The Inverse-Probability-of-Censoring Weighting (IPCW) Adjusted Win Ratio Statistic (IPCW-Adjusted Win Ratio): An Unbiased Estimator in the Presence of Censoring

Gaohong Dong, iStats Inc.

Lu Mao, University of Wisconsin

Bo Huang, Pfizer

Margaret Gamalo-Siebers, Pfizer

Jiuzhou (Joe) Wang, ImmunoGen

David C. Hoaglin, Univ. of Mass. Medical School

Duolao Wang, Liverpool School of Tropical Medicine, UK

Johan Verbeeck, University Hasselt, Belgium

Regulatory-Industry Statistics Workshop, Sep. 25, 2020

IPCW-Adjusted win ratio

Dong G, Mao L, Huang B, Gamalo-Siebers M, Wang J, Yu G, Hoaglin DC. The inverse-probability-of-censoring weighting (IPCW) adjusted win ratio statistic: an unbiased estimator in the presence of independent censoring. *J Biopharm Stat*. 2020;30(5):882-899.

Dong G, Huang B, Wang D, Verbeeck, Wang J, Hoaglin DC. Adjusting win statistics for dependent censoring. *Pharmaceutical Statistics* (Accepted)

Outline

- A background example
- Win ratio
- IPCW-Adjusted win ratio
- Examples
- Summary

Background example: CHARM program

- CHARM program: included 3 separate randomized trials comparing candesartan with placebo in subjects with chronic heart failure (CHF).
- Primary endpoint: Composite of cardiovascular (CV) death or hospitalization for CHF.
- The three CHARM trials were completed in 2003 with 7599 subjects with median follow-up 3.14 years

Background example : CHARM program (cont.)

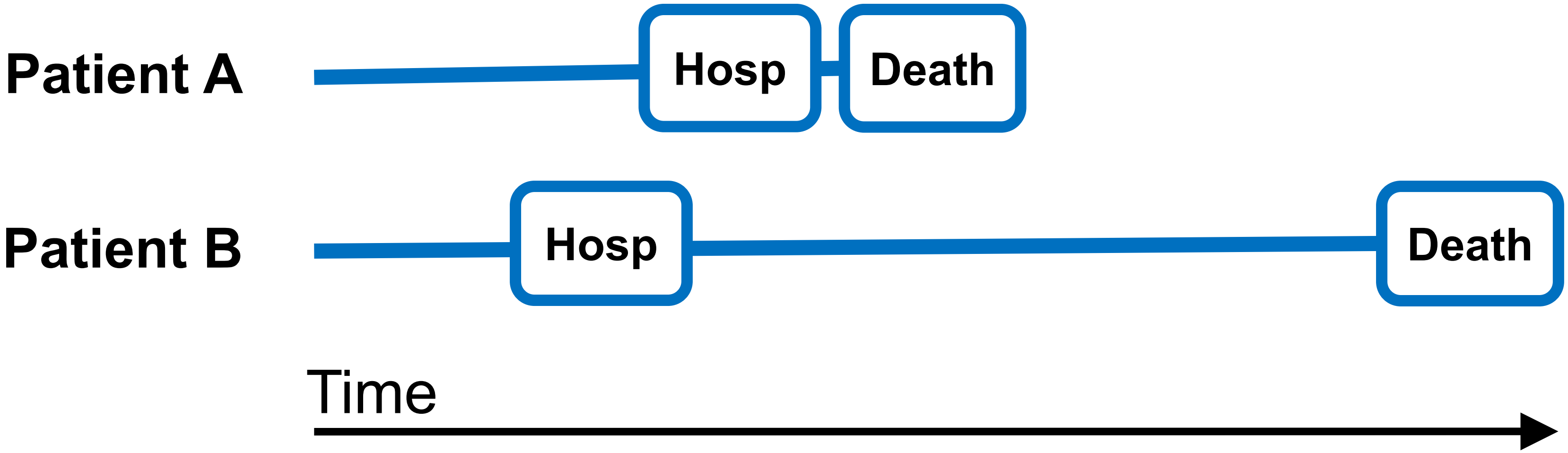
	CHARM Added		CHARM Alternative		CHARM Preserved	
Adjusted HR	0.85		0.70		0.86	
95% CI	0.75–0.96		0.60–0.81		0.77–1.00	
P-value	0.010		<0.0001		0.051	
	C	Pl	C	Pl	C	Pl
No. of patients	1276	1272	1013	1015	1514	1509
No. with primary composite event	483	538	334	406	333	366
No. of these which were CV death[a]	174	182	127	120	92	90
Total no. with CV death[a]	302	347	219	252	170	170

Only 54% of CV deaths contributed to the composite

Q: Could all CV deaths be considered for the analysis?

