# Introduction to TTE modeling: Workbook 3 Solutions

Summary measures from S(t) and comparing survival functions

2023-07-11

## Contents



## Preliminaries for R examples

```
library(tidyverse)
library(stringr)
library(survival)
library(survminer)
library(texreg)
library(mgcv)
library(flexsurv)
library(muhaz)
library(Hmisc)

theme_set(theme_bw())
```

```
load('../data/aedat.RDS')

aedat <-
  aedat %>%
  mutate(AETOXGR = factor(aedat$AETOXGR, 0:3, labels=c("None","Mild","Moderate","Severe")),
         ae_any = AETOXGR != 'None') %>%
  group_by(USUBJID) %>%
  # End of study for patients without a severe event
  mutate(TTE_SEVERE = case_when(
    STUDYID=="PROTA" ~ 2,
    STUDYID=="PROTB" ~ 6
  ),
  # Time of severe event for those that had one
  TTE_SEVERE = ifelse(AETOXGR=="Severe", TTE, TTE_SEVERE),
  AE_any = ifelse(AETOXGR!="None",1,0)
  )

# Both for EDA and for model-checking, it's generally helpful to have quartiles of exposure:
dat_use <-
  aedat %>% arrange(USUBJID, TTE_SEVERE) %>% slice(1) %>%
  group_by(PBO) %>%
  mutate(Quartile = ifelse(PBO == "PBO", "PBO",
                           paste0("Q", ntile(CAVGSS, n = 4)))) %>%
```

```
  ungroup() %>%
  mutate(rowid = 1:n())
```

Our goal here is to compare time to any AE between placebo and treated subjects. First, we'll compare summary measures, then we'll compare using the log-rank test.

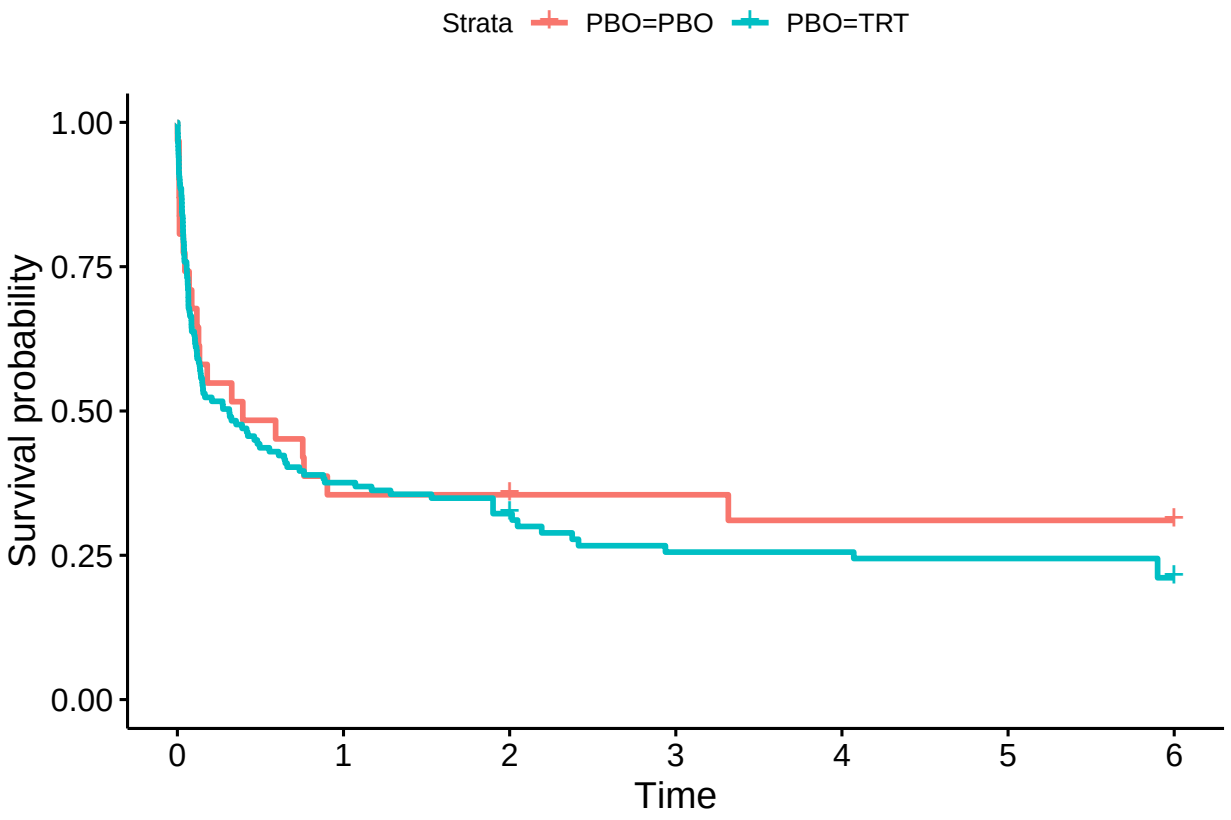
Let's start by estimating the survival function for time to any AE, stratified by treatment.

```
km_trt <- survfit(Surv(TTE,AE_any)~PBO, dat=dat_use)
print(km_trt)
```

```
. Call: survfit(formula = Surv(TTE, AE_any) ~ PBO, data = dat_use)
.
.           n events median 0.95LCL 0.95UCL
. PBO=PBO  31     21  0.394   0.117      NA
. PBO=TRT 149    111  0.313   0.136   0.649
```

