Applied Survival Analysis

Lecture 12. Composite Endpoints

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Outline

1. Definition and rationale
2. Clinical trials regulatory guidelines
3. Statistical methods (Time-to-first event; composite event process)

Composite Endpoint

- Complex outcome data involving multiple failure processes:
  - Multivariate failure times
  - Recurrent event
  - (Semi)-Competing risks
  - Repeated measures with survival endpoint
- Statistical methods:
  - Joint models (frailty, random effects)
  - Marginal models (component-wise robust methods, cumulative incidence)
- Composite endpoint:
  - Combine multiple outcomes into a single variable (e.g., time to first event, TFE)
  - Desirable for primary analysis of clinical trials

Composite Endpoint

- Examples:
  - Cardiovascular trials: major adverse cardiac events (**MACE**) including death and non-fatal events such as heart failure, myocardial infarction, and stroke
  - Cancer trials: death and the non-fatal event of tumor progression
- Death is usually the main outcome of interest, supplemented by one or several non-fatal event types as auxiliaries
- Notation:
  - Let D denote the time to death and write $N_D^*(t) = I(D \leq t)$
  - Use $N_1^*(t), \ldots, N_K^*(t)$ to denote the counting processes of K non-fatal event types
  - Total outcomes:

$$\boldsymbol{Y}(t) = \{N_D^*(u), N_1^*(u), \ldots, N_K^*(u) : 0 \leq u \leq t\}$$

Composite Endpoint

- Definition of composite endpoint: a many-to-one function that synthesizes the multivariate information into a **single process** (e.g., time to first event; TFE)

Definition 12.1. A composite endpoint is represented by a univariate process $\mathcal{C}(\boldsymbol{Y})(t)$, where $\mathcal{C}(\boldsymbol{Y})(t)$ is a function only of $\boldsymbol{Y}(t)$.

For example,

$$\mathcal{C}(\boldsymbol{Y})(t) = I\left\{N_D^*(t) + \sum_{k=1}^{K} N_i^*(t) \geq 1\right\} := N_F^*(t) \qquad (12.1)$$

is the counting process for the TFE, i.e., the event-free survival time.

Composite Endpoint

- Advantages of composite endpoint:
  - More events → higher statistical power
  - No need to adjust for multiplicity
  - A single measure of overall treatment effect
- Therefore, composite endpoints are recommended for use as the primary endpoints of clinical trials

Composite Endpoint – Regulatory Guidelines

- **ICH-E9** "Statistical Principles for Clinical Trials" (ICH, 1998):
  - "There should generally be only one primary variable"
  - "If a single primary variable cannot be selected from multiple measurements associated with the primary objective, another useful strategy is to integrate or combine the multiple measurements into a single or composite variable, using a predefined algorithm."
  - "(composite endpoint) addresses the multiplicity problem without adjustment to the type I error."
  - "The method of combining the multiple measurements should be specified in the protocol."
  - "…an interpretation of the resulting scale should be provided in terms of the size of a clinically relevant benefit."

Composite Endpoint – Regulatory Guidelines

- The European Network for Health Technology Assessment (**EUnetHTA**) guideline: “Endpoints used for Relative Effectiveness Assessment – Composite Endpoints” (EUnetHTA, 2015)
  - “All components of a composite endpoint should be separately defined as secondary endpoints and reported with the results of the primary analysis.”
  - “Components of similar clinical importance and sensitivity to intervention should preferably be combined.”
  - “If adequate, mortality should however be included if it is likely to have a censoring effect on the observation of other components.”

Composite Endpoint – Regulatory Guidelines

- **FDA** Guidance for Industry: "Multiple Endpoints in Clinical Trials" (FDA, 2017)
  - "Composite endpoints are often assessed as the time to first occurrence of any one of the components, …, it also may be possible to analyze total endpoint events."
  - "The treatment effect on the composite rate can be interpreted as characterizing the overall clinical effect when the individual events all have reasonably similar clinical importance."
  - "…analyses of the components of the composite endpoint are important and can influence interpretation of the overall study results."

