

Hazard Ratios (HRs)

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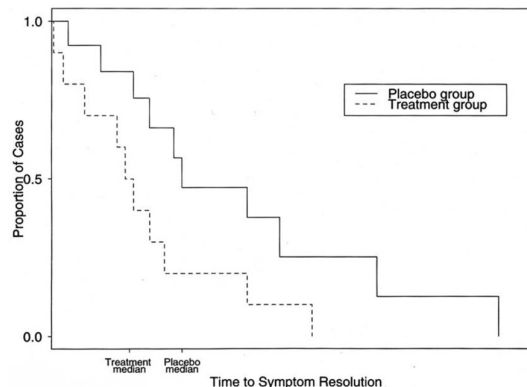
➤ HAZARD RATIO AND KAPLAN-MEIER CURVES

A **hazard ratio** (HR) is the probability of an event in a treatment group relative to the control group probability over unit of time.

A hazard ratio might seem like relative risk ratios (RRs) or odds ratios (ORs), but those assess risk at one point in time, such as the end of the study. In contrast, hazard ratios are used in survival analysis studies that record time-to-event data. Regression models derive the HRs from these data, representing the instantaneous risk at any given point during the study, not just at the end.

For instance, we could say that HR is an effect measure for time-to-event data. What does it mean exactly? In clinical trials, usually survival analysis, is recorded the timespan between the subject entering the study and reaching a predefined endpoint or event (Ex. Death), this is what we called time-to-event data. This data is recorded for both groups, the control, and the treatment, and then the hazard ratio could be determined.

To better understand this analysis of hazard ratio, **Kaplan-Meier curves** could graphically depict time-to-event data. These curves represent the proportion of subjects who have experienced an event (Y-axis) by the time intervals (X-axis). As time progresses the events are taking place so the proportion who have not experienced the event decreased among time. This decrease is displayed in the Kaplan-Meier curves as a downward slope that depicts the event probability over time, which analysis refer to as the **hazard rate**.



A **hazard ratio** is the ratio of two **hazard rates (R)** represented by the different slopes of the Kaplan-Meier curves of each condition (treatment and control). So, hazard ratios (HRs) are a single number that summarizes the magnitude of the difference between Kaplan-Meier curves.

$$HR = \frac{\text{Hazard rate in the treatment group}(R_A)}{\text{Hazard rate in the control group}(R_B)}; HR = \frac{\sum O_A / \sum E_A}{\sum O_B / \sum E_B}$$

where O and E are the observed and expected numbers of events, and A and B indicate the groups being compared.

➤ HAZARD RATIO INTERPRETATION

A **hazard ratio** tells us whether a subject in the treatment group unaffected at any given time has a greater, equal, or lower probability of experiencing the event during the next unit of time

than an unaffected subject in the control group. We can classify the hazard ratio into three group attending to the hazard rates of the treatment and the control group:

- **Hazard ratio = 1.** This means equivalence between the hazard rates of treatment and control groups, meaning that both would experience the same number of events in a period.
- **Hazard ratio > 1.** This means that the treatment group experiences a higher event probability within any given period than the control group.
- **Hazard ratio < 1.** This means that the treatment group experiences a lower event probability during a unit of time than the control group.

In addition to this **hazard ratio**, **confidence intervals (CI)** could be measured allowing to determine the statistical significance of this HR. The confidence intervals are the range of values that is likely to include the true population value and is used to measure the precision of the study's estimate, in this case the precision of the HR. The narrower the confidence interval, the more precise the estimation. If the CI includes 1, then the HR is not significant.

Let's see an example. If the endpoint or event is death and the **HR=0.5**, this would mean that the unaffected subject in the treatment group has half probability of experiencing the event, in this case death, within a time span than someone in the control group. On the contrary, if the **HR=2**, this would mean that the unaffected subject in the treatment group has twice probability of experiencing the event (death) within a time span than someone in the control group.

