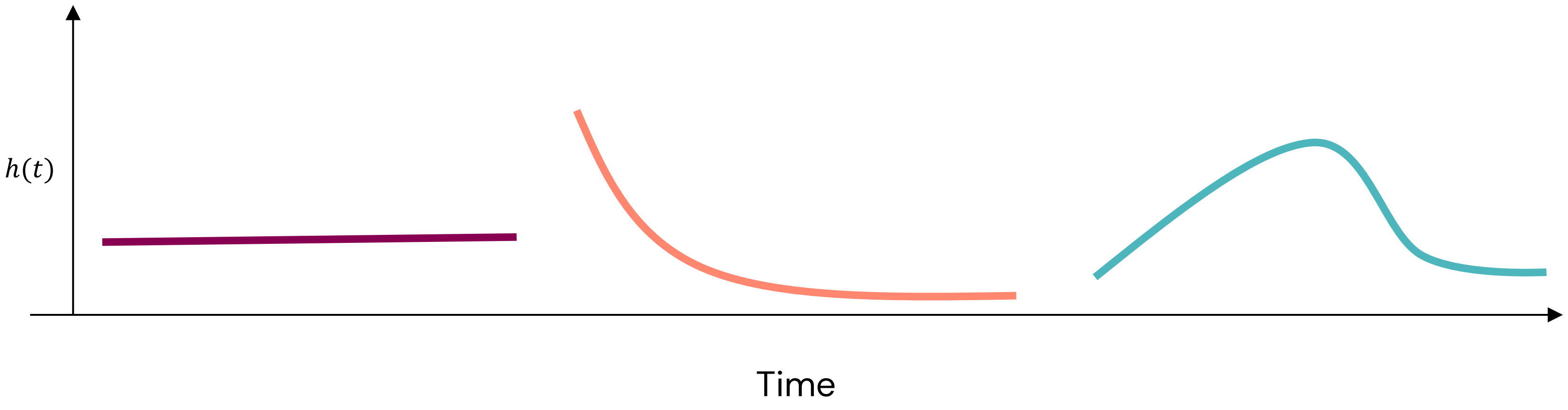
- The rate of transition is determined by the hazard rate
- Hazard rate function = $h(t)$

$$\boxed{\text{Healthy}} \xrightarrow{h(t)} \boxed{\text{Sick}}$$

- The hazard is a velocity
- $h(t) \geq 0$
- Higher hazard rate means both more events over time and events sooner

Hazard function examples

- The Hazard function can look very different depending on the mechanics of the transition



The Cumulative Hazard

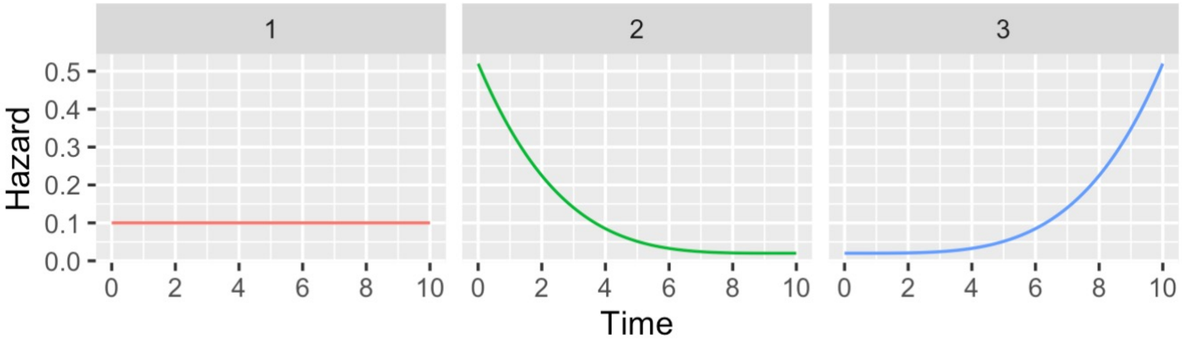
- The total accumulated hazard from *0* to *t*:

$$H(t) = \int_0^t h(u)du$$

- If the hazard is the velocity, the cumulative hazard is the total distance travelled
- How much hazard were you exposed to?
  - → A lot over a short time?
  - → A little over a long time?

