STAT 6390: Analysis of Survival Data

Textbook coverage: Chapter 2

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Survivor, hazard and cumulative hazard functions

- Suppose the actual (uncensored, untruncated) survival time of an individual is t and can be regarded as the observed value of a variable, T.
- 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 $F(t) = \mathrm{P}(T \leq t)$.
- The survival function of T is then defined as

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

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

Survivor, hazard and cumulative hazard functions

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

$$h(t) = \lim_{\delta \to 0} \frac{\mathrm{P}(t \leq T < t + \delta | T \geq t)}{\delta}. \tag{1}$$

- $\mathrm{P}(t \leq T < t + \delta | T \geq t)$ is a conditional probability.
- The conditional probability is then expressed as a probability per nit time by dividing by the time interval, δ, 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.

Survivor, 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 $\delta = 1$.
  - $\lim_{\delta \to 0}$ 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 $\mathrm{E}\{\mathrm{I}(\cdot)\} = \mathrm{P}(\cdot)$.
  - The part "given that the event..." might be ignored if events follow the Poisson process.

Survivor, hazard and cumulative hazard functions

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

$$(1) = \lim_{\delta \to 0} \frac{\mathrm{P}(t \leq T < t + \delta)}{\delta \cdot \mathrm{P}(T < t)} = \lim_{\delta \to 0} \frac{F(t+\delta) - F(t)}{\delta} \cdot \frac{1}{\mathrm{P}(T < t)} = \frac{\mathrm{d}F(t)}{\mathrm{d}t} \cdot \frac{1}{S(t)}.$$

- $h(t)$ 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

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

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

Survivor, hazard and cumulative hazard functions

- Equation (2) also implies

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

where $H(t) = \int_0^t h(u)\,\mathrm{d}u$ 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 $(0, t)$.

Survivor, hazard and cumulative hazard functions

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

Empirical survivor 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 there is a single sample of survival times, and none of these are censored.
- In this case, the survivor probability at t, $S(t)$, is defined as

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

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

Empirical survivor 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 survivor function

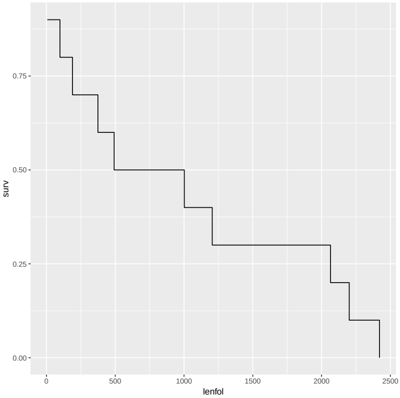
- The empirical estimates can be easily computed with `ecdf`.

```
> 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 survivor function

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

```
> whas20 %>% ggplot(aes(lenfol, surv)) + geom_step(size = 1.2)
```

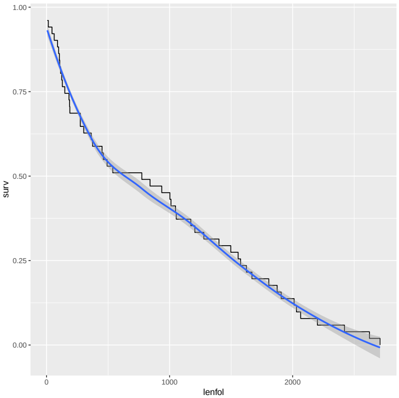


- The $\hat{S}_e(t)$ is 1 at $t = 0$ and 0 at the final death time.
- The $\hat{S}_e(t)$ is assumed to be constant between adjacent death times.

Empirical survivor 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 estiamtor

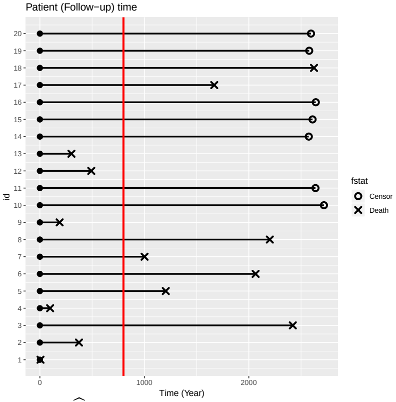
- With censoring, the same idea can be applied with proper adjustment.
- Kaplan-Meier estimator is the default estimator used by many packages.
- The basic idea is to decompose $\mathrm{P}(T > t)$ by conditioning on prior times.
- Suppose a sample size of n, $\mathrm{P}(T > t)$ can be decomposed as

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

  for a series of time intervals $0 \doteq t_{(0)} < t_{(1)} < \ldots < t_{(i)} < t$ for some $i \leq n$.
- In general, the series $\{t_{(1)}, \ldots, t_{(m)}\}$ denotes the m ordered death times.

Kaplan-Meier estiamtor

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



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

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

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

Why does $\widehat{S}_{KM}(800) = \hat{S}_e(800)$ here?

Kaplan-Meier estimator

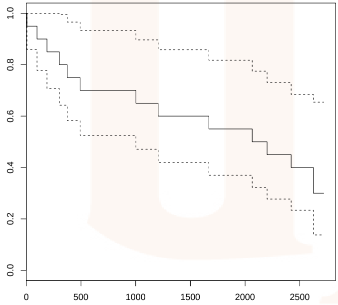
- The Kaplan-Meier estimator can be obtained with the `survfit` function.

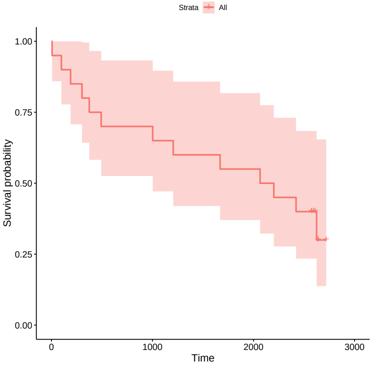
```
> library(survival)
> km <- survfit(Surv(lenfol, fstat) ~ 1, data = whas100, subset = id <= 20)
> summary(km)
Call: survfit(formula = Surv(lenfol, fstat) ~ 1, data = whas100, subset = id <=
    20)

