MODULE 12: INTRODUCTION TO SURVIVAL ANALYSIS

Summer Institute in Statistics for Clinical Research
University of Washington
July, 2017

Barbara McKnight, Ph.D.
Professor
Department of Biostatistics
University of Washington

OVERVIEW

- Session 1
  - Introductory examples
  - The survival function
  - Survival Distributions
  - Mean and Median survival time

- Session 2
  - Censored data
  - Risk sets
  - Censoring Assumptions
  - Kaplan-Meier Estimator and CI
  - Median and CI

- Session 3
  - Two-group comparisons: logrank test
  - Trend and heterogeneity tests for more than two groups

- Session 4
  - Introduction to Cox regression

OVERVIEW – MODULE 16

Module 16: Survival analysis in Clinical Trials

- Quick review of basics
- Estimating survival after Cox model fit
- More two-sample tests
  - Weighted logrank
  - Additional tests based on functionals and metrics
- Adjustment, precision and post-randomization variables
- Power
- Choice of outcome
- Information accrual in sequential monitoring

OVERVIEW – MODULE 20

Module 20: Survival analysis for Observational Data

- More complicated Cox models
  - Adjustment
  - Interaction
- Hazard function Estimation
- Competing Risks: Cox and Fine-Gray models
- Choice of time variable
- Left Entry/Truncation
- Immortal time bias
- Index event bias
- Time-dependent covariates

SESSION 1:
SURVIVAL DATA: EXAMPLES

Module 12: Introduction to Survival Analysis
Summer Institute in Statistics for Clinical Research
University of Washington
July, 2017

Barbara McKnight, Ph.D.
Professor
Department of Biostatistics
University of Washington

PRELIMINARIES

- No prior knowledge of survival analysis techniques assumed
- Familiarity with standard one- and two-sample statistical methods (estimation and testing) is assumed
- Emphasis on application rather than mathematical details
- Examples

SESSIONS/BREAKS

- 8:30 – 10:00
  - Break until 10:30
- 10:30 – 12:00
  - Break until 1:30
- 1:30 – 3:00
  - Break until 3:30
- 3:30 – 5:00

WHAT IS SURVIVAL ANALYSIS ABOUT?

- Studies the occurrence of an event over time
  - Time from randomization to death (cancer RCT)
  - Time from acceptance into a heart transplant program to death
  - Time from randomization to diagnosis of Alzheimer's Disease in a prevention trial
  - Time from randomization to ovarian cancer death in a randomized screening trial
  - Time from birth to removal of supplementary oxygen therapy
  - Time from first VTE diagnosis to recurrent VTE

YOUR EXAMPLES

WHAT IS SURVIVAL ANALYSIS ABOUT?

- Explores factors that are thought to influence the chance that the event occurs
  - Treatment
  - Age
  - Gender
  - Body Mass Index
  - Diet
  - Etc.

EXAMPLE 1

- Levamisole and Fluorouracil for adjuvant therapy of resected colon carcinoma
  Moertel et a. l, 1990, 1995
- 1296 patients, enrolled 1 – 5 weeks after surgery
- Stage B_2 or C
- 3 unblinded treatment groups in stage C (2:1:1 ratio)
  - Observation only
  - Levamisole (oral, 1yr)
  - Levamisole (oral, 1yr) + fluorouracil (intravenous 1yr)

Moertel CG, Fleming TR, Macdonald JS, et al. (1990) NEJM: 322(6):352–358.
Moertel CG. et al (1995). Annals of Internal Medicine: 122(5):321.

