Dynamic propensity scores matching to evaluate the impact of time-dependent exposures

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Best practices and recent advances in causal analyses, Bordeaux
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Plan

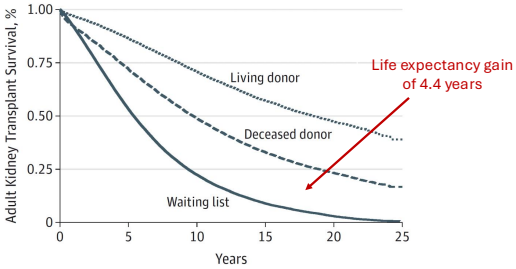
The benefit of kidney transplantation : which size ?

- Two treatments of end-stage renal disease : long-term dialysis and kidney transplantation (KT).
- KT is considered to be the best treatment since studies reflected its benefit in terms of life expectancy.
- Because it is impossible to randomize transplantation versus dialysis due to ethical reasons, the magnitude of this benefit remains uncertain.

JAMA Surgery ; 2015 ; 150(3) :252-259.1

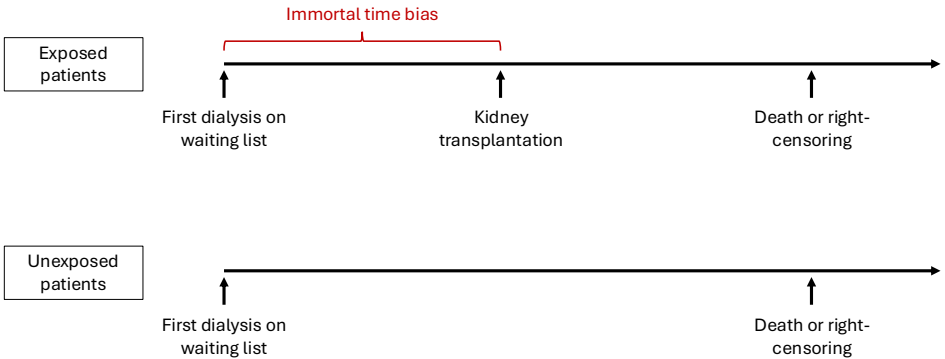
Survival Benefit of Solid-Organ Transplant in the United States

Abbas Rana, MD; Angelika Gruessner, PhD; Vatche G. Agopian, MD; Zain Khalpey, MD, PhD; Irbaz B. Riaz, MBBS; Bruce Kaplan, MD; Karim J. Halazun, MD; Ronald W. Busuttil, MD, PhD; Rainer W. G. Gruessner, MD

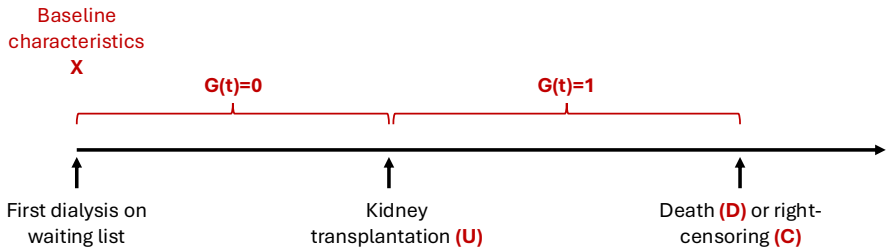


No. at risk						
Waiting list	239162	43202	7083	1472	275	32
Deceased donor	148292	74561	27850	8576	1859	16
Living donor	87387	50125	19255	5275	1115	8

An overestimation of the kidney transplantation benefit



Wolfe et al., New England Journal of Medicine 1999 ; 341 :1725-1730



$$\lambda(d \mid X, G(d)) = \lambda_0(d) \exp(\beta X + \gamma(d-u)G(d))$$

- $\lambda_0(.)$ is the baseline hazard function of the time-to-death.
- β are the regression coefficients associated with the baseline characteristics.
- $\gamma(.)$ is a time-dependent function according to the post-transplantation time.

