



Comparison of Standard Log-rank Test with Selected Alternatives

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INTRODUCTION

In oncology, randomized controlled trials (RCTs) of fundamental importance is choosing statistical methods that infer a difference in the survival distributions with censored time-to-event data. The standard log-rank (LR) test is widely used to compare the overall survival in superiority trials, and it is the most powerful and efficient test under the assumption of proportional hazards (PH). In the case of non-PH, the LR test has lower power and it might lead to an incorrect conclusion. New proposed alternative tests have shown power advantages.

We applied two alternative tests, Max-Combo (MC) and restricted mean survival time (RMST), on simulated data and reconstructed data to compare the power among the three tests. Our study focuses on small to moderate sample sizes since the three tests exhibit good properties for large samples. There are more alternative tests to LR, but we are focusing on MC and RMST, which are considered as the two most preferred methods.

METHODS

We used the open-source software R for the simulations and analyses. The data sets generated the following three scenarios: crossing curves (CC) and non-crossing curves (late effect and early effect). In the CC scenario, we generated the survival time of the treatment groups based on the Weibull distribution with a fix scale parameter of 1.4 and varying shape parameter that ranges from 1 (PH assumption is met) to 4 (PH assumption is violated). In the late effect and early effect scenarios, the survival time of the treatment group was generated from the combination of exponential distributions to ensure lower hazard rate in treatment group from the beginning of study (early effect) or from a particular point of the study (late effect). For each of these scenarios, we generated data sets with varying sample sizes (50, 100, or 200 subjects in each treatment group), treatment durations (1, 2, or 3), and different censoring probabilities ranging from 0.2 to 0.4. Considering every scenario and combination of parameters, we simulated data for 1000 studies to estimate the power of each of the three tests. In addition, the utility of the three tests is further evaluated on the individual patient data reconstructed from a FAKTION study (2020): a multicenter, randomized, controlled, phase 2 trial using the algorithm introduced by Guyot et al..