And then plot the estimates

```
ggsurvplot(km_trt)
```




- How do the median estimates compare? Which group is estimated to have the fastest onset of AEs? Which group is estimated to have the slowest? If you account for the uncertainty in the estimates, how do you think the medians compare to each other?

**Solution**:

Looking at the `survfit` output, the placebo group has a median of 0.394 and the treated group has a median of 0.313. Based on the median time to eventm the placebo group has a slightly slower onset rate, although the confidence intervals are largely overlapping.

- Why do you think the upper confidence limit for the placebo group is NA?

**Solution**:

The upper confidence limit being `NA` means that the upper confidence limit for the median time to event for the placebo group is not estimable (essentially, it's infinite). This may be due to a combination of factors including a small sample size, relatively short follow-up time, and true proportion of participants having an AE being less than 50%.

Note: You can use the quantile function to estimate other percentiles of the survival distribution.

```
quantile(km_trt, probs = 0.25)
```

```
. $quantile
.                  25
. PBO=PBO 0.04512747
. PBO=TRT 0.05557840
.
. $lower
.                  25
. PBO=PBO 0.01196842
. PBO=TRT 0.03467350
.
. $upper
.                  25
. PBO=PBO 0.32712369
. PBO=TRT 0.07518872
```

How do the 25th percentiles compare? Does the difference in one percentile (e.g., 25th or 50th) give you a full picture of the differences in the time to AE between these groups?

**Solution:**

The 25th percentiles seem to be very similar. In this case, where the survival curves are quite similar, one or two quantiles does convey much of the picture. However, in general, this is not the case.

We fit the log-rank test in R using the `survdiff` function:

```
survdiff(Surv(TTE,AE_any) ~ PBO, data=dat_use)
```

```
. Call:
. survdiff(formula = Surv(TTE, AE_any) ~ PBO, data = dat_use)
.
.           N Observed Expected (O-E)^2/E (O-E)^2/V
. PBO=PBO  31       21     23.9    0.3581      0.44
. PBO=TRT 149      111    108.1    0.0793      0.44
.
.  Chisq= 0.4  on 1 degrees of freedom, p= 0.5
```

**Exercise**

1. Repeat the steps abouve but comparing patient type or exposure quartile.
2. Does it appear that there is a difference between patient types or across exposure quartiles?

