Adjusting for treatment by centre interaction

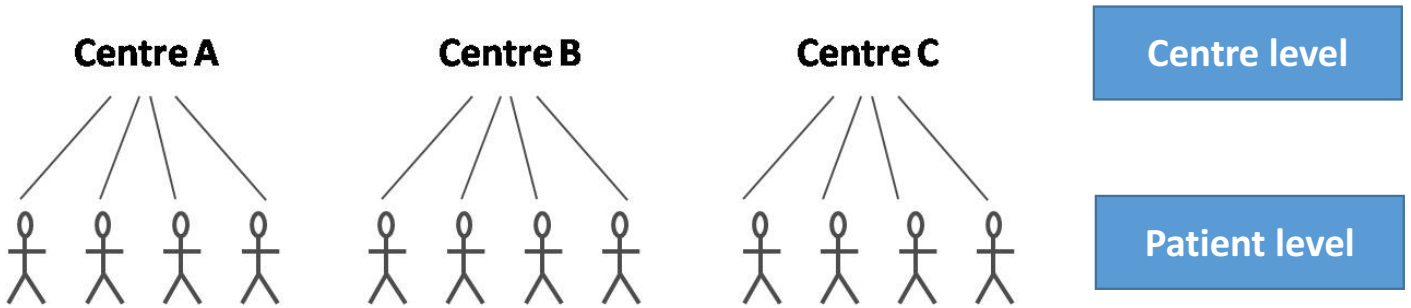
Lucie Biard, Matthieu resche-Rigon
ECSTRA Team, INSERM, UMR-S 1153, Paris, France

Statposium Program
Thursday November 9, 2017

Context (1)

- Multicentre studies, where patients are nested within institutions, medical units, or physicians

- Hierarchical structures : individuals are nested within centres



Context (2)

- Patients from the same centre usually share some known (observed or not) or unknown characteristics that may result in **correlated outcomes**

- These characteristics can be related to
  - patients' backgrounds (so-called case-mix)
  - healthcare environment (e.g., physicians' experience, nurse-to-patient ratio)

- The distribution of the endpoint may differ across centres, defining **heterogeneity across centres** : "**Centre effects**"

Motivating example (1)

- Haploidentical allogenic hematopoietic stem cell transplants (haplo-HSCT) in patient with high-risk leukaemia

- Two treatments to prevent graft-versus-host disease (GVHD)
  - T-cell depleted (TCD)
  - T-cell replete + post-transplant chemotherapy with cyclophosphamide (PTCY)

- Approaches known to require great expertise

- Centres tend to specialize in one GVHD prophylaxis strategy making it difficult to differentiate the treatment effect from the centre effect

Motivating example (2)