➤ **PROPORTIONAL HAZARDS**

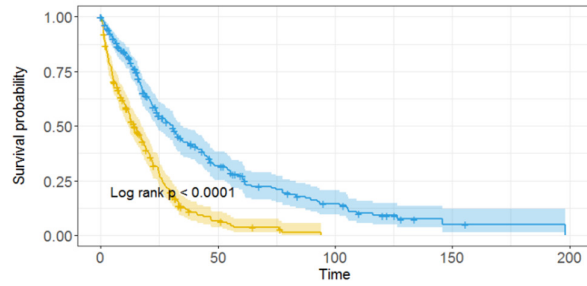
The **hazard ratio** compares the hazard of both treatments, most tests assume that **this ratio is constant over time** and differences are simply due to random sampling. This assumption is violated when hazard changes over time. For instance, comparing surgery (high initial risk, lower later risk) with medical therapy (less initial risk, higher later risk). In any case:

- If the proportional hazard assumption is accepted, you may use a **Hazard Ratio analysis (related to Cox model)**. The **log-rank method** or Mantel-Cox method calculates a p-value under this assumption.
- If the hazard is constant over time, then we may also use the **Ratio of median survival times (RMST)**. Where the median survival time would be the time when half of the patients in the control group have survived compared to the time when half of the patients in the treatment group have survived.

We would look for a direct relationship between the HR and the RMST to assume the proportional hazard hypothesis.

Proportional Hazard

HR= 0,5

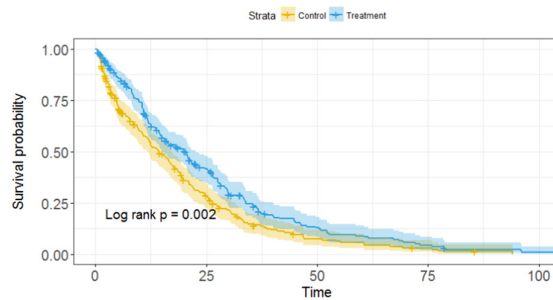


¿How to recognise a non-proportional Hazards?

We can differentiate between three different types of non-proportional Hazard (NPH) that would differ from the proportional ones on the distribution of the Kaplan- Meier Curves.

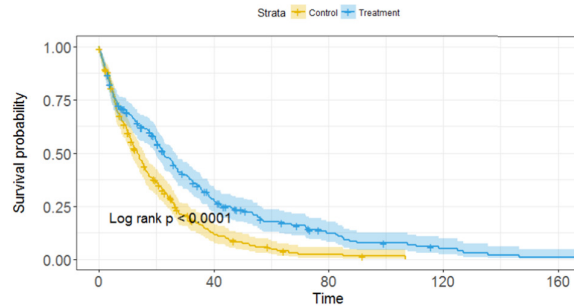
Early /Diminishing Effect

HR= 0,5 at first and then change to HR=1



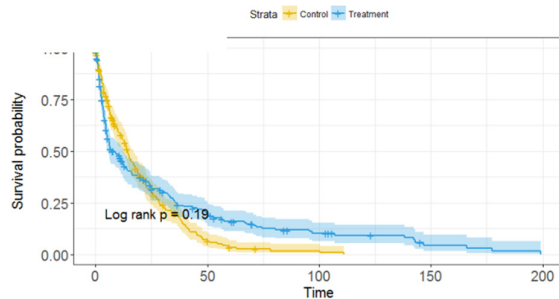
Late/Delayed Effect

HR= 1 and then change to HR=0,5

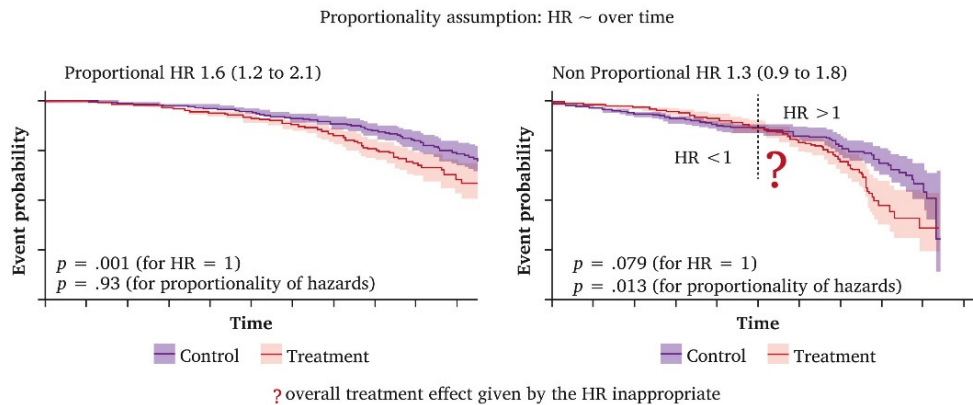


Crossing hazards

HR= 2 and the change to HR= 0,5



The proportionally assumption is based on the proportional relationship between the HR over time. In the Non-proportional Hazards this relationship is not maintained as we have seen, so the overall treatment effect given by the HR would be inappropriate because it is not maintained over time.