Wolfe et al., New England Journal of Medicine 1999 ; 341 :1725-1730

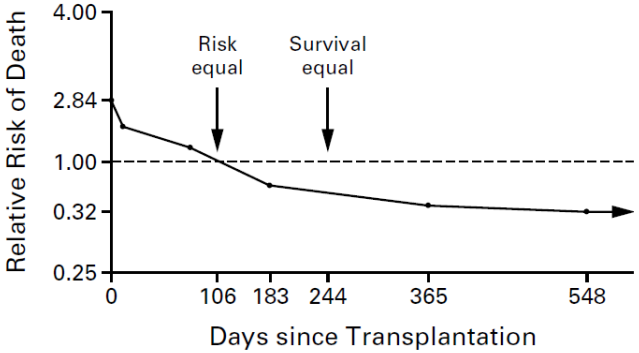


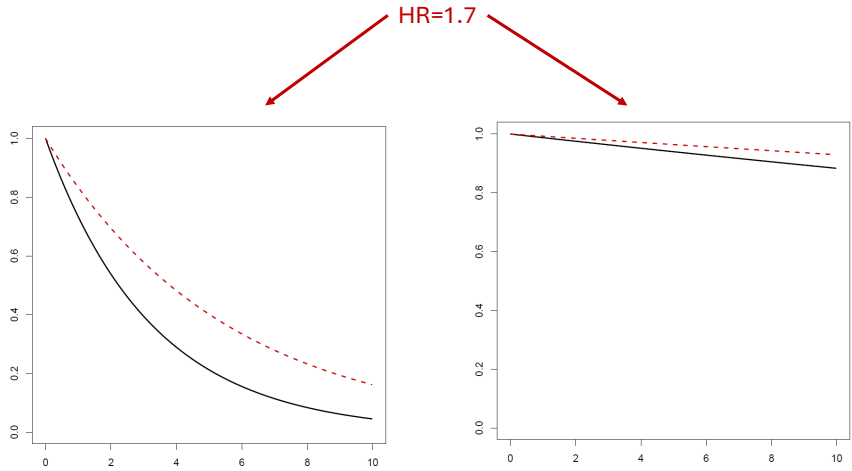
Figure 2. Adjusted Relative Risk of Death among 23,275 Recipients of a First Cadaveric Transplant.

The main limits of results from such an updated Cox model

$$\lambda(d \mid X, G(d)) = \lambda_0(d) \exp(\beta X + \gamma(d-u)G(d))$$

- Post-registration confounders $X(d)$ may bias the results.
- One can expect an overestimation of the KT effect : patients with a deteriorating health are less likely to be transplanted.
- The magnitude of the transplantation effect is difficult to interpret for Hazard Ratio (HR).

Interpretation of Hazard Ratios



Our objectives

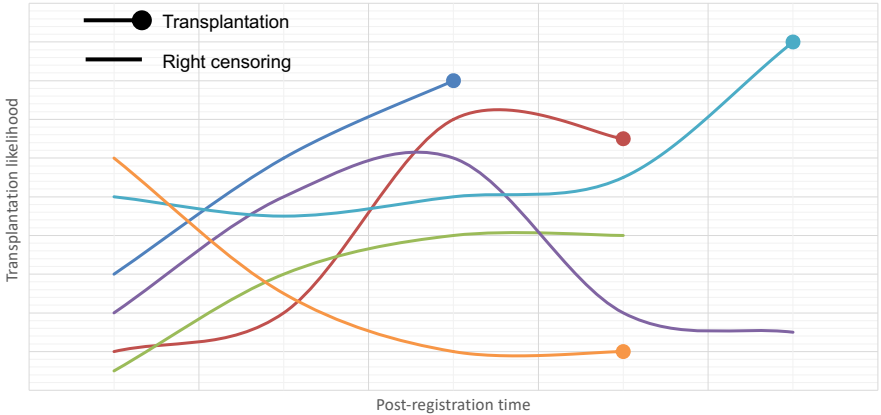
- To compare the life expectancy of KT recipients versus similar patients waiting for KT at the same time post-registration.
- To perform such analyses in the sub-population of obese patients.

Plan

Notations

- Transplantation group $(A = 1)$: patients who received a transplant at times U.
- Awaiting group $(A = 0)$: comparable patients who were not yet transplanted at U.
- Let $T = D - U$ and $S_a(t)$ the survival probabilities at the related time t for $A = a$.
- In terms of restricted mean survival times up to τ, one can define the two potential outcomes as $Y_a(\tau) = \int_0^\tau S_a(w)dw$.
- We aim to estimate the mean difference in life expectancy of the transplanted patients if they had not received a transplant at that time.