EXAMPLE 1

- Randomization
  - Dynamic method based on accrued:
  - For B_2, extent of invasion, time since surgery
  - For C, extent of invasion, time since surgery, number of lymph nodes involved

EXAMPLE 1

- Statistical analysis
  - Survival primary outcome (recurrence secondary)
  - Kaplan-Meier survival curves
  - Log-rank statistic
  - Cox proportional-hazards model for all multivariable analysis
  - Backward regression, maximal partial-likelihood estimate statistic
  - O'Brien-Fleming boundary for sequential monitoring; stopped early for stage C

EXAMPLE 1

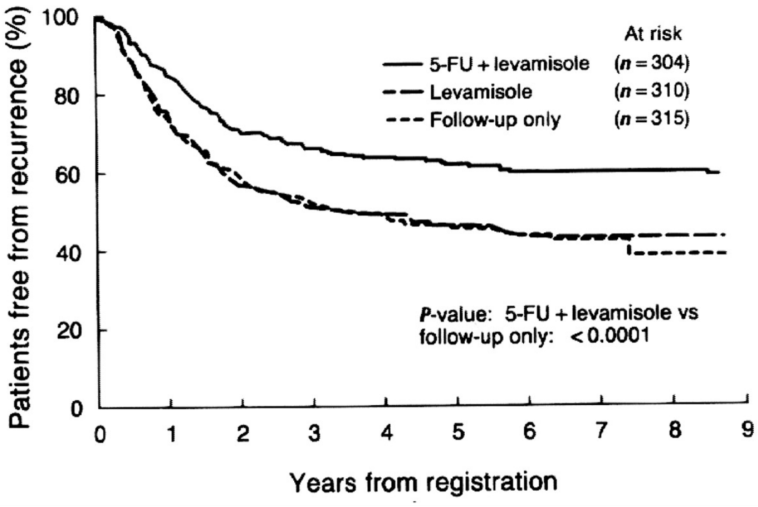


Figure 1: Recurrence-free interval according to treatment arm. Patients who died without recurrence have been censored. 5-FU = fluorouracil.

EXAMPLE 1

- Results (stage C) after 2nd interim analysis
- Fluorouracil + Levamisole reduced the
  - Recurrence rate by 41% (95% CI 23% - 54%) (p<0.0001)
  - Death rate by 33% (95% CI 10% - 50%) (p<0.006)
- Levamisole reduced the
  - Recurrence rate by 2%
  - Death rate by 6%
- Toxicity was mild (with few exceptions)
- Patient compliance excellent

EXAMPLE 1

- R survival package data "colon"
  - 929 eligible stage C patients (971 randomized – 42 ineligible)
  - Treatment groups (rx)
  - Sex, age
  - Obstruction of colon by tumor (obstruct)
  - Perforation of colon (perfor)
  - Adherence to nearby organs (adhere)
  - Number of lymph nodes with detectable cancer (nodes)
  - Days until event or censoring (time)
  - Censoring status (status)

EXAMPLE 1

- Multivariable analysis:
  - Proportional hazards model
  - "we kept the variable of treatment in the model and used backward regression for other covariates"
  - Other covariates (P < 0.01)
    - Depth of primary tumor invasion,
    - Invasion of adjacent structures
    - Regional implants
    - Number of metastatic lymph nodes
    - Histological differentiation
    - Preoperative carcinoembryonic antigen level

EXAMPLE 1

- Multivariable results: "After correction for the influence of prognostic factors through the use of a proportional hazards model, patients receiving fluorouracil plus levamisole were again found to have a significant survival advantage when compared with patients assigned to observation only; they had a 33% reduction in mortality rate (95% CI, 16% to 47%; *P* = 0.0007). Therapy with levamisole alone showed essentially no effect (6% reduction in death rate; *P* = 0.57."

Moertel et al (1995)

EXAMPLE 2 – ALZHEIMER'S

- Petersen et al. 2005, NEJM
- Subjects with amnestic subtype of mild cognitive impairment
- Adaptive randomization based on MMSE score, age, Apo ε4 genotype
- Three arms: Vitamin E, Donepezil, and Placebo
- Primary outcome: Time from randomization to possible or probable AD diagnosis
- Length of double-blind treatment: 3 years

Petersen RC, Thomas RG, Grundman M. et al. (2005) NEJM. 352(23):2379–2388.