Composite Endpoint – Regulatory Guidelines

- ICH-E9 (R1) Addendum: “Estimands and Sensitivity Analysis in Clinical Trials” (ICH, 2017)
  - “A central question for drug development and licensing is to quantify treatment effects.”
  - “…an estimand defines in detail what needs to be estimated to address a specific scientific question of interest.”
  - “Intercurrent events: Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation” (e.g., **death**)
  - “Intercurrent events need to be considered in the description of a treatment effect on a variable of interest”
  - “Composite strategy: The occurrence of the intercurrent event is taken to be a component of the variable.”
  - On the other hand, “…missing data and loss-to-follow-up are irrelevant to the construction of estimands.” (training material)

Composite Endpoint – Regulatory Guidelines

- To summarize, a composite endpoint should
  - be pre-specified in trial protocol
  - (ideally) consist of components of similar clinical importance
  - include mortality whenever appropriate
  - provide a meaningful scale for overall treatment effect
  - be followed with component-wise secondary analysis

Composite Endpoint – Statistical Methods

- Time to first event (TFE) analysis (KM curve; log-rank test; Cox model)
  - Unequal importance between components ignored (death vs non-fatal)
  - Information beyond the first event discarded

Fig. 12.1 In time-to-first analysis, a patient first hospitalized is treated the same as a patient who dies at the same time without being hospitalized.

- Solution:
  - Component-wise (cause-specific) weighting (Rauch et al., 2018b, Stats in Med)
  - Composite event process (Mao and Lin, 2016, Biostatistics)

Composite Endpoint – Statistical Methods

- Weighted composite event process

$$\mathcal{C}(\boldsymbol{Y})(t) = w_D N_D(t) + \sum_{k=1}^{K} w_k N_k^*(t) =: N_W^*(t)$$

  - where $w_D, w_1, \ldots, w_K$ are user-specified weights reflecting the importance of the corresponding events. Because death is more severe than the non-fatal events, one typically chooses $w_D > w_k (k = 1, \ldots, K)$

- Proportional means model

$$E\{dN_W^*(t) \mid Z\} = \exp(\beta^{\mathrm{T}} Z) \mathrm{d}\mu_0(t)$$

  - Ghosh-Lin-type inference procedure (due to semi-competing risk of death)

Composite Endpoint – A Cardiovascular Trial

- HF-ACTION: a randomized controlled clinical trial among heart failure (HF) patients.
- A total of 2331 medically stable outpatients with HF and reduced ejection fraction recruited over 4/2003--02/2007 at 82 centers in the USA, Canada, and France.
- Randomized to usual care alone or usual care plus aerobic exercise training that consists of 36 supervised sessions.
- Primary (composite) endpoint: all-cause death and all-cause hospitalization ($K = 1$)

Composite Endpoint – A Cardiovascular Trial

- Consider a subset of the study data consisting of 451 non-ischemic patients

ID	time	status	Training
1	7.2459016	2	0
1	12.5573770	0	0
2	0.7540984	2	0
2	45.9016393	0	0
5	0.2295082	2	0
5	0.3278689	1	0
6	47.4754098	2	0
6	47.9016393	0	0
7	32.5901639	0	1
8	0.9836066	2	0

Composite Endpoint – A Cardiovascular Trial

Table 12.1 Descriptive statistics for the non-ischemic subgroup in the HF-ACTION study.

	Exericise training	Usual care
N	220	231
Median follow-up	32 months	31 months
Death rate	0.036 per year	0.064 per year
Hospitalization rate	0.234 per year	0.274 per year

Composite Endpoint – A Cardiovascular Trial

- Cox model on TFE gives hazard ratio 0.80, 95% confidence interval (0.64, 1.01)
- For proportional means model, use `CompoML` function in the `WCE` package

```
obj.PM=CompoML(id,time,status,Training,w=c(1,1))#unweighted
obj.PM
```

The argument `w` specifies that death and non-fatal event are weighted by a 1-to-1 ratio. The output is as follows.

```
Point and interval estimates for mean ratios:
            Mean Ratio 95% lower CL  95% higher CL
Training     0.8298503    0.7149027       0.963280
```

