

ICC IN TIME-TO-EVENT STUDY

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OBJECTIVES

- 1) How to estimate ICC
- 2) Impact of ICC (Power and Sample Size)

CONTEXT:

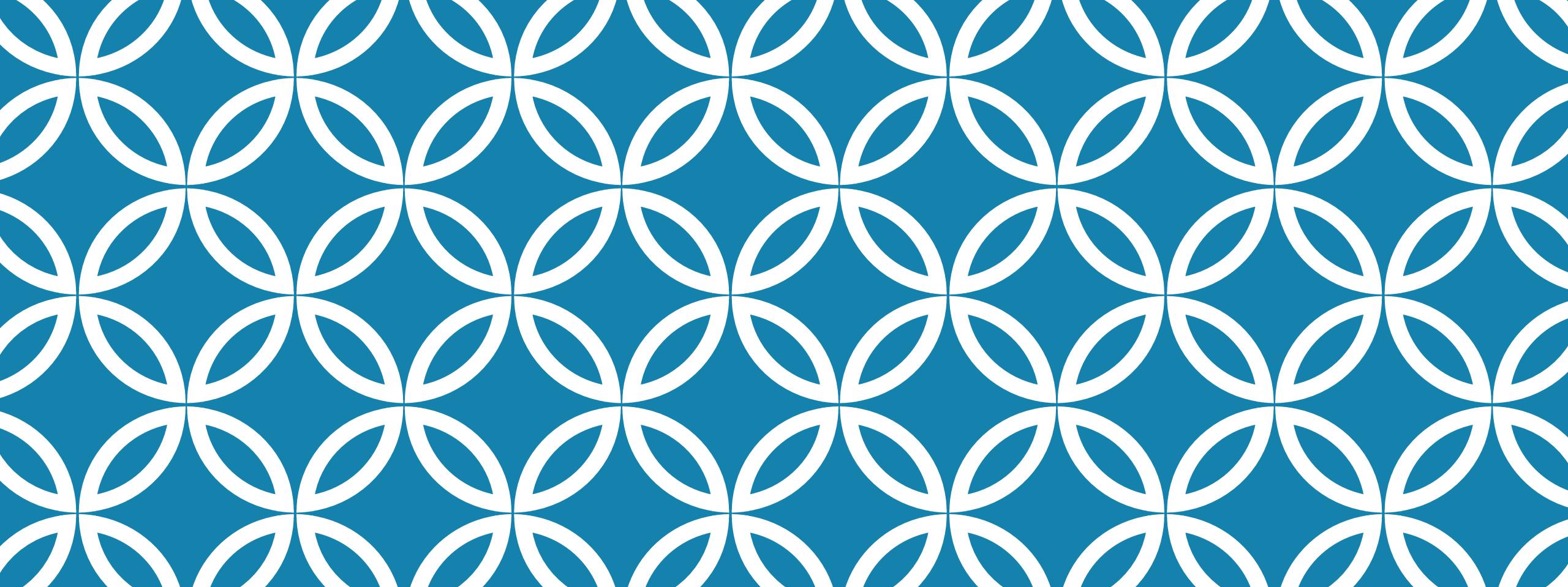
Intraclass Correlation Coefficient (ICC) quantifies the similarity between subjects belonging to the same cluster; higher values indicate greater correlation.

$$\text{ICC} = \frac{\text{Cluster variance}}{\text{Total variance}}$$

In **time-to-event data**, estimating the **ICC** is more complex due to:

- ◊ The **presence of censoring**
- ◊ The **non-Gaussian and often asymmetric distribution** of the outcome

Standard ICC estimation techniques require specific adaptations



PART 1: ESTIMATING ICC

METHODS FOR ESTIMATING ICC: LITERATURE REVIEW

The literature search began on PubMed using keywords such as '**ICC**' and '**time to event**', and was extended to references of selected papers (*backward citation searching*)

SUMMARY: ESTIMATION METHODS

#	Approach	Model type	ICC calculated from
1	Cox frailty	Cox + random frailty (Gamma / Log-normal)	Frailty variance relative to total variance
2	Parametric random effects	Weibull / Exponential + random intercept	Random intercept variance relative to total variance
3	Surrogate measures – Binary transformation	Dichotomized time-to-event / Discretize time	Between-cluster variance on the binary indicator relative to total variance (approximation)
4	Test/statistic-based: Log-rank based, KM	Variance of the log-rank test statistic or Kaplan–Meier estimator	Between- vs within-cluster variance of derived log-rank quantities (ANOVA)/of KM-based quantities

ESTIMATION METHODS - TABLE 1

N.	Paper	Method	Modeling Scale / Framework	Outcome Type	Approach #	Estimation type	ICC (ρ)	Notes
1	Williams (1995)	Analytical Log-Weibull formula	Log-time (a priori, theoretical)	Time-to-event	2	Closed-form	$\frac{\sigma_{\xi}^2}{\sigma_{\xi}^2 + \frac{\pi^2}{6\gamma^2}}$	Analytical ICC formula, used to simulate clustered survival data under a log-Weibull model
2	McCune (2025)	CoxME with Gaussian frailty	Log-hazard	Time-to-event	1/2	Regression / ML	$\frac{\sigma_{\text{random}}^2}{\sigma_{\text{random}}^2 + \frac{\pi^2}{6}}$	ICC derived from the random-effect variance in a Cox mixed-effects model with Gaussian frailty
3	McCune (2025)	Cox with Gamma frailty	Hazard	Time-to-event	1	Regression / ML	Estimated numerically via Laplace approximation	Non-parametric ICC estimated numerically via Laplace approximation
4A	McCune (2025) / Lam & Ip (2003)	GLMM (cloglog/logit) on discretized time	Log-hazard (discrete intervals)	Discrete-time survival	3	Regression / ML	$\frac{\sigma_{\text{random}}^2}{\sigma_{\text{random}}^2 + \frac{\pi^2}{6}}$ (cloglog) $\frac{\sigma_{\text{random}}^2}{\sigma_{\text{random}}^2 + \frac{\pi^2}{3}}$ (logit)	GLMM with random intercept on discretized survival intervals; link cloglog (McCune; Lam & Ip) or logit (Lam & Ip)
4B	McCune (2025)	CoxME on discretized time	Log-time	Discrete-time survival	3	Regression / ML	$\frac{\sigma_{\text{random}}^2}{\sigma_{\text{random}}^2 + \frac{\pi^2}{6}}$	CoxME model with Gaussian frailty on “exploded” discrete-time intervals

MSB = Mean Square Between groups - MSW = Mean Square Within groups

m = mean of patients for group - m_o = adjusted cluster size accounting for unequal cluster sizes

$\gamma^2 = 1$ in our example, proportional exponential risks

* codice già in parte in R

METODI DI STIMA DELL'ICC - TABELLA 2

N.	Paper	Method	Modeling Scale / Framework	Outcome Type	Approach #	Estimation type	ICC (ρ)	Notes
5	Kalia, Klar & Donner (2016)	Censoring indicators	Binary outcome	Binary	3	Regression / iterative	$\frac{MSB - MSW}{MSB + ((mo - 1) * MSW)}$	ANOVA-based ICC using 0/1 event indicators
6	Kalia, Klar & Donner (2016)	Observed event times	Event time	Time-to-event	3*	Regression / iterative	$\frac{MSB - MSW}{MSB + ((mo - 1) * MSW)}$	Based on ANOVA of observed event times, considering only uncensored events
7	Gagnon (2004)	Log-rank based	Martingale residuals from Cox	Time-to-event	4	Closed-form / ANOVA on residuals	Proportion of variance of log-rank statistic attributable to clusters	ICC derived from variance decomposition of log-rank statistic

MSB = Mean Square Between groups - MSB = Mean Square Between groups - MSW = Mean Square Within groups

m = mean of patients for group - m_o = adjusted cluster size accounting for unequal cluster sizes

$\gamma^2 = 1$ in our example, proportional exponential risks

* codice già in parte in R

METODI DI STIMA DELL'ICC - TABELLA 3

N.	Paper	Method	Modeling Scale / Framework	Outcome Type	Approach #	Estimation type	ICC (ρ)	Notes
8	Ying & Wei (1994)	Kaplan-Meier marginal survival functions	Survival probabilities within clusters	Time-to-event	4	Closed-form / ANOVA-type decomposition	Proportion of variance of KM-based quantities attributable to clusters	ICC from KM survival probabilities, accounts for censored data; fixed-effects approach
9	Oliveira et al. (2016)	Closed-form ICC from combined Weibull distribution with normal random effect	Time / Log-time (Weibull scale)	Time-to-event –	2	Closed-form / variance decomposition	$ICC = 1 - \xi$ Dove ξ rappresenta la parte di variabilità non dovuta al cluster (overdispersion)	ICC derived from variance decomposition of cluster and residual variability on the Weibull scale; ξ represents the proportion of variance not due to the cluster

MSB = Mean Square Between groups - MSW = Mean Square Within groups

m = mean of patients for group - m_o = adjusted cluster size accounting for unequal cluster sizes

$\gamma^2 = 1$ in our example, proportional exponential risks

* codice già in parte in R

IMPLEMENTATION IN R

Objective: compare different methods for estimating ICC

- ✓ Simulated cohort with reference ICC value
- ✓ Code implemented for each method
- ✓ ICC estimation for each approach
- ✓ Repetition across multiple scenarios

R CODE: COHORT GENERATION

```
# 1) Simulate survival cohort with NO interaction (hospital x treat) -----
#
# Input: ICC
#
# This function simulates a cohort of survival data with patients clustered
# within hospitals. The user provides:
#   - num_hosp      : number of hospitals (clusters)
#   - num_pat_group : number of patients per hospital
#   - icc          : intra-class correlation to define cluster effect
#   - pop_treat_effect : fixed treatment effect
#   - lambdas       : represents how frequently events occur
#   - gammas        : shape parameter (fixed to 1 for exponential baseline)
#   - maxt          : fixed 2*median
#
# Output: a data frame containing:
#   - id            : patient identifier
#   - hospital      : hospital/cluster identifier
#   - treat         : treatment assignment (0/1)
#   - eventtime     : observed survival/censoring time
#   - status         : event indicator (1=event, 0=censored)
#   - sigma_hosp    : standard deviation of hospital random effect
#   - cluster_eff   : hospital-specific random effect (frailty)
#
# Notes:
#   - Data simulation inspired by: Brilleman SL. "Simulating Survival Data Using the simsurv R Package"
#   - we use a weibull distribution (with gamma == 1, exponential) and a gaussian frailty term to model the cluster effect
#   - The hazard function assumes NO interaction between hospital and treatment:
#     
$$h_{ij}(t) = h_0(t) * \exp(\text{cluster\_eff}_j + \text{treat}_{ij} * \beta)$$

#     the treatment effect ( $\beta$ ) is the same across all hospitals.
#   - Sigma_hosp is derived from ICC using the inverse formula from Weibull & Williams (1995) e Crowder & Hand (1990).
#   - "funzioni altre" allow 1) specifying sigma_hosp for simulating
#     2) a model with treatment x hospital interaction: 
$$h_{ij}(t) = h_0(t) * \exp(\text{treat}_{ij} * (\beta + u_j))$$
 interaction model
#   - The maximum follow-up time (maxt) is chosen empirically (2x median expect) according to Klein & Moeschberger
#     ("Survival Analysis: Techniques for Censored and Truncated Data", 2nd edition, 2003)
```

R CODE

```
simulate_survival_cohort_no_interaction_icc <- function(num_hosp,
                                                       num_pat_group,
                                                       icc,
                                                       pop_treat_effect,
                                                       lambda,
                                                       gammas = 1,
                                                       maxt) {
  # Total number of patients
  tot_patients <- num_hosp * num_pat_group

  # Calculate residual variance for Weibull
  var_resid <- (pi^2) / (6 * gammas^2)

  # Calculate cluster effect variance from ICC
  sigma2_hosp <- abs((icc / (1 - icc)) * var_resid) ### from Williams 1995
  sigma_hosp <- sqrt(sigma2_hosp)

  # Covariates
  cov <- data.frame(
    id = 1:tot_patients,
    hospital = rep(1:num_hosp, each = num_pat_group),
    treat = rbinom(tot_patients, 1, 0.5))

  # Cluster effect for each hospital (random effect)
  cluster_effect <- rnorm(num_hosp, mean = 0, sd = sigma_hosp) ## gaussian frailty
  cov$cluster_eff <- cluster_effect[cov$hospital]

  # Betas: treatment effect and cluster_eff (= 1)
  beta <- c(treat = pop_treat_effect, cluster_eff = 1)

  # Simulate event times with "simsurv"
  dati_sopravvivenza <- simsurv(
    dist = "weibull",
    lambdas = lambda,
    gammas = gammas,
    x = cov[, c("treat", "cluster_eff")],
    betas = beta,
    maxt = 2*(log(2)/lambda)) ## maximum follow-up time; individuals with simulated event time > maxt will be right-censored

  # Merge covariates and simulated data
  coorte <- merge(cov, dati_sopravvivenza, by = "id")
  sigma_hosp <- rep(sigma_hosp, nrow(coorte))
  coorte <- cbind(coorte, sigma_hosp)
  coorte[] <- lapply(coorte, function(x) if(is.numeric(x)) round(x, 3) else x)
  return(coorte)}

#coorte <- simulate_survival_cohort_no_interaction_icc(icc= 0.01, pop_treat_effect = 0.3, num_pat_group = 20, num_hosp = 10, lambda = 0.01)
```

