

# STAT 6390: Analysis of Survival Data

Textbook coverage: Chapter 2

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# Survival, hazard and cumulative hazard functions

- Define  $T$  as the random variable of the actual (uncensored, untruncated) survival time of an individual.
- We assume the support of  $T$  is non-negative or  $(0, \infty)$ .
- We call  $T$  the *random variable* associated with the survival time, and we define  $T$  has a cumulative distribution function given by  $F(t) = P(T \leq t)$ .
- The survival function of  $T$  is then defined as

$$S(t) = 1 - P(T \leq t) = 1 - F(t).$$

- Why are we more interested in  $S(t)$ ?

# Survival, hazard and cumulative hazard functions

- The *hazard function* is widely used to survival analysis.
- The hazard function  $h(t)$  is defined below

$$h(t) = \lim_{dt \rightarrow 0} \frac{P(t \leq T < t + dt | T \geq t)}{dt}. \quad (1)$$

- $P(t \leq T < t + dt | T \geq t)$  is a conditional probability.
- The conditional probability is then expressed as a probability per unit time by dividing by the time interval,  $dt$ , to give a *rate*.
- The function  $h(t)$  is also referred to as the *hazard rate*, the *instantaneous death rate*, the *intensity rate*, or the *force of mortality*.
- Event rate at time  $t$ , conditional on the event not having occurred before  $t$ .

# Survival, hazard and cumulative hazard functions

- In terms of probability, if  $t$  is measured in days,  $h(t)$  is the approximate probability that an individual, who is *at risk of the event* occurring at the start of day  $t$ , experiences the event during that day.
  - In this case  $dt = 1$ .
  - $\lim_{dt \rightarrow 0}$  can be thought of as changing the unit from days to hours, minutes, seconds, milliseconds...
- If the event of interest is not death,  $h(t)$  can also be regarded as the *expected number of events* experienced by an individual in unit time, given that the event has not occurred before then.
  - Think of  $E\{I(\cdot)\} = P(\cdot)$ .
  - The part “given that the event...” might be ignored if events follow the Poisson process.

# Survival, hazard and cumulative hazard functions

- The definition in (1) leads to some useful relationships between survival and hazard functions:

$$(1) = \lim_{dt \rightarrow 0} \frac{P(t \leq T < t + dt)}{dt \cdot P(T \geq t)} = \lim_{dt \rightarrow 0} \frac{F(t + dt) - F(t)}{dt} \cdot \frac{1}{P(T \geq t)} = \frac{dF(t)}{dt} \cdot \frac{1}{S(t)}.$$

- $h(t)$  is approximately the probability that an individual experiences an event at this instant ( $t$ ) given that he/she is risk free up to  $t$ .
- If  $T$  is a continuous random variable, then we have

$$h(t) = \frac{f(t)}{S(t)}. \quad (2)$$

- This shows that from any one of the three functions,  $f(t)$ ,  $S(t)$ , and  $h(t)$ , the other two can be determined.

# Survival, hazard and cumulative hazard functions

- Equation (2) also implies

$$h(t) = -\frac{d}{dt} \{\log S(t)\} \text{ and } S(t) = e^{-H(t)},$$

where  $H(t) = \int_0^t h(u) du$  is the *cumulative hazard function*.

- Similarly, the cumulative hazard function can also be obtained from

$$H(t) = -\log S(t).$$

- The cumulative hazard function is the cumulative risk of an event occurring by time  $t$ .
- If the event is death, then  $H(t)$  summarizes the risk of death up to time  $t$ , given that death has not occurred by  $t$ .
- If the event is not death,  $H(t)$  can be interpreted as the expected number of events that occur in the interval  $(0, t)$ .

# Survival, hazard and cumulative hazard functions

- It is possible for  $H(t) > 1$ ,  $h(t) > 1$ , or  $f(t) > 1$ .
- $F(t)$ ,  $S(t)$  are bounded in  $[0, 1]$ .
- $F(t)$  and  $H(t)$  are non-decreasing;  $S(t)$  is non-increasing.
- $h(t)$  can go up and down.
- For example, suppose  $T \sim \exp(\lambda)$ , where  $\lambda$  is the rate. Then
  - $S(t) = e^{-\lambda t}$ .
  - $h(t) = \lambda$ .
  - $H(t) = \lambda t$ .

# Empirical survival function

- The  $S(t)$  can be estimated non-parametrically with the *product limit* estimator, which is also known as the *Kaplan-Meier* estimator.
- We first assume none of survival times are censored.
- In this case, the survival probability at  $t$ ,  $S(t)$ , is defined as

$$\hat{S}_e(t) = \frac{\# \text{ individuals with survival times } \geq t}{\# \text{ individuals in the data set}}. \quad (3)$$

- Equation (3) is called *empirical survival function*.
- Similarly,  $\hat{F}_e(t) = 1 - \hat{S}_e(t)$  is called the *empirical cumulative distribution function*.



# Empirical survival function

- We illustrate with the first 10 uncensored subjects in the `whas100` data.
- Make sure **tidyverse** package and `whas100` are properly loaded\*.

```
> whas10 <- whas100 %>% filter(fstat > 0) %>% filter(row_number() <= 10)
> whas10
# A tibble: 10 x 9
```

	id	admitdate	foldate	los	lenfol	fstat	age	gender	bmi
	<int>	<fct>	<fct>	<int>	<int>	<int>	<int>	<int>	<dbl>
1	1	3/13/1995	3/19/1995	4	6	1	65	0	31.4
2	2	1/14/1995	1/23/1996	5	374	1	88	1	22.7
3	3	2/17/1995	10/4/2001	5	2421	1	77	0	27.9
4	4	4/7/1995	7/14/1995	9	98	1	81	1	21.5
5	5	2/9/1995	5/29/1998	4	1205	1	78	0	30.7
6	6	1/16/1995	9/11/2000	7	2065	1	82	1	26.5
7	7	1/17/1995	10/15/1997	3	1002	1	66	1	35.7
8	8	11/15/1994	11/24/2000	56	2201	1	81	1	28.3
9	9	8/18/1995	2/23/1996	5	189	1	76	0	27.1
10	12	5/26/1995	9/29/1996	11	492	1	83	0	24.7

\* see note 1 for details.

