MASTER'S DEGREE THESIS

Interuniversity Master in Statistics and Operations Research

Title: Readability of the effect measures on health interventions

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FINAL MASTER THESIS

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Statistics and Operations Research

For everyone who has supported me
during the conduct of this memory.

"In scientific subjects, the natural remedy for dogmatism has been found in research"

Ronald Fisher

Executive summary

The objective is to empirically quantify the concordance between the inverse of Hazard Rate Ratio (HRR) and the Median Ratio (MR) in survival studies published in the New England Journal of Medicine. 120 pairs of HRR-MR measures were collected in 58 papers. Lin's concordance was 0.67, $CI_{95\%}$: 0.57 to 0.77.

Abstract

Introduction

The measure most used to report treatment effects in survival studies is the Hazard Rate Ratio (HRR). Patients should be able to make decisions about interventions based on information provided by a health expert. However, the medical literature is replete with erroneous interpretations of the HRR which threatens the decision-making process.

When confronted with a treatment which may affect a patient's longevity, the most fundamental question that both patients and doctors must face is: *Which option would allow me to live longer?* But HRR evaluates differences based on the proportions of survivors. Instead, the ratio of two survival medians (MR: Median Ratio) allows the comparison of times to event.

The ultimate goal is to improve the readability of the survival studies. Mainly, we focus on determining the relationship of the HRR with the MR. The specific objective is to empirically quantify the concordance between the inverse of HRR and MR in survival studies published in the *New England Journal of Medicine* (NEJM).

A post-hoc objective of this work is to evaluate whether there is a trend to publish clinical trials that have a more pronounced HRR effect than MR.

Methods

In the first part of the work, theoretical relationships between HRR and other measures such as MR and the Expected mean Ratio were studied. Moreover, we sought via simulations relationships between HRR and frequency measures such as Relative Risk

(RR), the Odds Ratio (OR) or Risk Difference (RD). Finally, the connection between HRR and the Area Under ROC Curve (AUC) was explained.

We conducted a literature search of survival studies published in the NEJM that reported HRR and the medians of both treatment groups. In summary, we have chosen survival Randomized Clinical Trials (RCTs) published in the last decade, reporting the HRR and the median time of Overall Survival (OS) and/or Progression Free Survival (PFS) outcomes.

All HRR^{-1} (inverse of the HRR) of the studies have been standardized so that they are less than 1. That is, all those HRR^{-1} with values greater than 1 and its corresponding MR were inverted.

In these papers, the concordance between both measures was assessed with Lin's coefficient and the Bland-Altman graphic. The publication bias was evaluated with a metaregression and a funnel plot.

Results

There is a theoretical equivalence between the HRR^{-1} and the MR in the Exponential distribution when the proportional hazard assumption is met. This equality does not remain in the Gompertz distribution.

With regard to the literature search, 58 articles were found with 120 HRR and MR measures that met the eligibility criteria. Since 21 (17.5%) median pairs were not reported in the text, they were obtained by visual estimation of the survival curves.

20.7% of papers (12/58) came from 2007 and 74.1% of them had at least two measures (43/58). With regard to the outcomes, 65.8% (79/120) were the primary endpoint and exactly half of them referred to OS and to PFS. The mean sample size of the collected studies was 537 (SD = 336) and the mean number of events was 389 (228). The outcome $Log\ HRR^{-1}$ has a mean of -0.369 (equivalent to HRR^{-1} of 0.69) with an SD = 0.30. The outcome *Log MR* had a mean of -0.338 (equivalent to MR of 0.71) with an SD = 0.27.

In 116 of 120 pairs of measures (96.7%, $CI_{95\%}$: 91.2 to 99.0) the HRR and the MR aim in the same direction as the treatment effect. The estimation of the paired difference

between the *Log MR* and *Log HRR*$^{-1}$ weighted by the inverse squared Standard Error (SE) of the *Log HRR* was 0.004, $CI_{95\%}$: -0.051 to 0.059.

The weighted Linn coefficient for *Log MR* and *Log HRR*$^{-1}$ is 0.67, $CI_{95\%}$: 0.57 to 0.77, a *fair* concordance.

There is no trend toward publishing studies with a greater HRR effect than MR effect (or vice versa). The estimate of publication bias in this sense was 0.37 $CI_{95\%}$: -0.49 to 1.24.

Discussion

This project attempts to relate HRR to MR for supposedly better readability. Empirically, it was observed that there is an almost perfect concordance on average, but this is not so clear at the individual level. The CIs for the individual measures indicate that 95% of observed MRs are within the interval of 65% above and 48% below the HRR^{-1}. This difference is too great to considerer that MR and HRR^{-1} are interchangeable. About the qualitative concordance, only a 3.3% of the pairs MR - HRR^{-1} have a disagreement in the direction of treatment efficacy.

A possible explanation for these discrepancies could be the use of adjusted HRR –the unadjusted was available only in 16 of the 120 measurements (13.3%). A sensitivity analysis using the available unadjusted HRR showed a higher concordance (Lin's coefficient: 0.78).

Keywords: Hazard Ratio, Median Ratio, Survival, Readability.

MSC2000: 62N99

ABBREVIATIONS

AUC: Area Under ROC Curve

CI: Confidence interval

DEFF: Design Effect

ER: Expected mean Ratio

HRR: Hazard Rate Ratio

ICC: Intraclass Correlation Coefficient

LL: Lower Limit of a confidence interval

MR: Median Ratio

NEJM: New England Journal of Medicine

NNT: Number Needed to Treat

OR: Odds Ratio

OS: Overall Survival

PFS: Progression Free Survival

RCT: Randomized Clinical Trial

RD: Risk Difference

ROC: Receiver Operating Characteristic

RR: Relative Risk

SE: Standard Error

UL: Upper Limit of a confidence interval

NOTATION

Subscript 0: Refers to control group

Subscript 1: Refers to treated group

f. density function

F: distribution function

λ: hazard function

Λ: cumulative hazard function

S: Survival function

GENERAL INDEX

1 Introduction

1.1 Motivation

When confronted with treatments that could have repercussions on longevity, the most important question that both doctor and patient must face is:

Which option would allow me to live longer?

In order to quantify a reliable answer to this question, it is necessary to find a reliable means of measuring outcomes of the various treatments at hand. The specific terminology for what is being measured is described as *time to an event* and one of the most employed effect measures is the Hazard Rate Ratio (HRR). The hazard rate at time t is the conditional probability of failure, conditional upon survival up to time t[1]. Expressed mathematically:

$$\lambda(t) = \lim_{\Delta t \to 0} \frac{P\left(t \le T \le t + \Delta t \mid T \ge t\right)}{\Delta t} = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \frac{F\left(t + \Delta t\right) - F\left(t\right)}{S(t)} \qquad (1)$$

Then, HRR is the ratio between the hazard rates in both groups:

$$HRR(t) = \frac{\lambda_1(t)}{\lambda_0(t)} \qquad (2)$$

It describes the relative risk of some undesired event based on the comparison of event rates. Despite this specific definition, there is widespread confusion among clinicians and statisticians over its interpretation. For example, a first common mistake is to interpret the hazard rate as a Relative Risk ratio[2] (RR). This is just a measure for comparing the event proportion between two groups in a fixed time and it is expressed as a ratio of the event proportion up to an arbitrary date occurring in the treatment group compared with the control group. In a constant HRR, the RR changes over time and this implies that its value can be overstated if an instant with a great difference between survival curves is chosen (see Appendix I). In addition, relative risk can lead bias if there are different censure patterns in the groups (see section 2.2.2).

Another misinterpretation of the meaning of the HRR is to handle it as a relative speed of the occurrence of an event[3]. That is, we can find in the literature that an HRR of 2 is identified with events that occur in the treatment group *twice as fast* as those in the control group. We will study how far this interpretation can be valid.

An informal explanation of HRR equal to 2 in a certain instant of time could be that a patient in the treated group is twice as likely to have the next event as one in the control group (assuming that neither had the event before).

There is no single way to estimate the HRR, but certainly the Cox proportional hazards model is the most widespread. The model assumes that the risk for any combination of covariate values is proportional to the baseline risk and with the same proportionality factor over time:

$$\lambda\left(t \mid \vec{Z}_1\right) = \exp\left\{\vec{\beta}' \cdot \vec{Z}_1\right\} \cdot \lambda\left(t \mid \vec{Z}_0\right) \qquad (3)$$

where $\vec{Z}_0$ is the baseline covariate vector, $\hat{\vec{\beta}}'$ is the model coefficients vector and $\exp\left\{\hat{\vec{\beta}}' \cdot \vec{Z}_1\right\}$ is the HRR estimation for an individual with covariates $\vec{Z}_1$. Attention should be paid so that this estimator does not depend on time.

But if the HRR is difficult to interpret, why is it the most used measure in survival studies? Mainly, there are two reasons. First, for practical purposes, the HRR is usually only used in cases where it can be assumed constant over time and in these cases the effect of an intervention (or the relationship with a covariate) can be summarized in a single value with its uncertainty. Secondly, the Cox model provides an estimator with good statistical properties[4]:

1. The $\hat{\beta}$ estimation obtained in the regression consistently estimates the vector of parameters β.
2. Because the estimation was made through partial likelihood, the asymptotic distribution of the statistic is Normal with a mean equal to the vector of the parameters and a variance equal to the inverse of the Fisher information matrix. This is useful for calculating CIs for the HRR.
3. Because of the semiparametric nature of this model, the baseline risk can take any form.

However, the HRR estimation through the Cox model is not completely efficient in the sense that it does not achieve the Cramer-Rao bound.

In this document, we will see that under certain distributions, especially the Exponential, there is an analytic relationship between HRR and other measures. The trouble is that most survival times in medical studies do not fit to this distribution (Appendix II summarizes the most common shapes for the hazard function in medical studies and if the proportionality assumption holds in these situations). However, sample size calculations in the follow-up studies may assume further strong premises, such as a constant hazard rate in order to use the ratio of medians to find the "n"[5]. If this premise is assumed in the design phase, why not extrapolate this assumption to the results interpretation?

1.2 Background

Several studies have attempted to establish a relationship between HRR and other indicators.

Moser et al. summarize the statistical techniques used in survival analysis[6]. There are two main types of measures: those that concern the time to the event occurrence (e.g. survival median time) and those that refer to the number of patients that experienced the event before a given time, (e.g., hazard rate). Both kinds of measures have limitations. For survival hazard rates to be useful, an instant of time has to be agreed on as having clinical interest (or alternatively, to make the assumption that it is constant). On the other hand, median survival may be highly deceptive; for example, in a published clinical trial[7], a difference in medians of 3 years corresponded to a reduction in risk of only 6.3% over 5 years.

Michiels et al. showed the relationship between HRR, Odds Ratio (OR) and MR when performing meta-analysis on survival studies[8]. Their conclusion was that these latter two outcomes are not a reasonable surrogate of the HRR: the MR and the OR provide, respectively, under- and overestimations of the treatment effect. In addition, 20% (25/128) of trials showed opposite directions of MR and HRR. That is, whereas one method suggested that treatment was beneficial, the other suggested that it was detrimental. However, table 2 of this study showed discrepancies among these measures too small to have neither clinical relevance, nor statistical significance.

Similarly, Symons et al. went into depth on the interrelationship between HRR, RR and OR, indicating that the HRR estimation was always between the values of RR (underestimation of the effect) and OR (overestimation of effect)[9]. Furthermore, 3 factors enlarge those discrepancies: longer durations of follow-up, higher occurrence of the event and larger treatment effect. In addition, a constant HRR implies that RR, OR and Risk Difference (RD) are not constant over time and that those statistics can only be applied to a fixed time (see again appendix I).

Finally, Moser et al. showed that in the case of proportional hazards, there was a clear relationship between HRR and the Area Under the Receiver Operating Characteristic (ROC) Curve (AUC); that is, between the HRR and the likelihood that a patient in the treated group had an event before another patient in the control group[10]. This property allows us to relate the Cox model with the logistic regression and the Mann-Whitney-Wilcoxon statistic as well as to quantify the HRR in terms of prediction uncertainty reduction (proportion of patient pairs correctly classified)

1.3 Objectives

The ultimate goal is to improve the readability of the survival studies by providing alternative reports on the effect measures in survival studies. Mainly, we focus on determining the theoretical

and empirical relationships between the HRR and the MR. The initial hypothesis is that the inverse of HRR is a measure that is interchangeable with the MR.

Secondary objectives address the relationships between HRR and Expected mean Ratio (ER), OR, RR, RD and AUC.

A post-hoc objective of this work was to evaluate whether there was a tendency to publish small clinical trials that had a more pronounced effect of the HRR than the MR.

The case of a single dichotomous factor has been addressed (usually representing an intervention of a clinical trial). Furthermore, issues such as interaction or collinearity have not been born in mind.

2 Theoretical relationship between HRR and other measures

2.1 Relationship between HRR, MR and ER

There is an important conceptual difference between HRR and MR. While the first measures the comparative probability of one individual experiencing an event as compared to another individual from another group (taking into consideration that they both have lived up to a certain point), the second quantifies the gain in lifetime of one group over another. Put sharply, the HRR evaluates differences in the vertical axis (changes in proportions of survivors) and the MR takes into account the differences in the horizontal axis (comparing times to the event.).

By analogy with an athletic competition, the HRR would measure the gain in the probability of winning and the MR would give the margin of the victory.

Within the group of common statistical distributions, there are only two that have the property of proportional hazard under certain parameters: the Weibull distribution (and the particular case of the exponential) and the Gompertz distribution[11]. In this section, we study the theoretical relationship between HRR, MR and ER in these distributions.

2.1.1 Weibull distribution

In the case that the survival times in two study groups fit to the Weibull distribution and there is a constant HRR, the relationship between HRR and MR and between HRR and ER can be found analytically through the expressions for the median times and hazards.

First of all, one must know under what parameter combination the proportional hazard assumption is met. We consider the Weibull density function with shape parameter k and scale parameter ρ:

$$f(t) = k\rho(t\rho)^{k-1} \cdot \exp\left\{-(t\rho)^{k}\right\} \qquad (4)$$

Then, the hazard functions in both groups are defined by the expressions:

$$\lambda_0(t) = k_0\rho_0(\rho_0 t)^{k_0-1}$$
$$\lambda_1(t) = k_1\rho_1(\rho_1 t)^{k_1-1} \qquad (5)$$

Consequently the HRR is:

$$HRR(t) = \frac{k_1 \rho_1 (\rho_1 t)^{k_1 - 1}}{k_0 \rho_0 (\rho_0 t)^{k_0 - 1}} = \frac{k_1}{k_0} \cdot \frac{\rho_1^{k_1}}{\rho_0^{k_0}} \cdot t^{k_1 - k_0} \quad (6)$$

The only way that the HRR does not depend on time is that the shape parameters are the same ($k_1=k_0=k$). In this case, HRR is constant over time, and its value corresponds to the ratio of scale parameters to the kth power.

$$HRR = \left(\frac{\rho_1}{\rho_0} \right)^k \quad (7)$$

On the other hand, the MR under these conditions is easily deduced from the analytic formulas of survival medians:

$$\left. \begin{aligned} Med_0 &= \frac{(\ln(2))^{1/k}}{\rho_0} \\ Med_1 &= \frac{(\ln(2))^{1/k}}{\rho_1} \end{aligned} \right\} \Rightarrow MR = \frac{Med_1}{Med_0} = \frac{\rho_0}{\rho_1} \quad (8)$$

In the case of expected mean values, the same procedure as in expression (8) can be performed:

$$\left. \begin{aligned} E_0(T) &= \frac{\Gamma\left(1 + \frac{1}{k}\right)}{\rho_0} \\ E_1(T) &= \frac{\Gamma\left(1 + \frac{1}{k}\right)}{\rho_1} \end{aligned} \right\} \Rightarrow ER = \frac{E_1(T)}{E_0(T)} = \frac{\rho_0}{\rho_1} \quad (9)$$

where Γ represents the Gamma function.

Therefore, theoretical MR and ER to the kth power are equivalent to the inverse of theoretical HRR when proportionality of risks over time holds in the case of two Weibulls.

$$HRR^{-1} = MR^k = ER^k \quad (10)$$

In the case of the exponential distribution, there is an equivalence between the inverse HRR and MR because the shape parameter is 1 in any case and the HRR is the ratio of both rates. Unfortunately, as mentioned earlier, the exponential model is unrealistic in most medical applications since it assumes a constant hazard.

2.1.2 Gompertz distribution

As before, we must find the parameter combination that allows us to meet the proportional hazard assumption. The following Gompertz density function with parameters ρ_1 and ρ_2 is considered:

$$f(t) = \rho_1 \cdot \exp\left\{ \rho_2 t - \frac{\rho_1}{\rho_2}\left(\exp\{\rho_2 t - 1\}\right)\right\} \qquad (11)$$

Then, the hazard functions in both groups are defined by the expressions:

$$\begin{aligned} \lambda_0(t) &= \rho_{10} \cdot \exp\{\rho_{20} t\} \\ \lambda_1(t) &= \rho_{11} \cdot \exp\{\rho_{21} t\} \end{aligned} \qquad (12)$$

Consequently the HRR is:

$$HRR(t) = \frac{\rho_{11} \cdot \exp\{\rho_{21} t\}}{\rho_{10} \cdot \exp\{\rho_{20} t\}} = \frac{\rho_{11}}{\rho_{10}} \cdot \exp\{(\rho_{21} - \rho_{20}) \cdot t\} \qquad (13)$$

As one can observe in expression (13), a constant HRR can only be obtained if the second parameters of both distributions are the same ($\rho_{21} = \rho_{20} = \rho_2$). In this case, HRR is constant over time, and its value corresponds to the ratio of first parameters.

$$HRR = \frac{\rho_{11}}{\rho_{10}} \qquad (14)$$

As the median does not have a closed analytical expression under some parameters and the mean has to be calculated by a numerical integral, these statistics were managed by simulating different scenarios for several parameter combinations in the treatment (ρ_{11} and ρ_2) and control (ρ_{10} and ρ_2) groups (see in Appendix III the simulation procedure and under what conditions the analytical median exists). Figure 1 shows the MR and ER as functions of HRR^{-1} for 12 different scenarios

(each one is represented for a single line). For the same scenario, different values of ρ_{10} provide different HRR^{-1}, MR and ER.

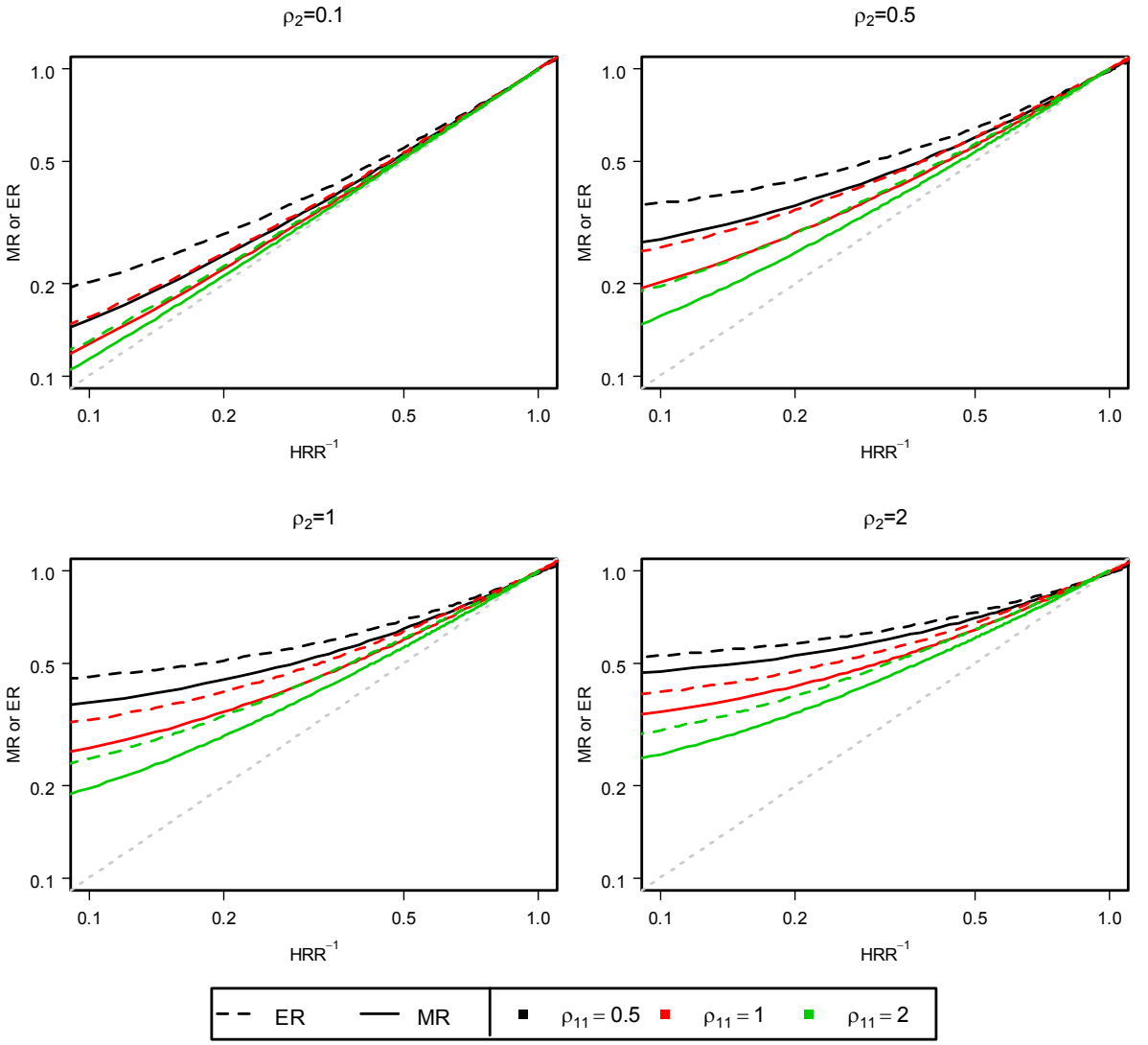


Figure 1. MR and ER as a function of HRR^{-1} in several scenarios. Dotted grey line represents the bisection, the region that represents the perfect concordance.

It can be seen that the equivalence between HRR^{-1}, MR and ER does not hold in the Gompertz distribution. Also, we can observe that, as the HRR effect increases, correspondence (bisection) with both MR and ER declines. Moreover, for lower values of ρ_2 (top-left) and higher values of ρ_{11}, correspondence increases. In any case, the treatment effect derived from the HRR is larger than the one derived from the MR or the ER (a smaller value implies a greater effect).

2.2 Relationships between HRR and RR, OR and RD in the reference group median

In some survival studies, a particular moment could be of particular clinical interest. Some statistics such as RR, OR or RD are useful for expressing the effect of an intervention at a given time. However, it is well known that different patterns of censure in both groups imply biased effect estimations.

In this section, a proposal is put forth for calculating these estimators through HRR; the advantage of this method is the robustness to different censure distributions in the groups.

From the proportional hazards assumption, the relationship between the survival curves can be deduced at each instant of time:

$$\lambda_1(t) = e^{\beta} \cdot \lambda_0(t) \Rightarrow \Lambda_1(t) = e^{\beta} \cdot \Lambda_0(t)$$
$$S_1(t) = \exp\{-\Lambda_1(t)\} = \exp\{-e^{\beta} \cdot \Lambda_0(t))\} = \exp\{-\Lambda_0(t))\}^{e^{\beta}} = S_0(t)^{e^{\beta}} \Rightarrow S_1(t) = S_0(t)^{HRR} \quad (15)$$

where β represents the coefficient of the Cox model; Λ is the cumulative hazard function and S represents the survival function.

The expression (15) is true for any time t, including the median survival for both groups:

$$S_1(Med_0) = S_0(Med_0)^{HRR} = \left(\frac{1}{2}\right)^{HRR}$$
$$S_0(Med_1) = S_1(Med_1)^{HRR^{-1}} = \left(\frac{1}{2}\right)^{HRR^{-1}} \quad (16)$$

One can use the last two equations to find the median survival time in the treated group from the reference distribution and the HRR (or to obtain the reference median survival from the treated group survival distribution and the HRR). Figure 2 shows that the median in the treated group is the moment at which the survival in the reference distribution is $(1/2)^{1/HRR}$ and, on the other hand, the reference median is the time point at which survival in the treated group distribution is $(1/2)^{HRR}$.

The interpretation of this result is the following: at the moment Med_0, 50% of patients have suffered the event in the control group and $(1-1/2^{HRR})\cdot 100\%$ of patients in the treated group were affected.

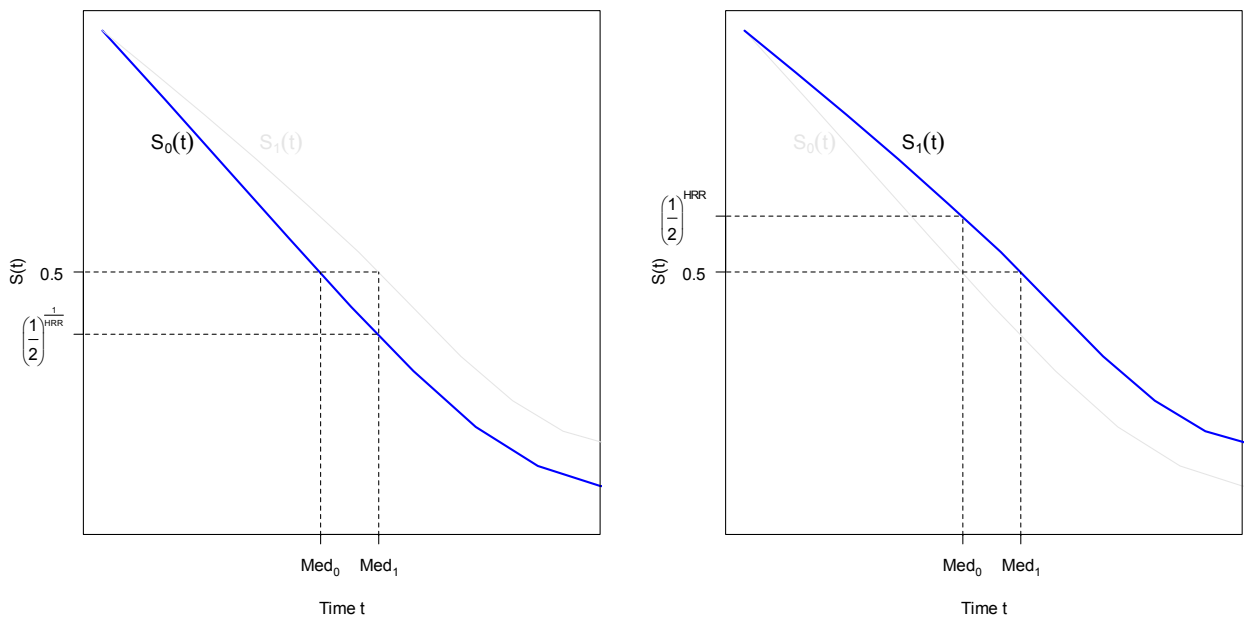


Figure 2. Blue lines represent the known distribution and grey lines represent the distribution whose median one want to know. Left: A way to obtain the median in the treated group from the reference distribution and the estimated HRR. Right: A way to get the median in the control group from the distribution of the treated group and the estimated HRR.

In order to have a measure of uncertainty for this estimation, the CI can be obtained directly from the CI of the HRR estimation (which in turn is derived from the CI of the coefficient β in the Cox proportional hazards model):

$$CI_{1-\alpha}(HRR) = [LL_{HRR}\ , UL_{HRR}] = [\exp\{\beta - Z_{1-\alpha/2} \cdot SE(\beta)\}, \exp\{\beta + Z_{1-\alpha/2} \cdot SE(\beta)\}]$$

$$CI_{1-\alpha}(S_1(Med_0)) = [0.5^{UL_{HRR}}\ , 0.5^{LL_{HRR}}] \qquad (17)$$

where $Z_{1-\alpha/2}$ is the quantile $(1 - \alpha/2)$ of the standard normal distribution.

It should be noted that this is a confidence interval for the proportion of survivors in the treated group on the real reference median (not in its estimation), because the uncertainty in the estimation of this median is not being considered.

2.2.1 Frequency effect measures

Once survival at any point can be estimated from the HRR, other indicators such as RR, OR and RD are easily deduced (see appendix I).

To illustrate the use of measurements such as the RD, RR or OR, let us suppose a study with fictitious data (sections 2.2.1.1, 0 and 2.2.1.3).

2.2.1.1 The Risk Difference, RD(Med_0) at the median control survival time point

A proposal for reporting results in survival studies could be based on Table 1, which contains a measure of the absolute risk in the median reference group survival.

$\hat{\beta}$	$SE(\hat{\beta})$	*HRR*	*RD(Med_0)*	*$CI_{95\%}$ (RD (Med_0))*	*NNT (Med_0)*
-0.5	0.25	0.61	0.16	0.08 to 0.22	6.25

Table 1. One proposal for reporting results in survival studies based on the RD.

Assuming that the reference group median was one year, a clinician might say to his/her patient: *"Look, if you use the standard care, you will have a 50% chance of living more than one year. However, if you choose the study treatment, you will have a 66% chance of living more than one year* with an uncertainty ranging from 58% to 72%*"*.

That is, the patients in the treated group will have a probability of surviving to the reference median from 0.08 to 0.22 higher than in the other group. Graphically, this RD is represented in Figure 3.

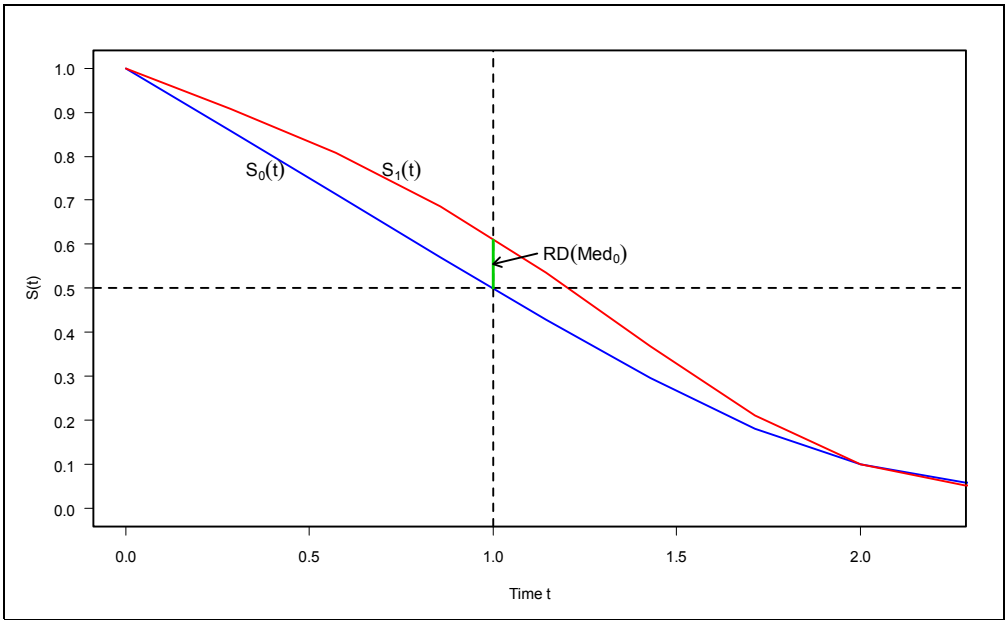


Figure 3. Graphical representation of RD between two groups in the median control survival time.

On the other hand, the Number Needed to Treat (NNT) represents the number of patients who should be treated in order to prevent one event. Therefore, a clinician might say to his/her manager: "*If you give me resources to treat 7 patients, I will avoid 1 event in one year*".

2.2.1.2 The Odds Ratio, OR(Med_0) at the median control survival time point

Alternative measures that can be considered at this particular point in time are the RR and the OR, through construction of the corresponding 2x2 table.

For example, assuming that there were 100 patients in each group and the same HRR and reference median as above, we get Table 2.

	Expected number of survivors in Med_0	Expected number of deaths in Med_0	Total
Treated group	66	34	100
Reference group	50	50	100
Total	116	84	200

Table 2. Expected number of survivors and deaths in both groups in median control time according to survival calculated using HRR.

Therefore, Table 1 can be transformed into Table 3 to report the OR(Med_0).

$\hat{\beta}$	$SE(\hat{\beta})$	*HRR*	*OR(Med_0)*	*$CI_{95\%}$ (OR (Med_0))*
-0.5	0.25	0.61	1.94	1.10 to 3.43

Table 3. One option for reporting results in survival studies based on the OR.

Assuming that the reference group median was 1 year, a clinician might say to his patient: *"Look, if you use the standard care, you will have a 50% chance of living more than a year. However, if you choose the study treatment, the odds of living longer increase by 94%* with an uncertainty ranging from 10% to 243%*"*.

The odds of surviving to the reference median is 1.94 ($CI_{95\%}$: 1.10 to 3.43) times higher in the treated group (Table 3).

2.2.1.3 The Relative Risk, RR(Med_0) at the median control survival time point

Also, Table 1 can be transformed into Table 4 to report the RR(Med_0).

$\hat{\beta}$	$SE(\hat{\beta})$	*HRR*	*RR(Med_0)*	*$CI_{95\%}$ (RR (Med_0))*
-0.5	0.25	0.61	1.32	1.04 to 1.68

Table 4. One option for reporting results in survival studies based on the RR.

Assuming that the reference group median was 1 year, a clinician might say to his patient: *"Look, if you use the standard care, you will have a 50% chance of living more than a year. However, if you choose the study treatment, the probability of living longer increases by 32%* with an uncertainty ranging from 4% to 68%*"*.

In other words, the probability of surviving to the reference median is 1.32 ($CI_{95\%}$: 1.04 to 1.68) times higher in the treated group (Table 4).

2.2.2 Bias of RR, OR and RD

As mentioned previously, these crude measures provide biased estimates in the presence of different censure patterns in both groups. The main advantage of calculation through the HRR is that it avoids this bias. A simulation procedure was defined to illustrate this fact. Box 1 describes it.

1. The theoretical RR, OR and RD in the reference group theoretical median were obtained assuming exponential times in both distributions with rates 1 and 0.8 and by applying the formulas of Appendix I with the modeled HRR (0.8).
2. For each group and each iteration, 50 exponential lifetimes with hazard rates 1 and 0.8 (controls and treated) were generated with the R function *rexp*.
3. The RR, OR and RD employing the full data in the reference group theoretical median were calculated using the resulting 2x2 table of survivors/deaths in front of treated/control at that moment.
4. A uniform censure was generated in order to have a 10% of censure proportion in the control group and a variable censure proportion in the treatment group (from 0 to 40% in steps of 2%). See Appendix IV for more detailed information about the censure generation procedure.
5. Employing the available data after applying the censure, the RR, OR and RD on the theoretical reference median were calculated. We used the 2x2 table resulting from the survivors/deaths in front of treated/control at that moment.
6. A Cox proportional hazards model was adjusted to obtain an HRR estimation.
7. The RR, OR, RD obtained by the HRR estimation were calculated using again the formulas of Appendix I.
8. Steps 2 to 7 were repeated 500 times.
9. The RR and OR for a specific censure proportion were estimated from the exponential of the mean logarithm estimations in the 500 simulations. The RD was the mean of RDs for the 500 values in each censure proportion.

Box 1. Simulation procedure to assess the bias of the RR, OR and RD with different censure proportion in both groups.

Figure 4, Figure 5 and Figure 6 show, respectively, the comparisons between modeled RR, OR and RD and the same measures obtained in three different ways (with uncensored data; with censored data through a 2x2 table; and with censored data from the HRR estimation). It can be seen that the RR, OR and RD calculated in a 2x2 table with the presence of censures provides biased estimations. The bias raised as the proportion of censored observations was more unbalanced in both groups.

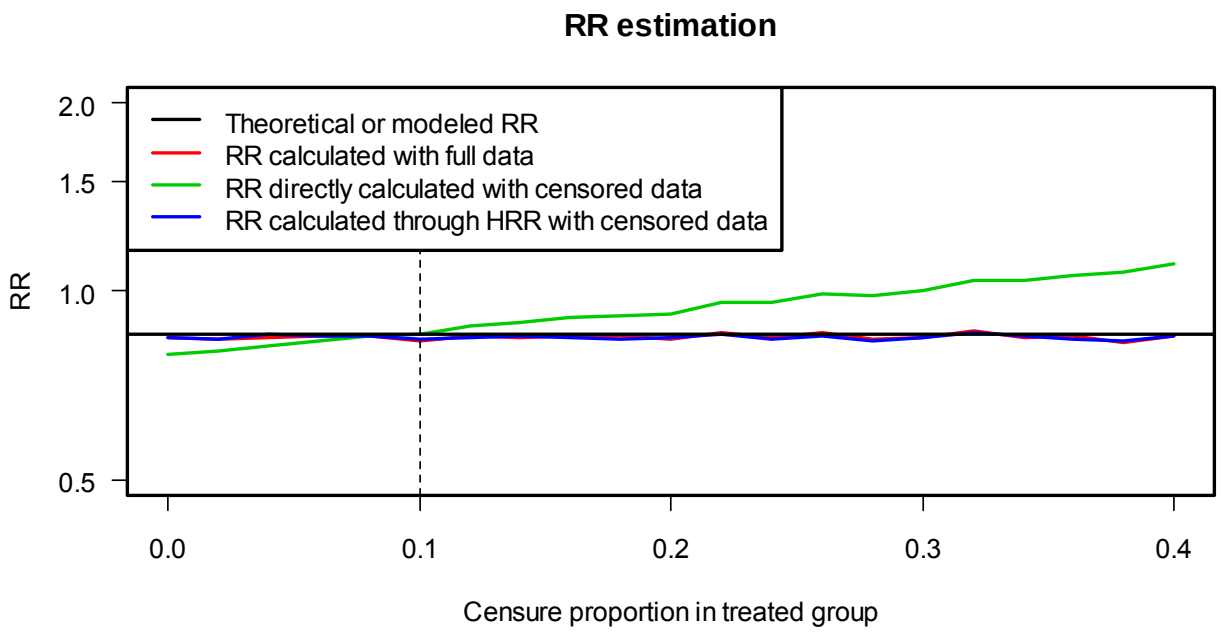


Figure 4. Theoretical RR (black) is the ratio of theoretical risks in Med_0. RR calculated with full data (red) is the ratio between risks over the uncensored exponential times generated with rates 1 and 0.8, respectively, on Med_0. RR calculated with censored data (green) has been calculated after adding 10% of censures in the control group and a variable censure proportion (x-axis) in the treated group. RR based on HRR (blue) has been calculated with the HRR estimated by the Cox model over the censored data. The vertical dotted line represents the censure proportion in the control group.

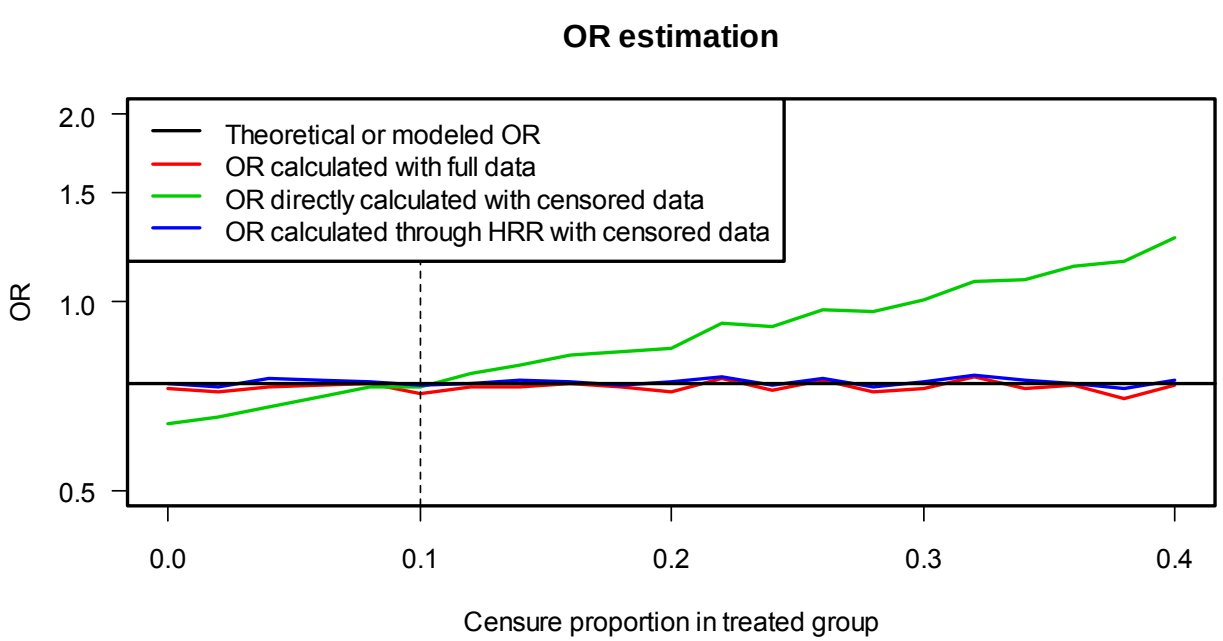


Figure 5. Theoretical OR (black) is the ratio of theoretical odds in Med_0. OR calculated with full data (red) is the ratio between odds over the uncensored exponential times generated with rates 1 and 0.8, respectively, on Med_0. OR calculated with censored data (green) has been calculated after adding 10% of censures in the control group and a variable censure proportion (x-axis) in the treated group. OR based on HRR (blue) has been calculated with the HRR estimated by the Cox model over the censored data. The vertical dotted line represents the censure proportion in the control group.

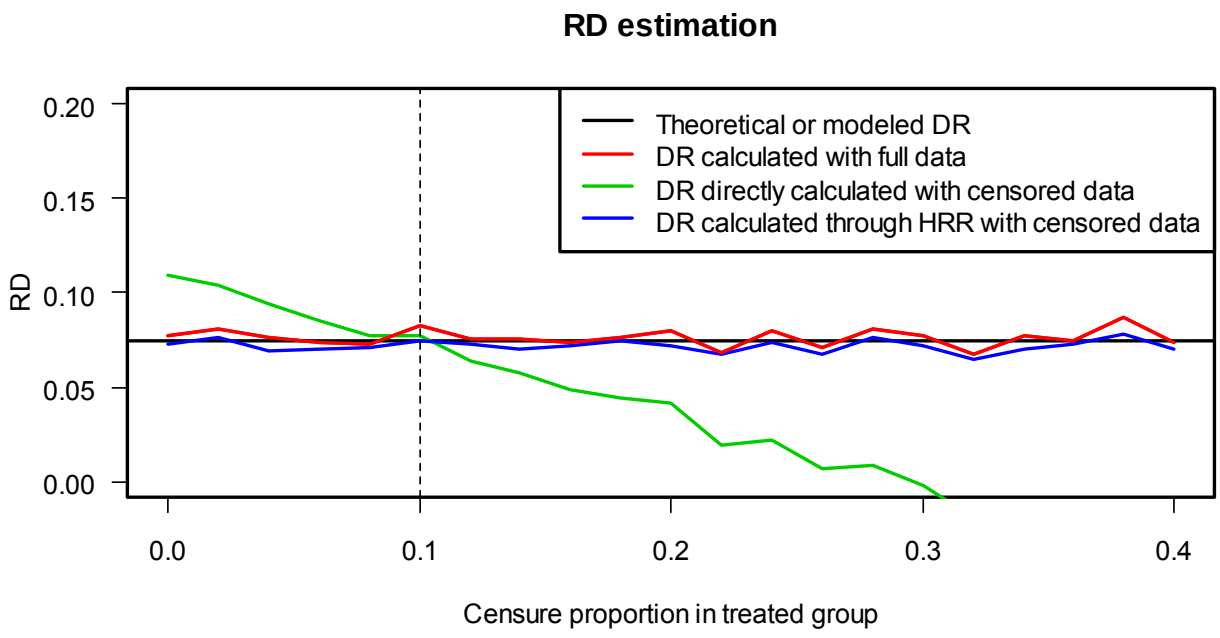


Figure 6. Theoretical RD (black) result from subtracting the theoretical $S_0(Med_0)$ from the theoretical $S_1(Med_0)$. RD calculated with full data (red) is the difference between $S_1(Med_0)$ and $S_0(Med_0)$ in the uncensored exponential times generated with rates 1 and 0.8, respectively. RD calculated with censored data (green) is the same quantity but calculated after adding 10% of censures in the control group and a variable censure proportion (x-axis) in the treated group. RD based on HRR (blue) is the difference between survivals in the reference group median calculated with the HRR estimation from the Cox model using the censored data. The vertical dotted line represents the censure proportion in the control group.

