Kidney transplant recipients survival : mortality prediction

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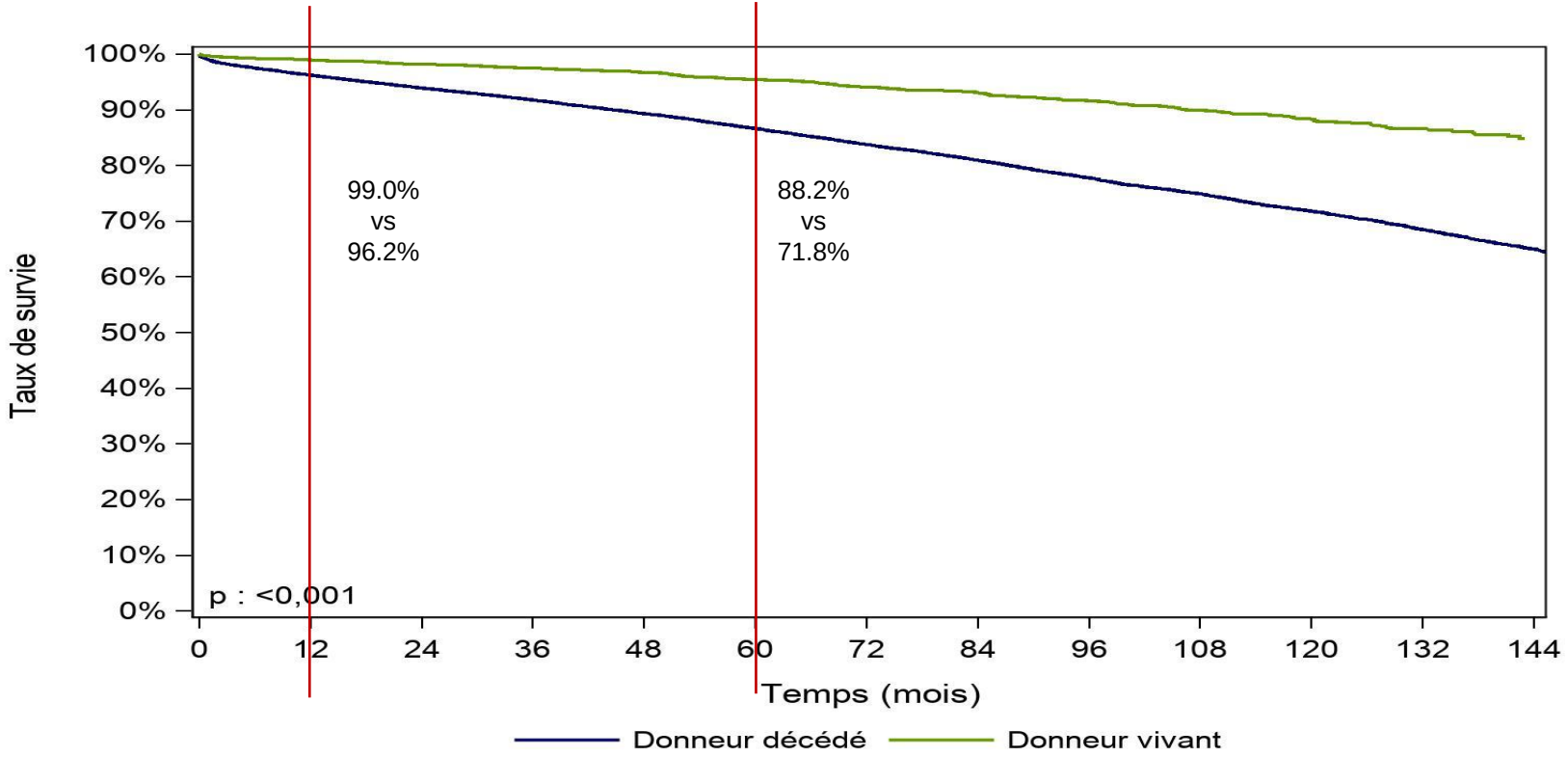
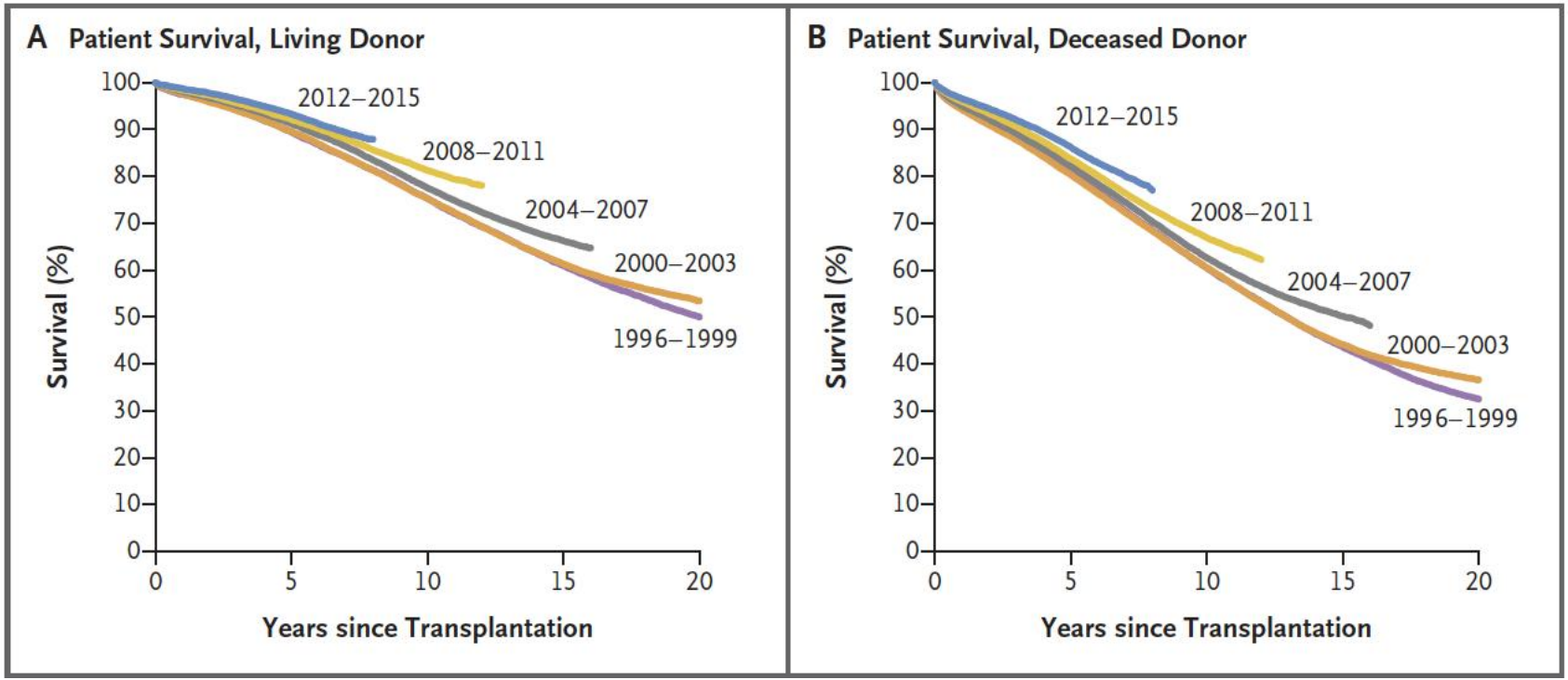
(MD, MPH)

Living vs Deceased donors (ABM)



Agence de la biomédecine, period 2007-2019.

The US experience



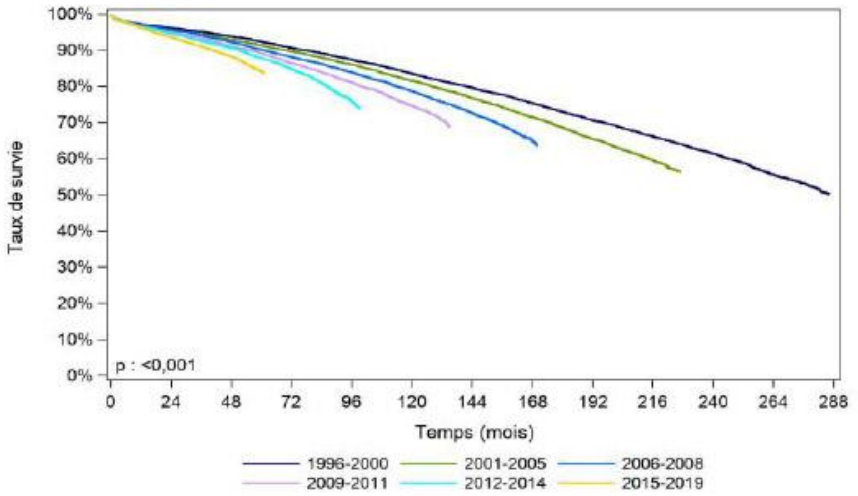
Graft and Patient Survival after Kidney Transplantation in the United States.
Kaplan–Meier estimates of patient after transplantation of grafts from living donors (Panel A) and deceased donors (Panels B), with the data grouped in 4-year cohorts from 1996 to 2015. There were gradual improvements in patient and graft survival from the 1996–1999 period to the 2012–2015 period.

N Engl J Med 2021;385:729-43.