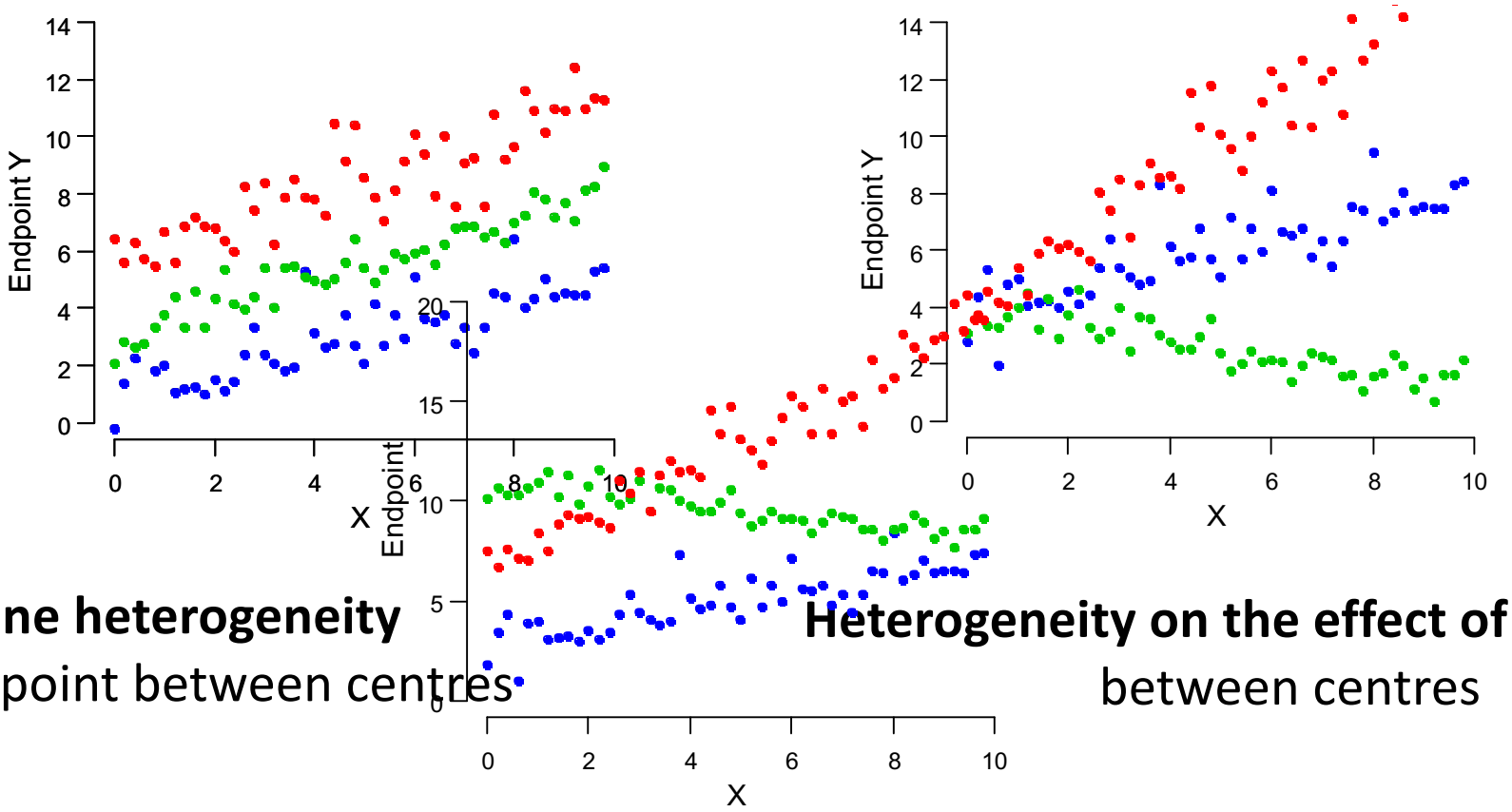
- EBMT registry : adult acute leukaemia patients who received a haplo HSCT between 2007 and 2013 in centres that performed both GVHD prevention strategies, TCD and PTCY

- 226 patients
- 20 centres, centres size ranged from 2 to 66 patients
- 127 patients relapse or died

- Endpoint : Leukemia Free survival (time to relapse or death)

- Model : Cox Model

Main types of centre effect



Baseline heterogeneity
on the endpoint between centres

Heterogeneity on the effect of a covariate
between centres

Modelling strategies in survival analysis

- Modelling centre effect of *K* centres:
  - Stratification
  - Centre as a fixed variable
  - Centre as a random variable

- Stratification cannot easily handle interaction between centre and covariates

- Adjustment on centre allows to estimate and test for centre effects

Cox model : Fixed effects

Baseline heterogeneity

Heterogeneity on the effect of X (interaction)

$$\lambda_k(t) = \lambda_0(t) e^{\alpha_k + \beta X + \gamma_k X}$$

$$\lambda_k(t) = \lambda_0(t) e^{\alpha_k} e^{(\beta + \gamma_k) X}$$

Centre-specific baseline hazard

Centre-specific effect of covariate X

- Fixed centre effect: testing hazard ratios to 1
  - Global test: H_0: $\alpha_1 = \cdots = \alpha_K = \gamma_1 = \cdots = \gamma_K = 0$
  - Partial tests: H_0: $\alpha_1 = \cdots = \alpha_K = 0$; $\gamma_1 = \cdots = \gamma_K = 0$
  - Likelihood ratio tests, inflated number of parameters, anticonservatism*

** Andersen, P. K., Klein, J. P., & Zhang, M. J. (1999). Testing for centre effects in multi-centre survival studies: a Monte Carlo comparison of fixed and random effects tests. Statistics in medicine, 18(12), 1489-1500.*

Random effects Cox model

Heterogeneity on the effect of X (interaction)