We adapted the method proposed by Lu (Biometrics ; 2005 ;61 :721-728)



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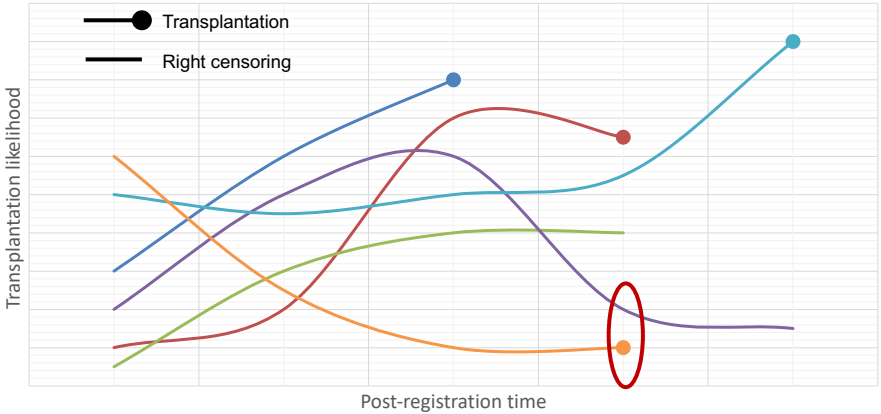

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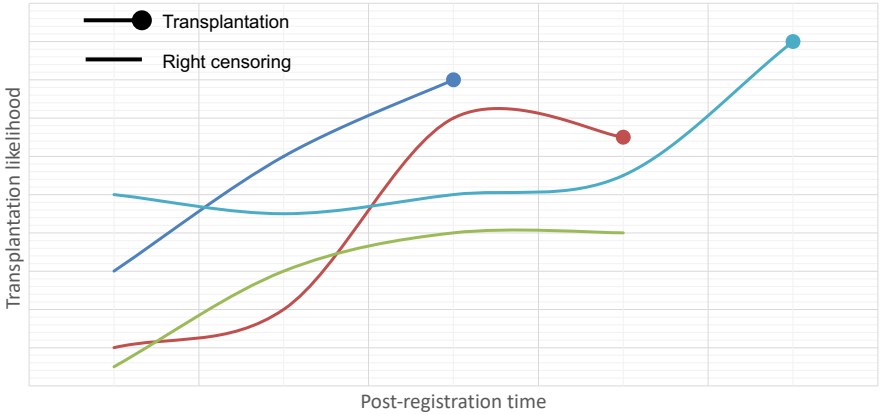

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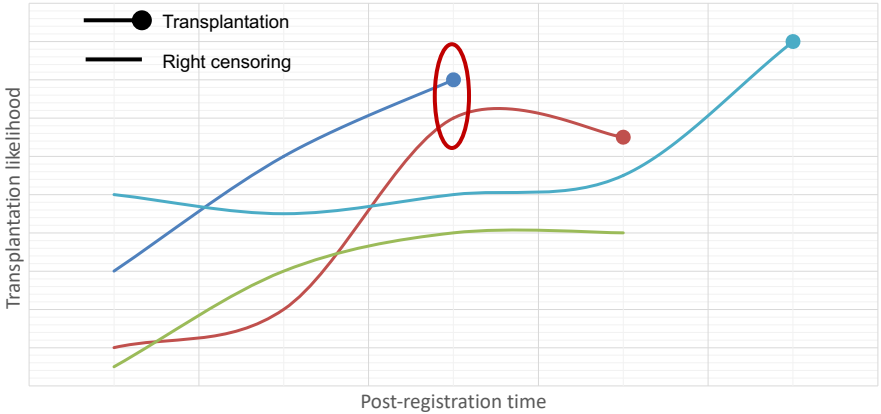

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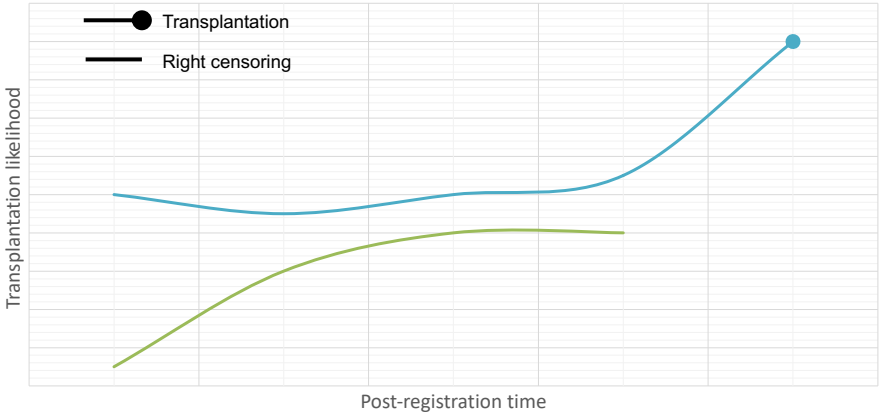


The first step : estimating the time-dependent likelihood of transplantation

- The hazard of receiving a kidney transplant at time u was estimated by using an updated Cox model :

$$\lambda(u \mid X(u)) = \lambda_0(u) \exp(\beta X(u))$$

- Death and waiting list removal were right-censored.
- We considered the following 10 covariates (drawing a directed acyclic graph) :
  - Time-fixed variables : age, sex, blood group, time from dialysis to registration, year of registration on the waiting list, duration of temporary contraindication, history of diabetes and living area.
  - Time-dependent variables : Body mass index, calculated panel reactive antibody.