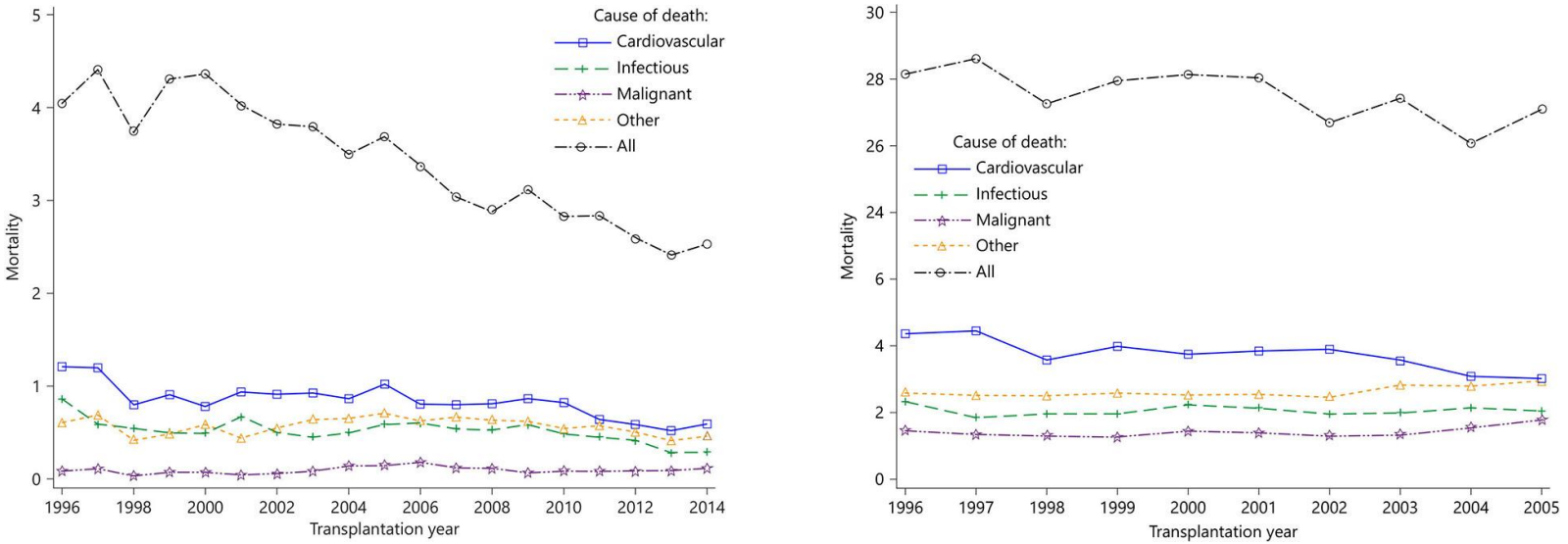
The French experience

Figure R16. Survie du receveur après greffe rénale selon la période

Période de greffe	N	Survie à 1 mois	Survie à 1 an	Survie à 5 ans	Survie à 10 ans	Survie à 15 ans	Médiane de survie (mois)
1996-2000	7753	99,30% [99,0% - 99,4%]	97,20% [96,9% - 97,6%]	92,40% [91,8% - 93,0%]	83,60% [82,7% - 84,4%]	73,00% [72,0% - 74,0%]	NO
nombre de sujets à risque*		7682	7495	7024	6190	5250	
2001-2005	9697	99,10% [98,9% - 99,2%]	97,10% [96,7% - 97,4%]	91,30% [90,7% - 91,9%]	81,50% [80,7% - 82,3%]	68,60% [67,7% - 69,6%]	NO
nombre de sujets à risque*		9596	9378	8708	7567	5185	
2006-2008	7232	99,20% [99,0% - 99,4%]	97,10% [96,7% - 97,5%]	90,20% [89,5% - 90,9%]	78,70% [77,7% - 79,6%]	NO	NO
nombre de sujets à risque*		7167	6997	6432	5334	0	
2009-2011	7403	99,20% [99,0% - 99,4%]	96,80% [96,3% - 97,1%]	89,30% [88,5% - 90,0%]	74,70% [73,6% - 75,7%]	NO	NO
nombre de sujets à risque*		7338	7147	6481	2327	0	
2012-2014	7978	99,10% [98,8% - 99,3%]	96,70% [96,3% - 97,1%]	87,80% [87,1% - 88,5%]	NO	NO	NO
nombre de sujets à risque*		7884	7660	6564	0	0	
2015-2019	15632	99,00% [98,9% - 99,2%]	96,30% [96,0% - 96,6%]	84,00% [83,0% - 85,0%]	NO	NO	NO
nombre de sujets à risque*		15247	13415	1156	0	0	



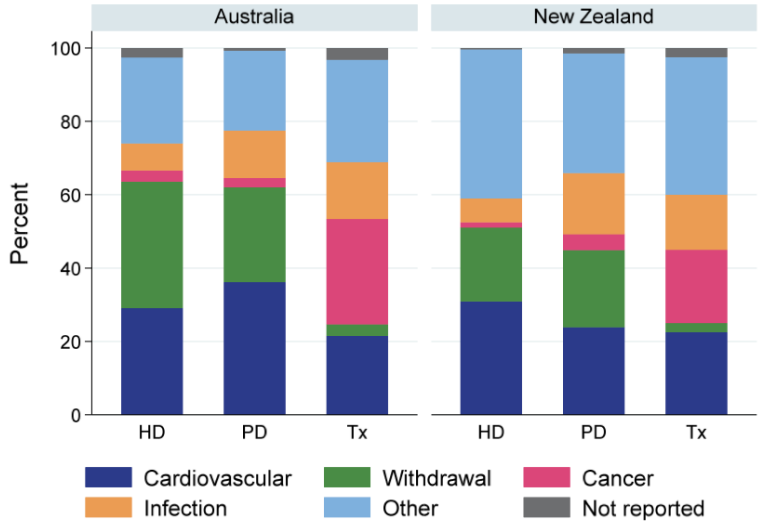
Causes of Death



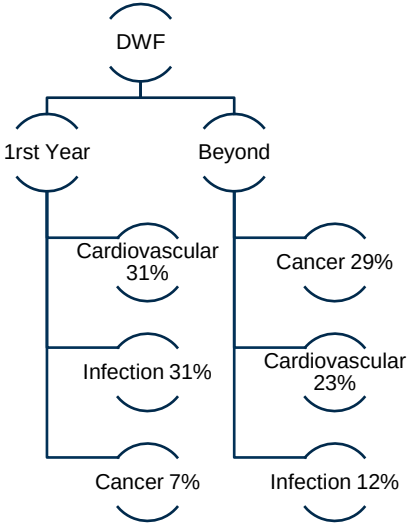
Trends of 1-year and 10 years all-cause and cause-specific mortality among KTRs in USA[1]

1. Awaan A.A. Am J Nephrol 2018;48:472-481,

Causes of Death



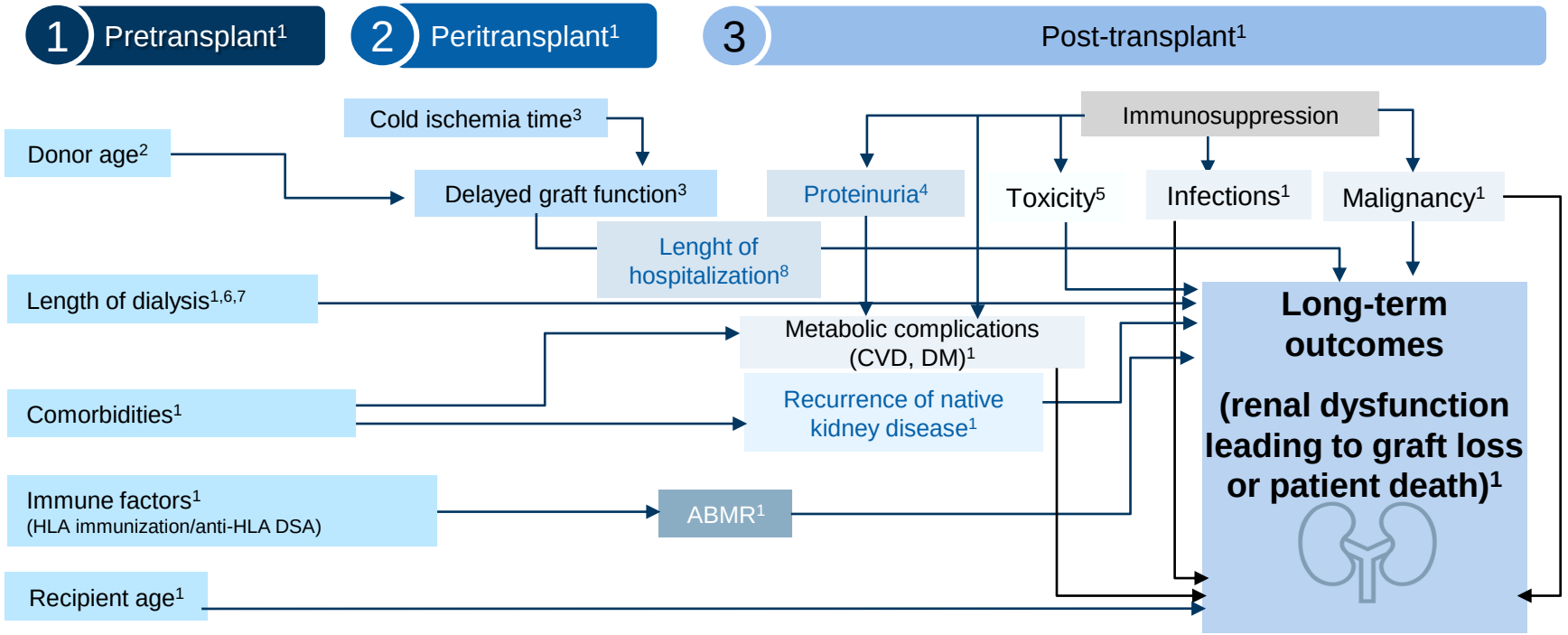
Cause of Death by Modality- Deaths Occuring 2020 in Australia & New Zealand [1].