RESULTS

Figure 1. (Simulation Study) Non-PH and crossing survival curves

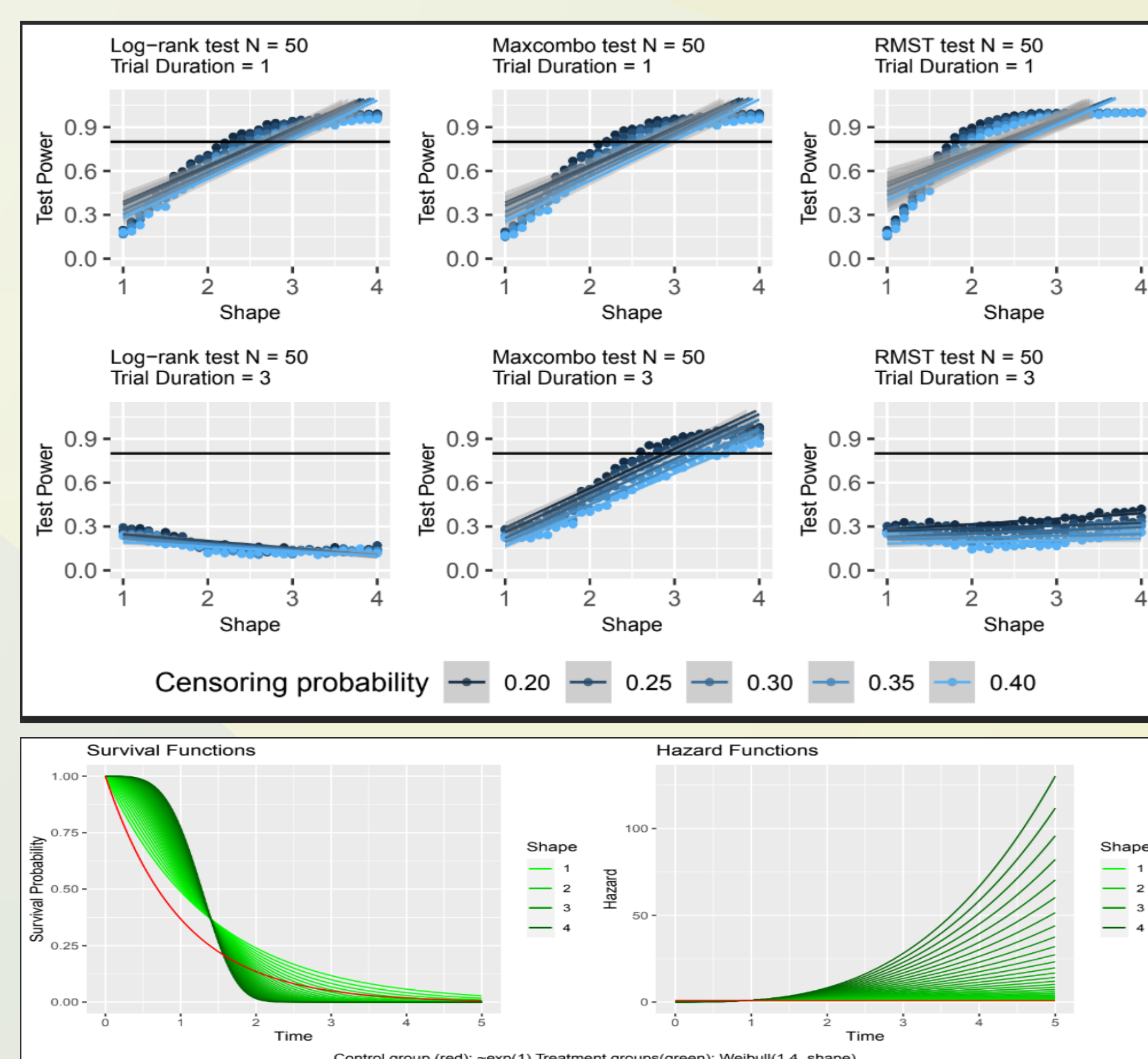


Figure 2. (Simulation Study) Non-PH and non-crossing survival curves Early Effect

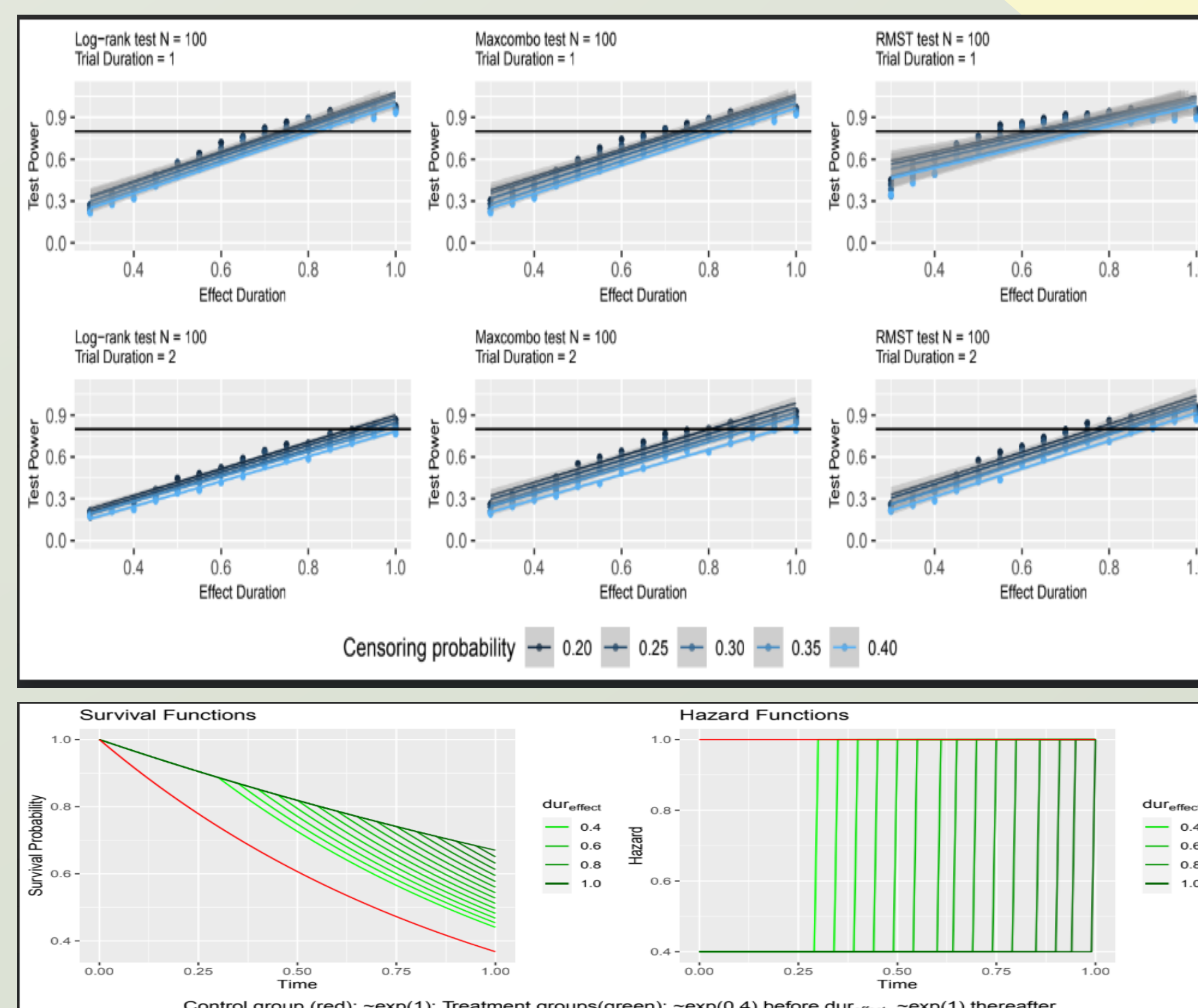
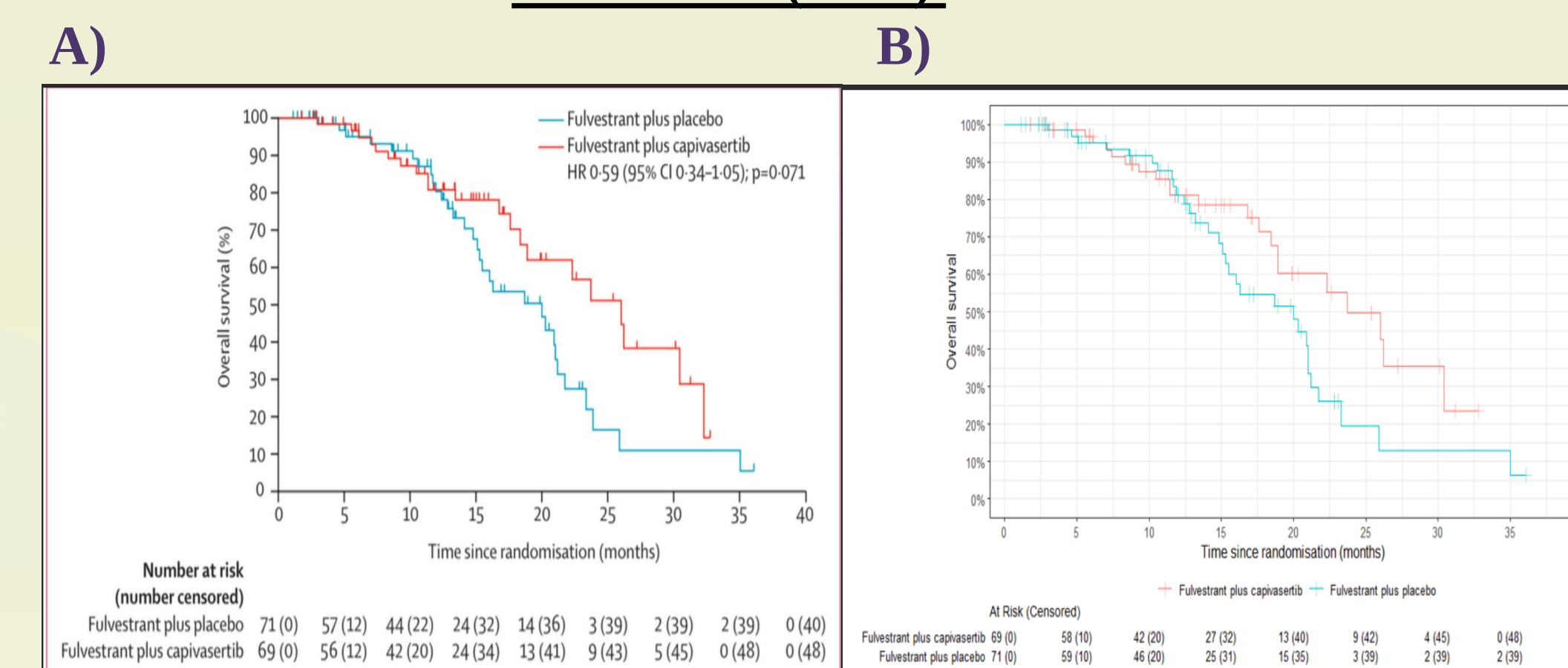


