Defining estimand for win ratio

How to separate true effect from censoring

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Outline

- **Background**
- **Censoring's impact on estimand**
  - Time frame of comparison
- **Two approaches to clarity**
  - **Nonparametric**: fix the time frame
  - **Semiparametric**: posit a time-constant feature
- **Summary and discussion**

Introduction

Composite Endpoint

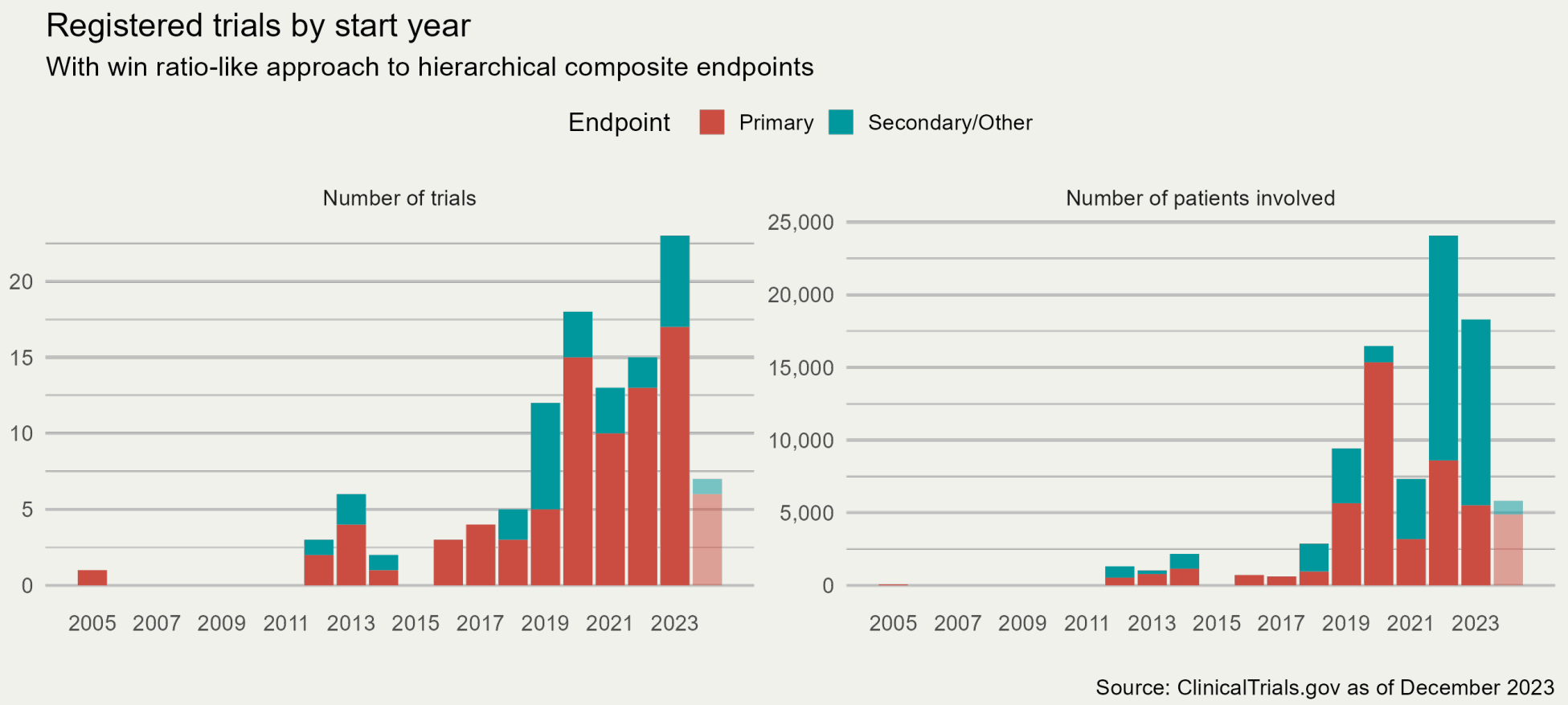
- **Traditional composite endpoint (TCE)**
  - **Time to first event**
    - Major adverse cardiac event (MACE): death, heart failure, myocardio-infarction, stroke, etc.
  - **Limitations**:
    - Lack of clinical priority
    - Statistical inefficiency (waste of data)
- **Hierarchical composite endpoint (HCE)**
  - **Example**: Death > nonfatal MACE > six-minute walk test (6MWT)/ NYHA class