Cause of Death with Function categorised by timing post-transplant [2]

1. Anzdata 44 annual report 2021 anzdata.org.au. 2. Anzdata 43RD Annual Report 2020 (data to 2019)

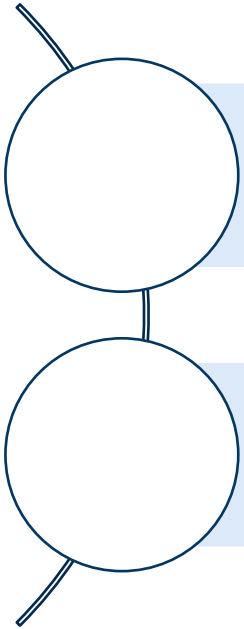
Several factors that can affect long-term Outcomes after Kidney transplantation



ABMR, antibody-mediated acute rejection; CVD, cardiovascular disease; DM, diabetes mellitus; DSA, donor-specific antibodies; HLA, human leukocyte antigen; I/R, 7 ischemia reperfusion.

1. Legendre C et al. *Transpl Int.* 2014;27:19-27; **2**. Foster BJ et al. *Transplantation* 2013;96: 469-475; **3**. Irish WD et al. *Am J Transplant*;.2010; 10: 2279–2286; 4. Halimi JM. *Transplantation* 2013;96:121-130; **5.** Nankivell BJ. *Transplantation*. 2004;78(4):557-565. **6**. Cosio et al**. 7**. Meier-Kriesche and Schold, Semin Dial. 2005, **8**. Lin SJ et al. Clin Transplant 2006:20: 245–252.

Why to perform mortality modelling?



To determine independantly **associated factors**

- Increase knowledge
- Allow intervention

To **predict** long-term events

- Inform medical decision and medical care
- Act as surrogate endpoint

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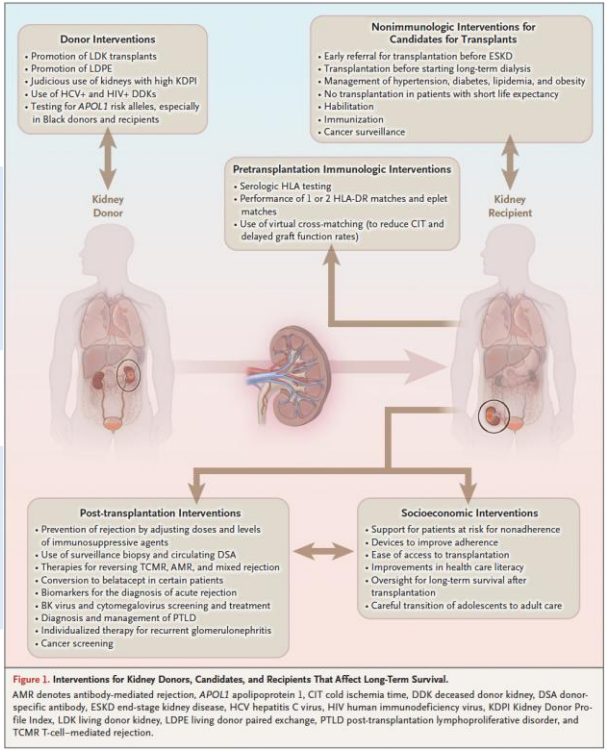


Figure 1. Interventions for Kidney Donors, Candidates, and Recipients That Affect Long-Term Survival.

AMR denotes antibody-mediated rejection, *APOL1* apolipoprotein 1, CIT cold ischemia time, DDK deceased donor kidney, DSA donor-specific antibody, ESKD end-stage kidney disease, HCV hepatitis C virus, HIV human immunodeficiency virus, KDPI Kidney Donor Profile Index, LDK living donor kidney, LDPE living donor paired exchange, PTLD post-transplantation lymphoproliferative disorder, and TCMR T-cell–mediated rejection.

Hariharan S, Israni AK, Danovitch G. Long-Term Survival after Kidney Transplantation. N Engl J Med. 2021 Aug 19;385(8):729-743.

Kidney transplantation outcomes and regulatory endpoints

How are outcomes measured and what are the endpoints currently used by the regulatory agencies (e.g. FDA, EMA) ?

Currently, one-year outcomes are relevant for regulatory agencies (Acute rejection, Graft loss or Death) to approve a new drug in transplantation

These one-year parameters are only restricted early after transplantation

Defining endpoints for next generation trials in Kidney transplantation

Limitations

Designing studies with 5- or 10-year graft and patient survivals

- Unrealistic in terms of cost

1-year graft and patient survivals

- Irrelevant today for superiority trials
- Already reached good graft patient survival in transplant population (~95%); further improvement is difficult

Need to define realistic and feasible endpoints for upcoming clinical trials

Haas M et al. *Am J Transplant.* 2018;18:293-307.

Need for a tool to predict long-term outcomes

Kidney transplantation currently lacks robust models to predict long-term patients' survival, which represents a major unmet need in clinical care and clinical trials[1,2]

Current major endpoints include 1-year patient and graft survival and incidence biopsy-proven rejection; however, these do not help assess long-term patients' survival [1]

There is a need for a novel endpoint that better predicts patients' life expenctancy[3]

A prognostic biomarker is needed – that will combine traditional factors and biomarker candidates to represent the complete spectrum of risk-predicting parameters[1,4,5]

BPAR, biopsy-proven acute rejection.

1. Stegall M et al. *Am J Transplant*. 2016;16:1094-1101; **2.** Mannon RB et al. *Am J Transplant*. 2020. doi: 10.1111/AJT.15833; **3**. Haas M et al. *Am J Transplant*, 2018;18(2):293–307; **4.** Loupy A, Aubert O et al. *B.Med J.* 2019;366:l4923; **5.** Schold JD, Kaplan B. *Am J Transplant*. 2010; 10: 1163-1166.

Mortality Prediction

- Many variables are associated with death (univariable models or with few covariables).

- Some mortality score have emerged during the past years with heterogenous performances.

Team Year	Baskin-Bey et al. RRS, 2009	Hernandez et al. 2009	Kasiske et al. 2010	Lorent et al. 2016
Country	USA	Espagne	USA	France
Computation time	Before transplantation	1 year post-transplant	1 year post-transplant (or D0 or D7)	1 year post-transplant
Predicted event	Death	Death at 3 years	Graft loss or death at 5 years	Death
Recipients variables prior to transplantation	Age Diabetes Dialysis duration Angor/Coronaropathy	Age Diabetes HCV Angor/Coronaropathy	Age Cause of CKD Ethnicity Assurance	Age Diabetes Dialysis duration Cardio-vascular event
Recipients variables up to 1 year post-transplantation		NODAT	Hospitalisation during first year	
Biological variables at one year		Creatinin Proteinuria	GFR	Creatinin
Follow-up variables		Tacrolimus or MMF		
Methodology	Cox	Cox	Cox	Cox
Performances	C-stat = 0.78 (for 5Y)	C-stat = 0.74 IC 95% = 0.70-0.77	C-stat = 0.72	AUC = 0.77 (4Y) et 0.78 (10Y)
Internal validation		Cross-validation	Cross-validation	Cross-validation
External validation	-	No	-	Yes: Suiss cohort

Objective of our study

- The aim of this study is to create a score at one-year post-transplantation that accurately predicts long-term patient mortality