➤ **EXAMPLE. Table 1:** Data set for Mantel-Haenszel log-rank test.

| Time | l'_A | l'_B | l'_T | O_A | O_B | O_T | E_A | $O_A - E_A$ | V | E_B | $O_B - E_B$ |
|----------|--------|--------|--------|-------|-------|-------|-----------------------------------|-------------|--------|--------|-------------|
| 3 | 35 | 45 | 80 | 0 | 1 | 1 | $\frac{35 \times 1}{80} = 0.4375$ | -0.4375 | 0.2461 | 0.5625 | 0.4375 |
| 7 | 35 | 44 | 79 | 0 | 1 | 1 | $\frac{35 \times 1}{79} = 0.4430$ | -0.4430 | 0.2468 | 0.5670 | 0.433 |
| 8 | 35 | 43 | 78 | 0 | 2 | 2 | $\frac{35 \times 2}{78} = 0.8974$ | -0.8974 | 0.2442 | 1.1026 | 0.8974 |
| 11 | 35 | 41 | 76 | 1 | 0 | 1 | $\frac{35 \times 1}{76} = 0.4605$ | 0.5395 | 0.2484 | 0.5395 | -0.5395 |
| 29 | 34 | 41 | 75 | 0 | 1 | 1 | $\frac{34 \times 1}{75} = 0.4533$ | -0.4533 | 0.2478 | 0.5467 | 0.4533 |
| 54 | 34 | 40 | 74 | 1 | 2 | 3 | $\frac{34 \times 3}{74} = 1.3784$ | -0.3784 | 0.2416 | 1.6216 | 0.3784 |
| Σ | | | | 2 | 7 | 9 | 4.0701 | -2.0701 | 1.4749 | 4.9399 | 2.0601 |

$l'_A, l'_B,$ and l'_T are the number of subjects in group A, group B, and the total, respectively; $O_A, O_B,$ and O_T are the number of failures (deaths or other events) in group A, group B, and the total, respectively; $E_A = \frac{O_T l'_A}{l'_T}$.

¿How to calculate the Hazard ratio (HR)?

If we take as an example the data shown in the **Table 1**, then:

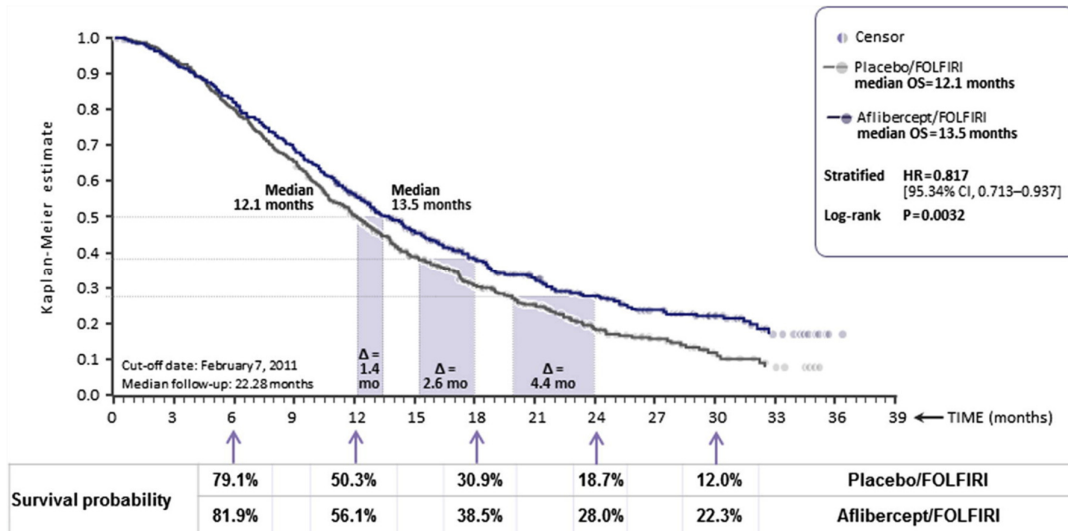
$$HR = \frac{\sum O_A / \sum E_A}{\sum O_B / \sum E_B} = \frac{2 / 4.0710}{7 / 4.9399} = 0.3468. \quad HR < 1$$

As $HR < 1$ this would mean that the treatment group experiences a lower event probability, in the survival analysis we would be talking about death, during a unit of time than the control group.