Win Ratio: Basics

- **A common approach to HCE**
  - **Proposed and popularized** by Pocock et al. (2012)
  - **Treatment vs control**: generalized pairwise comparisons
  - **Win-loss**: sequential comparison on components
    - Longer survival > fewer/later nonfatal MACE > better 6MWT/NYHA score
  - **Effect size**: WR = wins / losses
- **Alternative metrics**
  - **Proportion in favor** (net benefit): PIF = wins − losses
  - **Win odds**: WO = (wins + 2^{-1}ties) / (losses + 2^{-1}ties)

Win Ratio: Gaining Popularity

- More trials are using it…



Source: ClinicalTrials.gov as of December 2023

Estimand vs Censoring

An Important Caveat

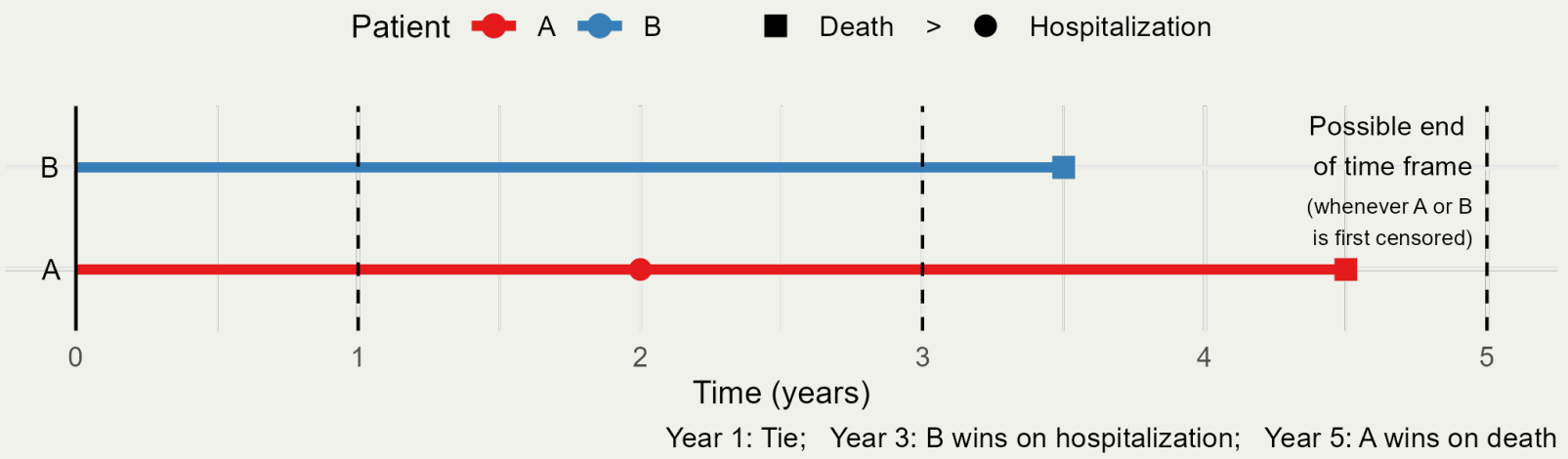
- **WR's estimand depends on censoring …**
  - Luo et al. (2015), Bebu & Lachin (2016), Oakes (2016), Mao (2019), Dong et al. (2020a), Li et al. (2024), etc.
- **What is an estimand?**
  - Population-level quantity to be estimated
    - Population-mean difference, (true) risk ratio, etc.
  - Specifies how treatment effect is measured
  - **ICH E9 (R1) addendum**: estimand construction one of the "*central questions for drug development and licensing*" (ICH, 2020)

Time Frame of Comparison

- **Cause of dependency on censoring**
  - Censoring $\rightarrow$ time frame of comparison $\rightarrow$ magnitude of win/loss probabilities
- **Example**
  - **Pair 1**: one patient censored at year 1, the other > 1 year
    - Compared over $[0, 1]$ year
  - **Pair 2**: neither patient censored until year 5
    - Compared over $> [0, 5]$ years
    - More events $\rightarrow$ fewer ties $\rightarrow$ higher win/loss proportions
    - Prioritized components more likely conclusive, harder to pass

Win-Loss Changes with Time

- **Illustration**
  - Win-loss status, and deciding component, changes with time



  - Longer follow-up …
    - **Parameters**: win/loss proportions ↑ (WR uncertain); tie proportion ↓
    - **Relative contribution**: prioritized ↑; deprioritized ↓

Trial-Dependent Estimand

- **Actual estimand**
  - Average WR mixing shorter-term with longer-term comparisons
  - Weight set (haphazardly) by censoring distribution
    - Staggered entry, random withdrawal $\rightarrow$ non-scientific
- **Testing vs estimation**
  - **Testing (qualitative)**: okay
    - Valid under H_0, powerful if treatment *consistently* outperforms control over time
  - **Estimation (quantitative)**: not okay
    - Needs a generalizable target quantity (scientific estimand)
    - Unaffected by length of trial, rates of patient accrual/loss to follow-up, etc.