QUESTIONS

- ◊ Overall correctness of the procedure?
- ◊ Is it ok to use the LW estimate as the reference parameter for ICC?

```
simulate_survival_cohort_no_interaction_icc <- function(num_hosp,
  num_pat_group,
  icc,
  pop_treat_effect,
  lambda,
  gammas = 1,
  maxt) {

  # Total number of patients
  tot_patients <- num_hosp * num_pat_group

  # Calculate residual variance for weibull
  var_resid <- (pi^2) / (6 ^ gammas^2)

  # Calculate cluster effect variance from ICC
  sigma2_hosp <- abs(icc / (1 - icc)) * var_resid ### from Williams 1995
  sigma_hosp <- sqrt(sigma2_hosp)

  # Covariates
  cov <- data.frame(
    id = 1:tot_patients,
    hospital = rep(1:num_hosp, each = num_pat_group),
    treat = rbinom(tot_patients, 1, 0.5))

  # Cluster effect for each hospital (random effect)
  cluster_effect <- rnorm(num_hosp, mean = 0, sd = sigma_hosp) ## gaussian frailty
  cov$cluster_eff <- cluster_effect[cov$hospital]

  # Betas: treatment effect and cluster_eff (= 1)
  beta <- c(treat = pop_treat_effect, cluster_eff = 1)

  # Simulate event times with "simsury"
  dati_sopravvivenza <- simsury(
    dist = "weibull",
    lambdas = lambda,
    gammas = gammas,
    x = cov[, c("treat", "cluster_eff")],
    betas = beta,
    maxt = 2*(log(2)/lambda)) ## maximum follow-up time; individuals with simulated event time > maxt will be right-censored

  # Merge covariates and simulated data
  coorte <- merge(cov, dati_sopravvivenza, by = "id")
  sigma_hosp <- rep(sigma_hosp, nrow(coorte))
  coorte <- cbind(coorte, sigma_hosp)
  coorte[] <- lapply(coorte, function(x) if(is.numeric(x)) round(x, 3) else x)
  return(coorte)

#coorte <- simulate_survival_cohort_no_interaction_icc(icc= 0.01, pop_treat_effect = 0.3, num_pat_group = 20, num_hosp = 10, lambda = 0.01)
```

SIMULATED DATA

id	hospital	treat	cluster_eff	eventtime	status	sigma_hosp
1	1	1	0.289	55.856	1	0.129
2	2	1	0.289	4.360	1	0.129
3	3	1	0.289	11.732	1	0.129
4	4	1	0.289	82.054	1	0.129
5	5	1	0.289	126.850	1	0.129
6	6	1	0.289	83.011	1	0.129
7	7	1	0.289	12.725	1	0.129
8	8	1	0.289	138.629	0	0.129
9	9	1	0.289	15.164	1	0.129
10	10	1	0.289	60.993	1	0.129
11	11	1	0.289	35.571	1	0.129
12	12	1	0.289	138.629	0	0.129
13	13	1	0.289	10.031	1	0.129
14	14	1	0.289	82.115	1	0.129
15	15	1	0.289	81.185	1	0.129
16	16	1	0.289	74.188	1	0.129
17	17	1	0.289	54.614	1	0.129
18	18	1	0.289	3.165	1	0.129
19	19	1	0.289	1.362	1	0.129
20	20	1	0.289	18.738	1	0.129
21	21	2	0.019	18.946	1	0.129
22	22	2	0.019	14.494	1	0.129
23	23	2	0.019	57.838	1	0.129
24	24	2	0.019	14.077	1	0.129
25	25	2	0.019	138.629	0	0.129

R CODE: ESTIMATING ICC + CI

```
# 2 Estimated ICC -----
# ICC is estimated using 10 methods from the literature, applied to a simulated cohort

| icc_estimation <- function(data) {

  # Method 1 - weibull - goal standard

  sigma2_xi <- unique(data$sigma_hosp)^2
  gamma_val <- 1
  var_epsilon <- pi^2 / (6 * gamma_val^2)

  # 3) Bootstrap ICC -----
  # This bootstrap samples entire clusters (e.g., hospitals) with replacement.
  # For each selected cluster, all subjects belonging to that cluster are included.
  # The ICC is calculated on each bootstrap dataset.

  bootstrap_icc <- function(data, B = 100, cluster_var = "hospital") {

    boot_results <- vector("list", B)

    # Cluster
    clusters <- unique(data[[cluster_var]])

    for (b in 1:B) {
      # --- Resampling for cluster ---
      sampled_clusters <- sample(clusters, length(clusters), replace = TRUE)

      # Assign unique cluster IDs to duplicated clusters to preserve all rows
      data_boot <- do.call(rbind, lapply(sea along sampled_clusters). function(i) {
```

Question/doubts: *review with someone the R codes for estimating ICC*

SIMULATED SCENARIOS

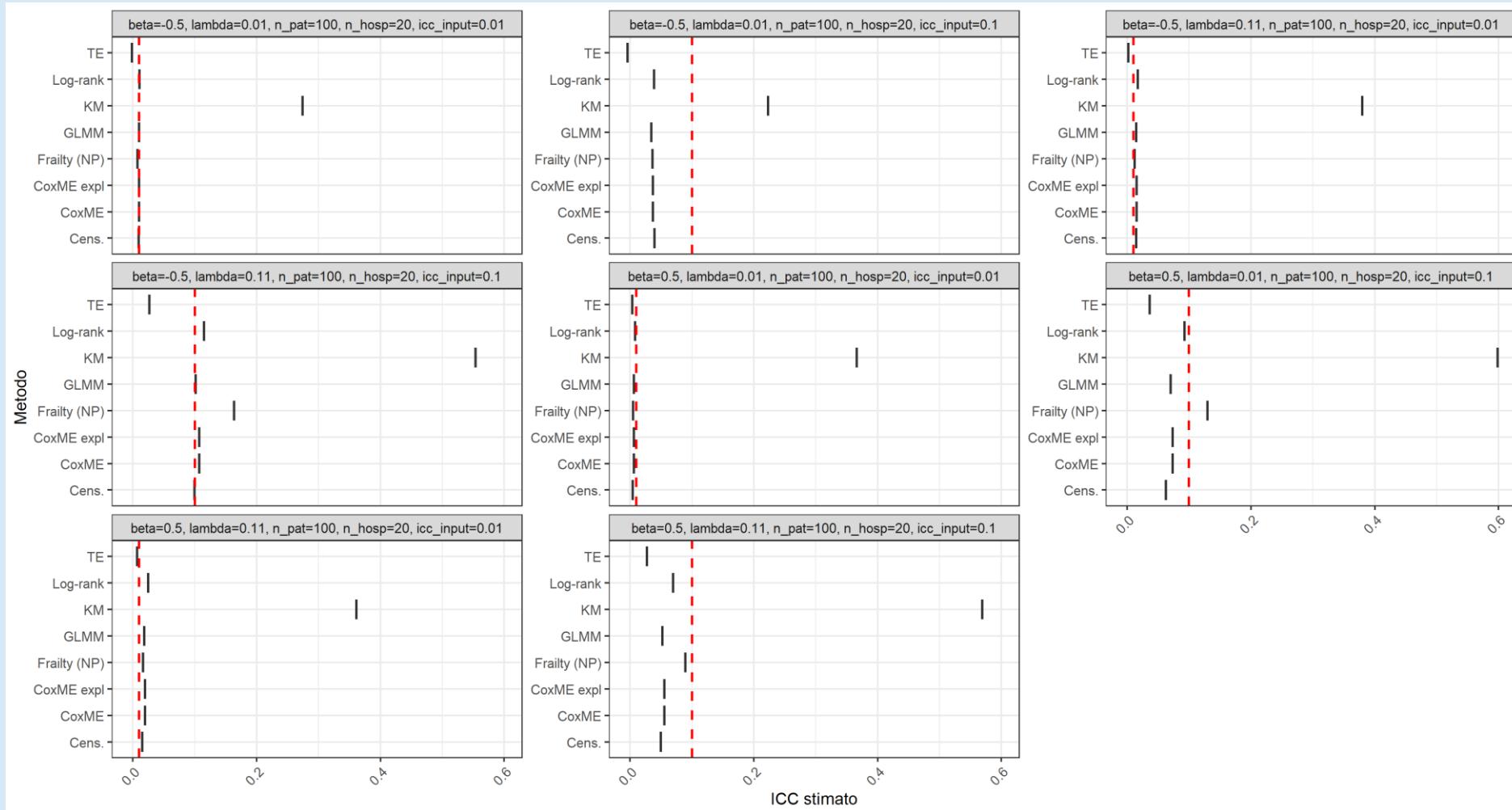
Beta (treatment effect)	Lambda	# patients for group (m)	# hospital	ICC
- 0,5 , 0,5	0.11, 0,1	100	20	0.01, 0.05, 0.1, 0.2
HR: 0.61, 1.65	Median 6 ; 60 months	-	-	-

Question: what other scenarios are useful to evaluate?