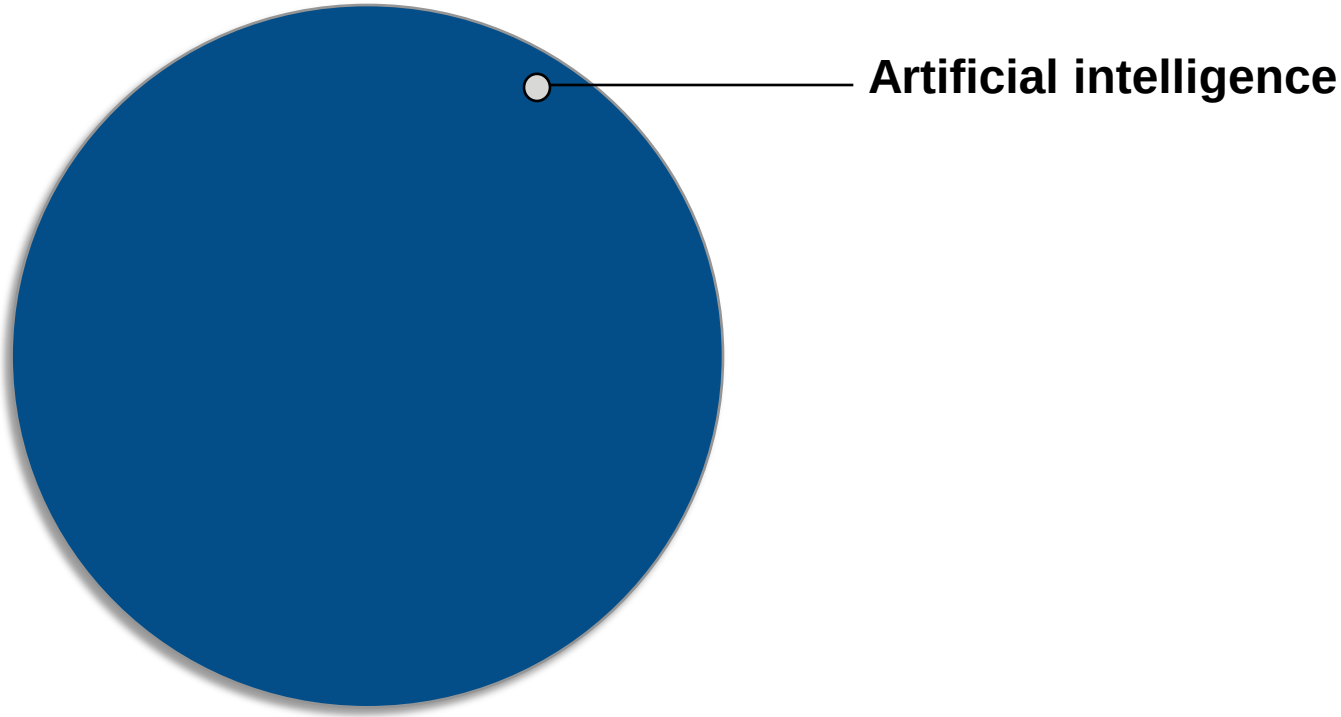
- Using Artificial Intelligence : traditional Cox model or Machine Learning methods.

Artificial intelligence: definition

Artificial intelligence is a science like mathematics or biology. It studies ways to build intelligent programs and machines that can creatively solve problems, which has always been considered a human prerogative

Artificial Intelligence vs. Machine Learning vs. Deep Learning: Essentials; Yulia Gavrilova, April 2020. Link: https://serokell.io/blog/ai-ml-dl-difference (Accessed May 2021)

Artificial intelligence, machine learning and deep learning: three different things



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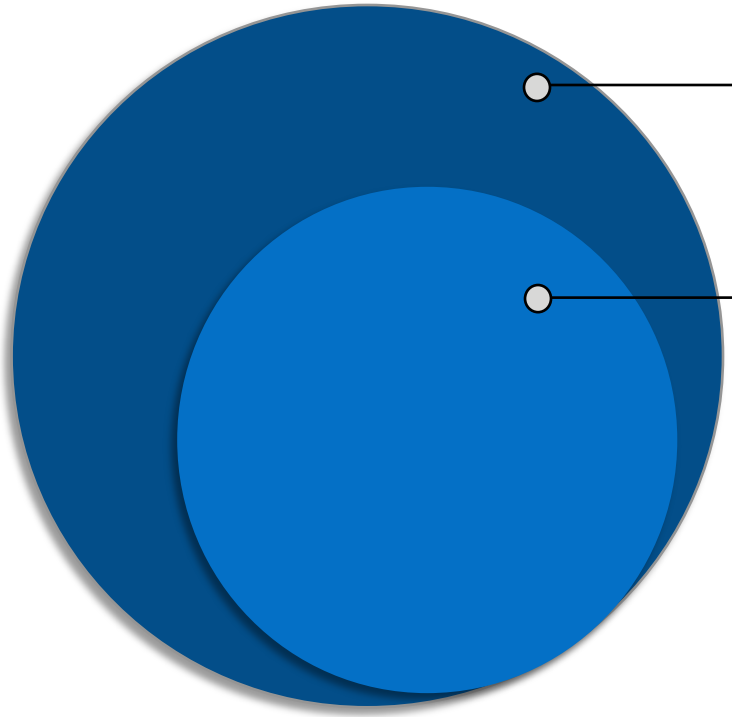

Artificial intelligence

Machine learning

Provides systems the ability to automatically learn and improve from experience without being explicitly programmed

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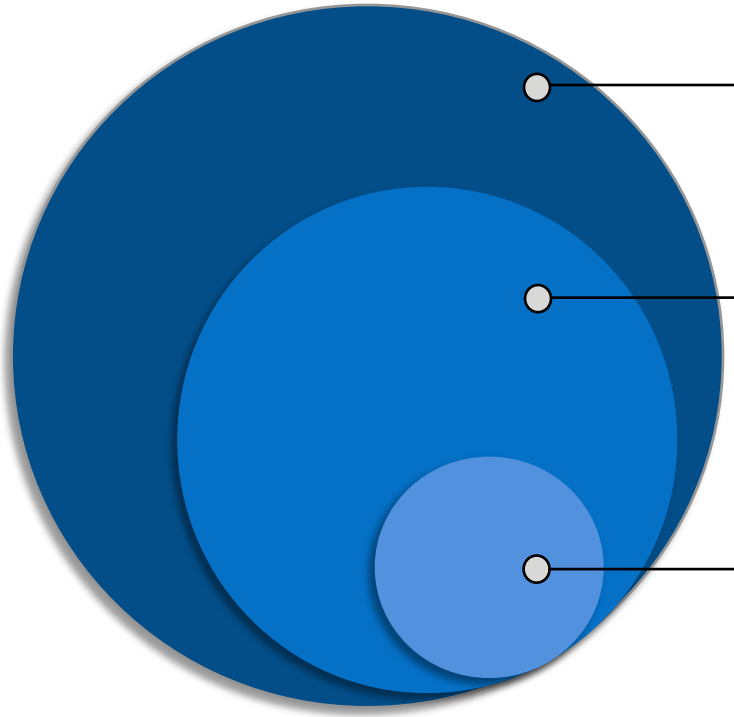

Artificial intelligence

Machine learning

Provides systems the ability to automatically learn and improve from experience without being explicitly programmed

Deep learning

Uses the neural networks to analyze different factors with a structure that is similar to the human neural system

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What includes ‘machine learning’?

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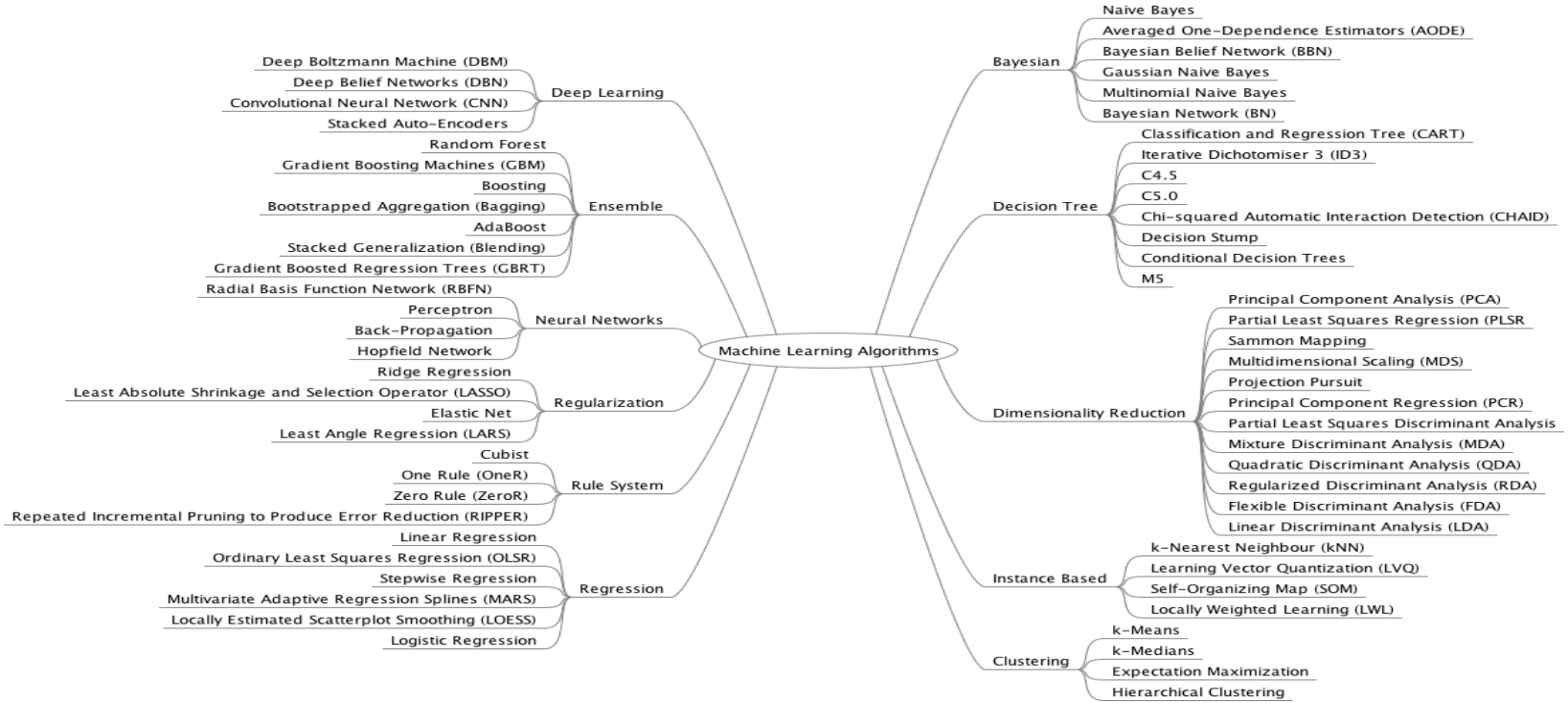