# Empirical survival function

- The empirical estimates can be easily computed with `ecdf`.

```
> whas10 <- whas10 %>% mutate(surv = 1 - ecdf(lenfol)(lenfol))
> whas10
```

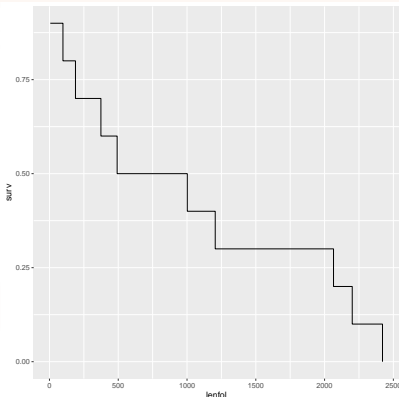
# A tibble: 10 x 10

	id	admitdate	foldate	los	lenfol	fstat	age	gender	bmi	surv
	<int>	<fct>	<fct>	<int>	<int>	<int>	<int>	<int>	<dbl>	<dbl>
1	1	3/13/1995	3/19/1995	4	6	1	65	0	31.4	0.9
2	2	1/14/1995	1/23/1996	5	374	1	88	1	22.7	0.6
3	3	2/17/1995	10/4/2001	5	2421	1	77	0	27.9	0
4	4	4/7/1995	7/14/1995	9	98	1	81	1	21.5	0.8
5	5	2/9/1995	5/29/1998	4	1205	1	78	0	30.7	0.3
6	6	1/16/1995	9/11/2000	7	2065	1	82	1	26.5	0.200
7	7	1/17/1995	10/15/1997	3	1002	1	66	1	35.7	0.4
8	8	11/15/1994	11/24/2000	56	2201	1	81	1	28.3	0.100
9	9	8/18/1995	2/23/1996	5	189	1	76	0	27.1	0.7
10	12	5/26/1995	9/29/1996	11	492	1	83	0	24.7	0.5

# Empirical survival function

- The empirical survival function is a non-increasing step function.

```
> whas10 %>% ggplot(aes(lenfol, surv)) + geom_step(size = 1.2)
```

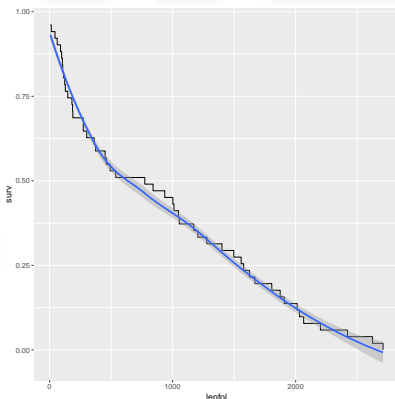


- The  $\hat{S}_e(t)$  is 1 at  $t = 0$  and 0 at the final death time.
- The  $\hat{S}_e(t)$  is assumed to be constant between adjacent death times.

# Empirical survival function

- Putting everything together, we could plot the empirical survival curve for all the uncensored subjects in `whas100`:

```
> whas100 %>% filter(fstat > 0) %>% mutate(surv = 1 - ecdf(lenfol)(lenfol)) %>%
+   ggplot(aes(lenfol, surv)) + geom_step() + geom_smooth()
```



- The pipeline between `ggplot` is “+” instead of “%>%”.

# Kaplan-Meier estimator

- With censoring, the same idea can be applied with proper adjustment.
- Kaplan-Meier estimator is the default estimator used by many packages.
- The basic idea is to decompose  $P(T > t)$  by conditioning on prior times.
- Suppose a sample size of  $n$ ,  $P(T > t)$  can be decomposed as

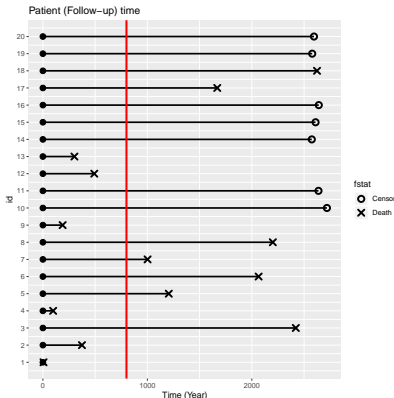
$$\hat{S}_{KM}(t) \doteq P(T > t) = P(T > t_{(0)}) \cdot P(T > t_{(1)} | T > t_{(0)}) \cdot P(T > t_{(2)} | T > t_{(1)}) \cdot \dots \cdot P(T > t | T > t_{(i)}),$$

for a series of time intervals  $0 \doteq t_{(0)} < t_{(1)} < \dots < t_{(i)} < t$  for some  $i \leq n$ .

- In general, the series  $\{t_{(1)}, \dots, t_{(m)}\}$  denotes the  $m$  ordered death times.

# Kaplan-Meier estimator

Suppose we want  $P(T > 800)$  among the first 20 patients in `whas1000`.



- There are 6 events before  $t = 800$ .
- The events occurred at

$t_{(0)}$	$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$
0	6	98	189	302	374	492

$$\begin{aligned}
 \hat{S}_{KM}(800) &= P(T > 800) = \\
 &= P(T > 0) \times P(T > 6 | T > 0) \times P(T > 98 | T > 6) \times \dots \times P(T > 492 | T > 374) \\
 &= 1 \times \frac{19}{20} \times \frac{18}{19} \times \frac{17}{18} \times \frac{16}{17} \times \frac{15}{16} \times \frac{14}{15} = \frac{14}{20} = 70\%
 \end{aligned}$$

$$\hat{S}_{KM}(800) = \hat{S}_e(800) \text{ here, why?}$$

# Kaplan-Meier estimator

- The Kaplan-Meier estimator can be obtained with the `survfit` function.