Baseline heterogeneity

$$\lambda_k(t) = \lambda_0(t)e^{\beta X + b_{1k}X + b_{2k}}$$

$$\lambda_k(t) = \lambda_0(t)e^{b_{2k}}e^{(\beta + b_{1k})X}$$

Centre-specific baseline hazard

Centre-specific effect of covariate X

$$b_k \sim \mathcal{N}(0, \Sigma)$$

$$\Sigma = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

- Random centre effect: testing centre variance to 0
  - Global test : H_0: $\Sigma = [0]$
  - Partial tests: H_0: $\sigma_1 = 0$; $\sigma_2 = 0$
  - Conventional tests: questionable validity under non asymptotic conditions (variance is strictly positive, bounded at 0)

Testing centre effects

- Global test:

$$H_0: \Sigma = 0 \text{ vs } H_1 : \Sigma = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

- Partial test (e.g. testing for interaction btw centre and treatment X):

$$H_0: \Sigma = \begin{pmatrix} 0 & 0 \\ 0 & \sigma_2^2 \end{pmatrix} \text{ vs. } H_1: \Sigma = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

- Partial test (e.g. testing for baseline heterogenity):

$$H_0: \Sigma = \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & 0 \end{pmatrix} \text{ vs. } H_1: \Sigma = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

** Biard L, Porcher R, Resche-Rigon M. Statist Med 2014;33:3047-57*
Biard L, Labopin M, Chevret S, Resche-Rigon M. SMMR 2016.

Testing random effects

- Case of a single random effect on the baseline hazard
- $H_0 : \sigma^2=0 \Rightarrow$ boundary of the parameter's space
- Wald or likelihood ratio test statistics distribution : mixtures of χ 2 distributions (conservative)
- Permutation procedures

** Drikvandi R, Verbeke G, Khodadadi A et al. Testing multiple variance components in linear mixed-effects models. Biostatistics 2013; 14(1): 144–159. DOI:10.1093/biostatistics/kxs028.*

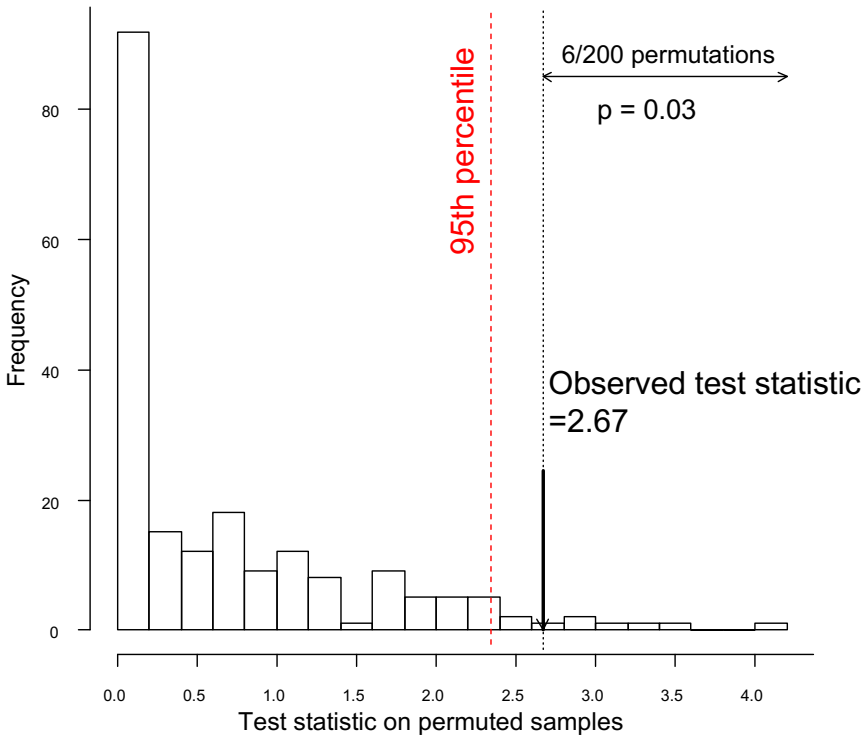
Permutation procedure

- If there is **no centre effect**, the endpoint distribution is independent of centres

