

# Survival Analysis in Economic Evaluation

The DARTH Workgroup

# Overview

- ▶ Motivation and introduction in Survival Analysis
- ▶ Survival modeling
- ▶ Non-Parametric modeling
- ▶ Semi-Parametric modeling
- ▶ Fully Parametric modeling
- ▶ Multistate models

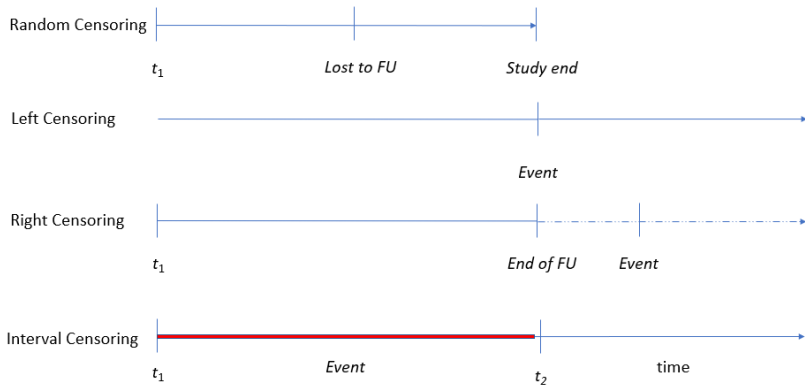
# It's all about the data!

- ▶ RCT evidence often not sufficient for Health Technology Assessment (HTA)
  - ▶ Short follow up
  - ▶ Patients lost during follow up
  - ▶ Often not reflective of real world
  - ▶ Right skewed
  - ▶ Information “flowing” over intervals
  - ▶ Extrapolation often necessary

## Bonus challenges in Oncology RCTs

- ▶ Overall Survival (OS), Progression-Free Survival (PFS)
- ▶ Trials powered to show differences on PFS and not OS
- ▶ Cross-over
- ▶ PFS and OS data are correlated
- ▶ Access to patient level OS data not always the case

# Censoring



## Informative Censoring

The case where survival time is dependent with whatever causes the censoring. Example: A patient in a community study is censored because they are hospitalized (hospitalization indicates severity)

In most of the examples throughout we will make the assumption of non-informative censoring

# What is survival analysis

- ▶ Set of statistical methods that can handle:
  - ▶ Data skewness
  - ▶ Censoring
  - ▶ (Time-dependent) Covariates
  - ▶ State transition processes
  - ▶ Recurrent events
  - ▶ The expectation of cure
- ▶ Used for both inference and extrapolation

## Key Concepts in survival analysis

- ▶ survival to time  $T$ : the random variable capturing time since the beginning of the event.
- ▶ Survival: the probability of not experiencing an event unit some time  $t$   $S(t) = Pr(T > t) = 1 - Pr(T \leq t)$
- ▶ Cumulative density function:

$$F(t) = Pr(T \leq t)$$

$$F(t) = 1 - S(t)$$

- ▶ Hazard function (the instantaneous rate of the event):

$$h(t) = \lim_{\delta t \rightarrow 0} \frac{1}{\delta t} \frac{F(t+\delta t) - F(t)}{S(t)}$$

