Win Ratio: A Different Way to Analyze Clinical Trials. Its Strengths and Weaknesses

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Introduced in 2012, the win ratio is an innovative approach to the analysis of combined endpoints in randomized clinical trials (RCTs). Its key strength is that it recognizes the different clinical importance of the components of a compound and prioritizes them in a clinical hierarchy. This approach also has the ability to incorporate repeat events, hospitalizations, and quantitative outcomes, as well as quality of life scores.

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The *win ratio* is a response to the limitations of conventional endpoints and their methods of analysis, as many clinical trials in medicine evaluate the efficacy of a treatment based on its impact on fatal and non-fatal events. In this context, the primary endpoint is often a combination of such events. For example, in the case of ischemic heart disease, endpoints may include cardiovascular death, stroke, myocardial infarction, or revascularization.

The analysis typically uses a proportional hazards model for time to first event, using the hazard ratio, its 95% confidence interval (CI), and the log-rank test. In traditional Cox analysis, the comparison is actuarial, and the proportional hazard, expressed as a hazard ratio (HR), requires the effect to be constant over time.

However, conventional endpoints do not directly account for the fact that combined events may vary in clinical importance (e.g., deaths are more important than non-fatal events). Although time-to-first-event analyses are often effective, they sometimes do not adequately reflect the results of an RCT. A weighted measure of the combined effect could take into account the clinical relevance of the different components, but difficulties in agreeing on an appropriate weighting and the resulting analytical complexity have limited its use. These limitations were the basis for the development of the win ratio.

Table 1. *We compare the time-to-first event (HR) studies with the win ratio*

Hazard Ratio	Win Ratio
Simple, reproducible.	Less experience, lack of familiarity.
Requires proportional hazards.	Does not require proportional hazards (uses pairs of comparisons).
Ignores occurrence of fatal events after non-fatal events.	Incorporates all fatal events of interest.
Does not consider the hierarchy of events.	Allows establishing a hierarchy of events and analyzing other patient-focused outcomes.
Estimates sample size and statistical power.	No estimate of sample size and statistical power.
Distinguishes between short-term and long-term events.	With a single "metric" it combines short- and long-term efficacy.

The *win ratio* is valuable because most composite outcomes have a hierarchy of components that reflect their clinical priorities. In its simplest form, with two time-to-event outcomes of interest, such as death and hospitalization, the hierarchy would be (i) death and (ii) hospitalization.

This hierarchy can be extended to include additional time-to-event outcomes, such as (i) death, (ii) stroke, (iii) myocardial infarction, and (iv) coronary revascularization. Alternatively, for repeated outcomes, the time-t- event can be replaced by the number of events, e.g., a hierarchy including (i) death and (ii) number of hospitalizations.

The principle is as follows: Consider an RCT comparing a new treatment (NT) with a control group (CG). In this approach, each patient receiving the NT is compared with each patient in the CG, i.e., paired NT × CG comparisons are performed. Within each pair, the hierarchical component scores are evaluated in descending order of importance, until one of the patients shows a better outcome than the other. If the NT patient has a better outcome, it is considered a "win", whereas if the CG patient has a better outcome, it is considered a "loss". Thus, among all paired comparisons, a total number of winners (NG), losers (NP) and the rest are ties. The ratio of wins is calculated as NG/NP.

Let us consider two alternatives for matching:

1- Matching by risk criterion.

In this approach, the first event considered is the most severe, in this case mortality. The possible situations are:

a. If neither patient in the pair dies, it is considered a tie.

b. If one of the CG patients dies, he/she is a loser and the patient in the intervention group is a winner (and vice versa).

c. If both patients die, the one who dies later will be considered the winner, and the other will be the loser.

2- "All against all" comparison.

Alternatively, it is proposed to compare each patient in one group with all the patients in the other group. The calculation of the *win ratio* is similar, but the statistical analysis requires a more complex approach.

Consider these examples:

Example 1.

180 X 180 = 32400 patient pairs				
	Wins	Draws	Losses	Difference wins vs. losses
Death	48%	18%	34%	14%
Re-hospitalization	12%	3%	3%	9%
				= 23%
Win Ratio	NG/NP = 60% (48+12)/37% (34+3) = 1,58 (IC 95%: 1,24-2,61); $p < 0,001$			

Example 2.

150 X 150 = 22500 patient pairs				
	Wins	Draws	Losses	Difference wins vs. losses
Death	14%	78%	8%	6%
Re-hospitalization	8%	59%	11%	-3%
KCCQ improvement > 10 pts	23%	29%	7%	16%
				= 19%
Win Ratio	NG/NP = 46% (14+8+23)/26% (8+11+7) = 1,73 (IC 95% 1,38-2,48); $p < 0,001$			

Example 3.

205 X 205 = 42025 patient pairs				
	Wins	Draws	Losses	Difference wins vs. losses
Death	4%	93%	3%	1%
Re-hospitalization	10%	80%	3%	7%
				= 8%
Win Ratio	NG/NP = 14% (4+10) / 6% (3+3) = 1,71 (IC 95% 1,25-3,62); $p < 0,001$			

In **Example 1**, we set the events in hierarchical order: (i) death and (ii) rehospitalization. The difference in the *win ratio* is 23%, which clearly reflects the impact of mortality when events are hierarchically ordered. Compared to the usual time-to-first-event analysis, the impact of mortality is more clearly seen without being "biased" by hospitalizations prior to death.

In **Example 2**, the overall *win ratio* is 19%, largely favored by quality of life (measured with the KCCQ questionnaire), with a minimal effect of mortality and no effect of hospitalization. This reveals more clearly that the study is primarily defined by an improvement in quality of life (a surrogate marker), but not by serious clinical events.

In **Example 3**, the difference in the win ratio is smaller because of the small number of events, as demonstrated by the "ties," since 80% of the patients survived or were not hospitalized. Of the endpoints, the difference lies in rehospitalization.

These examples allow us to identify the strengths and weaknesses of the method.

Strengths: One of the main strengths is the ability to have a global view of events in hierarchical order, that allows a more accurate assessment of the overall treatment effect. This approach is particularly useful when analyzing recurrent events, such as hospitalizations, or when incorporating quantitative outcomes, such as quality of life scores. It also allows us to observe the impact of these events in studies that may not have sufficient statistical power to detect effects on serious clinical events.

Weaknesses: One weakness is that the overall outcome can be difficult to interpret, unlike the classic time-to-first-event analysis, which provides an easily interpretable HR. Sometimes, as in **Example 2**, although the overall outcome is significant, it is highly dependent on a "softer" component (quality of life score), suggesting that all hierarchical events are "weighted" equally. This could imply that the final outcome is conditioned by events that are not clinically relevant. Another point of contention is the handling of "ties." Leaving these patients out of the analysis may distort the interpretation of the results, since omitting them implies not adequately representing the possibility of "winners" in the overall cohort. "Ties" represent the absence of a 'winner' and ignoring them could overstate the treatment effect. This could be more relevant in "lower risk" populations, as the number of events would be lower (e.g., in primary vs. secondary prevention).

In the literature, *win ratio* analysis is becoming increasingly common, so it is important to understand its methodology, which will favor the appropriate interpretation of the results.

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