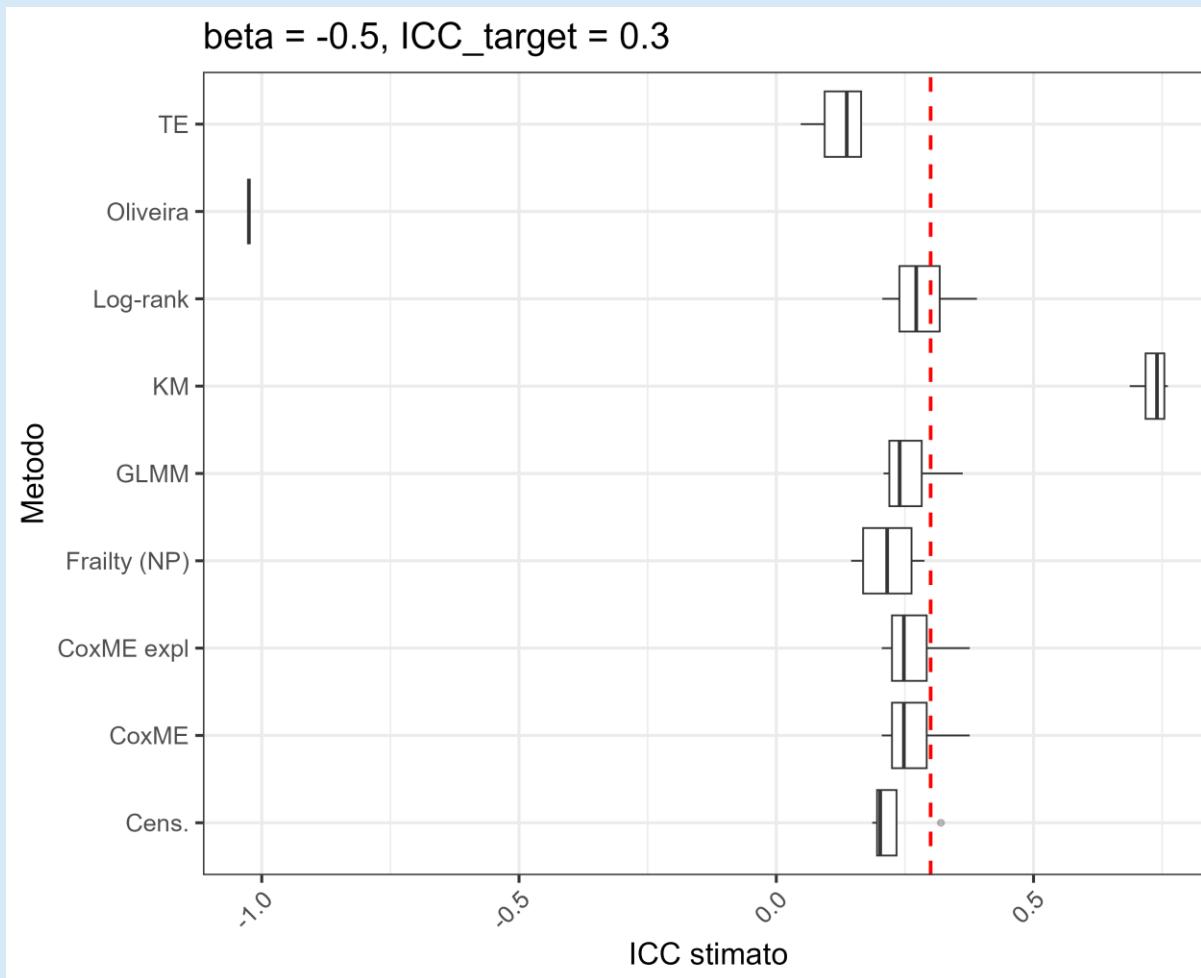
RESULTS - TABLE

	Method	Mean	SD	CI_low	CI_high	beta	lambda	num_pat_group	num_hosp	icc_input
1	weibull - goal standard	0.010000000	0.000000000	0.010000	0.010000	-0.5	0.11	100	20	0.01
2	CoxME Gaussian frailty	0.015400000	0.003589458	0.008950	0.020575	-0.5	0.11	100	20	0.01
3	Cox gamma frailty (NP)	0.012250000	0.003126710	0.006950	0.017525	-0.5	0.11	100	20	0.01
4	GLMM cloglog discretized	0.014850000	0.003773523	0.008475	0.020525	-0.5	0.11	100	20	0.01
5	CoxME discretized time	0.015400000	0.003589458	0.008950	0.020575	-0.5	0.11	100	20	0.01
6	Censoring indicators	0.014700000	0.005120650	0.006425	0.023625	-0.5	0.11	100	20	0.01
7	Observed event times	0.001800000	0.007445239	-0.007525	0.017000	-0.5	0.11	100	20	0.01
8	Log-rank based	0.017000000	0.003612843	0.010425	0.022050	-0.5	0.11	100	20	0.01
9	Kaplan-Meier ICC	0.380000000	0.038751570	0.310300	0.434300	-0.5	0.11	100	20	0.01
10	Oliveira	-0.017000000	0.000000000	-0.017000	-0.017000	-0.5	0.11	100	20	0.01
11	weibull - goal standard	0.010000000	0.000000000	0.010000	0.010000	0.5	0.11	100	20	0.01
12	CoxME Gaussian frailty	0.019650000	0.005234250	0.012475	0.029000	0.5	0.11	100	20	0.01
13	Cox gamma frailty (NP)	0.016650000	0.004826190	0.010000	0.026050	0.5	0.11	100	20	0.01
14	GLMM cloglog discretized	0.018600000	0.004870967	0.011950	0.026525	0.5	0.11	100	20	0.01
15	CoxME discretized time	0.019650000	0.005234250	0.012475	0.029000	0.5	0.11	100	20	0.01
16	Censoring indicators	0.015450000	0.004334379	0.008425	0.022525	0.5	0.11	100	20	0.01
17	Observed event times	0.006950000	0.004718106	-0.001625	0.014525	0.5	0.11	100	20	0.01
18	Log-rank based	0.024900000	0.006520413	0.015950	0.036050	0.5	0.11	100	20	0.01
19	Kaplan-Meier ICC	0.361400000	0.046300392	0.292025	0.439500	0.5	0.11	100	20	0.01
20	Oliveira	-0.017000000	0.000000000	-0.017000	-0.017000	0.5	0.11	100	20	0.01
21	weibull - goal standard	0.010000000	0.000000000	0.010000	0.010000	-0.5	0.01	100	20	0.01
22	CoxME Gaussian frailty	0.009700000	0.005795643	0.000950	0.019525	-0.5	0.01	100	20	0.01
23	Cox gamma frailty (NP)	0.007350000	0.004976524	0.000000	0.015000	-0.5	0.01	100	20	0.01
24	GLMM cloglog discretized	0.009789474	0.005513407	0.001450	0.018550	-0.5	0.01	100	20	0.01
25	CoxME discretized time	0.009700000	0.005795643	0.000950	0.019525	-0.5	0.01	100	20	0.01
26	Censoring indicators	0.009100000	0.006766014	-0.001575	0.021100	-0.5	0.01	100	20	0.01
27	Observed event times	0.001200000	0.002706717	0.005525	0.002575	0.5	0.01	100	20	0.01