The second step : matching pairs

- Because the baseline hazard function constant at each matching time point, one can match on the linear predictor $\beta X(u)$ from the Cox model.
- We used the nearest neighbor matching algorithm with a maximum caliper of 0.20.
- Exact matching was considered for the unbalanced covariates.
- We used random matching without replacement, meaning that once matched, a patient could not be matched again in another pair.

The third step : analysing the matched cohort

- The matching time corresponded to the pseudo-randomization $A = 1$ ou $A = 0$.
- From this baseline, the random variable T was the time-to-death with right censoring.
- We obtained $\hat{S}_a(t)$ by using the Kaplan-Meier estimator.
- The mean estimations and the related confidence intervals were derived by bootstrapping the full 3-step procedure.
- We respected an intention-to-treat approach : transplanted patients in group $A = 0$ were not censored/excluded.
- The cumulative probability of KT in the awaiting group was estimated by the Aalen-Johansen method.

Plan

Epidemiology ; 2021 ; 32 : 220-229

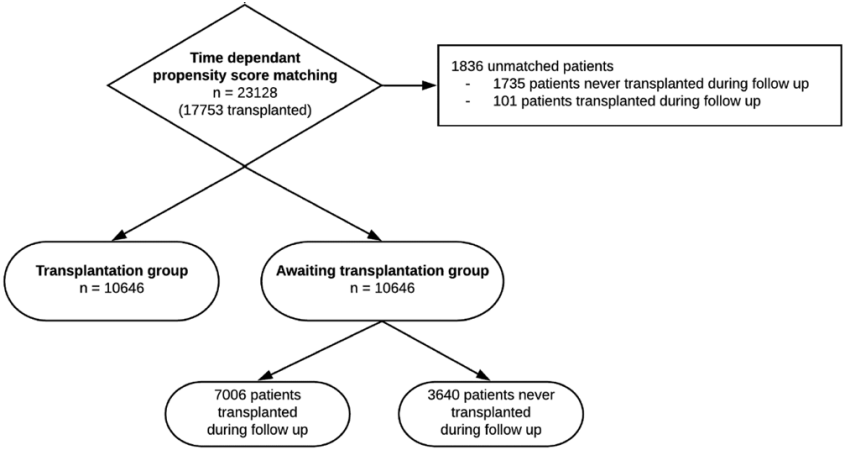
Clinical Trial Emulation by Matching Time-dependent Propensity Scores

The Example of Estimating Impact of Kidney Transplantation

Rémi Lenain,[a,b] *Julie Boucquemont,*[a] *Karen Leffondré,*[c] *Cécile Couchoud,*[d] *Mathilde Lassalle,*[d] *Marc Hazzan,*[b] *and Yohann Foucher*[a,e]

- 23,231 patients from the French REIN registry.
- First dialysis from 1 January 2005 to 31 December 2018.

Flowchart


Time dependant
propensity score matching
n = 23128
(17753 transplanted)
1836 unmatched patients
- 1735 patients never transplanted during follow up
- 101 patients transplanted during follow up
Transplantation group
n = 10646
Awaiting transplantation group
n = 10646
7006 patients
transplanted
during follow up
3640 patients never
transplanted
during follow up

