Simultaneous hypothesis testing for multiple competing risks in comparative clinical trials

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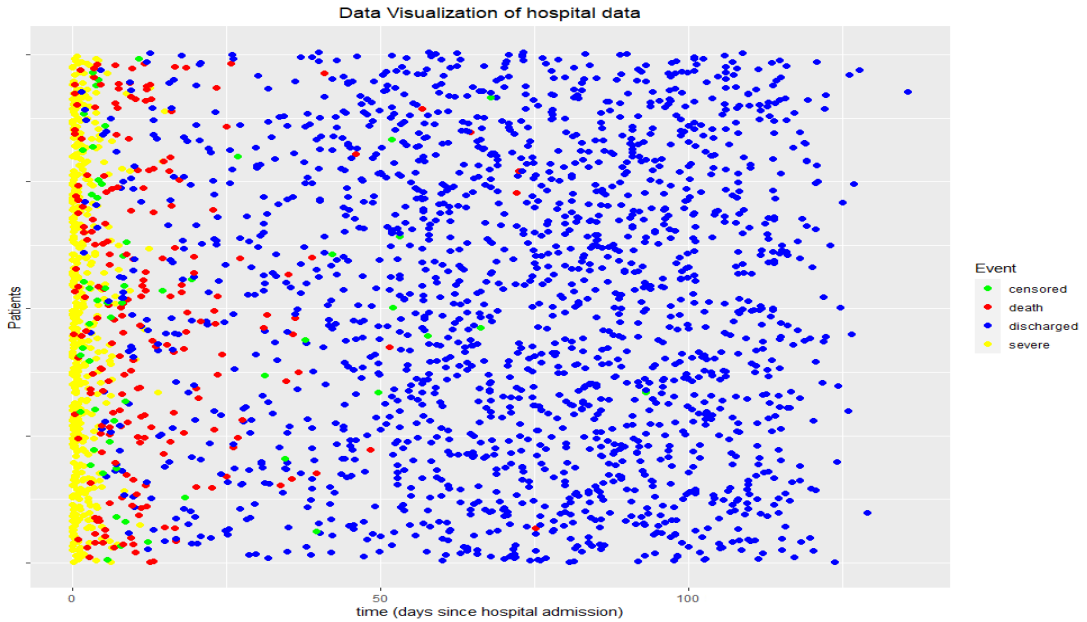
Disclosure

I have NO financial disclosure or conflicts of interest with the presented materials in this presentation.

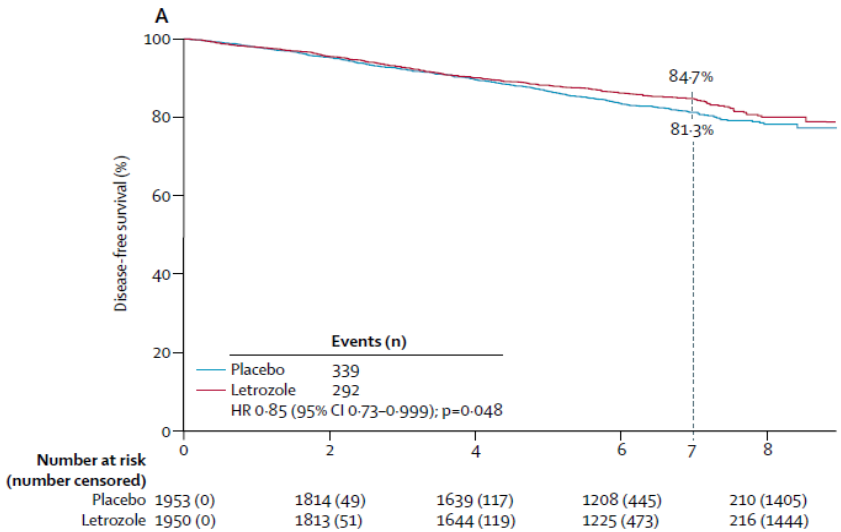
Motivating Example 1: COVID-19/ICU studies

Hospital data collected from 03/05/2020 to 07/17/2020 from 5 hospitals, the Johns Hopkins Medicine System.