Patients	Time	Death	Centre
1	6	0	A
2	4.5	1	A
3	0.5	1	A
4	3	0	B
5	2.5	1	B
6	5	0	B

- Centre indices are **exchangeable**

Permutation test procedure



1. Compute the statistic on the original sample
2. Randomly permute centre indices a large number of times
3. Compute the statistic on each permuted sample
4. Obtain an approximate distribution of the statistic under H_0
5. Reject H_0 if the observed statistic is greater than the 95th percentile (if 5% level test)

Testing centre effects

- Global test:

$$H_0: \Sigma = 0 \text{ vs } H_1 : \Sigma = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

- Drikvandi statistic

- If only a single centre effect on the baseline hazard equivalent to the estimated variance

** Drikvandi R, Verbeke G, Khodadadi A et al. Testing multiple variance components in linear mixed-effects models. Biostatistics 2013; 14(1): 144–159. DOI:10.1093/biostatistics/kxs028*

Testing centre effects

- Partial test (e.g. testing for interaction btw centre and treatment X):

$$H_0: \Sigma = \begin{pmatrix} 0 & 0 \\ 0 & \sigma_2^2 \end{pmatrix} \text{ vs. } H_1: \Sigma = \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}$$

- Only the tested centre effects are exchangeable under H0
- Indices permutation restricted to tested centre effect only

$$\lambda_k(t) = \lambda_0(t) e^{\widehat{b_{2k}}} e^{(\beta + b_{1k})X}$$

Offset $e^{\widehat{b_{2k}}}$ in the linear predictor of the instantaneous hazard

** Drikvandi R, Verbeke G, Khodadadi A et al. Testing multiple variance components in linear mixed-effects models. Biostatistics 2013; 14(1): 144–159. DOI:10.1093/biostatistics/kxs028*

Coding subtlety

- Usual coding X $\in$ {0;1}
- Treatment X=0 : $\lambda_k(t) = \lambda_0(t)e^{\beta X + b_{1k}X + b_{2k}}$

- Coding X $\in$ {-1/2;1/2}
- Imply equal variability in log hazard rate across trials for both treatment groups

Results

N=101 T-depleted
N=125 T-replete (ATG 62, PT-Cy 63)

Across 20 centers

Table 1: Patients characteristics according to GVHD prevention strategy.