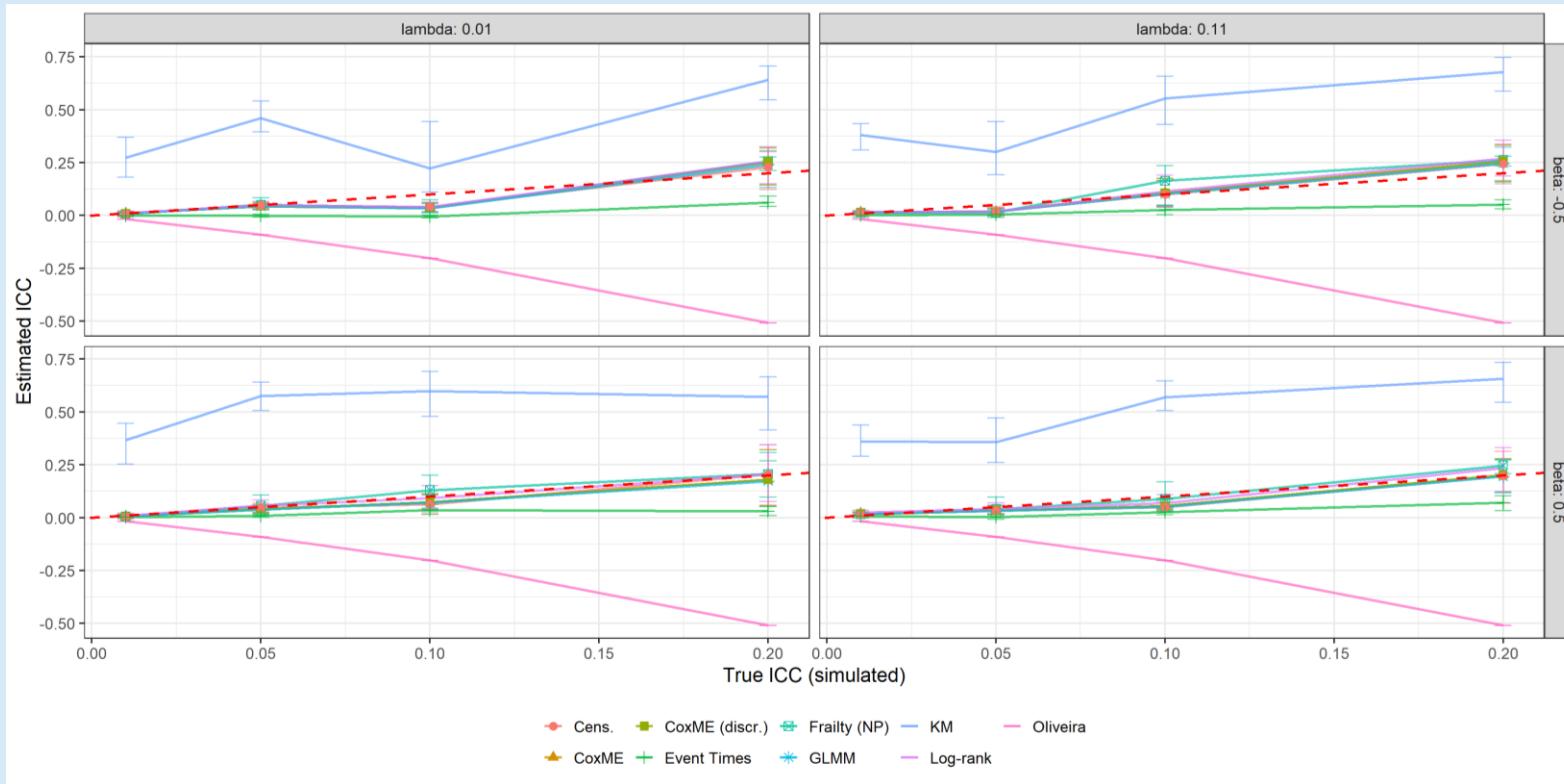
RESULTS - GRAPH 1



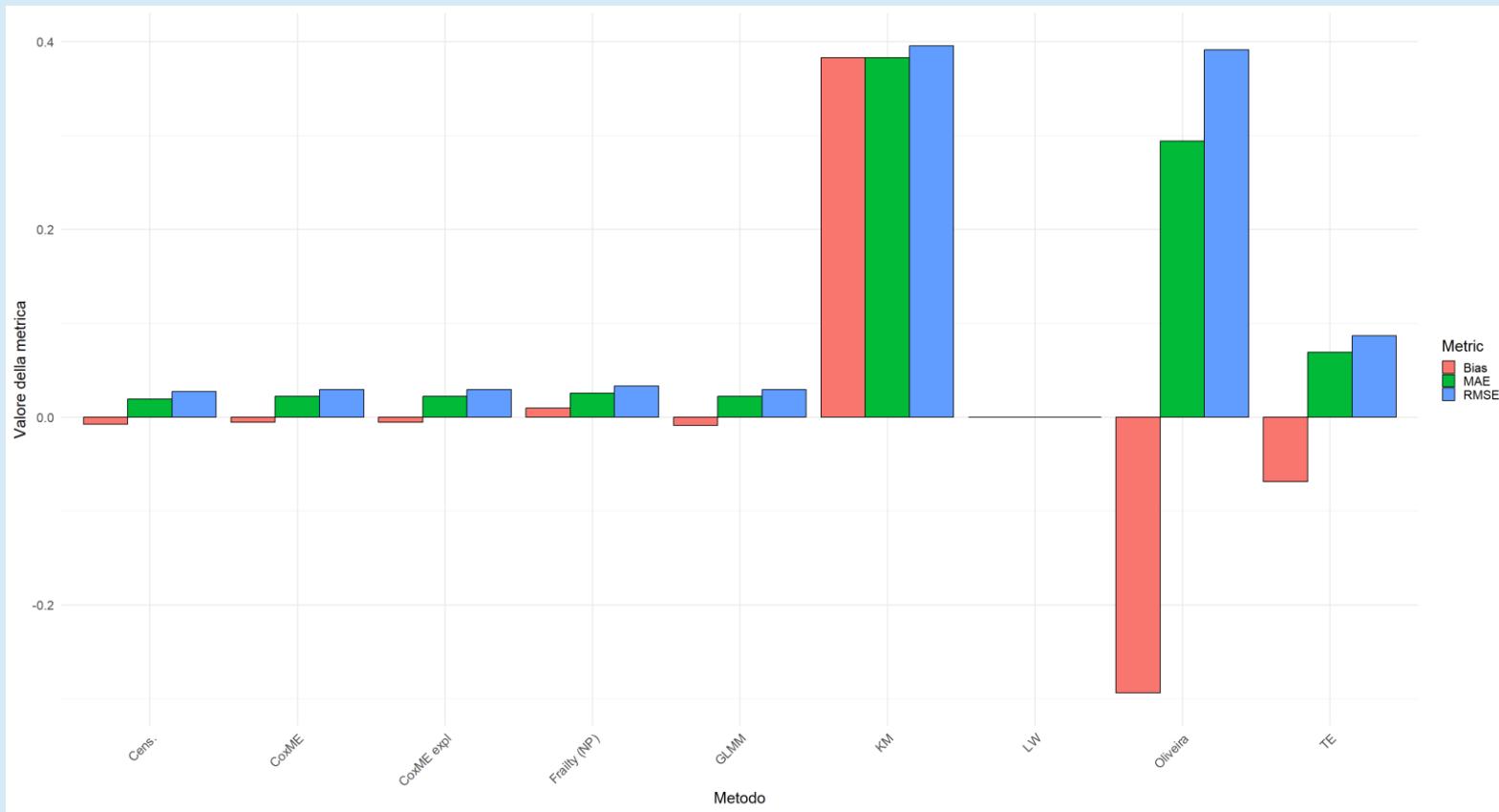
RESULTS - GRAPH 2



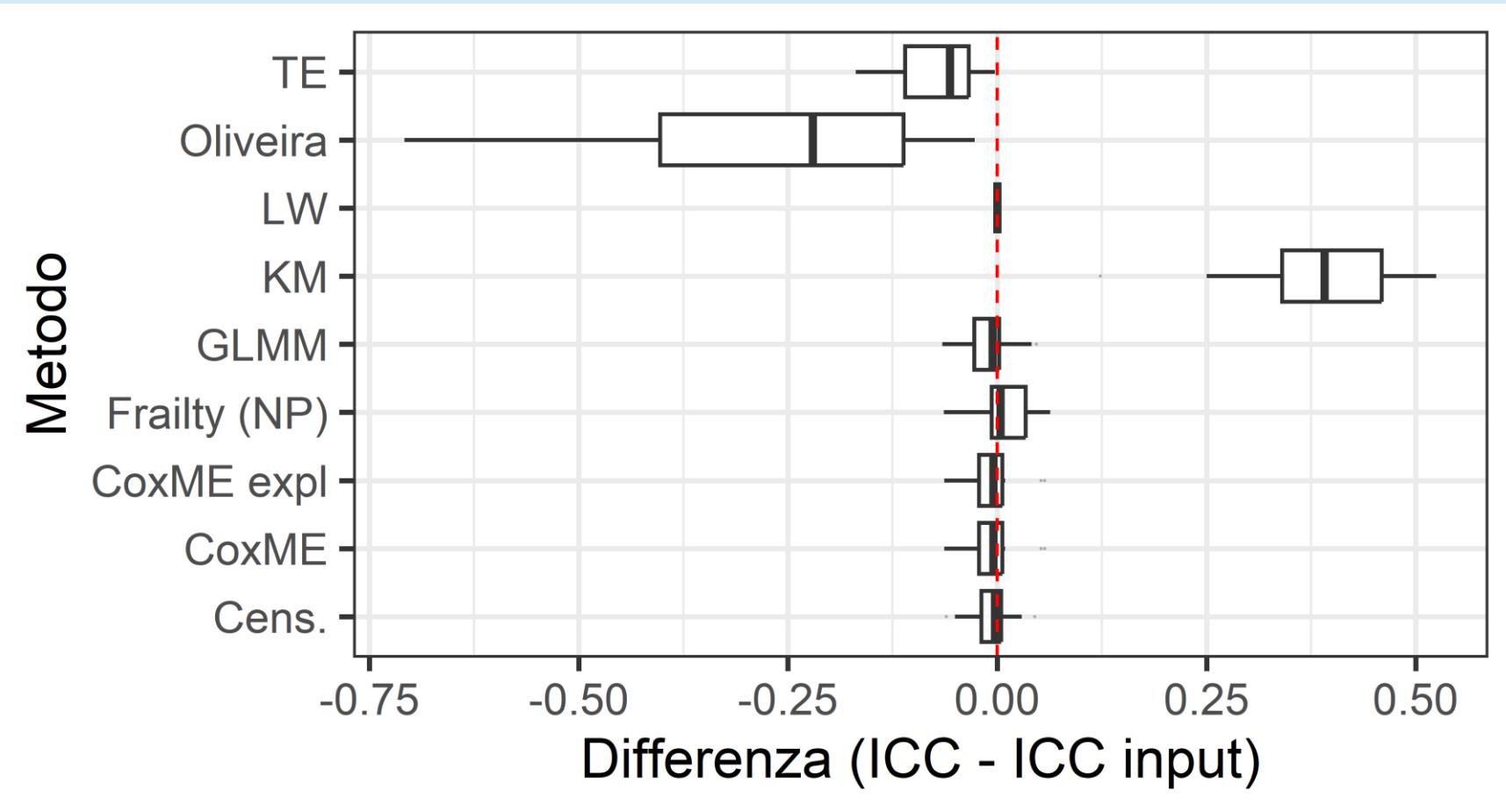
RESULTS - GRAPH 3

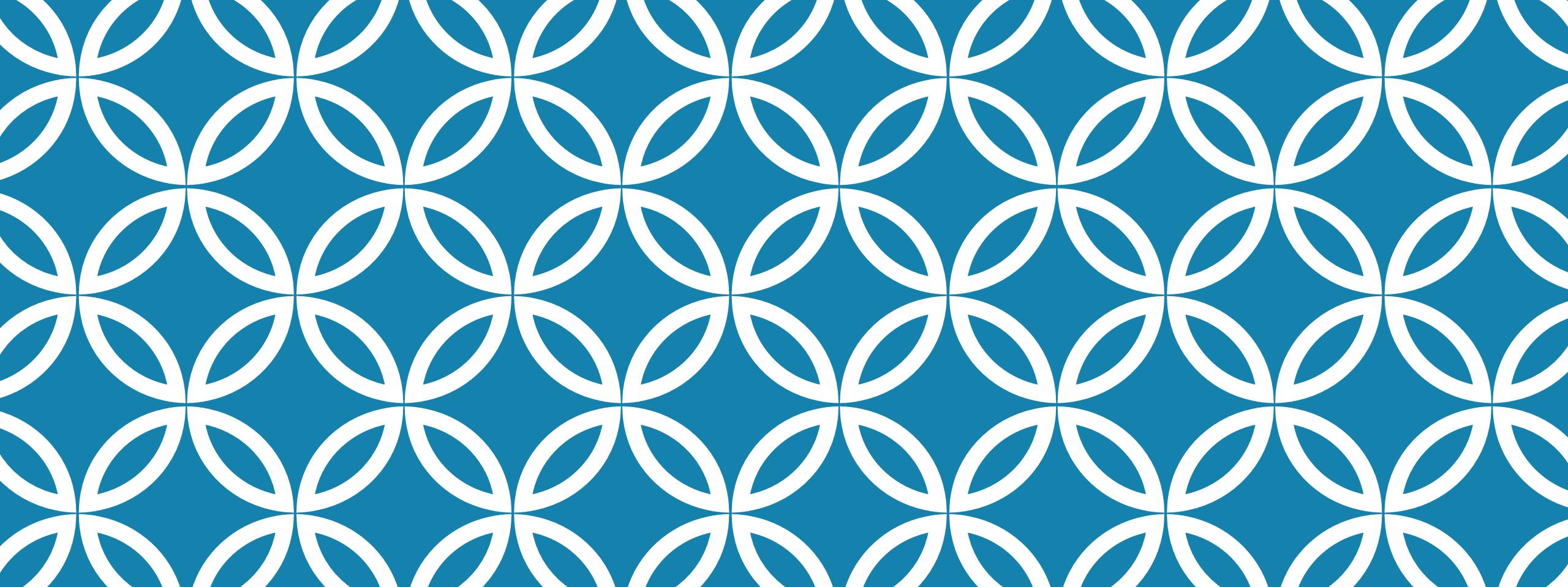


RESULTS - GRAPH 4



RESULTS - GRAPH 5





PART 2: PRACTICAL IMPLICATIONS

ICC – PRACTICAL IMPLICATIONS

- ◊ A high ICC reduces effective independent information
- ◊ Increases the sample size needed to maintain the same power
- ◊ It is crucial to consider it in trial planning

? How ICC impacts time-to-event data on:

- Statistical power
- Sample size

CORRECTION FOR ICC

$$n_{corr} = n \times DE$$

$$DE = 1 + (m - 1) \times ICC$$

Where:

- n_{corr} = corrected sample
- m = number of subjects per cluster
- ICC = intraclass correlation coefficient

ADJUSTING FOR ICC

Often the ICC is not known *a priori*. Possible strategies:

- ◊ Use data from previous pilot studies
- ◊ Refer to published estimates in the literature
- ◊ Conduct simulations to explore plausible scenarios

ICC VALUES FROM LITERATURE

Study	Design Type	Cluster Type	Outcome Type	ICC Value	Outcome Type
Ouyang et al. (2024)	Observational	Hospital Service Areas	Time-to-event (mortality, hospitalization, ED visits)	Median (IQR) Mortality: 0.001 (0, 0.002), Hospitalization: 0.010 (0.003, 0.023) ED Visit 0.017 (0.006, 0.052)	Clinical
Patton et al. (2020)	Observational	Hospitals	Surgical practice intensity	Mean (SD) Orthopedic: 0.14 (0.12, 0.20) Thoracic: 0.027 (0.17, 0.31), Neurotrauma: 0.008 (0.008, 0.012)	Processes
Haddad et al. (2012)	Observational	Hospitals	Severe maternal morbidity	Median (range) Total: 0.035 (< 0.001 to 0.508) Outcomes: 0.021 (< 0.001, 0.375 Process: 0.09 (0.001, 0.508)	Mixed
Vierron & Giraudeau (2007)	Secondary analysis (3 RCTs)	Hospitals	Treatment response, pain/disability measures, symptom improvement	Range: 0.08 – 0.16	Clinical
Adams et al. (2004)	Review + Secondary analysis 31 Study (19 RCTs)	Primary care organizations/ Physician	Vital signs and questionnaire health measures	Median (IQR): 0.010 (0, 0.032)	Clinical
Eldridge et al. (2004)	Review	Primary care organizations/ Physician	Primary care methods or outcomes	Median (IQR): 0.04 (0, 0.21)	Mixed
Gulliford et al. (1999)	Cross-sectional	District Health Authority	Health outcomes	. Most ICCs were below 0.01 Range: <0.01,	Clinical
Rysavy et al. (2015)	Observational, prospective cohort	Hospitals	Survival in preterm infants	Range: 0.03-0.13	Clinical
Thomson et al. (2001)	Observational, prospective cohort (Secondary analysis)	Primary care organizations	Practice variable	Range: 0.04 – 0.29	Processes
Jaiswal et al. (2025)	Observational	State & District	Under-five mortality	Range: 0.02 -0.05	Clinical
Pagel et al. (2011)	Observational / Cluster RCT	Communities	Mortality & Health Service	Mortality: 0–0.0034; Health Service: 0.021–0.154	Mixed

SIMULATION: ICC AND POWER

Regarding #2 ICC is usually small in human studies, typically between 0.01 and 0.02

Regarding #3 Simulation scenarios:

Beta (treatment effect)	Lambda	Patient for group (m)	# hospital	ICC
- 0,5 , 0,5	0.11, 0,1	20, 100	10, 50	0.01, 0.05, 0.1, 0.15, 0.2, 0.3, 0.4
HR: 0.61, 1.65	Median 6 ; 60 months	-	-	-

Question: what other scenarios are useful to evaluate?

R CODE – POWER

```
# -----
# FUNCTION: surv_power_function_def
# PURPOSE: Estimate statistical power for a survival study using Monte Carlo
#           simulations, both with and without accounting for clustering (ICC).
#
# HOW IT WORKS:
# 1. Generates 'nsim' simulated cohorts using the provided simulation function.
# 2. For each cohort, fits two Cox proportional hazards models:
#     - with clustering at the hospital level (coxph + cluster(hospital))
#     - without clustering (standard Cox model)
# 3. Records p-values for the treatment effect and counts how many simulations
#     are statistically significant ( $p < 0.05$ ).
# 4. Calculates:
#     - potenza_icc: proportion significant in the clustered model
#     - potenza_noicc: proportion significant in the unclustered model
#     - power_corrected_ICC: adjusted power accounting for the DE
#       starting from potenza_noicc (??)
# 5. Returns a tibble with the estimated powers, sample sizes, and other
#     relevant simulation details.
# -----
```

R CODE

Questions/doubts:

- ◊ The ICC_corr power should be smaller, but this is not observed...
- ◊ Is the DE correction correct?
- ◊ What “power” should I set in the power calculation?

