University of Waterloo

An Introduction to Survival Analysis

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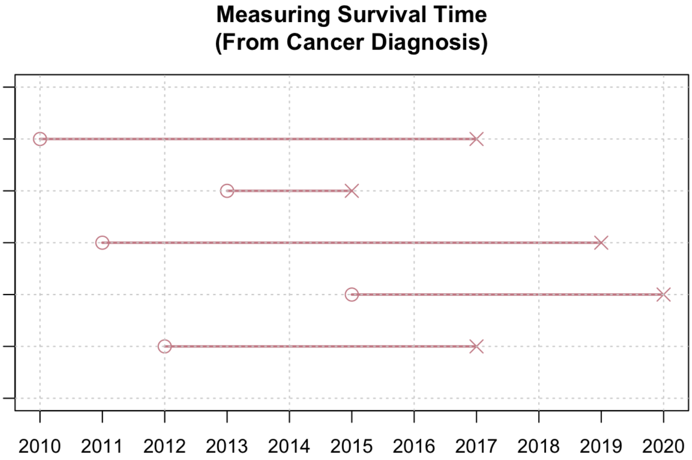
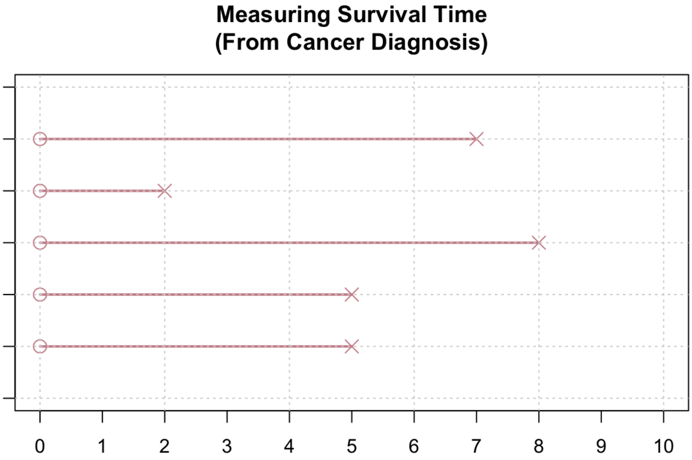
Outline

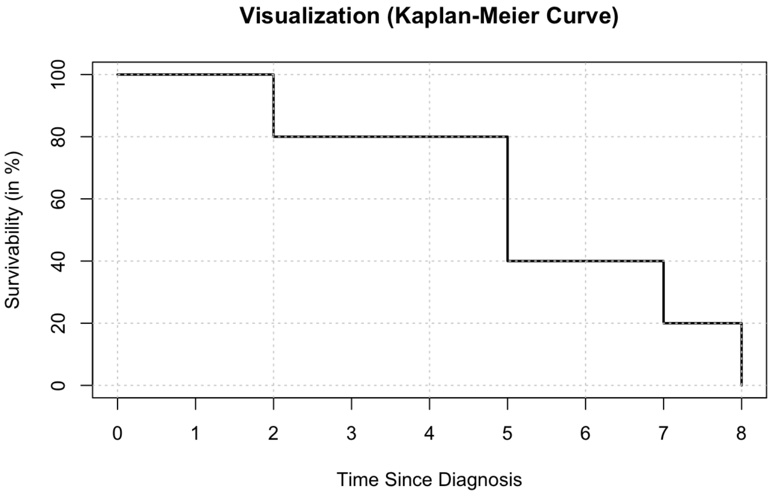
Intuition


Measuring Survival Time
(From Cancer Diagnosis)
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020

