Memorial Sloan Kettering Cancer Center

Survival Analysis

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Learning Objectives

- Understand what survival analysis is
- Understand when we need to use survival analysis methods
- Recognize key estimates

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Survival Analysis

- Statistical methods for analyzing data where the outcome is the time to an event
- Time-to-event means that we are interested in the time that elapses until the event or outcome occurs
- Examples of time-to-event outcomes:
  - Time-to-recurrence
  - Progression-free survival
  - Disease-free survival
  - Overall survival

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Survival Analysis Applications

- Applicable for data from single-arm clinical trials, randomized clinical trials, cohort studies, and other observational datasets
- Important for:
  - Studies where not all patients enter at the same time (staggered entry)
  - Data analyzed before all patients have experienced the outcome (censoring)

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Censoring

- Exact time event occurs is not known
- Different type of censoring:
  - Right censoring: event has not yet occurred
    - Most common type of censoring
    - Examples: study ends or patients are lost to follow-up
  - Interval censoring: event occurred between two time-points, but we don't know exactly when
    - Examples: outcome occurs between two scheduled follow-up visits
  - Left censoring: Event occurs before the study starts
    - Not usually found in clinical trials

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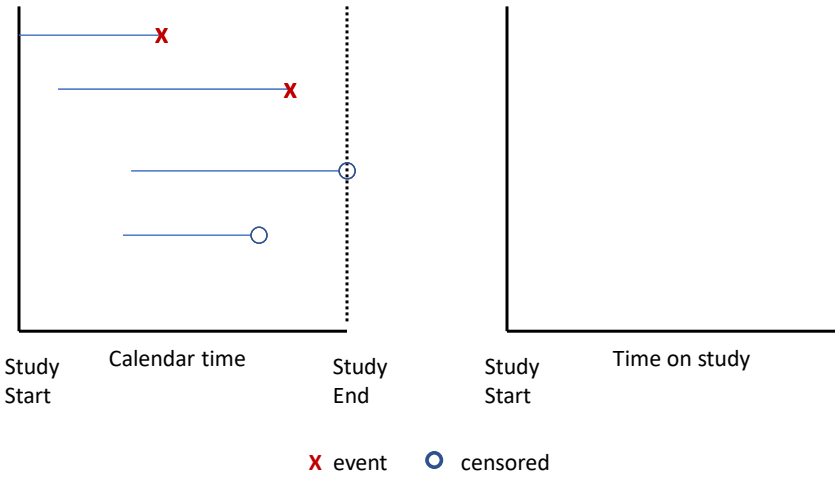
Survival Data Example



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Definitions

- Primary interest: *T* = the time until the event
- Instead observe:
  C = the time at which an observation is censored
  Event status (e.g. whether the patient died or not)
- Don't throw away information on *C*!
- Record and give to your statistician: event status, T, and C for everyone

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Survival Function

- $S(t) = \text{Prob}(T > t)$
- Interpretation: Probability an individual experiences the event after time *t;* probability of surviving beyond time *t*.
- Starts at 1 and decreases towards 0:
  - $S(t) = 1$ for $t=0$, $S(t) = 0$ for $t=\infty$
- Non-increasing function

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Hazard Function

- $h(t) = \lim_{\Delta t \to 0} \frac{\text{Prob}(t \le T \le \Delta t + t \mid T \ge t)}{\Delta t}$

- Interpretation: Probability of experiencing the event in the next instant given survival without the event until time *t*
- Also called hazard rate, instantaneous failure rate, age-specific failure rate
- Mathematically related to the survival function
- Can have many shapes but can never be negative ($h(t) \ge 0$)
- Hazard ratio is the ratio of two hazard functions

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Estimating the Survival Function

- To estimate $S(t)$ = Prob($T>t$), why not just take the proportion of people with event times greater than *t*?
  - Ignores censoring
- Two main ways:
  - Parametric estimate
    - Assumes the times-to-event follow a particular probability distribution function
  - Non-parametric estimate
    - Empirical estimate

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Kaplan-Meier Estimate

- $\hat{S}_{KM}(t) = \prod_{t_i \le t} \left(1 - \frac{D_i}{N_i}\right)$
  - N_i = Number of people at risk of having the event at the i^{th} time
  - D_i = Number of people having the event at the i^{th} time.
- Product-Limit estimator
- Most frequently used method for estimating the survival function
- Step function with jumps at the event times

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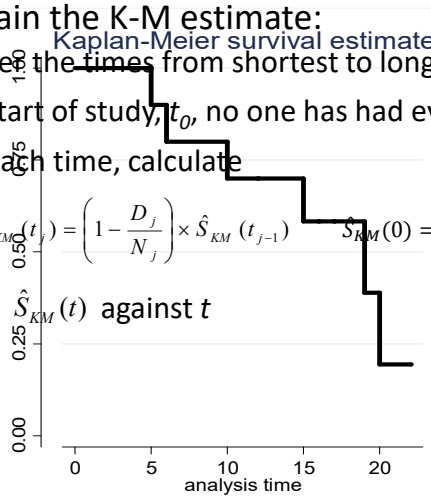
Kaplan-Meier Estimate