turns out  $h(t) = \frac{f(t)}{S(t)}$

- ▶ Cumulative hazard  $H(t) \int_0^t h(x) dx$

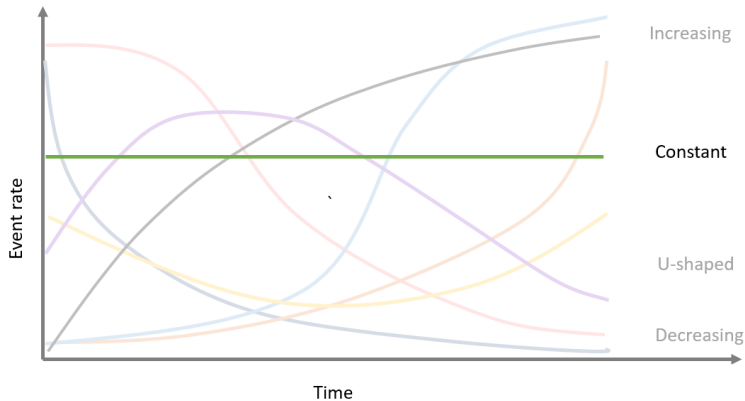
as well as  $S(t) = e^{-H(t)}$



## Example: the exponential distribution

- ▶  $H(t) = \lambda t$
- ▶  $S(t) = \exp(-\lambda t)$
- ▶  $f(t) = \lambda \exp(-\lambda t)$
- ▶ Weibull , gamma, lognormal etc. . .

# Some shapes of hazards



## common distributions and hazard shapes

- ▶ Exponential: constant hazard
- ▶ Weibull: hazard monotonically increases/decreases
- ▶ Gompertz: hazard monotonically increases/decreases, but the rate of change is exponential
- ▶ Log-logistic, log normal: hazard monotonically increases, and can then decrease

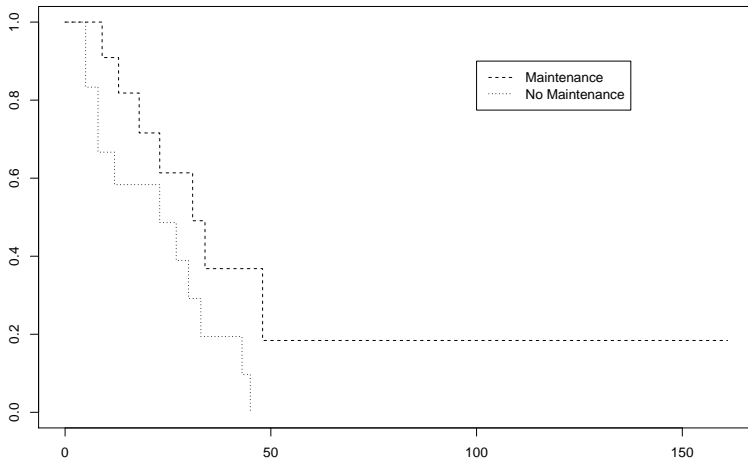
# Types of survival analysis models

- ▶ Non-parametric models (e.g. Kaplan Meier)
- ▶ Semi-Parametric models (e.g. Cox Proportional Hazard)
- ▶ Parametric models (e.g. Accelerated Failure Time)

# Non-Parametric models

- ▶ known as the “product-limit” estimator. The most used survival analysis method
- ▶ makes no parametric assumption on the data

**Kaplan–Meier Curves for AML Maintenance Study**



## Non-Parametric models

```
Call: survfit(formula = Surv(time, status) ~ x, data = aml)
```

x=Maintained

time	n.risk	n.event	survival	std.err	lower	95% CI	upper	95% CI
9	11	1	0.909	0.0867		0.7541		1.000
13	10	1	0.818	0.1163		0.6192		1.000
18	8	1	0.716	0.1397		0.4884		1.000
23	7	1	0.614	0.1526		0.3769		0.999
31	5	1	0.491	0.1642		0.2549		0.946
34	4	1	0.368	0.1627		0.1549		0.875
48	2	1	0.184	0.1535		0.0359		0.944

x=Nonmaintained

time	n.risk	n.event	survival	std.err	lower	95% CI	upper	95% CI
5	12	2	0.8333	0.1076		0.6470		1.000
8	10	2	0.6667	0.1361		0.4468		0.995
12	8	1	0.5833	0.1423		0.3616		0.941
23	6	1	0.4861	0.1481		0.2675		0.883
27	5	1	0.3889	0.1470		0.1854		0.816
30	4	1	0.2917	0.1387		0.1148		0.741
33	3	1	0.1944	0.1219		0.0569		0.664
43	2	1	0.0972	0.0919		0.0153		0.620
45	1	1	0.0000	NaN		NA		NA