2.3 Other relationships with HRR: AUC

In this section, we study what relationship exists between the HRR and the likelihood that a patient of a group suffers an event before the patient of another group.

2.3.1.1 AUC_{WMW} and AUC_{HRR}

It must be considered that the hazard is a rate rather than a probability. Note that in the formula (1) the expression to the right of the limit sign gives the ratio of two quantities. The numerator is the conditional probability we just discussed. The denominator (Δt) denotes a small time interval. By this division, we obtain a probability per unit of time, which is no longer a probability but a rate. In particular, the scale for this ratio is not 0 to 1, as for a probability, but rather ranges between 0 and infinite, and depends on whether time is measured in days, weeks, months, or years, etc[12].

Despite this fact, Moser et al.[9] and later Buyse[13] demonstrated that there is a clear relationship between HRR and the probability (θ) that a patient in the treated group is alive longer than one in the control group and suggested that this probability, as a measure, is more readable than the HRR itself.

$$\theta = \frac{HRR}{1 + HRR} \qquad (18)$$

The expression (18) is true in any situation with constant HRR and without censured times. A correction to θ based on a modified version of the Wilcoxon statistic should be applied in the case of having censure[14]. At the same time, this probability corresponds to the AUC —and to the Wilcoxon-Mann-Whitney (WMW) statistic— employed especially in diagnostic studies as a complementary result of the logistic regression to quantify the discrimination power. In section 5, we assess the concordance between the AUC calculated in the traditional way (through the WMW statistic) and the AUC estimated through the HRR from the Cox model.

2.3.1.2 HRR is sensitive to order but not to time

On the other hand, does the HRR not depend on the survival times at all but only on the relative order of these times in both groups? In order to answer this question, we will present a pair of comparisons of survival times in 2 groups. The aim will be illustrated by an example that the act of switching times without changing the original order does not update the HRR estimation. Obviously, a lone example only proves the non-equivalence, but serves to conceptualize the meaning of HRR.

Now, we will explain the choice of the time values. Times in the treated group are the same in both comparisons and they are 20 integers, equally spaced. Half of the times in the control group in the first comparison are inserted within the 10 lower times in the treatment and the other half is fixed to the largest integer smaller than the lowest time of the treated group. In the second comparison, the first half of the reference times are the same and the second half is set at value 1 (see Table 5). Attention should be paid to the fact that relative rank times between two groups are the same in both comparisons.

		Times																			
Comparison I	Treated	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
	Control	9	9	9	9	9	9	9	9	9	9	11	13	15	17	19	21	23	25	27	29
Comparison II	Treated	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
	Control	1	1	1	1	1	1	1	1	1	1	11	13	15	17	19	21	23	25	27	29

Table 5. Times employed in two comparisons of survival times. Times in the treated group are the same in two cases, while in the control group the times with values 9 in the first comparison switch to 1 in the second.

We realize that times constructed in this way do not meet the proportional hazards assumption and therefore the Cox model should not be applied. However, the purpose is not to assess whether the assumption is verified, but if the estimation changes from one comparison to another.

We made the 2 comparisons between the 2 groups of survival times. Figure 7 shows the survival curves of Kaplan-Meier for these comparisons. Although the time of life gained in the first comparison is lower (MR: 4.8 vs. 2.9), the HRR is the same in both cases (0.20 $CI_{95\%}$: 0.09 to 0.44).

Interestingly, the HRR estimation from the Cox model does not have the transitive property and the HRR between both control groups is different than 1 (HRR = 1.18 $CI_{95\%}$: 0.64 to 2.22).

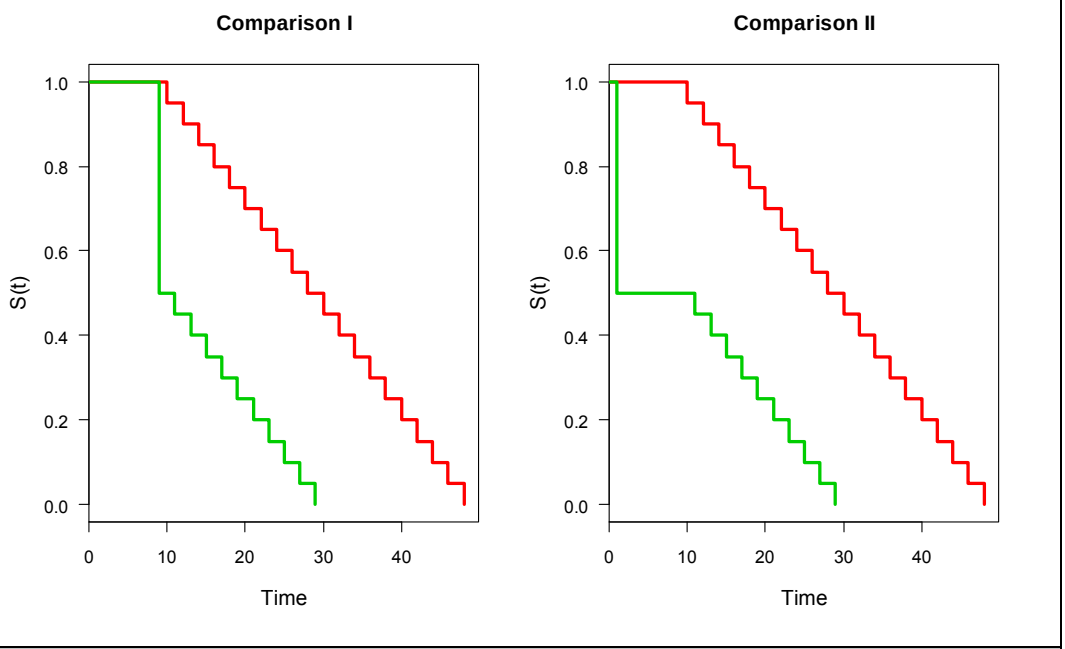


Figure 7. Kaplan-Meier survival curves in two comparisons.

3 Methods for empirical relationship between HRR and MR

In order to verify whether the analytical relationship between HRR and MR in the Exponential distribution was met in published studies, we conducted a literature search of survival studies published in the *New England Journal of Medicine* (NEJM) that reported HRR and the medians of the groups. The objective is to empirically quantify the concordance between HRR^{-1} and MR. In these papers, the concordance between both measures was assessed.

All HRR^{-1} (inverse of the HRR) of the studies have been standardized so that they were less than 1. That is, all those HRR^{-1} with values greater than 1 and its corresponding MR were inverted.

The statistical analysis were performed using the R software.

3.1 Bibliographical search

A Bibliographical search in the NEJM was performed with the criteria presented in Table 6 (Appendix V contains previous exploratory searches).

Search Code	Search Machine	Journal	Where	All words	Exact sentence	Some of the words	Year	Category
1	NEJM	NEJM	Text	-	Median Survival	Cox Hazard	2000-2010	Research
2	NEJM	NEJM	Text	Cancer	-	Cox Hazard	2000-2010	Research

Table 6. Bibliographical search criteria.

In summary, we have chosen survival trials published in the NEJM in the last decade, reporting the HRR and the median time of Overall Survival (OS) and/or Progression Free Survival (PFS) outcomes. The detailed eligibility criteria for the measures and for the studies are in Box 2.

Measures

1) Eligible survival measures refer either to Overall Survival (OS) or to Progression Free Survival (PFS) in any variant (Progression Free, Free Event, Disease Progression, Disease Free, Distant-Disease Free, etc.). Measures such as the duration of treatment were not included.

2) The adjusted or unadjusted HRR with its $CI_{95\%}$ are in the paper. If both are reported, adjusted HRR is chosen as a measure for analysis.

3) The median survival time in each group is reported, or alternatively, the survival curves that allow a graphical estimation are given.

4) Measures that are equivalent in the same study but evaluated differently were both included (for example, in one paper, the PFS may be considered by a radiological test or by symptomatology).

5) The measures relating to analysis of subgroups were not included unless the article only examines survival in the subgroups and does not make any global analysis (with all patients).

6) If there was a statistically significant interaction in the Cox proportional hazards model, then the measure was not included.

Articles/studies

7) The paper was published in the NEJM between January 2000 and December 2010.

8) Only Randomized Clinical Trials (RCTs) were included.

9) Studies with more than 2 treatment arms and with more than 2 comparisons were included.

Box 2. Eligibility criteria for the measures and for the articles/studies.

Box 3 shows the collected outcomes.

1) Search code with which the paper was found
2) Publication year of the article
3) Title of the paper
4) RCT (Yes/No)
5) Outcome category (Primary/Secondary)
6) Outcome type (OS/PFS)
7) HRR
8) Lower Limit (LL) of $CI_{95\%}$(HRR)
9) Upper Limit (UL) of $CI_{95\%}$(HRR)
10) Control group survival median
11) Treated group survival median
12) Number of patients in the control group
13) Number of patients in the treated group
14) Number of events in the control group (if available)
15) Number of events in the treated group (if available)
Box 3. Collected outcomes in bibliographical search.

3.2 Univariate descriptive

For categorical outcomes (publication year, measures by paper, outcome category and outcome type), the number and the percentage for each category are provided. In addition, bar charts are made.

For numerical outcomes (sample size, number of events, Log (HRR^{-1}) and Log (MR)), mean, Standard Deviation (SD) and boxplots are reported.

3.3 Concordance

3.3.1 Qualitative concordance

We have estimated a qualitative concordance as the proportion of pairs of measures where MR and HRR address the same treatment effect direction.

Also, a quantitative assessment of the concordance was performed in three ways (sections 3.3.2, 3.3.3 and 3.3.4).

3.3.2 Log (MR) - Log (HRR^{-1}) estimation

A paired weighted difference between Log (MR) and Log (HRR^{-1}) was estimated. To carry out the mean comparison, a linear regression weighted by the inverse of the variance of Log (HRR) was performed. The Standard Error (SE) of Log (HRR) was obtained as follows[15]:

$$SE_{Log(HRR)} = \frac{Log(UL_{HRR}) - Log(LL_{HRR})}{2 \cdot Z_{0.975}} \quad (19)$$

where UL_{HRR} and LL_{HRR} are the upper and lower limit of $CI_{95\%}$ for the HRR and $Z_{0.975}$ is the quantile 0.975 of the standard normal.

In the regression, the response was Log (MR) - Log (HRR^{-1}) and there was no explanatory variable, so that the intercept directly provides the estimation of the difference. The $CI_{95\%}$ was calculated from the SE and assuming normality in the estimator.

Due to the suspicion that the concordance was similar in measures of the same study, a repeated measures analysis was performed. We calculated the Intraclass Correlation Coefficient (ICC) for the response variable in studies that reported at least 2 pairs of measures. The ICC was calculated using a random effects model which considered the papers as blocks using the R function *lme* in *nlme* package. Subsequently, we calculated the Design EFFect (DEFF) using the formula:

$$DEFF = 1 + (m-1) \cdot ICC \quad (20)$$

where m is the number of measures per study (in our case, $m = 2$).

Finally, the previous $CI_{95\%}$ was increased by the DEFF.

3.3.3 Lin's concordance

The concordance between the Log (MR) and Log (HRR^{-1}) was assessed through Lin's coefficient (ρ_c), defined as follows[16]:

$$\rho_c = \frac{2 \cdot \sigma_{XY}}{\sigma_X^2 + \sigma_Y^2 + (\mu_X - \mu_Y)^2} \quad (21)$$

As population parameters were unknown, the sample estimators formula was employed instead of formula (21):

$$r_c = \frac{2 \cdot S_{XY}}{S_X^2 + S_Y^2 + \left(\bar{x} - \bar{y}\right)^2} \qquad (22)$$

All the statistics (means, variances and covariances) displayed in the expression (22) were weighted by the SE of the Log (HRR). The confidence interval for ρ_c was obtained assuming normality in the logarithms of the measures and using the following variance[17]:

$$\sigma_{\hat{\rho}_c}^2 = \frac{1}{n-2}\left[\frac{\left(1-\rho^2\right)\cdot\left(1-\rho_c^2\right)\cdot\rho_c^2}{\rho^2} + \frac{4\cdot\rho_c^3\cdot\left(1-\rho_c\right)\cdot u^2}{\rho} - \frac{2\cdot\rho_c^4\cdot u^4}{\rho^2}\right] \qquad (23)$$

where n is the number of observations; ρ is the Pearson correlation and u is the location shift relative to scale:

$$u = \frac{\mu_X - \mu_Y}{\sqrt{\sigma_X \cdot \sigma_Y}} \qquad (24)$$

As before, the unknown population parameters in (23) and (24) were replaced by weighted sample estimators.

Because this could be considered the primary analysis of the study, two sensitivity analyses were carried out. The first one consisted of obtaining the concordance by using the unadjusted HRRs. The second one tried to estimate the variance of Lin's coefficient through a bootstrap procedure with 10,000 simulations rather than analytically.

3.3.4 Bland-Altman concordance

The traditional bivariate scatter diagram (MR as a function of HRR^{-1}) is not a good graphical tool for assessing the agreement of 2 measures. In this graphic, the points tend to cluster around the regression line and it is difficult to observe differences between measures.

An alternative graphic for this purpose was presented by Bland and Altman[18]. This plot is a graphical technique for assessing the concordance between two measures that aim to evaluate the same response. It is constructed representing the differences as a function of the average of the two measures.

The location of points in the diagram allows an interpretation (Figure 8):

- A uniform cloud of points centered on zero of the y-axis indicates more concordance for smaller vertical dispersion to this center.

- A uniform cloud of points not centered on zero of the y-axis is an indication of a systematic error.
- A cloud of points increasing or decreasing along the x-axis indicates that the magnitude of the difference depends on the response value (therefore, the concordance is poor).
- Finally, a cloud of points with varying dispersion (usually increasing) along the x-axis indicates that the magnitude of the concordance depends on the response value.

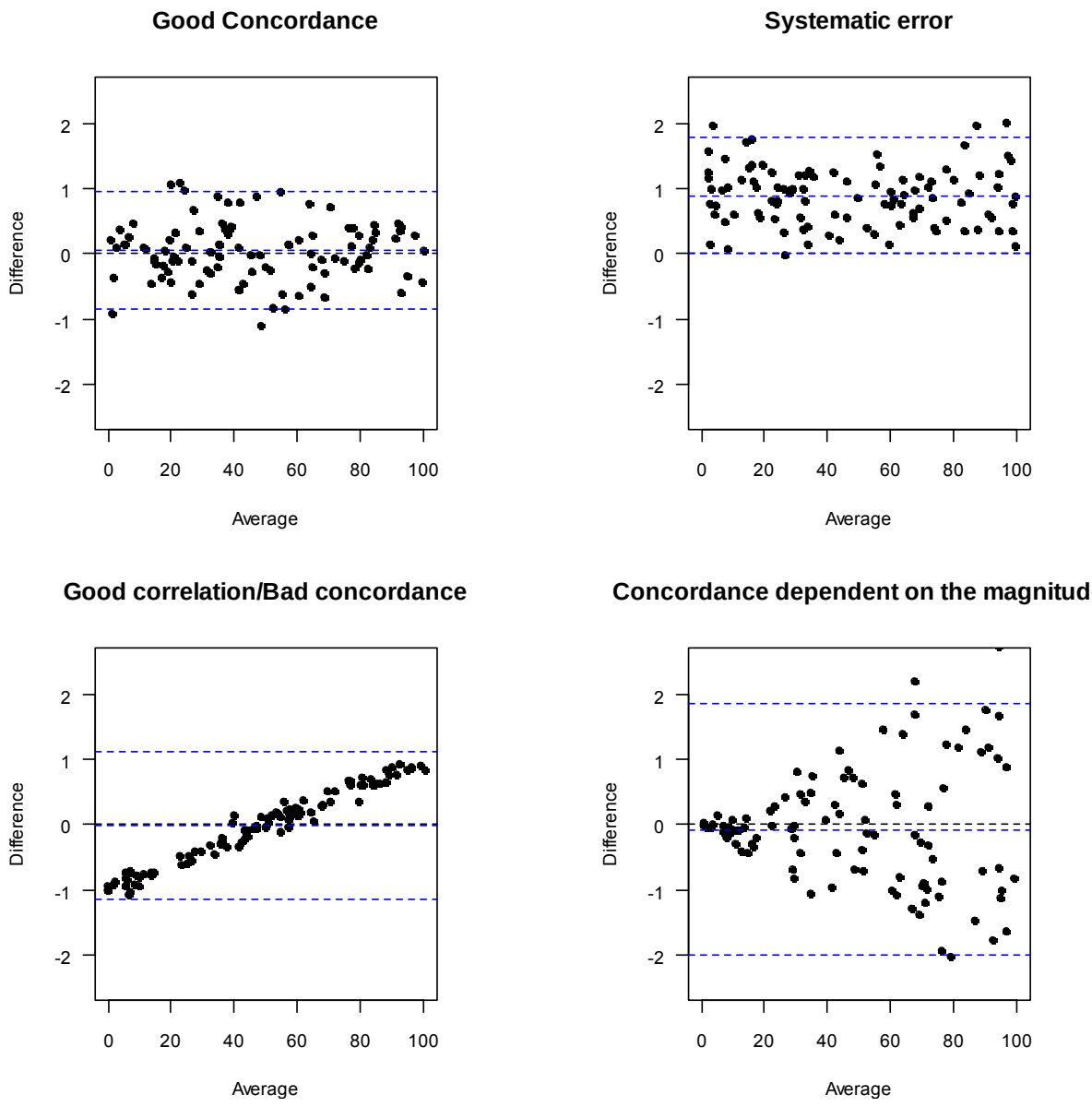


Figure 8. Examples of Bland-Altman graphic. The interpretation of each plot is summarized in the titles.

3.3.5 Concordance by subgroups

To evaluate the factors that could shrink the concordance subgroup, analyses were made according to the outcome type (OS / PFS) and the publication year (≤2005 / > 2005).

Also, in an exploratory way, we assessed whether the differences between the natural logarithms of the measures might depend on the censure proportion or on the total number of events. A bivariant graph of these differences in terms of these covariates was performed.

3.4 Publication bias

A post-hoc objective of this work was to evaluate whether there is a tendency to publish small clinical trials that had a more pronounced effect of the HRR than the MR (or vice versa). This issue was assessed with a Funnel plot and a metaregression.

3.4.1 Funnel Plot

A graphical tool used in the meta-analysis to evaluate this kind of bias is the funnel plot. Usually, it is built representing the effect on the horizontal axis (in our case, the x-axis represents the ratio between the MR and the HRR) and one of the following measures of accuracy in the vertical axis: the sample size, the SE, the inverse of the variance or the inverse of the SE[19].

Unfortunately, none of the above accuracy measures is applicable to our study. The sample size is not a good surrogate for the precision of the effect in survival studies (since there are censures and the number of events is not reported in many papers). On the other hand, we would like to have an SE estimation of Log (MR/HRR^{-1}), but from the information available in the studies only SE of Log (HRR) could be obtained. Therefore, in order to draw the funnel plot, the inverse SE of Log (HRR) was chosen as a surrogate measure of the inverse SE of Log (MR/HRR^{-1}). Appendix VI exposes some unsuccessfully attempts performed to obtain an SE estimation of Log (MR/HRR^{-1}).

A line in the funnel-plot separating the significant and the non-significant areas for a confidence level of 95% was represented using the SE of Log (HRR) and assuming normality[20] (we employed this SE because of the absence of SE of Log (MR/HRR^{-1})).

The $CI_{90\%}$ for the individual observations was estimated with a non-parametric bootstrap method. Box 4 explains the employed algorithm.

Parameters

m = 20	*number of points used in the estimation of each segment of the interval*
r =20	*number of points chosen with replacement of the previous m to perform an iteration of the bootstrap*
nboots = 100	*number of bootstrap iteration for each segment of the interval*
n = 120	*number of measures*

Algorithm

→ All measures of the ratios MR/HRR^{-1} are ranked according to the SE of Log (HRR) from lowest to highest and stored in a list (*List1*).

For *i* since 1 to $(n - m + 1)$

For *j* since 1 to *nboots*

1. The measures from *i* to $(i + m - 1)$ on the *List1* are selected in order to find a CI for these ones.
2. *r* of them are chosen with replacement.
3. The ratios MR/HRR^{-1} chosen in step 2 are ranked and stored in another list (*List2*).
4. The higher integer that is lower than or equal to *r*/20 and the lowest integer that is higher than or equal to (r-*r*/20) give us the positions in the *List2* that provides the li_j and ls_j values (the jth confidence limits)

End for

The mean of the *nboots* components of *li* and *ls* provide the *LL* and the *UL* of the $CI_{90\%}$ on the average height of the pertinent inverse SE (those points of *List1* from *i* to $(i+m-1)$.

End for

Remark. Generally, in step 4, for a $(1-\alpha)$ confidence level, the parameter *r* must be divided by 200α (bearing in mind that for non-integer values of $r/(200\alpha)$, the exact interval will not be obtained)

Box 4. Algorithm to calculate the $CI_{90\%}$ for the individual data in the funnel plot.

Interpretation

The value 1 of x-axis represents perfect concordance. Therefore, a remoteness of the geometric mean with respect to this value indicates a propensity for a greater effect on one of the two measures. Furthermore, if the geometric mean does not match the median, it is a symptom of asymmetry that would indicate that when the values of MR are greater than those of the HRR^{-1} this difference is greater than when the values of the HRR^{-1} are higher than those MR or vice versa.

There are two kinds of publication bias[21]. A first form of publication bias occurs when non-significant results are unlikely to be published (bilateral publication bias). In this case, the funnel plot is characterized by a hole in the center of the funnel for small studies. The other type is observed when studies with results that point to a non-desired effect are less likely to be published

(unilateral publication bias); they are characterized by the absence of one of the two tails in the funnel (Figure 9).

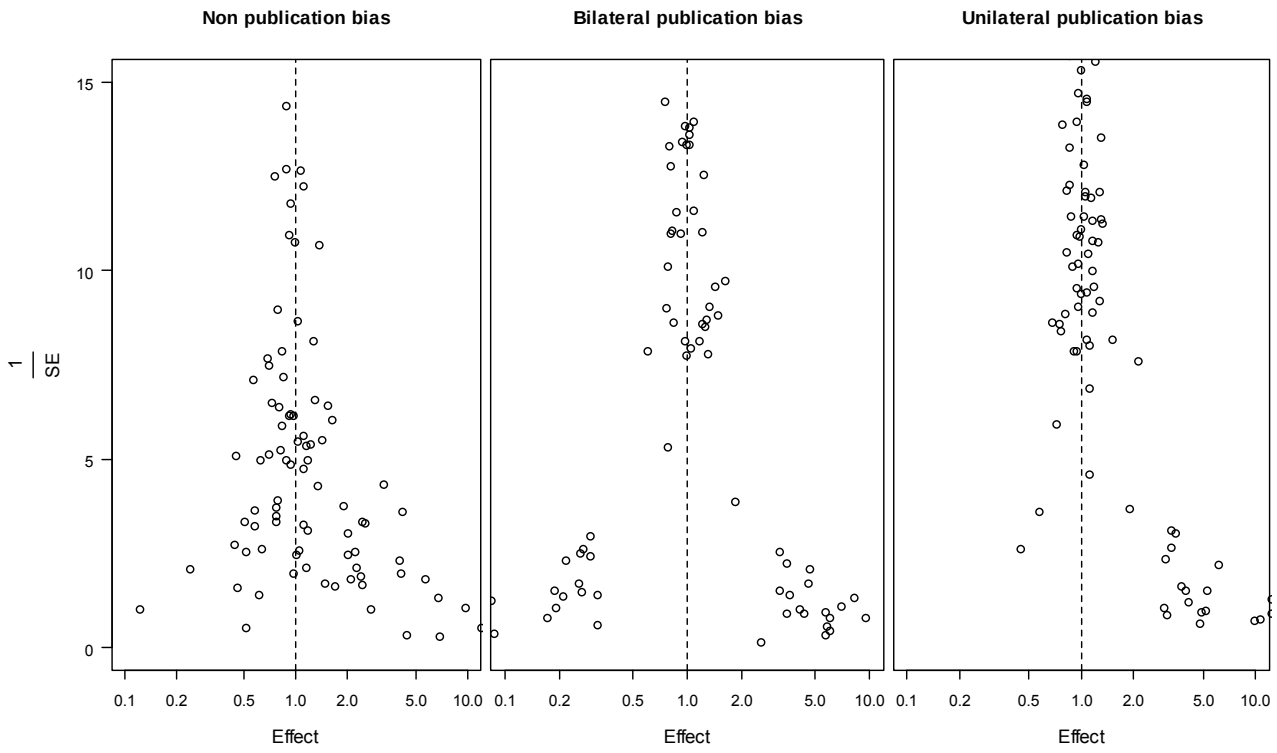


Figure 9. Examples for interpretation of funnel-plot.

3.4.2 Metaregression

Weighted linear metaregression was employed to formally test the unilateral publication bias hypothesis. The response outcome is the standardized difference of the logarithm measures:

$$\frac{Log(MR) - Log(HRR^{-1})}{SE} \qquad (25)$$

The explicative variable is the inverse of the SE of Log (HRR).

$$\frac{Log(MR) - Log(HRR^{-1})}{SE} = bias + slope \cdot \frac{1}{SE} \Rightarrow Log(MR) - Log(HRR^{-1}) = bias \cdot SE + slope \qquad (26)$$

The intercept of this regression represents the bias and it has a *t*-distribution with (*n*-2) degrees of freedom, *n* being the number of measures. This allows having a bias estimation with its CI[22].

4 Results of empirical relationship between HRR and MR

4.1 Bibliographical Search

Table 7 shows the search criteria results.

Search Code	Results	Accepted	Rejected	Repeatedly accepted	Repeatedly rejected
1	70	38	32	-	-
2	348	20	267	37	22

Table 7. Results of bibliographical search. *Results*: number of papers returned by the search engine; *Repeatedly accepted/rejected*: papers found in the second search that met/didn't meet the eligibility criteria and were accepted/rejected in the first search.

In total, 58 articles were found with 120 HRR and MR measures that met the eligibility criteria. Thirty-seven of the 38 papers accepted in the first search were also recovered in the second.

Since 21 (17.5%) median pairs were not reported in the text, they were obtained by visual estimation of the survival curves (Appendix VII quantifies how good those estimations are).

4.2 Univariate descriptive

20.7% of papers (12/58) came from 2007 and 74.1% had at least two measures (43/58). About the outcomes, 79/120 (65.8%) were the primary endpoint and exactly half of them referred to OS and to PFS (Figure 10).

The mean sample size of the collected studies was 537 (SD = 336) and the mean numbers of events was 389 (228). The outcome Log (HRR^{-1}) has a mean of - 0.369 (equivalent to HRR^{-1} of 0.69) with an SD = 0.30. The outcome Log (MR) has a mean of - 0.338 (equivalent to MR of 0.71) with an SD = 0.27 (Figure 11 and Table 8).

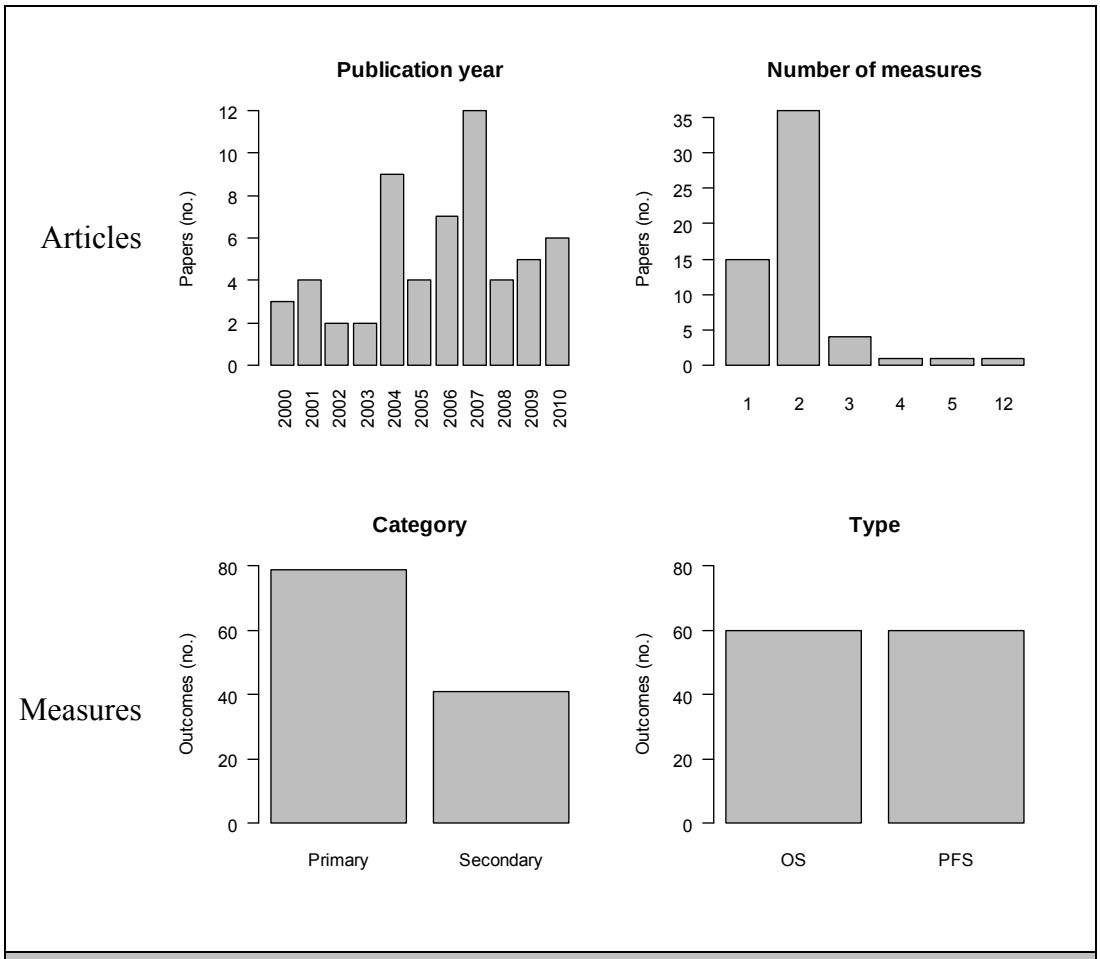


Figure 10. Univariate descriptive for the categorical outcomes: publication year of articles; number of measures per paper; outcome category; and outcome type.

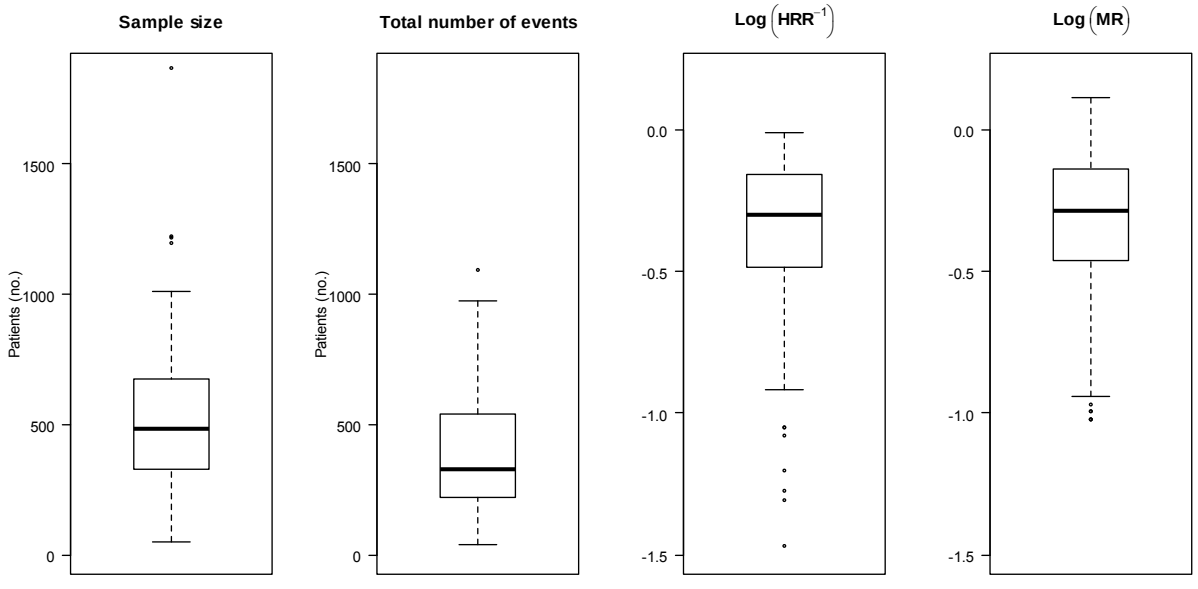


Figure 11. Univariate descriptive for numerical outcomes: sample size of the studies; total number of events per study; Log (HRR^{-1}) and Log (MR).

		n	%
Publication year	2000	3	5.2
	2001	4	6.9
	2002	2	3.4
	2003	2	3.4
	2004	9	15.5
	2005	4	6.9
	2006	7	12.1
	2007	12	20.7
	2008	4	6.9
	2009	5	8.6
	2010	6	10.3
Measures by paper	1	15	25.9
	2	36	62.1
	3	4	6.9
	4	1	1.7
	5	1	1.7
	12	1	1.7
Outcome category	Primary	79	65.8
	Secondary	41	34.2
Outcome type	OS	60	50.0
	PFS	60	50.0
			Mean (SD)
Sample size			537 (336)
Number of events			389 (228)
Log (HRR^{-1})			-0.369 (0.30)
Log (MR)			-0.338 (0.27)

Table 8. Numerical descriptive for main collected outcomes.

4.3 Concordance

4.3.1 Examples of high and low concordance in Kaplan-Meier survival curves

The aim here is to illustrate examples of Kaplan-Meier curves (extracted from the articles under study) where the concordance between the MR and the HRR^{-1} is either very high or very low (at the same time, this subgroup was subdivided into those cases with a higher HRR^{-1} effect or higher MR effect). Table 9, Table 10 and Table 11 show 3 examples of each type. For each measure, the MR, the HRR^{-1}, their ratio, the outcome type and the number of total events were reported.

4.3.1.1 High concordance

Table 9 shows no main feature in the curves with high concordance.

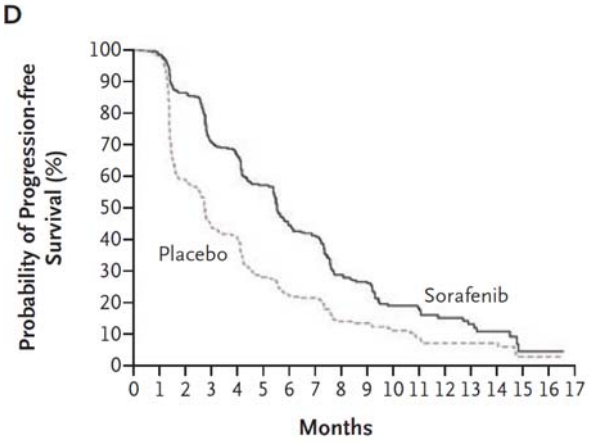
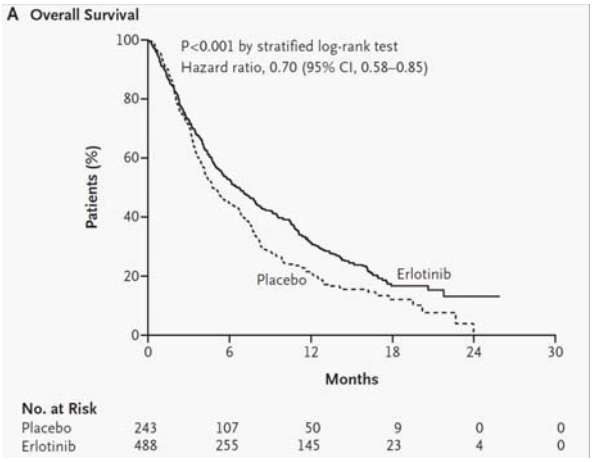
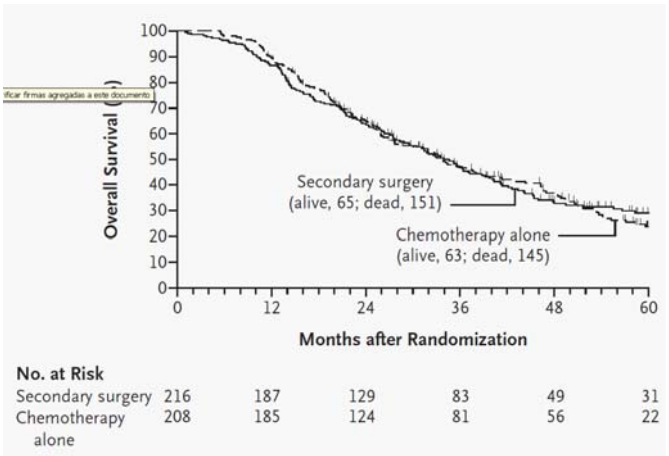
	MR = 0.51 HRR^{-1} = 0.51 MR/HRR^{-1} = 1.00 PFS Events (nº) = NA
	MR = 0.70 HRR^{-1} = 0.70 MR/HRR^{-1} = 1.00 OS Events (nº) = 587
	MR = 0.99 HRR^{-1} = 0.99 MR/HRR^{-1} = 1.00 OS Events (nº) = 296

Table 9. Examples of Kaplan Meier survival curves with high concordance between MR and HRR^{-1}.

4.3.1.2 Low concordance

Table 10 contains the 3 survival curves with a higher MR effect in respect to the HRR effect ($MR << HRR^{-1}$).

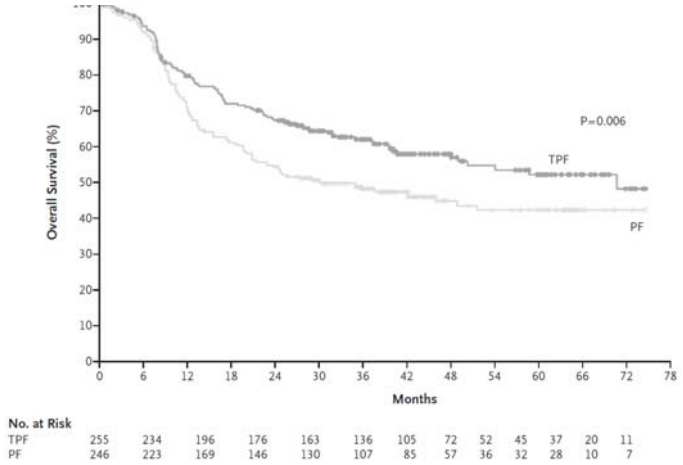
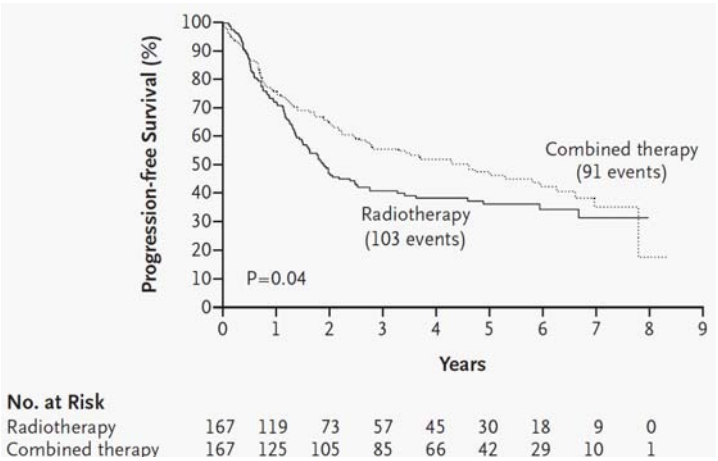
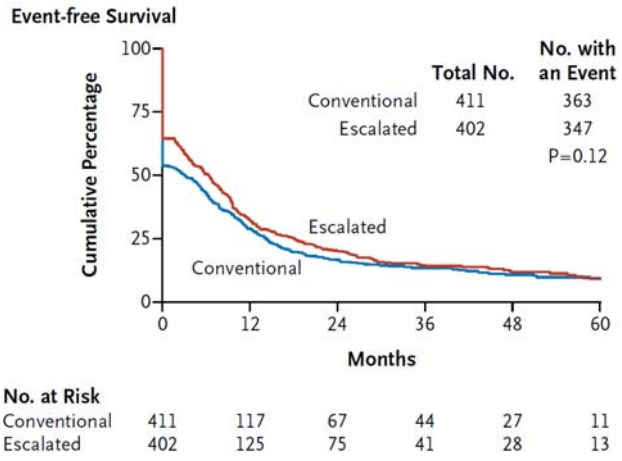
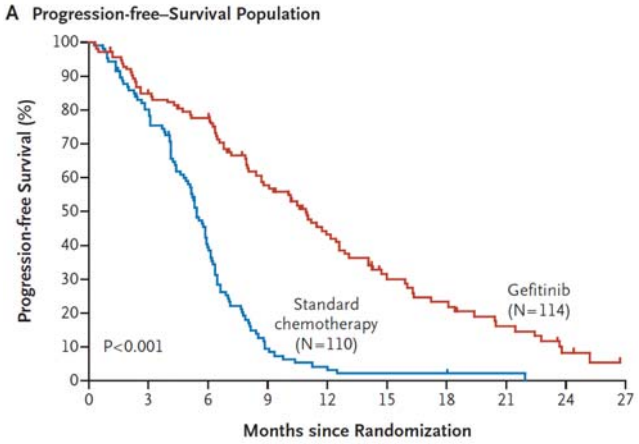
	MR = 0.36 HRR^{-1} = 0.71 MR/HRR^{-1} = 0.51 PFS Events = 198
	MR = 0.42 HRR^{-1} = 0.75 MR/HRR^{-1} = 0.56 PFS Events = 194
	MR = 0.50 HRR^{-1} = 0.89 MR/HRR^{-1} = 0.56 PFS Events = 710

Table 10.Examples of Kaplan Meier survival curves with low concordance between MR and HRR^{-1} and a higher MR effect. These curves correspond to the collected measures with a lower value of MR/HRR^{-1} (within the studies that reported the curves). It seems that the 3 curves show some proportion of patients having the event earlier, but then some stabilization occurs; it appears that patients who survive the first period, will not suffer the event.

Table 11 contains the 3 survival curves with higher HRR effect respect to the MR effect (HRR^{-1}<< MR).



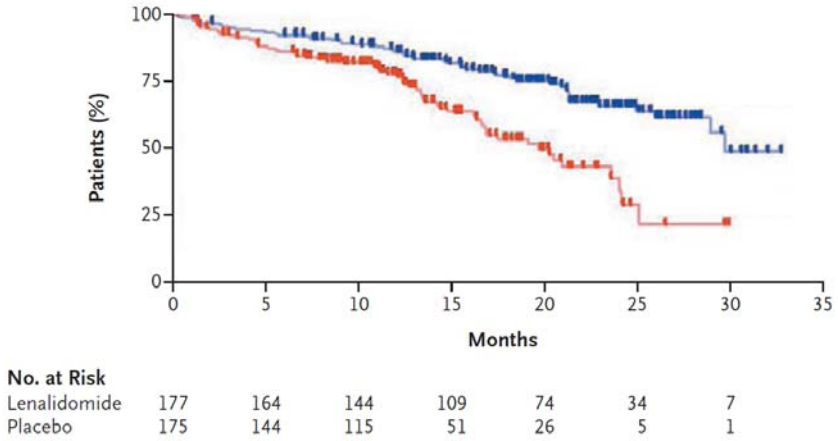
MR = 0.50

HRR^{-1} = 0.30

MR/HRR^{-1} = 1.67

PFS

Events = 218



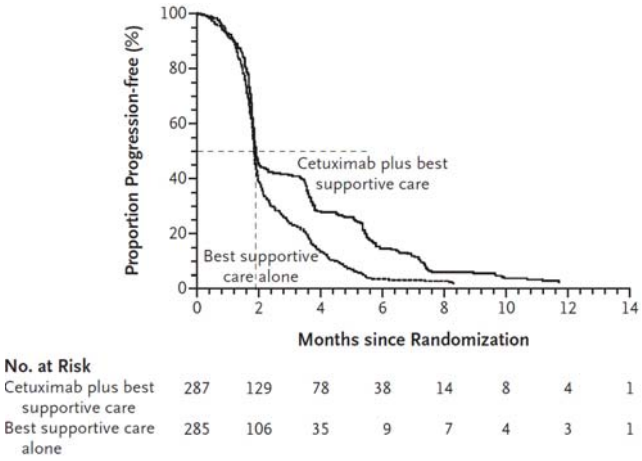
MR = 0.68

HRR^{-1} = 0.44

MR/HRR^{-1} = 1.55

OS

Events = 112



MR = 1.00

HRR^{-1} = 0.68

MR/HRR^{-1} = 1.47

PFS

Events = 542

Table 11. Examples of Kaplan Meier survival curves with low concordance between MR and HRR^{-1} and a higher HRR effect. Although it is difficult to check visually if the proportional hazards assumption holds, it seems that what they have in common is that the treatment effect is more pronounced in later times.