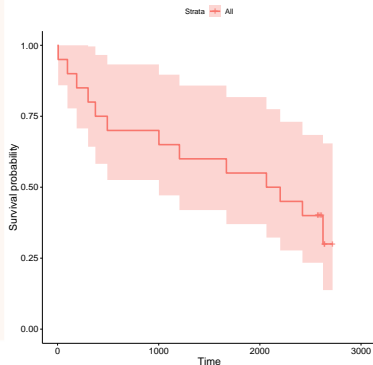
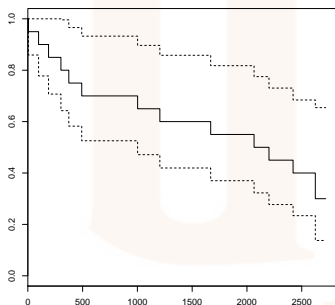
```
> library(survival)
> km <- survfit(Surv(lenfol, fstat) ~ 1, data = whas100, subset = id <= 20)
> summary(km)
Call: survfit(formula = Surv(lenfol, fstat) ~ 1, data = whas100, subset = id <=
20)
```

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
6	20	1	0.95	0.0487	0.859	1.000
98	19	1	0.90	0.0671	0.778	1.000
189	18	1	0.85	0.0798	0.707	1.000
302	17	1	0.80	0.0894	0.643	0.996
374	16	1	0.75	0.0968	0.582	0.966
492	15	1	0.70	0.1025	0.525	0.933
1002	14	1	0.65	0.1067	0.471	0.897
1205	13	1	0.60	0.1095	0.420	0.858
1669	12	1	0.55	0.1112	0.370	0.818
2065	11	1	0.50	0.1118	0.323	0.775
2201	10	1	0.45	0.1112	0.277	0.731
2421	9	1	0.40	0.1095	0.234	0.684
2624	4	1	0.30	0.1194	0.138	0.654

# Kaplan-Meier estimator

- The Kaplan-Meier curve can be plotted with `plot` or `ggsurvplot`.

```
> library(survminer)
> plot(km)
> ggsurvplot(km)
```

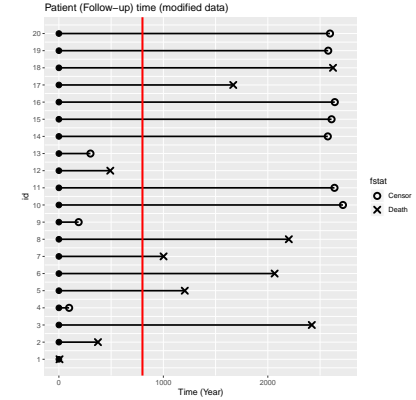


- Since **survminer** depends on the newest version of **survMisc**, you might need to update the latter to be able to use `ggsurvplot`.



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- There are 3 events before
- The events occurred at
 

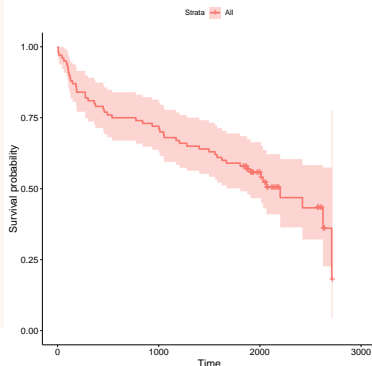
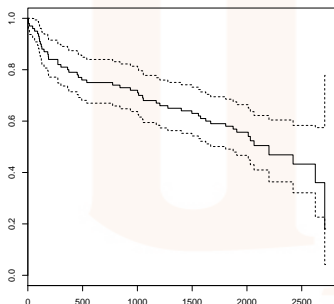
$t_{(0)}$	$t_{(1)}$	$t_{(2)}$	$t_{(3)}$
0	6	374	492
- In this modified data,  $t =$  are considered as censored

$$\begin{aligned}\hat{S}_{KM}(800) &= P(T > 800) = \\ &= P(T > 0) \times P(T > 6 | T > 0) \times P(T > 374 | T > 6) \times P(T > 492 | T > 374) \\ &= 1 \times \frac{19}{20} \times \frac{15}{16} \times \frac{14}{15} \approx 83.1\%\end{aligned}$$

# Kaplan-Meier estimator

- The Kaplan-Meier estimator for the whole data is

```
> library(survival)
> km <- survfit(Surv(lenfol, fstat) ~ 1, data = whas100)
> plot(km)
> ggsurvplot(km)
```



- If the last observed time corresponds to a censored observation, then the estimate of the survival function does not go to zero.

# Kaplan-Meier estimator

- Suppose we have a sample of  $n$  independent observations  $(t_i, c_i), i = 1, 2, \dots, n$ .
- Suppose there are  $m$  deaths and  $m \leq n$ .
- The series  $\{t_{(1)}, \dots, t_{(m)}\}$  are the  $m$  ordered death times.
- The Kaplan-Meier estimator has the form

$$\hat{S}_{KM}(t) = \prod_{t_{(i)} \leq t} \frac{n_i - d_i}{n_i} = \prod_{t_{(i)} \leq t} 1 - \frac{d_i}{n_i},$$

where  $n_i$  is the number of individual who are alive at  $t_{(i)}$  (at risk), and  $d_i$  is the number of individual who died at  $t_{(i)}$ .

- A potential problem with the Kaplan-Meier estimator is when  $n_i$  is small and  $n_i = d_i$  occurs at early time.

# Nelson-Aalen estimator

- An alternative estimate of  $\hat{S}_{KM}(t)$  is the *Nelson-Aalen estimator*:

$$\hat{S}_{NA}(t) = \prod_{t_{(i)} \leq t} \exp\left(-\frac{d_i}{n_i}\right).$$

- The main idea is to see  $d_i/n_i$  as the event rate, i.e.,  $h(t_{(i)}) = d_i/n_i$ .
- Recall the relationship  $h(t) = f(t)/S(t)$  and think of  $d_i/n$  and  $n_i/n$  are raw estimates of  $f(t)$  and  $S(t)$ .
- By the similar argument, we have

$$\hat{H}_{NA}(t) \doteq H(t) = \sum_{t_{(i)} \leq t} d_i/n_i, \text{ and } S(t) = e^{-\hat{H}_{NA}(t)} = \hat{S}_{NA}(t).$$

- $\hat{S}_{NA}(t)$  and  $\hat{S}_{KM}(t)$  are derived differently, but both based on  $d_i$  and  $n_i$ .
- In general  $\hat{S}_{NA}(t) \geq \hat{S}_{KM}(t)$  but  $\hat{S}_{NA}(t) \approx \hat{S}_{KM}(t)$ .