## Non-Parametric models - testing

- ▶ We can use a non parametric test to understand if group A lives longer than group B
- ▶ long-rank test: is the difference in survival times statistically different?
- ▶ relying on a  $\chi^2$  distribution

Call:

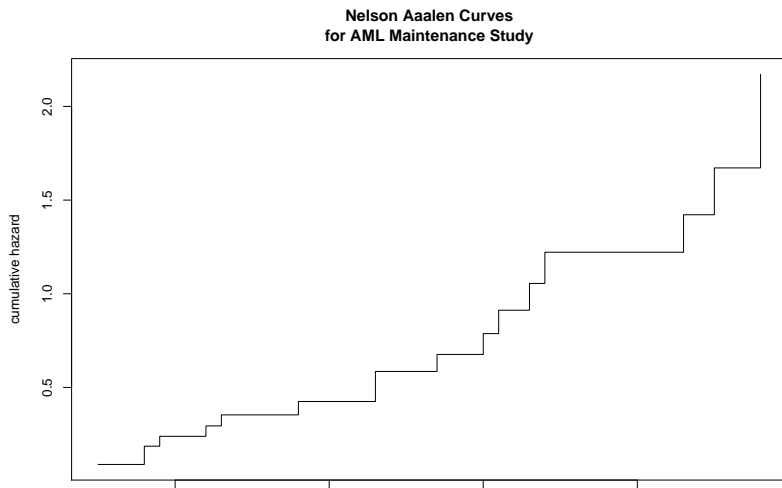
```
survdif(formula = Surv(time, status) ~ x, data = aml)
```

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
x=Maintained	11	7	10.69	1.27	3.4
x=Nonmaintained	12	11	7.31	1.86	3.4

Chisq= 3.4 on 1 degrees of freedom, p= 0.07

## Non-Parametric models

- ▶ Often, more intuitive to look at the results on the cumulative hazard rate
- ▶ Nelson Aalen cumulative hazard is the most common non parametric estimator





# Semi- Parametric models

- ▶ Cox proportional hazard model
  - ▶ Hazard: the instantaneous risk of an event at time  $t$ , conditional on survival to that time.
- ▶ Semi:
  - ▶ Baseline hazard modelled non parametrically (i.e effect of time)
  - ▶ Covariate effects (  $\beta$  's) modelled parametrically (like in a regression model)

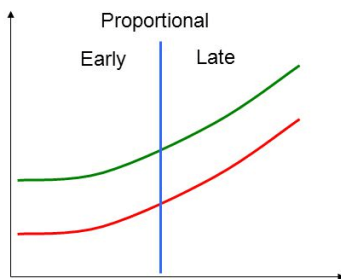
$h(t) = h_0(t)\exp(X\beta)$  where  $h_0(t)$  is estimated non-parametrically

Notice that the effect of the covariates is proportional on the baseline hazard..(that's why “proportional hazard” model)

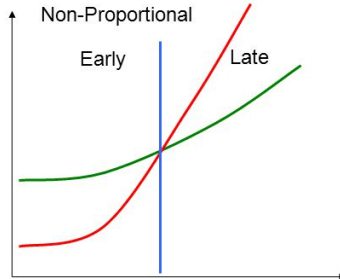
## The assumption of proportional hazards