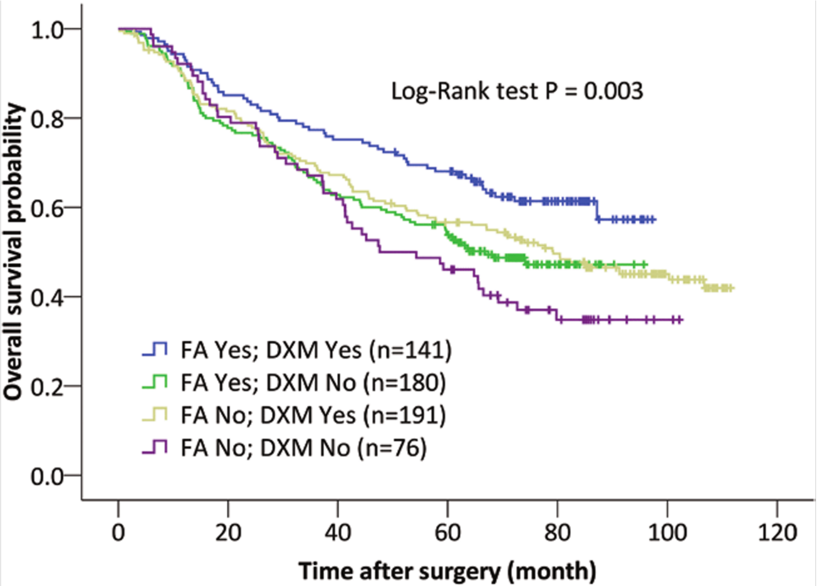
Intuition


Measuring Survival Time
(From Cancer Diagnosis)
0
1
2
3
4
5
6
7
8
9
10

Intuition


Visualization (Kaplan-Meier Curve)
Survivability (in %)
0
20
40
60
80
100
0
1
2
3
4
5
6
7
8
Time Since Diagnosis

Intuition


Log-Rank test P = 0.003
FA Yes; DXM Yes (n=141)
FA Yes; DXM No (n=180)
FA No; DXM Yes (n=191)
FA No; DXM No (n=76)
Overall survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
Time after surgery (month)

Introduction to Survival Analysis

Definition

- **Survival analysis** is a branch of statistics that measures the time until an event occurs.
- **Survival time** is the particular variable of interest.
  - Exposure $\rightarrow$ Event
  - Ex. Time of cancer diagnosis to death
- Survival Analysis doesn't have to just be involved with death, but in the same lens of cancer, it could be the time of complete remission to relapse

Censoring

Definition

- Censoring occurs when we don't know the exact time to event.
- We don't delete these observations
  - Make a note that the result was censored.
- Different types of censoring
  - Right censoring
  - Left Censoring
  - Interval censoring

Right Censoring

Definition

- Time to the event is GREATER than some value x
  - $t_i > x$
- Study: Estimating survival time after diagnosis of pancreatic cancer (Wahutu, 2016)
  - Consider: Patients still alive at the end of the study; Patients who are lost to follow up

Interval Censoring

Definition

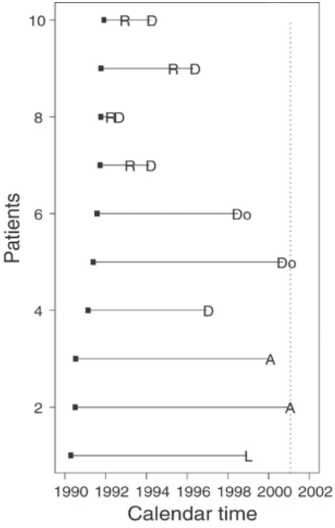
- Time to event is BETWEEN 2 values x_1 and x_2
  - $x_1 < t_i < x_2$
- Study: Oral lesion occurrence in immunosuppressed children (Rodrigues, 2018)
  - Consider: Lesion occurrence is identified by a specialist at regular checkups

Left Censoring

Definition

- Time to the event is LESS than some value x
  - $t_i < x$
- Study: Age at menarche cohort study (Wohlfahrt-Veje, 2016)
  - Consider: Young women enrolled in the study who have already begun menstruating

Intuition


Patients
10
8
6
4
2
R D
RD
R D
Do
Do
D
A
A
L
1990 1992 1994 1996 1998 2000 2002
Calendar time
Patients
10
8
6
4
2
0 2 4 6 8 10 12
Time from diagnosis (years)

Important Functions

Functions of interest

- Survival function: $S(t) = P(T > t)$
- Hazard function: $h(t)$ represents the instantaneous risk of occurrence of the event given the history

Kaplan-Meier Survival Curves

Purpose

A useful non-parametric way to estimate the survival function. We calculating using the formula

$$S(t_j) = S(t_{j-1}) \left(1 - \frac{d_j}{n_j}\right)$$

Where d_j is the number of deaths at time t_j and n_j is the number of subjects at risk.