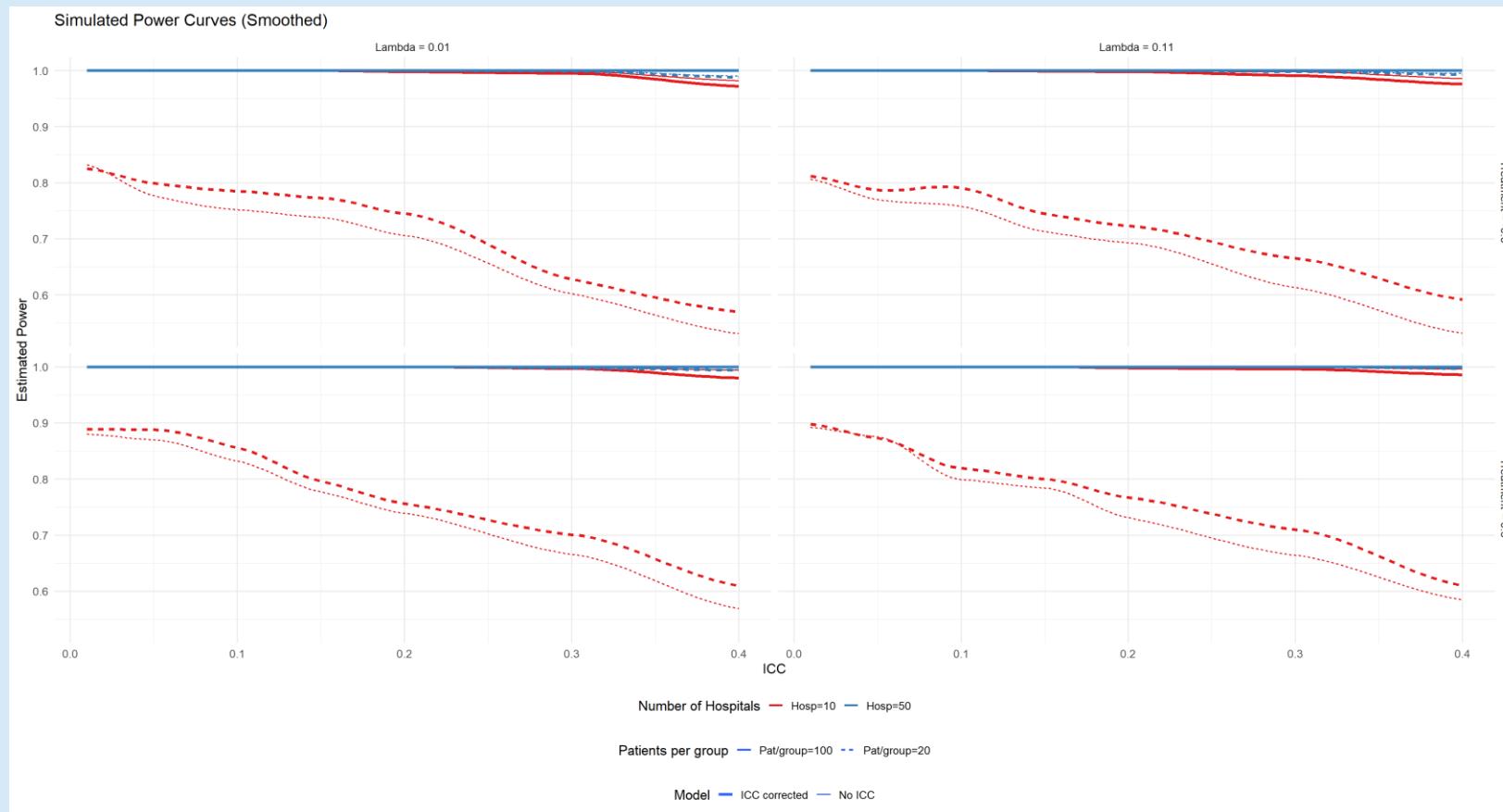
$$\text{Power}_{\text{corrected}} = \text{Power}_{\text{raw}} \cdot \sqrt{\frac{1}{DEFF}}$$

```
surv_power_function_def <- function(simula_coorte_fun, simula_args = list(),  
                                     nsim = 100) {  
  
  p_values_icc <- numeric(nsim)  
  significativi_icc <- logical(nsim)  
  
  p_values_noicc <- numeric(nsim)  
  significativi_noicc <- logical(nsim)  
  
  for (i in 1:nsim) {  
    coorte <- do.call(simula_coorte_fun, simula_args) # Genera coorte  
  
    if (i == 1) {  
      sigma_hosp <- unique(coorte$sigma_hosp)  
      icc <- simula_args$icc %||% 0 # prendi icc dagli argomenti  
      num_hosp <- length(unique(coorte$hospital))  
      num_pat_group <- nrow(coorte) / num_hosp  
      sample_size <- nrow(coorte) }  
  
    # Modello di Cox con e senza correzione cluster  
    mod_icc <- coxph(Surv(eventtime, status) ~ treat + cluster(hospital), data = coorte)  
    mod_noicc <- coxph(Surv(eventtime, status) ~ treat, data = coorte)  
  
    # p-value modello con ICC  
    p_val_icc <- summary(mod_icc)$coefficients["treat", "Pr(>|z|)"]  
    p_values_icc[i] <- p_val_icc  
    significativi_icc[i] <- p_val_icc < 0.05  
  
    # p-value modello senza ICC  
    p_val_noicc <- summary(mod_noicc)$coefficients["treat", "Pr(>|z|)"]  
    p_values_noicc[i] <- p_val_noicc  
    significativi_noicc[i] <- p_val_noicc < 0.05  
  
    # calcolo potenze  
    potenza_icc <- mean(significativi_icc)  
    potenza_noicc <- mean(significativi_noicc)  
  
    # correzione per DE  
    sample_size_corrected <- ceiling(sample_size * (1 + (num_pat_group - 1) * icc))  
    ## ss per avere potenza modello noicc  
    power_corrected_ICC <- potenza_noicc * sqrt(sample_size / sample_size_corrected)
```

RESULTS - TABLE

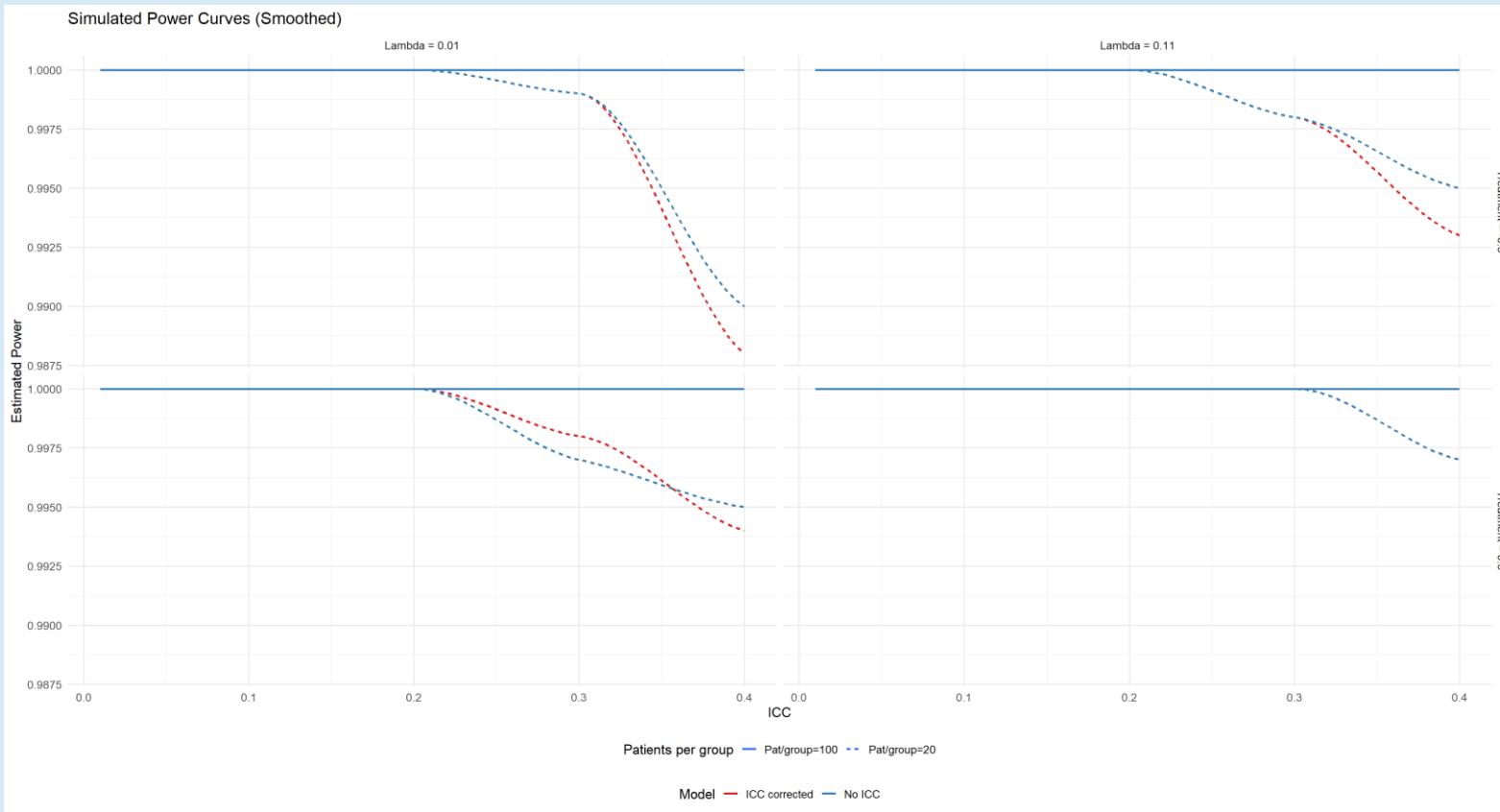
	nsim	icc	num_hosp	num_pat_group	sample_size	potenza_icc	potenza_noicc	power_corrected_ICC	sample_size_corrected	pop_treat_effect	lambda
1	1000	0.01	10	20	200	0.825	0.832	0.7626931	238	-0.5	0.01
2	1000	0.01	10	100	1000	1.000	1.000	0.7088812	1990	-0.5	0.01
3	1000	0.01	50	20	1000	1.000	1.000	0.9166985	1190	-0.5	0.01
4	1000	0.01	50	100	5000	1.000	1.000	0.7088812	9950	-0.5	0.01
5	1000	0.05	10	20	200	0.799	0.777	0.5557093	391	-0.5	0.01
6	1000	0.05	10	100	1000	1.000	1.000	0.4099600	5950	-0.5	0.01
7	1000	0.05	50	20	1000	1.000	1.000	0.7159313	1951	-0.5	0.01
8	1000	0.05	50	100	5000	1.000	1.000	0.4099600	29750	-0.5	0.01
9	1000	0.10	10	20	200	0.785	0.752	0.4412094	581	-0.5	0.01
0	1000	0.10	10	100	1000	1.000	1.000	0.3028913	10900	-0.5	0.01
1	1000	0.10	50	20	1000	1.000	1.000	0.5871190	2901	-0.5	0.01
2	1000	0.10	50	100	5000	1.000	1.000	0.3028913	54500	-0.5	0.01
3	1000	0.15	10	20	200	0.773	0.738	0.3761196	770	-0.5	0.01
4	1000	0.15	10	100	1000	1.000	1.000	0.2511802	15850	-0.5	0.01
5	1000	0.15	50	20	1000	1.000	1.000	0.5096472	3850	-0.5	0.01
6	1000	0.15	50	100	5000	1.000	1.000	0.2511802	79250	-0.5	0.01
7	1000	0.20	10	20	200	0.745	0.706	0.3220757	961	-0.5	0.01
8	1000	0.20	10	100	1000	0.998	0.999	0.2190452	20800	-0.5	0.01
9	1000	0.20	50	20	1000	1.000	1.000	0.4563879	4801	-0.5	0.01
0	1000	0.20	50	100	5000	1.000	1.000	0.2192645	104000	-0.5	0.01
1	1000	0.30	10	20	200	0.628	0.602	0.2325729	1340	-0.5	0.01
2	1000	0.30	10	100	1000	0.995	0.998	0.1801198	30700	-0.5	0.01
3	1000	0.30	50	20	1000	0.999	0.999	0.3859474	6700	-0.5	0.01
4	1000	0.30	50	100	5000	1.000	1.000	0.1804807	153500	-0.5	0.01
5	1000	0.40	10	20	200	0.570	0.531	0.1810169	1721	-0.5	0.01
6	1000	0.40	10	100	1000	0.972	0.982	0.1541163	40600	-0.5	0.01
-	1000	0.40	50	20	200	0.000	0.000	0.0000000	0.001	0.5	0.01