Hazard & Survival

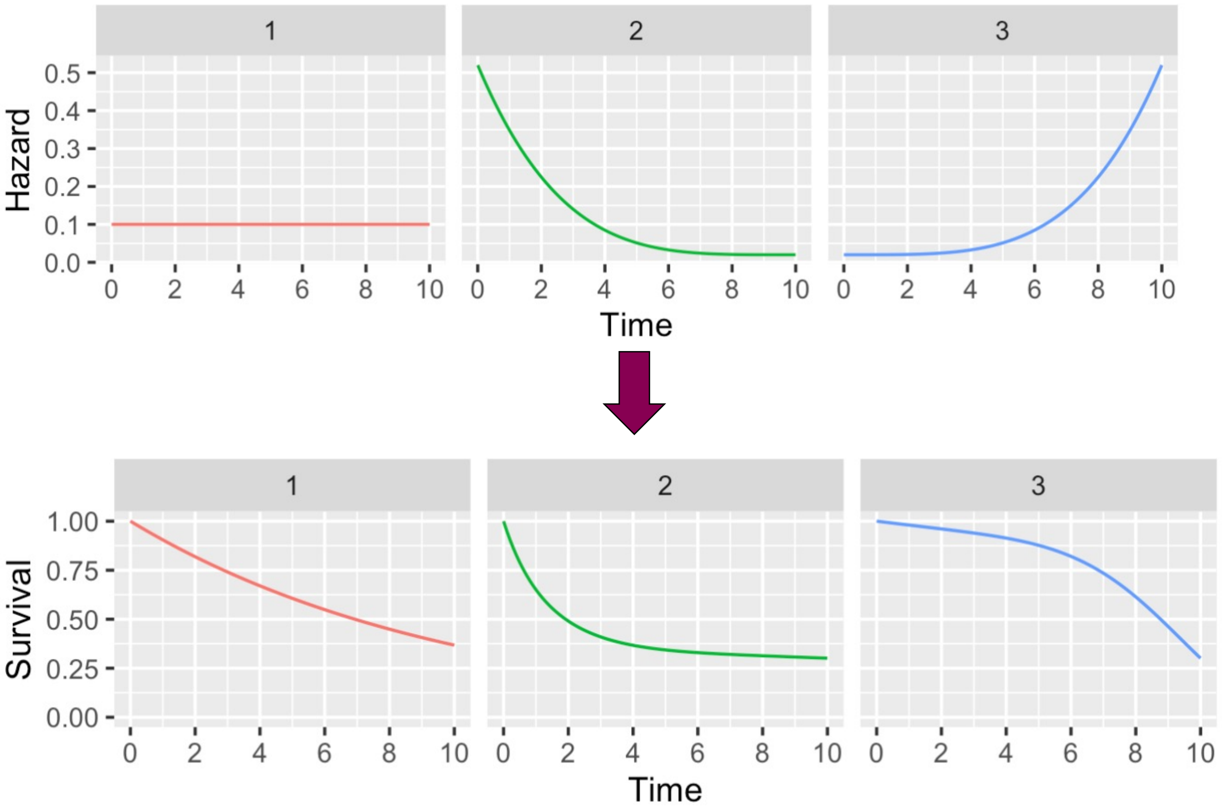
- How is the hazard function related to the survival function?



Hazard & Survival

- How is the hazard function related to the survival function?

- $S(t) = e^{-H(t)}$



Two Measures of Interest

- When doing survival analysis, we want to study two quantities:

1. The Survival (or Cumulative Incidence) over time for interesting comparisons
   → More practical outcome
     - e.g. survival after 5 years
     - treatment vs. no treatment
     - by smoking and age group (4 comparisons)
2. The Hazard function
   → Useful scale for exposure
   → e.g. carcinogens for developing cancer

Cox Proportional Hazards Regression

Proportional Hazards

- How do we compare hazards $h_1(t)$ and $h_2(t)$?