Assumptions

1. Random censoring
2. Non-informative censoring
3. Independence of censoring
4. Survival probabilities do not change over time
5. No competing risks

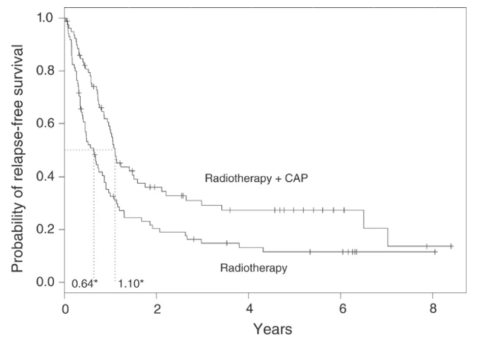
Example: Calculating KM Curves By Hand for Lung Cancer Trial

Figure 1

Radiotherapy (*n* =86)		Radiotherapy+CAP (*n* =78)	
Survival times (days)	**Kaplan–Meier survivor function *S*(*t*)**	**Survival times (days)**	**Kaplan–Meier survivor function *S*(*t*)**
18	1 × (1-1/86)=0.988	9	1 × (1-1/78)=0.987
23[a]	S(18) × (1-0/85)=0.988	22	S(18) × (1-1/77)=0.974
25	S(23) × (1-1/84)=0.977	35	S(22) × (1-1/76)=0.962
27	S(25) × (1-1/83)=0.965	53	S(35) × (1-1/75)=0.949
28	S(27) × (1-1/82)=0.953	76	S(53) × (1-1/74)=0.936
30	S(28) × (1-1/81)=0.941	81	S(76) × (1-1/73)=0.923
36	S(30) × (1-1/80)=0.930	94	S(81) × (1-1/72)=0.910
45	S(36) × (1-1/79)=0.918	97	S(94) × (1-1/71)=0.897
55	S(45) × (1-1/78)=0.906	103	S(97) × (1-1/70)=0.885
56	S(55) × (1-1/77)=0.894	114	S(103) × (1-1/69)=0.872
57	S(56) × (1-3/76)=0.859	115	S(114) × (1-1/68)=0.859
57	S(56) × (1-3/76)=0.859	121[a]	S(115) × (1-0/67)=0.859
57	S(56) × (1-3/76)=0.859	126	S(121) × (1-1/66)=0.846

Example: Comparing KM Curves

Figure 2



Observations

- Overall, Radiotherapy+CAP has a higher survival probability
- The Radiotherapy+CAP group has greater median survival time

Log-Rank Test

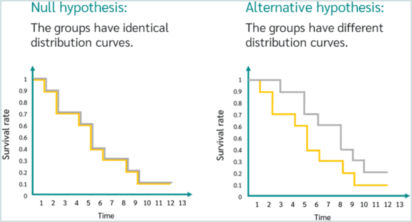
Purpose

A non-parametric test statistic used to compare two survival curves (independent from each other) by calculating

$$\chi^2 = \sum_{i=1}^{g} \frac{(O_i - E_i)^2}{E_i}$$

where O_i is the observed number of events and E_i is the total expected number of events in each group i.

Hypothesis



Back to Cancer Research Example

Log Rank Test for Lung Cancer Trial

	Radiotherapy (*n* =86)	**Radiotherapy+CAP (*n* =78)**
Number of relapses (O_i)	70	54
Median survival time(years) (95% CI)	0.64 (0.45–0.87)	1.10 (0.96–1.59)
Expected number of relapses (E_i)	53.4	70.6
Hazard ratio (95% CI)	0.58 (0.41–0.83)	
Logrank test	χ^2=9.1, 1 df, P<0.002	

df=degree of freedom: CAP=cytoxan, doxorubicin and platinum-based chemotherapy.

Observations

- Log rank test yields a χ^2 value of 9.1 on 1 degree of freedom (P<0.002)
- Hazard Ratio of 0.58 indicates that there is 42% less risk of relapse at any point in time among patients surviving in the combination treatment group compared to those treated with radiotherapy alone
- Indication is present that the combination treatment is more effective than radiotherapy treatment

The Cox Propotional Hazard model

Definition

$$h(t, \mathbf{X}) = h_0(t)e^{\sum_{i=1}^{p} \beta_i X_i}$$

$$\mathbf{X} = (X_1, X_2, \ldots, X_p) \quad \text{explanatory/predictor variables}$$

An expression for the hazard at time t for an individual with a given specification of a set of explanatory variables denoted by **X**.