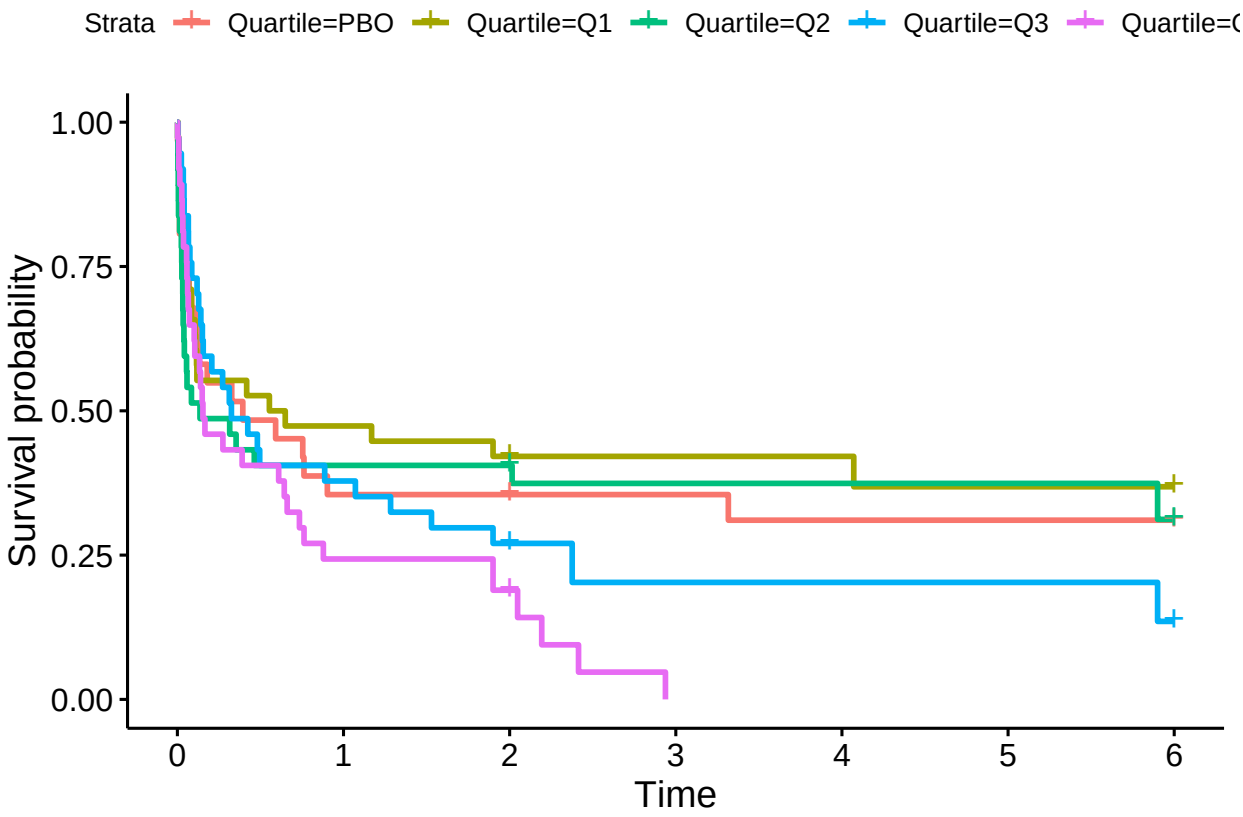
**Solution:**

*Effect of exposure quartile*

```
km_exposure <- survfit(Surv(TTE,AE_any)~Quartile, dat=dat_use)
print(km_exposure)
```

```
. Call: survfit(formula = Surv(TTE, AE_any) ~ Quartile, data = dat_use)
.
.                n events median 0.95LCL 0.95UCL
. Quartile=PBO 31     21  0.394  0.1172      NA
. Quartile=Q1  38     23  0.602  0.1061      NA
. Quartile=Q2  37     25  0.136  0.0392      NA
. Quartile=Q3  37     29  0.325  0.1503   1.529
. Quartile=Q4  37     34  0.154  0.1012   0.735
```

```
ggsurvplot(km_exposure)
```




```
survdiff(Surv(TTE,AE_any) ~ Quartile, data=dat_use)
```

```
. Call:
. survdiff(formula = Surv(TTE, AE_any) ~ Quartile, data = dat_use)
.
.                N Observed Expected (O-E)^2/E (O-E)^2/V
. Quartile=PBO 31       21     23.9    0.3581     0.440
. Quartile=Q1  38       23     30.1    1.6677     2.171
. Quartile=Q2  37       25     26.5    0.0802     0.103
. Quartile=Q3  37       29     27.8    0.0555     0.071
. Quartile=Q4  37       34     23.8    4.3986     5.458
.
.  Chisq= 6.7  on 4 degrees of freedom, p= 0.2
```