RESULTS - GRAPH 1



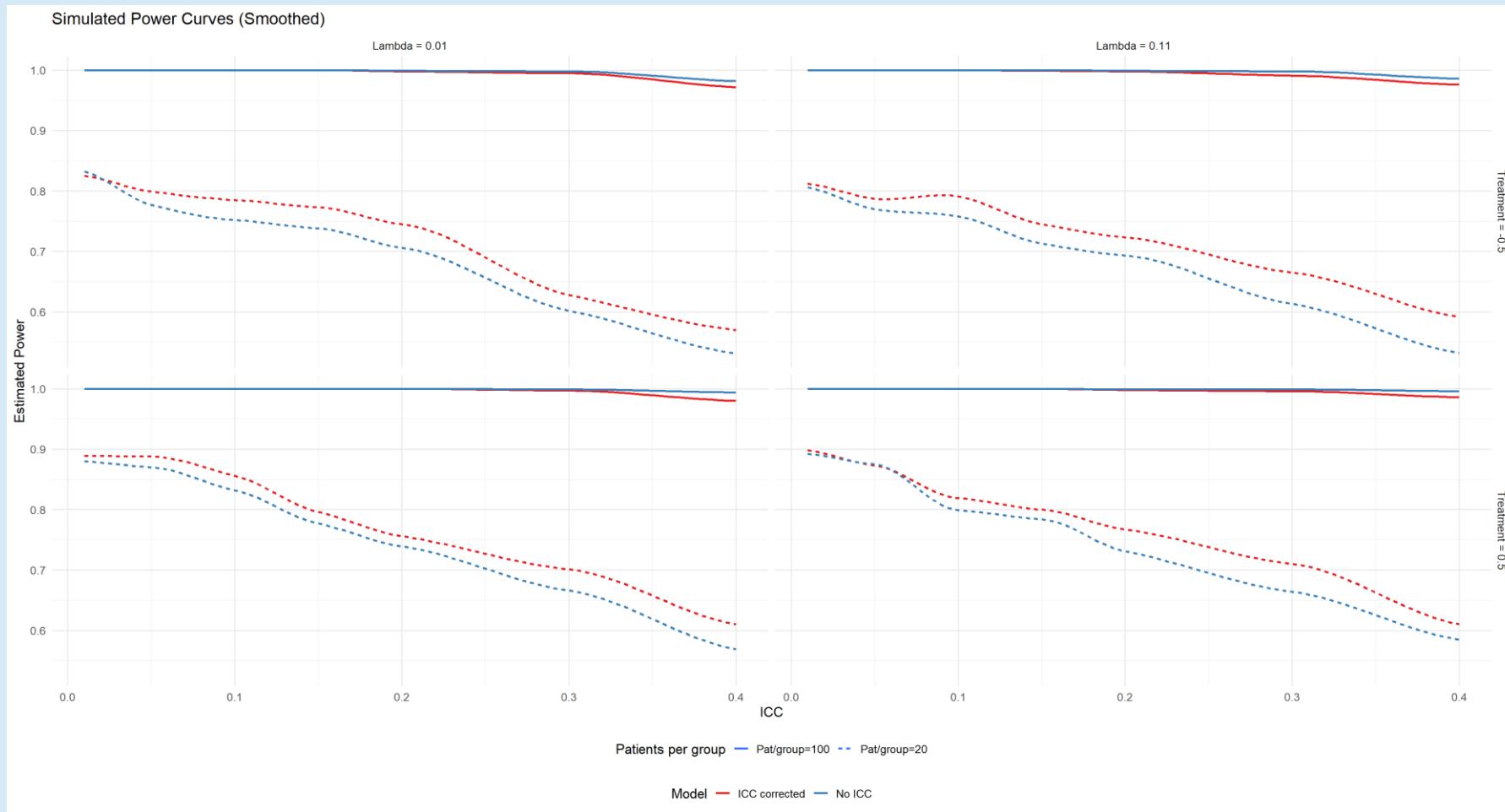
Question: Shouldn't the “corrected ICC” power be lower?

RESULTS - GRAPH 2

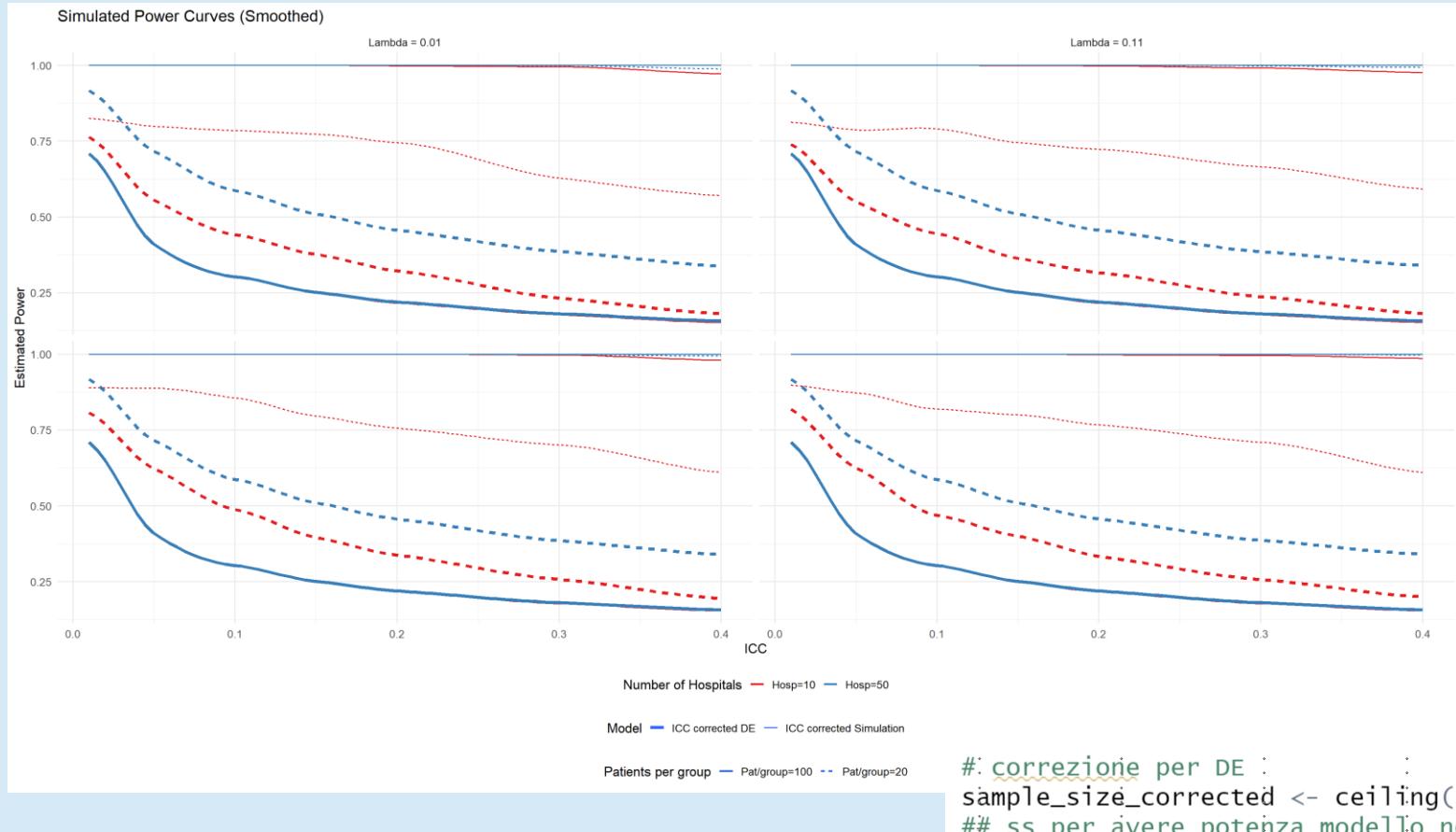


50 OSPEDALI

RESULTS - GRAPH 3



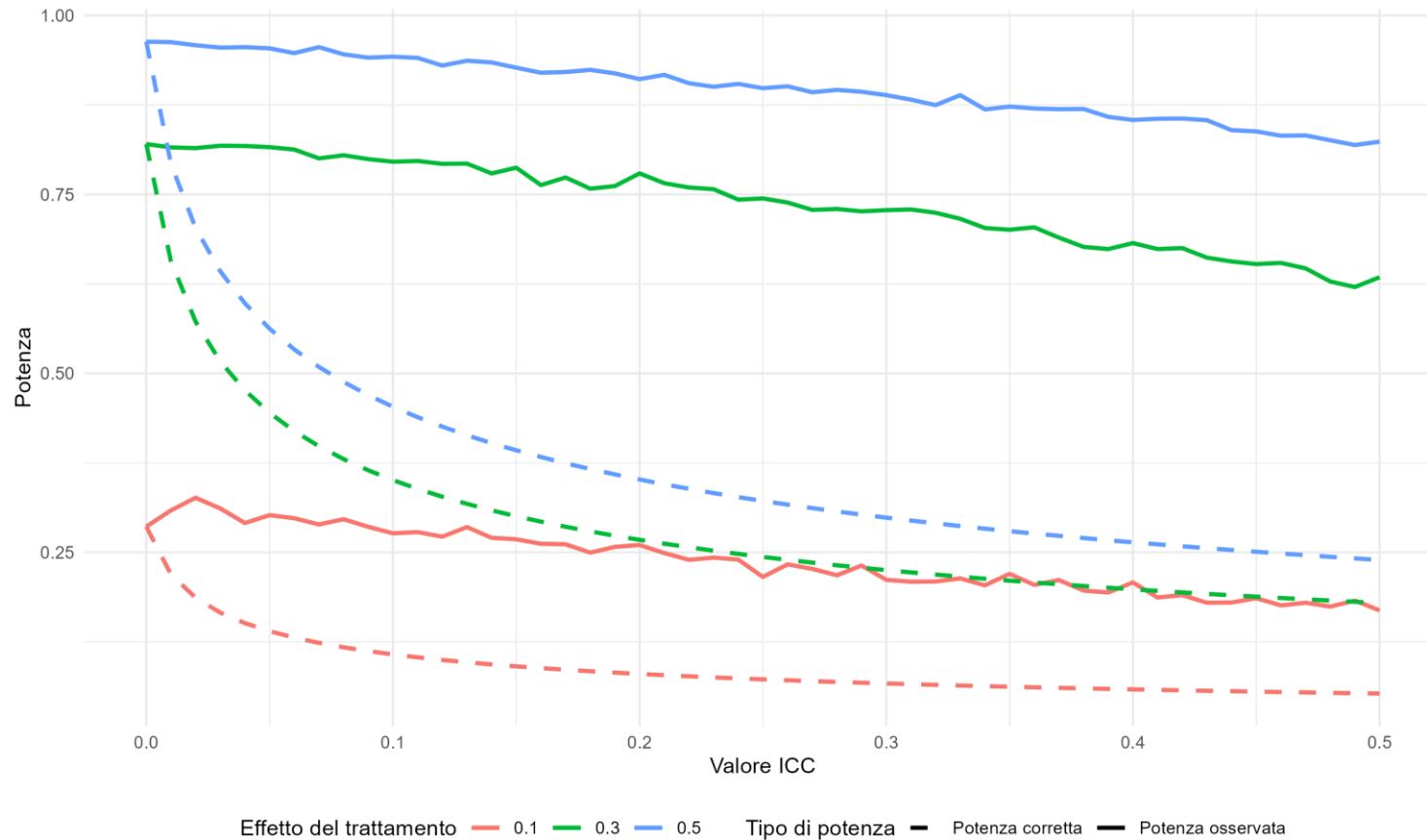
RISULTATI: DE CORRECTION



$$P_{cor} = P_0 \sqrt{SS_0/SS (cor)}$$

```
#: correzione per DE
sample_size_corrected <- ceiling(sample_size * (1 + (num_pat_group - 1) * icc))
## ss per avere potenza modello noicc
power_corrected_ICC <- potenza_noicc * sqrt(sample_size / sample_size_corrected)
```

POWER E CORREZIONE DE (VECCHIA SIMULAZIONE)



*Vecchia simulazione (luglio,
codici ora aggiornati)ma
risultati simili*

SAMPLE SIZE – R CODE

```
# -----
# FUNCTION: sample_size_icc
# PURPOSE: Estimate the minimum number of patients per group required to achieve
#          a target statistical power ( $\geq 0.8$ ) for a clustered survival study,
#          accounting for intraclass correlation (ICC) among hospitals.
#
# HOW IT WORKS:
# 1. Starts with an initial number of patients per group
# 2. Generates a simulated cohort
# 3. Runs 'nsim' Monte Carlo simulations, fitting a Cox proportional hazards
#    model with clustering at the hospital level, and calculates the proportion
#    of simulations where the treatment effect is statistically significant
#    ( $p < 0.05$ ) → this is the estimated power (potenza_icc).
# 4. Increments the number of patients per group until the target power is reached
# 5. Returns a tibble (...)
```

R CODE

Questions / doubts:

- ◊ *ICC = 0?? Methods*
- ◊ *It increases by 1 per hospital; if the number of hospitals is large, there is a big jump at each increment...*

```
sample_size_icc <- function(icc, num_hosp, pop_treat_effect, nsim = 500,
                             max_pat_group = 500, timeout_sec = 1000,
                             lambda = 0.1, gammas = 1) {

  npt <- 1 #10 # starting number of patients per group
  found_target <- FALSE
  candidate_npt <- NULL
  candidate_result <- NULL

  while (npt <= max_pat_group - 2) {
    message("➡ Testing NPT = ", npt)

    result <- tryCatch({
      withTimeout({
        significativi <- logical(nsim)

        for (i in 1:nsim) {
          # Coorte simulATA
          coorte <- simulate_survival_cohort_no_interaction_icc(
            num_hosp = num_hosp,
            num_pat_group = npt,
            icc = icc,
            pop_treat_effect = pop_treat_effect,
            lambda = lambda,
            gammas = gammas )

          # Modello Cox con clustering
          mod_icc <- coxph(Surv(eventtime, status) ~ treat + cluster(hospital), data = coorte) ##ok calcolarla così?
          ## o meglio mod_icc <- coxph(Surv(eventtime, status) ~ treat, data = coorte) ## se rho == 0?
          p_val <- summary(mod_icc)$coefficients["treat", "Pr(>|z)"]
          significativi[i] <- p_val < 0.05}

        potenza_icc <- mean(significativi)

        tibble(
          nsim = nsim,
          icc = icc,
          num_hosp = num_hosp,
          num_pat_group = npt,
          sample_size = npt * num_hosp,
          potenza_icc = potenza_icc ) }, timeout = timeout_sec, onTimeout = "silent")
    }, error = function(e) { message("✖ Error: ", conditionMessage(e)); NULL })

    valid <- !is.null(result) && !is.null(result$potenza_icc) && !is.na(result$potenza_icc)

    if (valid && result$potenza_icc >= 0.8) {
      found_target <- TRUE
      candidate_npt <- npt
      candidate_result <- result
      break }

    npt <- npt + 1 }

  if (!found_target) {
    return(tibble(
```

SIMULATION: ICC AND SAMPLE SIZE

Betas	Lambdas	# (m) pat for group	# hospital	ICC
- 0,5 , 0,5	0.11, 0,1	100	20	0.01, 0.05, 0.1, 0.2
HR: 0.61, 1.65	Mediana 6 ; 60 mesi	-	-	-

Question: what other scenarios are useful to evaluate?

