Supplement to Poster P077

Does the Winner Take it All? The Win Ratio Method

An Alternative Approach to Analyse Composite Endpoints

Corinna Miede, mainanalytics GmbH

1 Calculation of the Win Ratio

The calculation of the Win Ratio as outlined in the conference poster and this supplement is performed according to the **unmatched pair approach** that was first described in Finkelstein and Schoenfeld [1]. For deriving winners, losers and ties the algorithm proposed by Pocock et al. [2] is applied. The confidence interval and hypothesis testing is based on the variance estimator introduced in Dong et al. [3].

Let

- $i = 1, ..., N_T$ denote patient i in the active treatment group and
- $j = 1, ..., N_P$ denote patient j in the placebo group

For each pair (i, j) define

- $W_{ij} = 1$ if patient i wins over patient j
- $W_{ij} = -1$ if patient i loses to patient j
- $W_{ij} = 0$ if the pair (i, j) is a tie.

The number of winners N_W in the active treatment group can be expressed as:

$$N_W = \sum_{i=1}^{N_T} \sum_{j=i}^{N_P} \mathbf{1}\left(W_{ij} = 1\right).$$

Analogously, the number of losers is given by:

$$N_L = \sum_{i=1}^{N_T} \sum_{j=i}^{N_P} \mathbf{1}\left(W_{ij} = -1\right).$$

The Win Ratio is then defined as:

$$R_W = \frac{N_W}{N_L}.$$

Consequently, a win ratio greater than 1 indicates that active treatment is favorable over placebo. The number of winners in the active treatment group N_W as well as the number of losers in the active treatment group N_L are asymptotically normally distributed. The two-sided p-value testing

$$H_0 : R_W = 1 \text{ vs. } H_1 : R_W \neq 1$$

can be calculated as (see [3]):

$$p\text{-value} = 2 \cdot \left[1 - \Phi\left(\left|\frac{log(R_W)}{\sqrt{\widehat{\sigma^2_{log(R_W)}}}}\right|\right)\right].$$

Furthermore, the $(1-\alpha)\cdot 100\%$ confidence interval (CI) of the Win Ratio is obtained as follows:

$$(1-\alpha)\cdot 100\%\ \text{CI} = \left[\exp\left(log(R_W) - z_{1-\frac{\alpha}{2}} \cdot \sqrt{\widehat{\sigma^2_{log(R_W)}}}\right), \exp\left(log(R_W) + z_{1-\frac{\alpha}{2}} \cdot \sqrt{\widehat{\sigma^2_{log(R_W)}}}\right)\right].$$

For the derivation of $\widehat{\sigma^2_{log(R_W)}}$ and further details please refer to Dong et al. [3]. Additional information can be found in Finkelstein and Schoenfeld [1] and Pocock et al. [2].

2 Analysis Example

The analysis is based on an example study with $N_P = 50$ patients treated with placebo and $N_T = 50$ patients treated with active treatment comparing the active treatment vs. placebo.

The key results of the traditional composite time to first symptom worsening, hospitalisation or death analysis are outlined in the conference poster. This composite event consists of 3 components and only the first event is considered regardless of the event severity.

Additional details on the results of the Win Ratio analysis that is briefly summarized in the conference poster are provided in Table 1. The predefined hierarchy based on the severity of events is taken into account.

Table 1: Win Ratio analysis

	Placebo		Active treatment	
Number of patients	50	(100.0%)	50	(100.0%)
Number of pairs			2500	(100.0%)
Death (1st level)				
Patients with event	11	(22.0%)	7	(14.0%)
Pairs with event first	383	(15.3%)	130	(5.2%)
Hospitalisation (2nd level)				
Patients with event	27	(54.0%)	21	(42.0%)
Pairs with event first	636	(25.4%)	393	(15.7%)
Symptom worsening (3rd level)				
Patients with event	39	(78.0%)	40	(80.0%)
Pairs with event first	426	(17.0%)	314	(12.6%)
Win Ratio				
Pairs with event first	1445	(57.8%)	837	(33.5%)
Number of ties			218	(8.7%)
Win Ratio estimate			1.73	
95% confidence interval			(1.07, 2.78)	
p-value			0.0250	

References

[1] Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. Stat Med. 1999 Jun 15;18(11):1341-54.

[2] Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012 Jan;33(2):176-82.

[3] Dong G, Li D, Ballerstedt S, Vandemeulebroecke M. A generalized analytic solution to the win ratio to analyze a composite endpoint considering the clinical importance order among components. Pharm Stat. 2016 Sep;15(5):430-7.

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Contact Information

Corinna Miede
mainanalytics GmbH
Softwarecenter 5b
35037 Marburg
Germany
Corinna.Miede@mainanalytics.de