4.3.2 Qualitative concordance

In 116 of 120 pairs of measures (96.7%, $CI_{95\%}$: 91.2 to 99.0) the HRR and the MR aim in the same direction as the treatment effect. That is, MR and HRR^{-1} are either both less than 1 or both greater than 1.

4.3.3 Log (MR) - Log (HRR^{-1}) estimation

The estimation of the difference between the Log (MR) and Log (HRR^{-1}) weighted by the inverse of the squared SE of the Log (HRR) is:

$$\widehat{Log\left(\frac{MR}{HRR^{-1}}\right)} = 0.004 \qquad CI_{95\%} : -0.030 \; to \; 0.038$$

The estimated ratio between MR and HRR^{-1} is:

$$\widehat{\frac{MR}{HRR^{-1}}} = 1.004 \qquad CI_{95\%} : 0.970 \; to \; 1.039$$

The CI for the difference at the individual level will depend on the specific SE for any concrete study; therefore, to give a common CI at the individual level makes no sense.

Intraclass Correlation Coefficient

These CIs should be corrected by the ICC of agreement between measures of PFS and OS for each paper. A first assessment of the magnitude of the intraclass correlation concordance is shown in Figure 12.

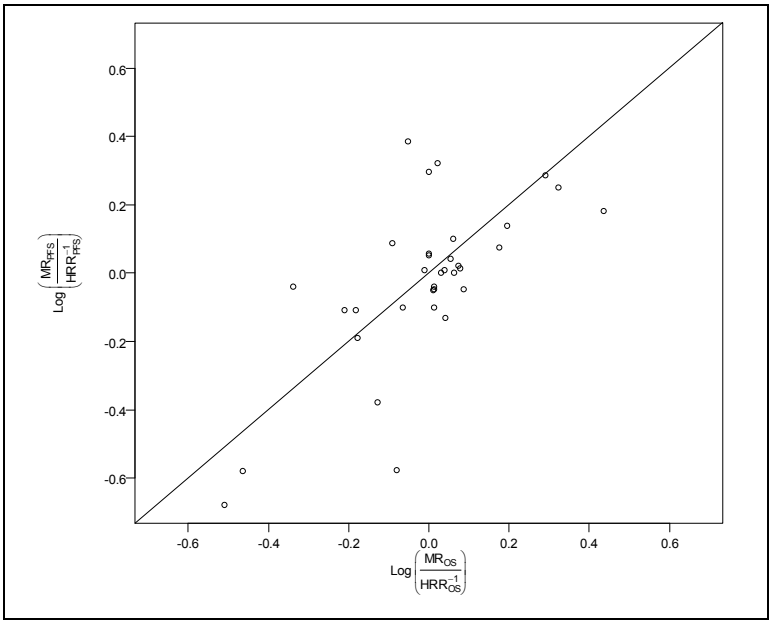


Figure 12. Difference in the natural logarithm of the PFS measures as a function of the same difference in OS measures.

An estimation of ICC obtained by a random effects model is 0.61. This is a very large value consistent with Figure 12. The Design Effect (DEFF) is:

$$DEFF = 1 + (m-1) \cdot ICC = 1 + ICC = 1.61$$

Now, the CI for the weighted difference between the Log (MR) and Log (HRR^{-1}) corrected by DEFF is:

$$\widehat{Log\left(\frac{MR}{HRR^{-1}}\right)} = 0.004 \qquad CI_{95\%} : -0.051 \; to \; 0.059$$

And the estimation of the ratio between the MR and HRR^{-1} is:

$$\widehat{\frac{MR}{HRR^{-1}}} = 1.004 \qquad CI_{95\%} : 0.950 \; to \; 1.061$$

4.3.4 Lin's concordance

The weighted Lin coefficient for the HRR^{-1} and MR logarithms was:

$$\hat{\rho}_c = 0.67 \qquad CI_{95\%} : 0.57 \; to \; 0.77$$

Given the lower limit of 0.57, this value can be considered as at least a *fair* concordance in the scale[23] of Box 5:

0.0-0.1	→	*independence*
0.1-0.3	→	*bad*
0.3-0.5	→	*poor*
0.5-0.7	→	*fair*
0.7-0.9	→	*good*
0.9-1.0	→	*almost perfect*

Box 5. Scale for Lin's coefficient

Two sensitivity analyses were performed: one concerning the point estimate and another uncertainty. The first consisted in finding the Lin coefficient using only the 16 available unadjusted HRRs. In this case, the point estimate was 0.78.

In addition, we estimated the bootstrap $CI_{95\%}$ for ρ_c with the original data (adjusted HRRs) and it resulted in a similar range: from 0.53 to 0.80.

4.3.5 Bland-Altman concordance

Figure 13 shows that there is equivalence between the two measures in the average of all studies; the weighted mean almost matches the perfect concordance. However, at the individual level, there is no equivalence; 95% of the individual MRs are located between an increase of 65% and a decrease of 48% in respect to the $HRRs^{-1}$.

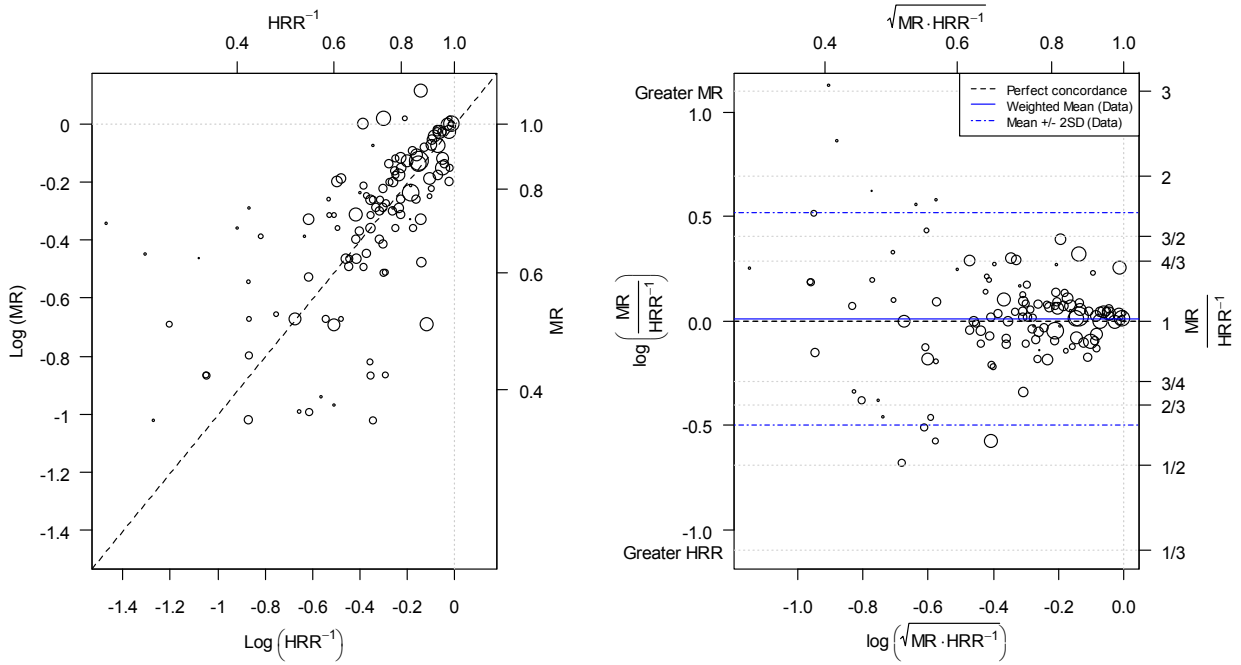


Figure 13. Left: Relationship between MR and HRR^{-1} (standardized to be less than 1). Right: Bland-Altman concordance plots discrepancies as function of averages. The size of the dots is proportional to the inverse of the SE of Log (HRR) obtained in the studies. The blue lines on the right graph represent the weighted mean (by the inverse of SE) of all observations and this average ± 2 SD.

4.3.6 Concordance by subgroups

The purpose of this section is to determine what factors may influence the concordance between the two measures. To this end, the concordances have been evaluated for various subgroups: by the outcome type (OS/PFS) and by the publication year (2 groups: before/during 2005 and after 2005). Also, we have studied if the censure proportion or the total number of events determines the concordance.

PFS / OS

A comparison of means between groups of PFS and OS for the variable | Log (MR) - Log (HRR^{-1}) | has been made. PFS measures have a greater difference between the two measures than in OS measures. Figure 14 shows that these differences seem to be higher for the PFS but unrelated to Log (HRR^{-1}) value.

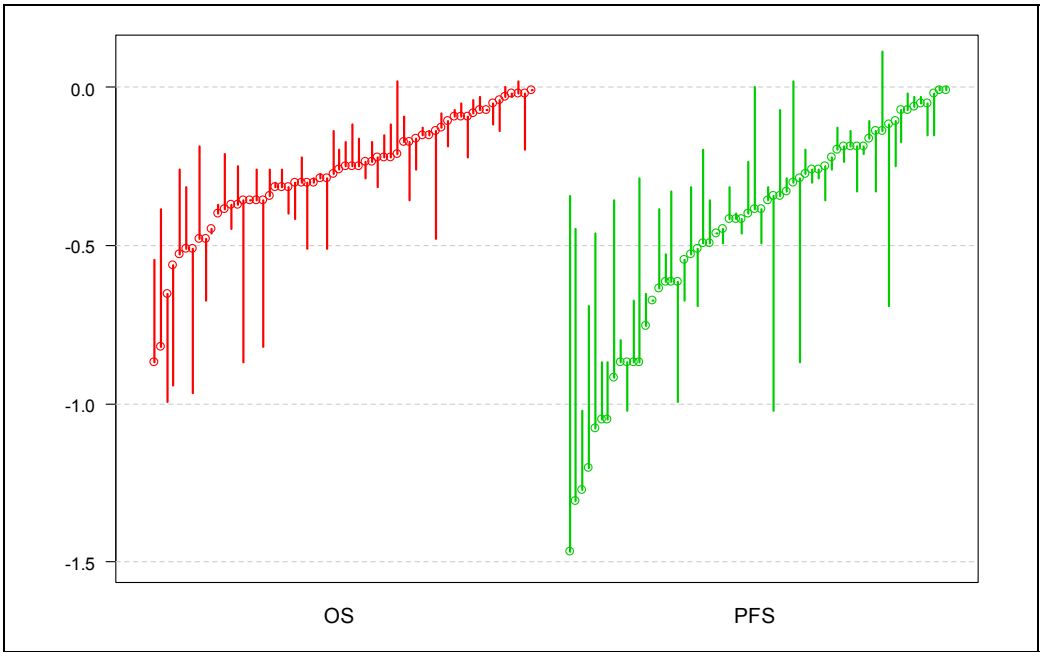


Figure 14. Dots represent the sorted Log (HRR^{-1}) in OS (red) and in PFS (green) on the y axis. Segments represent the difference between Log (MR) and Log (HRR^{-1}).

However, no significant differences exist between both groups (the explanation of the discrepancy with the Figure 14 is the use of weights in the comparison). The estimation of the difference corrected by DEFF is:

$$\overbrace{\left|\log\left(\frac{MR}{HRR^{-1}}\right)\right|_{PFS} - \left|\log\left(\frac{MR}{HRR^{-1}}\right)\right|_{OS}} = 0.07 \qquad CI_{95\%} : -0.01 \; to \; 0.15$$

This is equivalent to the following estimate of the ratio without logarithms*:

$$\frac{\overbrace{\max_{PFS}\left(\frac{MR}{HRR^{-1}}, \frac{HRR^{-1}}{MR}\right)}}{\max_{OS}\left(\frac{MR}{HRR^{-1}}, \frac{HRR^{-1}}{MR}\right)} = 1.07 \qquad CI_{95\%} : 0.99 \; to \; 1.16$$

* The exponential of the absolute value of the logarithm of a ratio is the same as the maximum between the ratio and its inverse. Let's look:

$$\exp\left\{\left|\log\left(\frac{A}{B}\right)\right|\right\} = \exp\left\{\left|\log(A) - \log(B)\right|\right\} = \exp\left\{\max\left\{\log(A) - \log(B), \log(B) - \log(A)\right\}\right\} =$$

$$= \exp\left\{\max\left\{\log\left(\frac{A}{B}\right), \log\left(\frac{B}{A}\right)\right\}\right\} = \max\left\{\exp\left(\log\left(\frac{A}{B}\right)\right), \exp\left(\log\left(\frac{B}{A}\right)\right)\right\} = \max\left\{\frac{A}{B}, \frac{B}{A}\right\}$$

Figure 15 shows the Bland-Altman graphic stratified by outcome type. The OS discordance seems to be greater for greater effect size. PFS points are generally further away from the perfect concordance (in either of the 2 directions) than the OS.

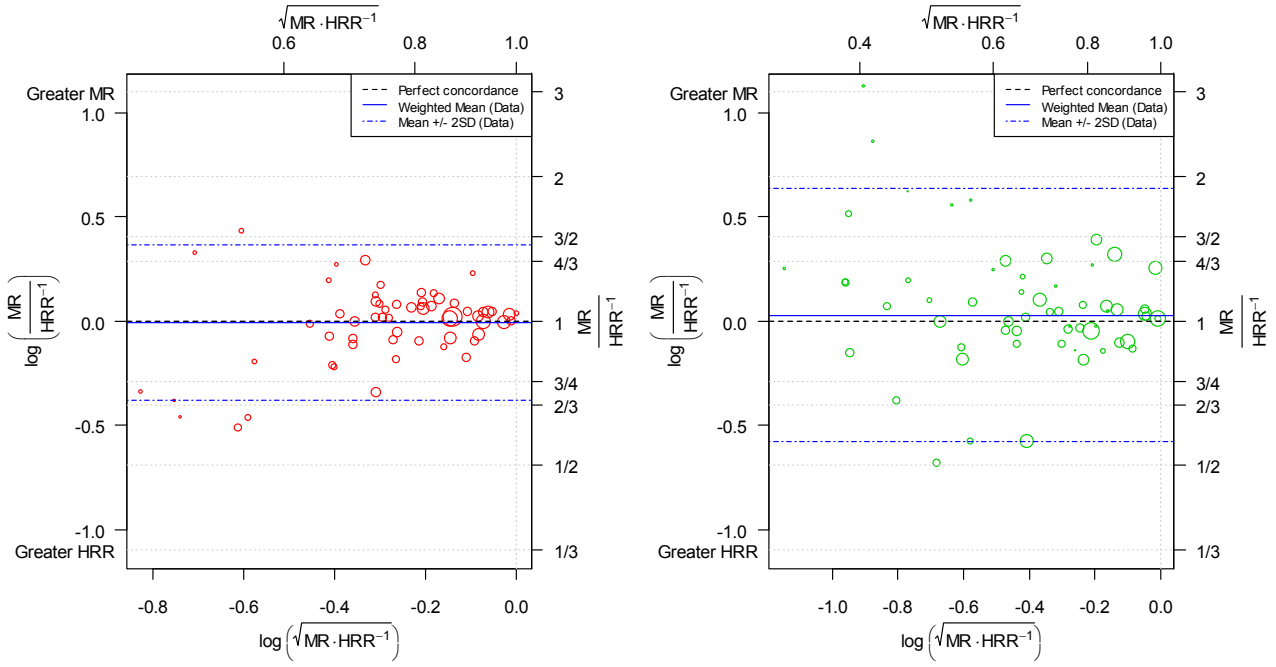


Figure 15. Left: Bland-Altman graphic for the measures of OS (red dots). Right: Bland-Altman graphic for the measures of PFS (green). The size of the dots is proportional to the inverse SE of Log (HRR) obtained in the studies. The blue lines represent the weighted average (by the inverse SE) of the pertinent observations and this average ± 2 SD.

However, despite a trend toward greater divergence in measures of PFS, the weighted OS concordance (r_c = 0.64) is similar to the PFS concordance (r_c = 0.65) due to the highest correlation presented in this last group. Calculations of overall and per group concordances are detailed below:

$$r_{global} = \frac{2 \cdot S_{XY}}{S_X^2 + S_Y^2 + (\bar{x} - \bar{y})^2} = \frac{0.045}{0.069 + 0.067 + (-0.300 + 0.310)^2} = 0.67$$

$$r_{OS} = \frac{2 \cdot S_{XY}}{S_X^2 + S_Y^2 + (\bar{x} - \bar{y})^2} = \frac{0.022}{0.043 + 0.026 + (-0.245 + 0.237)^2} = 0.64$$

$$r_{PFS} = \frac{2 \cdot S_{XY}}{S_X^2 + S_Y^2 + (\bar{x} - \bar{y})^2} = \frac{0.062}{0.091 + 0.099 + (-0.359 + 0.388)^2} = 0.65$$

where X represents Log (MR) and Y represents Log (HRR^{-1}). All statistics were weighted by the inverse SE of the Log (HRR^{-1}).

Before/during or after year 2005

Figure 16 supports the idea that there are no differences between the measures of older and recent studies.

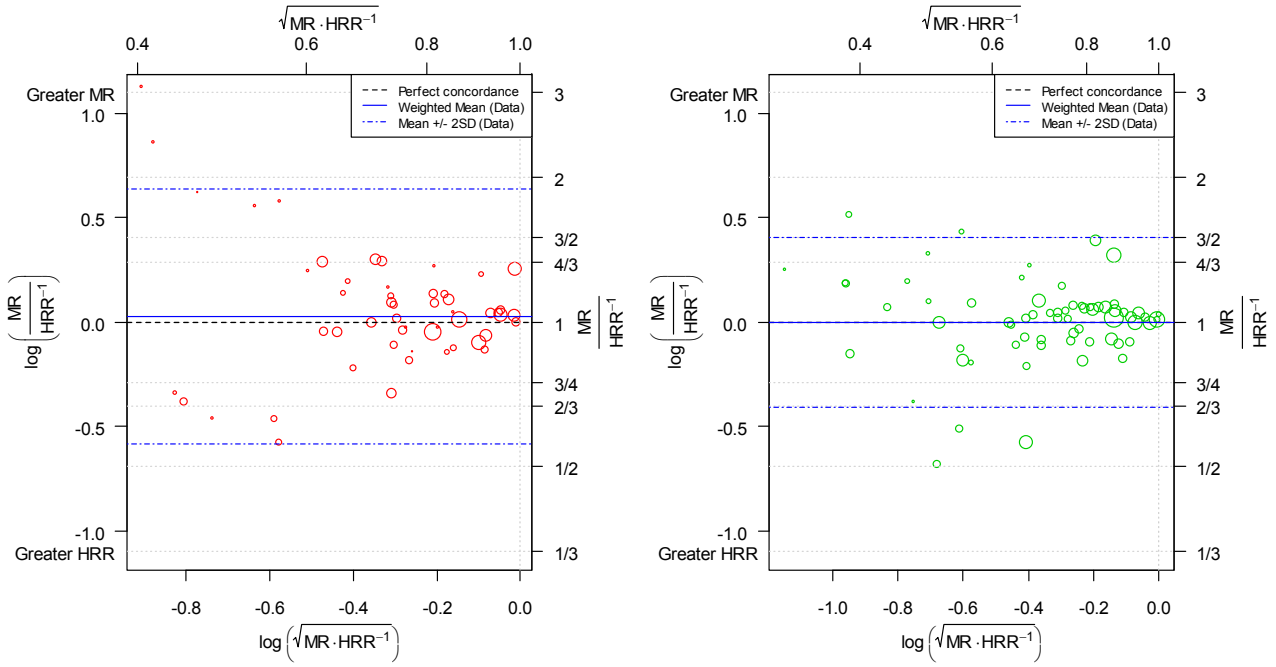


Figure 16. Left: Bland-Altman graphic for the study measures previous to 2006 (red dots). Right: Bland-Altman graphic for the measures after 2005 (green). The size of the dots is proportional to the inverse SE of Log (HRR) obtained in the studies. The blue lines represent the weighted average (by the inverse SE) of the pertinent observations and this average ± 2 SD.

No significant differences in the means of the | Log (MR) - Log (HRR-1) | depending on whether the study is before or after 2005. The estimation of the difference is:

$$\left|\log\left(\frac{MR}{HRR^{-1}}\right)\right|_{\leq 2005} - \left|\log\left(\frac{MR}{HRR^{-1}}\right)\right|_{>2005} = -0.013 \qquad CI_{95\%} : -0.099 \; to \; 0.073$$

Other covariates

Figure 17 shows that neither the censure proportion nor the total number of events seem to influence the difference between the measures under study.

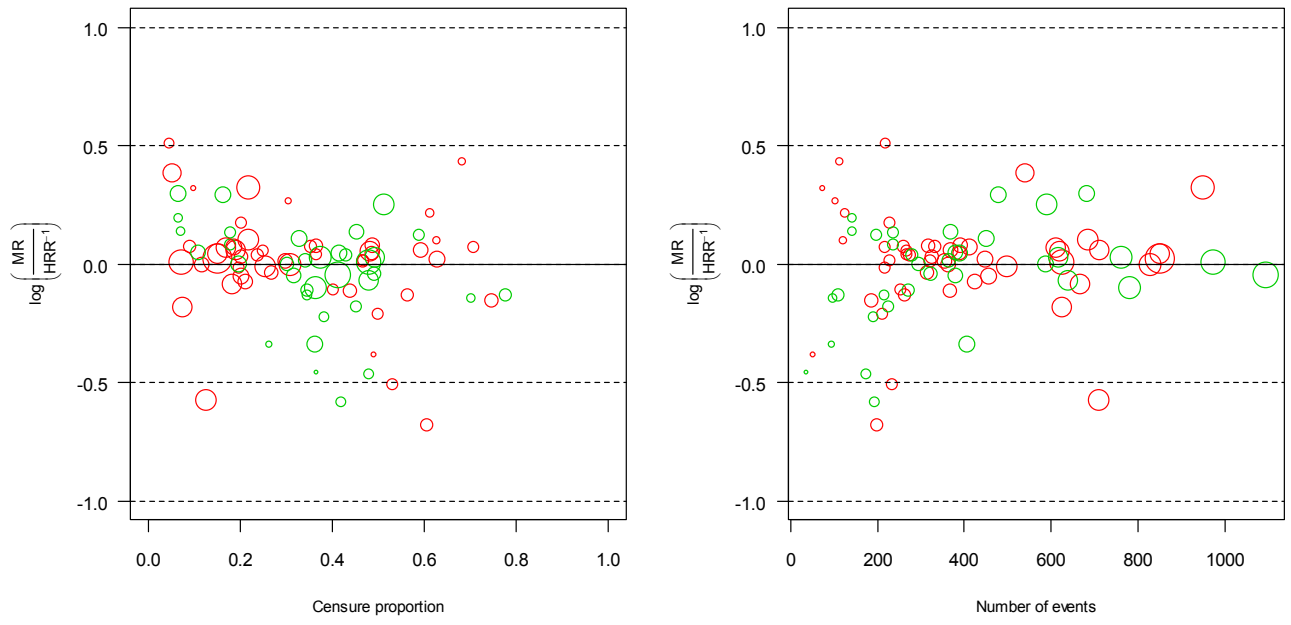


Figure 17. Left: Differences in natural logarithms of MR and HRR^{-1} as function of the censure proportion (if available). Right: Differences in natural logarithms of MR and HRR^{-1} as function of the number of events (if available).

4.4 Publication bias

In this section, the tendency to publish small clinical trials with a more pronounced effect of the HRR than the MR (or vice versa) was evaluated.

4.4.1 Funnel-Plot

Figure 18 shows the Funnel plot of the ratio between MR and HRR^{-1}.

- Points located on the left of the Funnel-Plot represent those responses with a greater observed MR effect than the observed HRR effect and vice versa (note that for greater effects, the value of the MR or the HRR^{-1} is lower).
- The geometric mean is slightly to the right of the perfect concordance. That is, the HRR^{-1} effect is slightly higher than the MR effect in the collected articles (this is equivalent to HRR^{-1} having smaller values).
- The mean and median coincide, as a sign of symmetry.

- There is a trend of the points for small studies to be located to the right. This could be indicative that those survival studies with small sample sizes that have a marked HRR effect compared with the MR effect were more published. To confirm this hypothesis, a metaregression was performed afterwards.
- Another less important interpretation of the low presence of points in the bottom of the graphic could be that the NEJM do not publish small studies.

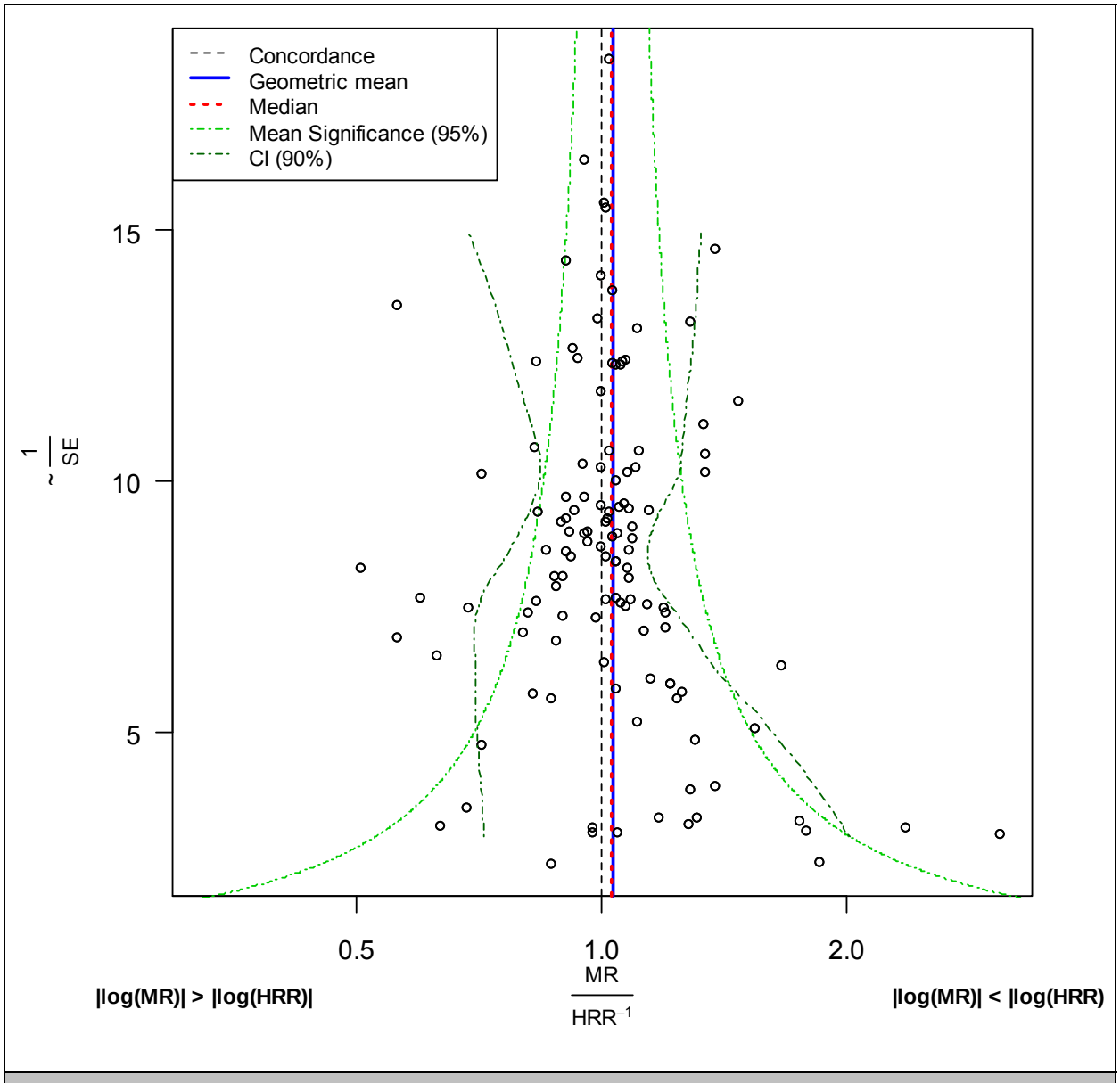


Figure 18. Funnel-plot of MR/HRR^{-1} in collected studies. Vertical axis represents the inverse SE of Log (HRR).

4.4.2 Metaregression

There is no evidence of bias (p = 0.40) to publish studies with an HRR effect more pronounced than the MR effect in small studies (large SE).

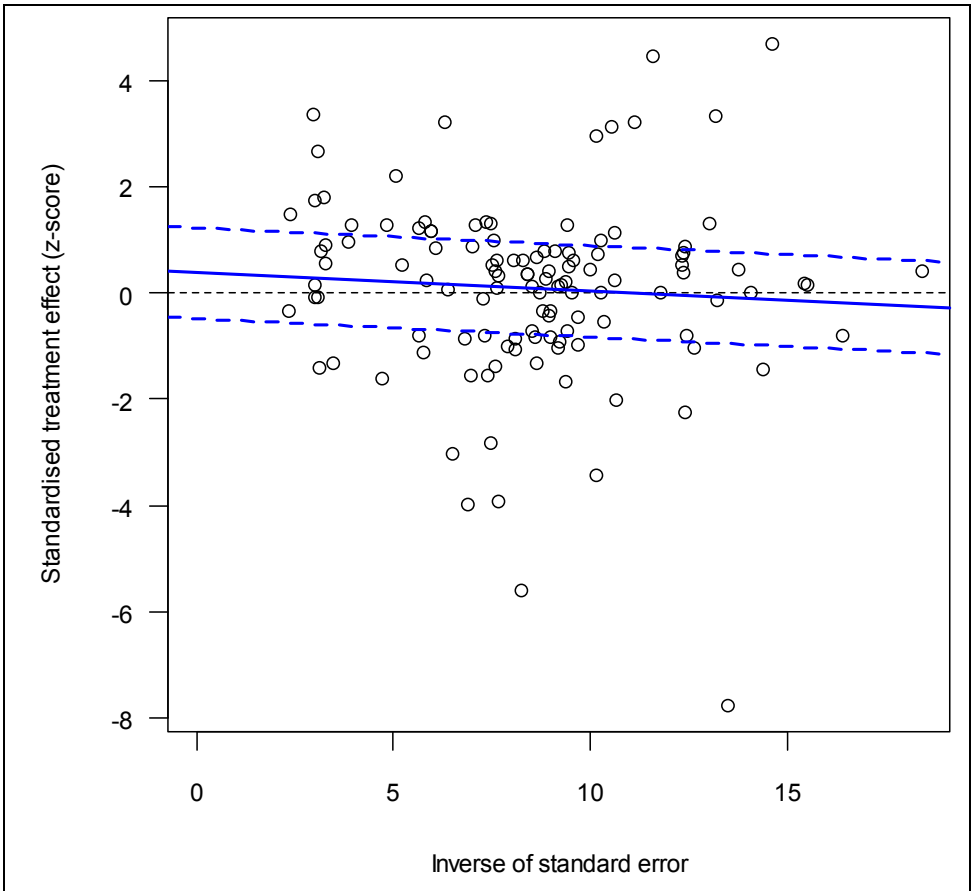


Figure 19. Weighted metaregression graphic of standardized Log (MR/HRR^{-1}) vs. the inverse of SE.

Interpretation

The estimated regression line (Figure 19) was:

$$\frac{D}{SE} = bias + slope \cdot \frac{1}{SE} = 0.37 - 0.03 \cdot \frac{1}{SE}$$

where *D* is the difference between the logarithm of the measures.

Consequently the point estimation for bias with its $CI_{95\%}$ was:

$$\widehat{Bias} = 0.37 \qquad CI_{95\%} : -0.49 \; to \; 1.24$$

Therefore, there is no evidence of publication bias, because it can not be excluded that the regression line runs through the origin.

5 AUC_{WMW} – AUC_{HRR} concordance by simulation

In this section, we mainly want to assess the concordance between the AUC_{HRR} based on formula (18) and the same probability AUC_{WMW} directly estimated as the proportion of treated-control pairs in which the treated patient suffers the event after the patient in the reference group. A simulation with uncensored exponential times was performed. Box 6 details the procedure.

A hundred simulations of the following steps were carried out:

1. Fifty exponential survival times per group were generated with rates 1 and 0.8 (control and treated) using R function *rexp*.
2. AUC_{WMW} was estimated exactly as the proportion of treated-control pairs in which the treated individual lives longer.
3. AUC_{HRR} was estimated with formula (18) using the estimated HRR from the Cox model.
4. Concordance between two probabilities was assessed with the Lin coefficient and Bland-Altman graphic.

Box 6. Simulation procedure to assess the concordance between AUC_{WMW} and AUC_{HRR}

Values of AUC_{WMW} ranged from 0.35 to 0.62 with a mean of 0.45 (SD = 0.06). Values of AUC_{HRR} ranged from 0.34 to 0.58 with a mean of 0.45 (0.05). It is noteworthy that the expected value is 0.44 (0.8/1.8). Paired mean difference was:

$$\overline{AUC_{HRR} - AUC_{WMW}} = -0.003 \qquad CI_{95\%} : \text{-0.018 to 0.011}$$

Figure 20 shows how strong the concordance is between the two estimators of the probability that an event occur earlier in one group than in another. Visually, it appears that the concordance is very high; specifically, it is:

$$\hat{\rho}_c = 0.86 \qquad CI_{95\%} : 0.81 \; to \; 0.91$$

Given the lower limit of 0.81, the concordance can be considered as at least a *good* concordance.

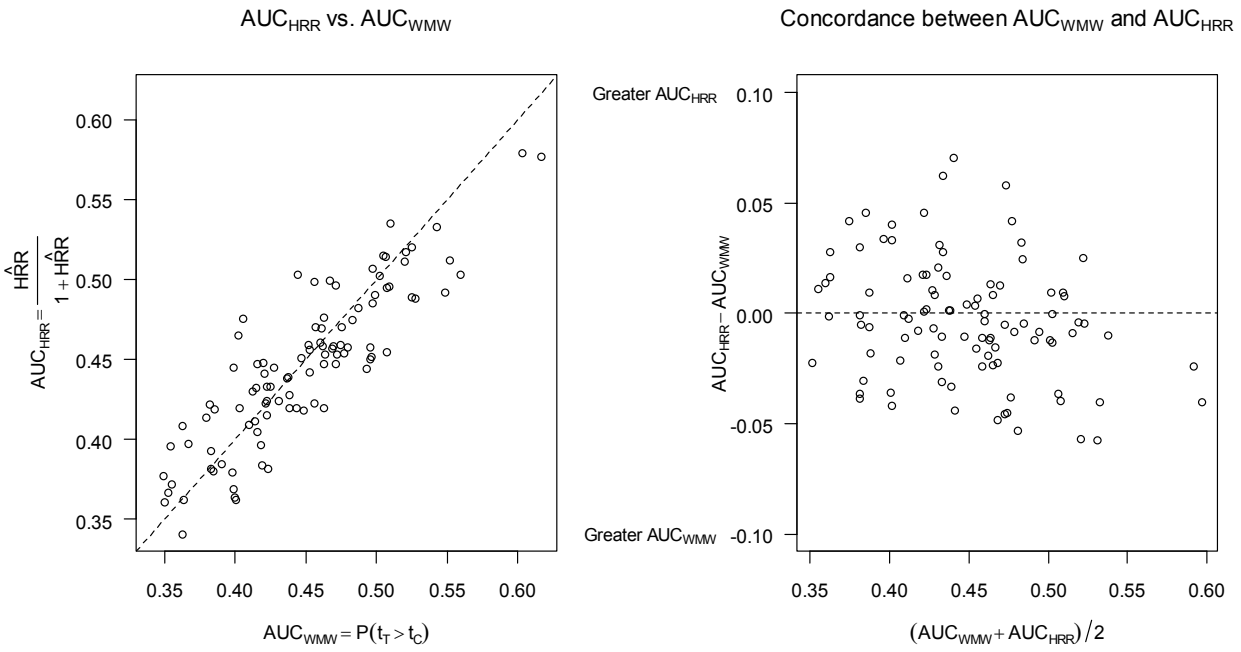


Figure 20. A hundred simulations of two exponentials with parameters 1 and 0.8 (for control and treated group) were employed. The sample size in each group was 50 patients. Left: Bivariant plot showing the relationship between the AUC_{WMW} and AUC_{HRR}. Right: Bland-Altman concordance for these 2 estimators.

6 Discussion

6.1 Key findings

This project has attempted to relate HRR to other statistical measures for supposedly better readability.

With regard to MR, we have seen a perfect theoretical concordance with HRR^{-1} in the Exponential distribution. In the measures of the NEJM papers, it was observed that there is a satisfactory concordance on average (the $CI_{95\%}$ indicates that the ratio between them ranges from 0.95 to 1.06), but this is not so clear at the individual level; 95% of observed MRs are within the interval of 65% above and 48% below the HRR^{-1}. This difference is too great to consider that MR and HRR^{-1} are interchangeable. About the qualitative concordance, only 3.3% of the pairs MR - HRR^{-1} have a disagreement in the direction of treatment efficacy. Although Figure 18 points toward a trend in publishing small studies with a greater HRR effect, the publication bias was not statistically significant.

Also, we have observed a theoretical equivalence between the ER with the HRR^{-1} (and, therefore, with the MR) in the Exponential distribution.

Assuming the proportional hazards assumption, there is a correspondence between the HRR and the AUC. This analytical relationship is met in the absence of censored data and, in the presence of censored data, a modified version of the Wilcoxon statistic must to be employed.

About the frequency measures, if censures are not taken into account, the effect estimations may be biased. In contrast, it has been observed that RR, OR and RD estimations based on HRR are unbiased in the case of exponential distribution and under different censure patterns.

6.2 Mechanisms and explanations

We can find 3 possible explanations for the relatively low empirical concordance found.

6.2.1 Proportional hazard assumption not met

Although there are formal statistical tests to assess the proportional hazards assumption, these tests are not usually reported in published articles. This fact leads us to suspect that in some cases, the premise can not be fulfilled.

As an example, we examine the 4 qualitatively discordant pairs of measures. In 3 of these 4 pairs, the survival curves of Kaplan-Meier were reported (Figure 21) in the papers. In all of them, the curves are crossing, making sense that the HRR was not constant over time.

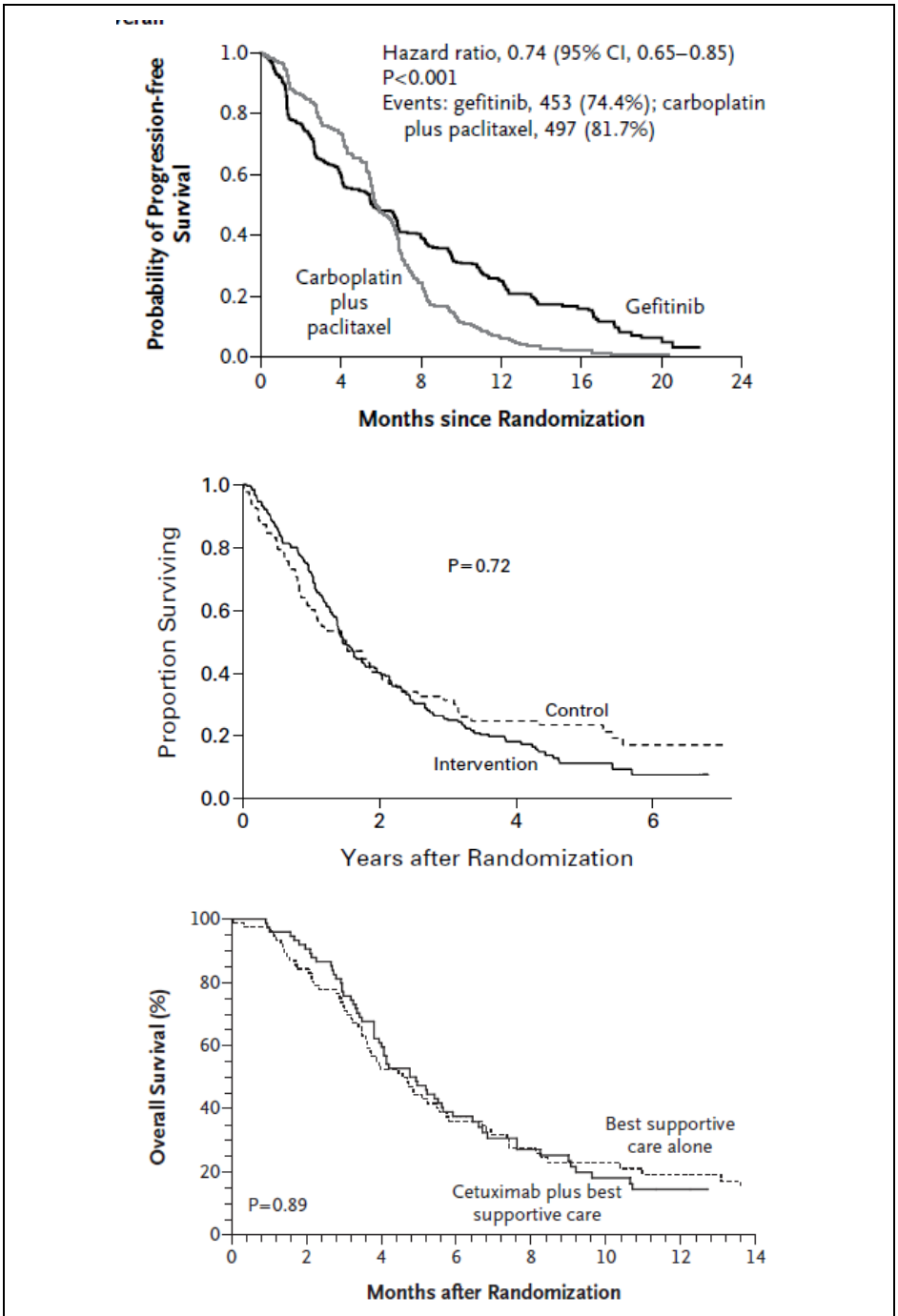


Figure 21. Three of the 4 survival curves for the measures in which the MR and HRR point to different directions of treatment.

6.2.2 Adjusted instead of unadjusted HRR

Another possible explanation about why greater empirical concordance was not achieved could stem from the use of adjusted HRRs in the analysis. The unadjusted HRRs were only available in 16 of the 120 measurements (13.3%), although reporting guidelines[24] advise the communication of both adjusted and unadjusted measures. In our specific case, the Lin coefficient increases from 0.67 to 0.78 when considering the unadjusted HRRs.

RCTs balance the different prognostic factors between groups and in the general linear model the absence of colinearity has the advantage that the adjusted treatment effect matches the unadjusted (sum squares decomposition theorem). Instead, this property does not apply to other models based on likelihood estimations (such as the Cox proportional hazards). In these situations, there are two effect measures: the adjusted or *specific effect on the unit* and the unadjusted or *overall effect on the population*[25].

6.2.3 Discordance due to systematic or random error

We studied whether the amount of discrepancy observed was due to systematic differences in the measures or to random fluctuations. Carrasco et al.[16] postulate that low concordance associated with high correlation implies a corrigible systematic error (i.e., one measure consistently takes values higher or lower than the other, such as in Figure 8 top-right) or a linear relationship between measures (Figure 8 bottom-left). If the correlation is too low it could mean that there is no concordance at all. That is, the random error is so large that concordance is fully diluted and can not be detected. In our case, a correlation between Log (MR) and Log (HRR^{-1}) of 0.68 is not large enough to ruling out a relevant random error.

On the other hand, a simulation explained in Appendix VIII was performed to see what would happen if the distributions in the studies had been exponential or Weibull. The aim was to assess the observed concordance between HRR^{-1} and MR in exponential distribution and between HRR^{-1} and MR^k in Weibull distribution. We wanted to study the Lin coefficient values in two situations where it is known that there is a perfect theoretical equivalence. In addition, we also assessed HRR^{-1} in front of MR in Weibull distribution.

Table 12 lists the concordances and global standard deviations for all data and for the subgroups of OS and PFS in the collected data (empirical distribution) and in simulations of exponential and Weibull distributions. The last two columns contain the average of the Lin coefficients and the SDs over 100 simulations.