RISULTATI SAMPLE SIZE: TABLE 1

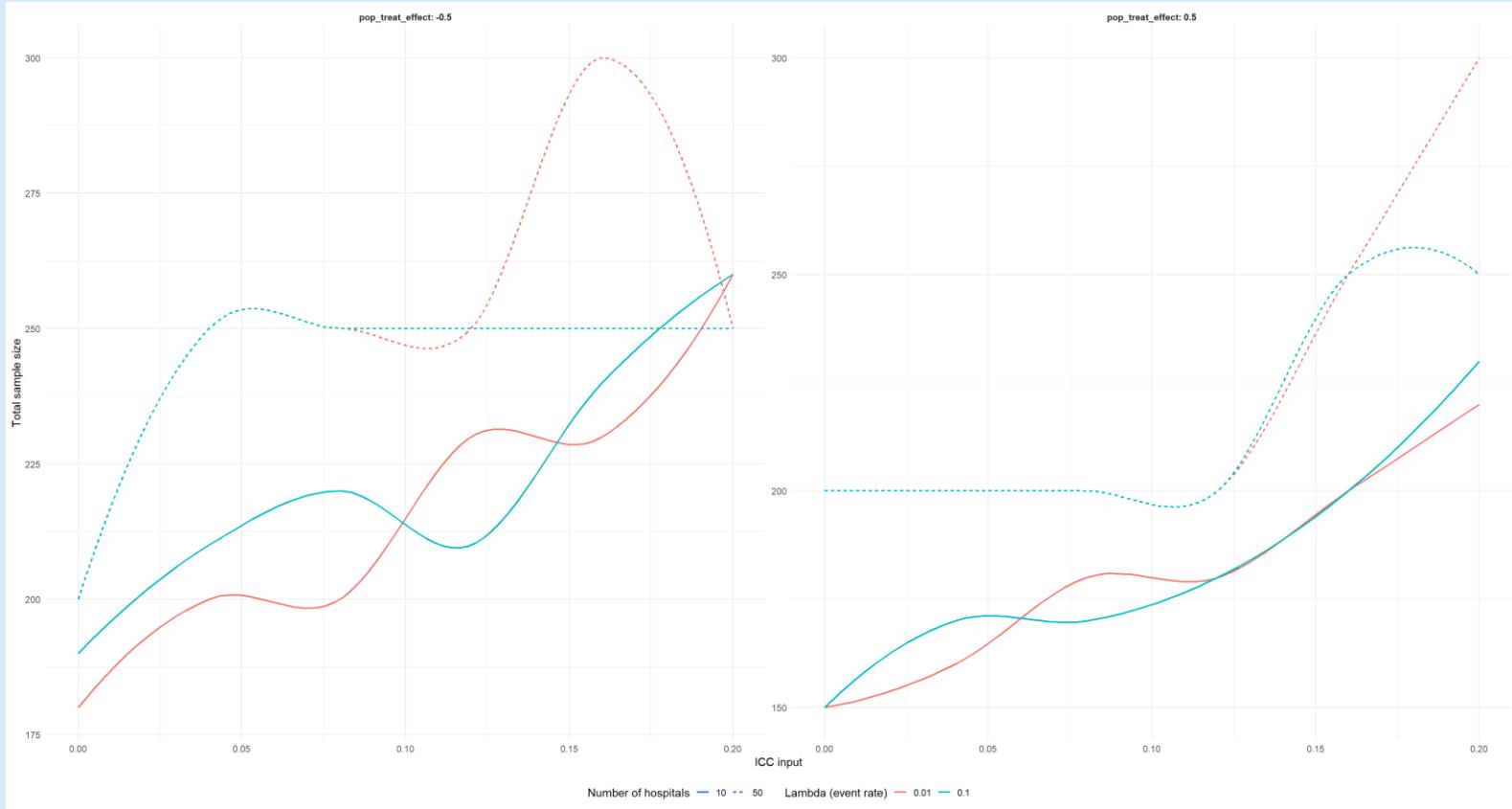
nsim	icc	num_hosp	num_pat_group	sample_size	lambda	potenza_icc	icc_input	pop_treat_effect
500	0.00	10	18	180	0.01	0.800	0.00	-0.5
500	0.04	10	20	200	0.01	0.834	0.04	-0.5
500	0.08	10	20	200	0.01	0.804	0.08	-0.5
500	0.12	10	23	230	0.01	0.804	0.12	-0.5
500	0.16	10	23	230	0.01	0.818	0.16	-0.5
500	0.20	10	26	260	0.01	0.822	0.20	-0.5
500	0.00	10	15	150	0.01	0.828	0.00	0.5
500	0.04	10	16	160	0.01	0.808	0.04	0.5
500	0.08	10	18	180	0.01	0.814	0.08	0.5
500	0.12	10	18	180	0.01	0.802	0.12	0.5
500	0.16	10	20	200	0.01	0.808	0.16	0.5
500	0.20	10	22	220	0.01	0.846	0.20	0.5
500	0.00	10	19	190	0.10	0.808	0.00	-0.5
500	0.04	10	21	210	0.10	0.836	0.04	-0.5
500	0.08	10	22	220	0.10	0.840	0.08	-0.5
500	0.12	10	21	210	0.10	0.820	0.12	-0.5
500	0.16	10	24	240	0.10	0.840	0.16	-0.5
500	0.20	10	26	260	0.10	0.818	0.20	-0.5
500	0.00	10	15	150	0.10	0.800	0.00	0.5
500	0.04	10	17	170	0.10	0.846	0.04	0.5

RESULTS – TABLE 2

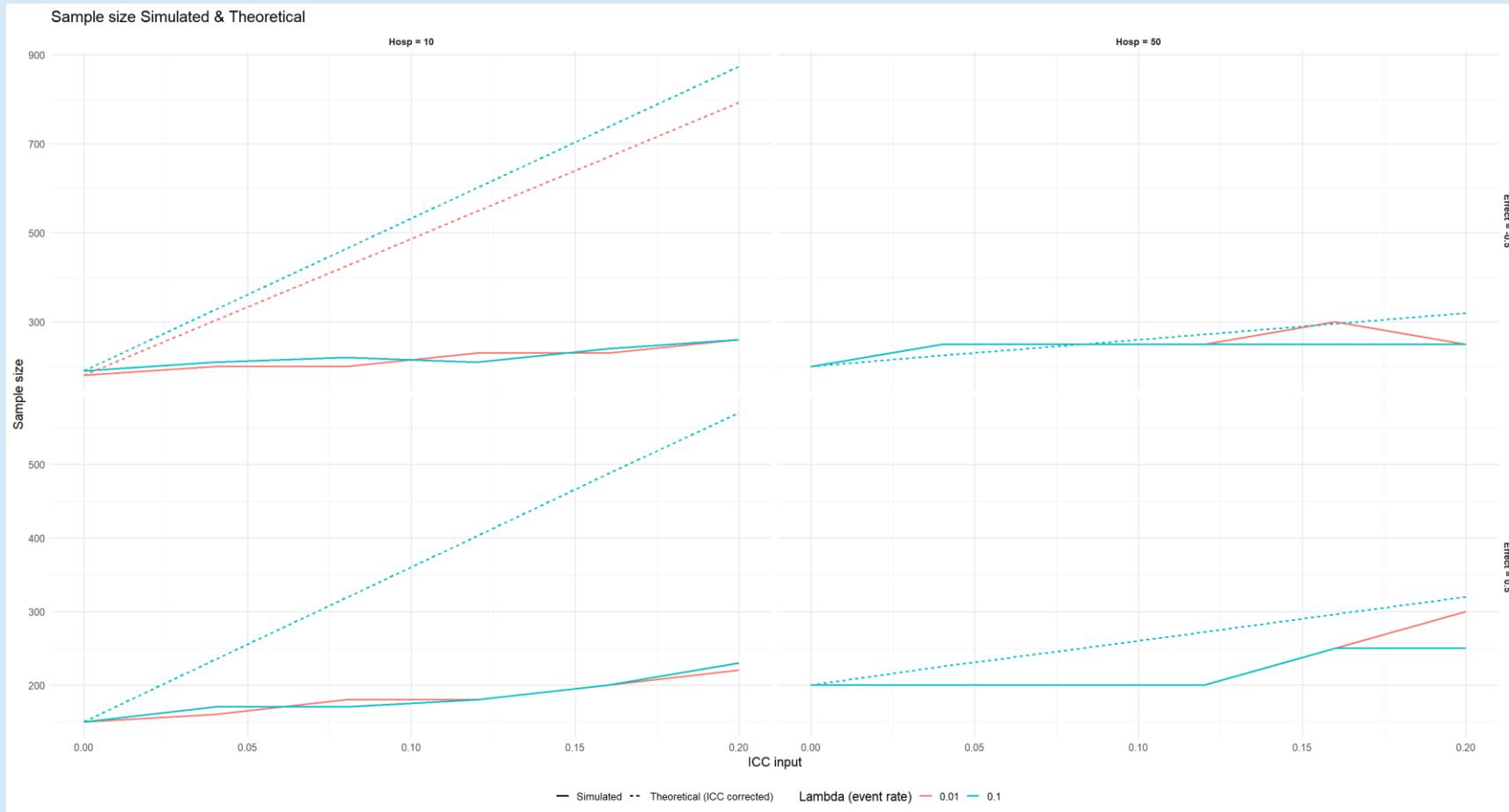
num_hosp	num_pat_group	sample_size	lambda	potenza_icc	icc_input	pop_treat_effect	sample_size_0	num_pat_group_0	sample_size_correct_icc	num_pat_group_correct_icc
10	18	180	0.01	0.800	0.00	-0.5	180	18	180	18.00
10	20	200	0.01	0.834	0.04	-0.5	180	18	303	30.30
10	20	200	0.01	0.804	0.08	-0.5	180	18	425	42.50
10	23	230	0.01	0.804	0.12	-0.5	180	18	548	54.80
10	23	230	0.01	0.818	0.16	-0.5	180	18	670	67.00
10	26	260	0.01	0.822	0.20	-0.5	180	18	793	79.30
10	15	150	0.01	0.828	0.00	0.5	150	15	150	15.00
10	16	160	0.01	0.808	0.04	0.5	150	15	234	23.40
10	18	180	0.01	0.814	0.08	0.5	150	15	318	31.80
10	18	180	0.01	0.802	0.12	0.5	150	15	402	40.20
10	20	200	0.01	0.808	0.16	0.5	150	15	487	48.70
10	22	220	0.01	0.846	0.20	0.5	150	15	570	57.00
10	19	190	0.10	0.808	0.00	-0.5	190	19	190	19.00
10	21	210	0.10	0.836	0.04	-0.5	190	19	327	32.70
10	22	220	0.10	0.840	0.08	-0.5	190	19	464	46.40
10	21	210	0.10	0.820	0.12	-0.5	190	19	601	60.10
10	24	240	0.10	0.840	0.16	-0.5	190	19	738	73.80

```
sample_size_db$sample_size_correct_icc <- ceiling(sample_size_db$sample_size_0 * (1 + (sample_size_db$num_pat_group_0 - 1) * sample_size_db$icc_input))
sample_size_db$num_pat_group_correct_icc <- sample_size_db$sample_size_correct_icc / sample_size_db$num_hosp
```