# Proportional Hazard Assumption

- In a piecewise model, coefficients would differ in non-proportional models



Here, the effect is the same in both time periods

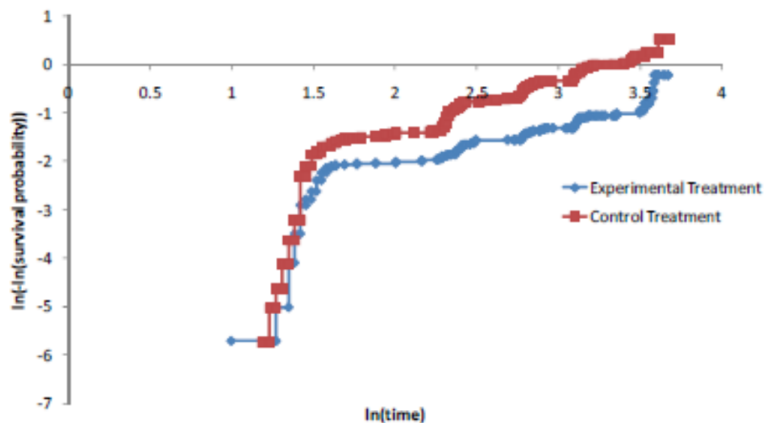


Here, the effect is negative in the early period and positive in the late period

# Assessing the proportionality assumption

The assumption can be assessed number of ways : visually

Figure 2: Log-cumulative hazard plot



<http://nicesdu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf>

Testing the non-zero slope of the Schoenfeld residuals

# Fully Parametric models (Accelerated Failure Time models)

- ▶ Usually model time-to-event directly rather than hazard
- ▶ Resemble a regression model but can capture censoring
- ▶ Fit a distribution to the (observed) time-to-event data
  - ▶ 1 parameter : exponential
  - ▶ 2 parameter : Weibull, lognormal, gamma etc
  - ▶ 3, 4 parameter: Gen. gamma , Gen F etc
- ▶ Assumption that censored patients will follow similar patterns to the observed.
- ▶ Temporal extrapolation possible !

## AFT and covariates

- ▶ We can incorporate covariates in a sort of similar way as we would do in a linear regression model  $\log(T) = \beta_0 + X\beta_1 + \epsilon$

$T$	$\log(T)$
Exponential	Extreme value
Weibull	Extreme value
Log-logistic	Logistic
Lognormal	Normal

# Choosing the “right” distribution

- ▶ Statistical considerations of goodness-of-fit
- ▶ Clinical plausibility
  - ▶ in-sample
  - ▶ extrapolations
  - ▶ out-of-sample

## Goodness of fit metrics

- ▶ Likelihood based metrics
- ▶ Akaike Information Criterion (AIC)
- ▶ Bayesian Information Criterion (BIC)
- ▶ Performance based metrics
- ▶ Sensitivity , Specificity
- ▶ (time dependent) Receiver Operating characteristic (ROC) curve
- ▶ Area Under the Curve (AUC)
- ▶ c- statistic

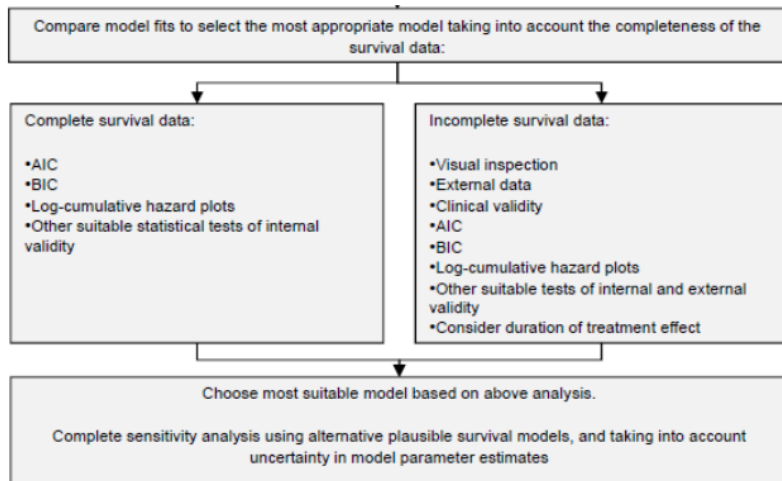
# Choosing the “right” distribution

- ▶ NICE Decision Support Unit
- ▶ Latimer et al 2011 : Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data
  - ▶ **Survival Model Selection Process algorithm:**
    - ▶ *recommendations for how survival analysis can be undertaken more systematically. This involves fitting and testing a range of survival models and comparing these based upon internal validity (how well they fit to the observed trial data) and external validity (how plausible their extrapolated portions are)*