# Nelson-Aalen estimator

- $\hat{S}_{NA}(t)$  has slightly nicer properties and is more stable.
- If the interest is in estimating the cumulative hazard function,  $H(t)$ , we can use either the  $\hat{H}_{NA}(t)$ , or  $\hat{H}_{KM}(t) = -\log \hat{S}_{KM}(t)$ .
- The  $\hat{H}_{KM}(t)$  follows directly from  $\hat{S}_{KM}(t)$ :

$$\hat{H}_{KM}(t) = - \sum_{t_{(i)} \leq t} \log \left( \frac{n_i - d_i}{n_i} \right).$$

- Problems with this estimator?

# Nelson-Aalen estimator

- $\hat{S}_{NA}(t)$  can be obtained with `coxph` of the **survival** package.

```
> args(coxph)
function (formula, data, weights, subset, na.action, init, control,
  ties = c("efron", "breslow", "exact"), singular.ok = TRUE,
  robust = FALSE, model = FALSE, x = FALSE, y = TRUE, tt, method = ties,
  ...)
NULL
```

- `coxph` refers to “Cox proportional hazard model” that has the form

$$h(t) = h_0(t)e^{X^T\beta}, \quad (4)$$

where  $X$  is the covariate matrix,  $\beta$  is the regression coefficient, and  $h_0(t)$  is called the **baseline hazard** function.

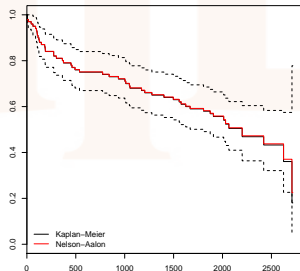
- More details will be given in Chapter 3.

# Nelson-Aalen estimator

- For now, we will assume  $\beta = 0$  in (4), which implies  $h(t) = h_0(t)$ .
- We will use  $h_0(t)$  to obtain  $\hat{S}_{NA}(t)$ .

```
> cox <- coxph(Surv(lenfol, fstat) ~ 1, data = whas100)
> H0 <- basehaz(cox)
> str(H0)
'data.frame': 95 obs. of  2 variables:
 $ hazard: num  0.0201 0.0303 0.0406 0.051 0.0616 ...
 $ time  : num   6 14 44 62 89 98 104 107 114 123 ...

> plot(km)
> lines(H0$time, exp(-H0$hazard), 's', col = 2)
```



# Life-table estimates

- When dataset is large, the  $\hat{S}_{KM}(t)$  and  $\hat{S}_{NA}(t)$  can be obtained with intervals of time, rather than exact time points.
  - The series  $\{t_{(1)}, \dots, t_{(m)}\}$  represents intervals.
  - $d_i$  represents the number of individual who died in  $t_{(i)}$ .
  - $n_i$  represents the number of individual who are alive in  $t_{(i)}$ .
- Potential problem with censoring?
- Adjustments under uniform assumption (p25).
- Better to adopt methods for data with interval censoring.



# Inference on $\hat{S}_{KM}(t)$

- The 95% confidence interval (CI) does not follow the usual form of

$$PE \pm 1.96 \times SE.$$

- This is mainly because  $\hat{S}_{KM}(t)$  needs to lie between 0 and 1.
- Two common methods to obtain the 95% CI for  $\hat{S}_{KM}(t)$  are the log and log-log transformations.
- The idea is to derive the standard errors on the transformed scale first, then back-transform these back.

# The Delta Method

- We need the Delta method to estimate the standard errors.
- The Delta method states that

$$\text{Var}\{g(X)\} \approx \text{Var}(X) \cdot \{g'(x_0)\}^2,$$

where  $g'(x_0)$  is the 1st derivative of  $g(\cdot)$  evaluates at constant  $x_0$ .

# The Delta Method

- A special case of the Delta method is when  $g(\cdot) = \log(\cdot)$ .
- Setting  $g(\cdot) = \log(\cdot)$ , we have

$$\text{Var}\{f(X)\} \approx \frac{\text{Var}(X)}{x_0^2}.$$

# Inference on $\hat{S}_{KM}(t)$

- We will first look at the log transformation.
- Recall

$$\hat{S}_{KM}(t) = \prod_{t_{(i)} \leq t} \frac{n_i - d_i}{n_i}.$$

- The variance of log-transformed  $\hat{S}_{KM}(t)$  gives

$$\text{Var} \left\{ \log \hat{S}_{KM}(t) \right\} = \text{Var} \left\{ \sum_{t_{(i)} \leq t} \log \left( \frac{n_i - d_i}{n_i} \right) \right\} = \sum_{t_{(i)} \leq t} \text{Var} \left\{ \log \left( \frac{n_i - d_i}{n_i} \right) \right\}.$$

- We assume independence between observations in the risk sets.
- For convenience, let's write  $p_i = (n_i - d_i)/n_i$ , and  $\hat{p}_i$  when  $n_i$  and  $d_i$  are known.