- HF patients in exercise training on average experience 83% as many composite events (death & hospitalization) as those in usual care

Composite Endpoint – A Cardiovascular Trial

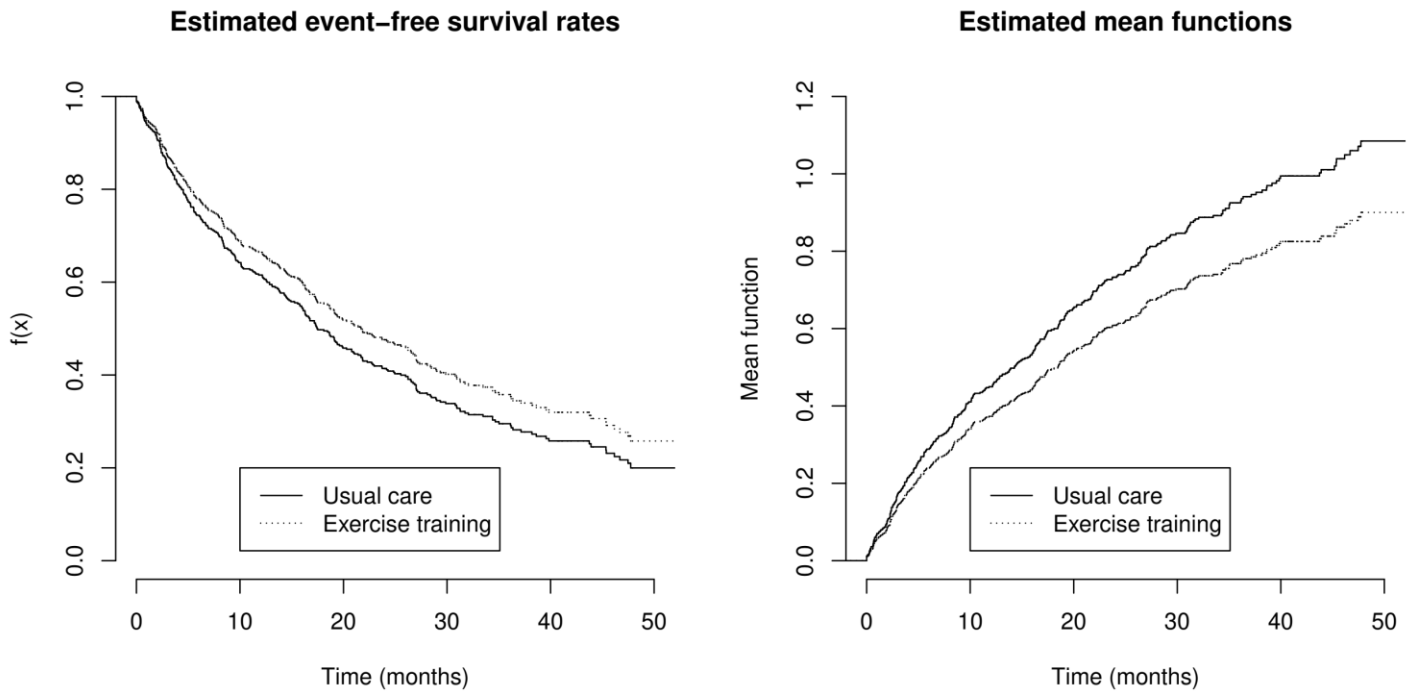

Fig. 12.2 Left, model-based event-free survival rates by arm; right, model-based mean frequency functions of all events by arm.

Summary

- Composite endpoint: univariatized process from multiple outcomes
  - Greater power; avoids multiplicity adjustment; overall effect size
- Regulatory guidelines (ICH, EUnetHTA, FDA)
- Challenges
  - Unequal importance between components; full use of data
- Statistical methods
  - Time to first event
  - Composite event process (`WCE::CompoML()`)
  - Other: proportion in favor; win ratio (to be discussed in next chapter)

HW5 (Due Apr 15)

- Problem 8.8
- Problem 10.2
- Problem 11.4

- Extra credit: 11.2