In COVID-19/ICU studies, both "death" and "recovery" are important endpoints. The analysis of one single endpoint cannot reveal a complete story of the disease.

Motivating Example 2: Oncology trials



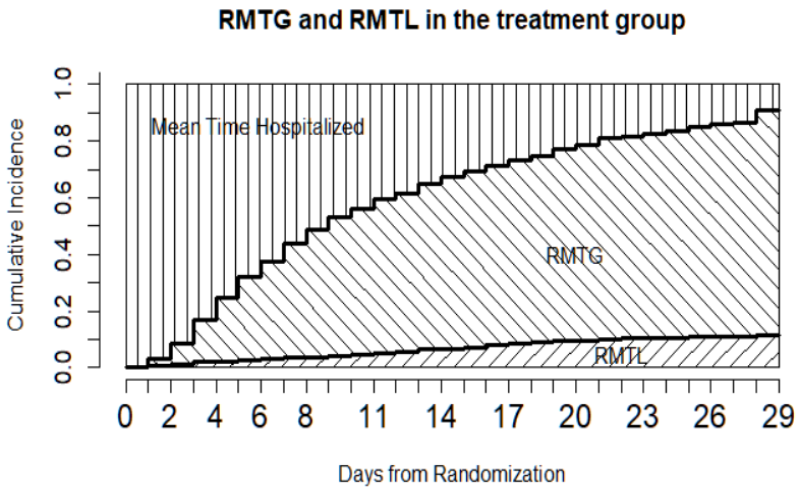
	Placebo group (n=1953)	Letrozole group (n=1950)
Distant recurrence	87 (4·5%)	61 (3·1%)
Local recurrence	33 (1·7%)	36 (1·8%)
Contralateral breast cancer	59 (3·0%)	30 (1·5%)
Second non-breast primary cancer	112 (5·7%)	104 (5·3%)
Death	48 (2·5%)	61 (3·1%)
Total first event	339 (17·4%)	292 (15·0%)
Alive, event free	1614 (82·6%)	1658 (85·0%)

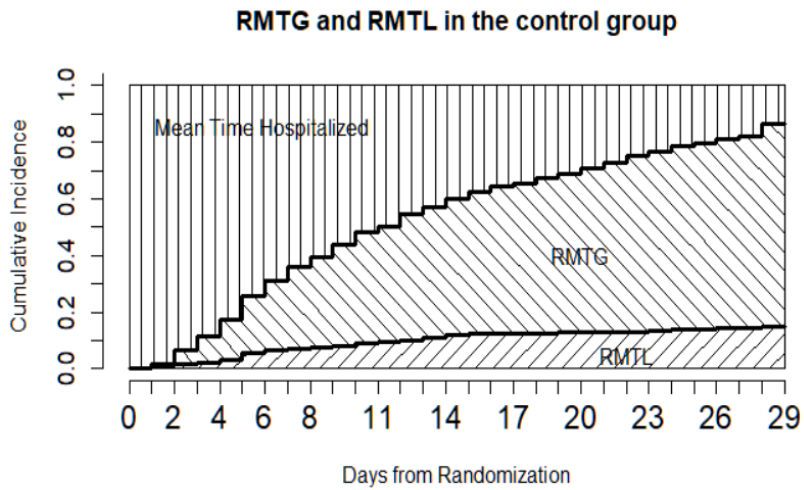
Data are n (%).

Table 2: Type of first events

- Novel interventions do not necessarily impact all components of a composite endpoint equally.
- Improvements (treatment effect) in breast cancer-specific outcomes would be "diluted" by the contribution of non-breast cancer deaths.

