

# G-computation et Inverse-Probability-Weighting en analyse de survie

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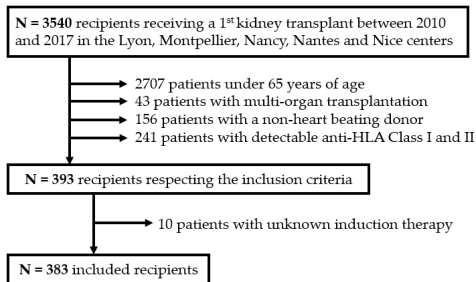
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GDR Stat&Santé – SFB – SFdS  
11 octobre 2019



# Vie réelle : Transplantation rénale

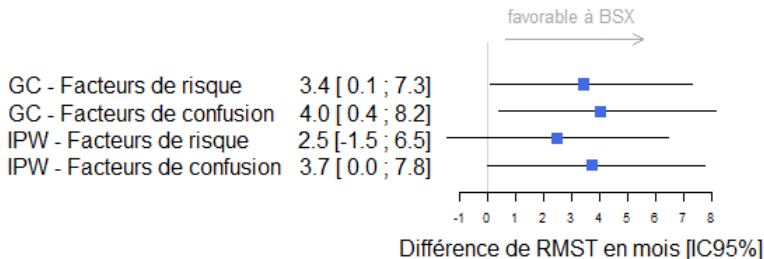
- Basiliximab (BSX) *versus* Thymoglobuline (ATG) sur la survenue d'une complication cardiaque à 3 ans<sup>1</sup>
- ATG  $\Rightarrow$  moins de rejet mais plus d'évènement indésirable



1. Masset, C., *et al.* (2019) Induction therapy in elderly kidney transplant recipients with low immunological risk. *Transplantation*, 1.

# Vie réelle : Transplantation rénale

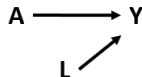
- ATG : 179 patients (dont 31% qui ont une complication cardiaque)
- BSX : 204 patients (dont 29% qui ont une complication cardiaque)



⇒ Variation importante de l'effet

# Score de propension

- Probabilité pour un patient  $i$  d'être exposé selon ses caractéristiques  $L_i$ 
  - $p_i = P(A_i = 1|L_i)$
- Classiquement estimé à partir d'une régression logistique
- Utilisable de différentes manières
  - 1 Stratification
  - 2 Ajustement
  - 3 Appariement  $\Rightarrow$  Critiqué<sup>1</sup>
  - 4 Pondération (IPW)  $\Rightarrow$  Meilleures performances<sup>2</sup>



1. King, G. and Nielsen, R. (2019) Why propensity scores should not be used for matching. Political Analysis, 1-20

2. Le Borgne, F., Giraudeau, B., Querard, A. H., Giral, M. and Foucher, Y. (2016) Comparisons of the performance of different statistical tests for time-to-event analysis with confounding factors : practical illustrations in kidney transplantation. Statistics in Medicine, 35, 1103–1116.

# Inverse-Probability-Weighting

- Pseudo-échantillon pondéré équilibré sur  $L$  entre les groupes
- Utilisation de poids stabilisés<sup>3</sup> :

$$\omega_i = A_i P(A_i = 1)/p_i + (1 - A_i) P(A_i = 0)/(1 - p_i)$$

- Survie ajustée par Kaplan-Meier pondéré<sup>4</sup>

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3. Xu, S., *et al.* (2010) Use of Stabilized Inverse Propensity Scores as Weights to Directly Estimate Relative Risk and Its Confidence Intervals. *Value in Health*, 13, 273–277.

4. Cole, S. R. and Hernán, M. A. (2004) Adjusted survival curves with inverse probability weights. *Computer methods and programs in biomedicine*, 75, 45–49.