 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)
```

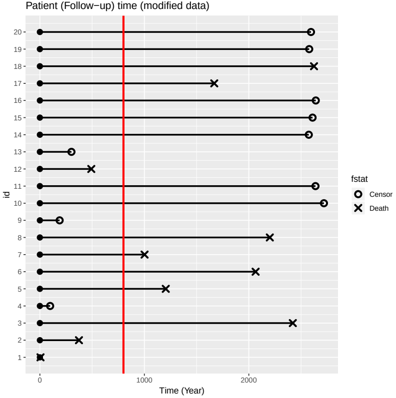




- Since **survminer** depends on the newest version of **survMisc**, you might need to update the latter to be able to use `ggsurvplot`.

Kaplan-Meier estimator

Suppose we want $\mathrm{P}(T > 800)$ based on the following modified data:



- There are 3 events before $t = 800$.
- The events occured at

$t_{(0)}$	$t_{(1)}$	$t_{(2)}$	$t_{(3)}$
0	6	374	492

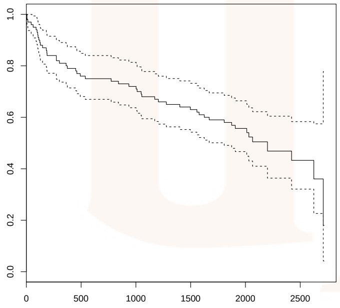
- In this modified data, $t = 98, 189, 302$ are considered as censored.

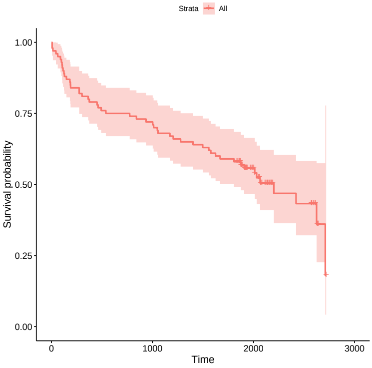
$$\widehat{S}_{KM}(800) = \mathrm{P}(T > 800) =$$
$$= \mathrm{P}(T > 0) \times \mathrm{P}(T > 6 | T > 0) \times \mathrm{P}(T > 374 | T > 6) \times \mathrm{P}(T > 492 | T > 374)$$
$$= 1 \times \frac{19}{20} \times \frac{15}{16} \times \frac{14}{15} \approx 83.1\%$$

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 $(t_i, c_i), i = 1, 2, \ldots, n$.
- There are m deaths and $m \leq n$.
- The series $\{t_{(1)}, \ldots, t_{(m)}\}$ are the m ordered death times.
- The Kaplan-Meier estimator has the form

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

  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-Aalon estimator

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

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

- 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 rough estimates of $f(t)$ and $S(t)$.
- By the similar argument, we have

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

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

Nelson-Aalon estimator

- $\widehat{S}_{NA}(t)$ 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 $\widehat{H}_{NA}(t)$, or $\widehat{H}_{KM} = -\log(\widehat{S}_{KM}(t))$.
- $\widehat{S}_{NA}(t)$ 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

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

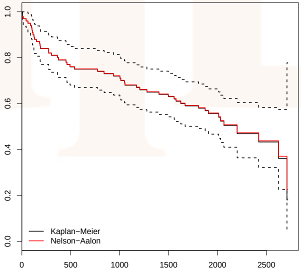
  where X is the covariate matrix, β is the regression coefficient, and $h_0(t)$ is called the *baseline hazard* function.
- More details will be given in Chapter 3.

Nelson-Aalon 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 $\widehat{S}_{NA}(t)$.

```
> 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 $\widehat{S}_{KM}(t)$ and $\widehat{S}_{NA}(t)$ 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).

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

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

$$\text{PE} \pm 1.96 \times \text{SE}.$$

- This is mainly because $\widehat{S}_{KM}(t)$ lies between 0 and 1.
- Two common methods to obtain the 95% confidence interval for $\widehat{S}_{KM}(t)$ 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

$$\mathrm{Var}\{f(X)\} \approx \mathrm{Var}(X) \cdot \{f'(x_0)\}^2,$$

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

The Delta Method

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

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

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

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

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

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

$$\mathrm{Var}\left[\log\left\{\widehat{S}_{KM}(t)\right\}\right] = \mathrm{Var}\left\{\sum_{t_{(i)} \le t} \log\left(\frac{n_i - d_i}{n_i}\right)\right\} = \sum_{t_{(i)} \le t} \mathrm{Var}\left\{\log\left(\frac{n_i - d_i}{n_i}\right)\right\}$$

- 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 $\widehat{S}_{KM}(t)$

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

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

- With the Delta method, we have

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

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

- From the above result, we have

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

- By the Delta method,

$$\mathrm{Var}\left[\log\{\widehat{S}_{KM}(t)\}\right] \approx \mathrm{Var}\{\widehat{S}_{KM}(t)\} \cdot \frac{1}{\widehat{S}^2_{KM}(t)}.$$

- Altogether, this gives

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

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

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

- With the Greenwood formula, the condifdence interval of $\widehat{S}_{KM}(t)$ can be obtained using the usual form of PE $\pm Z_{\alpha/2} \times$ SE.
- The bounds can still be less than zero or greater than one.