Restricted mean times (COVID-19 Example)





- Restricted Mean Time Gained (RMGT): area under CIF of discharge
  $\int_0^\tau F_1^{\text{sub}}(t)dt = \text{E}[\{\tau - T\} \times I(\eta = 1, T \leq \tau)]$
- Restricted Mean Time Lost (RMLT): area under CIF of death
  $\int_0^\tau F_2^{\text{sub}}(t)dt = \text{E}[\{\tau - T\} \times I(\eta = 2, T \leq \tau)]$
- Mean time Hospitalized: Measurement for healthcare resource utilization
  $\tau - \int_0^\tau F_1^{\text{sub}}(t)dt - \int_0^\tau F_2^{\text{sub}}(t)dt$

- Therefore we propose to use competing risks analysis and consider several endpoints simultaneously so that researchers can characterize different aspects of the disease progression at the same time and evaluate optimal treatments in the setting of clinical trials.
- We aim to develop joint hypothesis testing methods for competing risks data with two endpoints within restricted mean time analysis framework.

Joint inference of RMGT and RMLT

Denote RMGT as μ_1, RMLT as μ_2, and they can be estimated using Aalen-Johansen's estimator as $\hat{\mu}_j = \int_0^\tau \hat{F}_j(t)$.

The joint behaviors of the estimators are derived below:

Theorem

Under some regularity conditions, $\sqrt{n}\{\hat{\mu}_1 - \mu_1, \hat{\mu}_2 - \mu_2\}^T$ *has an asymptotically bivariate normal distribution with mean 0 and variance-covariance matrix* $\Sigma = (\sigma_{ij})$ *as* $n \to \infty$*, where* σ_{ij}*,* $i, j = 1, 2$ *can be found in the manuscript Appendix.*

In the clinical trials setting, let μ_{1k}, μ_{2k} denote RMTG and RMTL in group k, $k = 1, 2$ for control and treatment, respectively. We have proposed two joint hypothesis testing methods for

$$H_0 : \mu_{11} = \mu_{12} \text{ and } \mu_{21} = \mu_{22}$$

- Chi-Square Joint Test

$$X^2 = \left(\hat{\mu}_{11} - \hat{\mu}_{12}, \hat{\mu}_{21} - \hat{\mu}_{22}\right) \Sigma_c^{-1} \begin{pmatrix} \hat{\mu}_{11} - \hat{\mu}_{12} \\ \hat{\mu}_{21} - \hat{\mu}_{22} \end{pmatrix}$$

- Maximum Joint Test

$$T^* = max(|Z_1|, |Z_2|)$$

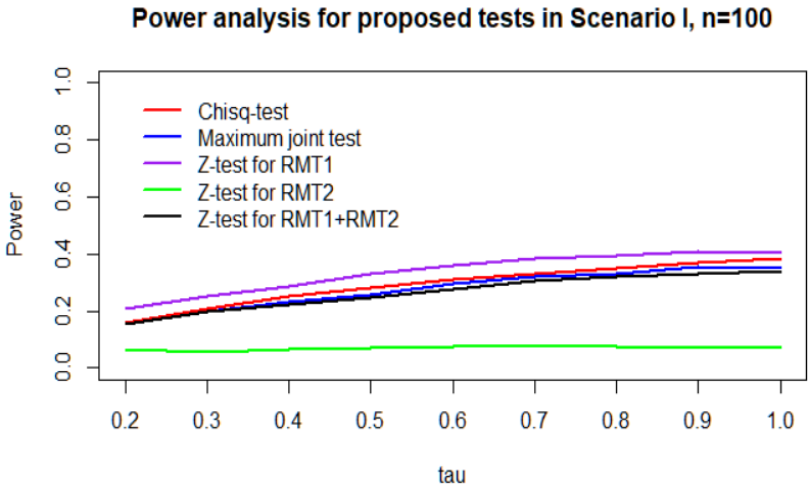
  in which Z_1 and Z_2 are standardized restricted mean differences.