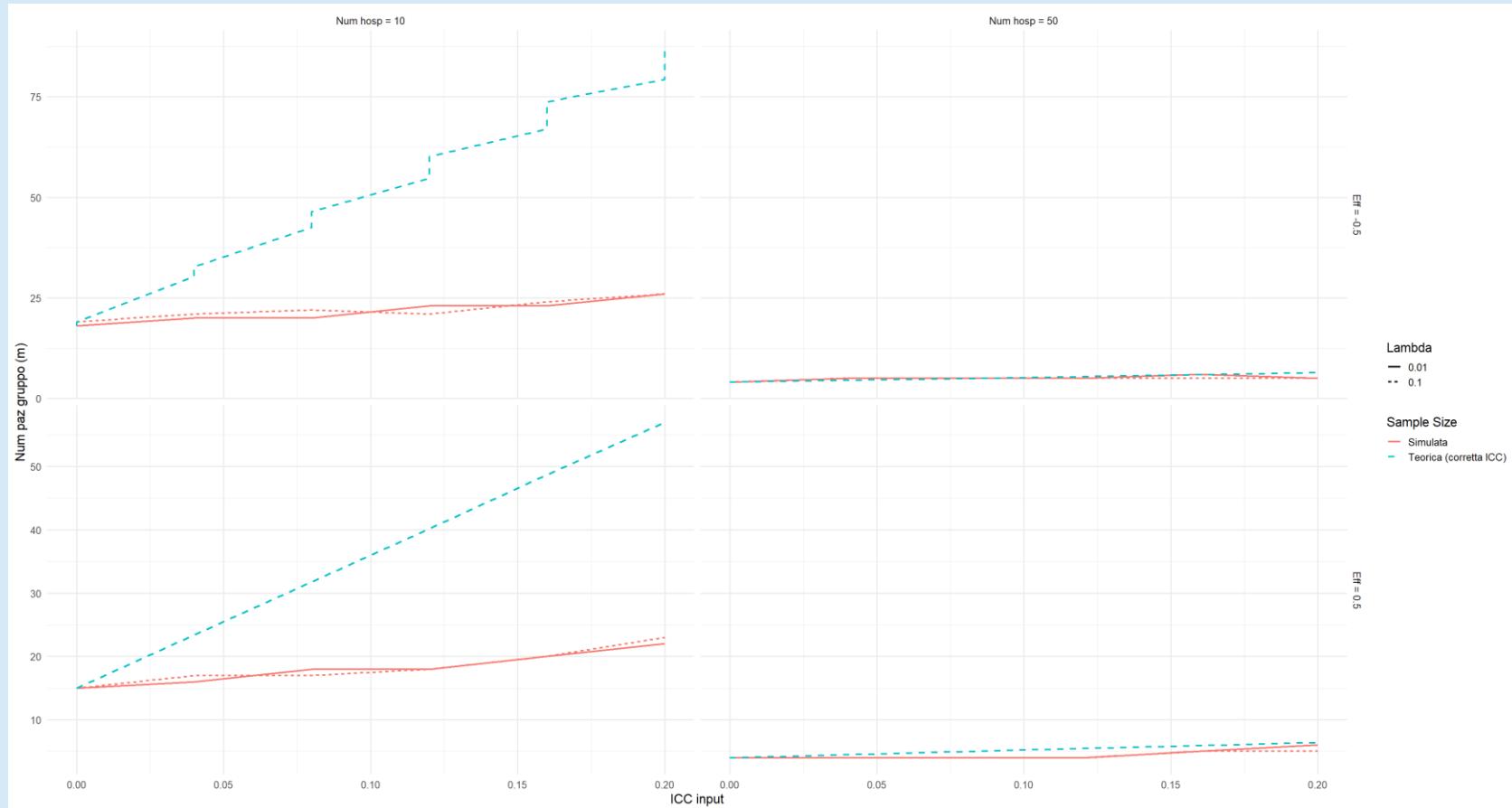
RESULTS - GRAPH 2: SS - M



RESULTS - SS SIMULATED E THEORETICAL (TOTAL)

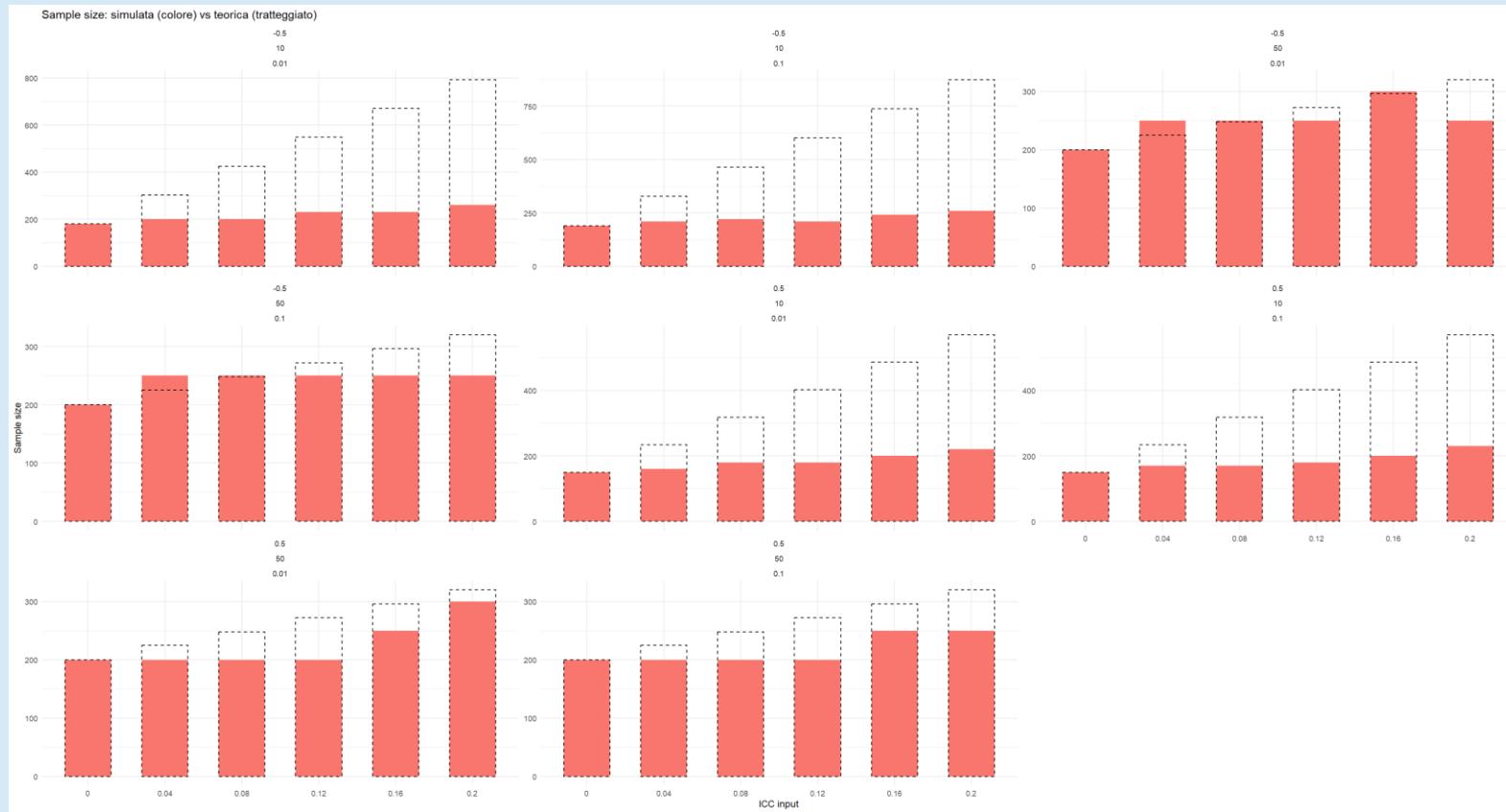


RESULTS - SS SIMULATED E THEORETICAL (M)

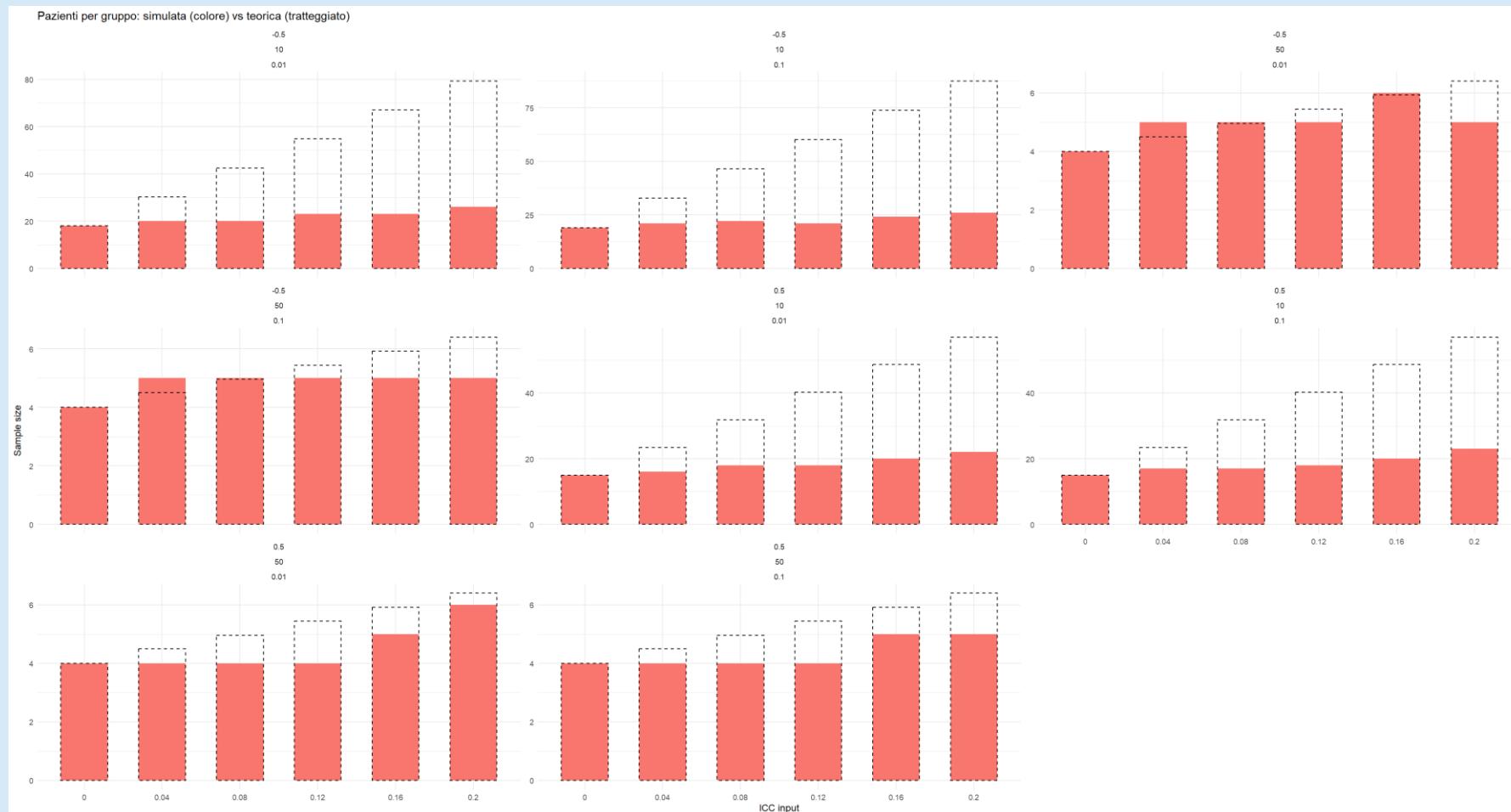


```
sample_size_db$sample_size_correct_icc <- ceiling(sample_size_db$sample_size_0 * (1 + (sample_size_db$num_pat_group_0 - 1) * sample_size_db$icc_input))  
sample_size_db$num_pat_group_correct_icc <- sample_size_db$sample_size_correct_icc/sample_size_db$num_hosp
```

RESULTS - SS SIMULATED E THEORETICAL (TOT2)



RESULTS - SS SIMULATED E THEORETICAL (M 2)



REAL STUDIES (ESTIMATION ICC)

Study	Fonte	Coxme	Coxph frailty gamma (non parametrico)	GLMM (cloglog) - esplosi	Censura	Tempi osservati
Etca-ned	-	0.048	0.034	0.045	0.018	0.019
Pbc3	SurvNet	0	0	NA	-0.003	0.028
Panitumumab Chemio	Project Data Sphere	0.050	0.035	0.048	0.048	0.059
Azienda 0 (injuries)	-	0.013	0.011	0.012	0.006	0.001

POSSIBLE FUTURES IMPLEMENTATION

- ◊ **other options for data simulation** (Include treat × effect interaction?)
- ◊ (explore other scenarios)
- ◊ **shiny app:** for sample size calculation from ICC/data; design optimization