# Inference on $\hat{S}_{KM}(t)$

- The key is to estimate  $\text{Var}\{\log(p_i)\}$  with the Delta method.
- For each  $t_{(i)}$ ,  $n_i$  is fixed but  $d_i$  is random.
- $n_i - d_i$  can be assumed to follow the binomial distribution with parameters  $n_i$  and  $1 - d_i/n_i$ . Then

$$\text{Var}(p_i) = \frac{\text{Var}(n_i - d_i)}{n_i^2} = \frac{\frac{d_i}{n_i} \cdot \left(1 - \frac{d_i}{n_i}\right)}{n_i}.$$

- With the Delta method, we have

$$\text{Var}\{\log(p_i)\} \approx \frac{\text{Var}(p_i)}{\hat{p}_i} = \frac{d_i}{n_i \cdot (n_i - d_i)}.$$

# Inference on $\hat{S}_{KM}(t)$

- From the above result, we have

$$\text{Var} \left\{ \log \hat{S}_{KM}(t) \right\} \approx \sum_{t_{(i)} \leq t} \frac{d_i}{n_i \cdot (n_i - d_i)}.$$

- By the Delta method (again),

$$\text{Var} \left\{ \log \hat{S}_{KM}(t) \right\} \approx \text{Var} \{ \hat{S}_{KM}(t) \} \cdot \frac{1}{\hat{S}_{KM}^2(t)}.$$

- Altogether, this gives

$$\text{Var} \{ \hat{S}_{KM}(t) \} \approx \hat{S}_{KM}^2(t) \cdot \sum_{t_{(i)} \leq t} \frac{d_i}{n_i \cdot (n_i - d_i)}.$$

- This result is known as the *Greenwood's formula*, or the log transformation.
- This estimator can be obtained from a counting process approach.

# Inference on $\hat{S}_{KM}(t)$

- The Greenwood formula is the default method for `survfit`.
- With the Greenwood formula, the  $100(1 - \alpha)\%$  confidence interval of  $\hat{S}_{KM}(t)$  can be obtained using the usual form of  $PE \pm Z_{\alpha/2} \times SE$ .
- The bounds can still be outside of  $[0, 1]$ .
- An alternative approach is to consider the log-log transformation.

# Inference on $\hat{S}_{KM}(t)$

- By the Delta method, we have

$$\text{Var} \left[ \log \left\{ -\log \hat{S}_{KM}(t) \right\} \right] \approx \frac{1}{\{-\log \hat{S}_{KM}(t)\}^2} \cdot \sum_{t_{(j)} \leq t} \frac{d_j}{n_j \cdot (n_j - d_j)}.$$

- This implies that the  $100(1 - \alpha)\%$  confidence interval can be constructed by inverting

$$\log \{-\log \hat{S}_{KM}(t)\} \pm Z_{\alpha/2} \times \text{SE} \left[ \log \{-\log \hat{S}_{KM}(t)\} \right]$$

- Since  $-\log$  of a survival function gives the cumulative hazard function, e.g.,  $-\log S(t) = H(t)$ , the log-log approach called the “log hazard” approach.



# Inference on $\hat{S}_{KM}(t)$

- Types of CI can be specified with `conf.type` in `survfit`.

```
> ?survfit.coxph
```

- Some options are available for `conf.type` depending on  $g(\cdot)$  used in the Delta method.

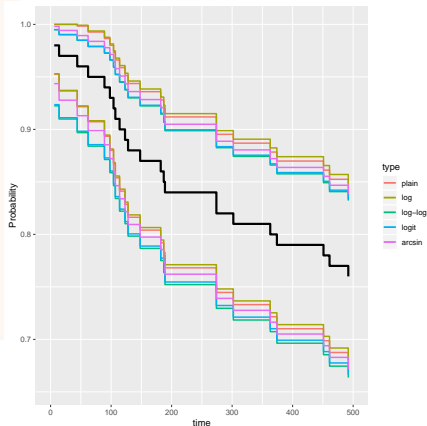
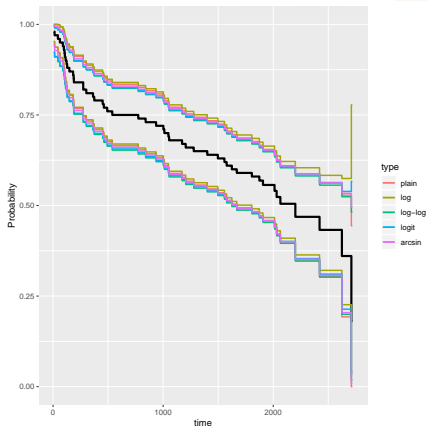
```
plain   $g(x) = x$ 
log      $g(x) = \log(x)$ 
log-log  $g(x) = \log\{-\log(x)\}$ 
logit    $g(x) = \log\left(\frac{x}{1-x}\right)$ 
arcsin   $g(x) = \arcsin \sqrt{x}$ 
```

- In addition, Peto et al. (1977) proposed to estimate  $\text{Var}\{\hat{S}_{KM}(t)\}$  from

$$\text{Var}\{\hat{S}_{KM}(t)\} = \frac{\hat{S}_{KM}(t) \cdot (1 - \hat{S}_{KM}(t))}{n_i}$$

# Inference on $\hat{S}_{KM}(t)$

- The following depict  $\hat{S}_{KM}(t)$  with the five `conf.type`'s for `whas100`.
- The CI's are quite close to each other.



# \*Inference on the median and percentiles

- Given a  $\hat{S}(t)$  ( $\hat{S}_{KM}(t)$  or  $\hat{S}_{NA}(t)$ ), the estimate of the  $p$ th percentile is

$$\hat{t}_p = \min\{t : \hat{S}(t) \leq (p/100)\}.$$

- The Delta method can be used again to obtain  $\text{Var}(\hat{t}_p)$ .
- Setting  $g(\cdot) = S(\cdot)$ , we have the relationship

$$\text{Var}\{\hat{S}(\hat{t}_p)\} \approx \text{Var}(\hat{t}_p) \cdot \{f(\hat{t}_p)\}^2,$$

where  $f(t) = d\hat{S}(t)/dt$ .

- The only unknown in the above equation is  $f(t)$ , which can be approximated by linear interpolation:

$$\hat{f}(\hat{t}_p) \approx \frac{\hat{S}(\hat{u}_p) - \hat{S}(\hat{l}_p)}{\hat{l}_p - \hat{u}_p},$$

where  $\hat{u}_p < \hat{t}_p < \hat{l}_p$ ,  $\hat{u}_p = \max\{t : \hat{S}(t) \geq p/100 + \epsilon\}$  and  $\hat{l}_p = \min\{t : \hat{S}(t) \leq p/100 - \epsilon\}$ , for some small constant  $\epsilon$ .