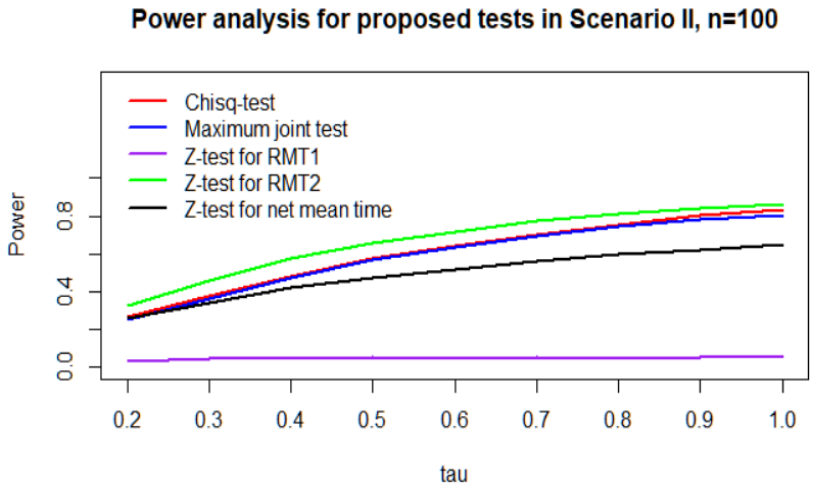
We can also perform Z test for linear combinations of restricted means.

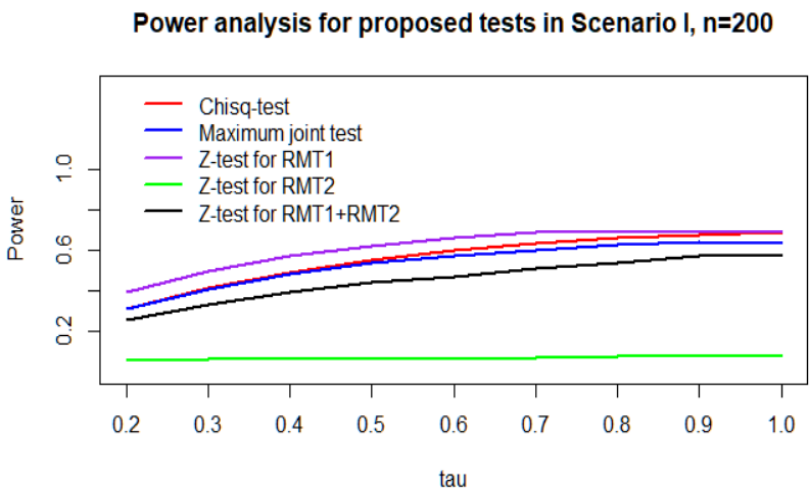
Simulation studies

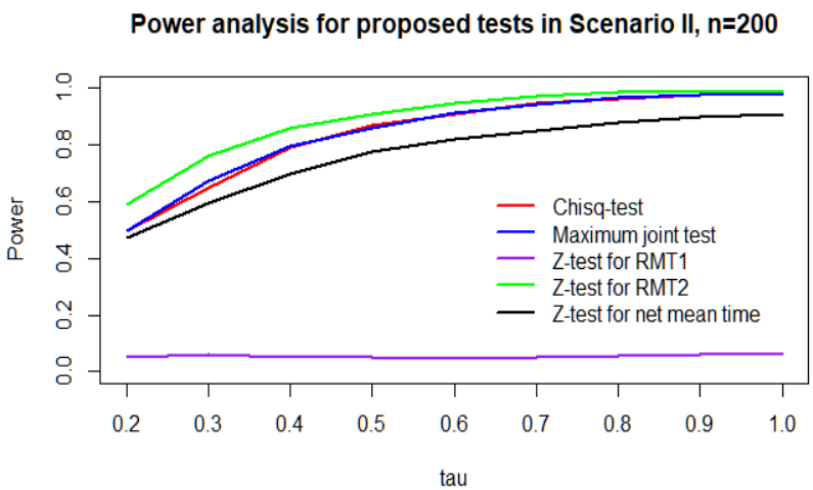
Monte Carlo simulations are used to evaluate the power of proposed test in clinical trials setting.