EXAMPLE 2 – ALZHEIMER'S

- Primary analysis: Cox regression adjusted for randomization influencing variables MMSE score, age and Apo E genotype
- 769 enrolled: 253 donepezil, 257 vitamin E, 259 placebo
- 230 dropped out: 92 donepezil, 74 vitamin E, 66 placebo
  - Treatment related toxicity: GI complaints, muscle aches, insomnia
- Dropout was observed to be related to MMSE score

EXAMPLE 2 – ALZHEIMER'S

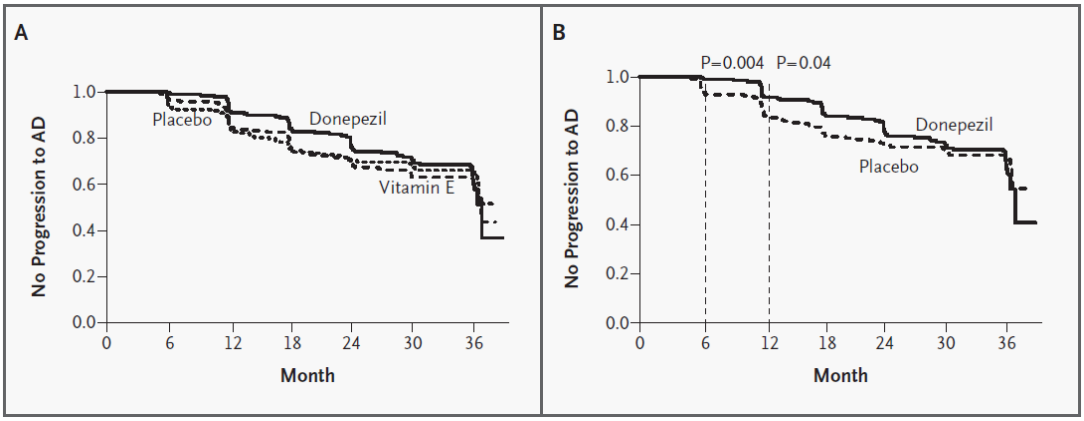
- 212 developed possible or probable AD
- "There were no significant differences … during the three years of treatment"
- Vitamin E vs Placebo
  - Hazard Ratio 1.02 (95% CI, 0.74, 1.41), p-value 0.91
- Donepezil vs Placebo
  - Hazard Ratio 0.80 (95% CI, 0.57, 1.13), p-value 0.42

EXAMPLE 2 – ALZHEIMER'S

- Prespecified analyses
- At 6 months intervals
  - Donepezil vs Placebo significantly reduced likelihood of progression to AD during the first 12 months (p-value 0.04)
  - Finding supported by secondary outcome measures
  - Subgroup ≥ 1 apolipoprotein E ϵ4 alleles significantly reduced likelihood of progression to AD over 3 years
  - Vitamin E vs Placebo: no significant differences
  - Vitamin E vs Placebo: also no significance for above subgroup
- Simulations assuming informative treatment-related dropout did not change primary conclusions