Distribution	Outcome	Concordance (Lin Average)	SD
Empirical	Global	0.67	0.25
	OS	0.64	0.19
	PFS	0.65	0.30
Exponential	Global	0.93	0.14
	OS	0.89	0.11
	PFS	0.93	0.17
Weibull	Global	0.95	0.14
(HRR^{-1} vs MR^{k})	*OS*	0.91	0.10
	PFS	0.96	0.18
Weibull	Global	0.70	0.32
(HRR^{-1} vs MR)	*OS*	0.61	0.25
	PFS	0.75	0.37

Table 12. Observed and simulated concordances and SD.

The simulated concordances are higher to the observed ones when there is theorical concordance, but similar when there is not. This result suggests that the discrepancies in the observed data could not be due solely to sampling variability. As an additional conclusion, we rule out that neither of these ones are the distributions of survival times in the most studies of the NEJM.

Appendix IX contains the Figure 30, which shows where the lines representing ± 2 SD would be located if the distributions were exponential or Weibull. Moreover, in the same Appendix, there are 4 simulations of the Bland-Altman graphic for these distributions. In any case, it is apparent that the random variability is not the cause of the observed empirical discrepancies.

6.3 Comparison with other relevant studies

The study of Michiels et al.[8] is the most similar to this work, although the objective was somewhat different (focused on meta-analysis). They did not formally assess concordance, but they found greater disagreements in the directions of the treatment effect between the HRR and the MR. By contrast, the quantitative relationship is very optimistic in the sense that the bivariant diagram of the Log (MR) versus Log (HRR) have almost all points close to the bisection. Despite this, in their discussion it is stated that the MR is not a reasonable alternative to HRR.

6.4 Challenges

There are some issues for improvement in this work that we will mention below.

Some questions remain for future research which could be noted. It should be studied if measures such as MR, ER, RR, OR, RD and AUC are more interpretable than the HRR for people involved in health decisions. A survey for doctors and patients could be conducted about the understanding of these measures.

No empirical study on mean survival was possible because medical papers with censored data do not report this information. Nevertheless, the biggest concern for a patient is the lifetime that is gained from a particular intervention, and this information is obtained directly through the survival means in each group. With the purpose offering an answer in this regard, we recommend future research on methods for estimating this statistic in the presence of censored times.

Finally, for simplicity, many of the simulations in this work are based on exponentially distributed times. We are aware that this modeling is not the most suitable to situations under study; for this reason, it should be checked that the results are robust in other settings.

6.5 Generability and conclusions

The data of this work is taken from a single medical journal. The reason for choosing only one is, first, to obtain more homogeneous data and, second, to speed up the data collection. The reason for choosing the NEJM is that it provides more results with the search criteria than other journals (for example, in 2010, NEJM published 168 RCTs with humans, while BMJ published 128, JAMA 60 and Annals of Internal Medicine 37) and, in turn, NEJM contained a higher proportion of eligible papers.

It is difficult to know whether the results are extrapolated to other studies of lower quality published in other journals. A hypothesis could be that these studies have a worse analysis process and that many of them, probably, do not meet the proportional hazards assumption, leading to lower concordance.

Although the MR is not interchangeable with the HRR^{-1}, they can be approximated from each other in studies that do not have a very large effect size. In addition, alternative measures to HRR can complement the information reported in survival papers.

ANNEX I. $S_1(t)$, RR, OR and RD en funció del HRR i de la $S_0(t)$

La Taula 13 mostra com per HRR constants i valors de $S_0(t)$ donats, els valors de $S_1(t)$, RR, OR i RD no són constants al llarg del temps. Els valors per cada estadístic han estat calculats amb les següents expressions:

$$S_1(t) = S_0(t)^{HRR}$$

$$RR(t) = \frac{1 - S_1(t)}{1 - S_0(t)}$$

$$OR(t) = \frac{\left(1 - S_1(t)\right) / S_1(t)}{\left(1 - S_0(t)\right) / S_0(t)} \qquad (27)$$

$$RD(t) = S_1(t) - S_0(t)$$

$S_1(t)$		**HRR**				
t (anys)	**$S_0(t)$**	**0.9**	**0.8**	**0.7**	**0.6**	**0.5**
1	**0.8**	0.82	0.84	0.86	0.87	0.89
2	**0.6**	0.63	0.66	0.70	0.74	0.77
3	**0.4**	0.44	0.48	0.53	0.58	0.63
4	**0.2**	0.23	0.28	0.32	0.38	0.45
RR(t)		**HRR**				
t (anys)	**$S_0(t)$**	**0.9**	**0.8**	**0.7**	**0.6**	**0.5**
1	**0.8**	0.91	0.82	0.72	0.63	0.53
2	**0.6**	0.92	0.84	0.75	0.66	0.56
3	**0.4**	0.94	0.87	0.79	0.70	0.61
4	**0.2**	0.96	0.91	0.84	0.77	0.69
OR(t)		**HRR**				
t (anys)	**$S_0(t)$**	**0.9**	**0.8**	**0.7**	**0.6**	**0.5**
1	**0.8**	0.89	0.78	0.68	0.57	0.47
2	**0.6**	0.88	0.76	0.64	0.54	0.44
3	**0.4**	0.85	0.72	0.60	0.49	0.39
4	**0.2**	0.81	0.66	0.52	0.41	0.31
RD(t)		**HRR**				
t (anys)	**$S_0(t)$**	**0.9**	**0.8**	**0.7**	**0.6**	**0.5**
1	**0.8**	0.02	0.04	0.06	0.07	0.09
2	**0.6**	0.03	0.06	0.10	0.14	0.17
3	**0.4**	0.04	0.08	0.13	0.18	0.23
4	**0.2**	0.03	0.08	0.12	0.18	0.25

Taula 13. Per una supervivència basal $S_0(t)$ (0.8, 0.6, 0.4 i 0.2) i un HRR (0.9, 0.8, 0.7, 0.6, 0.5) donats, valors de $S_1(t)$, del RR, del OR i del RD.

Es pot observar que (1) el RR pren valors superiors al HRR; (2) el OR pren valors inferiors al HRR; (3) les diferències es van ampliant a mesura que passa el temps i que el HRR disminueix.

ANNEX II. Principals distribucions en els estudis de medicina

Les distribucions dels temps de supervivència es poden classificar segons la forma de la seva funció de risc (λ). A continuació citem les formes més usuals i en quines situacions apliquen[26].

1) Funció de risc constant. Correspon a poblacions que no presenten envelliment respecte la variable resposta. La distribució que resulta és l'exponencial. És molt inusual i només es podria donar en determinats esdeveniments adversos. Per exemple, les hemorràgies digestives després de l'administració d'antiinflamatoris es diu que tenen el mateix risc sigui la primera o l'enèsima vegada que es prenen.

2) Funció de risc creixent: Es dóna en poblacions que envelleixen amb el pas del temps per l'edat o per desgast. Es pot trobar en l'anàlisi del temps de vida de pacients amb leucèmia que no responen al tractament.

3) Funció de risc decreixent: Correspon a poblacions amb una versemblança de fallada molt primerenca. Els individus s'enforteixen amb el pas del temps; es dóna en els pacients després d'un trasplantament o a l'inici de la vida de qualsevol persona.

4) Funció de risc amb forma de banyera: La funció de risc és decreixent a l'inici, constant durant un llarg període de temps i creixent al final. Apropiada com a model per a poblacions que es segueixen des del naixement. Moltes dades de mortalitat segueixen aquest tipus de corbes ja que al principi les morts resulten de les malalties infantils, després la baixa taxa de mortalitat s'estabilitza i es segueix un lent procés creixent a causa de l'envelliment de la població.

5) Funció de risc amb forma de gepa: La funció de risc creix a l'inici i al cap d'un temps comença a decréixer. Apropiada com a model per a la supervivència després de cirurgia ja que a l'inici hi ha un risc creixent de mort a causa de les infeccions i possibles hemorràgies, i aquest decreix a mesura que el pacient es recupera.

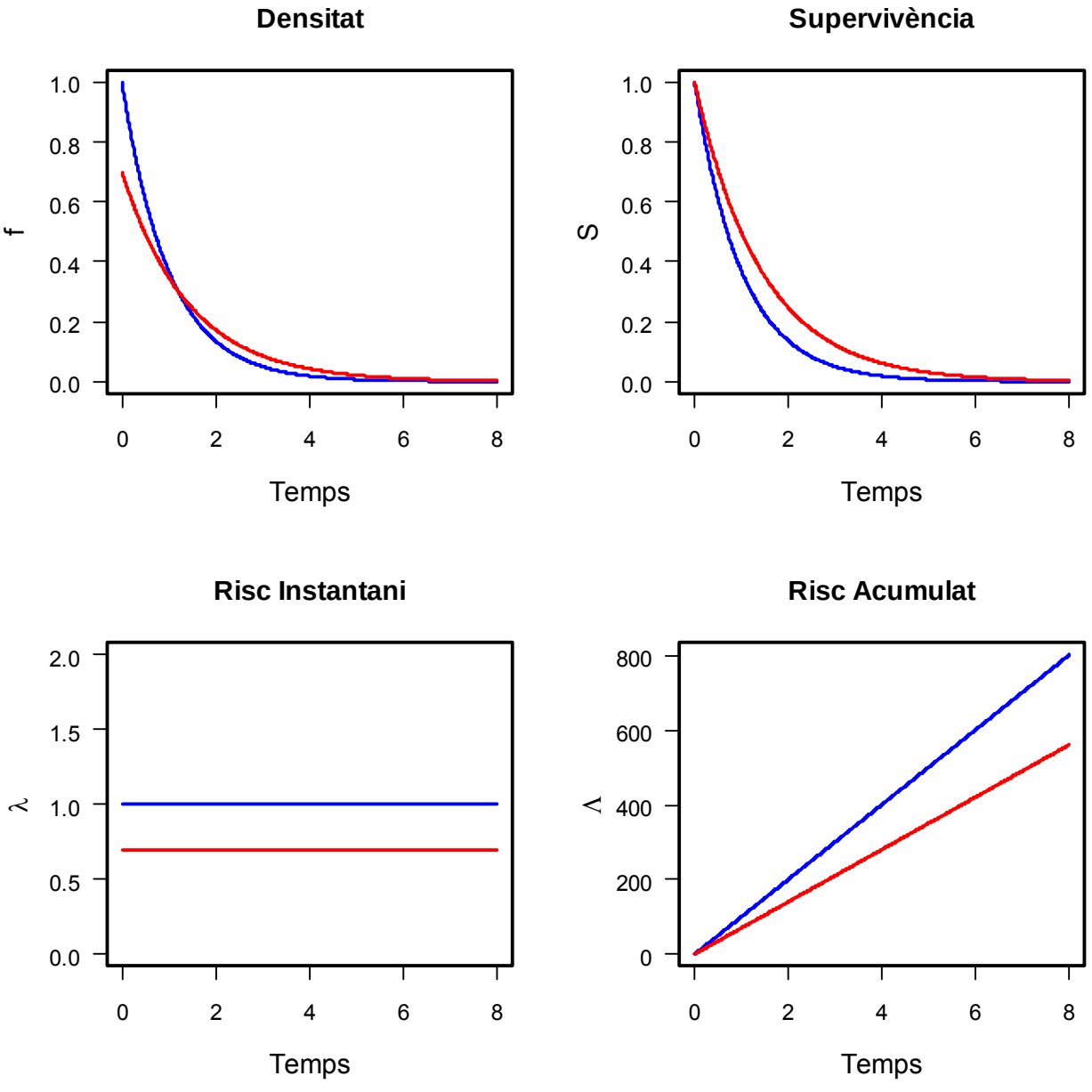
Amb l'objectiu d'aprofundir en el coneixement teòric de certes distribucions, en les següents planes, es representen les funcions de densitat (f), de supervivència (S), de risc (λ) i de risc acumulat (Λ) per algunes distribucions. En aquells casos que no es compleixi la premissa de riscos proporcionals, a més a més, s'ha dibuixat el HRR.

A la vista d'aquestes funcions, es pot concloure que la premissa de riscos proporcionals es inviable comprovar-la visualment a partir de les corbes de $f(t)$ o de $S(t)$, sent més assequible en les corbes de riscos i sobretot en la de $\Lambda(t)$. No obstant, el procediment ortodox per verificar-la és mitjançant un anàlisi formal dels residus.

Exemples de riscos proporcionals

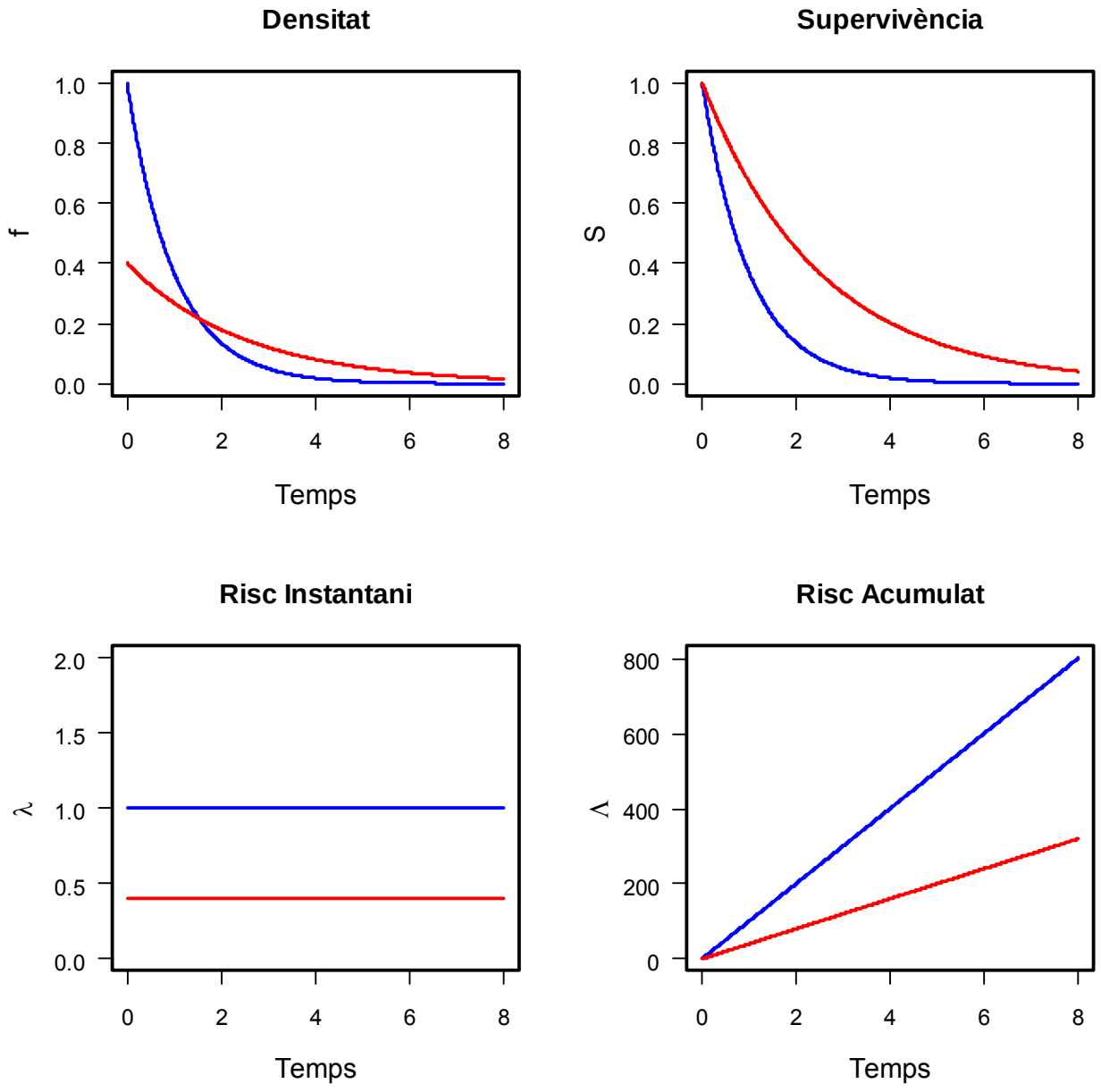
Exemple 1. Exponencial

	Distribució	Esperança	Mediana
—	Exp(λ = 0.7)	1.43	0.99
—	Exp(λ = 1)	1	0.69
Efectes			
MR	0.7		
HRR	1.43		



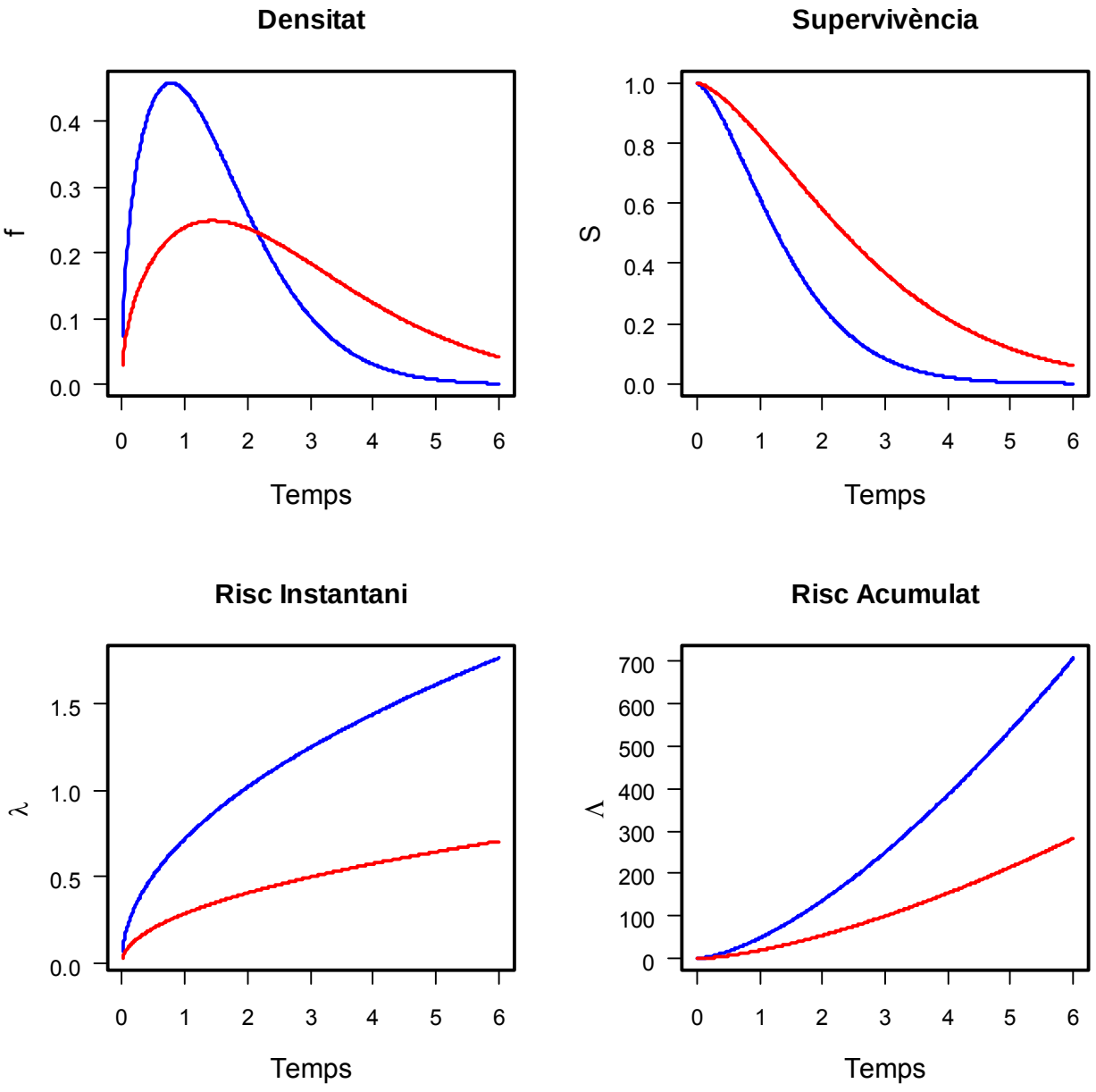
Exemple 2. Exponencial

	Distribució	Esperança	Mediana
—	Exp(λ = 0.4)	2.5	1.73
—	Exp(λ = 1)	1	0.69
	Efectes		
MR	0.4		
HRR	2.5		



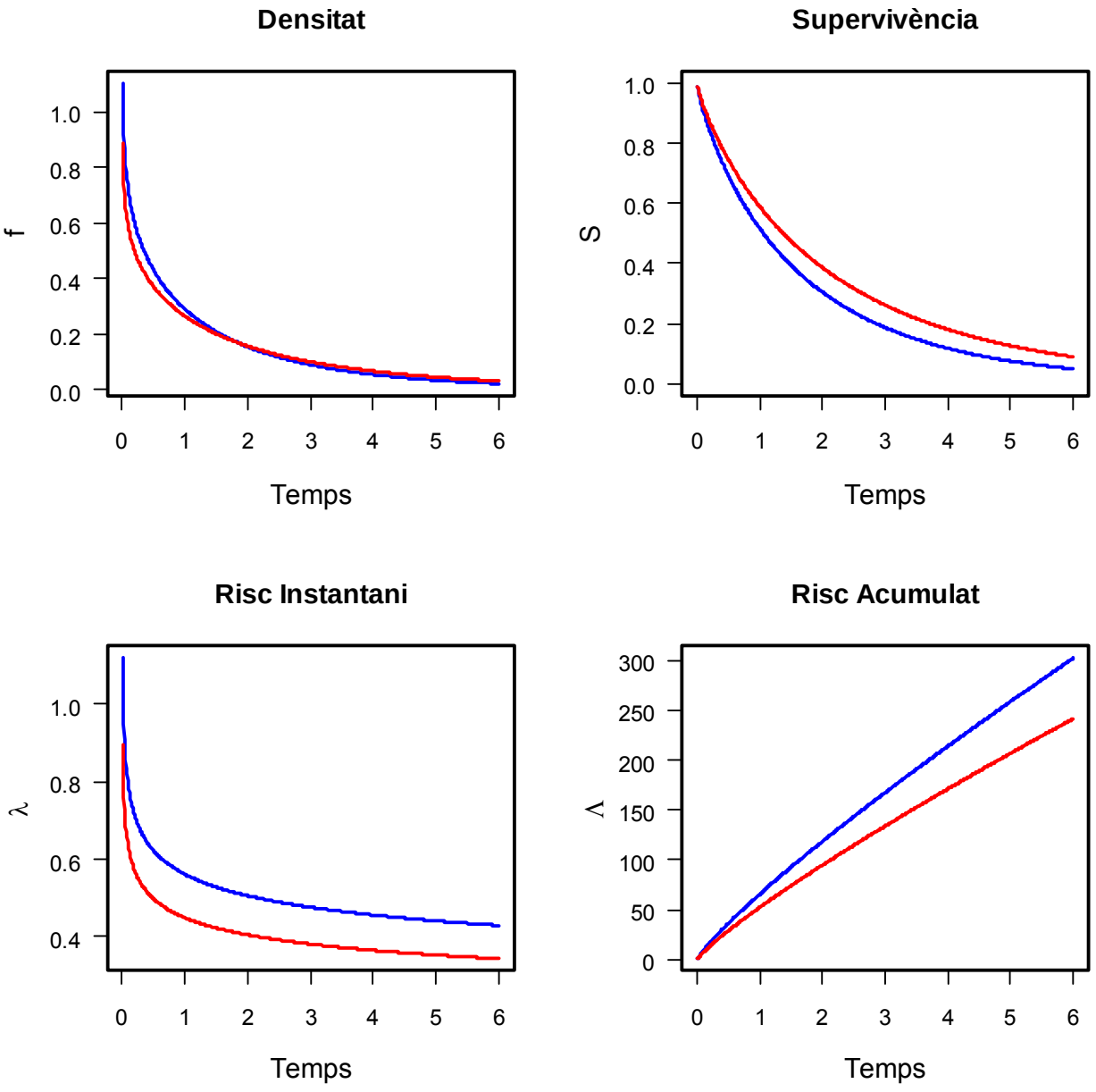
Exemple 3. Weibull (Risc creixent)

	Distribució	Esperança	Mediana
—	Weibull(k = 1.5, ρ = 3.00)	2.71	2.35
—	Weibull(k = 1.5, ρ = 1.63)	1.47	1.27
	Efectes		
MR	0.54		
HRR	2.5		



Exemple 4. Weibull (Risc decreixent)

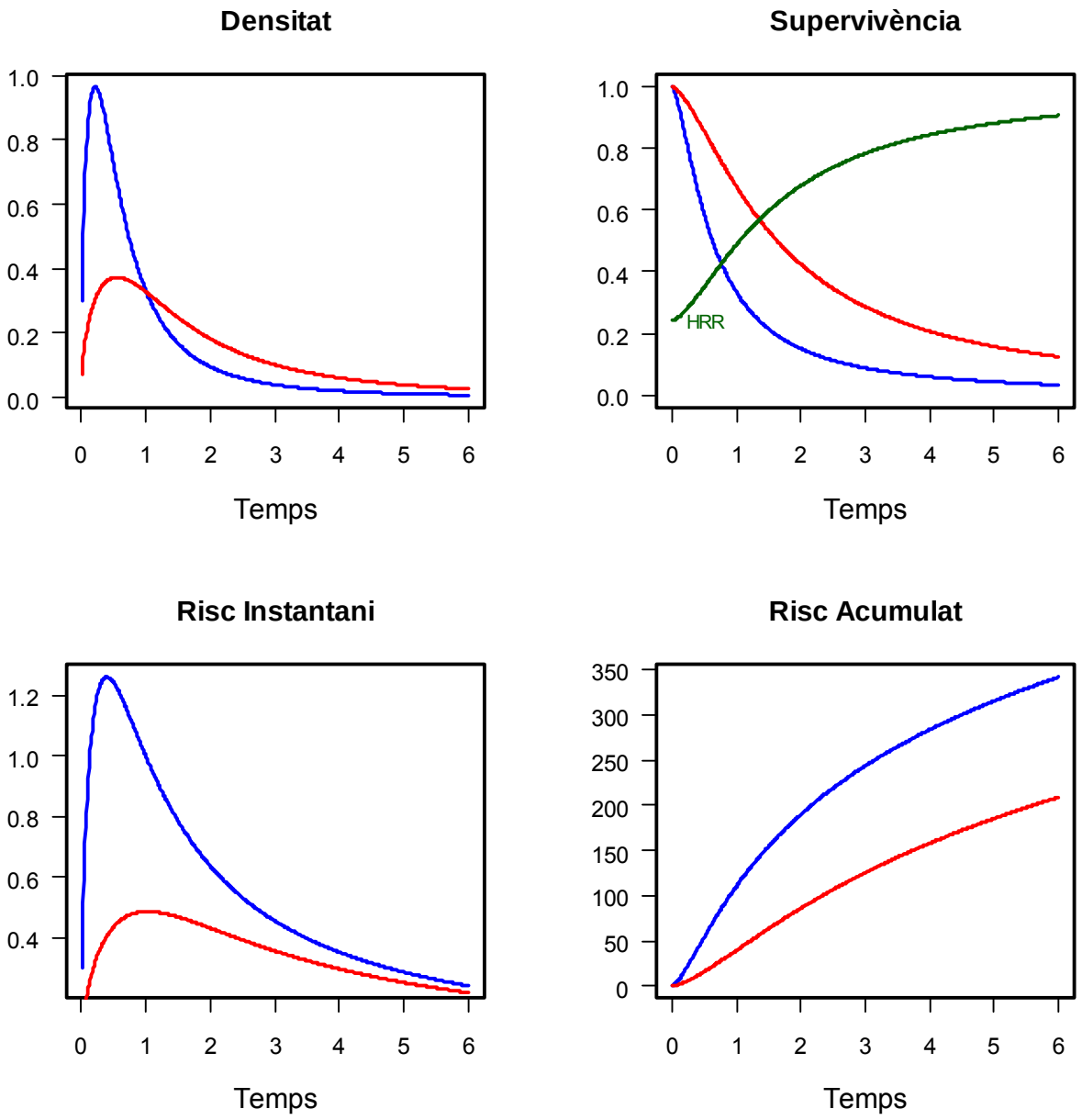
	Distribució	Esperança	Mediana
—	Weibull(k = 0.85, ρ = 2.12)	2.31	1.38
—	Weibull(k = 0.85, ρ = 1.63)	1.77	1.06
	Efectes		
MR	0.77		
HRR	1.25		



Exemples de riscos no proporcionals

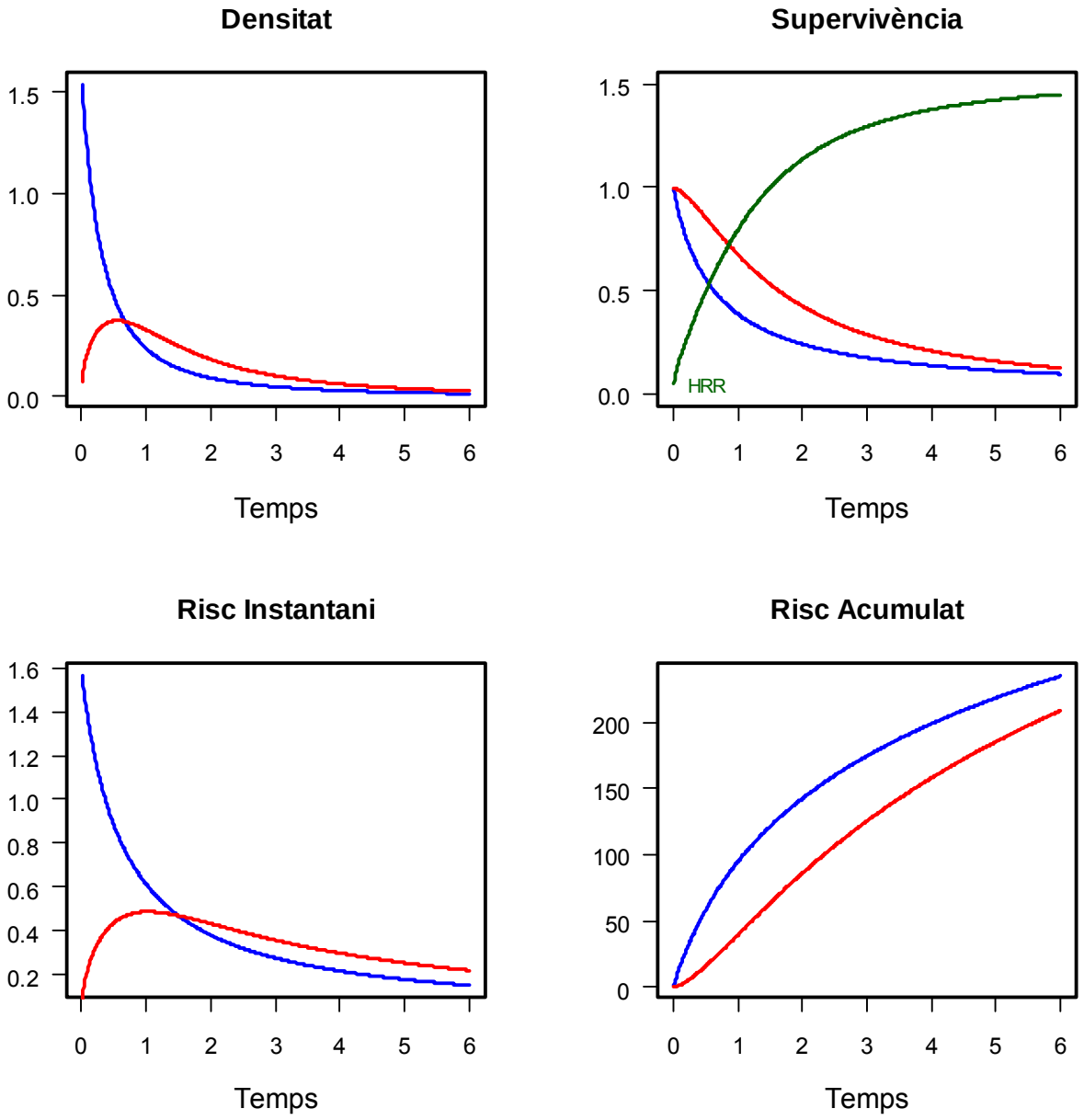
Exemple 1. Log-logística (Risc amb forma de gepa)

	Distribució	Esperança	Mediana
—	Log-logistic(k = 1.5, ρ = 1.63)	2.29	1.63
—	Log-logistic(k = 1.5, ρ = 0.63)	1.11	0.63
	Efectes		
MR	0.39		
HRR	-		



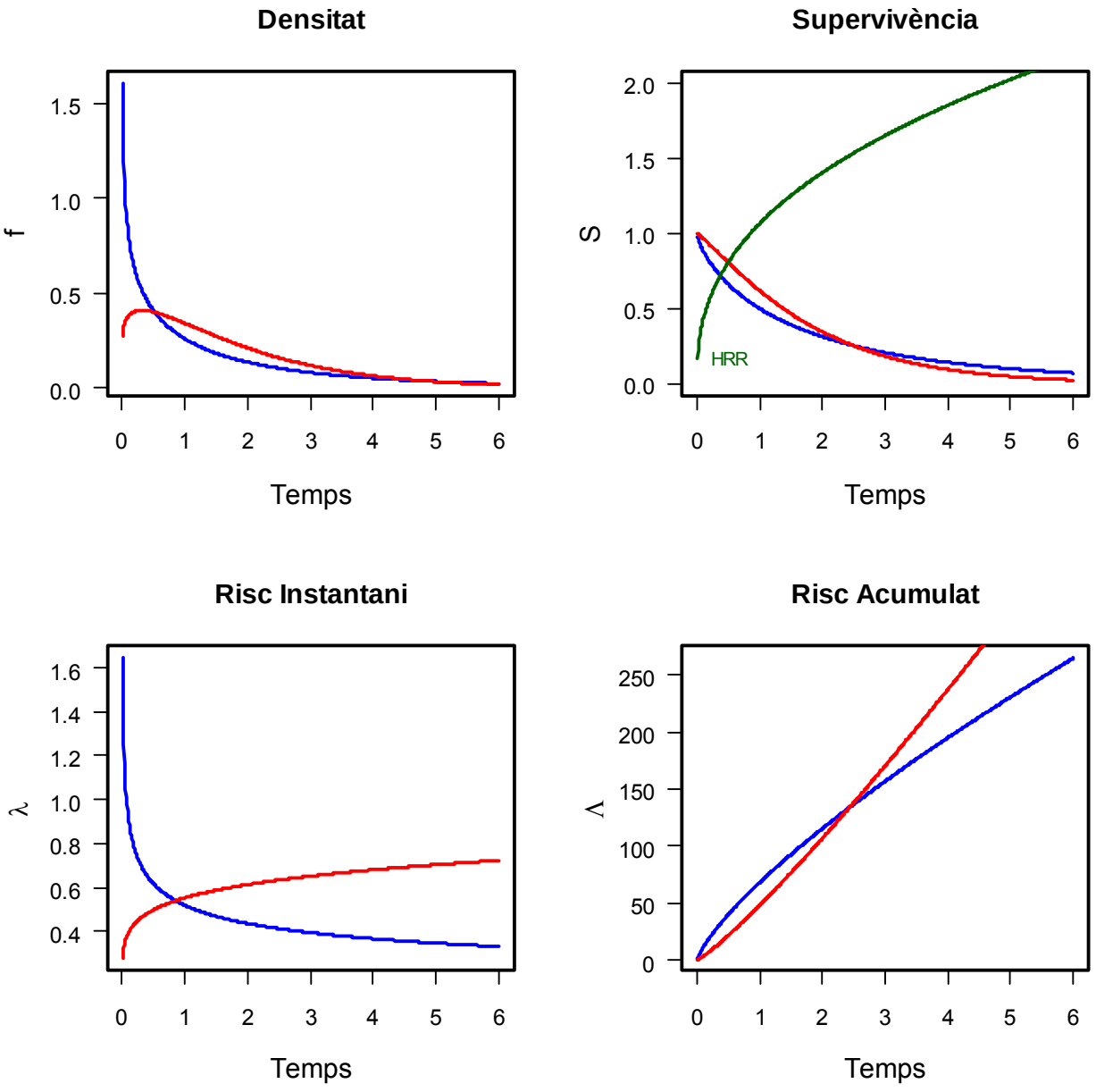
Exemple 2. Log-logística (Riscos amb formes de gepa i decreixent)

	Distribució	Esperança	Mediana
—	Log-logistic(k = 1.5, ρ = 1.63)	2.29	1.63
—	Log-logistic(k = 1, ρ = 0.63)	1.48	0.63
	Efectes		
MR	0.39		
HRR	-		



Exemple 3. Weibull (Riscos decreixent i creixent)

	Distribució	Esperança	Mediana
—	Weibull(k = 1.15, ρ = 1.89)	1.80	1.37
—	Weibull(k = 0.75, ρ = 1.63)	1.94	1.00
	Efectes		
MR	0.73		
HRR	-		



ANNEX III. Simulation procedure to generate the Gompertz distributions

Simulation procedure

Simulation scenarios were defined by all possible combinations of the following parameters:

ρ_{10}: 0.01, 0.02, …, 1.99, 2.00
ρ_{11}: 0.5, 1, 2
ρ_2: 0.5, 1, 2, 10

where ρ_{10}, ρ_{11} are the first parameter of the Gompertz distribution in the control and treated group respectively and ρ_2 is the second common parameter to both groups (necessary condition for a constant HRR).

Box 7 contains simulation procedure

For each combination of parameters, the next procedure was carried out:

1. Generation of 10,000 uncensored survival times for each group with the R function *rgompertz* of the library *eha*. Attention should be paid to the Gompertz parameterization; it is different from the parameterization presented in this work.
2. The HRR has been obtained analytically as the ratio of the parameters ρ_1 of each group (directly obtained from the expression of the hazard rate $\lambda(t) = \rho_1 \cdot exp\{\rho_2 t\}$)
3. Median and mean survival times for each group are calculated as the median and mean times on the generated data.
4. MR and ER are obtained as the ratio between both groups.

Box 7. Simulation procedure to find the relationship between HRR, MR and ER.

Analytic median

There is a necessary condition for the existence of the Gompertz analytical median: the ratio between two parameters must be lower than the following quantity:

$$\frac{\rho_1}{\rho_2} < e \cdot \left(1 + Log(2)\right) \qquad (28)$$

Let's see.

The F(t) of the Gompertz is:

$$F(t) = \exp\left\{1 - \frac{\rho_1}{\rho_2} \cdot e^{-1}\right\} - \exp\left\{1 - \frac{\rho_1}{\rho_2} \cdot e^{\rho_2 t - 1}\right\} \quad (29)$$

In order to obtain the median:

$$F(Med) = \frac{1}{2} \Rightarrow e \cdot \exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{-1}\right\} - e \cdot \exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{\rho_2 Med - 1}\right\} = \frac{1}{2} \Rightarrow \exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{-1}\right\} - \exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{\rho_2 Med - 1}\right\} = \frac{1}{2e} =$$

$$\exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{\rho_2 Med - 1}\right\} = \exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{-1}\right\} - \frac{1}{2e} \Rightarrow -\frac{\rho_1}{\rho_2} \cdot e^{\rho_2 Med - 1} = Log\left(\exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{-1}\right\} - \frac{1}{2e}\right) \Rightarrow$$

$$e^{\rho_2 Med - 1} = -\frac{\rho_2}{\rho_1} \cdot Log\left(\exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{-1}\right\} - \frac{1}{2e}\right) \Rightarrow \rho_2 Med - 1 = Log\left[-\frac{\rho_2}{\rho_1} \cdot Log\left(\exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{-1}\right\} - \frac{1}{2e}\right)\right] \Rightarrow$$

$$Med = \frac{1 + Log\left[-\frac{\rho_2}{\rho_1} \cdot Log\left(\exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{-1}\right\} - \frac{1}{2e}\right)\right]}{\rho_2}$$

For the existence of this median the following condition should be met:

$$\exp\left\{-\frac{\rho_1}{\rho_2} \cdot e^{-1}\right\} > \frac{1}{2e} \Rightarrow -\frac{\rho_1}{\rho_2} \cdot e^{-1} > Log\left(\frac{1}{2e}\right) \Rightarrow \frac{\rho_1}{\rho_2} \cdot e^{-1} < 1 + Log(2) \Rightarrow \frac{\rho_1}{\rho_2} < e \cdot (1 + Log(2))$$

For the different scenarios, the real median was compared with the analytical median. The results have been displayed in the Figure 22.

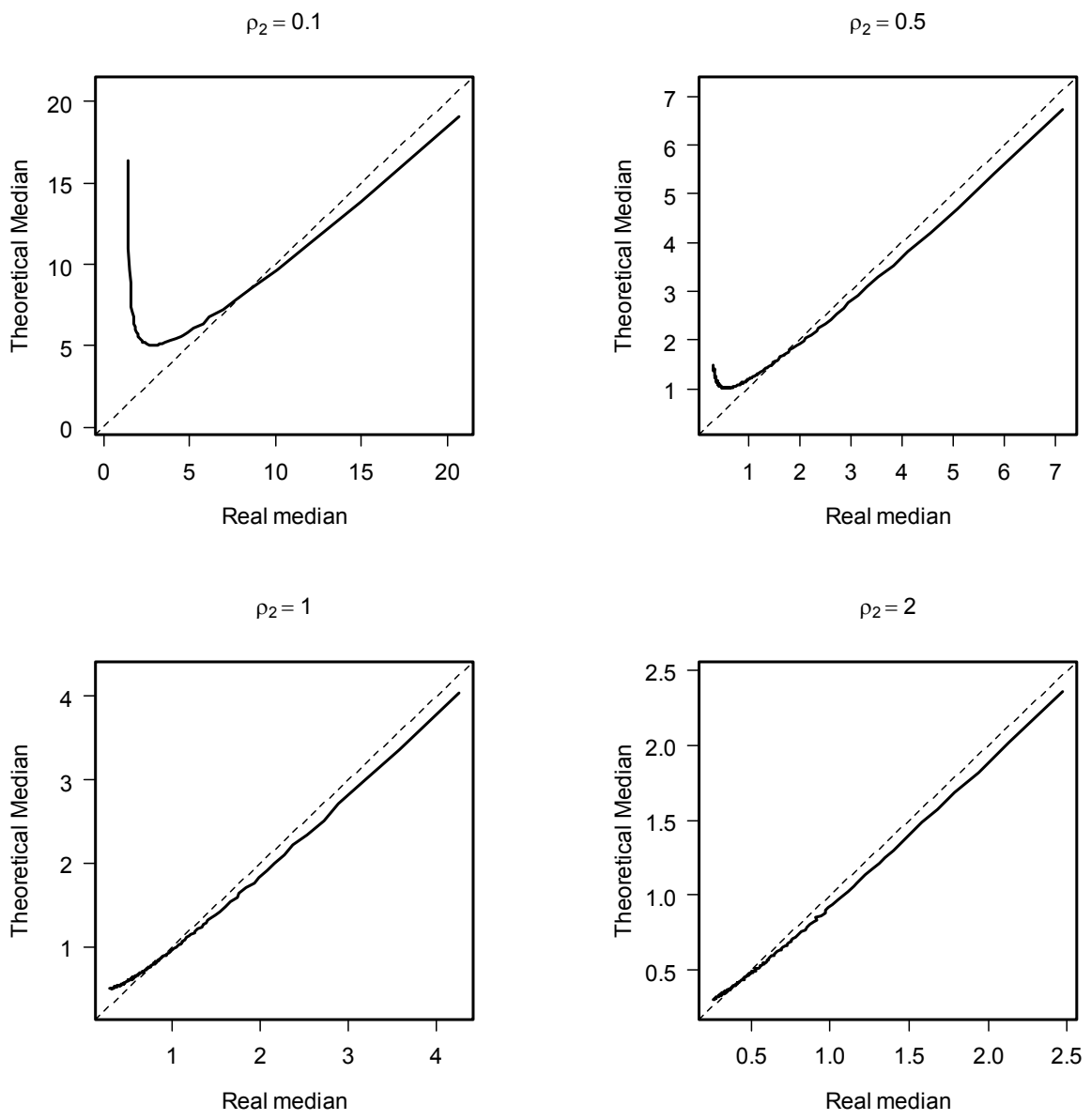


Figure 22. Analytic median as function of real median for different parameters combination. Dotted lines represent the equivalence. In some cases, the analytic median and median calculated via simulation have considerabe differences (see graphics on top).

ANNEX IV. Generació de les censures

El Quadre 8 detalla el procés de generació temps de vida exponencials censurats uniformement i amb un temps de reclutament i de seguiment establert. La Figura 23 il·lustra gràficament aquest procés.