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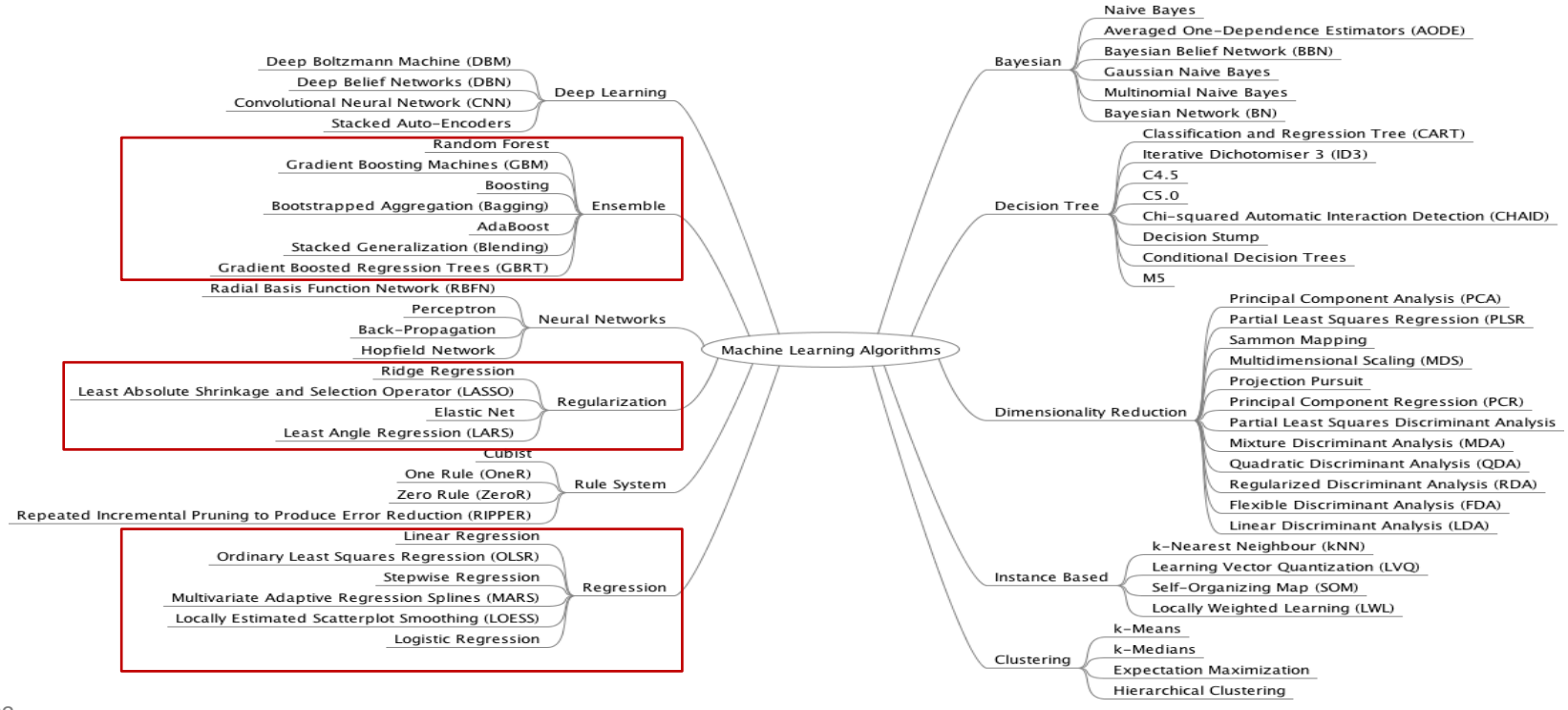
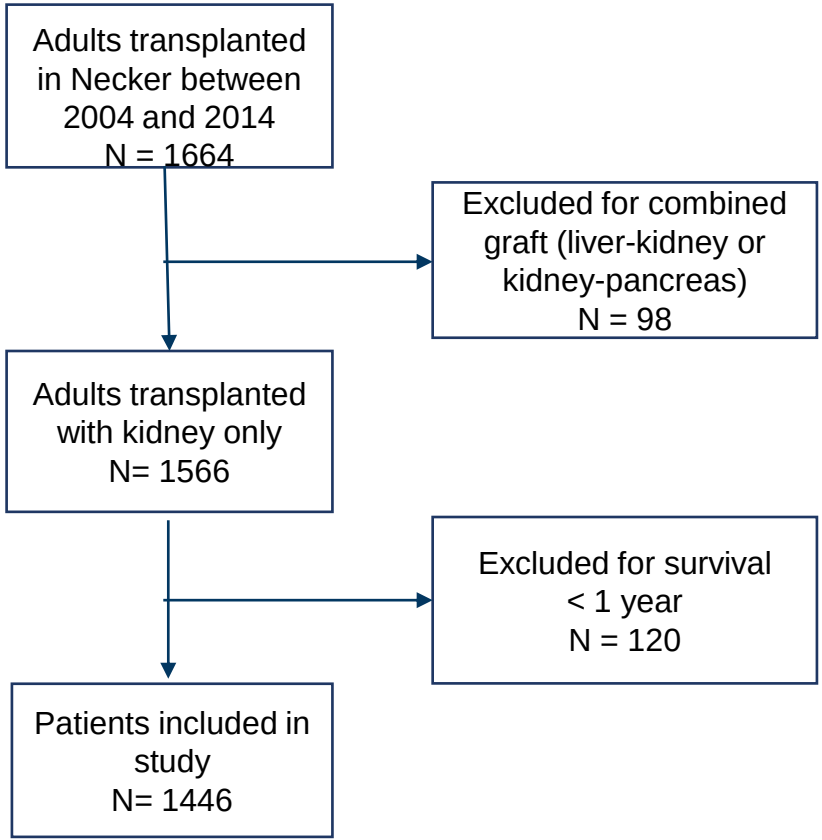


MORTALITY PREDICTION ALGORYTHM

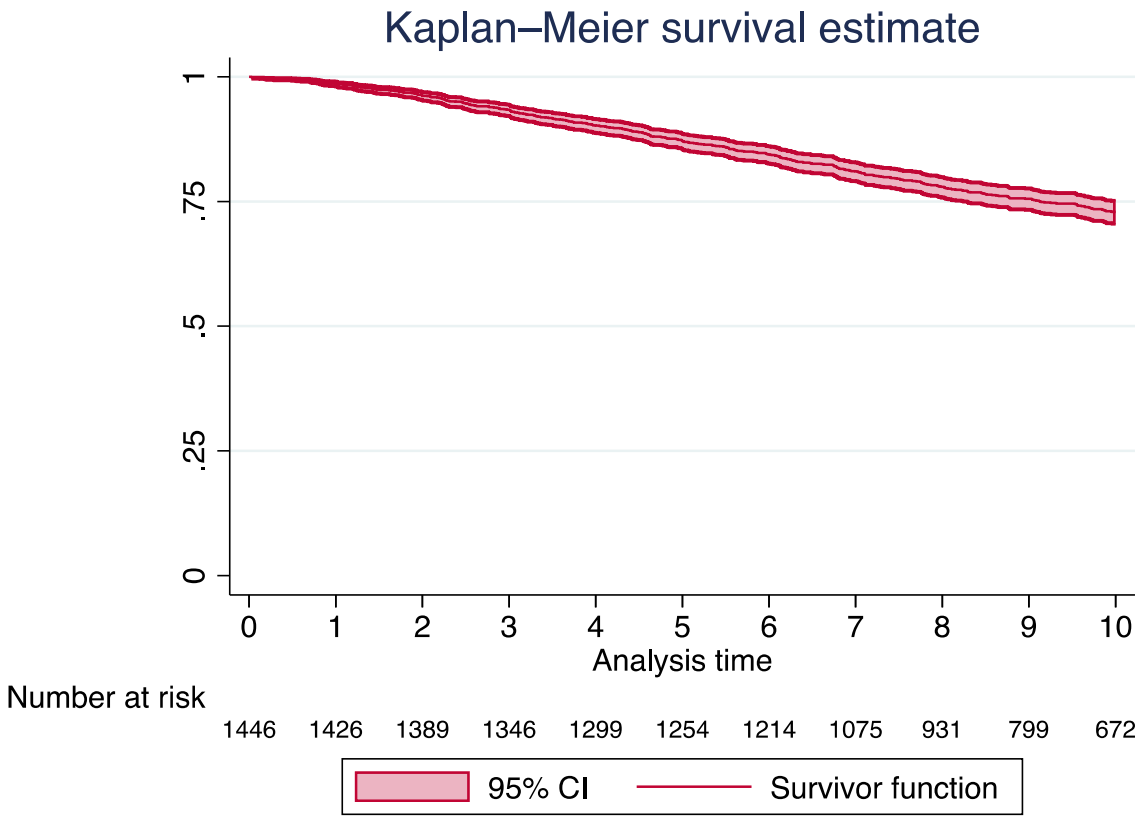
One-year prediction

STUDY DESIGN

- Consecutive kidney transplant recipients at Necker hospital
- Inclusion time : 2004-2014
- Evaluation at one year post-transplant
- 427 deaths during the study period
- Median follow-up : 10.6 years