- Hazard ratio: $\mathrm{HR(t)} = \frac{h_1(t)}{h_2(t)}$

- **Proportional hazards:**
  → The hazard ratio is constant over time
  → $h_1(t) = HR \cdot h_2(t)$

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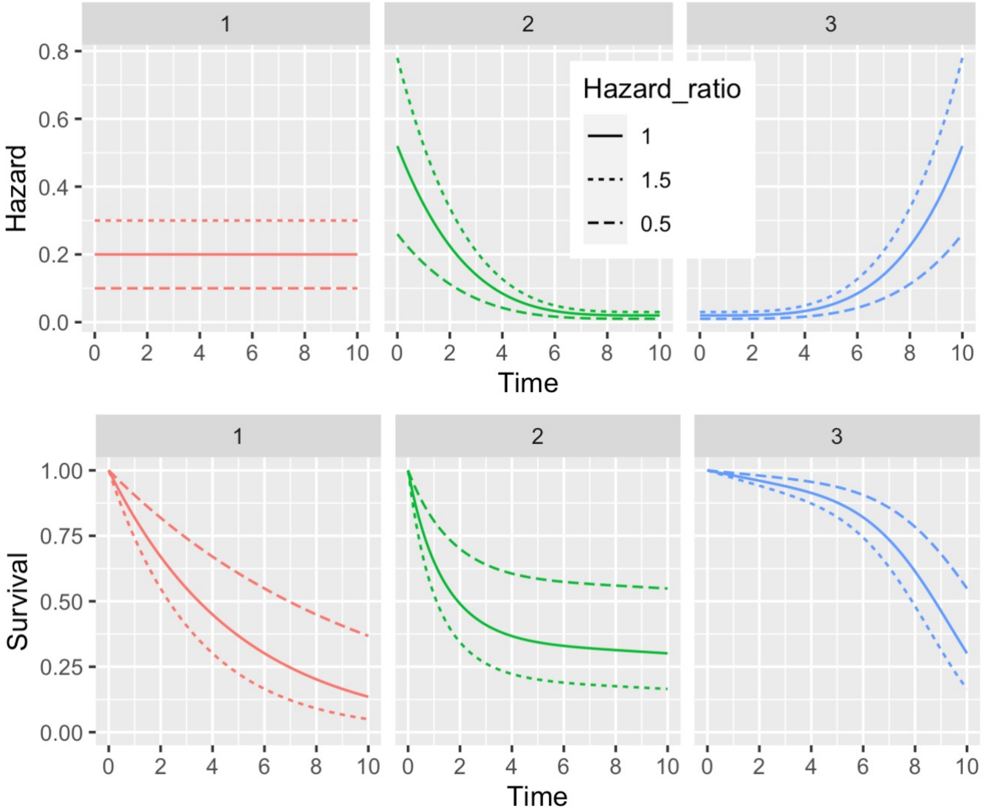


Cox Proportional Hazards Regression Models

- The workhorse for inference in survival analysis
- All subjects have an unknown hazard function specific to them
- We impose a rule:
  - → There is a common underlying shape to all the hazards, $\boldsymbol{h_0(t)}$
  - → All subjects' hazards are then **proportional to $\boldsymbol{h_0(t)}$** according to their covariates/risk factors
- Subject *i*'s hazard = $h_0(t) \cdot HR_i$

Cox Proportional Hazards Regression Models (2)

- Subject *i*'s hazard = $h_0(t) \cdot HR_i$

- Cox regression is regression on $\ln(HR_i)$:

$$\ln(HR_i) = \beta_1 X_{1i} + \beta_2 X_{2i} + \cdots \beta_m X_{mi}$$

- The β:s are estimated using the time-to-event outcome and the covariates

- $h_0(t)$ is not estimated! ("semi-parametric", "partial log-likelihood")

Interpreting Cox Models

$$\ln(HR_i) = \beta_1 X_{1i} + \beta_2 X_{2i} + \cdots \beta_m X_{mi}$$

- The β:s are "*log-hazard ratios*"
- e^{β_j} is the hazard ratio from a 1 unit increase in covariate X_j
  - → Binary (0/1): Change from treatment group 1 to treatment group 2
  - → Continuous: Change in BMI from 25 to 26
  - → Multiplicative, e.g. 2 unit change ⇒ $e^{\beta_j \cdot 2}$, etc.