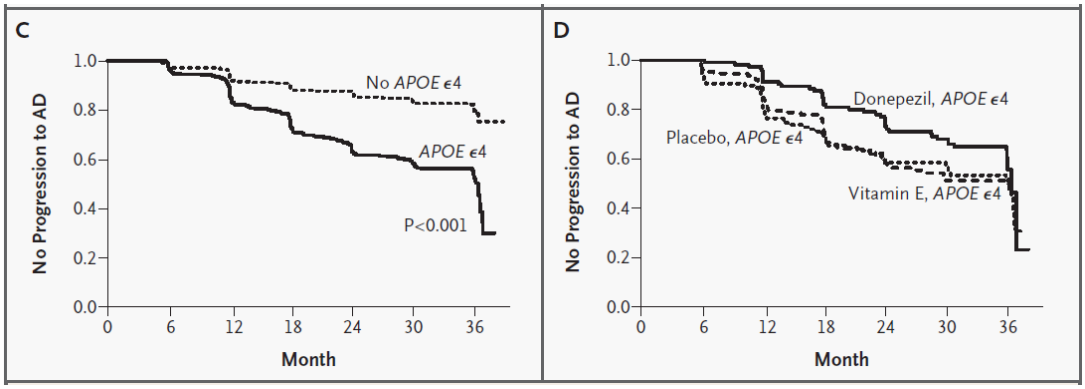
EXAMPLE 2 – RESULTS

- Overall and at 6 and 12 months



EXAMPLE 2 – RESULTS

- APOE ϵ4 results



EDITORIAL

- "long-awaited results"
- Donepezil standard therapy for AD
- "Implications …. Enormous"
  - Clear-cut negative findings for Vitamin E
  - Especially noteworthy
  - Despite dearth of evidence of its efficacy

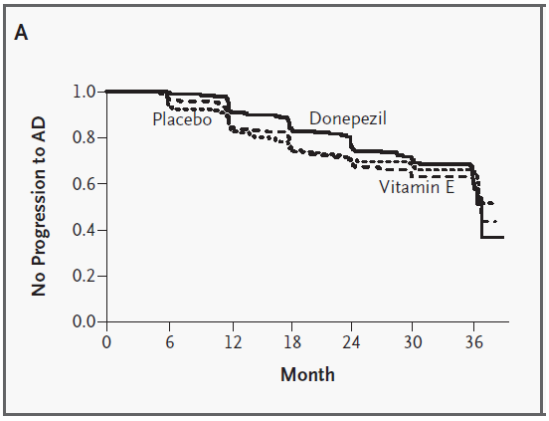
  - Findings for donepezil "much less clear"
  - "not quite as disappointing"

EDITORIAL COMMENTS

- "rate of progression … somewhat lower in the treatment group during the first year of the study"
- "by two years, even this small effect had worn off"
- Possible explanation: "Reduced statistical power later in the study as the number of subjects at risk declined owing to death, withdrawal and development of AD
- Secondary analyses suggest… benefits wore off

EXAMPLE 2 – RESULTS

- Interesting steps…..



SCREENING TRIAL

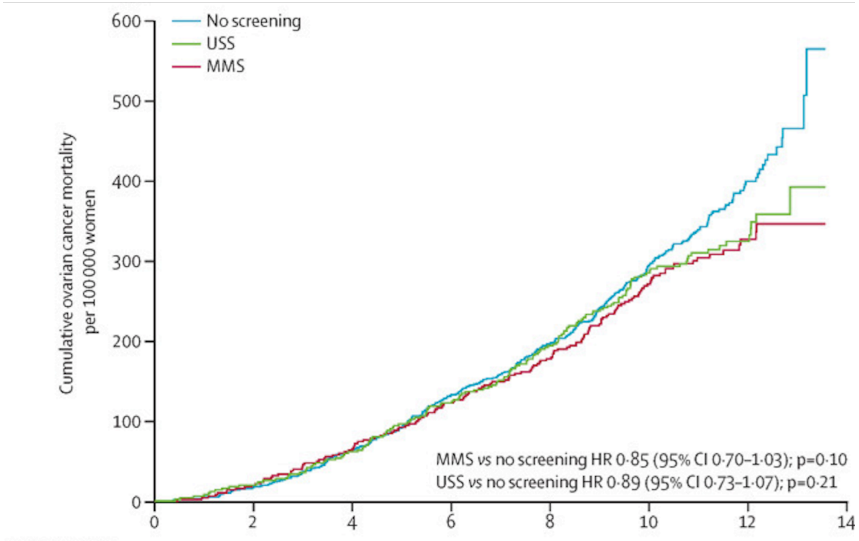
- 202,546 women 50-72 years of age, England, Wales, Northern Ireland
- Randomized to one of three arms in 1:1:2 ratio between June 1, 2001 and Oct 21, 2005.
  - Annual multimodal screening (serun CA 125 + algorithm)
  - Annual transvaginal ultrasound
  - No screening
- Screening ended Dec 31, 2011.
- Not blinded
- Primary outcome: death from ovarian cancer (by end of 2014)

Jacobs IJ, Menon U, Ryan A, et al. (2016) The Lancet. 387(10022):945–956.