# Estimateur de Kaplan-Meier : Rappel

- Probabilité de faire l'évènement entre  $t_{j-1}$  et  $t_j$  sachant que l'on était à risque à  $t_{j-1}$  est de  $d_{ja}/R_{ja}$  dans le groupe  $A = a$

- où

Nombre d'évènements  $d_{ja}^\omega = \sum_{i:t_i=t_j} \omega_i \delta_i \mathbb{1}(A_i = a)$

Nombre de sujets à risques  $R_{ja}^\omega = \sum_{i:t_i \geq t_j} \omega_i \mathbb{1}(A_i = a)$

$\omega_i = 1$  si analyse non-pondérée

⇒ Fonction de survie dans le groupe  $A = a$  :

$$\hat{S}_a^{IPW}(t) = \prod_{t_j \leq t} [1 - d_{ja}^\omega / R_{ja}^\omega]$$

# G-Computation (GC)

	L	A	T
Dumas	1	1	20
Orwell	0	0	18
Tolkien	0	1	13
Verne	1	0	10

- Estimer un modèle de Cox multivarié afin d'obtenir nos coefficients  $\hat{\gamma}$  et  $\hat{\beta}$

$$\Lambda(t) = \Lambda_0(t) \exp(\gamma A_i + \beta L_i)$$

- $\hat{\Lambda}_0(t)$  est obtenu par l'estimateur de Breslow<sup>5</sup>

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5. Breslow N. E. (1972) Discussion of the paper by D. R. Cox. Journal of the Royal Statistical Society series B. 34 :216–217

# G-Computation (GC)

- Créer les deux mondes contrefactuels

	L	A	T
Dumas	1	1	20
Orwell	0	1	18
Tolkien	0	1	13
Verne	1	1	10

	L	A	T
Dumas	1	0	20
Orwell	0	0	18
Tolkien	0	0	13
Verne	1	0	10

- Calculer ensuite :

$$\hat{S}_1^{GC}(t) = n^{-1} \sum_{i=1}^n \exp[-\hat{\Lambda}_0(t) \times \exp(\hat{\gamma} \times \mathbf{1} + \hat{\beta}L_i)]$$

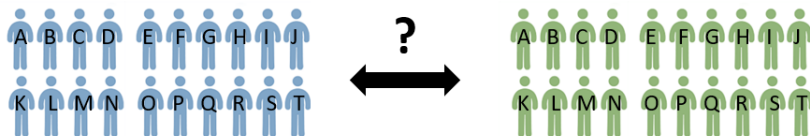
$$\hat{S}_0^{GC}(t) = n^{-1} \sum_{i=1}^n \exp[-\hat{\Lambda}_0(t) \times \exp(\hat{\gamma} \times \mathbf{0} + \hat{\beta}L_i)]$$

- Variance obtenue par bootstrap<sup>6</sup>

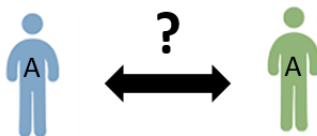
6. Austin, P.C. (2016) Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med 35, 5642–5655.



# Marginal *versus* conditionnel



# Marginal *versus* conditionnel



# Littérature

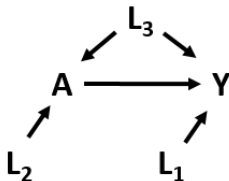
- 1 seule comparaison entre GC et IPW en survie<sup>7</sup>
  - ⇒ Variance plus faible en GC
- Mais :
  - Confusion dépendante du temps
  - 1 seul scénario de simulation
  - Pas de censure

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7. Daniel, R.M., Cousens, S.N., De Stavola, B.L., Kenward, M.G., Sterne, J.A.C. (2013) Methods for dealing with time-dependent confounding. *Statistics in Medicine* 32, 1584–1618.

# Littérature

- Pas de consensus sur la stratégie de sélection des covariables



- Score de propension  $\Rightarrow$  plutôt les facteurs de risque ( $L_1$  et  $L_3$ ) ou les facteurs de confusion ( $L_3$ )<sup>8 9</sup>
- GC  $\Rightarrow$  ?

8. Brookhart, M.A., *et al.* (2006) Variable selection for propensity score models. *American Journal of Epidemiology*, 163, 1149–1156.

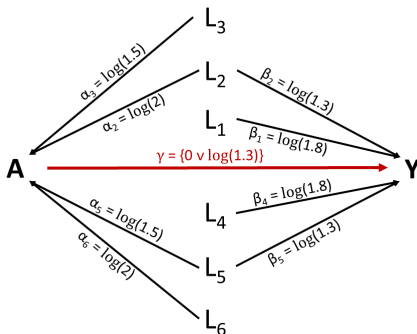
9. Austin, P. C., Grootendorst, P. and Anderson, G. M. (2007) A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects : a Monte Carlo study. *Statistics in Medicine*, 26, 734–753.