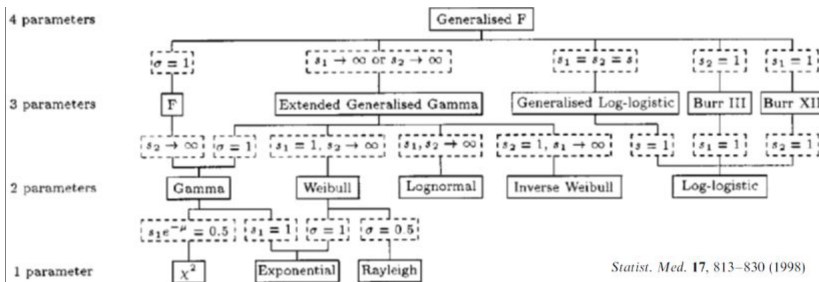
# Choosing the “right” distribution

Latimer et al 2011 (DSU 14)



# Flexible Survival models

- ▶ Multi - parameter distributions
  - ▶ Generalized Gamma
  - ▶ Generalized F
  - ▶ Data hungry - possibility of overfitting
  - ▶ Hypothesis testing possible

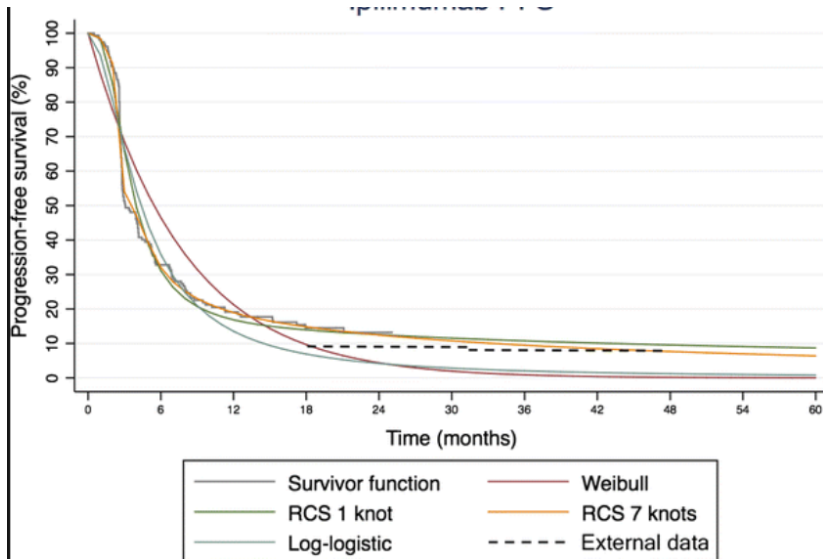


# Spline Survival models

- ▶ Survival models where the underlying hazard of an event is modelled as a smooth, piecewise polynomial function of time.
- ▶ Extrapolation of hazard possible
- ▶ Non-linear relation of time and hazard
- ▶ Conventionally *knots* are evenly spread on the (log)-time axis
- ▶ Overfitting with too many knots possible -sensitivity analysis
- ▶ AIC, BIC valid GoF tests
- ▶ TSD 2020

# Spline Survival models

Gibson et al (Pharmacoeconomics, 2017)



# Spline Survival models

From Gibson et al (Pharmacoeconomics, 2017)

*Spline-based models using a limited number of knots can provide an acceptable fit to trial data and generate extrapolated estimates supported by longer term evidence, with results that are stable in response to changes in knot placement.*

## Approaches in extrapolation

Modeler faced with more decisions: - Extrapolate using KM and “fitted” tails - Extrapolate using the fitted curve

- ▶ Fit separate curves to the data
- ▶ Extrapolate treatment effect as relative
- ▶ What is the behaviour of the relative effect post trial?
- ▶ Regardless of the approach, the implied (observed or predicted) treatment effect should be presented