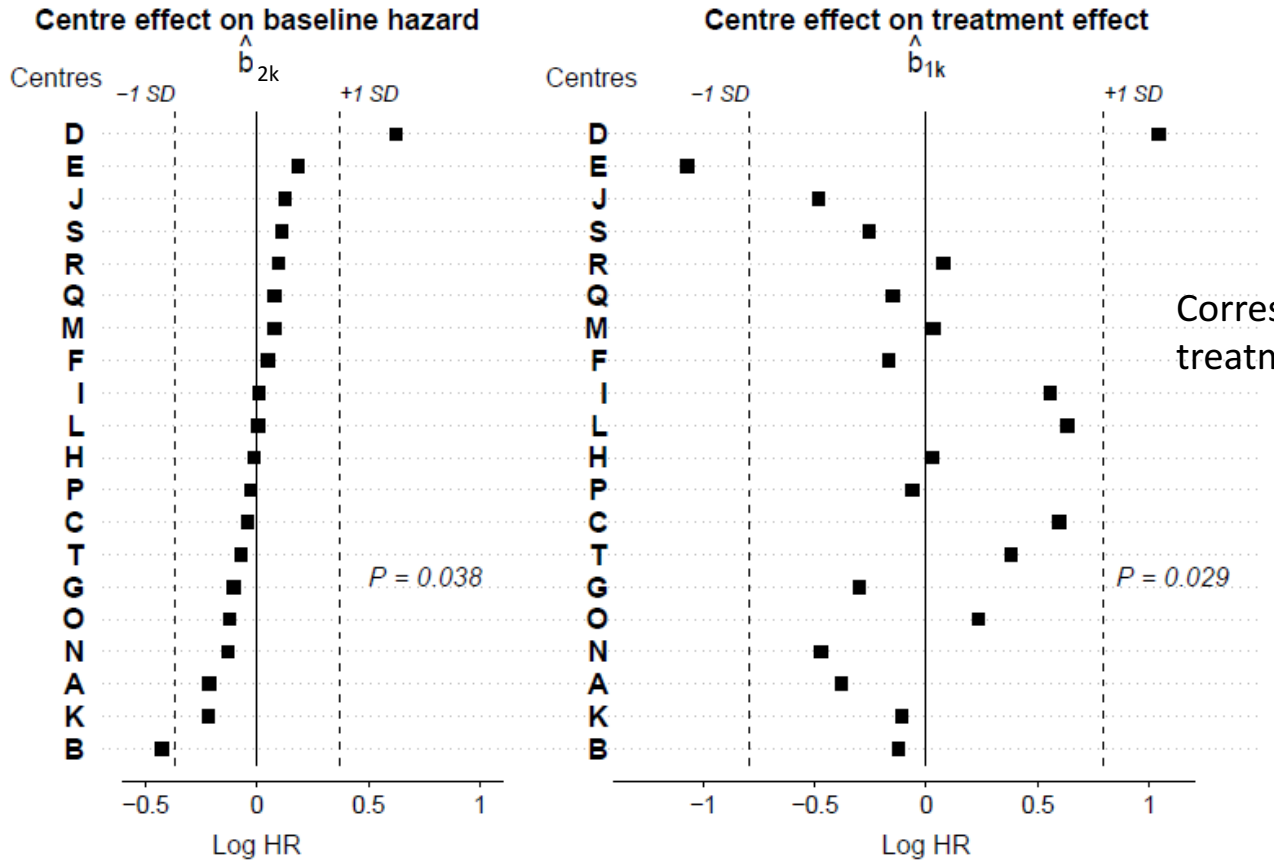
Variables	All	T-Cell replete	TCD
Total	226	125 (55)	101 (45)
Age at transplant	46 (31 to 58)	50 (37 to 59)	41 (26 to 55)
Male gender	123 (54)	71 (57)	52 (51)
Diagnosis			
AML	175 (77)	100 (80)	75 (74)
ALL	51 (23)	25 (20)	26 (26)
Type of transplant			
BM	48 (21)	39 (31)	9 (9)
PB	178 (79)	86 (69)	92 (91)
Disease status			
CR1	144 (64)	80 (64)	64 (63)
CR2	82 (36)	45 (36)	37 (37)
Secondary malignancy	39 (17)	26 (21)	13 (13)
Previous autologous transplant	16 (7)	11 (9)	5 (5)
Donor age	36 (26 to 48)	34 (25 to 44)	42 (30 to 53)
NA, nb.	86	44	42
Female-to-male transplant	68 (30)	38 (30)	30 (30)
CMV matching (donor/recipient)			
-/-	34 (16)	11 (9)	23 (25)
+/-	14 (7)	3 (2)	11 (12)
-/+	39 (18)	26 (22)	13 (14)
+/+	126 (59)	80 (67)	46 (49)
NA, nb.	13	5	8
Conditioning regimen			
MAC	107 (47)	53 (42)	54 (53)
RIC	119 (53)	72 (58)	47 (47)
TBI in MAC	46 (43)	15 (28)	31 (58)
NA, nb.	1	0	1
TBI in RIC	67 (56)	35 (49)	32 (68)

Results

Fixed-effect variable	$\hat{\beta}$ (SE)	P
GVHD prevention (PTCY *vs.* TCD)	-0.18 (0.31)	0.56
Random centre effects	$\hat{\sigma}$	P
Global test		0.007
Centre on baseline hazard	0.37	0.038
Centre × GVHD prevention	0.79	0.029

- Global test significant : at least one centre effect
- The effect of PTCY compared to TCD varied significantly across centres (P = 0.029)

Distribution of Centre effects



Corresponding IQR of the treatment effect : [0.50;1.42]

Limits

- The power of the permutation tests tended to decrease in the case of small centre sizes or in the case of high censoring
- May perform poorly in presence of too few events per centre
- Does not depend on the estimation procedure
- Relatively robust to distribution misspecification
- At least 200 permutations (1000 for the example)

Conclusions

- Random effects are an intuitive modelling choice for heterogeneity and treatment by centre interaction
- Permutation procedures are a straightforward tool for testing them.
- Applicable to single and multiple centre effects situations.
- Easy to implement on statistical software platforms.

But… it is not the end

- Testing for the existence of centre effects is a first step in identifying the source of heterogeneity

- Potential sources of centre effect:
  - Patient-related (case-mix)
  - Centre-related: physicians and paramedical team, transplant unit characteristics, institution