Product of Two Quantities

$$h_0(t) \times e^{\sum_{i=1}^{p} \beta_i X_i}$$

$h_0(t)$	$e^{\sum_{i=1}^{p} \beta_i X_i}$
Baseline hazard Involves t but not X's	Exponential Involves X's but not t (X's are time-independent)

Semi-Parametric Nature

What does semi-parametric mean?

- Combines parametric and non-parametric components.
- The baseline hazard, $h_0(t)$, is an unspecified function (non-parametric).
- The relationship between the covariates and the hazard rate is expressed parametrically.

Why is this important?

- The Cox PH model is a "robust" model, so that the results from using the Cox model will closely approximate the results for the correct parametric model.
- This property makes the Cox PH Model more flexible than fully parametric models while still allowing meaningful interpretation.

Interpretation

Hazard Ratio (HR)

$$\widehat{HR} = \frac{\hat{h}(t, \mathbf{X}^*)}{\hat{h}(t, \mathbf{X})}$$

Measures the relative risk of an event for different covariate levels.

Interval Estimation

- Large sample 95% confidence interval:

$$\exp\left[\hat{\beta}_1 \pm 1.96\sqrt{\mathsf{Var}(\hat{\beta}_1)}\right]$$

where

$$s_{\hat{\beta}_1} = \sqrt{\mathsf{Var}(\hat{\beta}_1)}$$

Cox PH Model Ovarian Dataset Example

Table 1 Hazard ratios from the Cox PH model for the ovarian dataset

From: Survival Analysis Part II: Multivariate data analysis – an introduction to concepts and methods

	Univariate analysis				Multivariate analysis			
Covariate	**Coefficient (b_i)**	**HR [exp(b_i)]**	**95% CI**	***P*-value**	**Coefficient (b_i)**	**HR [exp(b_i)]**	**95% CI**	***P*-value**
FIGO stage	0.809	2.24	(2.03–2.48)	<0.001	0.731	2.08	(1.82–2.37)	<0.001
Histology				<0.001				<0.001
Serous	(0.000)	(1.00)			(0.000)	(1.00)		
Mucinous	−0.727	0.48	(0.38–0.61)		−0.422	0.66	(0.50–0.85)	
Endometroid	−1.162	0.31	(0.22–0.45)		0.198	1.22	(0.80–1.85)	
Clear cell	−0.343	0.71	(0.52–0.97)		0.342	1.41	(0.99–2.00)	
Adenocarcinoma	0.119	1.13	(0.74–1.72)		0.501	1.65	(0.91–2.99)	
Undifferentiated	0.390	1.48	(0.81–2.70)		0.746	2.11	(1.03–4.29)	
Mixed mesodermal	0.614	1.85	(1.28–2.66)		0.789	2.20	(1.45–3.35)	
Grade				<0.001				<0.001
1	(0.000)	(1.00)			(0.000)	(1.00)		
2	1.116	3.05	(1.90–4.91)		0.885	2.42	(1.40–4.19)	
3	1.650	5.20	(3.31–8.18)		0.885	2.42	(1.40–4.18)	
Absence of ascites	−0.798	0.45	(0.37–0.55)	<0.001	−0.396	0.67	(0.54–0.84)	<0.001
Age (per 5-year increase)	0.153	1.17	(1.12–1.21)	<0.001	0.133	1.14	(1.09–1.19)	<0.001

HR=hazard ratio, CI=confidence interval.

References

- Log rank test tutorial.
- Survival analysis: Self learning book.
- M. J. Bradburn, T. G. Clark, S. B. Love, and D. G. Altman.
  Survival analysis part ii: Multivariate data analysis – an introduction to concepts and methods.
  Nature.
- T. G. Clark, M. J. Bradburn, S. B. Love, and D. G. Altman.
  Survival analysis part i: Basic concepts and first analyses.
  Nature.