# Objectifs

- 1 Estimer les performances de la GC et de l'IPW via une étude de simulation
- 2 Quelle stratégie de sélection des covariables envisager ?

# Plan de simulation

- $N = 100, 500$  ou  $2000$

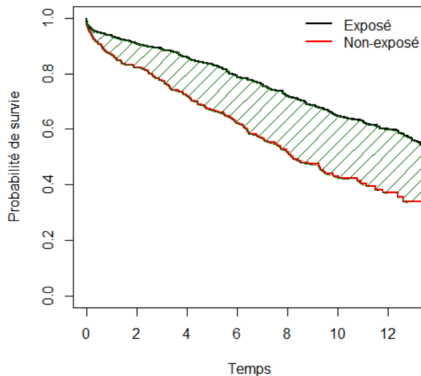


- Censure = 40% ou 90%
- 10 000 itérations

⇒ Hazard Ratio ou Restricted Mean Survival Time Difference ( $\Delta RMST$ )

# Restricted Mean Survival Time (RMST)<sup>10</sup>

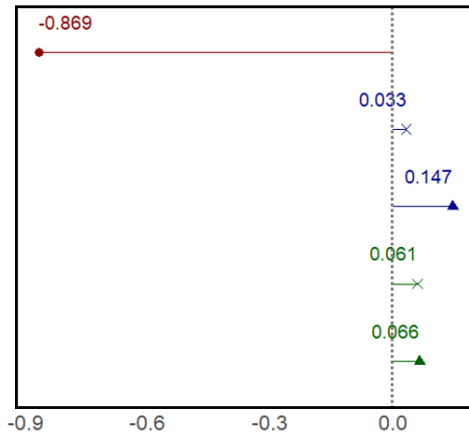
- $\Delta RMST = \int_0^T [S_1(t) - S_0(t)]dt$



10. Royston, P. and Parmar, M. K. (2013) Restricted mean survival time : an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Medical Research Methodology, 13, 152.

# Simulations : H1, N=500, censor=40%, $\Delta RMST$

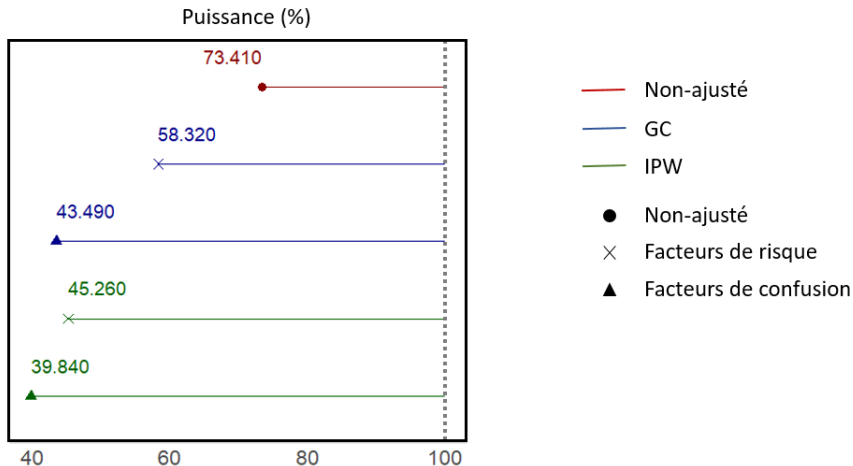
Biais absolu



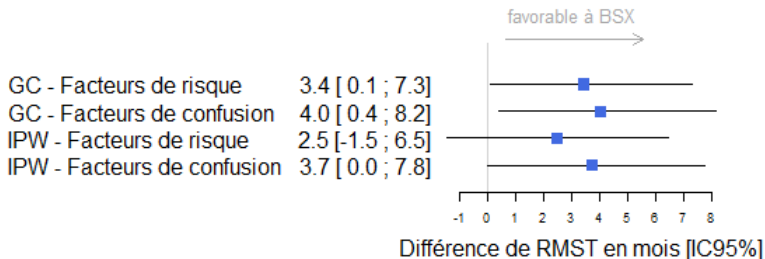
- Non-ajusté
- GC
- IPW
- Non-ajusté
- × Facteurs de risque
- ▲ Facteurs de confusion



# Simulations : H1, N=500, censure=40%, $\Delta RMST$



# Basiliximab *versus* Thymoglobuline



- 1 Effet varie selon la méthode et la stratégie de sélection
- 2 Intervalle de confiance plus étroit avec GC incluant tous les facteurs de risque
- 3 Conclusion différente selon la méthode

# Conclusion

- Résultats de l'application impactés par le choix des méthodes
- GC et IPW non-biaisés
- GC avec tous les facteurs de risque  $\Rightarrow$  à préférer car plus puissante
- Intérêt des estimateurs doublement robustes<sup>11</sup> ?