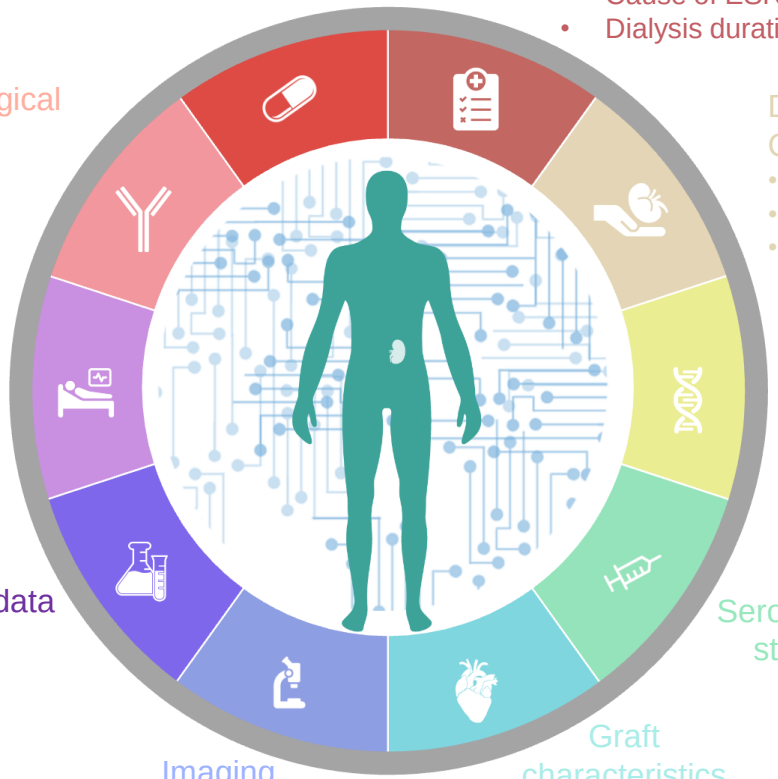


Kaplan-Meier curve



DATA COLLECTION

> 160 parameters



Treatments

Registry data
- Demographic data
- Cause of ESRD
- Dialysis duration

Immunological data

Donor Characteristics
- Age
- Sex
- History

Complications during first year

Recipient history

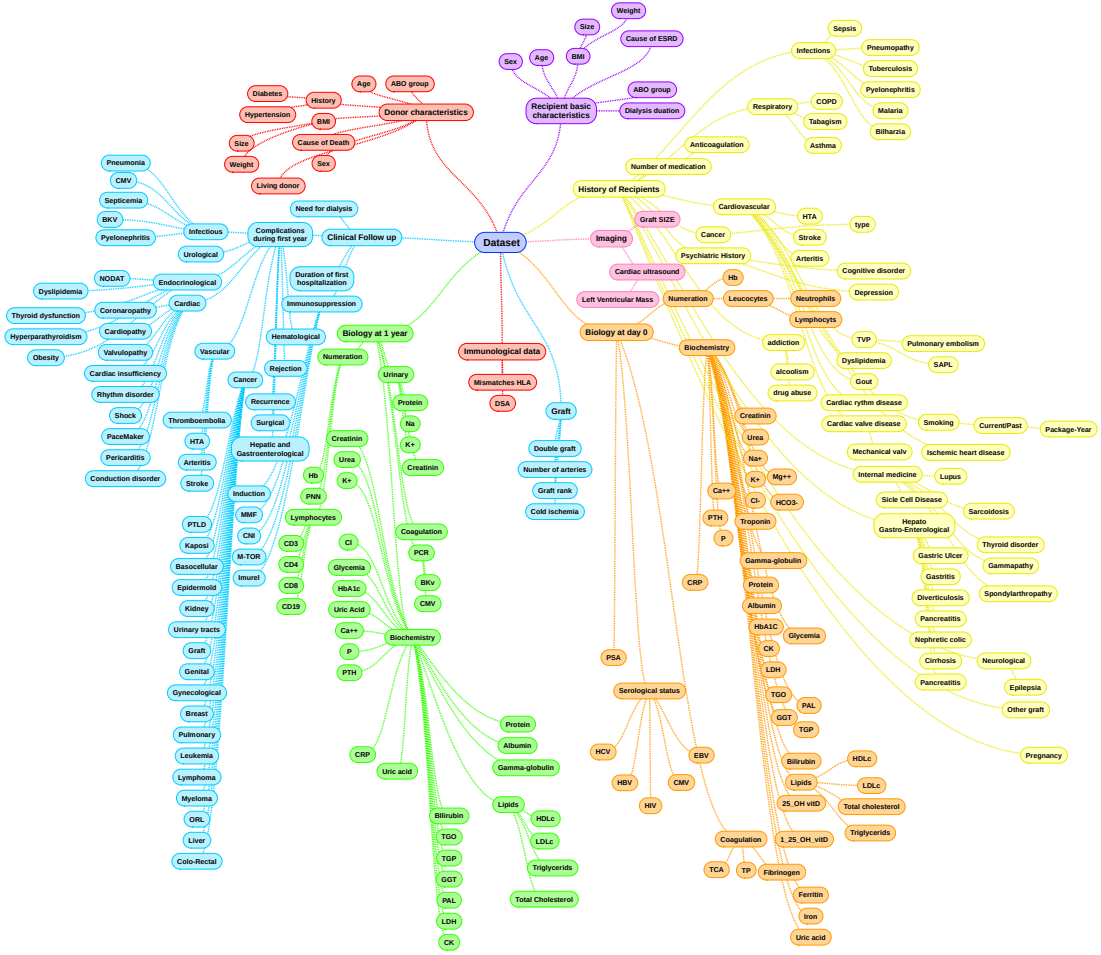
Biological data
- Day 0
- 1 year

Serological status

Imaging

Graft characteristics

MULTIPLE SOURCES OF DATA



- Recipient history
- Biology day 0
- Biology 1 year
- Clinical Follow-up
- Donor basic characteristic
- Recipient basic characteristic
- Imaging

Recipients characteristics

Recipient characteristics	n	Cohort
Age, mean (SD), years	1446	49.35 (14.19)
Gender male, No. (%)	1446	878 (60.72)
BMI, mean, kg/m2	1446	25.02 (4.52)
ESRD causes : **Glomerulonephritis, No. (%)** **PKD, No. (%)** **Diabetes, No. (%)** **Hypertension, No. (%)** **NIC** **Other, No. (%)** **Unknown, No. (%)**	1446	 407 (28.15) 144 (9.96) 117 (8.91) 59 (4.08) 222 (15.35) 173 (11.96) 309 (21.37)
Dialysis, No. (%)	1446	1164 (80.50)
Time since onset of dialysis, median (IQR)	1446	3.18 (0.82 - 6.25)
Cardiac echography **Left Ventricular Mass, mean (SD)**	1446	128.35 (29.24)
Kidney transplant imaging **Kidney size, mean (SD), cm**	1446	11.05 (0.82)

Donors characteristics

Donors characteristics	n	Cohort
Age, mean (SD), years	1446	53.47 (16.86)
Gender male, No. (%)	1446	758 (52.42)
BMI, mean, kg/m2	1446	25.42 (4.92)
Hypertension, No %	1446	404 (27.94)
Diabetes, No %	1446	101 (6.98)
Living Donor, No. (%)	1446	337 (23.31)
Vascular Death, No %	1109	639 (57.62)
Last creatinine ,mean (SD), µmol/L	1446	88.71 (52.20)

Transplant characteristics

Transplant characteristics	N	Cohorte
Graft rank **1** **2** **3** **4** **5**	1446	 1177 (81.40) 211 (14.59) 51 (3.53) 5 (0.35) 2 (0.14)
Dual kidney graft, No. (%)	1446	132 (9.13)
Number of renal arteries >1, No. (%)	1446	326 (22.54)
DSA, No. (%)	1446	315 (21.78)
HLA A/B/DR mismatchs, mean (SD), number	1446	3.61(0.04)
Duration of first hospitalization, mean (SD), days	1446	19.47 (11.16)
Dialysis après transplantation, No.(%)	1446	339 (23.44)
Follow-up (years), median (IIQ)	1446	10.59 (7.94 – 13.71)
Death events, No. (%)	1446	427 (29.53)
Graft loss, No. (%)	1446	277 (19.16)