1) Generació de n_1 y n_2 temps de vida (T_1 y T_2) amb distribucions exponencials de paràmetres λ_1 i λ_2 (mitjançant la instrucció *rexp* implementada en R).

2) Aplicació de una censura (C) uniforme [0, *Tmax*] escollint *Tmax* de manera que la proporció esperada de censures totals sigui igual a una proporció (p) nominal donada. Això és,

$$n_1 \cdot P(T_1 > C) + n_2 \cdot P(T_2 > C) = (n_1 + n_2) \cdot p \underset{n_1=n_2}{\Rightarrow} P(T_1 > C) + P(T_2 > C) = 2p$$

S'ha de resoldre l'equació següent per mètodes numèrics per trobar *Tmax:*

$$\frac{1 - exp\{-\lambda_1 \cdot T_{max}\}}{\lambda_1 \cdot T_{max}} + \frac{1 - exp\{-\lambda_2 \cdot T_{max}\}}{\lambda_2 \cdot T_{max}} = 2p$$

3) Addicció d'un temps de reclutament (R) uniforme en [0, *t.recluta*]. Simplement consisteix en desplaçar l'inici dels temps de vida un interval R cap a la dreta.

4) Addició d'un temps de seguiment (*tFollow*) que marqui la fi de l'estudi. Aquest temps pot ser fix (tots els temps de vida superiors a aquest temps queden censurats) o calculat a partir d'una proporció desitjada de censures per fi d'estudi (es fixa un temps de fi de seguiment que censuri la proporció desitjada).

5) Traslladar tots els temps a un origen comú amb la finalitat de realitzar l'anàlisi.

Quadre 8. Procés de generació de temps de vida exponencials censurats uniformement i amb un temps de reclutament i de seguiment fixats.

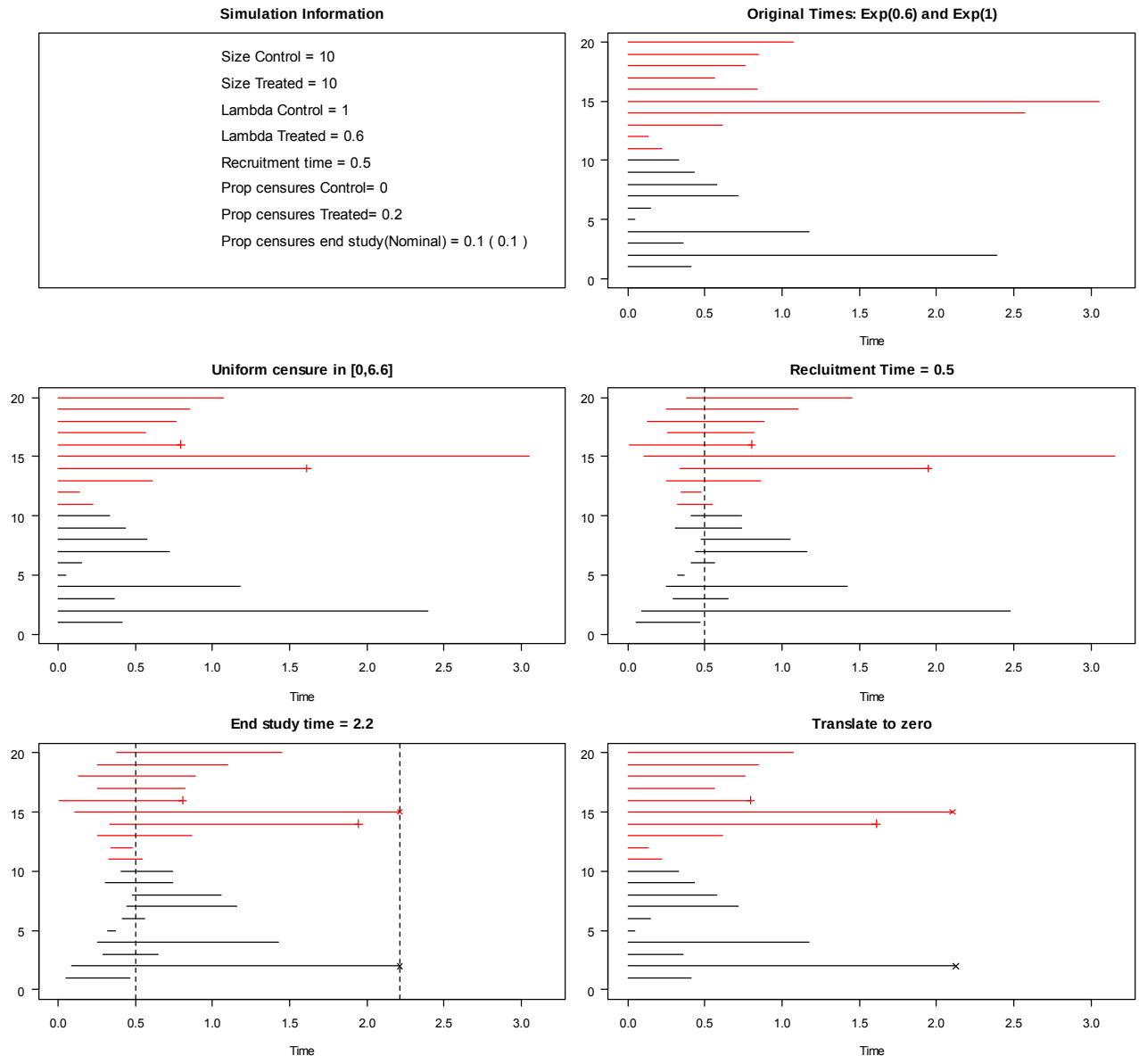


Figura 23. Explicació gràfica del procés de generació de censures. Els 5 gràfics de línees es corresponen als punts 1) a 5) explicats en el Quadre 8.

La Figura 24 aclareix el comportament dels temps de censura generats en funció del temps de seguiment. S'observa que la proporció d'individus censurats, lògicament, creix a mesura que hi ha més temps de seguiment.

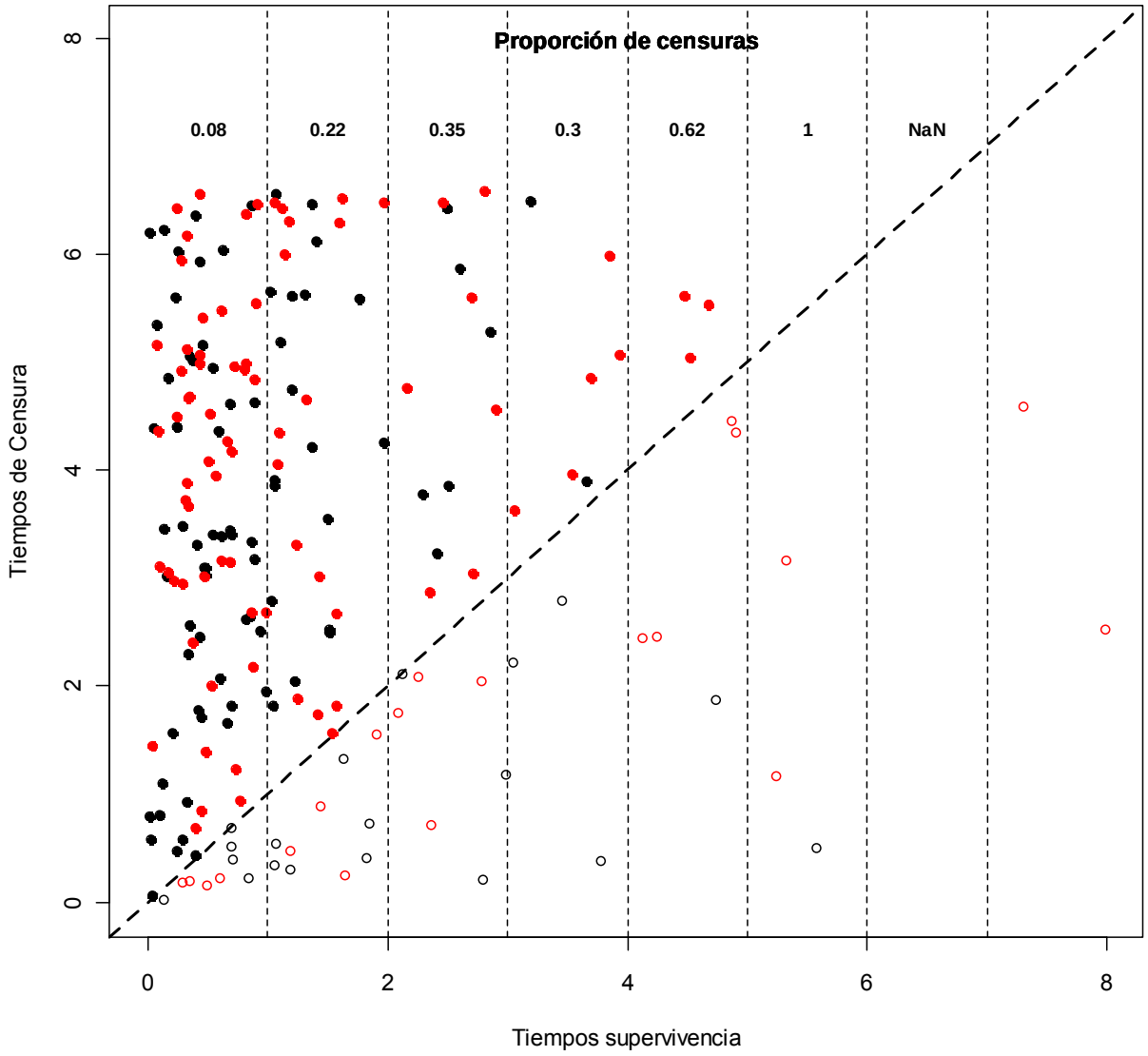


Figura 24. Temps de censura (C) en funció dels temps de seguiment (T) generats. Els punts vermells representen els temps del grup tractat (major supervivència) i els negres els del grup control. Els punts per sobre de la bisectriu (densos) són els temps observats i els situats per sota (buits) són temps censurats. S'observa que la proporció de censures creix a mesura que augmenta el temps de seguiment (p.ex., entre els que viuen menys d'una unitat de temps, hi ha un 8% de censures, mentre que en els que viuen entre 4 i 5 unitats de temps hi ha un 62% de censures). Aquestes dades han estat generats a partir de distribucions exponencials amb taxes de mort d'1 i 0.6 respectivament i amb una distribució de censures uniforme en [0, 6.6] que comporten una proporció global de censures esperades del 20%. La grandària mostral per grup és de 100 individus.

ANNEX V. Cerca bibliogràfica exploratòria.

En un primer conjunt de cerques exploratòries amb els paràmetres de la Taula 14 es van obtenir un total de 135 mesures corresponents a 79 articles de 4 revistes diferents (NEJM, Annals of Internal Medicine, JAMA i Lancet). En la recerca final es van descartar revistes diferents al NEJM, en algunes per la dificultat d'extreure articles que complissin els criteris d'elegibilitat (Annals of Internal Medicine: 2 de 12 elegibles, JAMA: 10 de 51) i per homogeneïtzar els resultats.

En resum, les cerques consistien en alternar les paraules Cox i Hazard dins del text amb les expressions exactes "Median Survival" o diferents tipus de càncer ("Colorectal cancer", "Lung cancer", ...) en diferents períodes de 2000 a 2010.

Codi	Cercador	Revista	On	Totes les paraules	Frase exacta	Any	Categoria
1	NEJM	NEJM	Text	Cox	Median survival	2009	Research
2	NEJM	NEJM	Abstract	Median Survival Cox	-	2008	Research
3	NEJM	NEJM	Text	Cox	Median survival	2008	Research
4	NEJM	NEJM	Text	Cox	Median survival	2007	Research
5	NEJM	NEJM	Text	Cox	Median survival	2006	Research
6	NEJM	NEJM	Text	Cox	Median survival	2005	Research
7	NEJM	NEJM	Text	Hazard	Median survival	2009	Research
8	NEJM	NEJM	Text	Hazard	Median survival	2008	Research
9	NEJM	NEJM	Text	Cox	Median survival	2004	Research
10	NEJM	NEJM	Text	Cox	Median survival	2003	Research
11	NEJM	NEJM	Text	Cox	Median survival	2002	Research
12	NEJM	NEJM	Text	median	Colorectal cancer	2005-2009	Research
13	NEJM	NEJM	Text	hazard	Colorectal cancer	2005-2009	Research
14	NEJM	NEJM	Text	hazard	Lung cancer	2005-2009	Research
15	NEJM	NEJM	Text	hazard	Esophageal cancer	2005-2009	Research
16	NEJM	NEJM	Text	hazard	stomach cancer	2005-2009	Research
17	NEJM	NEJM	Text	hazard	Hepatocarcinoma	2005-2009	Research
18	NEJM	NEJM	Text	hazard	Laryngeal cancer	2005-2009	Research
19	NEJM	NEJM	Text	hazard	Breast cancer	2005-2009	Research
20	NEJM	NEJM	Title	Chemotherapy followed	-	1812- Present	Research
21	NEJM	NEJM	Abstract	Median survival	-	2010	Research

Codi	Cercador	Revista	On	Totes les paraules	Frase exacta	Any	Categoria
22	NEJM	NEJM	Text	-	Median survival	2010	Research
23	Google Scholar	JAMA	Text	hazard	Median survival	2005-2010	-
24	Google Scholar	JAMA	Text	hazard trial	Median survival	2005-2010	-
25	Google Scholar	Ann Int. Med	Text	hazard trial	Median survival	2005-2010	-
26	Google Scholar	NEJM	Text	Hazard	Median survival	2005-2010	-
27	Google Scholar	NEJM	Text	Hazard	Median survival	2000-2004	-
28	Google Scholar	NEJM	Text	HR	Median survival	2000-2004	-
29	Google Scholar	JAMA	Text	hazard trial	Median survival	2000-2004	-
30	Google Scholar	Ann Int. Med	Text	hazard trial	Median survival	2000-2004	-
31	Google Scholar	LANCET	Text	hazard trial	Median survival	2005-2010	-

Taula 14. Criteris de cerca temptatius previs a la cerca definitiva.

El nombre de mesures acceptades i rebutjades en cada cerca es pot veure a la Taula 15 (s'ha de tenir en compte que les cerques es van realitzar en l'ordre que marca el seu codi, el que implica que cerques més tardanes tenien menys opcions de rebutjar o acceptar articles, ja que els articles repetits no es van comptabilitzar).

Codi	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Acceptats	2	10	0	15	11	9	0	0	5	0	0	0	3	8	0	0	0	0	1	0	0	5	5	4	3	0	11	3	0	0	39
Rebutjats	1	26	0	3	2	1	1	1	3	3	3	2	9	6	0	0	0	0	14	6	5	14	0	6	2	1	10	0	11	5	10

Taula 15. Resultats de la cerca segons el criteri emprat.

Els articles amb zeros a les dues caselles representen cerques que van retornar majoritàriament articles acceptats o rebutjats en cerques prèvies.

Les cerques anteriors del NEJM poden simplificarse agrupant-les en les categories de la Taula 16.

Codi	Cercador	Revista	On	Totes les paraules	Frase exacta	Any
2	NEJM	NEJM	Abstract	Median survival Cox		2008
1, 3, 4, 5, 6, 9, 10, 11	NEJM	NEJM	Text	Cox	Median survival	2002 -2009
13	NEJM	NEJM	Text	Hazard	Colorectal cancer	2005-2009
14	NEJM	NEJM	Text	Hazard	Lung cancer	2005-2009
19	NEJM	NEJM	Text	Hazard	Breast cancer	2005-2009
22	NEJM	NEJM	Text		Median survival	2010
26,27	Google Scholar	NEJM	Text	Hazard	Median survival	2000-2010

Taula 16. Agrupació dels criteris de cerca realitzats en el NEJM.

Es va provar un segon conjunt de cerques a través del cercador PubMed i del mateix cercador de la revista del NEJM (Taula 17 i Taula 18). El que es pot observar és que no aportaven articles nous ja que tots els articles acceptats per a l'any 2009 ja havien estat trobats en anteriors cerques.

Cerques provades en PubMed amb paraules clau

Paraula clau	Any	Trobats anteriorment	Resultats	Rebutjats	Acceptats	Solapats	No solapats
Survival Analysis	2009	4	58	54	4	4	0
Kaplan-Meier Estimates	2009	4	40	36	4	4	0
Proportional Hazard Models	2009	4	20	18	2	2	0

Taula 17. Segon conjunt de cerques provades en PubMed.

Cerques provades en NEJM amb paraules en el text

Paraula clau	Any	Trobats anteriorment	Resultats	Rebutjats	Acceptats	Solapats	No solapats
cox ó hazard ó survival	2009	4	115	111	4	4	0

Taula 18. Segon conjunt de cerques provades en NEJM.

ANNEX VI. Intents d'estimar l'error estàndard del Log (MR/HRR^{-1})

En aquest punt es plantegen quatre sistemes d'estimació de la variància del $Log\left(MR/HRR^{-1}\right)$ a partir de la informació disponible: la variància del *Log* (HRR^{-1}).

Mètode I: mètode Delta

Es provarà d'arribar a estimar la variància del *Log (MR/HRR-1)* a partir de la variància del *Log (HRR)* i de la variància de les medianes usant aproximacions de primer ordre de les sèries de Taylor i assumint els estimador com no esbiaixats.

$$V\left(\log\left(\frac{MR}{HRR^{-1}}\right)\right) = V\left(\log\left(MR\cdot HRR\right)\right) \approx \frac{V\left(MR\right)}{MR^2} + \frac{V\left(HRR\right)}{HRR^2}$$

$$V\left(MR\right) = V\left(\frac{Med_1}{Med_0}\right) = \frac{V\left(Med_2\right)}{Med_1^2} + \left(\frac{Med_2}{Med_1^2}\right)^2 \cdot V\left(Med_1\right)$$

Malauradament, la majoria d'estudis no comuniquen la variància de les medianes no i per tant, aquest mètode no serveix per tenir una estimació.

Mètode II: Empíric

Consisteix en estimar la variància de forma empírica. Per cada estudi es disposa de la variància del *Log (HRR)*. Es dividiran aquestes variàncies en 10 decils i s'agafarà com a representant d'aquest decil la mitjana de les variàncies. Per cada decil es calcularà la variabilitat mostral del $Log\left(MR/HRR^{-1}\right)$. Finalment, es farà una regressió lineal simple, amb aquestes dues variàncies per veure si es una es pot predir a partir de l'altra. El procés està més detallat en el Quadre 9.

1. Es divideixen les mesures del MR y del HRR^{-1} en 10 decils segons la magnitud del EE del Log (HRR) (obtingut en l'article).
2. Per cada decil es calcula la variància del $Log\left(MR/HRR^{-1}\right)$.
3. Es fa una regressió lineal simple amb la variable resposta la variància del $Log\left(MR/HRR^{-1}\right)$ en funció de la variància del Log (HRR^{-1}) escollint como representant de classe la mitjana de totes les variàncies corresponents a aquest decil.

Quadre 9. Mètode per obtenir una estimació empírica del $Log\left(MR/HRR^{-1}\right)$ a partir del $Log\left(HRR\right)$.

La sortida de R de la regressió lineal i el diagrama bivariant corresponent als 10 decils es troben en la Figura 25.

Es pot observar que una variabilitat és difícilment predictible a partir de l'altre. Malgrat el coeficient de determinació no és molt baix (R^2 = 0.65), en el gràfic s'observa que els decils amb baixa variabilitat queden mal predits. Per tant, s'han de buscar altres alternatives.

```
Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.02607    0.01019   2.557  0.03381 *
VLogHRR      0.77780    0.20164   3.857  0.00483 **
Residual standard error: 0.02462 on 8 degrees of freedom
Multiple R-squared: 0.6503,     Adjusted R-squared: 0.6066
F-statistic: 14.88 on 1 and 8 DF,  p-value: 0.004827
```

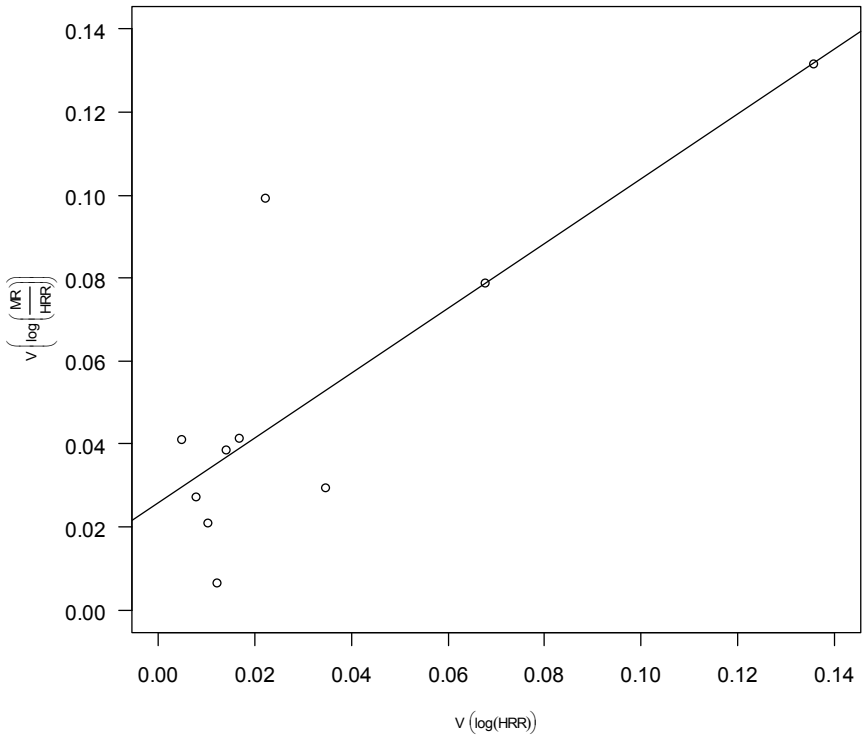


Figura 25. Sortida de R de la regressió (a dalt) i diagrama bivariant i recta de regressió (a baix) de la variància empírica de l'estimador d'interès en funció de la variància del *Log(HRR)*.

Mètode III: Simulació

Aprofitant la següent relació teòrica:

$$V\left(\log\left(\frac{MR}{HRR^{-1}}\right)\right) = V\left(\log(MR) - \log\left(HRR^{-1}\right)\right) =$$
$$V\left(\log(MR)\right) - 2\cdot Cov\left(\log(MR), \log\left(HRR^{-1}\right)\right) + V\left(\log\left(HRR^{-1}\right)\right)$$

Es pretenia predir mitjançant simulació la variància del $Log(MR/HRR^{-1})$. El procediment es detalla en el Quadre 10.

1. Es van realitzar 50 simulacions de la comparació de 2 mostres de temps de supervivència exponencials.
2. En cada simulació es van generar 2 paràmetres (λ_1 i λ_2) per les exponencials d'ambdós grups segons una distribució uniforme [1/3 , 1]. Es va usar la funció de R *runif*.
3. Per cada grup, es van generar 50 temps de vida exponencials amb paràmetres λ_1 i λ_2 amb la funció de R *rexp*.
4. Per a cada parella de paràmetres es van generar 50 repliques per tal d'estimar la variabilitat tant dels logaritmes del HRR y del MR, així com de la covariància d'ambdós.
5. Es van realitzar dues regressions. La resposta en ambdues va ser la variància del $Log\left(MR / HRR^{-1}\right)$. En la primera, la variable predictora va ser la variància del Log (HRR^{-1}) y en la segona va ser l'expressió:

$$\text{Log } (HRR^{-1})\text{-2Cov } (\text{Log}(HRR^{-1}) \text{ , Log } (MR))$$

Quadre 10. Procediment de simulació per intentar predir $Log\left(MR / HRR^{-1}\right)$ en distribucions exponencials.

La Figura 26 conté la sortida de R d'ambdues regressions i els gràfics corresponents.

Respecte a la primera regressió, el principal problema és que desconeixem si la relació observada en un cas molt concret (distribucions exponencials sense censura) seria generalitzable a altres situacions i, a més, l'R^2 és ínfim (Figura 26).

En la segona regressió el coeficient de la variable dependent hauria de ser proper a 1 (sabem que el valor real és 1) i el terme independent s'interpretaria com la variància del MR. No obstant això, aquest terme independent no és constant i invalida la informació que es pugui obtenir, a més no ens serveix perquè desconeixem la covariància, que és necessària per establir el predictor.

```
Residuals:
      Min        1Q    Median        3Q       Max
-0.019538 -0.007806  0.001699  0.007072  0.027846

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.043420   0.006535   6.644 2.59e-08 ***
V.LOG.HRRinv 0.015766   0.138343   0.114     0.91
---

Residual standard error: 0.009875 on 48 df.
Mult. R-squared: 0.0002705,  Adj. R-squared: -0.02056
F-statistic: 0.01299 on 1 and 48 DF,  p-value: 0.9097
```

```
Residuals:
      Min        1Q    Median        3Q       Max
-0.019563 -0.007954  0.001624  0.006963  0.027834

Coefficients:
                Estimate Std. Error t value Pr(>|t|)
(Intercept)     0.043854  0.004869   9.007 6.93e-12 ***
VLNMRHRRMIN2COV-0.007045 0.111907  -0.063     0.95
---

Residual standard error: 0.009876 on 48 df
Mult. R-squared: 8.255e-05,  Adj. R-squared: -0.02075
F-statistic: 0.003963 on 1 and 48 DF,  p-value: 0.95
```

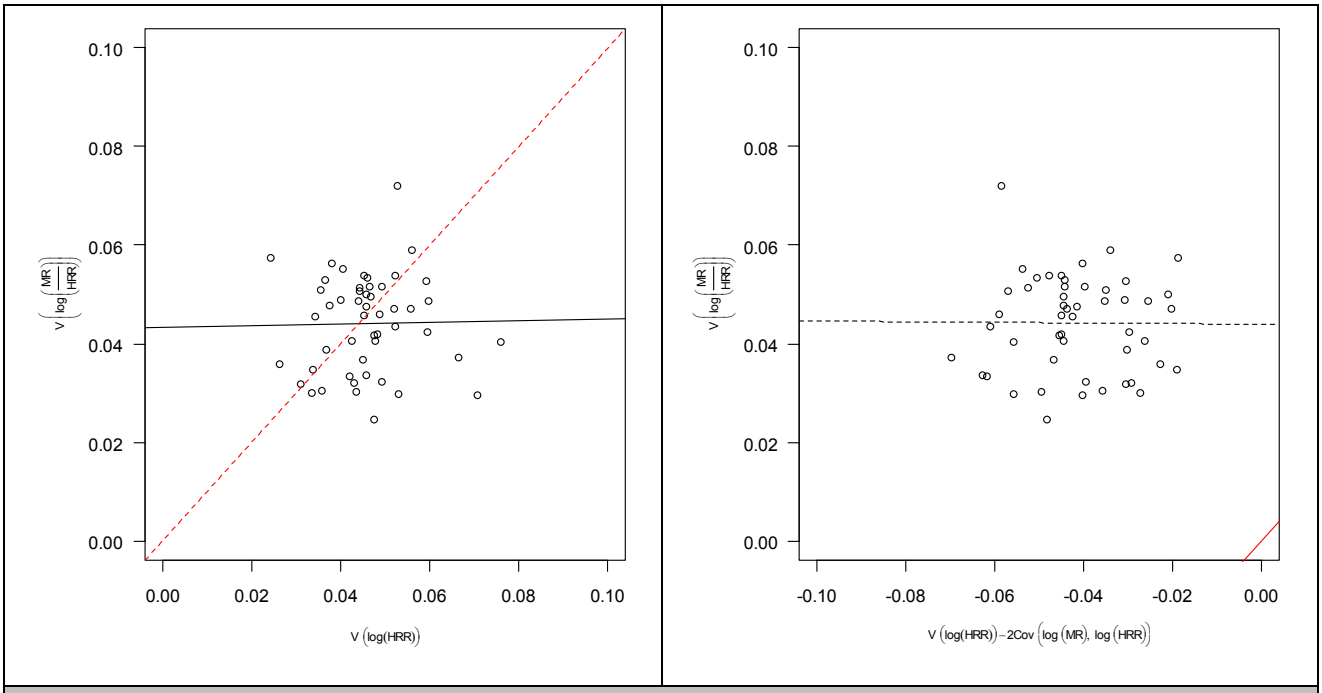


Figura 26. Sortida de R (a dalt) i diagrama bivariant (a baix) corresponents a les dues regressions realitzades. La línia vermella correspon a la bisectriu i la línia negra a la recta de regressió.

Mètode IV: A través del nombre d'esdeveniments o de la magnitud del HRR

L'objectiu d'aquest apartat és determinar si:

(1) la magnitud del HRR i

(2) la grandària mostral

influeixen en les variàncies i correlacions del MR i el HRR. Si es trobés que sí, podria estudiar-se en quina manera aquest resultat podria ser útil. El Quadre 11 mostra el procediment emprat.

1. Es van realitzar 50 simulacions de la comparació de 2 mostres de temps de supervivència exponencials.
2. En cada simulació els paràmetres λ_1 i λ_2 van ser generats amb sengles distribucions uniformes [1/3, 1].
3. Es van generar 50 temps de vida exponencials amb paràmetres λ_1 i λ_2.
4. Per cada parell de paràmetres, es van generar 100 rèpliques per estimar la variabilitat tant dels logaritmes del HRR i del MR, així com de la correlació entre ambdós.

Quadre 11. Procediment per esbrinar la influència de la magnitud del HRR en la variabilitat i correlació de les mesures.

La Figura 27 conté la sortida de R de la descriptiva dels estadístics estudiats i els diagrames bivariants corresponents a aquests estadístics enfront de la magnitud del HRR. S'observa que la magnitud del HRR no afecta a cap dels paràmetres d'estudi.

```
> summary(varLogMR)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.05838 0.07965 0.08827 0.08501 0.09410 0.10130
> summary(varLogHRR)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.03211 0.04058 0.04584 0.04592 0.04941 0.05926
> summary(varLogMRHRR)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
 0.1573  0.1976  0.2241  0.2175  0.2331  0.2716
> summary(corLogMRHRR)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
-0.7877 -0.7213 -0.6993 -0.6935 -0.6644 -0.6009
```

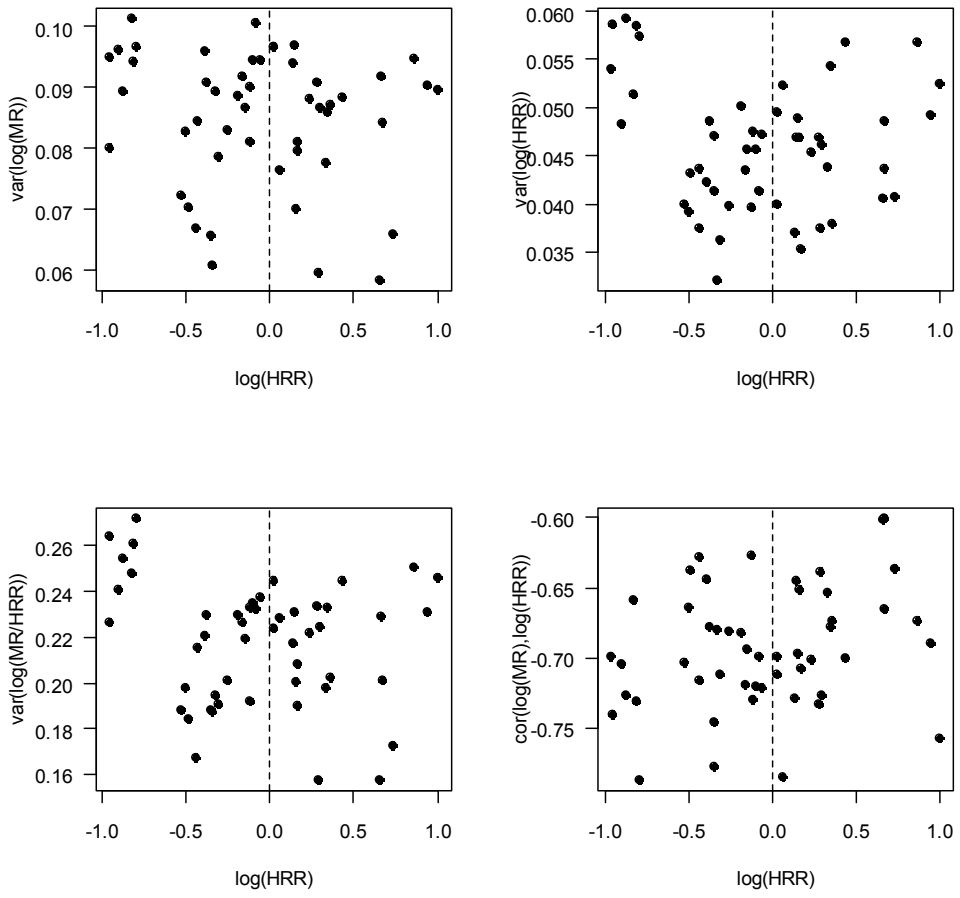


Figura 27. A dalt: Sortida de R dels estadístics descriptius de les variàncies del MR, del HRR, de la variància del seu quocient i de la correlació. A baix: Diagrames bivariants d'aquestes magnituds en funció de la magnitud del HRR.

El Quadre 12 mostra el procediment emprat per estudiar com varien aquestes magnituds en funció de la grandària mostral.

1. Per cada grandària mostral (de 10 a 200 individus per grup en intervals de 5), es va realitzar una simulació de la comparació de 2 mostres de temps de supervivència exponencials amb paràmetres $\lambda_1 = 1$ i $\lambda_2 = 0.8$ (es van mantenir constants atès que ja s'ha vist que el HRR no afectava les variàncies estudiades).
2. Per cada grandària mostral, es van generar 100 rèpliques per estimar la variabilitat tant dels logaritmes del HRR i del MR, així com de la correlació entre ambdós.

Quadre 12. Procediment per esbrinar la influència de grandària mostral en la variabilitat i correlació de les mesures.

Tot i que la inversa de la variància del logaritme del HRR està directament relacionada amb la grandària mostral (Figura 28), no passa el mateix amb la correlació. El que torna a fer inútil aquest sistema d'estimació.

```
> summary(varLogMR)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.01750 0.02709 0.04024 0.06662 0.07567 0.42410
> summary(varLogHRR)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.00840 0.01305 0.01878 0.03740 0.03690 0.30180
> summary(varLogMRHRR)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.04307 0.06613 0.09400 0.17300 0.17650 1.28400
> summary(corLogMRHRR)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
-0.7814 -0.7440 -0.6958 -0.6898 -0.6540 -0.5535
```

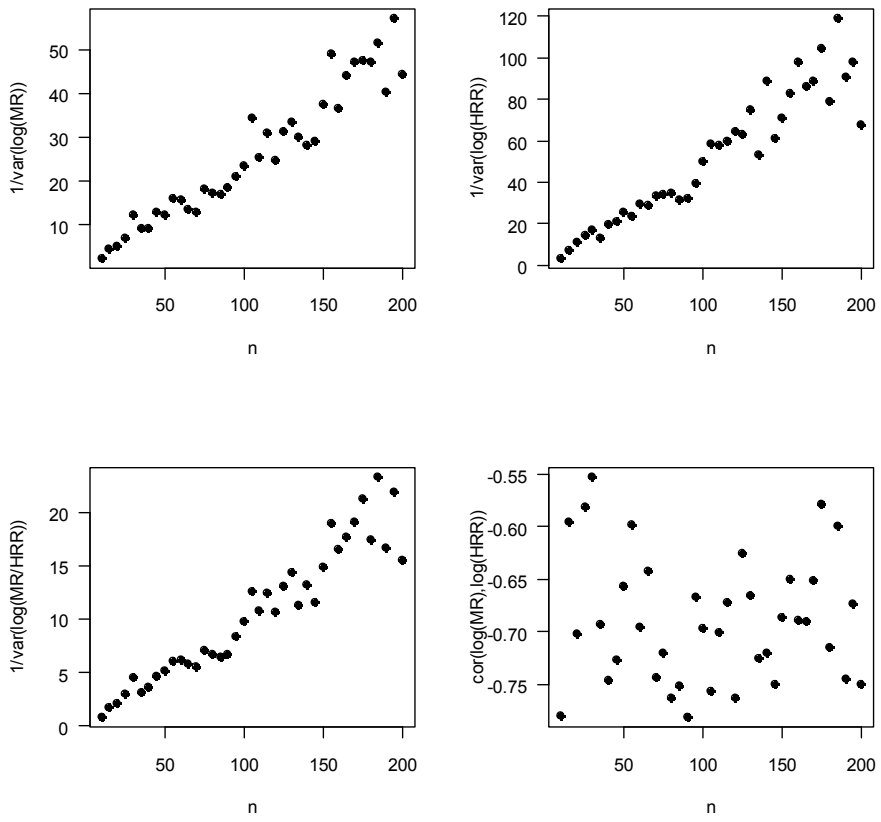


Figura 28. A dalt: sortida de R dels estadístics descriptius de les variàncies del MR, del HRR, de la variància del seu quocient i de la correlació. A baix: diagrames bivariants d'aquestes magnituds en funció de la grandària mostral.

ANNEX VII. Concordança entre les medianes estimades de forma gràfica

En aquells articles que no van comunicar les medianes en el text o en les taules, però que sí que donaven les corbes de supervivència estimades per Kaplan i Meier i aquestes assolien la proporció de 0.5 en tots els grups, les medianes es van estimar gràficament.

S'ha comprovat que la concordança entre les estimacions de dos avaluadors emmascarats (als valors reals i a l'estimació de l'altre avaluador) i les medianes reals de 14 mesures corresponents a 7 estudis és elevada (Figura 29).

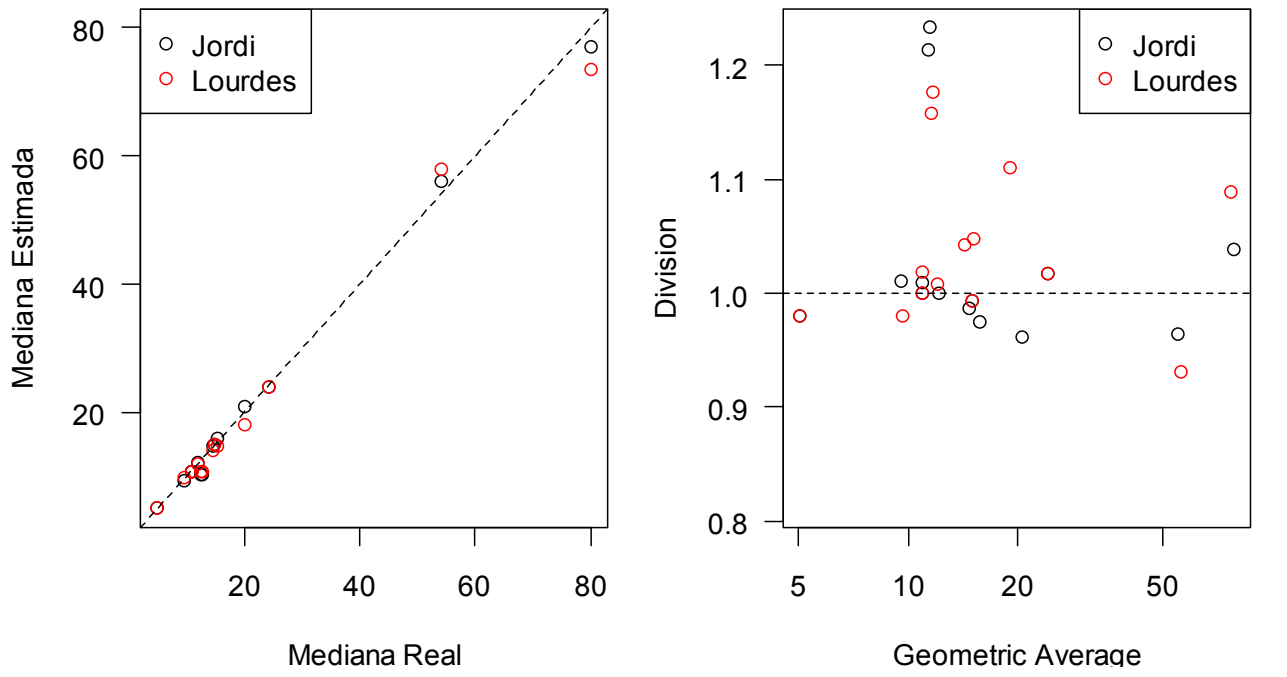


Figura 29. Esquerra: Diagrama bivariant de les medianes estimades per l'avaluador I (negre) i l'avaluador II (vermell) enfront de les medianes reals. Dreta: Gràfic de Bland-Altman de concordances.

Els coeficients de Lin per cada parella són els següents:

Concordança Avaluador 1 – Mediana Real:	0.998	$CI_{95\%}$: 0.993 a 0.999
Concordança Avaluador 2 – Mediana Real:	0.993	$CI_{95\%}$: 0.981 a 0.998
Concordança Avaluador 1 – Avaluador 2:	0.998	$CI_{95\%}$: 0.993 a 0.999

ANNEX VIII. Simulation procedure to generate Weibull and exponential distributions based on empirical data

Box 13 cointains the simulation procedure to generate Weibull and exponential data as similar as possible to empirical data; that is, with the same sample size, the same HRR and the same censure proportion.

Notation

i: group i = 0, 1

j: measure number j = 1, 2, …, 120

s: simulation number s = 1,2,…, 100 (Not listed in the below table)

Exponential	Weibull
1. Parameter estimation In the exponential distribution, the HRR is directly the rate ratio (i.e., the ratio of two parameters): $\rho_{0j} = 1$ (the jth rate for control group is always 1) ρ_{1j} = HRR_j (the jth rate for treated group is the jth HRR)	**1. Parameter estimation** The common shape parameter (k) of both groups and the two scale parameters (ρ_0, ρ_1) were obtained for each measure by solving a system of 3 equations with 3 unknowns. $$k_j = \frac{Log(HRR_j)}{Log(MR_j^{-1})}$$ $$\rho_{0j} = \frac{Med_{0j}}{Log(2)^{1/k}}$$ $$\rho_{1j} = \frac{Med_{1j}}{Log(2)^{1/k}}$$ This equations were obtained by solving the system: $$\begin{cases} HRR = \left(\frac{\rho_0}{\rho_1}\right)^k \\ Med_0 = \rho_0 \cdot (ln(2))^{1/k} \\ Med_1 = \rho_1 \cdot (ln(2))^{1/k} \end{cases} \quad (30)$$ If the shape parameter is negative due to the HRR and MR aim in opposite directions, then the measure was excluded from the simulation.

2. Time generation

n_{0j} (control group size) y n_{1j} (treated group size) lifetimes of the pertinent distribution were generated employing the R functions *rexp* and *rweibull*, respectively.

3. Censure proportion

If the total number of events in the jth measure was known, the global censure proportion (p_j) was equal to 1 minus the ratio of the number of events ($E_i = E_{0i} + E_{1i}$) divided by the number of patients ($n_i = n_{0i} + n_{1i}$) for that measure. If the number of events was not available, p_j was the average value equal to the total known number of events divided by the total number of patients in studies that reported the events.

4. Censure generation

A uniform censure in [0, T_{max}] was generated. T_{max} was calculated to provide an expected censure proportion equal to p_j. (See appendix IV)

5. MR calculation

Each median was calculated by Kaplan-Meier and their ratio was performed. If a median can not be estimated, the measure is removed in this simulation.

6. HRR calculation

Calculated by adjusting the Cox model

Exponential	**Weibull**
7. Lin concordance coefficient The weighted (by the inverse of SE obtained from the Cox model) concordance between Log (MR) and Log (HRR^{-1}) was calculated with the Lin coefficient. **8. SD** Standard deviation of $\left\lvert Log\left(\frac{MR_j}{HRR_j^{-1}}\right)\right\rvert$	**7. Lin concordance coefficient** The weighted (by the inverse of SE obtained from the Cox model) concordance between $k_j \cdot$Log (MR) and Log (HRR^{-1}) was calculated with the Lin coefficient. **8. SD** Standard deviation of $\left\lvert Log\left(\frac{MR_j^k}{HRR_j^{-1}}\right)\right\rvert$

Box 13. Simulation process in a single iteration to generate exponential and Weibull time distributions similar to empirical data. This process was repeated 100 times**.**

Regarding Weibull simulations, 6.7% (8/120) of the parameters could not be calculated because of the negative values of the shape parameters. Between 4.5% (5/112) and 5.4% (6/112) – depending on the simulation – of the remaining measures were removed during the simulation because medians could not be estimated from Kaplan-Meier survival. Therefore, the final Weibull simulations were made with 106 or 107 pairs of measures. The concordance and the SD for each distribution were estimated as the average of the Lin coefficients and SDs over the 100 simulations, respectively.