Description of the unmatched patients

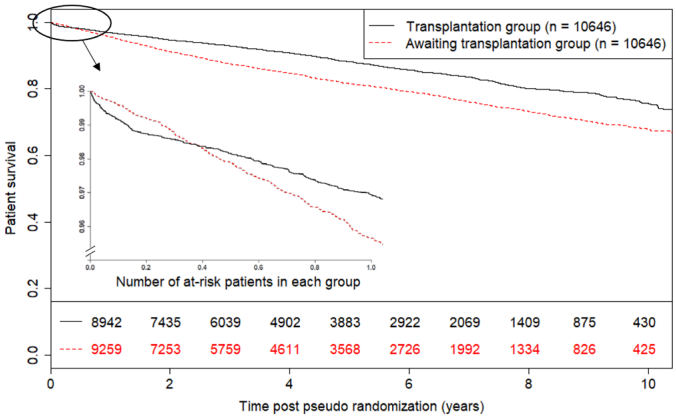
Median [interquartile range] Effective (%)	**Unmatched patients (N=1836)**	**Matched patients (N=21292)**	**p-value**
Recipient age (years)	57.7 [49.3;64.2]	54.8 [43.9;63.4]	<0.01
Male recipient	1184 (65%)	13635 (64%)	0.72
Recipient BMI (kg/m²)	26.0 [22.8;30.1]	24.9 [22.1;28.4]	<0.01
Year of inscription on waiting list			<0.01
- 2005-2007	48 (2.6%)	2702 (13%)	
- 2008-2010	179 (9.7%)	5830 (27%)	
- 2011-2013	448 (24%)	7016 (33%)	
- 2014-2016	1161 (63%)	5744 (27%)	
Primary cause of end stage renal disease			<0.01
- Diabetic nephropathy	446 (24%)	2605 (12%)	
- Hypertension	351 (19%)	3237 (15%)	
- Other	238 (13%)	3400 (16%)	
- Polycystic Kidney Disease	198 (11%)	3480 (16%)	
- Primary glomerulopathy	283 (15%)	5034 (24%)	
- Pyelonephritis	78 (4.2%)	1037 (4.9%)	
- Unknown	242 (13%)	2499 (12%)	
Recipient blood group			<0.01
- A	574 (31%)	8428 (40%)	
- AB	61 (3.3%)	874 (4.1%)	
- B	314 (17%)	2546 (12%)	
- O	887 (48%)	9444 (44%)	
Dialysis technique			<0.01
- Hemodialysis	1630 (89%)	17981 (85%)	
- Peritoneal dialysis	206 (11%)	3310 (16%)	
Time from dialysis to inscription (days)	245.0 [21.5;496.0]	193.0 [-1.0;414.0]	<0.01
Calculated Panel Reactive Antibody > 0%	1270 (69%)	7835 (37%)	<0.01
Potential matched donors	277.0 [93.0;518.2]	424.0 [179.0;634.0]	<0.01
Positive anti-HLA class I antibodies	513 (28%)	4453 (21%)	<0.01
Positive anti-HLA class II antibodies	315 (17%)	2923 (14%)	<0.01
History of diabetes	724 (39%)	4412 (21%)	<0.01

Well-balanced characteristics at the matching time

TABLE 2. Patient Characteristics in the Transplantation and Awaiting Transplantation Groups at the Time of Pseudo-Randomization

	Awaiting Transplantation Group (N = 10,646)	Transplantation Group (N = 10,646)	Standardized Difference (%)
Recipient age (years), median (IQR)	56.9 (45.8 to 65.1)	55.3 (44.5 to 64.0)	8.6
Male recipient, effective (%)	6782 (64)	6853 (64)	1
Recipient BMI (kg/m^2), median (IQR)	25.1 (22.3 to 28.6)	25.0 (22.1 to 28.4)	3.7
Year of inscription on waiting list, effective (%)			0
2005–2007	1351 (13)	1351 (13)	
2008–2010	2915 (27)	2915 (27)	
2011–2013	3508 (33)	3508 (33)	
2014–2016	2872 (27)	2872 (27)	
Primary cause of end-stage renal disease, effective (%)			4.3
Diabetic nephropathy	1316 (12)	1289 (12)	
Hypertension	1688 (16)	1549 (15)	
Other	1688 (16)	1712 (16)	
Polycystic kidney disease	1727 (16)	1753 (17)	
Primary glomerulopathy	2453 (23)	2581 (24)	
Pyelonephritis	517 (4.9)	520 (4.9)	
Unknown	1257 (12)	1242 (12)	
Recipient blood group, effective (%)			42
A	3243 (30.5)	5185 (48.7)	
AB	327 (3.1)	547 (5.1)	
B	1477 (13.9)	1069 (10.0)	
O	5599 (52.6)	3845 (36.1)	
Dialysis technique, effective (%)			3.1
Hemodialysis	9053 (85)	8928 (84)	
Peritoneal dialysis	1592 (15)	1718 (16)	
Time from dialysis to inscription (days), median (IQR)	201.0 (2.0 to 424.0)	185.0 (−3.0 to 404.0)	2.2

Survival curves and *HR*



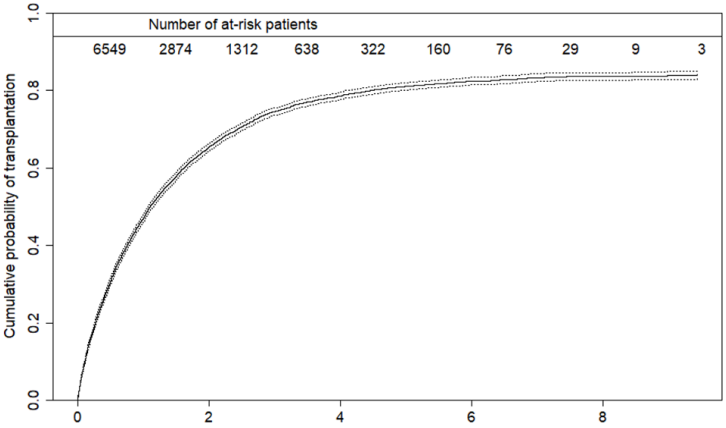
- The HR was 1.45 (95% CI = 1.11-1.90) during the first 3 months.
- The HR was 0.6 (95% CI = 0.55-0.65) afterwards.