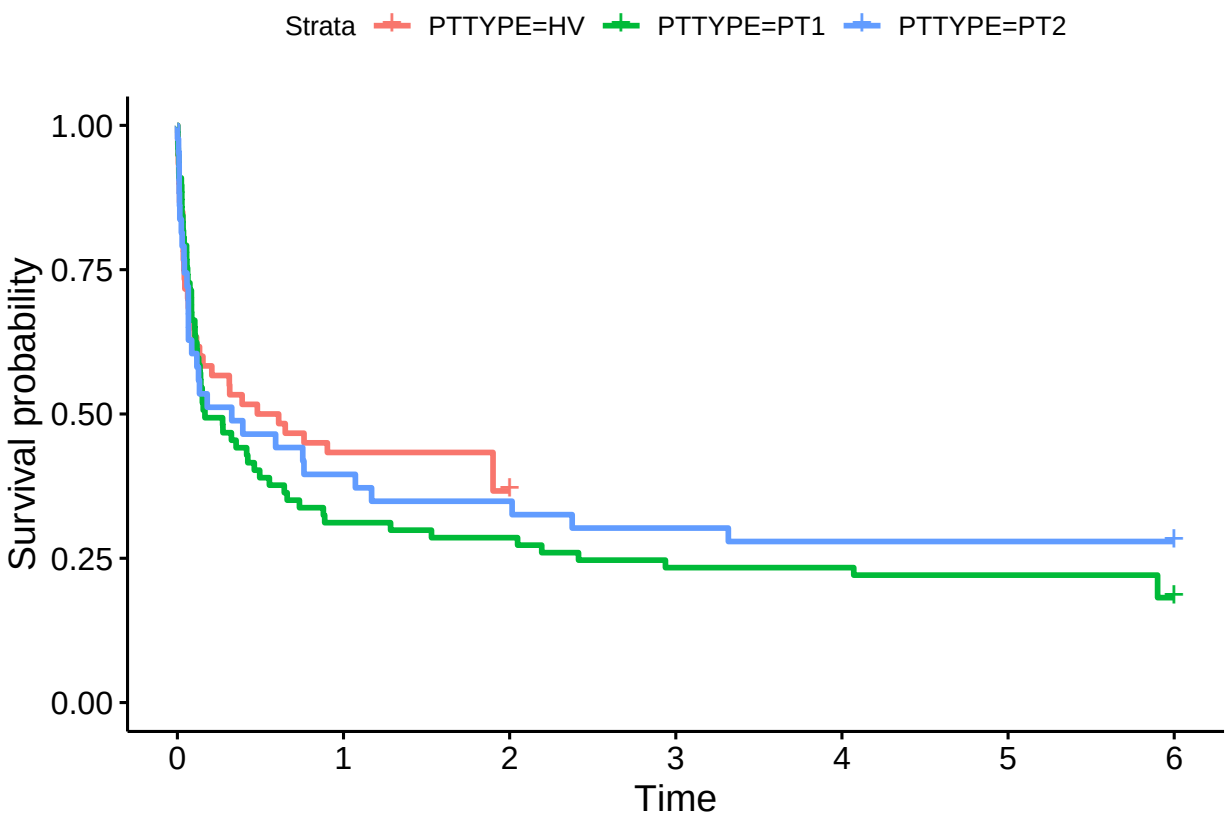
There doesn't appear to be any clear difference between the exposure groups nor any monotonic relationship between exposure and the risk of an event.

*Effect of patient type:*

```
km_pttype <- survfit(Surv(TTE,AE_any)~PTTYPE, dat=dat_use)
print(km_pttype)
```

```
. Call: survfit(formula = Surv(TTE, AE_any) ~ PTTYPE, data = dat_use)
.
.             n events median 0.95LCL 0.95UCL
. PTTYPE=HV  60     38  0.545  0.1334      NA
. PTTYPE=PT1 77     63  0.166  0.1186   0.643
. PTTYPE=PT2 43     31  0.327  0.0667   2.376
```

```
ggsurvplot(km_pttype)
```




```
survdiff(Surv(TTE,AE_any) ~ PTTYPE, data=dat_use)
```

```
. Call:
. survdiff(formula = Surv(TTE, AE_any) ~ PTTYPE, data = dat_use)
.
.             N Observed Expected (O-E)^2/E (O-E)^2/V
. PTTYPE=HV  60       38       42     0.381     0.587
. PTTYPE=PT1 77       63       57     0.641     1.146
. PTTYPE=PT2 43       31       33     0.126     0.171
.
.  Chisq= 1.2  on 2 degrees of freedom, p= 0.6
```

While it appears that the median time to AE is shorter in PT1 than in the HV or PT2 groups, the difference does not reach statistical significance as measured by the log-rank test. This may be due, in part, to the fact

that the standard log-rank test gives relatively higher weights to the early events. In this case, the survival curves do not show much difference early on (where most of the events occur).