Two Approaches to Meaningful Estimand

General Strategies

- **Goal**: a meaningful, generalizable WR estimand
  - Unaffected by censoring distribution
- **Key strategy**
  - Be *proactive* on time frame of comparison
- **Approaches**
  - Choose a fixed time (nonparametric)
  - Model time trajectory with a constant parameter (semiparametric)

Time Restriction - Univariate

- **Outcome data**
  - $D^{(a)}$: survival time for a patient in group a (1: treatment; 0: control)
    - $S^{(a)}(t) = P(D^{(a)} > t)$
- **Time restriction: a familiar concept**
  - *Five-year* survival rate of breast cancer patients
    - Estimand: $S^{(1)}(\tau) - S^{(0)}(\tau)$
  - *Five-year* average survival time
    - Estimand: $E\{\min(D^{(1)}, \tau)\} - E\{\min(D^{(0)}, \tau)\}$
    - Restricted mean survival time (RMST)
  - **Restriction time** $\tau = 5$ years (pre-specify)

Time Restriction - WR

- **Two-tiered composite**
  - $D^{(a)}$: survival time; $T^{(a)}$: time to (first) nonfatal MACE
- **Restricted win/loss probability**
  - Image all patients followed up to τ

$$w_{a,1-a}(\tau) = \underbrace{P\{D^{(1-a)} < \min(D^{(a)}, \tau)\}}_{\text{win on survival}} + \underbrace{P\{\min(D^{(1)}, D^{(0)}) > \tau, T^{(1-a)} < \min(T^{(a)}, \tau)\}}_{\text{tie on survival, win on nonfatal event}}$$

  - **Restricted WR**: $\mathrm{WR}(\tau) = w_{1,0}(\tau)/w_{0,1}(\tau)$

Time Restriction - Estimation

- **General case**
  - Formulate win/loss probability as function of time based on *uncensored* outcomes
  - Pick restriction time τ
- **Estimation**: must handle censoring properly
  - **Inverse probability censoring weighting** (IPCW, Dong et al., 2020b, 2021)
    - **R-package**: `WINS` (Cui & Huang, 2023)
  - **Multiple imputations** for data censored before τ (T. Wang et al., 2023, 2024)

Time Restriction - A Variation

- **Take time difference into account**
  - $w_{a,1-a}(\tau)$: win probability by $\tau \rightarrow$ average win time by τ
  - Restricted mean time in favor: $w_{1,0}(\tau) - w_{0,1}(\tau)$ (Mao, 2023)
    - **R-package**: `rmt` (**rmt?**)
    - **Colon cancer trial**: levamisole + fluorouracil ($n = 304$) vs control ($n = 314$)

Table 1: Restricted mean times in favor of treatment in a colon cancer trial by τ = 7.5 years.

	Estimate (yrs)	**95% CI (yrs)**	**P-value**
Death	0.62	(0.20, 1.04)	0.004
Recurrence	0.35	(0.21, 0.49)	<0.001
Overall	0.97	(0.47, 1.46)	<0.001

Temporal Modeling

- **Cox proportional hazards (PH) model**
  - Time-varying hazard $\xrightarrow{\text{PH}}$ time-constant hazard ratio (global effect)
  - Checking proportionality: score residuals
- **A proportional win-fractions (PW) model**
  - Time-varying win-loss probability $\xrightarrow{\text{PW}}$ time-constant win ratio (global effect) (Mao & Wang, 2021; T. Wang & Mao, 2022)