Mean life expectancy according to several follow-up times

	Transplantation Group Mean Life Expectancy		Awaiting Transplantation Group Mean Life Expectancy		Mean Life Expectancy Difference		Relative Mean Life Expectancy Gain	
Time (years)	**RMST**	**95% CI**	**RMST**	**95% CI**	**ΔRMST**	**95% CI**	**%**	**95% CI**
1	0.98 years	0.98, 0.98	0.98 years	0.98, 0.98	0.03 months	–0.01, 0.08	0.27	–0.08, 0.65
3	2.9 years	2.9, 2.9	2.8 years	2.8, 2.8	0.93 months	0.7, 1.1	2.8	2.2, 3.4
5	4.7 years	4.7, 4.7	4.5 years	4.5, 4.5	2.4 months	2.0, 2.9	4.5	3.7, 5.3
10	8.8 years	8.7, 8.9	8.2 years	8.1, 8.3	6.8 months	5.5, 8.2	6.9	5.5, 8.3

RMST indicates restricted mean survival time.

Probability to be transplanted in the awaiting transplantation group



Plan

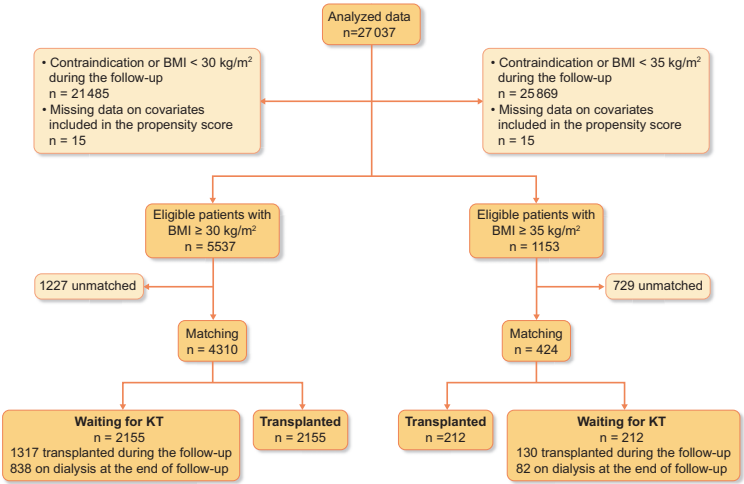
Nephrology Dialysis Transplantation ; 2022 ; 37 : 1768-1776

Impact of kidney transplantation in obese candidates: a time-dependent propensity score matching study

Christel Castelli [1,2], Yohann Foucher [1,3], Julie Boucquemont [4], Mathilde Prezelin-Reydit[5], Magali Giral[6], Emilie Savoye [7], Marc Hazzan[8] and Rémi Lenain [1,8]

- Same inclusion criteria compared to the first application.
- Two analyses by the exclusion of :
  - patients with BMI < 30 kg/m2 during the follow-up.
  - patients with BMI < 35 kg/m2 during the follow-up.