Source: Pocock et al. (2012)

Win ratio (Pocock et al., 2012)



Who wins?

- First-event analysis: Patient A wins on Hospitalization
- Win ratio: Patient B wins on Death

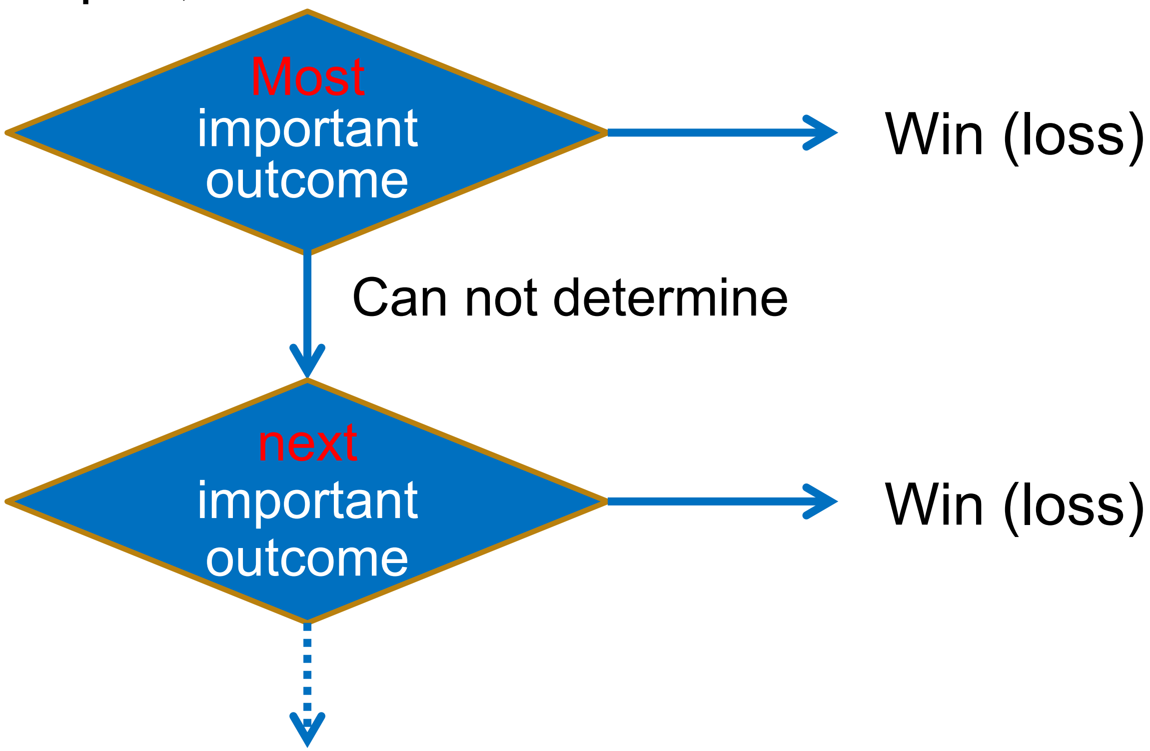
Win ratio (cont.)

Based on pairwise comparisons: each patient in the Treatment group is compared with every patient in the Control group.

		TRT win	Con win	Tied
Treatment Patient 1	Control Patient 1	✓		
	Control Patient 2		✓	
	… …			
	Control Patient N_c	✓		
… …	… …			
Treatment Patient N_t	Control Patient 1			✓
	Control Patient 2	✓		
	… …			
	Control Patient N_c		✓	

Win ratio (cont.)

- For each pair,



- $$Win\ ratio = \frac{Number\ of\ wins\ for\ Treatement}{Number\ of\ wins\ for\ Control}$$

Determine wins

Rule: Patient i in Treatment wins (K_{ij} = **1**) if $min(T_i, C_i, C_j) > T_j$

Patient j in Control wins (L_{ij} = **1**) if $min(T_j, C_j, C_i) > T_i$

Pair	Patient		K_{ij} (i wins)	L_{ij} (j wins)
1	i	T_i	1	
	j	T_j		0
2	i	C_i	1	
	j	T_j		0
3	i	T_i	0	
	j	C_j		0
4	i	C_i	0	
	j	C_j		0

Win ratio (Cont.)