*Merci de votre attention*

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11. Vansteelandt, S., Keiding, N., 2011. Invited Commentary : G-Computation-Lost in Translation ? American Journal of Epidemiology 173, 739–742.

# Références

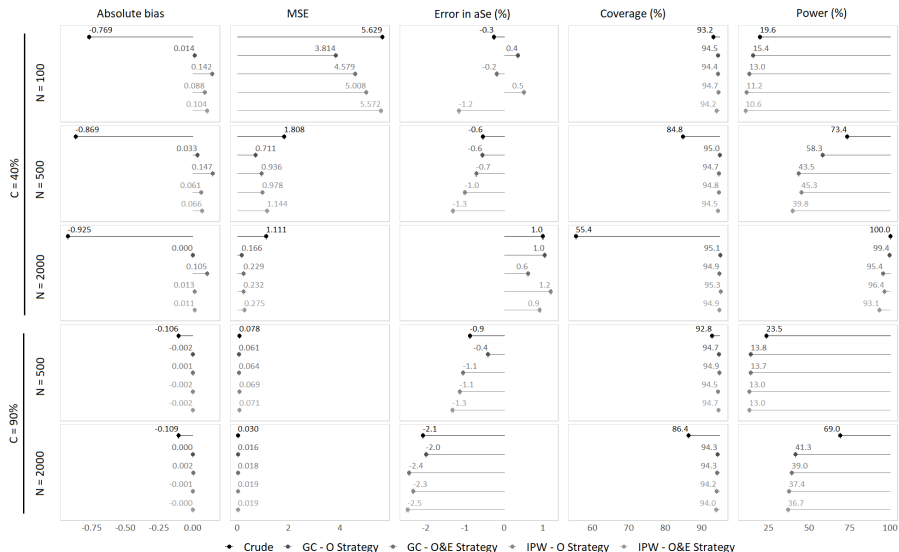
- ① King, G. and Nielsen, R. (2019) Why propensity scores should not be used for matching. *Political Analysis*, 1-20
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- ④ Cole, S. R. and Hernán, M. A. (2004) Adjusted survival curves with inverse probability weights. *Computer methods and programs in biomedicine*, 75, 45–49.
- ⑤ Breslow N. E. (1972) Discussion of the paper by D. R. Cox. *Journal of the Royal Statistical Society series B*. 34 :216–217
- ⑥ Austin, P.C. (2016) Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. *Stat Med* 35, 5642–5655.
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- ⑧ Brookhart, M.A., *et al.* (2006) Variable selection for propensity score models. *American Journal of Epidemiology*, 163, 1149–1156.
- ⑨ Austin, P. C., Grootendorst, P. and Anderson, G. M. (2007) A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects : a Monte Carlo study. *Statistics in Medicine*, 26, 734–753.
- ⑩ Royston, P. and Parmar, M. K. (2013) Restricted mean survival time : an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Medical Research Methodology*, 13, 152.
- ⑪ Vansteelandt, S., Keiding, N., 2011. Invited Commentary : G-Computation-Lost in Translation ? *American Journal of Epidemiology* 173, 739–742.