ANNEX IX. Simulacions del gràfic de Bland-Altman sota les distribucions exponencial i Weibull

La Figura 30 mostra on es situarien las línees de ± 2 DE en el cas de les dades reals i sota les simulacions de la distribució Weibull i Exponencial.

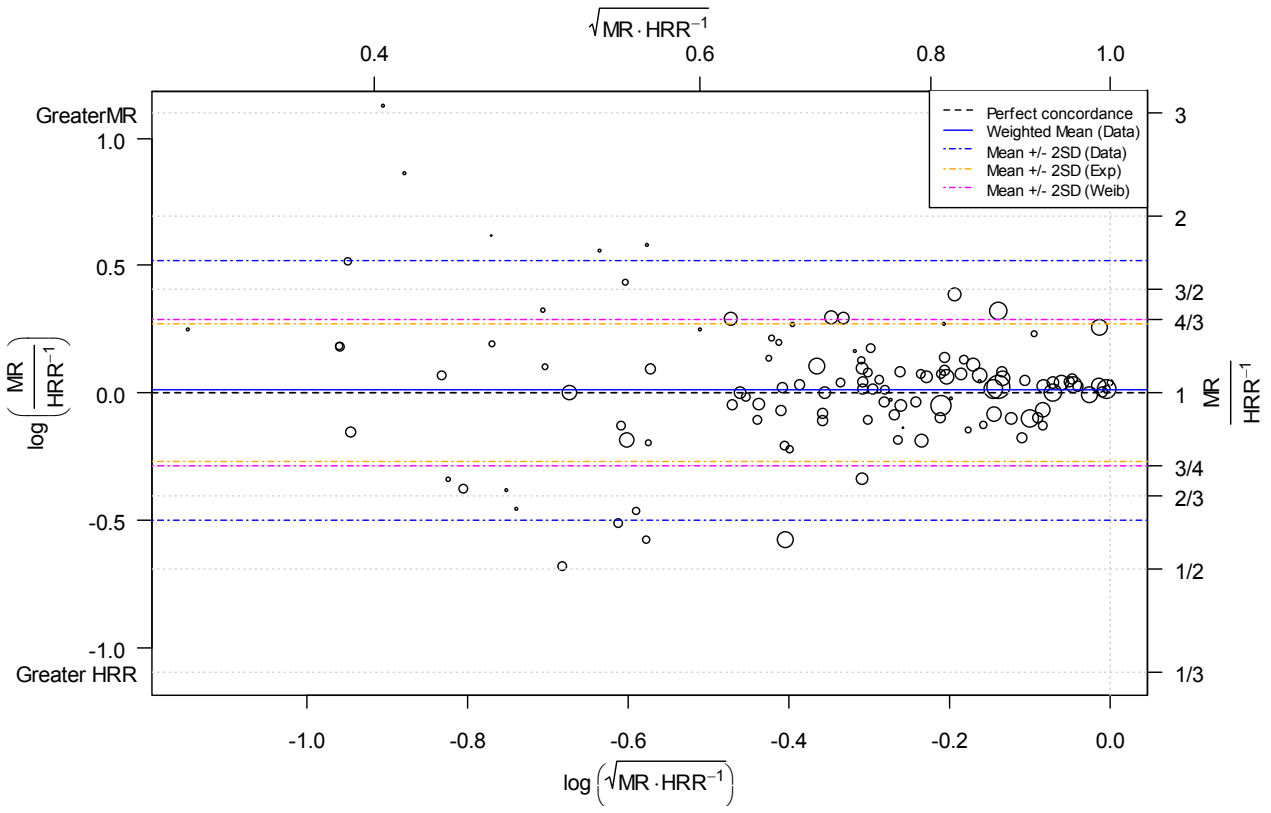


Figura 30. El gràfic de Bland-Altman de concordança de les discrepàncies en funció de les mitjanes. La grandària dels punts és proporcional a la inversa de la SE del Log (HRR). Les línies blaves representen la mitjana ponderada (per la inversa de la SE) i aquesta mitjana ± 2 DE. Les línies taronges representen on es trobarien les línies corresponents a ± 2 DE si totes les distribucions de temps fossin exponencials i les línies de color rosa tindrien el mateix significat pel cas de la distribució Weibull.

En 4 de les 100 simulacions de les dades dels estudis assumint distribucions exponencials o Weibulls, el gràfics de Bland-Altman es van generar amb l'objectiu de veure com quedaven els punts distribuïts sota la premissa de concordança teòrica perfecta (Figura 31 i Figura 32).

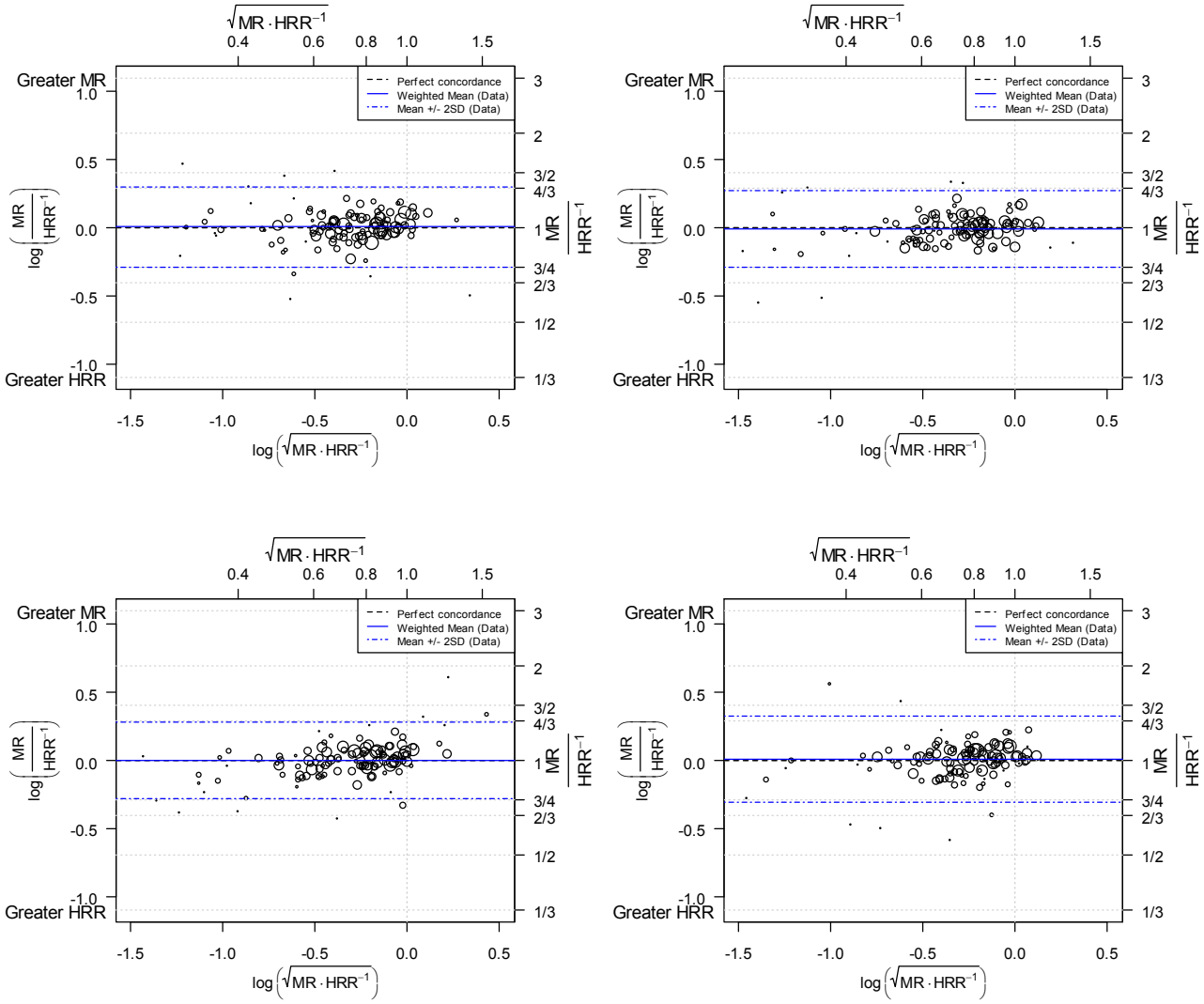


Figura 31. Simulació de 4 gràfics de Bland-Altman sota la distribució Exponencial. El coeficients de Lin en els 4 gràfics (d'esquerra a dreta i de dalt a baix) són 0.92, 0.94, 0.93 i 0.92 respectivament.

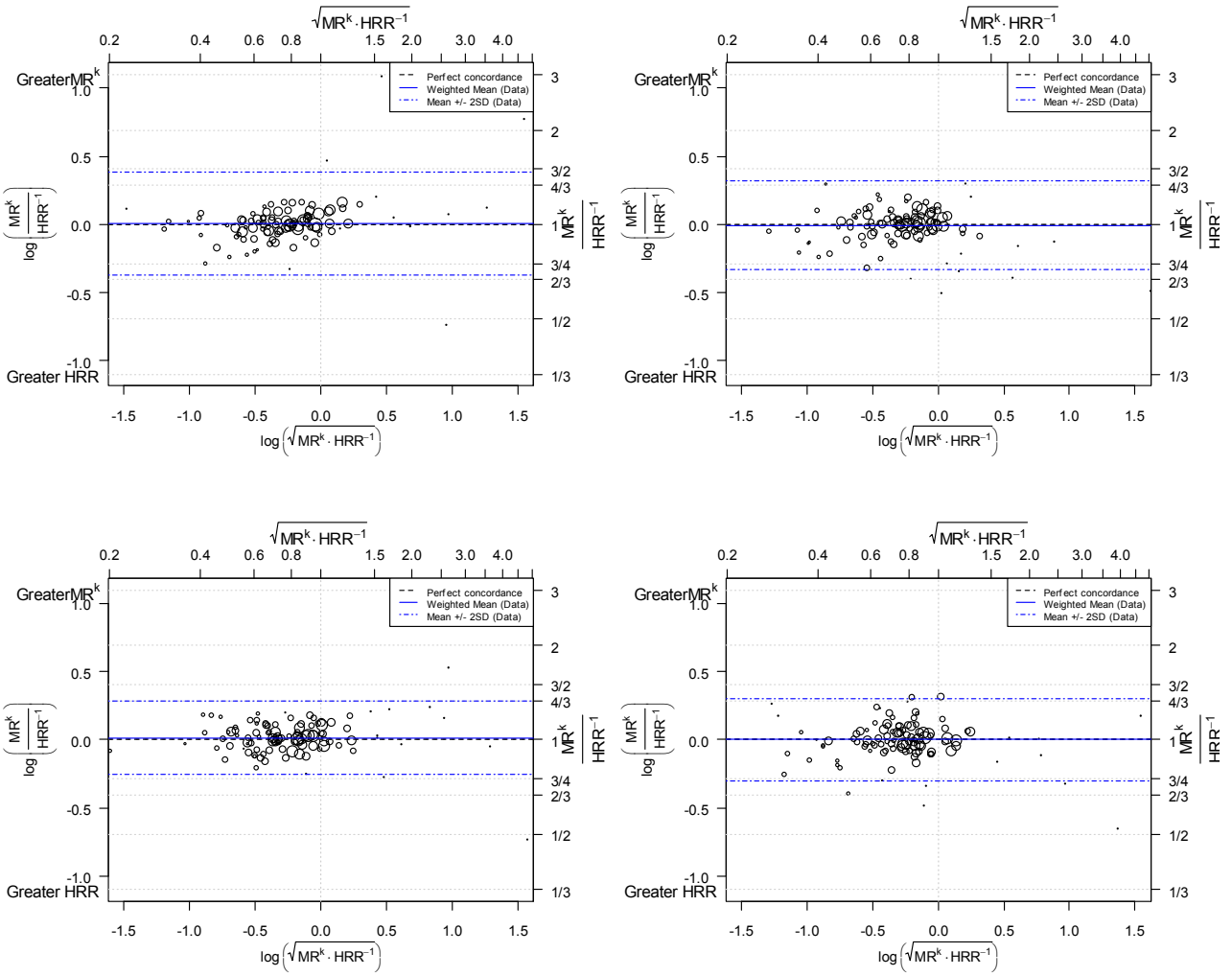


Figura 32. Simulació de 4 gràfics de Bland-Altman sota la distribució Weibull. El coeficients de Lin en els 4 gràfics (d'esquerra a dreta i de dalt a baix) són 0.95, 0.94, 0.96 i 0.94 respectivament.

ANNEX X. Scripts en R

Script 1. Script principal que realitza la lectura de les dades, els gràfics de Bland-Altman, el Funnel-plot, i les figures dels annexos VI i VII.

```
################################################################################
# Script per l'anàlisi de les dades NEJM                                       #
# Autor: Jordi Cotés Martínez                                                  #
# Data: Maig de 2011                                                           #
# Objetiu principal: Examinar la concordancia entre el HRR^-1 i el Median Ratio#
################################################################################

rm(list=ls())

####################### Carregar funcions i llibreries #########################
setwd('E:\\TFM\\RecercaHRRvsMediana\\Scripts')
source('Functionsv1.r')


####################### Lectura de les dades ###################################
setwd('E:\\TFM\\RecercaHRRvsMediana')
NEJM <- read.csv2('NEJM3.csv',header=TRUE,dec='.')


####################### Inspecció de les dades #################################
head(NEJM) ; names(NEJM) ; dim(NEJM)


####################### Seleccionar les variables que ens interesen ############
columns <-  c("CodeArt","Num","CodiSearch","Year","Outcome","Type","HRR_Adj",
              "LI_Adj","LS_Adj","MedianC","MedianT","HRR","LI","LS","MedRat",
              "MR.HRR","GeoMean","N","NC","NT","E","EC","ET")


####################### Seleccionar els ECA's ##################################
selCT <- which(NEJM[,"CT"]=="Yes")
dades <- NEJM[selCT,columns]


####################### Inspecció de les dades  i descriptiva ##################
names(dades) ; summary(dades) ; table(dades$Year)
NumDescript(dades)
GraphDescript(dades)


####################### Selecció de les dades per l'anàlisi ####################
dades2 <- dades
n <- dim(dades2)[1]



################################################################################
##                                                                            ##
##                                                                            ##
##                                Gràfics                                     ##
##                                                                            ##
##                                                                            ##
################################################################################

################################################################################
#                    Grafic 1: Diagrama bivariant                              #
################################################################################

##### Generar el marc
win.graph(WinSize(100),100)
par(mfrow=c(1,2),las=1,mar=c(4.1,6,5,4.5),cex.lab=0.9,cex.axis=0.9)

##### Grandaria dels punts del gràfic (proporcional al EE del log (HRR))
esc <- 8                                  # Paràmetre d'escala per la grandaria dels punts
EE <- with(dades2,(log(LS)-log(LI))/(2*1.96)) # EE del HRR
size <- round(1/(esc*EE),2)               # Grandària dels punts en funció de EE i size

##### Color pels punts dels gràfics
colOS <- ifelse(dades2$Type=="OS",2,3)         # Color en funció de PFS (verd) o OS (vermell)
colYear <- ifelse(dades2$Year>2005,2,3)        # Color en funció de <=2005 (verd) o >2005 (vermell)
```

```
##### Gràfic sense eixos
HRR <- dades2$HRR
MR <-  dades2$MedRat
xymin <- min(HRR,MR) ; xymax <- max(HRR,MR)
plot(HRR,MR,xlim=c(xymin,xymax),ylim=c(xymin,xymax),pch=1,log='xy',cex=size,
      xlab=expression(Log~bgroup("(",HRR^-1,")")),ylab="Log (MR)",main="",
      xaxt="n",yaxt="n",col=1)
abline(0,1,lty=2)                   # bisectriu

##### Afegir els eixos
AxisPlot1(dades2)


################################################################################
#                                 Gràfic 2: BA                                 #
################################################################################
BlandAltman(x=log(dades2$HRR),y=log(dades2$MedRat),
            tit="",size=size,co=1,ID=NULL,limx=NULL,limy=3)
AxisBlandAltman(dades2$MedRat,dades2$HRR,EE=EE,Type="Global",addlines=F)


################################################################################
#                                 Gràfic 2a: BA en subgrup OS                  #
################################################################################
par(mfrow=c(1,2), las=1)
dadesOS <- subset(dades,dades$Type=="OS")
EEOS <- with(dadesOS,(log(LS)-log(LI))/(2*1.96))  # EE del HRR
sizeOS <- round(1/(esc*EEOS),2)                   # Grandària dels punts
colOS2 <- ifelse(dadesOS$Type=="OS",2,3)
BlandAltman(x=log(dadesOS$HRR),y=log(dadesOS$MedRat),
            tit="",size=sizeOS,co=colOS2,ID=NULL,limx=NULL,limy=3)
AxisBlandAltman(dadesOS$MedRat,dadesOS$HRR,EE=EEOS,Type="OS",addlines=F)


################################################################################
#                                 Gràfic 2b: BA en subgrup PFS                 #
################################################################################
dadesPFS <- subset(dades,dades$Type=="PFS")
EEPFS <- with(dadesPFS,(log(LS)-log(LI))/(2*1.96))  # EE del HRR
sizePFS <- round(1/(esc*EEPFS),2)                    # Grandària dels punts
colPFS2 <- ifelse(dadesPFS$Type=="OS",2,3)
BlandAltman(log(dadesPFS$HRR),log(dadesPFS$MedRat),"",sizePFS,colPFS2,ID=NULL,limy=3)
AxisBlandAltman(dadesPFS$MedRat,dadesPFS$HRR,EE=EEPFS,Type="PFS",addlines=F)


################################################################################
#                                 Gràfic 2c: BA en subgrup <=2005              #
################################################################################
par(mfrow=c(1,2), las=1)
dadesBefore <- subset(dades,dades$Year<=2005)
EEBefore <- with(dadesBefore,(log(LS)-log(LI))/(2*1.96))  # EE del HRR
sizeBefore <- round(1/(esc*EEBefore),2)                    # Grandària dels punts en funció de EE i
size
BlandAltman(log(dadesBefore$HRR),log(dadesBefore$MedRat),"",sizeBefore,2,ID=NULL,limy=3)
AxisBlandAltman(dadesBefore$MedRat,dadesBefore$HRR,EE=EEBefore)
################################################################################
#                                 Gràfic 2c: BA en subgrup >2005               #
################################################################################
dadesAfter <- subset(dades,dades$Year>2005)
EEAfter <- with(dadesAfter,(log(LS)-log(LI))/(2*1.96))  # EE del HRR
sizeAfter <- round(1/(esc*EEAfter),2)                     # Grandària dels punts en funció de EE i
size
BlandAltman(log(dadesAfter$HRR),log(dadesAfter$MedRat),"",sizeAfter,3,ID=NULL,limy=3)
AxisBlandAltman(dadesAfter$MedRat,dadesAfter$HRR,EE=EEAfter)


################################################################################
#                Gràfic 2e: Diferències entre log(MR) y log(HRR-1)             #
################################################################################
par(las=1)
plot(NULL,xlim=c(0,n+5),ylim=c(-1.5,0.1),xaxt="n",xlab="",ylab="")
mtext("OS",1,line=1,at=30,cex=1.2)
mtext("PFS",1,line=1,at=95,cex=1.2)
abline(h=seq(-1.5,0,0.5),lty=2,col="grey80")
```

```
### OS
HRR_OS_Sort <- sort(with(dadesOS,log(HRR)))                          # HRR ordenados
MR_OS_Sort <- with(dadesOS,log(MedRat[order(with(dadesOS,HRR))]))  # MR ordenados
nOS <- length(HRR_OS_Sort)
points(1:nOS,HRR_OS_Sort,cex=1.1,col=2)
segments(1:nOS,HRR_OS_Sort,1:nOS,MR_OS_Sort,col=2,lwd=2)

### PFS
HRR_PFS_Sort <- sort(with(dadesPFS,log(HRR)))                          # HRR ordenados
MR_PFS_Sort <- with(dadesPFS,log(MedRat[order(with(dadesPFS,HRR))])) # MR ordenados
nPFS <- length(HRR_PFS_Sort)
points((nOS+6):(n+5),HRR_PFS_Sort,cex=1.1,col=3)
segments((nOS+6):(n+5),HRR_PFS_Sort,(nOS+6):(n+5),MR_PFS_Sort,col=3,lwd=2)


##############################################################################
#                                  Gràfic 3: Funnel- Plot                    #
##############################################################################
par(mfrow=c(1,1),mar=c(5,6,5,3),las=1)
ma <- with(dades2,max(MedRat/HRR,HRR/MedRat))
plot(dades2$MedRat/dades2$HRR,1/EE,pch=1,xlab=expression(frac(MR,HRR^-1)),ylab=expression(paste("~
",frac(1,SE))),
    main="Funnel plot",log="x",xlim=c(1/ma,ma),cex.lab=0.8,cex=0.9)
abline(v=1,lty=2,col=1)
#text(dades2$MedRat/dades2$HRR,1/EE,dades2[,1],cex=0.5,pos=4)
FunnelLines(dades2)
FunnelEmpiric(dades2,EE)


##############################################################################
#                 Gràfic 4: Log(MR/HRR) vs. proporció de censures            #
##############################################################################
par(las=1,mar=c(5,6,3,1),mfrow=c(1,2))
pCens <- 1- dades2$E/dades2$N
plot(pCens,log(dades2$MedRat/dades2$HRR),pch=1,xlab='Censure
proportion',ylab=expression(log~bgroup("(",frac(MR,HRR^-1),")")),
    main="",log="",xlim=c(0,1),cex.lab=0.8,ylim=c(-1,1),cex=1.5*size,col=colOS,cex.axis=0.9)
abline(h=0,lty=1)
abline(h=seq(-1,1,0.5),lty=2)


##############################################################################
#                 Gràfic 4: Log(MR/HRR) vs. nombre d'events                  #
##############################################################################
par(las=1,mar=c(5,6,3,1))
nE <- dades2$E
plot(nE,log(dades2$MedRat/dades2$HRR),pch=1,xlab='Number of events',
       ylab=expression(log~bgroup("(",frac(MR,HRR^-1),")")),
    main="",log="",cex.lab=0.8,ylim=c(-1,1),cex=1.5*size,col=colOS,cex.axis=0.9)
abline(h=0,lty=1)
abline(h=seq(-1,1,0.5),lty=2)







##############################################################################
#                                                                            #
#                                                                            #
#                                    Anàlisi                                 #
#                                                                            #
#                                                                            #
##############################################################################

##############################################################################
#                                  Concordança                               #
##############################################################################

############################### Qualitativa ##################################
### Proporció d'estudis on el HRR y el MR apunten en el mateix sentit
e <- with(dades2,sum(MedRat>1))
n <- dim(dades2)[1]
prop.test(n-e,n)

### Correlació
cor(dades2$HRR,dades2$MedRat)
```

```
################### Quantitativa: Coeficient de Lin ############################
Lin1 <- epi.ccc(log(dades2$MedRat),log(dades2$HRR))$rho.c # Sense ponderar
Lin1bis <- LinWeigth(dades2,size)[1]                      # Sense ponderar (calculat a mà)
LinPond <- LinWeigth(dades2,size)[2]                      # Ponderant (calculat a mà)
cat("Coeficiente de Linn (con función de R):",Lin1[[1]],
       "\nCoeficiente de Linn (calculado a mano):",Lin1bis,
       "\nCoeficiente de Linn ponderado (calculado a mano):",LinPond,"\n")
LinInterpretation()

### Subgrup OS
(LinPondOS <- LinWeigth(dadesOS,sizeOS)[2])

### Subgrup PFS
(LinPondPFS <- LinWeigth(dadesPFS,sizePFS)[2])

############################ Anàlisi de sensibilitat 1 ##########################
### IC per bootstrap
nboot <- 10000
LinPondBoot <- c()
for (i in 1:nboot){
  mostra <- sample(1:n,n,rep=T)
  LinPondBoot[i] <- LinWeigth(dades2[mostra,],size)[2]
  print(i)
}
sdLin <- sd(LinPondBoot)
z <- qnorm(0.975)
LILinPond <- LinPond - z*sdLin
LSLinPond <- LinPond + z*sdLin
cat("El intervalo de confianza calculado por bootstrap para el coeficiente de Lin Ponderado es: ",
    round(LILinPond,2)," to ", round(LSLinPond,2),"\n")

############################ Anàlisi de sensibilitat 2 ##########################
##### Càlcul del coeficient de Lin pels HRR ajustats
columns2 <-  c("CodeArt","Num","CodiSearch","Year","Outcome","Type","HRR_Unadj",
               "LI_Unadj","LS_Unadj","MedianC","MedianT","HRR","LI","LS","MedRat",
               "MR.HRR","GeoMean","N","NC","NT","E","EC","ET")
selCT_NA <- which(NEJM[,"CT"]=="Yes" & !is.na(NEJM[,"HRR_Unadj"]))
dadesUnadj <- NEJM[selCT_NA,columns2]
dadesUnadj$HRR <- dadesUnadj$HRR_Unadj
sizeUnadj <- with(dadesUnadj,LS_Unadj-LI_Unadj)
(LinPondUnadj <- LinWeigth(dadesUnadj,sizeUnadj)[2])




################################################################################
#         CCI (Intraclass correlation coefficient) para la concordança         #
################################################################################

############################ Arreglar les dades ################################
##### Convertir les dades en una llista d'articles amb almenys dues mesures
dades3 <- DataForICC(dades2)
##### Converteix la llista anterior en una matriu de dues columnes amb les diferències per OS i PFS
MR_HRRMatrix <- DataForICC2(dades3)

############################## Gràfic ##########################################
### Paràmetres
xymin <- min(MR_HRRMatrix) ; xymax <- max(MR_HRRMatrix)
xy <- max(abs(c(xymin,xymax)))
labx <- expression(Log~bgroup("(",frac(MR[OS],HRR[OS]^-1),")"))
laby <- expression(Log~bgroup("(",frac(MR[PFS],HRR[PFS]^-1),")"))

### plot
par(mfrow=c(1,1),las=1,mar=c(5,7,5,2),mgp=c(3.2,0.5,0))
plot(MR_HRRMatrix[,1],MR_HRRMatrix[,2],asp=I,xlim=c(-xy,xy),ylim=c(-xy,xy),
      xlab=labx,ylab=laby,las=1,main="All data")
abline(0,1)
#text(MR_HRRMatrix[,1],MR_HRRMatrix[,2],sel,pos=4,cex=0.5)

############################ ICC ###############################################

### ICC calculat amb funció de R
ICC1 <- icc(MR_HRRMatrix,model = "twoway",type = "consistency",unit="single", r0 = 0, conf.level =
0.95)

### ICC calculat amb model d'efectes aleatoris
ICC <- ICCEfectesAleatoris(MR_HRRMatrix)
```

```
##############################################################################
#                  Diferències entre les dues mesures                        #
##############################################################################

##### IC de la diferència ponderada
logMRHRR <- log(dades2$MedRat)-log(dades2$HRR)
mod.lm <- lm(logMRHRR~1,weights= 1/(EE^2))
EstRatio2 <- coef(mod.lm)
EEglobal <- coef(summary(mod.lm))[2]
CI <- confint(mod.lm)
est <- mod.lm[[1]]
cat("Diferencia entre el logaritmo de MR y el logaritmo HRRinv ponderada es:"
       ,round(est,3),"[",round(CI[1],3),",",round(CI[2],3),
    "]\nCociente de MR y HRRinv ponderado
        es:",round(exp(est),3),"[",round(exp(CI[1]),3),",",round(exp(CI[2]),3),"]\n")

##### IC de la diferència ponderada i corregida pel DEFF
DEFF <- 1+ICC
amplitud <- DEFF*(CI[2]-est)
CI2 <- c()
CI2[1] <- est-amplitud
CI2[2] <- est+amplitud
cat("Diferencia entre el logaritmo de MR y el logaritmo HRRinv ponderada
        es:",round(est,3),"[",round(CI2[1],3),",",round(CI2[2],3),
    "]\nCociente de MR y HRRinv ponderado
        es:",round(exp(est),3),"[",round(exp(CI2[1]),3),",",round(exp(CI2[2]),3),"]\n")




##############################################################################
#                  Diferències per subgrups                                  #
##############################################################################


############################## PFS y OS ######################################
abslogMRHRR <- abs(logMRHRR)
mod.lm <- lm(abslogMRHRR~dades2$Type,weights=1/EE^2)
summary(mod.lm)
CI <- confint(mod.lm)[2,]
est <- mod.lm[[1]]["dades2$TypePFS"]
cat("La estimación de la diferencia del valor absoluto de log(MR·HRR) entre PFS y OS
        es:",round(est,2),"[",round(CI[1],2),",",round(CI[2],2),"]\n")
cat("La estimación del cociente de MR·HRR entre PFS y OS
        es:",round(exp(est),2),"[",round(exp(CI[1]),2),",",round(exp(CI[2]),2),"]\n")
##### IC de la diferència ponderada i corregida pel DEFF
amplitud <- DEFF*(CI[2]-est)
CI2 <- c()
CI2[1] <- est-amplitud
CI2[2] <- est+amplitud
cat("Diferencia entre el logaritmo de MR y el logaritmo HRRinv ponderada
        es:",round(est,3),"[",round(CI2[1],3),",",round(CI2[2],3),
    "]\nCociente de MR y HRRinv ponderado
        es:",round(exp(est),3),"[",round(exp(CI2[1]),3),",",round(exp(CI2[2]),3),"]\n")



########################## Abans de 2005 vs. després #########################
YearCat <- as.factor(ifelse(dades2$Year>2005,">2005","<=2005"))
mod.lm <- lm(abslogMRHRR~YearCat,weights=1/EE^2)
CI <- confint(mod.lm)[2,]
est <- mod.lm[[1]]["YearCat>2005"]
cat("La estimación de la diferencia del valor absoluto de log(MR·HRR) entre después y antes de 2005
        es:",round(est,2),"[",round(CI[1],2),",",round(CI[2],2),"]\n")
cat("La estimación del cociente de MR·HRR entre después y antes de 2005
        es:",round(exp(est),2),"[",round(exp(CI[1]),2),",",round(exp(CI[2]),2),"]\n")
##### IC de la diferència ponderada i corregida pel DEFF
amplitud <- DEFF*(CI[2]-est)
CI2 <- c()
CI2[1] <- est-amplitud
CI2[2] <- est+amplitud
cat("Diferencia entre el logaritmo de MR y el logaritmo HRRinv ponderada
        es:",round(est,3),"[",round(CI2[1],3),",",round(CI2[2],3),
    "]\nCociente de MR y HRRinv ponderado
        es:",round(exp(est),3),"[",round(exp(CI2[1]),3),",",round(exp(CI2[2]),3),"]\n")
```

```
##############################################################################
# Medianes gràfiques                                                         #
# Concordança entre la mediana real, l'observada gráficament per Lourdes  i per#
# mi mateix                                                                  #
##############################################################################

medianas <- read.csv2('E:\\TFM\\RecercaHRRvsMediana\\EstimacionGraficaMedianas\\
       Medianasgraficas.csv',dec='.',header=TRUE)
MedianConcordance(medianas)

##############################################################################
#                                  Publication Bias                          #
##############################################################################

############################## Funnel plot alternatiu ##########################
effect <- with(dades2,log(MedRat)-log(HRR))
par(mfrow=c(1,1),mar=c(6,6,3,1),las=1,cex.lab=0.8,cex.axis=0.8)
funnelplot(effect, EE, plot.conf=FALSE,mirror=FALSE,
           xlab=expression(log~bgroup("(",frac(MR,HRR^-1),")")),ylab=expression(frac(1,EE)))
abline(v=0,lty=2)
radial(effect,EE)

############################## Meta-regresión ##################################
# Efecto global y varianza global
TE.fixed <- EstRatio2
seTE.fixed <- EEglobal
par(mfrow=c(1,1),las=1,lwd=1,cex=1.2)
(linreg <- metabias(effect, EE,method = "linreg",plotit = TRUE, correct = FALSE))


### Estimación puntual y IC del sesgo
# If method is "linreg", the test statistic is based on a weighted linear
# regression of the treatment effect on its standard error (Egger et al., 1997).
# The test statistic follows a t distribution with number of studies - 2 degrees
# of freedom.
Bias <- linreg$est[1]
BiasSE <- linreg$est[2]
CIbias <- Bias + c(-1,1)*qt(0.975,n-2)*BiasSE
abline(h=0,lty=2)
abline(Bias,linreg$est[3],col=4,lwd=2)
abline(CIbias[1],linreg$est[3],col=4,lty=2,lwd=2)
abline(CIbias[2],linreg$est[3],col=4,lty=2,lwd=2)

# text(1/EE,effect/EE,rownames(dades2),cex=0.5,pos=4)
# metabias(effect, EE,method = "mm",plotit = TRUE, correct = FALSE)
# metabias(effect, EE, TE.fixed, seTE.fixed,method = "rank",plotit = TRUE, correct = FALSE)
# abline(v=0,lty=2,lwd=1)


##############################################################################
#                      Estimació de la variança del log(MR/HRR)              #
##############################################################################

setwd('E:\\TFM\\RecercaHRRvsMediana\\Scripts')
source('VariabilidadMR.r')

### Mètode 1: Ajust empíric
AjusteEmpirico(dades2,EE)

### Mètode 2: Simulació
AjusteSimula(n=50,nsim=50,replic=50)

### Mètode 3: Simulació en funció de log(HRR)
AjusteSimula2(n=50,nsim=50,replic=50)

### Mètode 4: Simulació en funció de n
AjusteSimula3(ene=seq(10,200,5),replic=100)
```