Treatment group:	**Control group:**
Patient *i* (*i* = 1, 2, …, N_t)	**Patient *j* (*j* = 1, 2, …, N_c)**
K_{ij} = **1** if Patient *i* wins over Patient *j* = **0** otherwise	L_{ij} = **1** if Patient *j* wins over Patient *i* = **0** otherwise
# of wins $$n_t = \sum_{i=1}^{N_t}\sum_{j=1}^{N_c}[K_{ij} = 1]$$	# of wins $$n_c = \sum_{i=1}^{N_t}\sum_{j=1}^{N_c}[L_{ij} = 1]$$
Win proportion $$P_t = n_t/\ N_t N_c$$	Win proportion $$P_c = n_c/\ N_t N_c$$
Win ratio = $n_t/\ n_c = P_t/\ P_c$	

Win ratio (cont.)

- Main advantages
  - Consider the most important outcome (e.g. death) first, then next important event, … etc.
  - Can handle a composite of multiple outcomes in any data type (e.g., time-to-event, ordinal, continuous, …)
  - Enable project specific rules defining winners (losers) and ties
  - Can handle non-proportional hazards situations (vs conventional HR and log-rank test).

- Challenges
  - Censoring can cause bias
  - Sample size and power calculation via simulations
  - Regression

Bias due to censoring

Pair	Patient		K_{ij} (i wins)	L_{ij} (j wins)
1	i	T_i	1	
	j	T_j		0
2	i	C_i	1	
	j	T_j		0
3	i	T_i	0	
	j	C_j		0
4	i	C_i	0	
	j	C_j		0

Bias due to censoring (cont.)

- Rule: Patient i in Treatment wins (K_{ij} = **1**) if $min(T_i, C_i, C_j) > T_j$

  Patient j in Control wins (L_{ij} = **1**) if $min(T_j, C_j, C_i) > T_i$

- Win probability for Treatment group

$$\tilde{\pi}_t = Prob(\min(T_i, C_i, C_j) > T_j)$$

- However, we are interested in π_t without an impact from censoring

$$\pi_t = Prob(T_i > T_j)$$

- The estimate of the win ratio based on $\tilde{\pi}_t$ can be biased due to censoring

IPCW-Adjusted win ratio

- IPCW (inverse probability of censoring weighting) technique can be applied to correct for censoring bias
- Independent censoring ssumption: *T* and *C* are independent.

$$\tilde{\pi}_t = E\left(K_{ij}\right) = E\left\{I\left(\min(T_i, C_i, C_j) > T_j\right)\right\}$$

$$= E\{I(T_i > T_j)\boxed{I(C_i > T_j)}I(C_j > T_j)\}$$

$$= Prob(T_i > T_j)\boxed{G^{(t)}(T_j)}G^{(c)}(T_j)$$

$$= \pi_t\boxed{G^{(t)}(T_j)}G^{(c)}(T_j)$$

- $G^{(t)}(x)$and $G^{(c)}(x)$: Survival functions of censoring (not event) at x

IPCW-Adjusted win ratio (cont.)

$$\tilde{\pi}_t = E(K_{ij}) = E\{I(\min(T_i, C_i, C_j) > T_j)\} = \pi_t G^{(t)}(T_j) G^{(c)}(T_j)$$

$$E\left(\frac{K_{ij}}{G^{(t)}(T_j)G^{(c)}(T_j)}\right) = \pi_t = Prob(T_i > T_j)$$

Therefore, $\frac{\boldsymbol{K_{ij}}}{\boldsymbol{G^{(t)}(T_j)G^{(c)}(T_j)}}$ is an unbiased estimator for the win probability π_t.

$\frac{\mathbf{1}}{\boldsymbol{G^{(t)}(T_j)}}$ and $\frac{\mathbf{1}}{\boldsymbol{G^{(c)}(T_j)}}$ are inverse-probability-of-censoring weights.

Similar work applies for dependent censoring

$\frac{\mathbf{1}}{\boldsymbol{G^{(t)}(T_j)}}$ and $\frac{\mathbf{1}}{\boldsymbol{G^{(c)}(T_j)}}$ can be estimated via KM method for independent censoring or Cox model for dependent censoring.

IPCW-Adjusted win ratio (cont.)

