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# Methods for survival analysis with competing risks

Phuse 2018, Frankfurt, Laura Marquis, Leonie Wagner

## Agenda

- Motivation
- Data
- Methods/ SAS procedures/ Results
- Conclusion

## Motivation

- Survival analysis is a part of clinical trials
- An event can be defined as death
- Risks for competing events possible
- Methods for analysis are available
- Theoretical and practical basics

## Data Structure

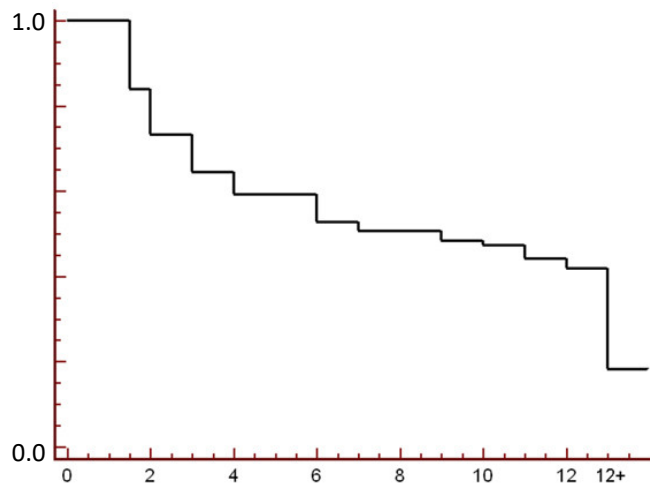
- Dummy data
- Utilization of the uniform distribution for time variable
- 100 subjects, 50 for each of both treatments
- 20 subjects died of cancer
- 20 subjects due to other circumstances
- 60 subjects are censored

# ADTTE

| Subject ID | Treatment | Event | Death Flag | Time |
|------------|-----------|-------|------------|------|
| 10001001   | 1         | 1     | Y          | 95   |
| 10001002   | 1         | 2     | Y          | 105  |
| 10001003   | 1         | 0     |            | 430  |
| 10001004   | 2         | 0     |            | 70   |
| 10001005   | 2         | 1     | Y          | 320  |

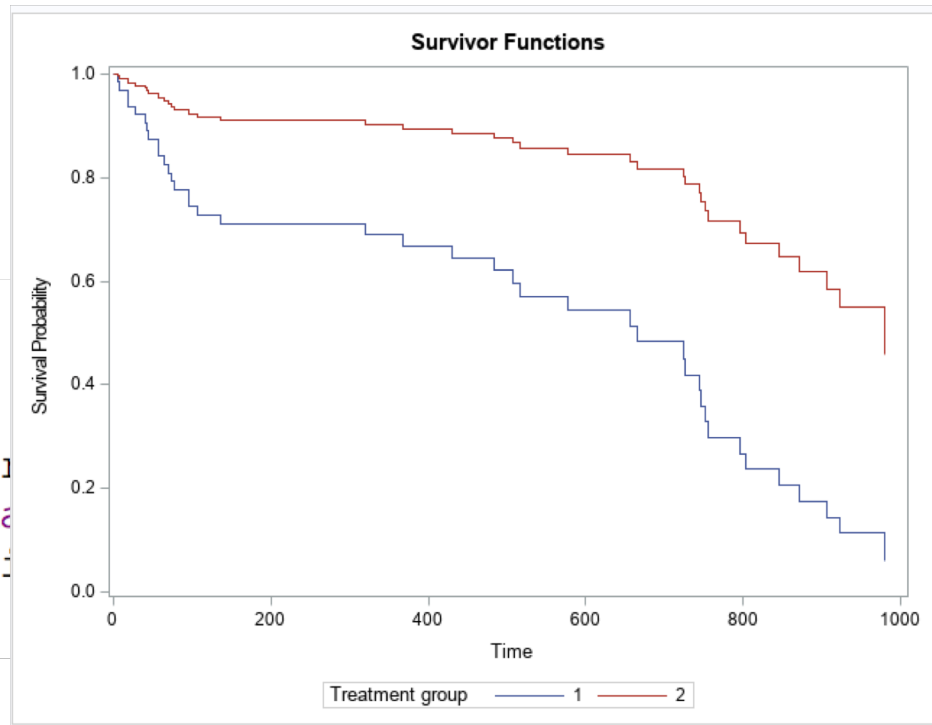
## Survival Analysis

- ADTTE: Events and censored observation
- Overall survival (OS),  
Progression free survival (PFS)
- Kaplan-Meier curves
- Hazard ratio (HR)



# Survival Analysis, HR

```
/*standard Cox model*/  
proc phreg data=death plots=  
    class trt;  
    model time*event(0)=trt;  
    hazardratio 'Hazard Ratio'  
    baseline covariates=reference  
run;
```



- The hazard ratio is 3.6

## Competing Events

- Event that
  - can occur within the time of observation
  - hinders the observation of the main event
- One or more concurrent events
- Example:
  - For Oncology studies and Overall survival:  
→ patients can die in car accidents

## Cause-Specific Hazards (CSH)

- Intuitive approach
- Censor the competing events  
→ perform analysis (Cox-regression)
- Direct risk for an event
- Condition: no other event happened before
- Only one event can occur

## Survival Analysis, CSH

```
/*cause specific hazards*/  
proc phreg data=death;  
    class trt;  
    model time*event(0,2)=trt;  
    hazardratio 'Cause-specific Hazards' trt / diff=pairwise;  
    baseline covariates=risk out=_null_ / rowid=trt;  
run;
```