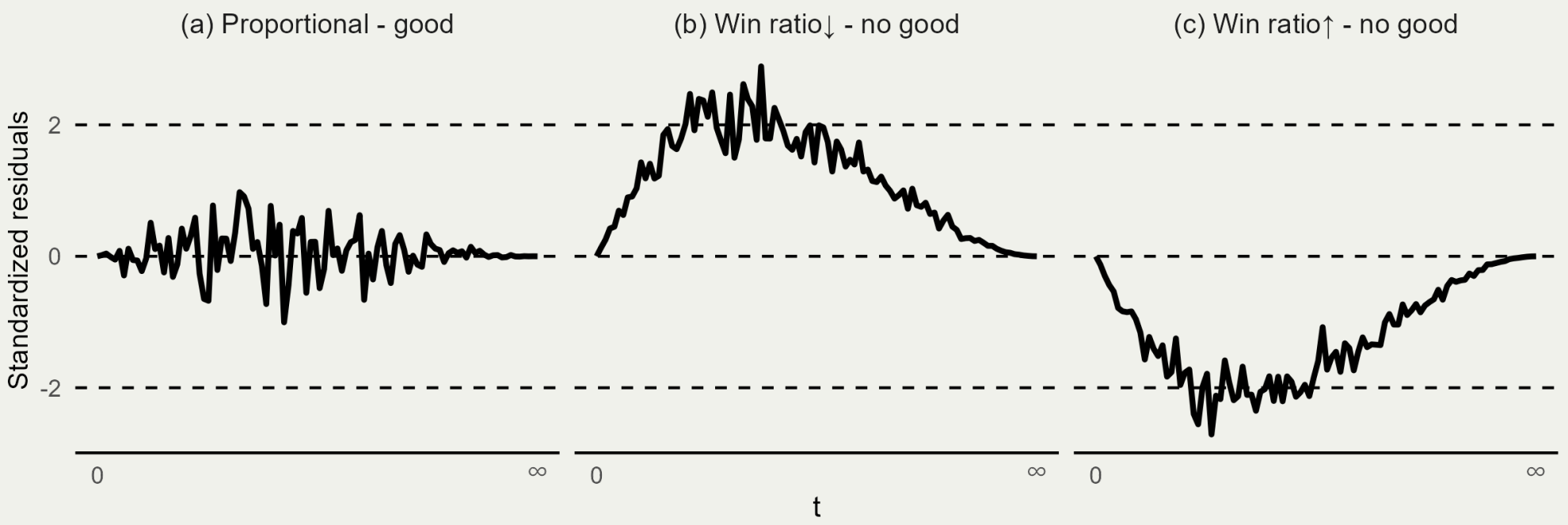
$$\frac{w_{1,0}(t)}{w_{0,1}(t)} = \exp(\theta) \text{ for some } \theta \text{ and all } t$$

    - $\exp(\hat{\theta})$: standard or time-weighted WR statistic
    - **R-package**: `WR` (**WR?**)

Checking Proportionality

- **Cumulative residuals**

$$\hat{\text{resid}}(t) = (\text{Observed wins by } t) - (\text{Model-based wins by } t)$$



Covariate Adjustment

- **HF-ACTION trial**
  - **Exercise training** $(n = 1051)$ vs **usual care** $(n = 1054)$

$$\frac{w_{z,z'}(t)}{w_{z',z}(t)} = \exp\{\theta(a - a') + \beta^{\mathrm{T}}(x - x')\} \text{ for all } t$$

  - **Covariates** x: sex, etiology, CPX, medical history, etc.

Table 2: Multiple PW regression for death > hospitalization in HF-ACTION.

	Win ratio	**95% CI**	**P-value**
Training v usual	1.06	(0.95, 1.19)	0.275
Male vs female	0.72	(0.63, 0.82)	<0.001
Ischemic vs non-ischemic	0.87	(0.76, 0.98)	0.027
CP exercise test (minute)	1.11	(1.09, 1.13)	<0.001
Atrial fibrillation	0.80	(0.70, 0.92)	0.002

Conclusion

Summary

- **How to separate true effect from censoring**
  - Make a conscious choice on time frame of comparison
    - Fix it (nonparametric) or model it (semiparametric)
- **Time restriction vs temporal modeling**
  - **Restricted win-loss**: model-free estimand, less efficient (`WINS`, `rmt`)
  - **PW regression**: may be more efficient *if proportionality (constant WR) holds* (`WR`)
- **Combine the two**
  - IPCW + working model for locally efficient estimation?
  - Nonparametric estimand but semiparametric inference

Future Work

- **Sample size estimation**
  - **Standard tests**: Gasparyan et al. (2021), Mao et al. (2022), Yu & Ganju (2022), B. Wang et al. (2023), etc.
  - **Restricted WR**: ??
- **Intercurrent event**
  - Treatment non-response/toxicity/discontinuation (ICH, 2020)
  - **Hypothetical**: win/lose had treatment continued $\rightarrow$ imputation?
  - **Composite**: death > *treatment failure* > lesser events?
  - **Principal strata**: win/lose among those who would not experience treatment failure if assigned to either group (identifiability)

For More

- **Main paper**

> Mao, L. (2024). Defining estimand for the win ratio: separate the true effect from censoring. *Clinical Trials*, 21, 584-594. https://doi.org/10.1177/17407745241259356

- **Slides URL**: https://lmaowisc.github.io/ce/win_ratio_estimand.html

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