- Like all other regressions we can get confidence intervals and p-values for each β

Example: Primary Biliary Cholangitis & Death

- PBC: Autoimmune disease destroying the bile ducts in the liver
- Causes scarring (fibrosis) $\Longrightarrow$ Cirrhosis $\Longrightarrow$ Liver failure $\Longrightarrow$ Death

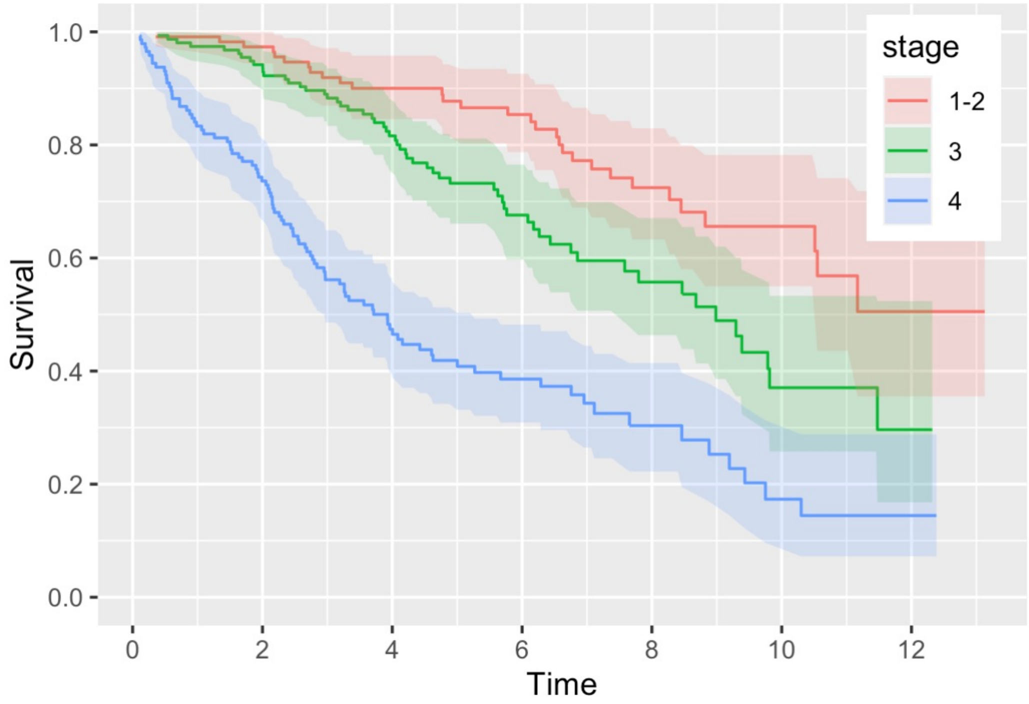
- *What is your prognosis based on current fibrosis stage (1–4)?*

- 412 PBC patients from the Mayo clinic
- Stage 1+2: 113 Stage 3: 155 Stage 4 (cirrhosis): 144
- 182 died or underwent liver transplant over up to 12 years (median 5 years)

- data("pbc", package="survival") in R

Example: Primary Biliary Cholangitis & Death (2)

- Kaplan-Meier curves:



- Can do log-rank test, but…
  → Age is potential confounder!
    - risk of death
    - fibrosis progression (time)
  → Overall quantification of the difference
- Cox regression let's us do all this **and** test for differences between stages

Example: Primary Biliary Cholangitis & Death (3)

- Cox model: $\ln(HR) = \beta_1[age] + \beta_2[sex\ (f)] + \beta_3[stage\ 3] + \beta_4[stage\ 4]$

Estimates:

Hazard Ratios:

Significance tests:

Example: Primary Biliary Cholangitis & Death (3)

- Cox model: $\ln(HR) = \beta_1[age] + \beta_2[sex\ (f)] + \boxed{\begin{matrix}\text{Stage 1–2:}\\ \beta_3 \cdot 0 + \beta_4 \cdot 0\end{matrix}}$

Estimates:	Hazard Ratios:	Significance tests:

Example: Primary Biliary Cholangitis & Death (3)

- Cox model: $\ln(HR) = \beta_1[age] + \beta_2[sex\ (f)] + \boxed{\begin{array}{c}\text{Stage 3:}\\ \beta_3 \cdot 1 + \beta_4 \cdot 0\end{array}}$