OVARIAN CANCER SCREENING TRIAL

- Primary analysis: Cox regression (proportional hazards)
  - MMS vs. no screening: Mortality reduction = (1 – HR)100 = 15% (95% CI: -1% – 33%) P = .10
  - USS vs. no screening: Mortality reduction = (1 – HR) 100 = 11% (95% CI: -7% - 27%) P = .21

OVARIAN CANCER SCREENING TRIAL



Number at risk

No screening	101299	100720	99662	98238	96632	75582	25252
MMS	50624	50343	49846	49176	48345	37758	12592
USS	50623	50338	49838	49192	48363	37768	12689

OVARIAN CANCER SCREENING TRIAL

- Why the delayed difference?

OVARIAN CANCER SCREENING TRIAL

- Secondary analyses, excluding prevalent cases:
- Post-hoc Weighted* logrank test:
  - MMS mortality reduction = 22% (3-38%) P = .023
  - USS mortality reduction = 20% (0 – 35%) P = .049

  * by pooled cumulative mortality

"COUNTER" EXAMPLE

- Resuscitation Outcomes Consortium
  - Out-of-hospital cardiac arrest
  - Traumatic injury
- Prehospital interventions
- Exception from informed consent
- 10 Regional Centers
  - 7 US
  - 3 Canada

"COUNTER" EXAMPLE

- Times
  - Event (cardiac arrest, traumatic injury)
  - 911 call
  - Arrival of EMS
  - Treatment start
  - Potential outcomes
    - Return of spontaneous circulation (Cardiac arrest)
    - ED admission
    - Survival to hospital discharge
    - Neurologically intact survival
    - 28-day survival
    - 6-month neurological outcomes

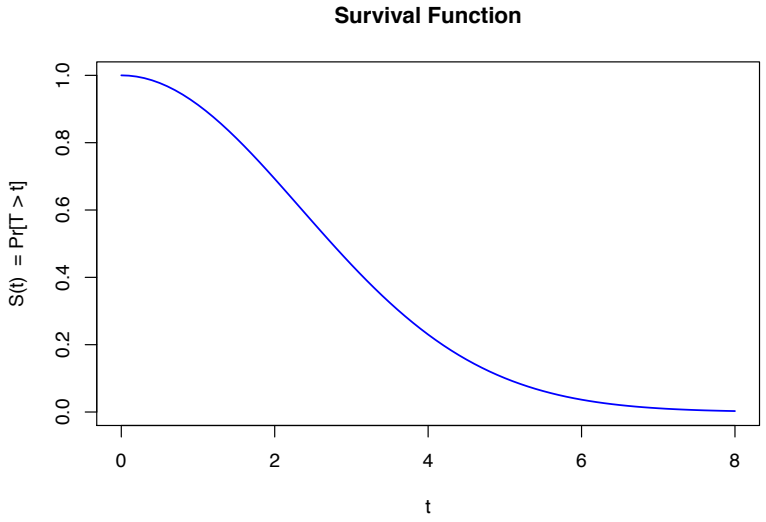
"COUNTER" EXAMPLE

- Time of injury/cardiac arrest
  (ordinarily unknown)
- 911 call
- Cardiac arrest: Many deaths before admission to hospital
- Trauma: Many deaths within the first 24 – 48 hours

SURVIVAL DATA AND FUNCTION

- Original applications in biometry were to survival times in cancer clinical trials
- Many other applications in biometry: eg. disease onset ages
- Interest centers not only on average or median survival time but also on probability of surviving beyond 2 years, 5 years, 10 years, etc.
- Best described with the entire survival function S(t).
  - For T = a subject's survival time, $S(t) = P[T > t]$.
  - Characterizes the entire distribution of survival times T.
  - Gives useful information for each t.