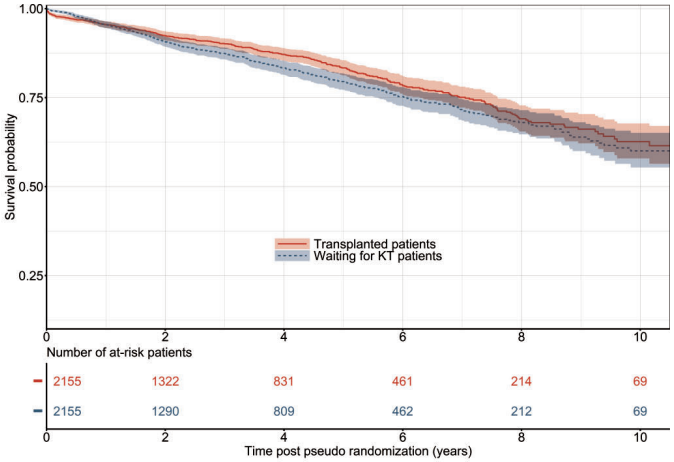
Flowchart of the studies



Description of two PS-matching cohorts

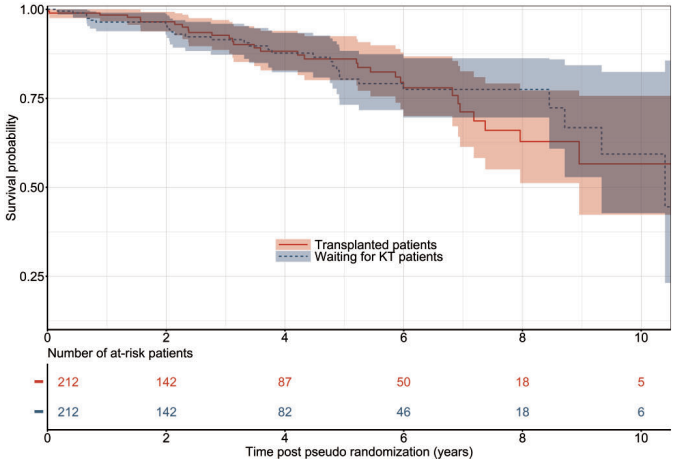
Characteristics	BMI ≥30 kg/m²			BMI ≥35 kg/m²		
	Waiting group ($n = 2155$)	Transplantation group ($n = 2155$)	Standardized difference (%)	Waiting group ($n = 212$)	Transplantation group ($n = 212$)	Standardized difference (%)
Recipient age (years), mean (SD)	57.3 (11.8)	57.2 (11.7)	1.3	55.5 (11.3)	54.8 (11.9)	5.6
Recipient sex (men)	1283 (59.5)	1232 (57.2)	3.7	94 (44.3)	96 (45.3)	1.6
Recipient BMI (kg/m²), mean (SD)	32.8 (2.5)	32.8 (2.5)	1.2	37.3 (2.1)	37.3 (2.2)	2.6
Primary cause of ESRD[a]			8.8			23
Diabetic nephropathy	519 (24.1)	493 (22.9)		60 (28.3)	55 (25.9)	
Hypertension	384 (17.8)	361 (16.8)		33 (15.6)	22 (10.4)	
Other	232 (10.8)	271 (12.6)		20 (9.4)	31 (14.6)	
Polycystic kidney disease	263 (12.2)	261 (12.1)		17 (8.0)	21 (9.9)	
Primary glomerulopathy	435 (20.2)	407 (18.9)		48 (22.6)	45 (21.2)	
Pyelonephritis	92 (4.3)	113 (5.2)		7 (3.3)	8 (3.8)	
Unknown	230 (10.7)	249 (11.6)		27 (12.7)	30 (14.2)	
Recipient ABO group			6.8			20.5
A	934 (43.3)	937 (43.5)		92 (43.4)	82 (38.7)	
AB	78 (3.6)	107 (5.0)		9 (4.2)	17 (8.0)	
B	233 (10.8)	225 (10.4)		16 (7.5)	23 (10.8)	
O	910 (42.2)	886 (41.1)		95 (44.8)	90 (42.5)	
ECD (among deceased donor)	–	1295 (70.6)		–	111 (62.7)	
KDPI >80	–	959 (52.5)		–	68 (38.2)	
Dialysis technique (hemodialysis)	1900 (88.2)	1862 (86.4)	5.1	190 (89.6)	192 (90.6)	3.1
Time from dialysis to registration (days), mean (SD)	266.8 (519.6)	280.4 (560.5)	2.5	245.1 (437.7)	284.5 (506.2)	8.3
Contraindication cumulative time (days), mean (SD)	192.0 (301.9)	188.9 (299.3)	1	206.2 (294.3)	187.1 (325.6)	6.2
cPRA (>0)	894 (41.5)	920 (42.7)	2.1	113 (53.3)	107 (50.5)	4.6
Positive anti-HLA class I antibodies	520 (24.1)	480 (22.3)	4.1	59 (27.8)	60 (28.3)	1
Positive anti-HLA class II antibodies[a]	314 (14.6)	292 (13.5)	2.8	45 (21.2)	32 (15.1)	15.1

Survival of patients with a BMI $\geqslant$ 30 kg/m2



- The survival at 10 years was 0.63 (95% CI 0.55-0.71) in the KT group ($A = 1$).
- This value was 0.60 (95% CI 0.52-0.68) in the awaiting group ($A = 0$).

Survival of patients with a BMI $\geqslant$ 35 kg/m2



- The survival at 10 years was 0.57 (95% CI 0.28-0.85) in the KT group ($A = 1$).
- This value was 0.59 (95% CI 0.27-0.92) in the awaiting group ($A = 0$).