- To obtain the K-M estimate:
  - Order the times from shortest to longest
  - At start of study, t_0, no one has had event,
  - At each time, calculate

$$\hat{S}_{KM}(t_j) = \left(1 - \frac{D_j}{N_j}\right) \times \hat{S}_{KM}(t_{j-1}) \qquad \hat{S}_{KM}(0) = 1$$

  - Plot $\hat{S}_{KM}(t)$ against t



i	t_i	D_i	N_i	(1)	$\hat{S}_{KM}(t)$
0	0		10		1
1	5	1	10	(1-1/10) x 1	0.90
2	6	1	9	(1-1/9) x .90	0.80
3	10	1	8	(1-1/8) x .80	0.70
4	12	0	---		---
5	15	1	6	(1-1/6) x .70	0.58
6	16	0	---		---
7	17	0	---		---
8	19	1	3	(1-1/3) x .58	0.39
9	20	1	2	(1-1/2) x .39	0.19
10	22	0	---		----

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Caveats

- Assume probability an observation is censored is unrelated to the probability of having an event
  - Uninformative censoring
- Estimates can be unstable at the tail of the Kaplan-Meier curve when the number of patients remaining at risk gets small
- If the last observation is censored the Kaplan-Meier estimate will not reach 0.

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Comparing Two Survival Functions

- H_o: $S_1(t) = S_2(t)$
- Can use:
  - Log-rank test
    - Most frequently used test
    - Most powerful against consistent differences
  - Modified Wilcoxon test
    - Most powerful against early differences
- Equivalent to testing H_0: Hazard Ratio = 1.
- State in advance what test you will use
- Sample size/power depends on the number of events

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Time-Dependent ROC Curves

- Disease status changes over time
- ROC curves that change as a function of time
- Can define based on the survival function

Heagerty *et al. Biometrics* 2000

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Time-Dependent ROC Curves

- Treat sensitivity and specificity as time-dependent functions and use Bayes theorem:

$$\text{Sensitivity}(c,t) = \text{Prob}(X > c \mid D(t) = 1) = \frac{\{1 - S(t \mid X > c)\}P(X > c)}{1 - S(t)}$$

$$\text{Specificity}(c,t) = \text{Prob}(X \le c \mid D(t) = 0) = \frac{\{1 - S(t \mid X \le c)\}P(X \le c)}{S(t)}$$

where X is the biomarker value

Heagerty *et al. Biometrics* 2000

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Time-Dependent ROC Curves:
Example using Strain in Chronic Heart Failure

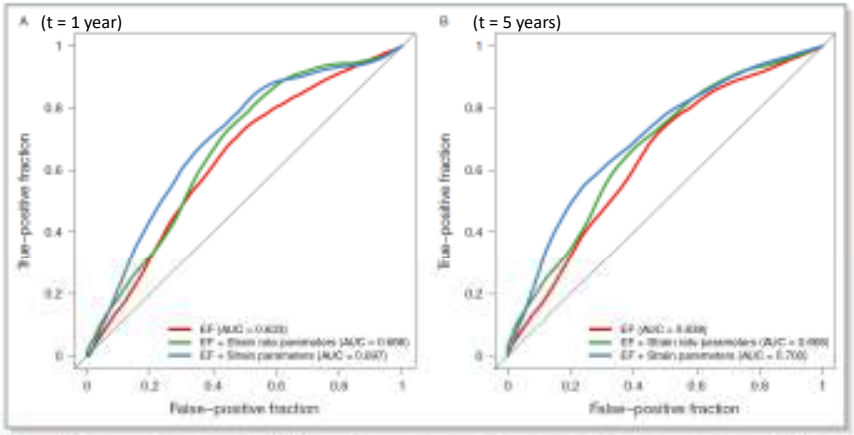

Figure 3. Receiver operating characteristic (ROC) curves. In comparison to EF alone, strain and EF demonstrated an improved AUC at both 1 year (0.697 versus 0.633, $P=0.032$) (A) and 5 years (0.700 versus 0.688, $P=0.014$) (B). In comparison to EF alone, strain rate and EF did not provide incremental value (0.666 versus 0.633, $P=0.16$) at 1 year (A) and 5 years (0.668 versus 0.638, $P=0.13$) (B). AUC indicates area under the ROC curve; EF, ejection fraction.

Zhang *et al. J Am Heart Assoc*. 2013

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Summary

- With time-to-event data, important to properly account for unobserved events
- When planning studies, think in terms of the number of events that will be observed
- Consider incorporating time-dependent ROC curves into planned analyses with time-to-event outcomes

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