# Descriptif de l'application

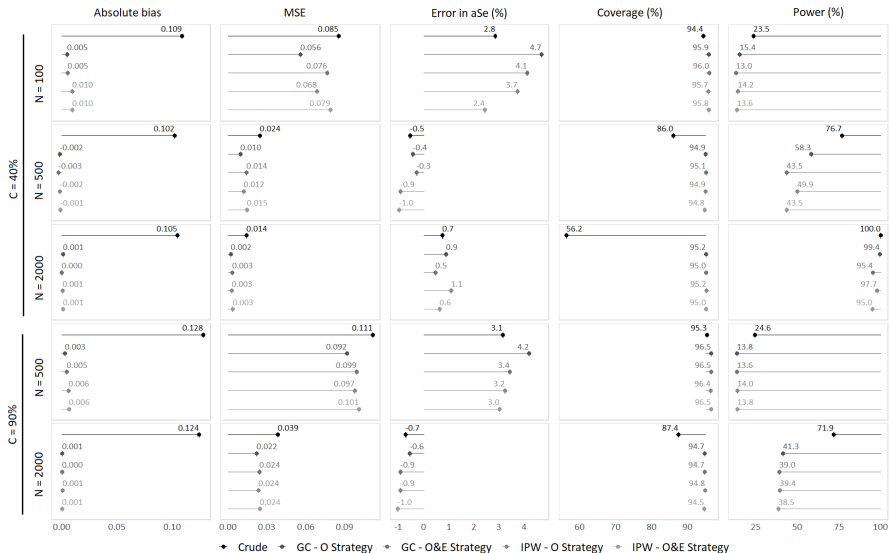
**Table 2.** Description of the kidney's transplantation cohort according to induction therapy.

	Overall (n=383)			ATG (n=179)			BSX (n=204)			p-value
	missing	n	%	missing	n	%	missing	n	%	
Male recipient	0	284	74.2	0	137	76.5	0	147	72.1	0.3180
Recurrent causal nephropathy	0	63	16.4	0	29	16.2	0	34	16.7	0.9024
Preemptive transplantation	1	61	16.0	1	18	10.1	0	43	21.1	0.0035
History of diabetes	0	123	32.1	0	64	35.8	0	59	28.9	0.1530
History of hypertension	0	327	85.4	0	150	83.8	0	177	86.8	0.4124
History of vascular disease	0	109	28.5	0	53	29.6	0	56	27.5	0.6405
History of cardiac disease	0	153	39.9	0	75	41.9	0	78	38.2	0.4651
History of cardiovascular disease	0	203	53.0	0	99	55.3	0	104	51.0	0.3973
History of malignancy	0	94	24.5	0	42	23.5	0	52	25.5	0.6457
History of dyslipidemia	0	220	57.4	0	92	51.4	0	128	62.7	0.0250
Positive recipient CMV serology	5	230	60.8	4	119	68.0	1	111	54.7	0.0082
Male donor	0	187	48.8	0	93	52.0	0	94	46.1	0.2510
ECD donor	1	372	97.4	1	172	96.6	0	200	98.0	0.5244
Use of machine perfusion	12	208	54.3	6	86	48.0	6	122	59.8	0.0684
Vascular cause of donor death	0	275	71.8	0	126	70.4	0	149	73.0	0.5655
Donor hypertension	11	224	60.2	9	103	60.6	2	121	59.9	0.8927
Positive donor CMV serology	0	240	62.7	0	115	64.2	0	125	61.3	0.5486
Positive donor EBV serology	1	370	96.9	1	172	96.6	0	198	97.1	0.8102
HLA-A-B-DR incompatibilities >4	5	97	25.7	3	41	23.3	2	56	27.7	0.3256
		<i>mean</i>	<i>sd</i>		<i>mean</i>	<i>sd</i>		<i>mean</i>	<i>sd</i>	
Recipient age (years)	0	70.8	4.8	0	70.5	4.8	0	71.0	4.8	0.3733
Recipient BMI (kg/m <sup>2</sup> )	3	26.7	4.0	3	26.9	4.2	0	26.5	3.9	0.2796
Duration on waiting list (months)	16	16.5	19.0	11	17.9	18.9	5	15.4	19.1	0.2082
Donor age (years)	1	72.7	8.8	1	72.1	10.0	0	73.1	7.5	0.2739
Donor creatininemia (μmol/l)	1	82.9	39.5	0	85.5	41.0	1	80.7	38.0	0.2331
Cold ischemia time (hours)	3	15.6	5.0	1	15.9	5.2	2	15.3	4.8	0.2820
Abbreviations: ATG, Thymoglobulin; BMI, Body mass index; BSX, Basiliximab; CMV, Cytomegalovirus; EBV, Epstein-Barr virus; ECD, Expanded criteria donor; HLA, Human leucocyte antigen; and sd, Standard deviation.										

# Résultats des simulations ( $\Delta RMST$ )



# Résultats des simulations (Marginal Hazard Ratio)



# Estimateur d'intérêt

- Hazard ratio marginal contesté
- Distribution des facteurs de confusion varie au cours du temps