Script 2. Funcions auxiliars emprades per l'script principal.

```
######################## Carregar llibreries ###################################
library(epiR)     # Concordancia de Lin. epi.ccc
library(irr)      # CCI (Intraclass correlation coefficient) para la concordancia (cci)
library(nlme)     # ICC con modelos de efectos aleatorios (lme)
library(psych)    # geometric.mean
library(rmeta)    # (funnelplot) Funnel plot alternativo
library(meta)     # (metabias) Evaluar el sesgo de publicación



#############################################################################################
# Realitza la descriptiva gràfica
# dades: les dades de les quals s'ha de fer la descriptiva
#############################################################################################

GraphDescript <- function(dades){

  attach(dades)
  DifZero <- function(x){sum(x!=0)}   # Funció auxiliar

  ############################## Gràfics categòriques ############################

  ##### Descriptiva per articles
  par(mfrow=c(2,2),las=1)
  YearT <- apply(table(CodeArt,Year),2,DifZero)
  barplot(YearT,main="Publication year",ylab = "Papers (no.)",las=2)
  barplot(table(table(CodeArt)),main="Number of measures",ylab = "Papers (no.)")

  ##### Descriptiva per mesures
  barplot(table(Outcome),main="Category",ylab = "Outcomes (no.)",ylim=c(0,80))
  barplot(table(Type),main="Type",ylab = "Outcomes (no.)",ylim=c(0,80))
  detach(dades)


  ############################## Gràfics numèriques ##############################

  dadesAux <- subset(dades,dades$Num==1)  # Seleccionem un representant de cada estudi

  ##### Box-plots
  win.graph() ; par(mfrow=c(1,4),las=1)
  boxplot(dadesAux$N,ylim=c(0,1850),ylab="Patients (no.)",main="Sample size")
  boxplot(dades$E,ylim=c(0,1850),ylab="Patients (no.)",main="Total number of events")

  #win.graph() ; par(mfrow=c(1,2),las=1)
  boxplot(log(dades$HRR),ylim=c(-1.5,0.2),main=expression(bold(Log~bgroup("(",HRR^-1,")"))))
  boxplot(log(dades$MedRat),ylim=c(-1.5,0.2),main=expression(bold(Log~bgroup("(",MR,")"))))

  ##### Gràfics de segments
  win.graph(300,150)
  par(mfrow=c(1,3),las=1,cex.axis=1.1)

  ### All data
  plot(NULL,xlim=c(0,1),ylim=c(-1.5,0.1),xaxt="n",xlab="",ylab="",main="All data")
  axis(1,at=c(0,1),label=c(expression(Log~bgroup("(",HRR^-1,")")),expression(Log~bgroup("(",MR,")"))))
  segments(0,log(dades$HRR),1,log(dades$MedRat),col=1)

  ### OS
  selType <- which(dades$Type=="OS")
  plot(NULL,xlim=c(0,1),ylim=c(-1.5,0.1),xaxt="n",xlab="",ylab="",main="OS")
  axis(1,at=c(0,1),label=c(expression(Log~bgroup("(",HRR^-1,")")),expression(Log~bgroup("(",MR,")"))))
  segments(0,log(dades$HRR[selType]),1,log(dades$MedRat[selType]),col=2)

  ### PFS
  plot(NULL,xlim=c(0,1),ylim=c(-1.5,0.1),xaxt="n",xlab="",ylab="",main="PFS")
  axis(1,at=c(0,1),label=c(expression(Log~bgroup("(",HRR^-1,")")),expression(Log~bgroup("(",MR,")"))))
  segments(0,log(dades$HRR[-selType]),1,log(dades$MedRat[-selType]),col=3)
}
```

```
################################################################################
# Realitza la descriptiva numèrica
# dades: les dades de les quals s'ha de fer la descriptiva
################################################################################

NumDescript <- function(dades){

  attach(dades)
  DifZero <- function(x){sum(x!=0)}   # Funció auxiliar
  YearT <- apply(table(CodeArt,Year),2,DifZero)
  detach(dades)
  dadesAux <- subset(dades,dades$Num==1)  # Seleccionem un de cada estudi

  ############################## Descriptiva numèrica ############################

  ##### Proporcions dels articles
  cat("\n---------------------- Proportions -------------------------------\n")
  cat("Publication year\n")
  print(round(prop.table(YearT),2))
  cat("\n")
  print(round(prop.table(table(table(dades$CodeArt),dnn="Measures by paper")),2))
  cat("\n")
  print(round(prop.table(table(dades$Outcome,dnn="Outcome category")),2))
  cat("\n")
  print(round(prop.table(table(dades$Type,dnn="Outcome Type")),2))
  cat("\n")
  print(table(dades$CodiSearch,dnn="Criterio de búsqueda por medidas"))
  cat("Criterio de búsqueda por artículos\n")
  print(table(dades$Num,dades$CodiSearch)[1,])
  cat("\n")


  ##### Taules de contingència
  cat("\n-------------------------- n -----------------------------------\n")
  Papers <- subset(dades,Num=="1")
  cat("\nYear") ;  print(table(Papers$Year))
  cat("\nNumber of measures") ;  print(table(tapply(dades$Num,dades$CodeArt,max)))
  cat("\nMain outcome") ;  print(table(dades$Outcome))
  cat("\nOutcome type") ;  print(table(dades$Type))

  ##### Estadístics variables contínues
  cat("\n------------------- Continue outcomes ------------------------------")
  cat("\nSample Size\n") ; print(summary(dadesAux$N))
  cat("SD: ",sd(dadesAux$N),"\n")
  cat("\nEvents\n") ; print(summary(dades$E))
  cat("SD: ",sd(dadesAux$E,na.rm=T),"\n")
  cat("\nLog(HRR)\n") ; print(summary(log(dades$HRR)))
  cat("SD: ",sd(log(dades$HRR)),"\n")
  cat("\nLog(MR)\n") ; print(summary(log(dades$MedRat)))
  cat("SD: ",sd(log(dades$MedRat)),"\n")
}







################################################################################
# Crea finestres per gràfics amb mateixa escala en x e y amb mfrow=c(1,2)
# heigth: Alçada del gràfic
################################################################################

WinSize <- function (heigth){
       margin <- par('mar')-0.1
       plotSize <- heigth - sum(margin[c(1,3)])
       widthSize <- 2*(plotSize + sum(margin[c(2,4)]))
       correction <- 118/125
       widthSize2 <- correction*widthSize
}
```

```
##############################################################################
# Dibuixa els eixos i les etiquetes en el digrama bivariant
# dades2: dades per fer el gràfic
##############################################################################

AxisPlot1 <- function(dades2){
  ##### Eixos en escala logarítmica
  B <- exp(seq(-2,0,0.2))
  Bchar <- formatC(seq(-2,0,0.2))
  axis(1,at=B,labels=Bchar,cex=0.9)
  axis(2,at=B,labels=Bchar,cex=0.9)

  ##### Eixos en escala normal
  A <- seq(0.2,1,0.2)
  Achar <- formatC(A,1,format="f")
  axis(3,at=A,labels=Achar,cex=0.9)
  axis(4,at=A,labels=Achar,cex=0.9)

  ### Etiquetes
  mtext(expression(HRR^-1),3,line=2,at=sqrt(xymin*xymax),cex=0.9,las=0)
  mtext("MR",4,line=2,at=sqrt(xymin*xymax),cex=0.9,las=0)

  ### Ablines per veure discordances
  abline(v=1,lty=3,col="grey80")
  abline(h=1,lty=3,col="grey80")
}




##############################################################################
# Gràfic Bland-Altman de concordança
# x: valors de x
# y: valors de y
# tit: títol del gràfic
# size: grandaria punts
# co: color dels punts
# ID: identificador pels punts
# limx: vector amb els límits per l'eix de les x's  (per defecte, ho ajusta als valors)
# limy: valor positiu limit per l'eix de les y's (per defecte, ajusta als valors conservant simetria
vertical)
##############################################################################
BlandAltman <- function(x,y,tit="Bland-Altman",size,co,ID=NULL,limx=NULL,limy=NULL){

       Bmean <- (x+y)/2
       Bdif <- y-x

  ##### Límit de l'eix de les y's
       if (is.null(limy))  ymax <- max(abs(Bdif),na.rm=T)
       if (!is.null(limy)) ymax <- limy

  ##### Gràfic
       plot(Bmean ,Bdif ,ylim=log(c(1/ymax,ymax)),xlim=limx,main=tit,cex=size,col=co,
        xlab=expression(log~bgroup("(",sqrt(MR%.%HRR^-1),")")),
                  ylab=expression(log~bgroup("(",frac(MR,HRR^-1),")")))

  ##### Etiquetes
  mtext("Greater MR",2,line= 0.5,at=log(ymax),adj=1,cex=0.9)
       mtext("Greater HRR",2,line= 0.5,at=-log(ymax),adj=1,cex=0.9)

  ##### Identificador
       if(!is.null(ID)) text(Bmean,Bdif,ID,pos=4,cex=0.6)

  ##### Linees verticals i horizontals en el zero
       abline(h=0,lty=2)
       abline(v=0,lty=3,col="grey80")
}
```

```
#####################################################################
# Dibuixa els eixos i les etiquetes en el gràfic de Bland Altman
# x: 1a variable
# y: 2a variable
# xtick: vector con número de puntos
# ytick: vector con número de puntos

AxisBlandAltman <- function(x,y,xtick=NULL,ytick=NULL,EE=NULL,Type=NULL,addlines=FALSE){
  ### Punts on va l'eix Y
  Puntsya <- log(c(1/(5:3),1:4/2:5,1,5:3/4:2,2:5))
  PuntsCharya <- c(paste("1/",5:3,sep=""),paste(1:4,"/",2:5,sep=""),1,c(paste(5:3,"/",4:2,sep=""),2:5))
  if(is.null(ytick)){
    Puntsy <- Puntsya[c(2:6,8,10:14)]
    PuntsChary <- PuntsCharya[c(2:6,8,10:14)]
  }
  if(!is.null(ytick)){
    Puntsy <- Puntsya[ytick]
    PuntsChary <- PuntsCharya[ytick]
  }
  ### Punts on va l'eix X
  Puntsxa <- log(c(seq(0.2,1,0.2),seq(1.5,5,0.5)))
  PuntsCharxa <- formatC(c(seq(0.2,1,0.2),seq(1.5,5,0.5)),1,format="f")

  if(is.null(xtick)){
    Puntsx <- Puntsxa
    PuntsCharx <- PuntsCharxa
  }
  if(!is.null(xtick)){
    Puntsx <- Puntsxa[xtick]
    PuntsCharx <- PuntsCharxa[xtick]
  }
  ### Dibuixar eixos
  xymin <- min(log(sqrt(x*y))) ; xymax <- max(log(sqrt(x*y)))
  axis(3, at = Puntsx , labels = PuntsCharx,cex=0.9)
  axis(4, at = Puntsy, labels = PuntsChary,cex=0.9)

  ### Ablines
  abline(h=Puntsy,lty=3,col="lightgrey")
  abline(h=0,lty=2)

  ### Label
  mtext(expression(sqrt(MR%.%HRR^-1)),3,line=2,at=mean(c(xymin,xymax)),cex=0.9)
  mtext(expression(frac(MR,HRR^-1)),4,line=3,at=0,cex=0.9,las=0)

  ### Confidence intervals
  MR <- x
  HRR <- y
  M <- ifelse(is.null(EE),mean(log(MR/HRR)),weighted.mean(log(MR/HRR),1/EE))
  SD <- sd(log(MR/HRR),na.rm=TRUE)
  cat("SD (data):",SD,"\n")
  abline(h=M,col=4,lwd=1)
  abline(h=M+c(2*SD,-2*SD),lty=4,col=4)

  ### Lectura de les desviacions
  if(addlines){
    setwd('E:\\TFM\\RecercaHRRvsMediana\\Concordancias simuladas')
    ExpAll <- mean(read.table('ExpPartialdataAllResponse.txt',header=T)[,2])
    ExpOS <- mean(read.table('ExpPartialdataOS.txt',header=T)[,2])
    ExpPFS <- mean(read.table('ExpPartialdataPFS.txt',header=T)[,2])

    WeibAll <- mean(read.table('WeibPartialdataAllResponse.txt',header=T)[,2])
    WeibOS <- mean(read.table('WeibPartialdataOS.txt',header=T)[,2])
    WeibPFS <- mean(read.table('WeibPartialdataPFS.txt',header=T)[,2])

    # Datos sacados de las simulaciones SimulaBlandAltman.r
    SDExp <- ifelse((is.null(Type) | Type=="Global"),ExpAll,ifelse(Type=="OS",ExpOS,ExpPFS))
    SDWei <- ifelse((is.null(Type) | Type=="Global"),WeibAll,ifelse(Type=="OS",WeibOS,WeibPFS))

    abline(h=c(-2*SDExp,2*SDExp),lty=4,col="orange")
    abline(h=c(-2*SDWei,2*SDWei),lty=4,col=6)
    legend('topright',c("Perfect concordance","Weighted Mean (Data)",
               "Mean +/- 2SD (Data)","Mean +/- 2SD (Exp)","Mean +/- 2SD (Weib)"),
               lty=c(2,1,4,4,4),col=c(1,4,4,"orange",6),lwd=1,cex=0.7,bg="white")
  }
  if(!addlines){
    legend('topright',c("Perfect concordance","Weighted Mean (Data)","Mean +/- 2SD (Data)"),
           lty=c(2,1,4),col=c(1,4,4),lwd=1,cex=0.7,bg="white")
  }
}
```

```
##############################################################################
# Dibuixa els IC del 95% teòrics i la mitja geomètrica i la mediana en B-A
##############################################################################
FunnelLines <- function(dades2){
  gm <- geometric.mean(dades2$MedRat/dades2$HRR)
  med <- median(dades2$MedRat/dades2$HRR)
  abline(v=gm, lwd=2,col=4)
  abline(v=med, lwd=2, col=2,lty=3)
  legend('topleft',c("Concordance","Geometric   mean","Median","Mean   Significance   (95%)","Individual
significance (90%)"),lty=c(2,1,3,4,4),col=c(1,4,2,3,"darkgreen"),lwd=c(1,2,2,1,1),cex=0.8)

  ### Línies de significació
  yizq <- seq(0,20,0.01)
  xizq1 <- log(gm)+1.96*1/yizq
  xizq2 <- log(gm)-1.96*1/yizq
  lines(exp(xizq1),yizq ,lty=4,col=3)
  lines(exp(xizq2),yizq ,lty=4,col=3)
  points(dades2$MedRat/dades2$HRR,1/EE,cex=0.8)

  ### Etiquetes
  mtext("|log(MR)| > |log(HRR)|",side=1,line=2.4,at=1/ma,adj=0.5,cex=0.8,font=2)
  mtext("|log(MR)| < |log(HRR)|",side=1,line=2.4,at=ma,adj=0.5,cex=0.8,font=2)
  mtext("HRR<1",side=3,line=0.5,at=1,cex=0.9,font=2)

}

##############################################################################
# IC empírico del 90% por bootstrap
# 1. Se cogen los m (20) puntos con menor EE (es decir con mayor 1/EE)
# 2. Se seleccionan r (20) de ellos con reposición
# 3. Se mira donde cae el cociente MR/HRR segundo (es decir el que deja un 5% de los puntos por
#    la izquierda) y el MR/HRR (r-1) (es decir el que deja un 5% de los puntos por la derecha)
# 4. El promedio de nboots (100) de los puntos segundos será el LI del IC a la altura promedio
#    de los 1/E de estos 20 puntos. Para el LS del IC se hará con el punto 19
# 5. Se repite el proceso para los puntos del 2 al 21 con menor EE
##############################################################################
FunnelEmpiric <- function(dades2,EE){
  m <- 10
  r <- 20
  nboots <- 100
  sortEE <- sort(EE)
  ordenEE <- order(EE)
  MR <- dades2$MedRat
  HRR <- dades2$HRR
  MRHRR <- MR/HRR
  MRHRRorder <- MRHRR[ordenEE]
  L <- length(EE)

  EEinv <- c()
  LI <- c()
  LS <- c()

  for (i in 1:(L-m+1)){
    primero <- i
    ultimo <- (i+m-1)
    EEinv[i] <- mean(1/sortEE[primero:ultimo])
    mpuntos <- MRHRRorder[primero:ultimo]
    linf <- c()
    lsup <- c()
    for (j in 1:nboots){
      muestra <- sort(sample(mpuntos,r,replace=TRUE))
      linf[j] <- muestra[2]
      lsup[j] <- muestra[r-1]
    }
    LI[i] <- geometric.mean(linf)
    LS[i] <- geometric.mean(lsup)
  }
### Lineas
  lowessLI <- lowess(EEinv,LI)
  yLI <- lowessLI$x
  xLI <- lowessLI$y

  lowessLS <- lowess(EEinv,LS)
  yLS <- lowessLS$x
  xLS <- lowessLS$y

  lines(xLS,yLS,lty=4,col="darkgreen")
  lines(xLI,yLI,lty=4,col="darkgreen")
}
```

```
##############################################################################
# Coeficient de Lin ponderat per size
# Retorna un vector amb el Lin sense ponderar calculat a mà (Article de Lin) i
# el coeficient ponderat
##############################################################################


LinWeigth <- function(dades,size){
  WT <- size/sum(size)
  x <- log(dades$MedRat)
  y <- log(dades$HRR)

  COV.WT <- cov.wt(cbind(x,y),wt = WT)
  mux.WT <- weighted.mean(x, WT)
  muy.WT <- weighted.mean(y, WT)

  co <- COV.WT$cov[2,1]
  varx <- COV.WT$cov[1,1]
  vary <- COV.WT$cov[2,2]
  cat('Para los logaritmos:')
  cat ('mu(MR):',mux.WT,'var(MR):',varx,'mu(HRR):',muy.WT,'var(HRR):',vary,'Covar(M,HRR):',co,'\n')

  Lin <- (2*cov(x,y))/(var(x)+var(y)+(mean(x)-mean(y))^2)
  LinWeight <- (2*co)/(varx+vary+(mux.WT-muy.WT)^2)

  ############ Interval de confiança (article biometrics Lin original p.258-9) ######
  u <- (mux.WT-muy.WT)/sqrt(varx*vary)
  rho <- co/sqrt(varx*vary)
  rhoc <- LinWeight
  n <- length(x)
  #A <- ((1-rho^2)*rhoc^2)/((1-rhoc^2)*rho^2)
  #B <- (4*rhoc^3*(1-rhoc^2)*u^2)/((1-rhoc^2)^2*rho)
  #C <- (2*(rhoc*u)^4)/((1-rhoc^2)^2*rho^2)

  A <- ((1-rho^2)*(1-rhoc^2)*rhoc^2)/(rho^2)
  B <- (4*rhoc^3*(1-rhoc)*u^2)/rho
  C <- (2*(rhoc*u)^4)/(rho^2)

  VarLinWeight <- (A+B-C)/(n-2)
  z <- qnorm(0.975)
  LI <- LinWeight-z*sqrt(VarLinWeight)
  LS <- LinWeight+z*sqrt(VarLinWeight)
  cat("Intervalo de confianza: ",round(LI,2)," to ",round(LS,2)," \n")

  return(c(Lin,LinWeight))
}



##############################################################################
# Printa la interpretació del coeficient de Lin
##############################################################################

LinInterpretation <- function(){
  cat("Valoració de la concordança:\n")
  cat("0.0-0.1: Independence\n")
  cat("0.1-0.3: Bad\n")
  cat("0.3-0.5: Poor\n")
  cat("0.7-0.9: Good\n")
  cat("0.9–1.0: Almost perfect\n\n")
  cat("Referencia principal: Mail de Josep LLuís carrasco \n")
  cat("Referencia: Robust estimators of the concordance correlation coefficient.\n")
  cat("Referencia:       http://www.niwa.co.nz/our-services/online-services/statistical-calculators/lins-
concordance.\n")

cat("http://www.fi.adeptnordic.com/products/dataanal/genstat/htmlhelp/samplesize/SLinsConcordance.htm\n")
}
```

```
##############################################################################
#
# Fa gràfics de BA de concordança entre jo, Lourdes i la real i calcula el coeficient de Lin
#
##############################################################################


MedianConcordance <- function(medianas){
  ### Plot
  par(mfrow=c(1,2),cex=1.2,mar=c(4,4,1,1))
  plot(medianas$Real,medianas$Jordi,xlab="Mediana Real",ylab="Mediana Estimada",las=1)
  points(medianas$Real,medianas$Lourdes,col=2)
  legend("topleft",c("Jordi","Lourdes"),col=1:2,pch=1)
  abline(0,1,lty=2)


  ### Bland-Altman Normal
  xJ <- (medianas$Real+medianas$Jordi)/2
  yJ <- (medianas$Real-medianas$Jordi)
  xL <- (medianas$Real+medianas$Lourdes)/2
  yL <- (medianas$Real-medianas$Lourdes)
  xmin <- min(c(xJ,xL))
  xmax <- max(c(xJ,xL))
  ymax <- max(abs(c(yJ,yL)))
  plot(xJ,yJ,xlab="Average",ylab="Difference",xlim=c(xmin,xmax),ylim=c(-ymax,ymax))
  points(xL,yL,col=2)
  abline(h=0,lty=2)
  legend("topleft",c("Jordi","Lourdes"),col=1:2,pch=1)

  ### Plot
  win.graph()
  par(mfrow=c(1,2),cex=1.2,mar=c(4,4,1,1))
  plot(medianas$Real,medianas$Jordi,xlab="Mediana Real",ylab="Mediana Estimada",las=1)
  points(medianas$Real,medianas$Lourdes,col=2)
  legend("topleft",c("Jordi","Lourdes"),col=1:2,pch=1)
  abline(0,1,lty=2)

  ### Bland-Altman logaritmic
  xJ <- sqrt(medianas$Real*medianas$Jordi)
  yJ <- (medianas$Real/medianas$Jordi)
  xL <- sqrt(medianas$Real*medianas$Lourdes)
  yL <- (medianas$Real/medianas$Lourdes)
  xmin <- min(c(xJ,xL))
  xmax <- max(c(xJ,xL))
  ymax <- max(abs(c(yJ,yL)))
  plot(xJ,yJ,xlab="Geometric Average",ylab="Division",
       xlim=c(xmin,xmax), ylim=c(1/ymax,ymax),log=c("x","y"))
  points(xL,yL,col=2)
  abline(h=1,lty=2)
  legend("topright",c("Jordi","Lourdes"),col=1:2,pch=1)

  ### icc
  M <- medianas[,3:5]
  concRJ <- epi.ccc(medianas$Real,medianas$Jordi)$rho.c
  concRL <- epi.ccc(medianas$Real,medianas$Lourdes)$rho.c
  concLJ <- epi.ccc(medianas$Lourdes,medianas$Jordi)$rho.c
  cat("Concordancia entre la mediana Real y la mediana evaluada por Jordi:\n")
  print(concRJ)
  cat("Concordancia entre la mediana Real y la mediana evaluada por Lourdes:\n")
  print(concRL)
  cat("Concordancia entre la mediana evaluada por Lourdes y la evaluada por Jordi:\n")
  print(concLJ)

}
```

```
#############################################################################
#
# Converteix les dades en una llista d'articles amb 2 mesures de OS i PFS en
# aquest ordre
#
#############################################################################

DataForICC <- function(dades2){

  ### Seleccionar los estudios con al menos una medida de PFS y una de OS
  Aux <- split(dades2,dades2$CodeArt)         # Lista con cada artículo un ítem
  nArt <- length(Aux)                         # Número de artículos
  elim <- c()                                 #
  for (i in 1:nArt){
    if(length(unique(Aux[[i]]$Type))!=2) elim <- c(elim,i)
  }
  Aux2 <- Aux[-elim]

  ### Seleccionar el primer PFS y el primer OS de cada estudio
  nArt2 <- length(Aux2)
  for (i in 1:nArt2){
    selOS <- min(which(Aux2[[i]]$Type=="OS"))
    selPFS <- min(which(Aux2[[i]]$Type=="PFS"))
    Aux2[[i]] <- Aux2[[i]][c(selOS,selPFS),]
  }
  return(Aux2)
}


#############################################################################
#
# Converteix lla llista anterior en una matriu de dues columnes amb les
# diferències per OS i PFS
#
#############################################################################

DataForICC2 <- function (dades3){
  Npapers <- length(dades3)
  DiscrepanciesMatrix <- matrix(NA,ncol=2,nrow=0)
  for (i in 1:Npapers){
    Dis <- with(dades3[[i]],log(MedRat)-log(HRR))
    DiscrepanciesMatrix <- rbind(DiscrepanciesMatrix,Dis)
  }
  rownames(DiscrepanciesMatrix) <- names(Aux2)
  colnames(DiscrepanciesMatrix) <- c("OS","PFS")
  MR_HRRMatrix <- DiscrepanciesMatrix
}



#############################################################################
#
# Converteix lla llista anterior en una matriu de dues columnes amb les
# diferències per OS i PFS
#
#############################################################################

ICCEfectesAleatoris <- function(MR_HRRMatrix){
  logMR_logHRR <- c(as.numeric(MR_HRRMatrix[,1]),as.numeric(MR_HRRMatrix[,2]))
  Paper <- as.factor(c(1:Npapers,1:Npapers))
  mod.lme <- lme(logMR_logHRR ~ 1,random = ~ 1|Paper)
  StdDevR <- mod.lme$sigma
  StdDevI <- sqrt(mod.lme$apVar[1,1])
  ICC <- StdDevI^2/(StdDevI^2+StdDevR^2)
  return(ICC)
}
```

Script 3. Funcions auxiliars usades en l'script principal per estimar la variabilitat del log(MR/HRR^{-1})

```
################################################################################
#                                                                              #
# Estimació de la Var(log(MR/HRR)) en funció de la Var(log(1/HRR))             #
#                                                                              #
################################################################################

################################################################################
# Mètode 2
# 1. Dividir els punts en decils segons X=1/Var(Log(HRR))
# 2. Calcular la Y=Var(Log(MR/HRR)) dins de cada decil de forma empírica
# 3. Fer regressió Y vs X
################################################################################

AjusteEmpirico <- function(dades2,EE){
  # 1. Dividir en deciles (Se debe haber ejecutado antes el script principal)
  Xaux <- (EE)^2
  brk <- quantile(Xaux, probs = seq(0, 1, 0.1))     # Tallo els EE en decils
  X <- (brk[1:10]+brk[2:11])/2                      # Agafo els representants de classe
  brk[1] <- brk[1]-0.0004                           # Resto un epsilon al primer

  DecilFactor <- cut(Xaux,brk)

  # 2. Calcular Var(Log(MR/HRR)) para cada decil
  Yaux <- with(dades2,log(MedRat/HRR))
  Y <- tapply(Yaux,DecilFactor,var)

  # 3. Regressió
  mod.lm <- lm(Y~X)
  par(mfrow=c(1,1),mar=c(5,5,5,1),las=1)
  plot(X,Y,xlab=expression(V~bgroup("(",log(HRR),")")),
       ylab=expression(V~bgroup("(",log~bgroup("(",frac(MR,HRR),")"),")")),
      cex.lab=0.65,xlim=c(0,0.14),ylim=c(0,0.14))
  coeff <- coef(mod.lm)
  abline(coeff[1],coeff[2])
}
```

```
#############################################################################
# Mètode 3
# 1. Simular temps de vida exponencials per dos tractaments
# 2. Confrontar la variabilitat del logaritme de MR/HRR i del logaritme de HRR amb
#    diferents lambdas. La variabilitat del logaritme de quocients és la suma de variancies
#    dels seus logaritmes
# 3. Fer regressió
# n: Grandària mostral;
# nsim: Número de simulacions;
# replic:repliques per estimar la variància del logaritme del rati de medianes
#############################################################################

AjusteSimula <- function(n,nsim,replic){
  set.seed(12345)
  V.LOG.HRRinv <- c()              ; log.hrrinv <- c()
  V.LOG.MR.HRRinv <- c()           ; log.mr.hrrinv <- c()
  V.LOG.MR.HRRinv.MINUS.2COV <- c() ; log.mr <- c()

  for (i in 1:nsim){
    lambda1 <- runif(1,1/4,1) ; lambda2 <- runif(1,1/4,1)       # Paràmetres de l'exponencial

    for (j in 1:replic){
      A <- rexp(n,lambda1) ;    B <- rexp(n,lambda2)            # Temps de vida
      Resposta <- c(A,B)
      Treatment <- as.factor(c(rep(0,n),rep(1,n)))
      status <- rep(1,2*n)
      simSurv <- Surv(Resposta,status)
      simSurvfit <- survfit(simSurv~Treatment)
      cox.mod <- coxph(simSurv~Treatment)
      Tab <- summary(simSurvfit)$table
      MR <- Tab["Treatment=1","median"]/Tab["Treatment=0","median"]

      log.hrrinv[j] <- (-cox.mod[[1]])                    # Log(HRR)
      log.mr[j] <- log(MR)                                # Log(MR)
      log.mr.hrrinv[j] <- log.mr[j] - log.hrrinv[j]       # Log(MR)-Log(HRR)
    }

    # Variància del logaritme del HRR
    V.LOG.HRRinv[i] <- var(log.hrrinv)

    # V(log(HRR))- 2*Cov(log(HRR),log(MR))
    V.LOG.MR.HRRinv.MINUS.2COV[i] <- var(log.hrrinv) - 2*cov(log.mr,log.hrrinv)
    V.LOG.MR.HRRinv[i] <- var(log.mr.hrrinv)
  }

  par(mfrow=c(1,2),las=1,mar=c(5,5,5,1))

  ### Y=Var(log(MR/HRR)) vs X=Var(log(HRR))
  plot(V.LOG.HRRinv,V.LOG.MR.HRRinv,xlim=c(0,0.1),ylim=c(0,0.1),
       xlab=expression(V~bgroup("(",log(HRR),")")),
      ylab=expression(V~bgroup("(",log~bgroup("(",frac(MR,HRR),")"),")")),cex.lab=0.65)
  mod.lm <- lm(V.LOG.MR.HRRinv~V.LOG.HRRinv)
  coeff <- coef(mod.lm)
  abline(coeff[1],coeff[2])
  abline(0,1,col=2,lty=2)


  ### Y =Var(log(MR/HRR)) vs X2 = Var(log(HRR))-2*Cov(log(MR),log(HRR))
  plot(V.LOG.MR.HRRinv.MINUS.2COV,V.LOG.MR.HRRinv,xlim=c(-0.1,0),ylim=c(0,0.1),
       xlab=expression(V~bgroup("(",log(HRR),")")-2*Cov~bgroup("(",list(log~bgroup("(",MR,")"),
              log~bgroup("(",HRR,")")),")")),
       ylab=expression(V~bgroup("(",log~bgroup("(",frac(MR,HRR),")"),")")),cex.lab=0.65)

  mod.lm <- lm(V.LOG.MR.HRRinv~V.LOG.MR.HRRinv.MINUS.2COV)
  coeff <- coef(mod.lm)
  abline(coeff[1],coeff[2],lty=2)
  abline(0,1,col=2)

  return(cbind(X2,Y,log(MR)))
}
```

```
#############################################################################
# Mètode 4.1
# 1. Simular temps de vida exponencials per dos tractaments
# 2. Calcular la variança del logaritme del HRR, del MR y de MR/HRR, així
# com la seva correlació amb el logaritme del HRR i amb la grandaria mostral.
# 3. Fer regressió
# n: Grandaria mostral;    nsim: Número de simulacions;
# replic:rèpliques per estimar la variància del logaritme del rati de medianes
#############################################################################

AjusteSimula2 <- function(n,nsim,replic){


  ### 1. Avaluar l'efecte de l'efecte en les variàncies

  set.seed(12345)
  varLogMR <- c() ;  varLogHRR <- c()
  varLogMRHRR <- c();  covarLogMRHRR <- c()
  corLogMRHRR <- c();  corLogMRHRRinv <- c()
  logMR <- c();  logHRR <- c();  logMRHRR <- c();  HRR <- c()

  for (i in 1:nsim){
    lambda1 <- runif(1,1/3,1)         # Taxes entre 1/3 y 1
    lambda2 <- runif(1,1/3,1)         # Taxes entre 1/3 y 1
    for (j in 1:replic){
      A <- rexp(n,lambda1)
      B <- rexp(n,lambda2)
      Resposta <- c(A,B)
      Treatment <- c(rep(0,n),rep(1,n))
      status <- rep(1,2*n)
       simSurv <- Surv(Resposta,status)
       simSurvfit <- survfit(simSurv~Treatment)
       SS <- summary(simSurvfit)
       cox.mod <- coxph(simSurv~Treatment)
       Tab <- SS$table
       M1 <- Tab["Treatment=1","median"]          # Mediana 1
       M0 <- Tab["Treatment=0","median"]
       logMR[j] <- log(M1/M0)
       logHRR[j] <- cox.mod[[1]]
       logMRHRR[j] <- logMR[j]-logHRR[j]
    }

    varLogMR[i] <- var(logMR)
    varLogHRR[i] <- var(logHRR)
    varLogMRHRR[i] <- var(logMRHRR)
    corLogMRHRR[i] <- cor(logMR,logHRR)
    corLogMRHRRinv[i] <- cor(logMR,1/logHRR)
    covarLogMRHRR[i] <- cov(logMR,logHRR)
    HRR[i] <- lambda1/lambda2
  }

  par(mfrow=c(2,2),las=1)
  plot(log(HRR),varLogMR,pch=19,xlab="log(HRR)",ylab="var(log(MR))")
  abline(v=0,lty=2)
  plot(log(HRR),varLogHRR,pch=19,xlab="log(HRR)",ylab="var(log(HRR))")
  abline(v=0,lty=2)
  plot(log(HRR),varLogMRHRR,pch=19,xlab="log(HRR)",ylab="var(log(MR/HRR))")
  abline(v=0,lty=2)
  plot(log(HRR),corLogMRHRR,pch=19,xlab="log(HRR)",ylab="cor(log(MR),log(1/HRR))")
  abline(v=0,lty=2)


  ### Descriptiva
  print(summary(varLogMR))
  print(summary(varLogHRR))
  print(summary(varLogMRHRR))
  print(summary(corLogMRHRR))
}
```

```
##############################################################################
# Mètode 4.2
# 1. Simular temps de vida exponencials per dos tractaments
# 2. Calcular la variança del logaritme del HRR, del MR y de MR/HRR, així
# com la seva correlació amb el logaritme del HRR i amb la grandaria mostral.
# 3. Fer regressió
# ene: Grandària mostral;replic:repliques para estimar la var. del logaritme del rati de medianes
##############################################################################
AjusteSimula3 <- function(ene,replic){
  varLogMR <- c() ;  varLogHRR <- c()
  varLogMRHRR <- c();  covarLogMRHRR <- c()
  corLogMRHRR <- c();  corLogMRHRRinv <- c()
  logMR <- c();  logHRR <- c();  logMRHRR <- c();  HRR <- c()

  ### 2. Avaluar l'efecte de la grandaria en les variàncies
  nsim <- length(ene)

  set.seed(12345)
  varLogMR <- c()
  varLogHRR <- c()
  varLogMRHRR <- c()
  covarLogMRHRR <- c()
  corLogMRHRR <- c()
  HRR <- c()

  for (i in 1:nsim){
    lambda1 <- 0.8
    lambda2 <- 1
    n <- ene[i]
    for (j in 1:replic){
      A <- rexp(n,lambda1)
      B <- rexp(n,lambda2)
      Resposta <- c(A,B)
      Treatment <- c(rep(0,n),rep(1,n))
      status <- rep(1,2*n)

       simSurv <- Surv(Resposta,status)
       simSurvfit <- survfit(simSurv~Treatment)
       cox.mod <- coxph(simSurv~Treatment)
       Tab <- summary(simSurvfit)$table
       M1 <- Tab["Treatment=1","median"]
       M0 <- Tab["Treatment=0","median"]

       logMR[j] <- log(M1/M0)
       logHRR[j] <- cox.mod[[1]]
       logMRHRR[j] <- logMR[j]-logHRR[j]
    }

    varLogMR[i] <- var(logMR)
    varLogHRR[i] <- var(logHRR)
    varLogMRHRR[i] <- var(logMRHRR)
    covarLogMRHRR[i] <- cov(logMR,logHRR)
    corLogMRHRR[i] <- cor(logMR,logHRR)
    HRR[i] <- lambda1/lambda2
  }

  par(mfrow=c(2,2),las=1)
  plot(ene,1/varLogMR,pch=19,xlab="n",ylab="1/var(log(MR))")
  abline(v=0,lty=2)
  plot(ene,1/varLogHRR,pch=19,xlab="n",ylab="1/var(log(HRR))")
  abline(v=0,lty=2)
  plot(ene,1/varLogMRHRR,pch=19,xlab="n",ylab="1/var(log(MR/HRR))")
  abline(v=0,lty=2)
  plot(ene,corLogMRHRR,pch=19,xlab="n",ylab="cor(log(MR),log(HRR))")
  abline(v=0,lty=2)

  ### Descriptiva
  print(summary(varLogMR))
  print(summary(varLogHRR))
  print(summary(varLogMRHRR))
  print(summary(corLogMRHRR))
}
```

Script 4. Script per a la realització de la Figure 1.

```
##############################################################################
# Script que demostra que la distribució Gompertz no té HRR^(-1)=MR malgrat tenir
# riscos proporcionals
##############################################################################
rm(list=ls())

##### Carregar llibreries
library(eha)
library(survival)

##### Paràmetres
rho11 <- c(0.5,1,2)
rho10 <- seq(0.01,2,0.01)
rho2 <- c(0.5,1,2,10)

n1 <- length(rho10)
n2 <- length(rho11)
nrho2 <- length(rho2)

##### Objectes per emmagatzemar resultats
MR <- c() ; HRR <- c() ; AR <- c()

MR1 <- matrix(0, nrow=n1, ncol=nrho2)                          # Mediana 1 Real
MT1 <- matrix(0, nrow=n1, ncol=nrho2)                          # Mediana 1 teórica
colnames(MR1) <- as.character(rho2) ; colnames(MT1) <- as.character(rho2)
rownames(MR1) <- as.character(rho10) ; rownames(MT1) <- as.character(rho10)
MR2 <- matrix(0, nrow=n2, ncol=nrho2)                          # Mediana 2 Real
MT2 <- matrix(0, nrow=n2, ncol=nrho2)                          # Mediana 2 teórica
colnames(MR2) <- as.character(rho2) ; colnames(MT2) <- as.character(rho2)
rownames(MR2) <- as.character(rho11) ; rownames(MT2) <- as.character(rho11)

##### Inicialitzar gràfic
layout(matrix(c(1,2,3,4,5,5), 3, 2, byrow = TRUE),heights = c(1,1,0.2))
par(las=1,lwd=2,mar=c(5,4,5,1),xpd=F,cex.lab=1.2,cex.axis=1.2)

for (k in nrho2:1){

  scale1 <- rho2[k]                 # Paràmetres d'escala (idèntics)
  scale2 <- rho2[k]

  for (j in 1:n2){
       shape2 <- rho11[j]           # Paràmetre de forma (tractats)
       for (i in 1:n1){

         shape1 <- rho10[i]    # Paràmetre de forma (controls)

         ### Generació dels temps (Atenció: parametrització Gompertz en R)
         time1 <- rgompertz(10000,shape1,scale1)
         time2 <- rgompertz(10000,shape2,scale2)

         ##################### Medianes #####################################
         med1 <- median(time1)
         med2 <- median(time2)

         ### Emmagatzemar medianes reals
         MR1[i,k] <- med1
         MR2[j,k] <- med2

         ### Càlcul medianes teòriques
         A <- exp(-shape1*scale1*exp(-1))
         B <- 1/(2*exp(1))
         C <- (-1/(scale1*shape1)*log(A-B))
         MT1[i,k] <- (1+log(C))*scale1

         A <- exp(-shape2*scale2*exp(-1))
         C <- (-1/(scale2*shape2)*log(A-B))
         MT2[j,k] <- (1+log(C))*scale2

         ### Mitjanes
         mean1 <- mean(time1)
         mean2 <- mean(time2)

         HRR[i] <- shape2/shape1            # Hazard Ratio
         MR[i] <- med2/med1                 # Median Ratio
         AR[i] <- mean2/mean1               # Rati de mitjanes
       }
```

```
        ###################### Gràfic ###################################
        if(j==1){
                plot(lowess(1/HRR,MR),xlim=c(0.1,1),ylim=c(0.1,1),asp=I,type="l",col=j,
                log="xy",xlab=expression(HRR^-1),ylab="MR or ER")

                ### En el títol s'ha d'invertir rho2 perqué la parametrització és diferent
                title(main=bquote(bold(paste(rho[2],"=",.(1/rho2[k])))),cex.main=1.5)
                lines(lowess(1/HRR,AR),lty=2,col=j)
                abline(0,1,lty=3,col="grey80")
        }
        if(j!=1){
                lines(lowess(1/HRR,MR),col=j)
                lines(lowess(1/HRR,AR),lty=2,col=j)
        }
  }
}
###################### Llegenda ###################################
par(mar=c(0,0,0,0))
plot(NULL,xaxt="n",yaxt="n",xlim=c(0,1),ylim=c(0,1),xlab="",ylab="n",bty="n")
legend(0.5,0.9,c("ER","MR",expression(bold(rho[11]==0.5)),
                expression(bold(rho[11]==1)),
                expression(bold(rho[11]==2))),
                horiz=T, xjust=0.5, col=c(1,1,1,2,3), lwd=c(2,2,rep(NA,3)),
                lty=c(2,1,rep(NA,3)), pch=c(NA,NA,rep(15,3)), cex=1.5)
segments(0.42,0.4,0.42,0.9,lwd=2)

################ Mediana teòrica versus real ##########################
par(mfrow=c(2,2),mar=rep(5,4))
for (i in 4:1){
  minxy <- min(c(MR1[,i],MT1[,i]),na.rm=T)
  maxxy <- max(c(MR1[,i],MT1[,i]),na.rm=T)
  plot(MR1[,i],MT1[,i],type="l",xlim=c(minxy,maxxy),ylim=c(minxy,maxxy),xlab="Real median",
       ylab="Theoretical Median", main=bquote(paste(bold(rho[2]==""),.(1/rho2[i]))))
  abline(0,1,lty=2,lwd=1)
}
```

Script 5. Script per a la realització de la Figure 2.

```
rm(list=ls())

##### Exemple
x0 <- c(0,1,2,3,4); y0 <- c(1,0.5,0.1,0.05,0)
x1 <- c(0,1,2,3,4); y1 <- c(1,0.615,0.1,0.08,0.04)

##### Paràmetres
n <- length(x0)
par(mfrow=c(1,1))
sp0 <- spline(x0,y0,method="natural")
sp1 <- spline(x1,y1,method="natural")
plot(sp0$x,sp0$y,type='l',xlim=c(0,2.2),ylim=c(0,1),xlab="Time
t",ylab="S(t)",col=4,lwd=2,yaxp=c(0,1,10), main="")
lines(sp1$x,sp1$y,col="red",lwd=2)
abline(h=0.5,lty=2)
abline(v=1,lty=2)
segments(1,0.5,1,0.61,lwd=3,col=3)
text(0.38,0.77,expression(S[0](t)),font=2,cex=1.2)
text(0.75,0.77,expression(S[1](t)),font=2,cex=1.2)
text(1.25,0.58,expression(RD(Med[0])),font=2,cex=1.2)
arrows(1.12,0.58,1,0.555,length = 0.1)

HRR <- 0.7
##### Punts Grup Control
x0 <- c(0,1,2,3,4)
y0 <- c(1,0.5,0.1,0.05,0)
##### Punts Grup Tractat
x1 <- c(x0,1.27)
y1 <- c(y0^HRR,0.5)

# Paràmetros
n <- length(x0)

par(mfrow=c(1,2),las=1)
##### 1r gràfic
##### Corva grup control
sp0 <- spline(x0,y0,method="natural")
plot(sp0$x,sp0$y,type='l',xlim=c(0,2.2),ylim=c(0,1),xlab="Time
t",ylab="S(t)",col=4,lwd=2,yaxp=c(0,1,10), main="",xaxt="n",yaxt="n")

##### Corva grup Tractat
sp1 <- spline(x1,y1,method="natural")
lines(sp1$x,sp1$y,col="grey90",lwd=1)

##### Eixos i ablines
point <- 0.5^(1/0.7)
axis(1,at=c(1,1.27),labels=c(expression(Med[0]),expression(Med[1])))
axis(2,at=c(0.5,point),labels=c(0.5,expression(bgroup("(",frac(1,2),")")^frac(1,HRR))))
# segments(-10,0.5,1,0.5,lty=2)
segments(-10,0.5,1.27,0.5,lty=2)
segments(-10,point,1.27,point,lty=2)
segments(1,-10,1,0.5,lty=2)
# segments(1.27,-10,1.27,point,lty=2)
segments(1.27,-10,1.27,0.5,lty=2)
text(0.32,0.77,expression(S[0](t)),font=2,cex=1.2)
text(0.82,0.77,expression(S[1](t)),font=2,cex=1.2,col="grey90")

##### 2on gràfic
plot(sp0$x,sp0$y,type='l',xlim=c(0,2.2),ylim=c(0,1),xlab="Time t",ylab="S(t)",col="grey90",
       lwd=1,yaxp=c(0,1,10), main="",xaxt="n",yaxt="n")
lines(sp1$x,sp1$y,col=4,lwd=2)
point <- 0.5^0.7
axis(1,at=c(1,1.27),labels=c(expression(Med[0]),expression(Med[1])))
axis(2,at=c(0.5,point),labels=c(0.5,expression(bgroup("(",frac(1,2),")")^HRR)))

text(0.32,0.77,expression(S[0](t)),font=2,cex=1.2,col="grey90")
text(0.82,0.77,expression(S[1](t)),font=2,cex=1.2,col=1)

segments(-10,0.5,1.27,0.5,lty=2)
segments(-10,point,1,point,lty=2)
segments(1,-10,1,point,lty=2)
segments(1.27,-10,1.27,0.5,lty=2)
```

Script 6. Script per a la realització de la Figure 4, Figure 5 i Figure 6

```
############ RR, OR, and DR
rm(list=ls())
library(survival)
source('E:\\TFM\\Simulaciones\\CensuraFunctions.r')

######################### Paràmetres ##############################################
n <- 50                     # Grandaria mostral
nsim <- 100                 # Nombre de simulacions
prop0 <- 0.1                # Proporció censures controls
prop1 <- seq(0,0.4,0.02)    # Proporció censures tractats
nprop1 <- length(prop1)     # Número de proporcions
lambda0 <- 1                # Paràmetre exponencial tractats
lambda1 <- 0.8              # Paràmetre exponencial controls

###### Valors teòrics en la mediana de referencia teòrica
Mediana0 <- log(2)/lambda0  # Mediana teòrica

S0 <- 0.5                   # Supervivència controls
S1 <- 0.5^lambda1           # Supervivència tractats

RR_Teo <- (1-S1)/(1-S0)
OR_Teo <- ((1-S1)/S1)/((1-S0)/S0)
RD_Teo <- S1 - S0

###### Objectes per emmagatzemar resultats
### Matriu per emmagatzemar OR, RR i RD
M <- matrix(NA, nrow=9, ncol=nprop1)
rownames(M) <- c("RR_Real","OR_Real","RD_Real","RR_Cens","OR_Cens","RD_Cens",
                 "RR_HRR","OR_HRR","RD_HRR")
colnames(M) <- prop1

### Matriu per emmagatzemar supervivències
M2 <- matrix(NA, nrow=6, ncol=nprop1)
rownames(M2) <- c("SKM","LI_SKM","LS_SKM","SHRR","LI_SHRR","LS_SHRR")
colnames(M2) <- prop1

RR_Real <- c() ; OR_Real <- c() ; RD_Real <- c()
RR_Cens <- c() ; OR_Cens <- c() ; RD_Cens <- c()
RR_HRR <- c() ; OR_HRR <- c() ; RD_HRR <- c()

SKM <- c() ; LISKM <- c() ;LSSKM <- c()
SHRR <- c() ; LISHRR <- c() ; LSSHRR <- c()

###### Simulació
for (i in 1:nprop1){
       for (j in 1:nsim){
         time1 <- rexp(n,lambda1)
         time0 <- rexp(n,lambda0)

         ### Real
         Sreal0 <- sum(time0>Mediana0)/n
         Sreal1 <- sum(time1>Mediana0)/n
         RR_Real[j] <- (1-Sreal1)/(1-Sreal0)
         OR_Real[j] <- ((1-Sreal1)/Sreal1)/((1-Sreal0)/Sreal0)
         RD_Real[j] <- Sreal1 - Sreal0

         ### Amb dades censurades
         AddCensure1 <- AddCensure(time1,time0,lambda1,lambda0,t.recluta=0,prop.cens=prop1[i],
                                   pFollow=0,tFollow=NULL,graph=FALSE,distribution="Exponential",
                                   sh=NULL,sca1=NULL,sca2=NULL)
         AddCensure0 <- AddCensure(time1,time0,lambda1,lambda0,t.recluta=0,prop.cens=prop0,
                                   pFollow=0,tFollow=NULL,graph=FALSE,distribution="Exponential",
                                   sh=NULL,sca1=NULL,sca2=NULL)

         timeCens1 <- AddCensure1[1:n,1]
         status1 <- AddCensure1[1:n,2]
         timeCens0 <- AddCensure0[(n+1):(2*n),1]
         status0 <- AddCensure0[(n+1):(2*n),2]

         n0 <- sum(status0)
         n1 <- sum(status1)
         Scens0 <- sum(timeCens0>Mediana0 & status0==1)/n0
         Scens1 <- sum(timeCens1>Mediana0 & status1==1)/n1
         RR_Cens[j] <- (1-Scens1)/(1-Scens0)
         OR_Cens[j] <- ((1-Scens1)/Scens1)/((1-Scens0)/Scens0)
         RD_Cens[j] <- Scens1 - Scens0
```

```
        ### Amb dades censurades a través del HRR
        time <- c(timeCens0,timeCens1)
        status <- c(status0,status1)
        times.Surv <- Surv(time,status)
        treatment <- c(rep(0,n),rep(1,n))
        mod.cox2 <- coxph(times.Surv~treatment)
        HRR <- exp(mod.cox2$coef)

        SHRR0 <- 0.5
        SHRR1 <- 0.5^HRR

        RR_HRR[j] <- (1-SHRR1 )/(1-SHRR0)
        OR_HRR[j] <- ((1-SHRR1 )/SHRR1)/((1-SHRR0)/SHRR0)
        RD_HRR[j] <- SHRR1 - SHRR0

        ### Supervivència KM + IC en Med0
        times.survfit <- survfit(times.Surv~treatment)
        timestreat <- times.survfit$time[(n+1):(2*n)]
        timestreatSort <- sort(timestreat)
        sel <- min(which(timestreat>Mediana0))

        Streat <- times.survfit$surv[(n+1):(2*n)]
        LIStreat <- times.survfit$lower[(n+1):(2*n)]
        LSStreat <- times.survfit$upper[(n+1):(2*n)]
        sel2 <- min(which(Streat<0.5))
        cat("sel1: ",sel,"sel2:",sel2,"\n")
        SKM[j] <- Streat[sel]
        LISKM[j] <- LIStreat[sel]
        LSSKM[j] <- LSStreat[sel]

        ### Supervivencia HRR
        LIHRR <- summary(mod.cox2)$conf.int[3]
        LSHRR <- summary(mod.cox2)$conf.int[4]
        SHRR[j] <- 0.5^HRR
        LISHRR[j] <- 0.5^LSHRR
        LSSHRR[j] <- 0.5^LIHRR

      }
      M[1,i] <- exp(mean(log(RR_Real))) ;
      M[2,i] <- exp(mean(log(OR_Real))) ;
      M[3,i] <- mean(RD_Real)
      M[4,i] <- exp(mean(log(RR_Cens))) ;
      M[5,i] <- exp(mean(log(OR_Cens))) ;
      M[6,i] <- mean(RD_Cens)
      M[7,i] <- exp(mean(log(RR_HRR)))  ;
      M[8,i] <- exp(mean(log(OR_HRR)))  ;
      M[9,i] <- mean(RD_HRR)

      M2[1,i] <- mean(SKM)  ;      M2[2,i] <- mean(LISKM)   ;   M2[3,i] <- mean(LSSKM)
      M2[4,i] <- mean(SHRR) ;      M2[5,i] <- mean(LISHRR)   ;  M2[6,i] <- mean(LSSHRR)
}
```

```
############################ Gràfics ##########################################

##### RR
par(lwd=2,las=1,mfrow=c(1,1))
plot(prop1,M[1,],type="l",col=2,main="RR estimation",ylim=c(0.5,2),
       xlab="Censure proportion in treated group",ylab="RR",log="y")
lines(prop1,M[4,],col=3)
lines(prop1,M[7,],col=4)
abline(h=RR_Teo)
abline(v=0.1,lty=2,lwd=1)
legendLabel <- c("Theoretical or modeled RR","RR calculated with full data",
                 "RR directly calculated with censored data",
                 "RR calculated through HRR with censored data")
legend("topleft",legendLabel,col=1:4,lwd=2,bg="white")


##### OR
par(lwd=2,las=1)
plot(prop1,M[2,],type="l",col=2,main="OR estimation",ylim=c(0.5,2),
       xlab="Censure proportion in treated group",ylab="OR",log="y")
lines(prop1,M[5,],col=3)
lines(prop1,M[8,],col=4)
abline(h=OR_Teo)
abline(v=0.1,lty=2,lwd=1)
legendLabel <- c("Theoretical or modeled OR","OR calculated with full data",
               "OR directly calculated with censored data",
               "OR calculated through HRR with censored data")
legend("topleft",legendLabel,col=1:4,lwd=2,bg="white")


##### DR
par(lwd=2,las=1)
plot(prop1,M[3,],type="l",col=2,main="RD estimation",ylim=c(0.00,0.2),
       xlab="Censure proportion in treated group",ylab="RD")
abline(h=RD_Teo)
lines(prop1,M[6,],col=3)
lines(prop1,M[9,],col=4)
lines(prop1,M[3,],col=2)
abline(v=0.1,lty=2,lwd=1)
legendLabel <- c("Theoretical or modeled DR","DR calculated with full data",
               "DR directly calculated with censored data",
               "DR calculated through HRR with censored data")
legend("topright",legendLabel,col=1:4,lwd=2,bg="white")


#### Supervivència KM versus Supervivència HRR
par(las=1,mfrow=c(1,1),lwd=2)
plot(prop1,M2[1,],type="l",col=2,main="KM Survival vs. HRR Survival",ylim=c(0,1),
       xlab="Censure proportion in treated group",ylab="S(t)")
lines(prop1,M2[2,],col=2,lty=2)
lines(prop1,M2[3,],col=2,lty=2)
lines(prop1,M2[4,],col=3,lty=1)
lines(prop1,M2[5,],col=3,lty=2)
lines(prop1,M2[6,],col=3,lty=2)
```