## \*Inference on the median and percentiles

- Replacing the unknown quantities with their empirical estimates, the  $100(1 - \alpha)\%$  CI can be obtained through  $\hat{t}_p \pm Z_{\alpha/2} \times \text{SE}(\hat{t}_p)$ .
- Clinicians are specifically interested in median survival (follow-up) time, because survival time data often tend to be skewed to the right.
- Other quantity of interest is the semi-interquartiles range (SIQR):

$$\text{SIQR} = \frac{t_{75} - t_{25}}{2}.$$

- Like the variance, the larger the SIQR, the more dispersed is the survival time distribution.

# \*Inference on the median and percentiles

- Median survival time is printed by `survfit`.

```
> survfit(Surv(lenfol, fstat) ~ 1, data = whas100)
Call: survfit(formula = Surv(lenfol, fstat) ~ 1, data = whas100)
```

n	events	median	0.95LCL	0.95UCL
100	51	2201	1806	NA

- Median follow-up time does not always exist.

```
> survfit(Surv(lenfol, fstat) ~ 1, data = whas100[81:100,])
Call: survfit(formula = Surv(lenfol, fstat) ~ 1, data = whas100[81:100,
])
```

n	events	median	0.95LCL	0.95UCL
20	9	NA	1577	NA

- A more practical approach?

# Counting processes

- As is seen from before, the focus in survival analysis is on observing the occurrence of events over time.
- Such occurrences constitute point (counting) process; counting number of events as they come along.
- There is a very neat collection of theories for counting processes.
- More in-depth details can be found in Fleming and Harrington (2011); Kalbfleisch and Prentice (2011).

# Counting processes

- Appendix 2 gives a short introduction of counting processes, in the case of right censoring.
- We start by focusing on a *single type* of event without censoring.
- For a given time  $t$ , let  $N(t)$  be the number of events over the time period  $(0, t]$ , then  $N(t)$  is a counting process.
- The counting process  $N(t)$  is *continuous from the right*, with jump size 1.

# Poisson process

- A well-known example of a counting process is the homogeneous Poisson process.
- Jumps occur randomly and independently of each other (independent increment property).
- A homogeneous Poisson process is described by its *intensity*  $\lambda$ .
- The  $\lambda$  is the probability of occurrence of an event in a small interval divided by the length of the interval.
- We will apply this idea to modeling counting process.



# Counting processes

- Suppose the intensity function that describes  $N(t)$  is  $\lambda(t)$ .
- Under our assumption that a subject can experience at most one event, consider a small time interval  $[t, t + dt)$ ,  $\lambda(t)$  is

$$\lambda(t)dt = P(dN(t) = 1 | \text{past}),$$

where  $dN(t)$  denotes the # of events in  $[t, t + dt)$ , or  $N(t + dt) - N(t)$ .

- Formally speaking, the “past” represents the *filtration* of the process up to but not including time  $t$ .

# Counting processes

- Under our assumption,  $dN(t)$  is binary, and

$$\lambda(t)dt = E\{I(dN(t) = 1)|past\} = E\{dN(t)|past\}.$$

- Then it follows

$$E(dN(t) - \lambda(t)dt|past) = 0. \quad (5)$$

- If we define a new process

$$M(t) = N(t) - \int_0^t \lambda(s)ds, \quad (6)$$

then we have  $E(dM(t)|past) = 0$ .

- It turns out  $M(t)$  is a zero-mean martingale.

# Counting processes

- Definition (6) can be written as

$$dN(t) = \lambda(t)dt + dM(t), \quad (7)$$

reflecting the relationship *observation = signal + noise*.

- Think of  $M(t)$  as the sum of random errors.
- Let

$$\Lambda(t) = \int_0^t \lambda(s)ds,$$

(5) and (6) implies  $\Lambda(t)$  is the cumulative expected # of events in  $(0, t]$ , or  $\Lambda(t) = E\{N(t)\}$ .

- $\Lambda(t)$  versus  $H(t)$ ?

# Counting processes

- Now we will look at the scenario when there is only *one event type* and a subject can experience *at most one event* (no ties in event times).
- In this case, the counting process  $N(t) = I(T \leq t)$ , where  $T$  is the survival time with hazard  $h(t)$ .
- The  $N(t)$  defined above has a jump size 1 at  $T$ .
- We then have

$$P(dN(t) = 1 | \text{past}) = \begin{cases} h(t)dt & \text{if } T \geq t \\ 0 & \text{if } T < t \end{cases} = h(t)I(T \geq t)dt.$$

- The relationship above implies the intensity process  $\lambda(t) = h(t) \cdot I(T \geq t)$ .

# Counting processes

- Building onto our assumption, now assume we have *n independent subjects*, each with  $T_i$ ,  $i = 1, \dots, n$ , and hazard  $h_i(t)$ .
- Suppose  $h_i(t) = h(t)$  for all  $i$ .
- From the last example, we have

$$N_i(t) = I(T_i \leq t) \text{ and } \lambda_i(t) = h_i(t)I(T_i \geq t).$$

- Define the *aggregated* process by adding together the individual processes:

$$N(t) = \sum_{i=1}^n N_i(t).$$

- This process counts the # of individuals who experienced the event by  $t$ .
- Is  $N(t)$  here a proper counting process?

# Counting processes

- Assuming continuous survival times, and the aggregated process jumps one unit at a time,

$$E(dN(t)|\text{past}) = \sum_{i=1}^n E(dN_i(t)|\text{past})$$

implies the aggregated intensity satisfies  $\lambda(t)dt = \sum_{i=1}^n \lambda_i(t)dt$  and

$$\lambda(t) = h(t)Y(t),$$

where  $Y(t) = \sum_{i=1}^n I(T_i \geq t)$  is the number of individuals at risk right before  $t$ , e.g.,  $Y(t) = n - N(t^-)$ .

- Plug  $\lambda(t)$  into Equation (7) gives the Nelson-Aalen estimator for  $H(t)$ .