	Unadjusted	IPCW-adjusted
Kernel	K_{ij} = **1** if Patient i wins over Patient j = **0** otherwise	$\boldsymbol{K_{ij}^A} = \dfrac{\mathbf{1}}{\boldsymbol{G^{(t)}(T_j)G^{(c)}(T_j)}}$ if Patient i wins = **0** otherwise
# of wins	$n_t = \sum_{i=1}^{N_t} \sum_{j=1}^{N_c} K_{ij}$	$n_c^A = \sum_{i=1}^{N_t} \sum_{j=1}^{N_c} \boldsymbol{K_{ij}^A}$
Win proportion	$P_t = n_t / N_t N_c$	$P_t^A = n_t^A / N_t N_c$
Win ratio	$WR = P_t / P_c$	$WR^A = P_t^A / P_c^A$

Example 1: Cardiovascular (CV) trial data

- A CV trial with the composite of death and hospitalization
- Selected the first 800 patients (419 vs 381 in two groups),
  - Used the data up to 3 years,
  - Excluded patients who dropped out prior to Year 3

  $\Rightarrow$ Estimate the “true” win ratio

  in the absence of censoring (early dropouts)
- Artificially applied 25% and 50% **independent** censoring
- Generated 1000 datasets for each censoring scheme

Example 1: Cardiovascular (CV) trial data (Cont.)

Censoring		Unadjusted			IPCW-adjusted		
Distribution	%	Median win proportion (%)		Win ratio Median (95 % CI)	Median win proportion (%)		Win ratio Median (95 % CI)
		Treatment	Control		Treatment	Control	
No censoring	0	38.4	31.1	1.23 (1.00, 1.52)			
Exp(0.0004)	25	31.0	23.9	1.30 (1.03, 1.64)	39.1	31.5	1.24 (1.00, 1.55)
Exp(0.001)	50	24.4	17.5	1.40 (1.07, 1.83)	39.6	31.3	1.26 (1.00, 1.63)

- Unadjusted win proportions decrease substantially as % of censoring increases
  = > Unadjusted estimates of the win ratio are biased due to censoring
- IPCW-adjusted win proportions are almost same as the “true” proportions.
  => IPCW-adjusted estimates of the win ratio are unbiased
- 95% CIs for the IPCW-adjusted win ratio are narrower than the unadjusted ones, but wider than the “true” 95% CI.

Example 2: Bone marrow transplant

- A bone marrow transplant study with relapse-free survival (Klein and Moeschberger, 2003)
- We compared ALL (n=38) vs high risk AML (n=45) groups
  - Used the data up to 1 year,
  - Excluded 1 ALL patient who dropped out prior to Year 1

  $\Rightarrow$ Estimate the “true” win ratio in the absence of censoring
- Artificially applied 20% and 50% dependent censoring
  - Censoring dependent on patient age (a baseline variable)
  - Censoring dependent on platelet recovery (a time-dependent variable)
- Generated 1000 datasets for each censoring scheme

Example 2: Bone marrow transplant (Cont.)

Scenario 1: censoring is artificially generated depending on patient age (a baseline covariate)

Censoring (%)	Method	Median win proportion (%)		Win ratio
		ALL	High risk AML	Median (95 % CI)
0		50.6	28.9	1.75 (1.22, 2.51)
20	Unadjusted	39.6	24.2	1.66 (1.14, 2.43)
	IPCW-adjusted	49.4	30.8	1.61 (1.11, 2.37)
	Baseline CovIPCW-Adjusted	50.7	28.9	1.76 (1.22, 2.59)
40	Unadjusted	29.2	18.2	1.59 (1.06, 2.55)
	IPCW-adjusted	48.8	32.9	1.48 (1.01, 2.32)
	Baseline CovIPCW-Adjusted	50.6	29.0	1.74 (1.15, 2.80)

Example 2: Bone marrow transplant (Cont.)

Scenario 2: censoring is artificially generated depending on time to platelet recovery (a time-dependent covariate)

Censoring (%)	Method	Median win proportion (%)		Win ratio
		ALL	High risk AML	Median (95 % CI)
0		50.6	28.9	1.75 (1.22, 2.51)
20	Unadjusted	40.4	22.6	1.78 (1.21, 2.68)
	IPCW-adjusted	48.5	27.8	1.74 (1.19, 2.61)
	Time-dependent CovIPCW-Adjusted	50.1	28.9	1.73 (1.17, 2.60)
40	Unadjusted	33.1	18.3	1.82 (1.18, 2.81)
	IPCW-adjusted	46.7	26.8	1.75 (1.15, 2.67)
	Time-dependent CovIPCW-Adjusted	49.9	28.6	1.74 (1.10, 2.72)

Summary

- Conventional analysis uses time to the first event. The first event analyzed may not be the most important outcome

- Win ratio considers the importance order of multiple outcomes. It provides an alternative way to analyze composite endpoints.

- For time-to-event outcomes, due to censoring, unadjusted estimate of the win ratio is biased. Amount of bias depends on the extent of censoring.

- IPCW-adjusted (independent censoring) and CovIPCW-adjusted (dependent censoring) win ratios give an unbiased estimate of treatment effect.