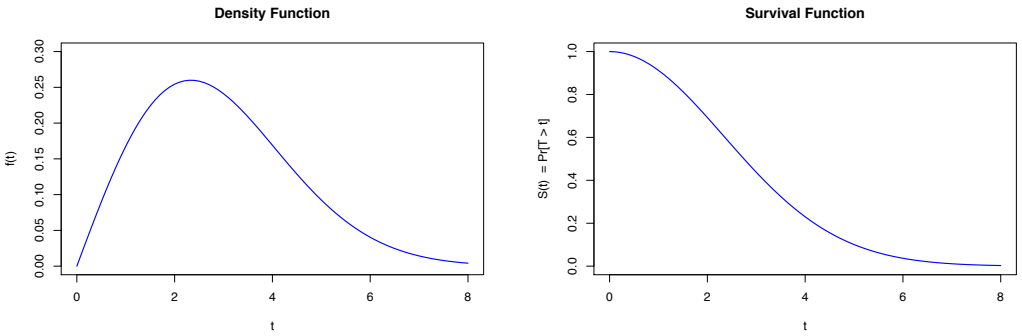
SURVIVAL FUNCTION



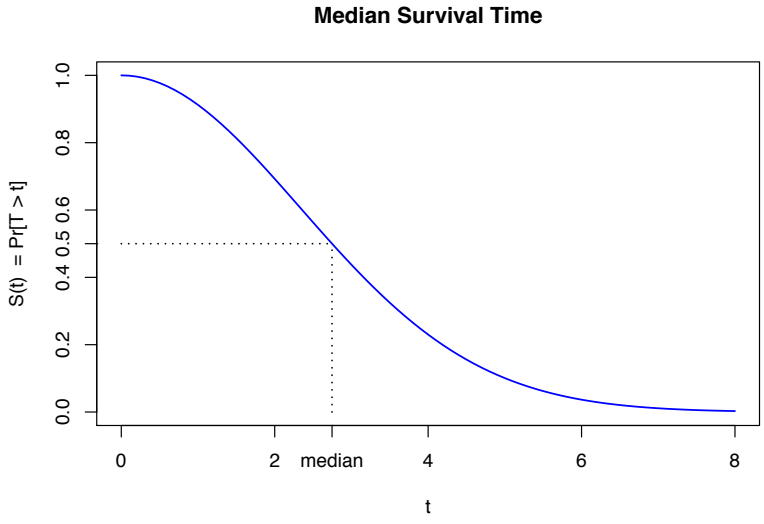
SURVIVAL DISTRIBUTION

- Continuous probability distribution of times T
- Only non-negative T's are possible: $\Pr(T<0)=0$
- Density function $f(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \Pr(t \le T < t + \Delta t)$
- Area under the $f(t)$ curve between two points is the probability T is between the two points.