Figure 3. (Real Study): Reconstructed KM curves of OS from FAKTION (2020)



A) KM plot [FAKTION study (2020)]:
HR: 0.59 (95%CI 0.34-1.05), p = 0.071

B) Reconstructed data statistics:
HR: 0.61 (95%CI 0.34-1.06), p = 0.082
Alternative Tests: MC test p = 0.110 and RMST p = 0.051

SUMMARY

In many RCTs, one of the main challenges is to pre-specify an efficient weighting scheme under non-PH to determine the trial power. In the non-PH and crossing survival curves (treatment may offer short-term benefit but does not provide long-term advantages), we observe that for shape values greater than 1 and less than 2.5 the LR is under power vs alternative tests MC and RMST. For the small sample size population with a low censoring rate and short trial duration, the RMST test slightly outperformed the MC test. The MC test provides robust power under non-PH, early and late survival differences, or crossing survival curves alternatives, and it is the preferred test in the settings of a clinical trial where there are one or more interim analyses.

The quality of the reconstructed data is examined to be sufficiently satisfactory, as shown in Figure 3 along with the p-values from the three tests.

Further investigation on the characteristics of the alternative tests under different non-PH patterns will provide better guidance for the design of a trial.

CONTACT INFO

Your comments and questions are valued and encouraged.

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