Script 7. Script per a la realització de la Figure 20.

```
### ¿HRR =~AUC?

################################################################################
par(lwd=1)
BlandAltman <- function(x,y,tit="Bland-Altman",size,co,ID=NULL,limy=NULL){

        Bmean <- (x+y)/2
        Bdif <- y-x
        ymax <- max(abs(Bdif),na.rm=T)

        plot(Bmean ,Bdif ,ylim=c(-0.1,0.1),
                    xlab=expression((theta[1]+hat(theta)[2])/2),
                    ylab=expression(hat(theta)[2]-theta[1]),
                    main=tit,pch=1,cex=size,col=co)
        abline(h=0,lty=2)
        mtext(expression(paste("Greater ",hat(theta)[2])),2,line= 3.5,at=0.1,adj=1,cex=0.9)
        mtext(expression(paste("Greater ",theta[1])),2,line= 3.5,at=-0.1,adj=1,cex=0.9)
        if(!is.null(ID)) text(Bmean,Bdif,ID,pos=4,cex=0.6)  # identificador
        abline(v=0,lty=3,col="grey80")
}


################################################################################

library(survival)

n <- 20
treatment <- c(rep(0,n),rep(1,n))
status <- rep(1,2*n)

################################################################################
# Opció 1
################################################################################
A1 <- seq(10,48,2)
B1 <- c(rep(9,10),seq(11,29,2))
times1 <- c(A1,B1)
times.Surv1 <- Surv(times1,status)
times.survfit1 <- survfit(times.Surv1~treatment)
mod.cox1 <- coxph(times.Surv1~treatment)
summary(mod.cox1)


################################################################################
# Opció 2
################################################################################
A2 <- seq(10,48,2)
B2 <- c(rep(1,10),seq(11,29,2))
times2 <- c(A2,B2)
times.Surv2 <- Surv(times2,status)
times.survfit2 <- survfit(times.Surv2~treatment)
mod.cox2 <- coxph(times.Surv2~treatment)
summary(mod.cox2)

par(mfrow=c(1,2),las=1,cex.lab=1.2)
plot(times.survfit1,lwd=3,col=2:4,main="Comparison I",xlab="Time",ylab="S(t)")
plot(times.survfit2,lwd=3,col=2:4,main="Comparison II",xlab="Time",ylab="S(t)")


################################################################################
# Comparació entre controls
################################################################################
times4 <- c(B1,B2)
times.Surv4 <- Surv(times4,status)
times.survfit4 <- survfit(times.Surv4~treatment)
mod.cox4 <- coxph(times.Surv4~treatment)
summary(mod.cox4)
```

```
##########################
# AUC
##########################

set.seed(12345)

# Càlcul de fita
n <- 50
treatment <- c(rep(0,n),rep(1,n))
status <- rep(1,2*n)
Fita1 <- c()
Fita2 <- c()

for(k in 1:100){
       A3 <- rexp(n,0.8)
       B3 <- rexp(n,1)
       times3 <- c(A3,B3)
       times.Surv3 <- Surv(times3,status)
       times.survfit3 <- survfit(times.Surv3~treatment)
       mod.cox3 <- coxph(times.Surv3~treatment)
       HRR[k] <- exp(-mod.cox3$coef)
       summary(mod.cox3)

       GanaA <- 0
       GanaB <- 0
       Total <- n^2
       for (i in 1:n){
              for (j in 1:n){
                     if (A3[i]<B3[j]) GanaA <- GanaA+1
              }
       }
       Fita1[k] <- GanaA/Total
       Fita2[k] <- HRR[k]/(1+HRR[k])
       print(k)
}
boxplot(HRR)
maxxy <- max(c(Fita1,Fita2))
minxy <- min(c(Fita1,Fita2))
par(mfrow=c(1,2),las=1,cex.lab=1,mar=c(5,7,5,2))
plot(Fita1,Fita2,xlim=c(minxy,maxxy),ylim=c(minxy,maxxy),
       xlab=expression(theta[1]==P(t[T]<t[C])),ylab=expression(hat(theta)[2]==frac(hat(HRR),1+hat(HRR))),
       main=expression(paste(hat(theta)[2]," vs. ",theta[1])))
abline(c(0,1),lty=2)

BlandAltman(Fita1,Fita2,
       tit=expression(paste("Concordance between ",theta[1]," and ",hat(theta)[2])),1,1,ID=NULL,limy=0.2)

install.packages("epiR")
library(epiR)
epi.ccc(Fita1,Fita2)$rho

summary(Fita2)
summary(Fita1)
summary(Fita2-Fita1)
```

Script 8. Script per a la realització de la Figure 8.

```
### BA graphic
BlandAltman <- function(x,y,tit="Bland-Altman",size,co,ID=NULL,limx=NULL,limy=NULL){

        Bmean <- (x+y)/2
        Bdif <- y-x

        if (is.null(limy))  ymax <- max(abs(Bdif),na.rm=T)
        if (!is.null(limy)) ymax <- limy

        plot(Bmean ,Bdif ,ylim=c(-ymax,ymax),xlim=c(0,100),xlab="Average",
                    ylab="Difference",main=tit,pch=19,cex=size,col=co)
        abline(h=0,lty=2,lwd=2)
        if(!is.null(ID)) text(Bmean,Bdif,ID,pos=4,cex=0.6)  # identificador
        linessd <- mean(Bdif)+2*c(0,sd(Bdif),-sd(Bdif))
        abline(h=linessd,lty=2,col=4)
}


par(mfrow=c(2,2),las=1)
### Good Concordance
x <- runif(100,0,100)
y <- x + rnorm(100,0,0.5)
BlandAltman(x,y,tit="Good Concordance",size=0.9,co=1,limy=2.5)

### Systematic error
x <- runif(100,0,100)
y <- x + 0.8 +rnorm(100,0,0.5)
BlandAltman(x,y,tit="Systematic error",size=0.9,co=1,limy=2.5)

### Good correlation/Bad concordance
x <- runif(100,0,100)
y <- 1.02*x - 1 + rnorm(100,0,0.1)
BlandAltman(x,y,tit="Good correlation/Bad concordance",size=0.9,co=1,limy=2.5)

### Concordance dependent on the magnitude of the response
x <- runif(100,0,100)
y <- x + rnorm(100,0,0.02*x)
BlandAltman(x,y,tit="Concordance dependent on the magnitude",size=0.9,co=1,limy=2.5)
```

Script 9. Script per a la realització de la Figure 9.

```
library(psych)
# Funnel-plot examples
par(las=1,mar=c(5,6,5,0),lwd=1,cex=1.2)
mat <- matrix(c(1,2,3),nrow=1)
layout(mat, widths = c(0.95,0.8,0.8))
###################################### Sin sesgo  ##############################################
plot(NULL,xlim=c(0.1,10),ylim=c(0,15),log="x",xlab="Effect",ylab=expression(frac(1,SE)),
    main="Non publication bias",cex.lab=1.2)
abline(v=1,lty=2)
x <- c()
y <- c()

for (i in 1:100){
  y[i] <- rexp(1,0.2)
  x[i] <- exp(rnorm(1,0,2/y[i]))
  points(x[i],y[i],cex=1.2)
}
###################################### Con sesgo tipo I ########################################
par(mar=c(5,0.5,5,0))
plot(NULL,xlim=c(0.1,10),ylim=c(0,15),log="x",xlab="Effect",ylab=expression(frac(1,SE)),
    main="Bilateral publication bias",cex.lab=1.2,yaxt="n")
abline(v=1,lty=2)
x <- c()
y <- c()
npoints <- 0

while (npoints<100){
  Y <- rexp(1,0.2)
  X <- exp(rnorm(1,0,2/Y))
  if (Y>7.5 | (Y<=7.5 & (X>3 | X<1/3))){
    npoints <- npoints +1
    points(X,Y,cex=1.2)
    y[npoints] <- Y
    X[npoints] <- X
  }
  else{
    probPrint <- runif(1)
    if (probPrint<0.04){
          npoints <- npoints +1
          points(X,Y,cex=1.2)
          y[npoints] <- Y
          x[npoints] <- X
    }
  }
}
###################################### Con sesgo tipo II #######################################
par(mar=c(5,0.5,5,1))
plot(NULL,xlim=c(0.1,10),ylim=c(0,15),log="x",xlab="Effect",ylab=expression(frac(1,SE)),
    main="Unilateral publication bias",cex.lab=1.2,yaxt="n")
abline(v=1,lty=2)
x <- c()
y <- c()
npoints <- 0

while (npoints<100){
  Y <- rexp(1,0.2)
  X <- exp(rnorm(1,0,2/Y))
  if (Y>7.5 | (Y<=7.5 & X>3)){
    npoints <- npoints +1
    points(X,Y,cex=1.2)
    y[npoints] <- Y
    X[npoints] <- X
  }
  else{
    probPrint <- runif(1)
    if (probPrint<0.04){
          npoints <- npoints +1
          points(X,Y,cex=1.2)
          y[npoints] <- Y
          x[npoints] <- X
    }
  }
}
```

Script 10. Script per a la realització de les figures de l'Annexe II.

```
#############################################################################
#       EXPONENCIAL
#############################################################################
library(survival)
par(cex.lab=1.2)
xe <- seq(0,8,0.01)
n <- length(xe)

lambda1 <- 1      # Azul
lambda2 <- 0.4    # Rojo

distribucion_e1 <- pexp(xe, lambda1)
distribucion_e2 <- pexp(xe, lambda2)

supervivencia_e1 <- 1-distribucion_e1
supervivencia_e2 <- 1-distribucion_e2

densidad_e1 <- dexp(xe, lambda1)
densidad_e2 <- dexp(xe, lambda2)

riesgo_e1 <- densidad_e1/supervivencia_e1
riesgo_e2 <- densidad_e2/supervivencia_e2

riesgoacum_e1 <- cumsum(riesgo_e1)
riesgoacum_e2 <- cumsum(riesgo_e2)

ymin <- min(c(supervivencia_e1,supervivencia_e2,densidad_e1,densidad_e1,
riesgo_e1,riesgo_e2,riesgoacum_e1,riesgoacum_e2))

ymax <- max(c(supervivencia_e1,supervivencia_e2,densidad_e1,densidad_e1,
       riesgo_e1,riesgo_e2,riesgoacum_e1,riesgoacum_e2))

par(mfrow=c(2,2),lwd=2,las=1)

plot(xe,densidad_e1,type='l', xlab='Temps',ylab="f", col='blue')
lines(xe,densidad_e2,col="red")
title('Densitat')

plot(xe,supervivencia_e1,type='l', xlab='Temps',ylab="S", col='blue')
lines(xe,supervivencia_e2,col="red")
ytext <- max(c(supervivencia_e1,supervivencia_e2))
#text(6,0.9,paste("HRR =", round(lambda1/lambda2,2)),adj=1,cex=0.9)
#text(6,1,paste("MR =", round(lambda2/lambda1,2)),adj=1,cex=0.9)
title('Supervivència')

plot(xe,riesgo_e1,type='l',xlab='Temps',ylab=expression(lambda), col='blue',ylim=c(0,2))
lines(xe,riesgo_e2,col="red")
title('Risc Instantani')

plot(xe,riesgoacum_e1,type='l', xlab='Temps',ylab=expression(Lambda), col='blue')
lines(xe,riesgoacum_e2,col="red")
title('Risc Acumulat')


#############################################################################
#       WEIBULL
#############################################################################

aux <- 6
x_w1 <- seq(0.01,aux,0.01)
n <- length(x_w1)
k1 <- 0.75          # Para HRR constante k1=k2
k2 <- 1.15
scale1 <- 1.63
HRR <- 1/0.9
# scale2 <- (HRR)^(1/k1)*scale1
scale2 <- 1.89

distribucion_w1 <- pweibull(x_w1, shape=k1, scale = scale1, log = FALSE)
distribucion_w2 <- pweibull(x_w1, shape=k2, scale = scale2, log = FALSE)

supervivencia_w1 <- 1-distribucion_w1
supervivencia_w2 <- 1-distribucion_w2

densidad_w1 <- dweibull(x_w1, shape=k1, scale = scale1, log = FALSE)
densidad_w2 <- dweibull(x_w1, shape=k2, scale = scale2, log = FALSE)
```

```
riesgo_w1 <- densidad_w1/supervivencia_w1
riesgo_w2 <- densidad_w2/supervivencia_w2

riesgoacum_w1 <- cumsum(riesgo_w1)
riesgoacum_w2 <- cumsum(riesgo_w2)

par(mfrow=c(2,2),lwd=2,las=1)

plot(x_w1,densidad_w1,type='l', xlab='Temps', col='blue',ylab="f")
lines(x_w1,densidad_w2,col='red')
title('Densitat')

plot(x_w1,supervivencia_w1,type='l', xlab='Temps', col='blue',ylim=c(0,2),ylab="S")
lines(x_w1,supervivencia_w2,col='red')
lines(x_w1,riesgo_w2/riesgo_w1,col="darkgreen")
text(x_w1[1],riesgo_w2[1]/riesgo_w1[1],"HRR",col="darkgreen",pos=4,cex=0.8)
#text(aux,0.9,paste("HRR =", round((scale2/scale1)^k1,2)),adj=1,cex=0.9)
#text(aux,1,paste("MR =", round(scale1/scale2,2)),adj=1,cex=0.9)
title('Supervivència')
#abline(h=0.5,,lty=2,lwd=1)
#abline(v=c(1.28,1.63),lty=2,lwd=1)

ymin <- min(c(riesgo_w1,riesgo_w2))
ymax <- max(c(riesgo_w1,riesgo_w2))
plot(x_w1,riesgo_w1,type='l', xlab='Temps', col='blue',ylim=c(ymin,ymax),ylab=expression(lambda))
lines(x_w1,riesgo_w2,col='red')
title('Risc Instantani')

plot(x_w1,riesgoacum_w1,type='l', xlab='Temps', col='blue',ylab=expression(Lambda))
lines(x_w1,riesgoacum_w2,col='red')
title('Risc Acumulat')

### Estadístics
(mean1 <- scale1*gamma(1+1/k1))
(mean2 <- scale2*gamma(1+1/k2))

(med1 <- scale1*log(2)^(1/k1))
(med2 <- scale2*log(2)^(1/k2))


#############################################################################
#       LOG-LOGISTICA
#############################################################################
library(actuar)
aux <- 6
xllg <- seq(0,aux,0.01)[-1]
k1 <- 1.5
k2 <- 1.5
scale1 <- 0.63
scale2 <- 1.63

distribucionllg1 <- pllogis(xllg, shape=k1, scale = scale1, log = FALSE)
distribucionllg2 <- pllogis(xllg, shape=k2, scale = scale2, log = FALSE)


supervivenciallg1 <- 1-distribucionllg1
supervivenciallg2 <- 1-distribucionllg2

densidadllg1 <- dllogis(xllg, shape=k1, scale = scale1, log = FALSE)
densidadllg2 <- dllogis(xllg, shape=k2, scale = scale2, log = FALSE)

riesgollg1 <- densidadllg1/supervivenciallg1
riesgollg2 <- densidadllg2/supervivenciallg2

riesgoacumllg1 <- cumsum(riesgollg1)
riesgoacumllg2 <- cumsum(riesgollg2)


par(mfrow=c(2,2),lwd=2,las=1)
plot(xllg,densidadllg1,type='l', xlab='Temps',ylab="", col='blue')
lines(xllg,densidadllg2,col='red')
title('Densitat')

plot(xllg,supervivenciallg1,type='l', xlab='Temps',ylab="", col='blue',ylim=c(0,1))
lines(xllg,supervivenciallg2,col='red')
lines(xllg,riesgollg2/riesgollg1,col="darkgreen")
text(xllg[1],riesgollg2[1]/riesgollg1[1],"HRR",col="darkgreen",pos=4,cex=0.8)
title('Supervivència')
```

```
#abline(h=0.5)
#abline(v=c(scale1,scale2))

plot(xllg,riesgollg1,type='l', xlab='Temps',ylab="", col='blue')
lines(xllg,riesgollg2,col='red')
title('Risc Instantani')

plot(xllg,riesgoacumllg1,type='l', xlab='Temps',ylab="", col='blue')
lines(xllg,riesgoacumllg2,col='red')
title('Risc Acumulat')


### Estadístics
# Esperanza aprox
(mean1 <- sum(0.01*supervivenciallg1))
(mean2 <- sum(0.01*supervivenciallg2))

(med1 <- scale1)
(med2 <- scale2)
(MR <- med1/med2)
```

Script 11. Script per a la realització de les figures de l'Annexe IX.

```
#########################################################################
# Script para simular gráfico de BA con exponencial y Weibull
# Objetivo: Examinar concordancia entre HRR y Median Ratio y cociente de esperanzas
#########################################################################


### Carregar funcions i llibreries ####################
rm(list=ls())
library(survival)
setwd('E:\\TFM\\RecercaHRRvsMediana\\Scripts')
source('Functionsv1.r')
source('FunctionForSimulaBA.r')

setwd('E:\\TFM\\Simulaciones')
source('CensuraFunctions.r')

### Lectura ###############################################
setwd('E:\\TFM\\RecercaHRRvsMediana')
NEJM <- read.csv2('NEJM3.csv',header=TRUE,dec='.')
names(NEJM)

### Paràmetres Simulació
nsim <- 1
opc11 <- 1      # 1=Todo ; 2=OS ; 3=PFS
opc2 <- 2       # 1=Todos los datos 2=Sólo ECA's
opc3 <- 1       # 1=BA 2= gráfico JAG

### Enmagatzemar resultats
concordancia <- c()
SD <- c()
M <- matrix(NA,nrow=3,ncol=4)
colnames(M) <- c("concordanceExp","SDExp","concordanceWeib","SDWeib")
rownames(M) <- c("global","OS","PFS")

################################### Lectura ##############################################
for (opc1 in opc11){

  ### Dades
  if(opc2==1) dades1 <- NEJM
  if(opc2==2) dades1 <- subset(NEJM,NEJM$CT=="Yes")
  if(opc2==1) filename <- "Alldata"
  if(opc2==2) filename <- "Partialdata"

  if(opc1==1) dades <- dades1
  if(opc1==2) dades <- subset(dades1,dades1$Type=="OS")
  if(opc1==3) dades <- subset(dades1,dades1$Type=="PFS")
  if(opc1==1) filename <- paste(filename,"AllResponse.txt",sep="")
  if(opc1==2) filename <- paste(filename,"OS.txt",sep="")
  if(opc1==3) filename <- paste(filename,"PFS.txt",sep="")


  ##########################################################################
  #
  # Exponencial
  #
  ##########################################################################

  NumMeasures <- dim(dades)[1]                  # Número de casos

  # Proporció de censures
  NEJMwithEvents <- subset(dades,!is.na(dades$E))
  pc2 <- 1- with(NEJMwithEvents,sum(E)/sum(N))  #Proporció de censures promig
  pc1 <- 1-dades$E/dades$N                      #Proporció de censures
  prop.cens <- ifelse(!is.na(dades$E),pc1,pc2)

  # Paràmetres
  lambda1 <- 1
  lambda2 <- dades$HRR
  t.recluta <- 0
  prop.censFollow <- 0

  n1 <- dades$NC
  n2 <- dades$NT

  #if (opc3==1) {win.graph() ; par(las=1,mfrow=c(2,2),mar=c(7,7,4,4))}
```

```
    if (opc3==2){
    win.graph()
    par(mfrow=c(1,1),las=1,mar=c(8,6,3,3))
    lim <- 1.2
    plot(NULL,xlim=c(-lim,lim),ylim=c(-lim,lim),main="Exponencial",
          xlab=expression(log~bgroup("(",frac(MR,HRR^-1),")")),
           ylab=expression(log~hat(bgroup("(",frac(MR,HRR^-1),")"))), cex.lab=0.7)
  }


propMRremove <- c()
for (j in 1:nsim){
    ### Inicialitzar vectors
    MR <- c()
    HRR <- c()
    size <- c()

    for (i in 1:NumMeasures){

        time1 <- rexp(n1[i],lambda1)
        time2 <- rexp(n2[i],lambda2[i])

        AC <- AddCensure(time1,time2,lambda1,lambda2[i],t.recluta,
               prop.cens[i],prop.censFollow,tFollow=NULL,graph=FALSE)
        times <- AC[,1]   # Temps: Fins n són del grup control y a partir de (n+1) del tractat
        status <- AC[,2]  # Censures: Fins n són del grup control y a partir de (n+1) del tractat
        treatment <- as.factor(c(rep("Control",n1[i]),rep("Treated",n2[i])))
        time.Surv <- Surv(times,status)              # Tiempos en un vector con su estado

        MR[i] <- ObtenerMR(time.Surv,treatment)

        mod.cox <- coxph(time.Surv~treatment)
        HRR[i] <- exp(coef(mod.cox))
        size[i] <- 1/sqrt(mod.cox$var)

        ### Gráfico JAG
        if (opc3==2){
          greycol <- as.character(100-min(round((size[i])*10),100))
          co <- paste("grey",greycol,sep="")
          points(log(dades$MedRat[i]/dades$HRR[i]),log(MR[i]/HRR[i]),pch=19,col=co,cex=0.7)
        }
    }
    EliminarNAs(variable=MR,MR,HRR,size)


    if (opc3==1){
      xymin <<- min(c(HRR,MR),na.rm=T) ; xymax <<- max(c(HRR,MR),na.rm=T)
      BlandAltman(log(HRR),log(MR),"",1/8*size,1,ID=NULL,limx=c(-1.5,0.5),limy=3)
      AxisBlandAltman(MR,HRR,EE=1/size,Type=ifelse(opc1==1,"Global",ifelse(opc1==2,"OS","PFS")))
    }

    # Iteración
    cat('Exp',opc1,opc2,'--> ite:',j,"\n")

    # Concordancia
    concordancia[j] <- CalculoLin(MR,HRR,size)


    # SD
    SD[j] <- sd(log(MR)-log(HRR))
    cat("SD:",SD[j],"\n")


  }
  M[opc1,1:2] <- c(mean(concordancia),mean(SD))

  filename2 <- paste("Exp",filename,sep="")
  cat(filename2,"Concordancia: ",mean(concordancia))
  cat(filename2,"SD: ",mean(SD))
  write.table(cbind(concordancia,SD), file = filename2, sep = "\t", row.names = FALSE)
```

```
#########################################################################
#
# Weibull
#
#########################################################################


# Proporción de censuras
NEJMwithEvents <- subset(dades,!is.na(dades$E))
pc2 <- 1- with(NEJMwithEvents,sum(E)/sum(N))  #Proporció de censures promig
pc1 <- 1-dades$E/dades$N                      #Proporción de censuras
prop.censa <- ifelse(!is.na(dades$E),pc1,pc2)

# Praàmetres
t.recluta <- 0
prop.censFollow <- 0
n1a <- dades$NC
n2a <- dades$NT

# Càlcul paràmetres de la Weibull
ka <- with(dades,log(HRR)/log(MedRat))
rho2a <- with(dades,ifelse(HRR_Adj<0,MedianC,MedianT))/(log(2)^(1/ka))
rho1a <- with(dades,ifelse(HRR_Adj<0,MedianT,MedianC))/(log(2)^(1/ka))

# Elimina las k's que son Na, negatives o infinit
elim1 <- which(is.na(ka) | ka+1==ka | ka<0)
k <- ka[-elim1]
rho1 <- rho1a[-elim1]; rho2 <- rho2a[-elim1]
n1 <- n1a[-elim1]; n2 <- n2a[-elim1]
prop.cens <- prop.censa[-elim1]


NumMeasures <- length(k)


#if (opc3==1) {win.graph() ; par(las=1,mfrow=c(2,2),mar=c(7,7,4,4))}

### 3 lineas para gráfico JAG
if (opc3==2){
  win.graph()
  par(mfrow=c(1,1),las=1,mar=c(8,6,3,3))
  lim <- 1.2
  plot(NULL,xlim=c(-lim,lim),ylim=c(-lim,lim),main="Weibull",
             xlab=expression(log~bgroup("(",frac(MR,HRR^-1),")")),
             ylab=expression(log~hat(bgroup("(",frac(MR,HRR^-1),")"))),cex.lab=0.7)
}

for (j in 1:nsim){
  ### Inicializar vectores
  MR <- c()
  HRR <- c()
  size <- c()
  for (i in 1:NumMeasures){
      time1 <- rweibull(n1[i],k[i],rho1[i])
      time2 <- rweibull(n2[i],k[i],rho2[i])

      AC <- AddCensure(time1,time2,lambda1,lambda2[i],t.recluta,prop.cens[i],prop.censFollow,
                    tFollow=NULL,graph=FALSE,"Weibull",sh=k[i],sca1=rho1[i],sca2=rho2[i])
      times <- AC[,1]  # Temps: Fins n són del grup control y a partir de (n+1) del tractat
      status <- AC[,2]  # Censures: Fins n són del grup control y a partir de (n+1) del tractat
      treatment <- as.factor(c(rep("Control",n1[i]),rep("Treated",n2[i])))
      time.Surv <- Surv(times,status)
      MR[i] <- ObtenerMR(time.Surv,treatment)
      mod.cox <- coxph(time.Surv~treatment)
      HRR[i] <- exp(coef(mod.cox))
      size[i] <- 1/sqrt(mod.cox$var)

      ### Gráfico JAG
      if (opc3==2){
        greycol <- as.character(100-min(round((size[i])*10),100))
        co <- paste("grey",greycol,sep="")
        points(log(dades$MedRat[i]/dades$HRR[i]),log(MR[i]/HRR[i]),pch=19,col=co,cex=0.7)
      }
  }

  propMRremove[j] <- EliminarNAs(variable=MR,MR,HRR,size)

  if (opc3==1){
    xymin <<- min(c(HRR,MR),na.rm=T) ; xymax <<- max(c(HRR,MR),na.rm=T)
```

```
      BlandAltman(log(HRR),log(MR),"",1/8*size,1,ID=NULL,limx=c(-1.5,1.5),limy=3)
      AxisBlandAltman(MR,HRR,EE=1/size,Type=ifelse(opc1==1,"Global",ifelse(opc1==2,"OS","PFS")))
    }

    # SD
    SD[j] <- sd(log(MR)-log(HRR))
    cat("SD:",SD[j],"\n")

  }
  M[opc1,3:4] <- c(mean(concordancia),mean(SD))


  filename2 <- paste("Weib",filename,sep="")
  cat(filename2,"Concordancia: ",mean(concordancia))
  cat(filename2,"SD: ",mean(SD))
  write.table(cbind(concordancia,SD), file = filename2, sep = "\t", row.names = FALSE)

}
summary(propMRremove)
length(elim1)

# Antes de leer los datos, hay que copiar los ficheros en el directorio
# E:\\TFM\\RecercaHRRvsMediana\\Concordancias simuladas

### Leer datos
setwd('E:\\TFM\\RecercaHRRvsMediana\\Concordancias simuladas')
EAA <- read.table('ExpPartialdataAllResponse.txt',header=T)
EAOS <- read.table('ExpPartialdataOS.txt',header=T)
EAPFS <- read.table('ExpPartialdataPFS.txt',header=T)

WAA <- read.table('WeibPartialdataAllResponse.txt',header=T)
WAOS <- read.table('WeibPartialdataOS.txt',header=T)
WAPFS <- read.table('WeibPartialdataPFS.txt',header=T)

A <- cbind(EAA,EAOS,EAPFS,WAA,WAOS,WAPFS)
colnames(A) <- paste(rep(c("Concordance","SD"),6),c(rep("Exp",6),rep("Weib",6)),
               rep(c("All","All","OS","OS","PFS","PFS"),2))
summary(A)
```

Script 12. Funcions usades en l'script 11.

```
ObtenerMR <- function(time.Surv,treatment){
      time.survfit <- survfit(time.Surv~treatment)  # Cálculo de Kaplan-Meier
      median1 <- summary(time.survfit)$table["treatment=Control","median"]
      median2 <- summary(time.survfit)$table["treatment=Treated","median"]
      MR <- median1/median2
      return(MR)
}



EliminarNAs <- function(variable,MR,HRR,size){
  l <- length(variable)
  elim <<- which(is.na(variable))
  if(length(elim)!=0){
    MR <<- MR[-elim]
    HRR <<- HRR[-elim]
    size <<- size[-elim]
  }
  return(length(elim/l))  # proporción de MR eliminados
}




CalculoLin <- function(MR,HRR,size){
  dades2 <- data.frame(cbind(MR,HRR))
  colnames(dades2) <- c("MedRat","HRR")
  concordancia <- LinWeigth(dades2,1/8*size)[2]
  cat("Coeficiente de Linn ponderado:",concordancia,"\n")
  return(concordancia)
}
```

Script 13. Funcions per generar les censures.

```
#######################################################################
# Use this fuction to add censure to times with a expected proportion
# of not random censures in each group and
# exact proportion of censures for end of follow-up
# time1, time2: times of events
# lambda1,lambda2: parameters of exponential
# t.recluta: recruitment time
# prop.cens: proportion of expected censures during the follow-up
# pFollow: proportion of exact censures due to finsih of study
# (if tFollow is not NULL, then this parameter is ignored)
# tFollow: time of follow-up
# graph: if TRUE, then print the process of censure (recommended for small sample sizes)
#
# Return a matrix with  times in first colum and censures in second colum:
# (1: not censured, 0:censured)
# This function calls the fuctions below
#######################################################################

AddCensure <- function (time1,time2,lambda1,lambda2,t.recluta,prop.cens,pFollow=NULL,tFollow=NULL,
                            graph=FALSE,distribution="Exponential",sh=NULL,sca1=NULL,sca2=NULL){
    # Tiempos originales (time)
    time <- c(time1,time2)

    ### Tamaños de muestra
    n1 <- length(time1)
    n2 <- length(time2)
    n <- n1+n2

    # Añadir tiempos de censura Uniforme entre [0,Tmax] (timeb).
    # Primero se debe calcular Tmax1 y Tmax2 (17/10/10 de la llibreta)
    if (distribution=="Exponential") timeAux <- CensuraUnif2(time1,time2,lambda1,lambda2,prop.cens)
    if (distribution=="Weibull") timeAux <- CensuraWeibull(time1,time2,sh,sca1,sca2,prop.cens)
    time1a <- timeAux[[1]]
    time2a <- timeAux[[2]]
    timea <- c(time1a,time2a)

    # Tiempos con periodo de reclutamiento  (timeb)
    timeAux <- CensuraRecruit(time1a,time2a,t.recluta)
    time1b <- timeAux[[1]]
    time2b <- timeAux[[2]]
    timeb <- c(time1b,time2b)         # Se añade el tiempo de reclutamiento a los tiempos generados

    # Tiempos con finalización del estudio  (timec)
    timec <- CensuraEnd(timeb,pFollow,tFollow,t.recluta)

    # Trasladamos los tiempos al cero (timed)
    timed <- timec-entry

    # Incluir censuras en la variable e-status
    status <- rep(1,n)
    for (i in 1:n){
        if(timec[i]==tFollowAux | timea[i]==Cens[i]){status[i] <- 0}
    }

    ######################################### Graphics ##############################################
    if (graph){
    ### Printar resultados
    PrintSet(time1,time2,time1a,time2a,time1b,time2b,tFollowAux,status,Cens1,Cens2,
               n1,n2,lambda2,prop.cens,pFollow)

     CensGraphics(time1,time2,timea,timeb,timec,timed,tFollowAux,t.recluta,n,n1,n2,
                      lambda1,lambda2,Cens,Cens1,Cens2,prop.cens,pFollow,Tmax)
    }
    return(cbind(timed,status))

}
```

```
##############################################################################
# Para 2 conjuntos de tiempo cualesquiera time1 y time2 genera dos conjuntos de
# tiempos time1a y time2a censurados uniformemente entre 0 y Tmax
##############################################################################

CensuraUnif <- function(time1,time2,Tmax){

    n1 <- length(time1)
    n2 <- length(time2)

    Cens1 <<- runif(n1,0,Tmax)
    Cens2 <<- runif(n2,0,Tmax)
    Cens <<- c(Cens1,Cens2)

    time1a <- pmin(time1,Cens1)
    time2a <- pmin(time2,Cens2)

    return(list(time1a,time2a))
}


##############################################################################
# Para 2 conjuntos de tiempo exponenciales time1 y time2 con tasas lambda1 y
# lambda2 genera dos conjuntos de tiempos time1a y time2a censurados uniformemente
# con una proporción de censuras globales ESPERADAS de prop.cens.
# Si los tiempos no son exponenciales NO funciona
##############################################################################

CensuraUnif2 <- function(time1,time2,lambda1,lambda2,prop.cens){

    n1 <- length(time1)
    n2 <- length(time2)

    if (prop.cens!=0){

      f <- function (x,prop.cens,lambda1,lambda2,n1,n2) {
        term1 <- n1*(exp(-lambda1*x)-1)/(lambda1*x)
        term2 <- n2*(exp(-lambda2*x)-1)/(lambda2*x)
        term3 <- (n1+n2)*prop.cens
        sol <- term1+term2+term3
        return(sol)
      }

      Tmax <<- uniroot(f,interval=c(0.01,500),tol=0.0001,prop.cens=prop.cens,
        lambda1=lambda1,lambda2=lambda2,n1=n1,n2=n2)$root

      Cens1 <<- runif(n1,0,Tmax)
      Cens2 <<- runif(n2,0,Tmax)
      Cens <<- c(Cens1,Cens2)

      time1a <- pmin(time1,Cens1)
      time2a <- pmin(time2,Cens2)
    }

    if (prop.cens==0){

      Tmax <<- 10^20

      Cens1 <<- rep(Tmax,n1)
      Cens2 <<- rep(Tmax,n2)
      Cens <<- c(Cens1,Cens2)

      time1a <- time1
      time2a <- time2
    }

    return(list(time1a,time2a))
}
```

```
##############################################################################
# Para 2 conjuntos de tiempo Weibull time1 y time2 con tasas lambda1 y
# lambda2 genera dos conjuntos de tiempos time1a y time2a censurados uniformemente
# con una proporción de censuras globales ESPERADAS de prop.cens.
# Si los tiempos no son Weibull NO funciona
##############################################################################

CensuraWeibull <- function(time1,time2,sh,sca1,sca2,prop.cens){

    n1 <- length(time1)
    n2 <- length(time2)

    if (prop.cens!=0){                                          # Libreta 29/4/11
      f1 <- function(y,sh,sca) exp(-(y/sca)^sh)
      f <- function (x,prop.cens,sh,sca1,sca2,n1,n2) {
        term1 <- n1*integrate(f1,0,x,sh,sca1)$value
        term2 <- n2*integrate(f1,0,x,sh,sca2)$value
        term3 <- (n1+n2)*prop.cens*x
        sol <- term1+term2-term3
        return(sol)
      }

      Tmax <<- uniroot(f,interval=c(0.01,10^5),tol=0.0001,prop.cens=prop.cens,
               sh=sh,sca1=sca1,sca2=sca2,n1=n1,n2=n2)$root

      Cens1 <<- runif(n1,0,Tmax)
      Cens2 <<- runif(n2,0,Tmax)
      Cens <<- c(Cens1,Cens2)

      time1a <- pmin(time1,Cens1)
      time2a <- pmin(time2,Cens2)
    }

    if (prop.cens==0){

      Tmax <<- 10^20

      Cens1 <<- rep(Tmax,n1)
      Cens2 <<- rep(Tmax,n2)
      Cens <<- c(Cens1,Cens2)

      time1a <- time1
      time2a <- time2
    }
    # Aux <<- cbind(time1,time1a,Cens1,time2,time2a,Cens2)
    return(list(time1a,time2a))
}


##############################################################################
# Para 2 conjuntos de tiempo cualesquiera time1 y time2 genera dos conjuntos de
# tiempos time1b y time2b desplazados a la derecha un tiempo de reclutamiento
# entre 0 y t.recluta
# Esta función solo tiene sentido usarla si luego se va añadir censura por
# finalización del estudio
##############################################################################


CensuraRecruit <- function(time1a,time2a,t.recluta){
    n1 <- length(time1a)
    n2 <- length(time2a)

    entry1 <<- runif(n1,0,t.recluta)   # tiempos de entrada en el estudio  (grupo1)
    entry2 <<- runif(n2,0,t.recluta)   # tiempos de entrada en el estudio (grupo2)
    entry <<- c(entry1,entry2)
    time1b <- time1a+entry1
    time2b <- time2a+entry2
    return(list(time1b,time2b))
}
```

```
##############################################################################
# Para un conjunto de tiempo cualesquiera time,
# 1. Si tFollow es NULL censura una proporción pFollow de tiempos por finalización de estudio.
# 2. Si tFollow no es NULL censura tosos los tiempos superiores a tFollow
# Retorna timec, que son los tiempos censurados.
# Se repestará pFollow siempre que sto no suponga que la finalización del estudio
# sea previa al fin del reclutamiento
##############################################################################


CensuraEnd <- function(time,pFollow,tFollow,t.recluta){

    if(!is.null(tFollow)){
      tFollowAux <<- tFollow
      if (tFollow<t.recluta){
        print("El tiempo de seguimiento debe ser mayor que el tiempo de reclutamiento")
      }
      if (tFollow>=t.recluta){
        timec <- pmin(time,tFollow)
        return(timec)
      }

    }

    if(is.null(tFollow)){
      if(pFollow!=0){
        n <- length(time)
        timebAux <-  sort(time,decreasing=TRUE)
        ncens <- ceiling(pFollow*n)
        tFollow0 <- ifelse(ncens!=0, mean(timebAux[ncens:(ncens+1)]),max(time))
        tFollowAux <<- pmax(tFollow0,t.recluta)
        timec <- pmin(time,tFollowAux)
        return(timec)
      }
      if(pFollow==0){
        tFollowAux <<- 10^20
        return(time)
      }
    }
}

##############################################################################
# Función auxiliar para printar un resumen del proceso
##############################################################################


PrintSet <- function(time1,time2,time1a,time2a,time1b,time2b,tFollow,
                status,Cens1,Cens2,n1,n2,lambda2,prop.cens,pFollow){
    timeb <- c(time1b,time2b)
    cat('------------------------------------------------------------------------\n')
    cat("lambda 1=",lambda1,"lambda 2=",lambda2,"Expected cens during study=",
                prop.cens,"Exact cens End study=",pFollow,"\n")
    cat("Proporción de censuras en grupo 1 uniformes
        (antes añadir cens por fin estudio):",sum(time1>Cens1)/n1,"\n")
    cat("Proporción de censuras en grupo 2 uniformes
        (antes añadir cens por fin estudio):",sum(time2>Cens2)/n2,"\n")
    cat("Proporción de censuras en grupo 1 uniformes:",
        sum(time1a!=time1 & time1b<tFollow)/n1,"\n")
    cat("Proporción de censuras en grupo 2 uniformes:",sum(time2a!=time2 & time2b<tFollow)/n2,"\n")
    cat("Proporción de censuras por fin de estudio:",sum(timeb>tFollow)/n,"\n")
    cat("Proporción total de censuras: ",sum(status==0)/n,"\n")
}
```

```
#####################################################
# Hace el gráfico de censuras (útil para n's pequeñas)
# -------------+
# ---
# ------------------+
# --------
#####################################################

CensGraphics <- function(time1,time2,timea,timeb,timec,timed,tFollow,t.recluta,
                n,n1,n2,lambda1,lambda2,Cens,Cens1,Cens2,prop.cens,pFollow,Tmax){

      time <- c(time1,time2)

      ### Tiempo máximo para los gráficos
      xmax <- max(c(time1,time2,timea,timeb,timec))

      par(mfrow=c(3,2),las=1,mar=c(4,2,3,1))

      # Información de la simulación
      plot(NULL,xlim=c(0,xmax),ylim=c(0,n),xlab="",ylab="",xaxt="n",yaxt="n",
        main="Simulation Information")
      h <- n-1                        # altura texto
      s <- (n-2)/8
      text(xmax/3,h,paste("Size Control =",n1),adj=0,cex=1.2)
      text(xmax/3,h-s,paste("Size Treated =",n2),adj=0,cex=1.2)
      text(xmax/3,h-2*s,paste("Lambda Control =",lambda1),adj=0,cex=1.2)
      text(xmax/3,h-3*s,paste("Lambda Treated =",lambda2),adj=0,cex=1.2)
      text(xmax/3,h-4*s,paste("Recruitment time =",t.recluta),adj=0,cex=1.2)
      text(xmax/3,h-5*s,paste("Prop censures Control=",round(sum(time1>Cens1)/n1,2)),adj=0,cex=1.2)
      text(xmax/3,h-6*s,paste("Prop censures Treated=",round(sum(time2>Cens2)/n2,2)),adj=0,cex=1.2)
      text(xmax/3,h-7*s,paste("Prop censures end study(Nominal) =",round(sum(timeb>tFollow)/n,2),
              "(",pFollow,")"),adj=0,cex=1.2)


      # Tiempos originales

      plot(NULL,xlim=c(0,xmax),ylim=c(0,n),xlab="Time",ylab="Individual",
        main=paste("Original Times: Exp(",lambda2,") and Exp(",lambda1,")",sep=""))
      for(i in 1:n){
        co <- ifelse(i<=n1,1,2)
        segments(0,i,time[i],i,col=co)
      }

      # Añadir tiempos de censura Uniforme entre [0,Tmax]
      tit1 <- paste("Uniform censure in [0,",round(Tmax,1),"]",sep="")
      tit2 <- "Without censure"
      tit <- ifelse(prop.cens==0,tit2,tit1)
      plot(NULL,xlim=c(0,xmax),ylim=c(0,n),xlab="Time",ylab="Individual",main=tit)
      for(i in 1:n){
        co <- ifelse(i<=n1,1,2)
        segments(0,i,timea[i],i,col=co)
        if(i<=n1 & timea[i]==Cens[i]){points(timea[i],i,col=1,pch=3)}
        if(i>n1 & timea[i]==Cens[i]){points(timea[i],i,col=2,pch=3)}
      }

      # Tiempos con periodo de reclutamiento
      plot(NULL,xlim=c(0,xmax),ylim=c(0,n),xlab="Time",ylab="Individual",
        main=paste("Recluitment Time =",t.recluta))
      for(i in 1:n){
        co <- ifelse(i<=n1,1,2)
        segments(entry[i],i,timeb[i],i,col=co)
        if(timea[i]==Cens[i]){points(timeb[i],i,col=co,pch=3)}
      }
      abline(v=t.recluta,lty=2)

      # Tiempos con finalización del estudio
      tit1 <- paste("End study time =",round(tFollow,1))
      tit2 <- "Without end time of study"
      tit <- ifelse(pFollow==0,tit2,tit1)
      plot(NULL,xlim=c(0,xmax),ylim=c(0,n),xlab="Time",ylab="Individual",main=tit)
      for(i in 1:n){
        co <- ifelse(i<=n1,1,2)
        segments(entry[i],i,timec[i],i,col=co)
        if(timec[i]==tFollow){points(timec[i],i,col=co,pch=4)}
        if(timec[i]!=tFollow & timea[i]==Cens[i]){points(timec[i],i,col=co,pch=3)}
      }
      abline(v=c(t.recluta,tFollow),lty=2)

      # Trasladamos los tiempos al origen
```

```
      plot(NULL,xlim=c(0,xmax),ylim=c(0,n),xlab="Time",ylab="Individual",
        main="Translate to zero")
      for(i in 1:n){
        co <- ifelse(i<=n1,1,2)
        segments(0,i,timed[i],i,col=co)
        if(timec[i]==tFollow){points(timed[i],i,col=co,pch=4)}
        if(timec[i]!=tFollow & timea[i]==Cens[i]){points(timea[i],i,col=co,pch=3)}
      }
      win.graph()
      CensVsTime(n1,n2,Cens,time)
}


#######################################################
# Hace el gráfico de censuras contra el tiempo
# No esta adaptado para hacer gráficos con tiempos de cualquier magnitud
#######################################################

CensVsTime <- function(n1,n2,Cens,time){
    par(mfrow=c(1,1))
    co <- c(rep(1,n1),rep(2,n2))
    pc <- ifelse(Cens>time,19,1)
    maxT <- max(time)
    maxC <- max(Cens)
    ma <- max(maxT,maxC)
    plot(time,Cens,col=co,xlab="Tiempos supervivencia",ylab="Tiempos de Censura",
          xlim=c(0,ma),ylim=c(0,ma),pch=pc)
    abline(0,1,lty=2,lwd=2)

    p <- c()
    M <- cbind(time,Cens)
    maI <- floor(maxT)
    for(i in 1:maI){
      Maux <- as.matrix(M[which(time<i & time>=(i-1)),],byrow=TRUE)
      total <- dim(Maux)[1]
      p[i] <- sum(Maux[,1]>Maux[,2])/total
      print(i)
      print(total)
      print(sum(Maux[,1]>Maux[,2]))
      abline(v=i,lty=2)
      text(i-0.5,0.9*ma,round(p[i],2),cex=0.8,font=2)
      text(ma/2,ma,"Proporción de censuras",adj=0.5,font=2)
    }
}
```

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