Survival Analysis Part I

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Overview

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• This type of outcome creates many complications.
• First, I will review data complications.
• Second, I will review study design complications.
• Third, I will review basic survival analyses.
• Fourth, I will conclude with an example in Stata.
Data

- “Clean” vs “Dirty” data.
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• Most tutorial examples: data are clean.
• Data from clinical registries are “dirty.”
• Survival analysis requires very specific data formatting.
• Stata requires special formatting before it will give you any results for a survival analysis.
• Such formatting is a key part of “cleaning” the data for analysis.
Data Notation

Typically, we need to create:

\[ Y_i = \text{the duration until the event occurs, ie. 12 months} \]
Dates

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• Handling dates in Stata is a key first step.
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• Handling dates in Stata is a key first step.
• Date variables need to be converted to date format using the date() command.
Dates

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2. Date command requires you to know format of your date.
3. Date might be recorded as 31jan2000 or 1/31/2000.
4. You must know the difference.
Dates

• The date command: date(string, “FMT”, 201X)

  • FMT is DMY for 31jan2000.
  • FMT is MDY for 1/31/2000.

  • Final part is topyear–most recent year in your data.
Dates

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• Key parts FMT and 201X
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- Stata saves dates as number of days since Jan 1, 1960.

The command:

- `format date1 %td`
- converts date from numeric form to date format.
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  - `format date1 %td`
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Calculating Duration

• Stata: gen duration = date2 - date1
• This gives survival time in days.
• Next, we must develop a censoring variable.
Censoring

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- What is censoring?
- Censoring loosely refers to missing outcome data.
- For some individuals, duration is known but survival time is unknown.
- Most common is administrative censoring.
Administrative Censoring

- Survival analysis requires a stopping point data collection.
Administrative Censoring

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Administrative Censoring

• Survival analysis requires a stopping point data collection.
• Some patients may not have experienced the event when the data is collected.
• For these patients, we don’t observe their survival time.
• We have a duration but survival time is missing, since the recorded time span is qualitatively different from patients that experienced the event.
Administrative Censoring

- Outcome: disease free survival after adj. chemo.
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- Data collection stops on Dec 1, 2021.
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• Data collection stops on Dec 1, 2021.
• All patients that have yet to recur when data collection stops are censored.
• We observe their duration but not the time to event, since the event has yet to occur.
• The survival time is missing.
Administrative Censoring

- We must record observations that are censored.
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- Create new variable: $C = 1$ is an uncensored observation, $C = 0$ is a censored observation.
Competing Events Censoring

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- Example: time to transplant.
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- Example: time to transplant.
- Patient dies before transplant.
- These patient should be considered censored.
- Competing events are study specific.
- Need to be defined by the researcher.
- Widespread competing events makes interpretation of results difficult.
Effects of Censoring

- Censoring reduces power.
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- If censoring is systematic, estimates from multivariate models can be biased.
Follow-up Time

• Follow-up time is the time from an event of interest: i.e. time since randomization.
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Baseline Time Point

- All subjects should be untreated at $t = 0$. 

E.g.: Effect of Lipitor on time to cardiac event. No one should be on Lipitor at $t = 0$. 
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Example Data

<table>
<thead>
<tr>
<th>id</th>
<th>duration</th>
<th>censor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>
Stata stset

- Stata requires all survival data to be stset.
- Syntax: stset surv_var, failure(censor)
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• Syntax: stset surv_var, failure(censor)
• Stata creates: _t0, _t1, _d, and _st
• time span, censoring, and relevant.
Survival Curves

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- Kaplan-Meier method is the most common.
Survival Curves

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• Kaplan-Meier method is the most common.
• Displays probability of event for those at risk.
Survival Curves

• We have $N$ observations.
• $n_t$ = the number of observations “at risk” for the event at time $t$. 

$\hat{S}(t^k) = \prod_{t \leq t^k} \frac{n_t - d_t}{n_t}$

This is known as the “Kaplan–Meier” estimate of the survivor function.
Survival Curves

• We have $N$ observations.
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For any particular time $t = k$, we can get an estimate of the survival function $\hat{S}(t_k)$ as the product of the conditional proportions of all survivors to that point

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Estimating Survival Curves - An Example

<table>
<thead>
<tr>
<th>Time</th>
<th>No. at risk</th>
<th>No. failed</th>
<th>No. censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
## Estimating Survival Curves

<table>
<thead>
<tr>
<th>Time</th>
<th>No. at risk</th>
<th>No. failed</th>
<th>No. censored</th>
<th>$p$</th>
<th>$\hat{S}(t)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>5/6</td>
<td>5/6</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>3/5</td>
<td>1/2</td>
</tr>
<tr>
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<td>0</td>
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<td>1</td>
<td>1/2</td>
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<tr>
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<td>2</td>
<td>1</td>
<td>0</td>
<td>1/2</td>
<td>1/4</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<th>No. censored</th>
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<td>1</td>
<td>1/4</td>
</tr>
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\[
(6 - 1) / 6 = 5/6 \\
(5 - 2) / 5 = 3/5 \\
5/6 \times 5/6 = 1/2
\]
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\[
\frac{(6-1)}{6} = \frac{5}{6}
\]

\[
\frac{(5-2)}{5} = \frac{3}{5} \times \frac{5}{6} = \frac{1}{2}
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Survival Curves

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• Stratify by key covariate: treatment, sex, etc.
• Inference is now important: are the curves statistically different?
If we’re interested in inference, or just want to know the uncertainty surrounding our estimates, we need some measure of the variability of these estimates. The most commonly–used of these is the “Greenwood” variance estimator:

\[
\text{Var}[\hat{S}(t_k)] = [\hat{S}(t_k)]^2 \sum_{t \leq t_k} \frac{d_t}{n_t(n_t - d_t)}
\]
Log-rank Test

We have two groups; treatment \((=1)\) and placebo \((=0)\), and we want to know if the survival curves are statistically different. Standard test is the log-rank test.
Log-rank Test

<table>
<thead>
<tr>
<th>Event</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td>$d_{1t}$</td>
<td>$d_{0t}$</td>
<td>$d_t$</td>
</tr>
<tr>
<td>No Event</td>
<td>$n_{1t} - d_{1t}$</td>
<td>$n_{0t} - d_{0t}$</td>
<td>$n_t - d_t$</td>
</tr>
<tr>
<td>Total</td>
<td>$n_{1t}$</td>
<td>$n_{0t}$</td>
<td>$n_t$</td>
</tr>
</tbody>
</table>

Normally, we’d do a $\chi^2$ test here, using the observed and expected number of events per cell.

The same general intuition applies, except that we conduct a similar test for each time period $t$. 
Log-rank Test

\[ \hat{e}_{1t} = \frac{n_{1t} d_t}{n_t} \]

is the “expected” number of events in that time period.
Log-rank Test

\[ \hat{Q} = \frac{\left[ \sum_t (d_{1t} - \hat{e}_{1t}) \right]^2}{\left[ \frac{n_{1t}n_{0t}d_{0t}(n_t - d_t)}{n_t^2(n_t - 1)} \right]} \]

The numerator of \( \hat{Q} \) is the sum of the (squared) observed minus expected events. We use this to test the null hypothesis of no difference between the treatment and placebo groups.

\( \hat{Q} \) is distributed as \( \chi^2_1 \).
Unadjusted Survival Analysis

• The analysis thus far assumes treated and control groups are exchangeable.
• Only reason survival curves differ is treatment—not some baseline characteristic of the treated group.
• Next time we take up methods to control for confounders.
Conclusion

• Data cleaning is a key step in survival analysis.
• May require several consequential choices.