Estimates:	Hazard Ratios:	Significance tests:

Example: Primary Biliary Cholangitis & Death (3)

Stage 4:

- Cox model: $\ln(HR) = \beta_1[age] + \beta_2[sex\ (f)] + \boxed{\beta_3 \cdot 0 + \beta_4 \cdot 1}$

Estimates:	Hazard Ratios:	Significance tests:

Example: Primary Biliary Cholangitis & Death (3)

- Cox model: $\ln(HR) = \beta_1[age] + \beta_2[sex\ (f)] + \beta_3[stage\ 3] + \beta_4[stage\ 4]$

Estimates:

	coef	exp(coef)
age	0.011160	1.011222
sexf	-0.276887	0.758140
stage3	0.588064	1.800500
stage4	1.463718	4.321997

Hazard Ratios:

Significance tests:

Example: Primary Biliary Cholangitis & Death (3)

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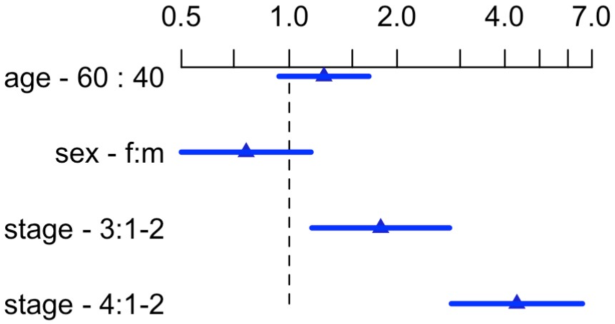

Significance tests:

HR age 60 vs 40: $e^{0.011\cdot(60-40)} = 1.25$

Example: Primary Biliary Cholangitis & Death (3)

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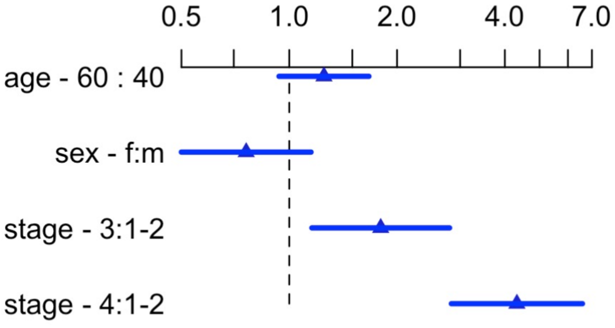


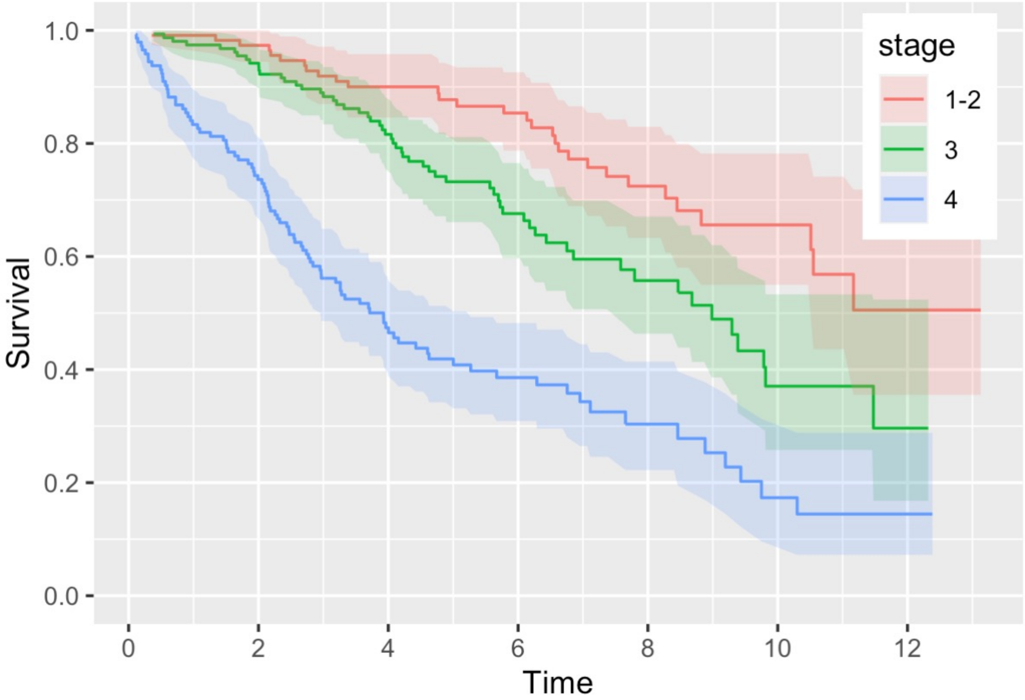
Significance tests:

Factor	Chi-Square	d.f.	P
age	2.29	1	0.1301
sex	1.70	1	0.1929
stage	55.57	2	<.0001
TOTAL	69.00	4	<.0001

HR age 60 vs 40: $e^{0.011\cdot(60-40)} = 1.25$

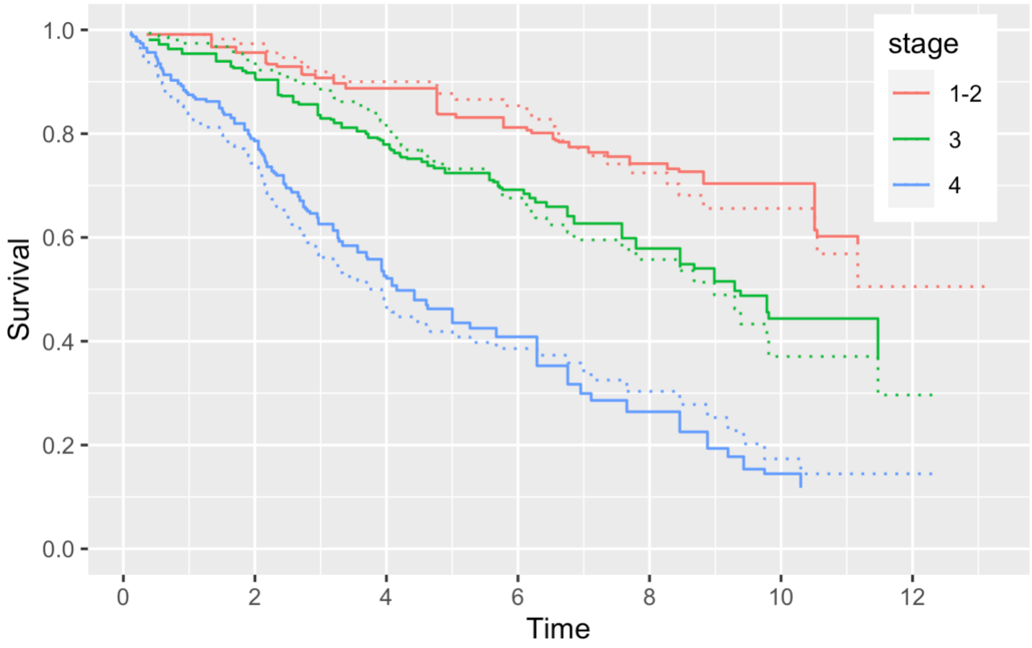
Checking the Proportional Hazards Assumption

- **Do the curves look like they have proportional hazards?**



Checking the Proportional Hazards Assumption

- **Do the curves look like they have proportional hazards?**
- If they did, according to the the Cox model:
- Important to check!
- What to do?
  → Flexible parametric survival model (advanced)



Checking the Proportional Hazards Assumption

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- Important to check!