- The cause-specific hazard ratio is 3.2

## Subdistribution Hazards (SDH)

- Immediate risk for a specific event
- Condition: no other event happened before
- No censoring of competing events, although no other event can happen
- Model of Fine and Gray (1990):  
Effects of covariates in direct coherence to CIF

## **Risk Set of SDH, Fine and Gray (1990):**

- Risk set is defined with weights
- Depending on the time
- For each time there is a weight for each subject
- Not known → needs to be derived
- Before SAS 9.4 → manual derivation
- SAS 9.4 → PROC PHREG

## The idea of Fine and Gray

- Censoring times for competing events not given
- Weight to be in the risk set:
  - Before any event:  $\text{weight}=1$
  - After event or censoring:  $\text{weight}=0$
  - After competing event:  $\text{weight}$  is between 1 and 0
  - Weight decreases over time
  - Depends on the survival function

## Survival Analysis, SDH

- SAS 9.4

```
/*sub-distribution hazards*/  
proc phreg data=death plots(overlay=stratum)=cif;  
  class trt;  
  model time*event(0)=trt /eventcode=1;  
  hazardratio 'Subdistribution Hazards' trt / diff=pairwise;  
  baseline covariates=risk out=_null_ / rowid=trt;  
run;
```

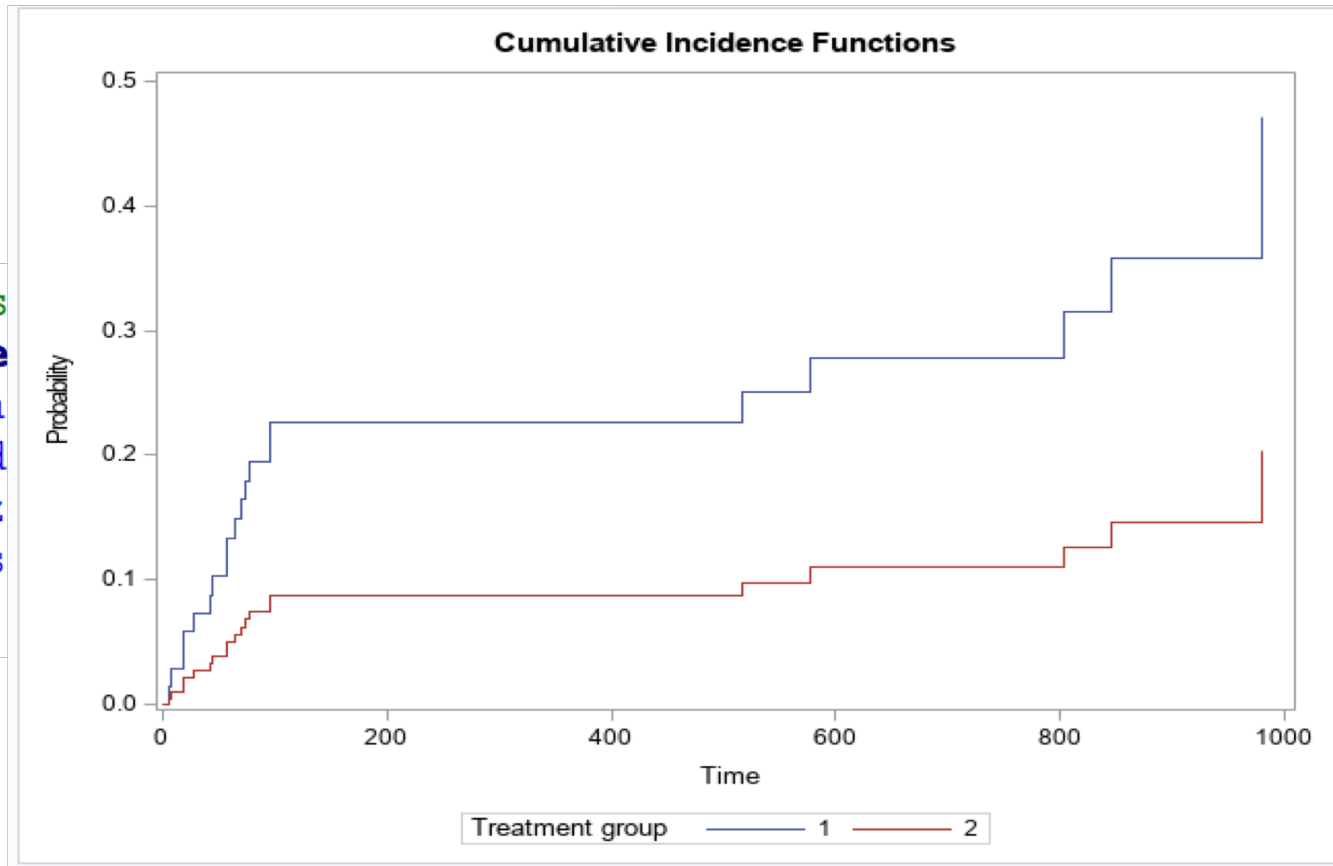
- The sub-distribution hazard ratio is 2.8

## Cumulative Incidence function (CIF)

- Percentage of subjects with events
  - Assumption: other events can happen
  - Computation divided into two parts
  - Hazard function: all competing events censored
  - Survival function: only one event possible
- Dependency of other events

## CIF

```
/*sub-dis  
proc phre  
    cla  
    mod  
    haz  
    bas  
run;
```



ewise;

## Conclusion

- Hazard Ratios:
- PROC PHREG in SAS 9.4 for SDH
- Main difference is definition of the risk sets
- Risk difference smaller for SDH
- Interpretation of the results according to method

| HR  | CSH | SDH |
|-----|-----|-----|
| 3.6 | 3.2 | 2.8 |

Thank you!

## References

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