- Scenario I: Positively correlated competing risks data to mimic cancer trials.
- Scenario II: Negatively correlated competing risks data to mimic COVID-19 setting.
- Sample size is set to be 100, 200, 300.
- Censoring is introduced by uniform distribution to achieve 20% rate.
- Compare the power of proposed joint tests and Z tests.


Power analysis for proposed tests in Scenario I, n=100
Power
tau
Chisq-test
Maximum joint test
Z-test for RMT1
Z-test for RMT2
Z-test for RMT1+RMT2


Power analysis for proposed tests in Scenario II, n=100
Power
tau
Chisq-test
Maximum joint test
Z-test for RMT1
Z-test for RMT2
Z-test for net mean time


Power analysis for proposed tests in Scenario I, n=200
Power
tau
Chisq-test
Maximum joint test
Z-test for RMT1
Z-test for RMT2
Z-test for RMT1+RMT2


Power analysis for proposed tests in Scenario II, n=200
Power
tau
Chisq-test
Maximum joint test
Z-test for RMT1
Z-test for RMT2
Z-test for net mean time

ACTT-1 real data analysis

- Adaptive COVID-19 Treatment Trial (ACTT-1).
- A double-blind, randomized, placebo-controlled phase III trial.
- The aim is to evaluate intravenous remdesivir in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection.
- We apply the proposed testing methods to see the benefits of using remdesivir.

TABLE 1 Restricted mean time analysis in ACTT-1 Study

	Treatment group (days)	Control Group (days)
	Day 15	
Restricted Mean Time Lost (RMTL)	0.521 (0.342-0.700)	0.948 (0.708-1.188)
Difference (95% CI)	**0.427 (0.127-0.727), p-value=0.005**	
Restricted Mean Time Gained (RMTG)	5.254 (4.843-5.665)	3.888 (3.496-4.281)
Difference (95% CI)	**1.366 (0.798-1.934), p-value<0.0001**	
"Net" Mean Time Gained (RMTG-RMTL)	4.733 (4.249-5.216)	2.940 (2.432-3.448)
Difference (95% CI)	**1.793 (1.091-2.494), p-value<0.0001**	
Chi-square joint test	**χ^2=25.246, p-value<0.0001**	
Maximum joint test	**T^*=4.712, p-value<0.0001**	
	Day 29	
Restricted Mean Time Lost (RMTL)	1.896 (1.429-2.364)	2.808 (2.212-3.403)
Difference (95% CI)	**0.912 (0.154-1.668), p-value=0.018**	
Restricted Mean Time Gained (RMTG)	15.094 (14.261-15.928)	12.351 (11.502-13.201)
Difference (95% CI)	**2.743 (1.552-3.933), p-value<0.0001**	
"Net" Mean Time Gained (RMTG-RMTL)	13.198 (12.070-14.326)	9.543 (8.309-10.778)
Difference (95% CI)	**3.655 (1.982-5.327), p-value<0.0001**	
Chi-square joint test	**χ^2=20.537, p-value<0.0001**	
Maximum joint test	**T^*=4.516, p-value<0.0001**	

Conclusions and Discussion

- Joint asymptotic behaviors of restricted means in the competing risks settings are developed.
- Joint testing statistics are constructed.
- Simulations and data applications show the validity of our proposed methods.
- We perform secondary analysis of ACTT-1 data obtained from NIH. The diversity/equity is fully addressed in the design stage.
- Further topics can be joint modelling of cumulative incidence functions and account for diversity/equity by incorporating covariates.

Thank you!

References

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