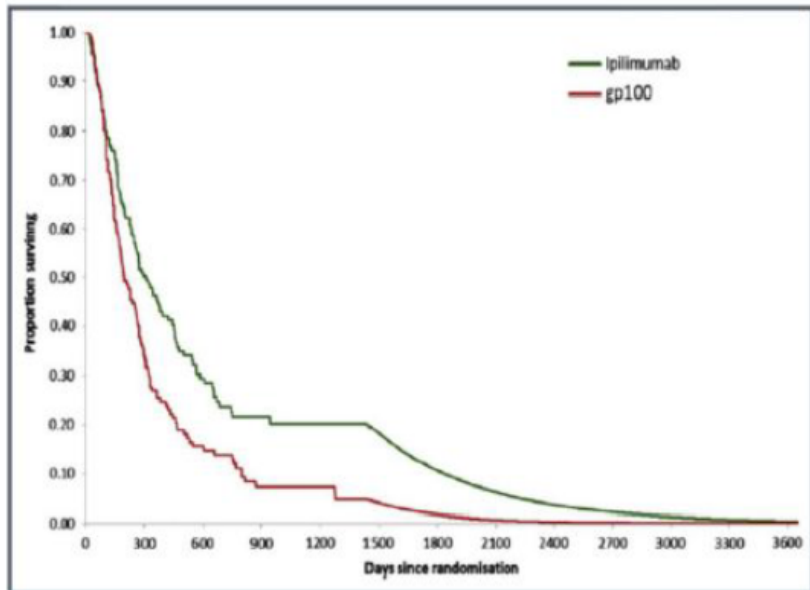


# The Ends Justify the Mean: Outcome Measures for Estimating the Value of New Cancer Therapies

Andrew Davies, MSc<sup>a</sup>, Andrew Briggs, DPhil<sup>b</sup>, John Schneider, PhD<sup>b</sup>, Adrian Levy, PhD<sup>c</sup>, Omar Ebeid, MPH<sup>b</sup>, Samuel Wagner, PhD<sup>d</sup>, Srividya Kotapati, PharmD<sup>d</sup>, Scott Ramsey, MD, PhD<sup>e</sup>

## Approaches in extrapolation

- ▶ Extrapolate using KM and “fitted” tails





► Extrapolate using the fitted curve

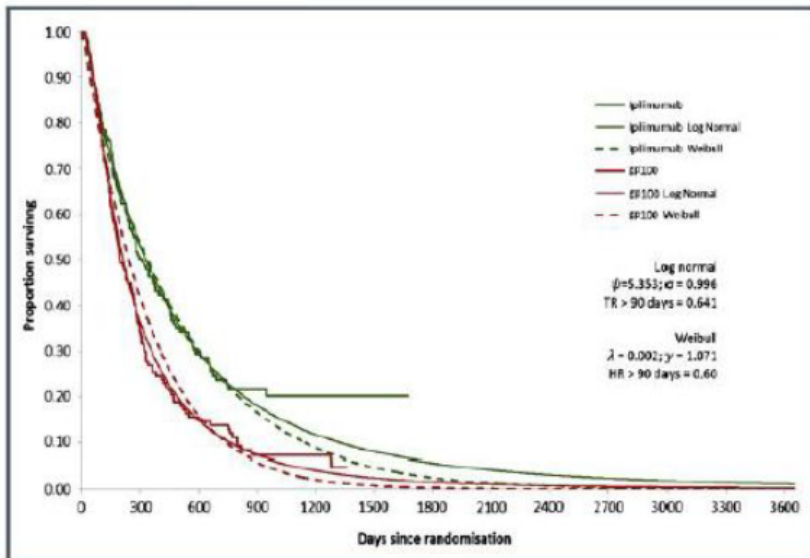


FIGURE 7: Case study showing empiric Kaplan-Meier curves and log-normal survivor functions.

# Extrapolating a relative treatment effect

Drummond, et al (2015). Methods for the economic evaluation of health care programmes. Oxford university press.