Univariable Analysis

- Age
- BMI
- CMV
- VHC
- Hypertension
- MACCE
- Dyslipidemia
- Diabetes
- Cardiac rhythm disorder
- Valvulopathy
- COPD
- Smoking
- Asthma
- Tuberculosis
- Gastic Ulcer
- Diverticulosis
- Cancer
- Monoclonal Gammapathy
- Psychiatric disorder
- Number of medication
- Dialysis history
- Immunosuppression
- Left ventricular mass
- Kidney transplanted size
- Mismatches HLA, DSA
- Cold ischemia time, dual kidney transplantation, Living donor,
- Donor : Sex, BMI, Hypertension, Diabetes
- Complications:
  - Recurrency, Vascular, Cardiac, infection, surgical, anemia, urological, cancer, NODAT
- Biology :
  - GFR, RPCU
  - Albumin, Na, Cl, K, Uric acid, LDH,PTH, GGT, CK, triglycerids, CRP, HbA1C,
  - Hb, Neutrophils, Lymphocytes

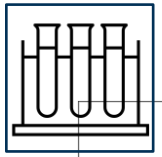
VARIABLES INCLUDED IN THE FINAL MULTIVARIABLE COX MODEL

Recipient's History

- Age (HR=1.07, CI: 1.06-1.08)
- Major CV events. (HR=1.71, CI:1.35-2.16)
- Psychiatric history (HR=2.62, CI:1.75-3.92)
- HCV status (HR=1.59, CI:1.11-2.29)
- Left Ventricular Mass (HR = 1.01, CI:1.001-1.008)
- DSA before transplantation (HR = 1.32, CI: 1.03-1.71)

Complications during the First Year

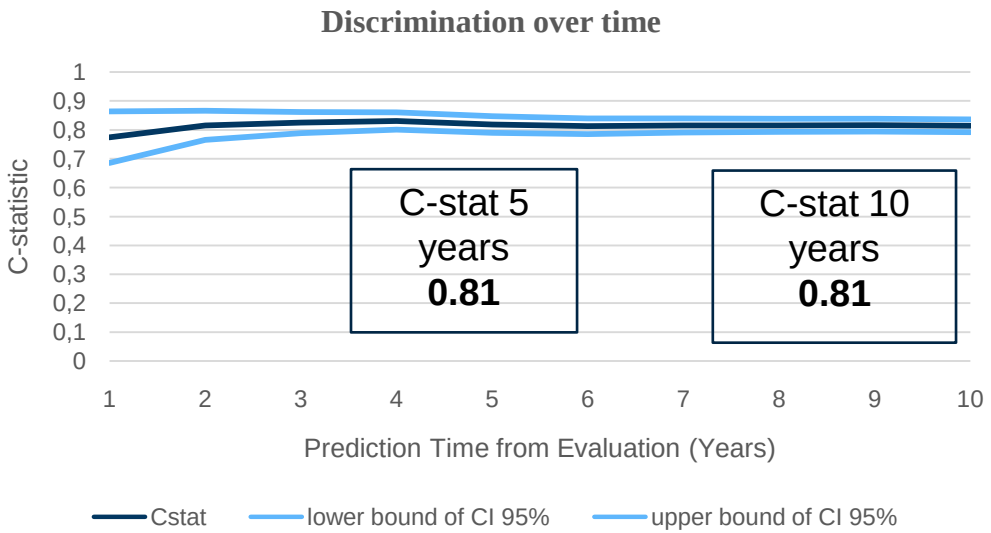
- Cardiac complication (HR=1.38, CI:1.11-1.72)
- Vascular complication (HR=1.29, CI: 1.03-1.61)
- Cancer (HR=1.94, CI: 1.32-2.84)
- Anemia. (HR=1.28, CI :1.03-1.61)



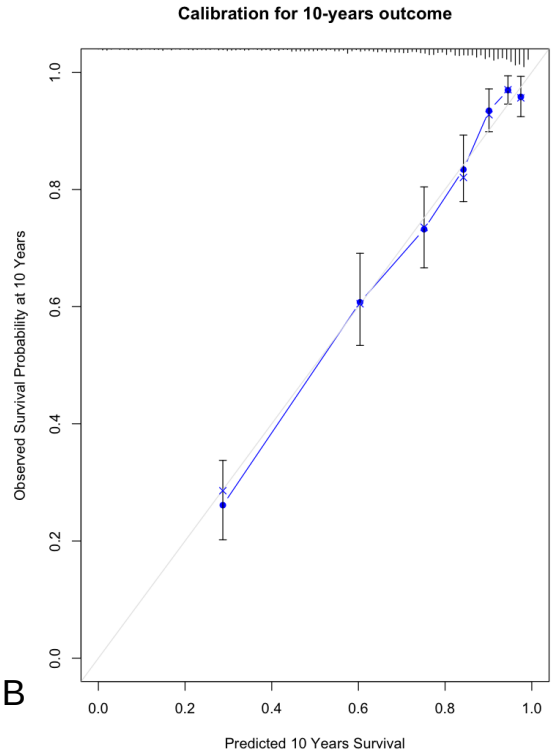
Biology M12

- UPCR (HR=1.22, CI:1.11-1.35)
- HbA1C (HR=1.13, CI: 1.03-1.25)
- Uric acid (HR=1.01, CI: 1.01-1.01)
- Gamma-gt (HR=1.18, CI:1.05-1.34)
- Lymphocytes (HR=0.85, CI:0.73-0.98)
- Neutrophils (HR=1.12, CI: 1.06-1.18)