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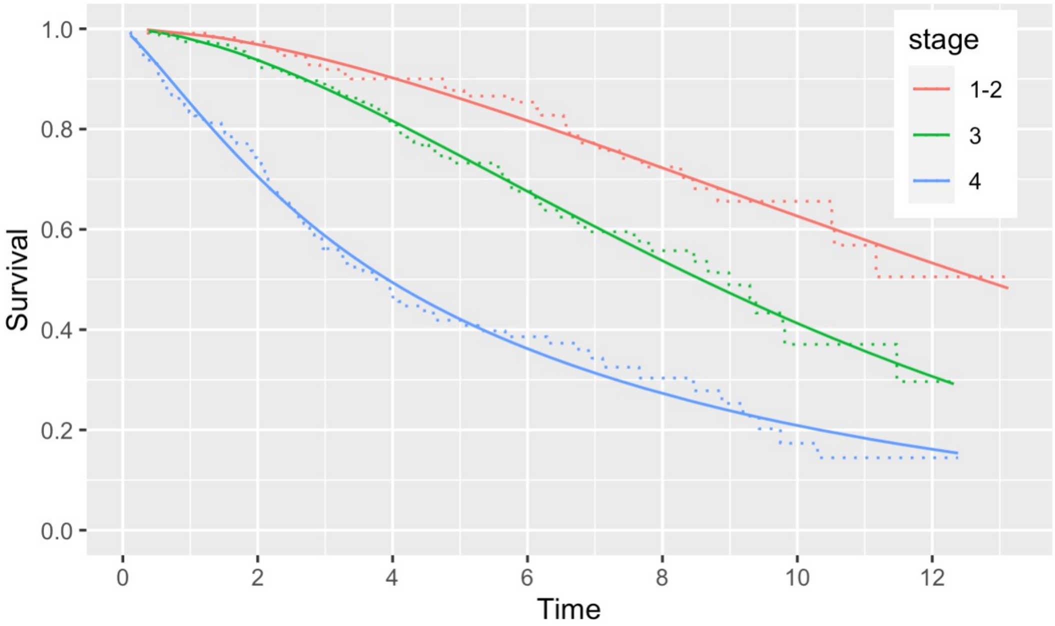

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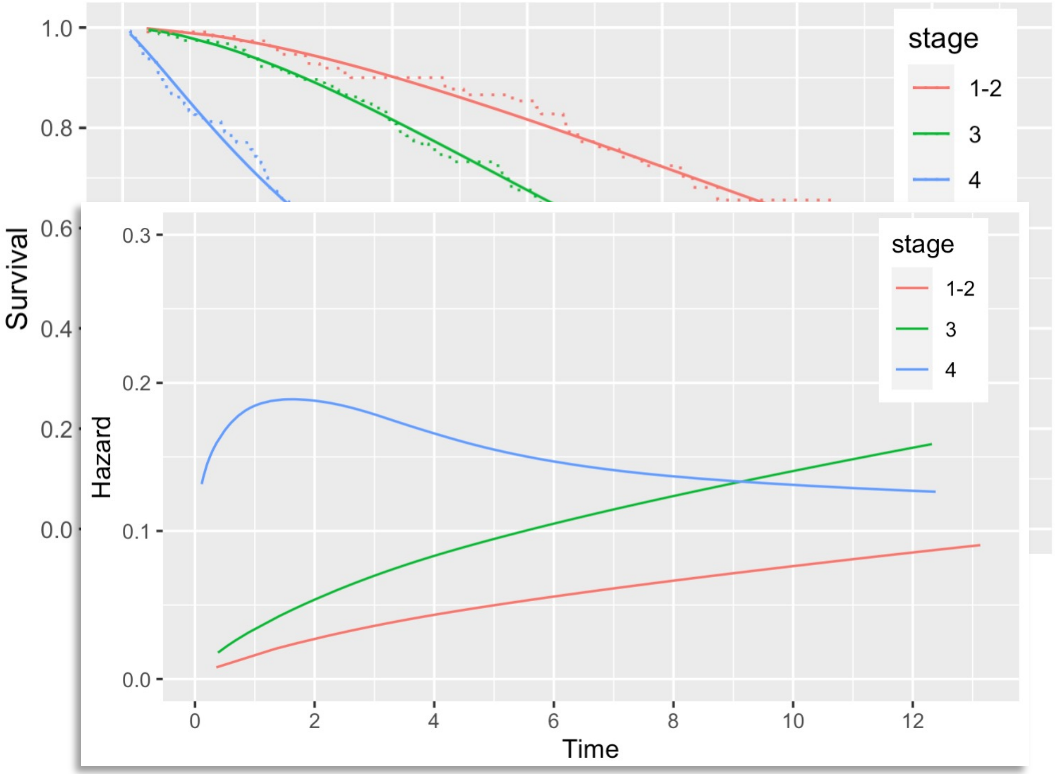

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