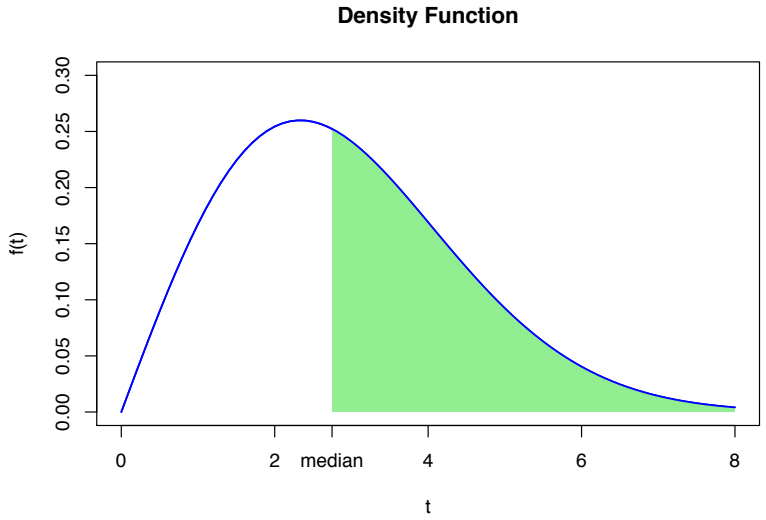
DENSITY AND SURVIVAL FUNCTIONS



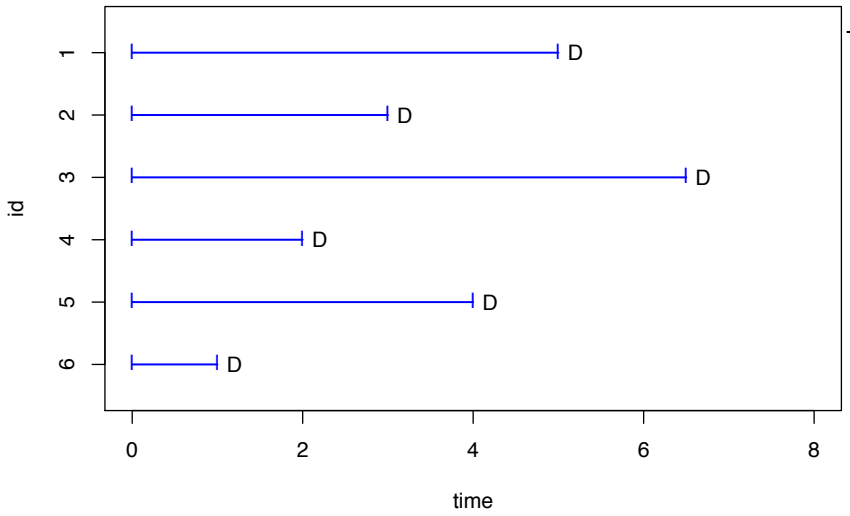
MEDIAN SURVIVAL TIME



MEDIAN SURVIVAL TIME



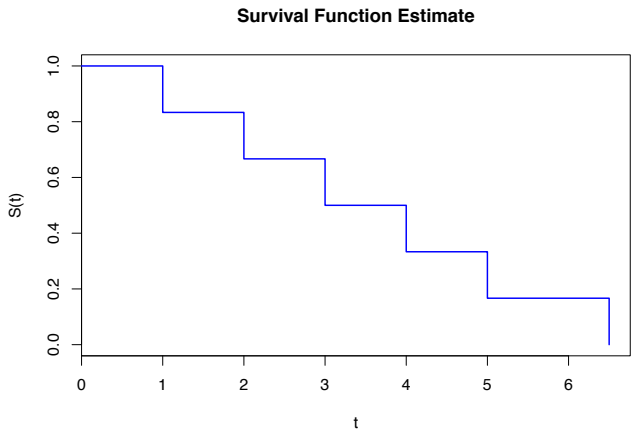
ILLUSTRATIVE DATA



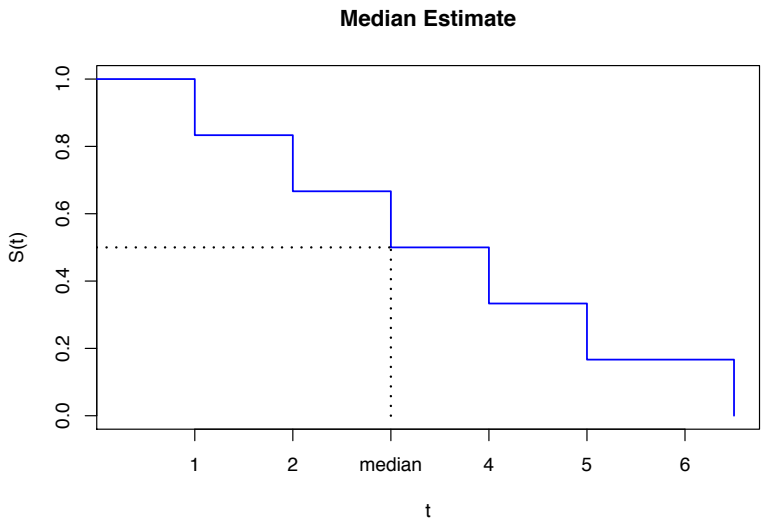
id	Y
1	5
2	3
3	6.5
4	2
5	4
6	1

SURVIVAL FUNCTION ESTIMATE

- Nonparametric Estimate: reduce estimate by 1/n every time there is an event (death): Empirical survival function estimate