# Derivation of $\hat{H}_{NA}(t)$

- Plug  $\lambda(t)$  into Equation (7), we have

$$dN(t) = h(t)Y(t)dt + dM(t)$$

- Intergrating both side after diving by  $Y(t)$  gives

$$\int_0^t \frac{1}{Y(t)} dN(t) - \int_0^t h(t)dt = \int_0^t \frac{1}{Y(t)} dM(t)$$

- The right-hand side is a stochastic integral with respect to a zero-mean martingale.
- The first term in the left-hand side gives  $\hat{H}_{NA}(t) = \sum_{t_{(i)} \leq t} \frac{1}{n_i}$ .
- Then  $E \left\{ \hat{H}_{NA}(t) - \hat{H}(t) \right\} = 0$  and  $\hat{H}_{NA}(t)$  is an unbiased estimator of  $\hat{H}(t)$ .
- The variance estimator can be derived using the *variation processes* or with transformation through the Delta methods.

# Counting processes

- Consider the same assumptions but allowing ties in event times.
- Two common approaches to deal with tied event times depend on how tied event times arise.
  - Two event times coincide due to rounding.

$$\hat{H}_{NA}(t) = \sum_{t_{(i)} \leq t} \sum_{k=1}^{d_i} \frac{1}{n_i - k}.$$

- Event times are genuinely discrete, so that tied event times are real and not due to rounding.

$$\hat{H}_{NA}(t) = \sum_{t_{(i)} \leq t} \frac{d_i}{n_i}.$$

- More discussion on large number properties with tied event times can be found in Anderson et al. (1993).



# Counting processes

- For nonparametric or semi-parametric methods, we do not need to have a distributional assumption on the censoring time,  $C$ .
- Rather, we will assume independent censoring:

$$P(t \leq T_i < t + dt, \Delta_i = 1 | T_i \geq t, \text{past}) = P(t \leq \tilde{T}_i < t + dt | \tilde{T}_i \geq t),$$

where  $T_i = \min(\tilde{T}_i, C_i)$  and  $\Delta_i = I(\tilde{T}_i < C_i)$ , for  $i = 1, \dots, n$ .

- In the presense of right censoring, the counting process is specified as

$$N_i(t) = I\{T_i \leq t, \Delta_i = 1\}, i = 1, \dots, n,$$

and  $\lambda_i(t)dt = P(dN_i(t) = 1 | \text{past})$ .

- Applying the independent censoring assumption, the intensity process for  $N_i(t)$  takes the form  $\lambda_i(t) = h_i(t) Y_i(t)$ , where  $Y_i(t) = I(T_i \geq t)$  is the at risk indicator for individual  $i$ .

# Counting processes

- As in the uncensored example, the *aggregated* process is

$$N(t) = \sum_{i=1}^n N_i(t) = \sum_{i=1}^n \mathbf{I}(T_i \leq t, \Delta_i = 1),$$

and the *aggregated* intensity process is

$$\lambda(t) = \sum_{i=1}^n \lambda_i(t) = \sum_{i=1}^n h_i(t) Y_i(t).$$

- In the case where  $h_i(t) = h(t)$  for all  $i$ , the intensity process takes the form  $\lambda(t) = h(t) Y(t)$ , where  $Y(t) = \sum_{i=1}^n Y_i(t)$ .
- The Nelson-Aalen estimator can be derived similarly.

# Counting processes

- Counting processes are non-decreasing.
- Martingales associated with  $M(t)$  are sub-martingales.
- Doob-Meyer decomposition guarantees the relationship

$$N(t) = h(t)Y(t) + M(t).$$

- Martingale central limit theorem.

# Comparison of survival functions

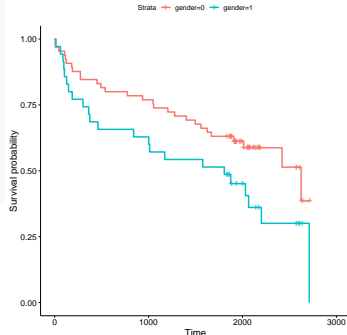
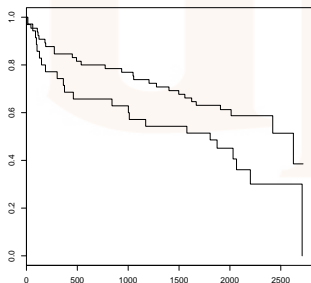
- The simplest way of comparing the survival functions is to plot them on the same axe.

```
> km <- survfit(Surv(lenfol, fstat) ~ gender, data = whas100)
> km
```

```
Call: survfit(formula = Surv(lenfol, fstat) ~ gender, data = whas100)
```

	n	events	median	0.95LCL	0.95UCL
gender=0	65	28	2624	2012	NA
gender=1	35	23	1806	841	NA

- ggsurvplot gives more informative output.



# Comparison of survival functions

- In the `whas100` study, the survival function for female patients (`gender = 0`) is always greater than that for male patients.
- Two explanations for the observed difference:
  - A real difference between the survival times of the two groups.
  - The difference has been observed is the result of chance variation.
- Procedures such as the *hypothesis test* is needed to distinguish the two possible explanations.

# Hypothesis testing

- As the hypothesis tests commonly encountered, the testing procedure here consists of the following major steps:
  - 1 State the *null hypothesis* and the *alternative hypothesis*.
  - 2 Formulate a *test statistic* that measures the extent to which the observed data depart from the null hypothesis.
  - 3 Calculate the *p*-value; the probability of obtaining a value as extreme or more extreme than the observed value, when the null hypothesis is true.

# Hypothesis testing

- $p$ -value can be interpreted as a measure of the strength of evidence against the null hypothesis.
- A  $p$ -value of 0.000 should be interpreted as  $p < 0.001$ .
- A one-sided hypothesis test is only appropriate when there is no interest in departures from the null hypothesis in the opposite direction.
- We will look at non-parametric procedures including the log-rank test and the Wilcoxon test.