➤ INTERPRETATION OF SURVIVAL ANALYSIS

Bearing in mind all above said, the survival analysis interpretation would be based on the Hazard ratios (HRs) and Median Survival Time ratio (RMST or MR).

The next example is extracted from a clinical trial called VELOUR (ClinicalTrials.gov NCT00561470) which was a large, international, randomised, placebo-controlled phase III trial comparing the efficacy and safety of FOLFIRI plus aflibercept and FOLFIRI plus placebo in patients with mCRC who had received prior treatment with oxaliplatin as published previously. The results were analysed by a survival analysis shown in the figure below.



To summarise:

- The graphic representation is a Kaplan-Meier Curve
- The Hazard Ratio measured was 0.817 ($HR < 1$) which means that the treatment group experiences a lower event probability during a unit of time than the control group.
- The CI of the HR does not include 1 so HR is significant.
- The Median survival times were also measured:
 - 12.1 months for Placebo/FOLFIRI group
 - 13.5 months for Aflibercept/FOLFIRI group
- The Ratio Median survival time (RMST) would be $12.1 / 13.5 = 0.89$
- $RMST = 0.89$ and $HR = 0.82$, being a direct relationship between the median ratio and the hazard ratio.

Here there are some articles and blogs showing further information about survival analysis and Hazard ratios:

- Spruance SL, Reid JE, Grace M, Samore M. Hazard ratio in clinical trials. *Antimicrob Agents Chemother.* 2004 Aug;48(8):2787-92. doi: 10.1128/AAC.48.8.2787-2792.2004. PMID: 15273082; PMCID: PMC478551. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC478551/>
- <http://www.sthda.com/english/wiki/cox-proportional-hazards-model>
- <https://s4be.cochrane.org/blog/2016/04/05/tutorial-hazard-ratios/>
- <https://bmcmusculoskeletaldisord.biomedcentral.com/articles/10.1186/s12891-021-04379-2>
- <https://statisticsbyjim.com/probability/hazard-ratio/>

- Ruff, P., Ferry, D. R., Lakom, R., Prausová, J., van Hazel, G. A., Hoff, P. M., Cunningham, D., Arnold, D., Schmoll, H. J., Moiseyenko, V. M., McKendrick, J. J., ten Tije, A. J., Vishwanath, R. L., Bhargava, P., Chevalier, S., Macarulla, T., & van Cutsem, E. (2015). Time course of safety and efficacy of aflibercept in combination with FOLFIRI in patients with metastatic colorectal cancer who progressed on previous oxaliplatin-based therapy. *European Journal of Cancer*, 51(1), 18–26. <https://doi.org/10.1016/J.EJCA.2014.10.019>
- Julien I.E. Hoffman, Chapter 35 - Survival Analysis, Editor(s): Julien I.E. Hoffman, Basic Biostatistics for Medical and Biomedical Practitioners (Second Edition), Academic Press, 2019, Pages 599-619, ISBN 9780128170847, <https://doi.org/10.1016/B978-0-12-817084-7.00035-8>.
- The figures about the three types of non-proportional Hazard are extracted from: <https://www2.amstat.org/meetings/biopharmworkshop/2018/onlineprogram/ViewPresentation.cfm?file=300719.pdf>
- The Hazard of Non-proportional Hazards in Time to Event Analysis. Meuli, Lorenz et al. *European Journal of Vascular and Endovascular Surgery*, Volume 62, Issue 3, 495 – 498 [https://www.ejves.com/article/S1078-5884\(21\)00454-8/fulltext](https://www.ejves.com/article/S1078-5884(21)00454-8/fulltext)
- Explicative videos:
 - Kaplan Meier Curve: https://www.youtube.com/watch?v=L_ziqYhksG8&ab_channel=DATAtab
 - Hazard ratio and Cox model: https://www.youtube.com/watch?v=DpZoRqqDgXA&ab_channel=DATAtab