MEDIAN ESTIMATE



By convention: median is earliest time where survival estimate ≤ .5

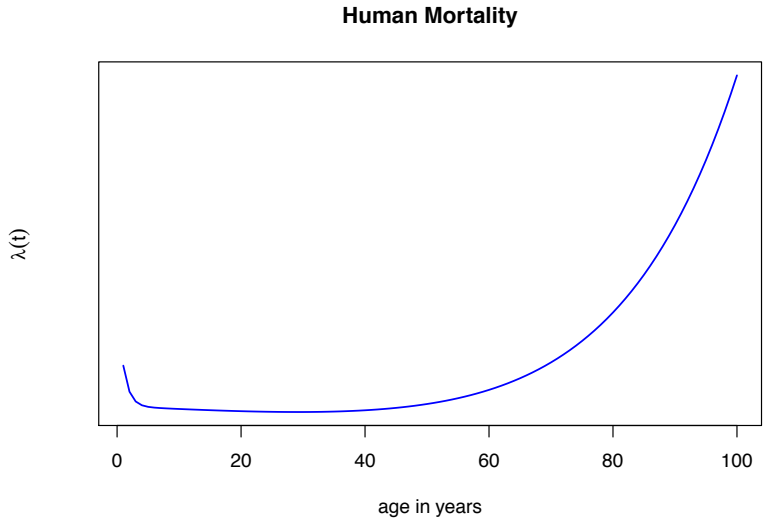
OTHER WAYS TO DESCRIBE A SURVIVAL DISTRIBUTION

- So far we have looked at the density function and survival function S(t).
- Also of interest: "hazard" function λ(t)

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \Pr[t \leq T < t + \Delta t | T \geq t]$$

- Instantaneous rate at which death occurs at t in those who are alive at t
- Examples:
  - Age-specific death rate
  - Age-specific disease incidence rate

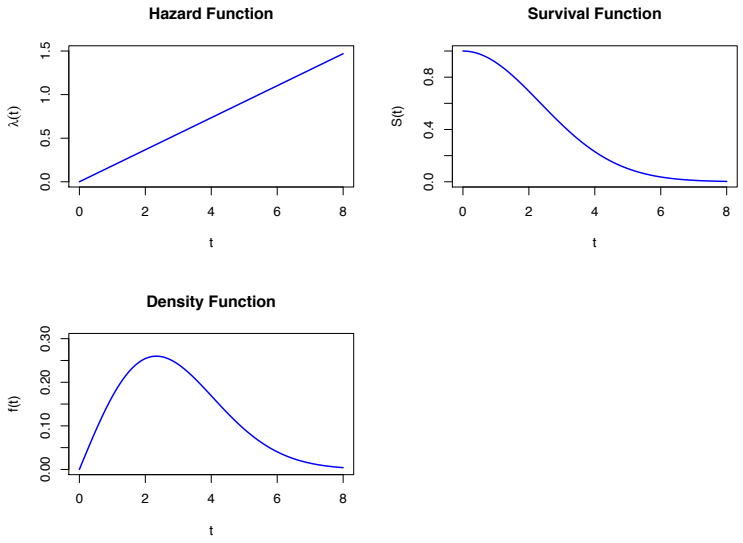
HAZARD FUNCTION FOR HUMANS



EQUIVALENT CHARACTERIZATIONS

- Any <u>one</u> of the density function(f(t)), the survival function(S(t)) or the hazard function(λ(t)) is enough to determine the survival distribution.
- They are each functions of each other:
  - $S(t) = \int_t^{\infty} f(s)ds = e^{-\int_0^t \lambda(s)ds}$
  - $f(t) = -\frac{d}{dt}S(t) = \lambda(t)e^{-\int_0^t \lambda(s)ds}$
  - $\lambda(t) = \frac{f(t)}{S(t)}$

EQUIVALENT CHARACTERIZATIONS



EQUIVALENT CHARACTERIZATIONS