# The log-rank test

- If we are willing to assume survival data follow a particular parametric distribution, we can construct a test based on likelihood theory.
- We will derive a nonparametric test using a rank-based procedure.
- Suppose the population survival curves are  $S_1(t)$  and  $S_0(t)$ .
- Ideally, we would like to test  $H_o : S_1(t) = S_0(t)$  versus  $H_a : S_1(t) > S_0(t)$ ,  $S_1(t) < S_0(t)$ , or  $S_1(t) \neq S_0(t)$ .
- Unfortunately, this is difficult because  $H_a$  can take a wide range of forms.
- Instead, it is more feasible to consider the *Lehman alternative*:

$$H_a : S_1(t) = [S_0(t)]^\theta, \text{ for } \theta > 0. \quad (8)$$



# The log-rank test

- The hypothesis in (8) can be view in terms of the hazard functions:

$$H_o : \lambda_1(t) = \lambda_0(t) \text{ versus } H_a : \lambda_1(t) = \theta \lambda_0(t).$$

- Either way, we could rewrite the hypothesis test as

$$H_o : \theta = 1 \text{ versus } H_a : \theta > 1, \text{ or } \theta < 1, \text{ or } \theta \neq 1.$$

- One can interpret the results solely based on  $\theta$  too.
- For example, under  $H_a : \theta > 1$ , then
  - $S_1(t)$  will be uniformly lower than  $S_0(t)$ .
  - $h_1(t)$  will be uniformly higher than  $h_0(t)$ .

# The log-rank test

- Following the notations defined previously, we assume
  - the two independent random samples are of size  $N_0$  and  $N_1$ .
  - $D$  is the total number of events in the combined sample (size  $N_0 + N_1$ ).
  - $\{t_{(1)}, \dots, t_{(D)}\}$  is the ordered event times.
  - Let  $d_{0i}$  and  $d_{1i}$  are the number of events in group 0 and 1, respectively.
  - Let  $n_{0i}$  and  $n_{1i}$  are the number of at risk in group 0 and 1, respectively.

# The log-rank test

- For the  $i$ th event time, we construct the following two-by-two table:

	Group 1	Group 0	Total
Failure	$d_{1i}$	$d_{0i}$	$d_i$
Non-failure	$n_{1i} - d_{1i}$	$n_{0i} - d_{0i}$	$n_i - d_i$
At risk	$n_{1i}$	$n_{0i}$	$n_i$

- Suppose the numbers of failures in two groups are independent, holding the margins fixed, then the distribution of  $d_{1i}$  (or  $d_{0i}$ ) follows a *hypergeometric distribution*.
- This gives

$$E(d_{1i}) = \frac{n_{1i} \cdot d_i}{n_i}, \text{ and } \text{Var}(d_{1i}) = \frac{n_{1i} \cdot n_{0i} \cdot d_i \cdot (n_i - d_i)}{n_i^2 \cdot (n_i - 1)}.$$

# The log-rank test

- Using the idea from the  $\chi^2$  tests, the test statistic has the form

$$Q = \frac{\left[ \sum_{i=1}^D \omega_i \{d_{1i} - E(d_{1i})\} \right]^2}{\sum_{i=1}^D \omega_i^2 \text{Var}(d_{1i})}, \quad (9)$$

where  $\omega_i$  is a possibly data-dependent weight.

- When there is no tied failure times,  $\text{Var}(d_{1i}) = \frac{n_{1i} \cdot n_{0i}}{n_i^2}$ .
- Under the null,  $Q$  follows the  $\chi^2$  distribution with one degree of freedom.
- The log-rank test sets  $\omega_i = 1$  (Peto and Peto, 1972).

# The log-rank test

- Different selections of  $\omega_i$  were studied.
- Most common expression has the form of

$$\omega_i = \left\{ \hat{S}(t_{(i)}) \right\}^{\rho}, \text{ for } \rho \in [0, 1],$$

where  $\hat{S}(t)$  is the survival estimator from the combined sample, ignoring group.

- This is called the Fleming-Harrington  $G(\rho)$  test (e.g. Cox and Oakes, 1984; Harrington and Fleming, 1982).
  - $\rho = 0$  gives the log-rank test
  - $\rho = 1$  gives the Wilcoxon test.
  - $\rho = 0.5$  gives the Tarone and Ware (1977) test.

# The log-rank test

- The  $G(\rho)$  test is implemented in `survdif` of the **survival** package

```
> args(survdif)
function (formula, data, subset, na.action, rho = 0)
NULL
> survdif(Surv(lenfol, fstat) ~ gender, data = whas100)
Call:
survdif(formula = Surv(lenfol, fstat) ~ gender, data = whas100)
```

	N	Observed	Expected	(O-E)^2/E	(O-E)^2/V
gender=0	65	28	34.6	1.27	3.97
gender=1	35	23	16.4	2.68	3.97

```
Chisq= 4 on 1 degrees of freedom, p= 0.05
```

- The log-rank test shows gender is marginally significant at  $\alpha = 0.05$ .

# The log-rank test

- Varying  $\rho$  shows similar results here.
- In general, when the tests give different results, then more than one result should be reported.
- It is important to also consult the plot to ascertain the directional effect of stratification or treatment.

# The log-rank test

- As in the Pearson's  $\chi^2$  test, a continuity correction could be considered when sample sizes are too small:

$$Q^* = \frac{\left[ \sum_{i=1}^D \omega_i \{ |d_{1i} - E(d_{1i})| - 0.5 \} \right]^2}{\sum_{i=1}^D \omega_i^2 \text{Var}(d_{1i})}.$$



# The log-rank test

- A problem can occur if the estimated survival (hazard) functions cross one another.
- This is similar to the proportional hazard assumption in the Cox models.
- In `whas100` data, the two survival curves (by gener) crossed one another at early  $t$ , despite being so different in large  $t$ .
- Fleming et al. (1987) proposed supremum versions of the log-rank tests, but have not been implemented in any software packages.

# The log-rank test

- The tests discussed here can be extended to comparison more than two survival functions simultaneously.
- $K$ -by- $K$  tables instead of two-by-two tables at each event time.
- When there are many groups to compare, it might be more convenient to consider regression models.

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