Plan

Interpretation of the results

- We did not compared KT versus long-term dialysis but early versus delayed KT.
- Overall population :
  - The life expectancy gain due early KT was 6.8 months (95% CI = 5.5-8.2).
  - It confirms the benefit of early KT when possible.
- Obese population :
  - We did not reported an increase of the life expectancy gain due early KT.
  - With the current organ shortage, our results suggest the possibility of delaying KT :
    - Other candidates may benefit from early KT.
    - This period could be used for weight loss of KT candidates.

Limitations of the results

- We did not consider the quality of life.
- We may have missed possible confounders.
- Other indicators can better characterize obesity, such as those discussed waist circumference.

Methodological points to keep in mind

- When using time-dependent propensity scores ?
  - To compare early versus delaying exposure/intervention.
  - To deal with immortal time bias.
  - To consider possible time-dependent confounders.
- The entire 3-step procedure must be bootstrapped.
- The analyses must respect the intended-to-treat principal.
- Check the balance of the possible confounders.
- Discuss the possible selection bias of unmatched individuals.

References

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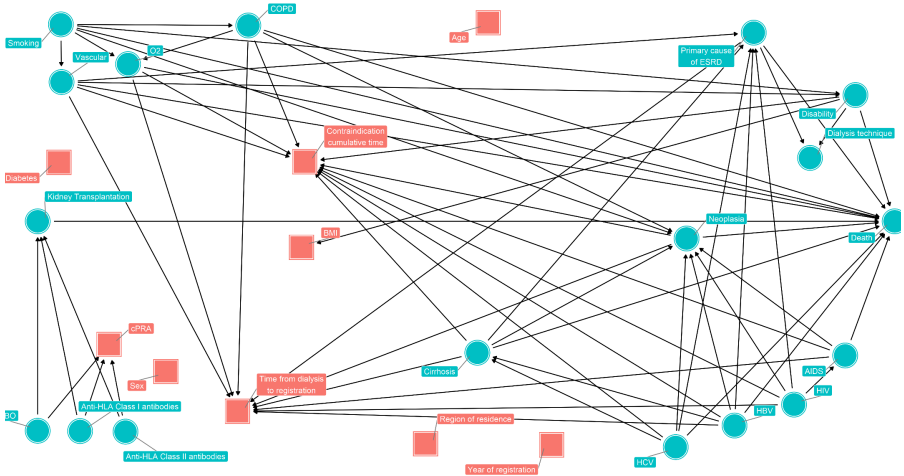
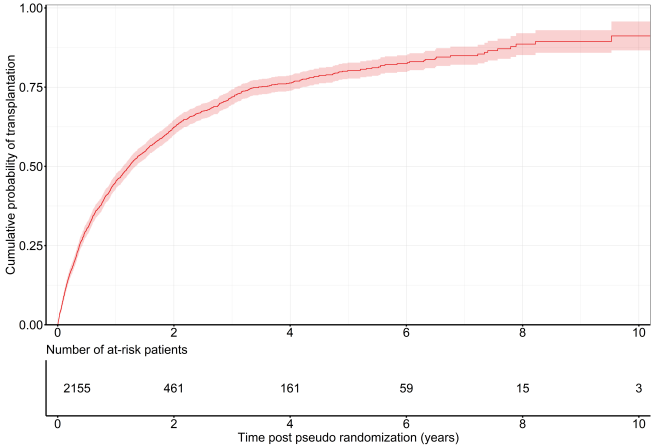
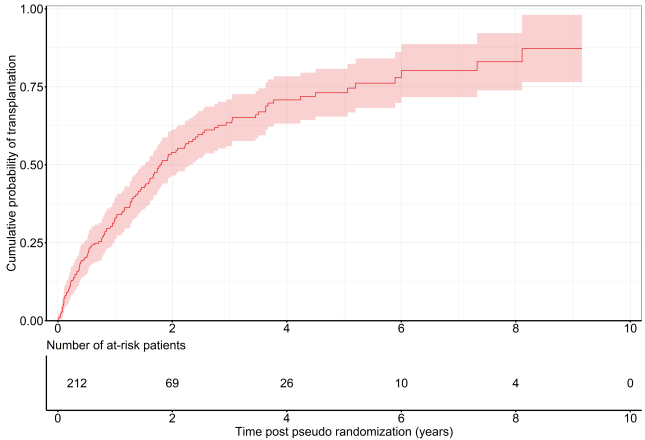
Directed acyclic graph



Cumulative probabilities of KT in the waiting group $\geqslant$ 30 kg/m2



Cumulative probabilities of KT in the waiting group $\geqslant$ 35 kg/m2



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