MODEL PERFORMANCES DISCRIMINATION & CALIBRATION

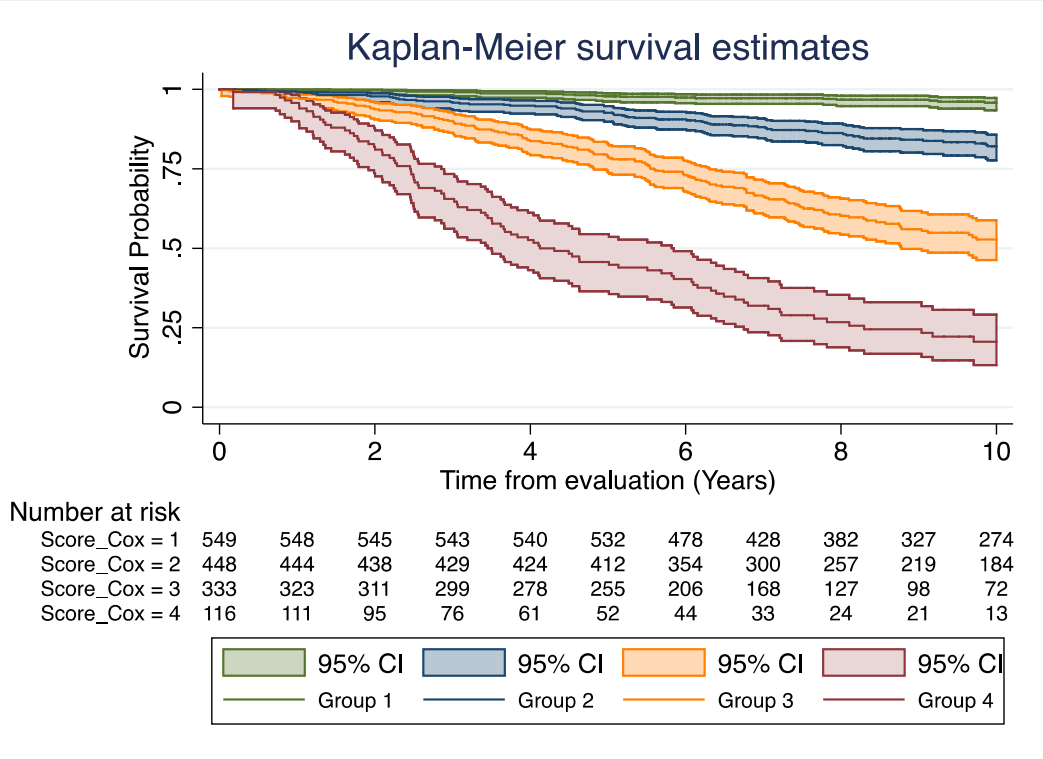


A

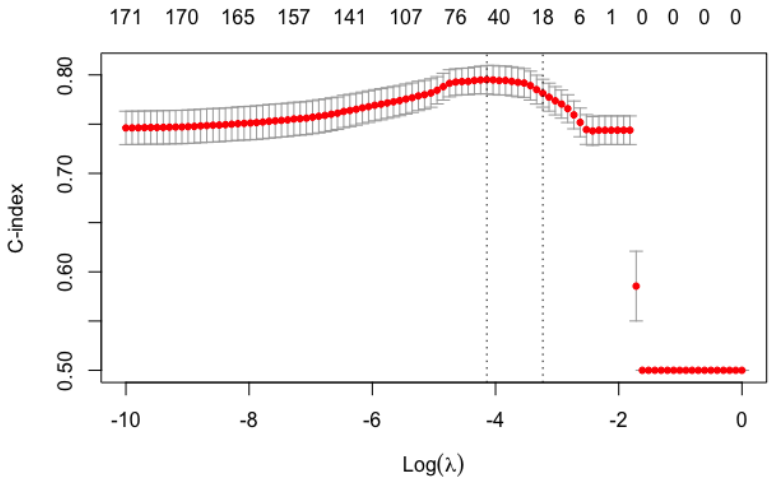


B

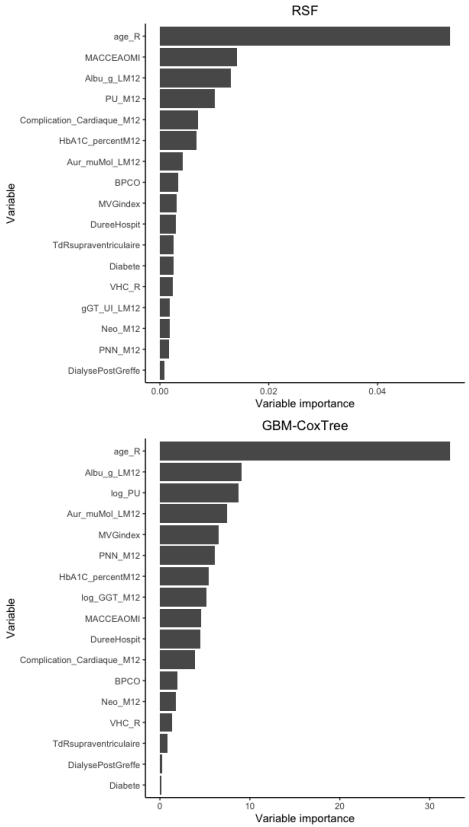
DISTINCT SURVIVAL GROUPS



Other models for variables' selection and mortality prediction

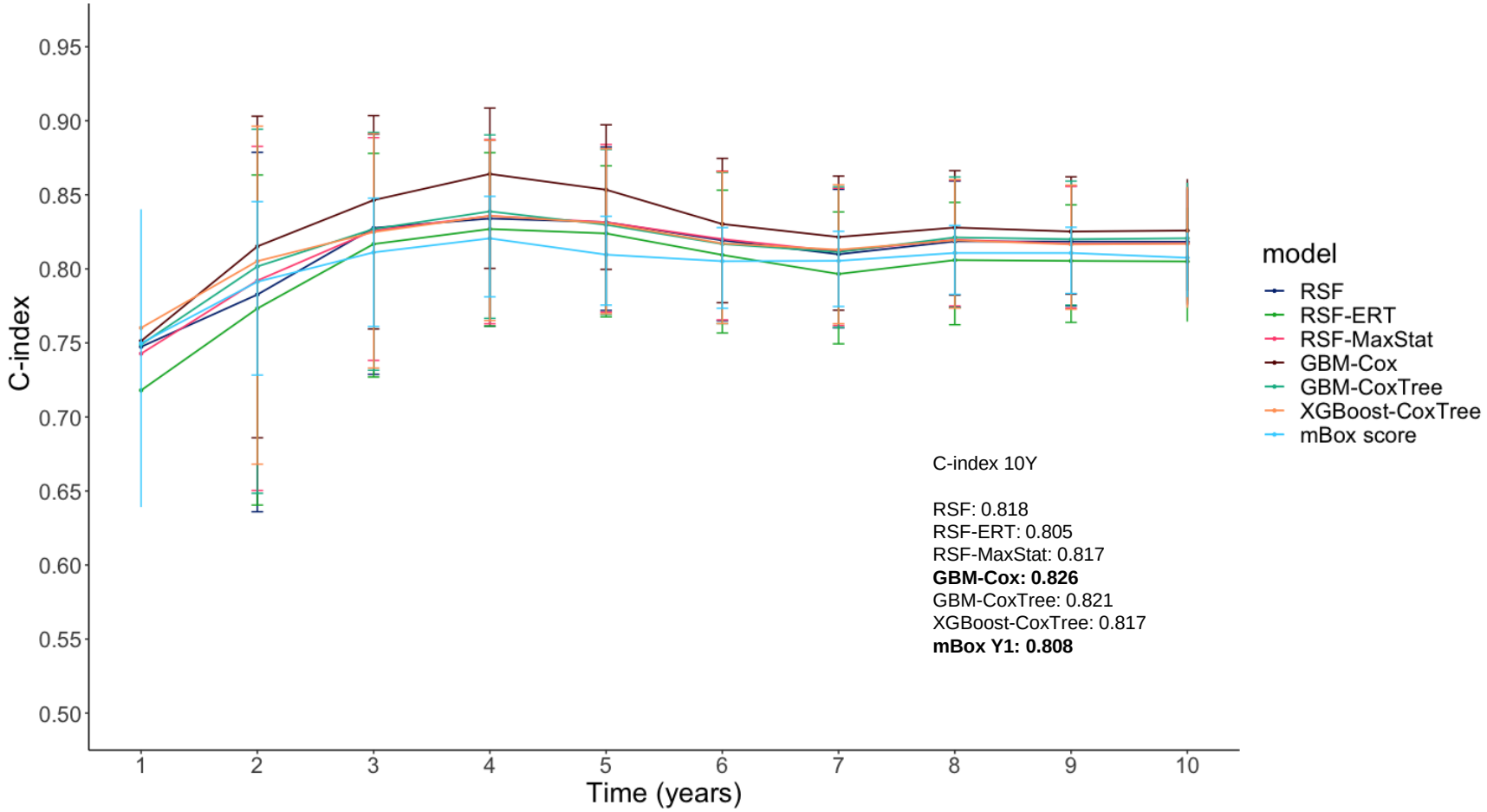


Lasso

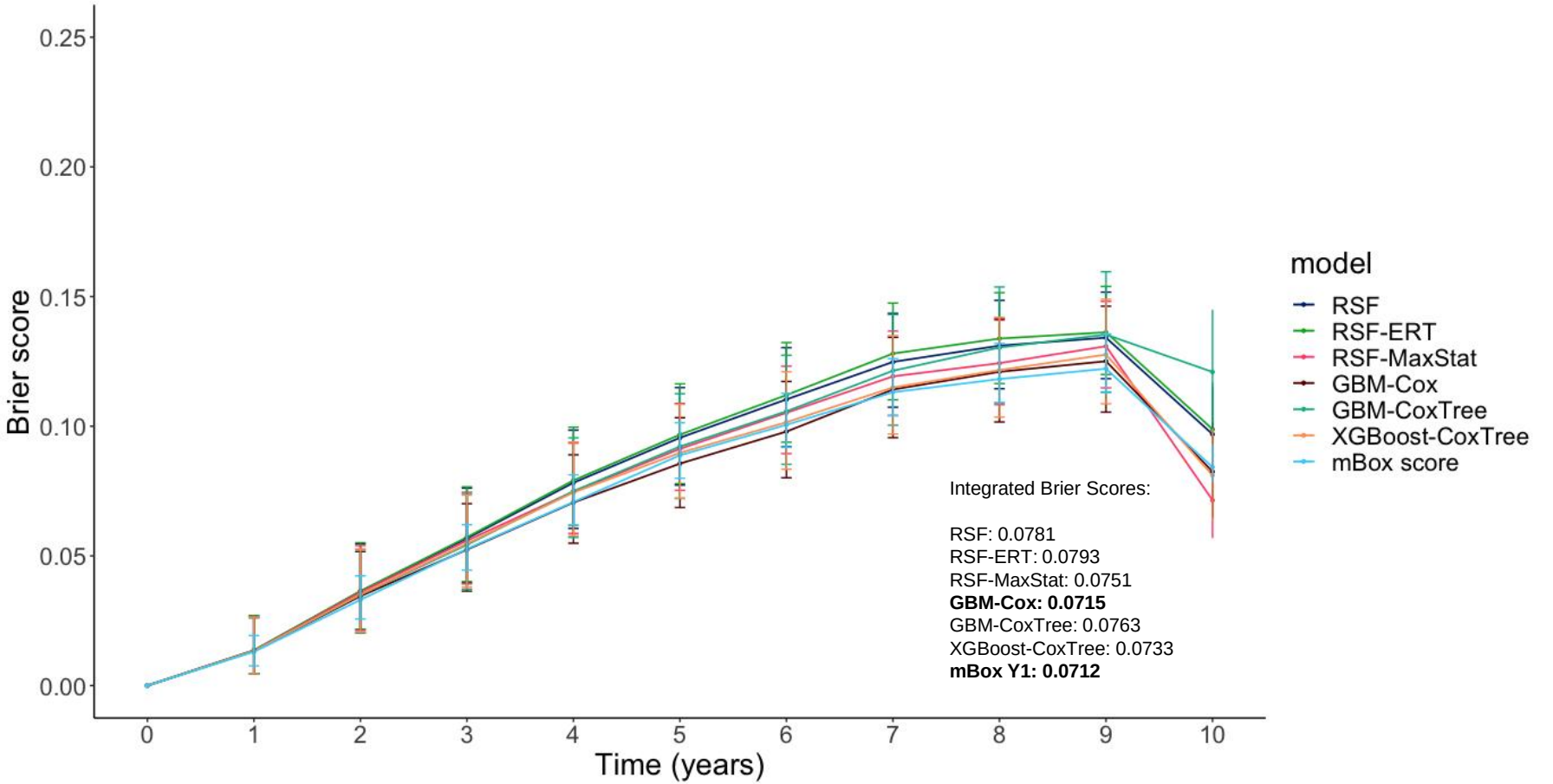


Cox	Lasso	ElasticNet	RSF	Gradient Boosting
Age of recipient	Age of recipient	Age of recipient	Age of recipient	Age of recipient
Major CV events	Major CV events	Major CV events	Major CV events	Major CV events
Psychiatric history	Psychiatric history	-	Ventricular Mass	Ventricular Mass
HCV status	HCV status	-	HCV status	HCV status
-	Diabetes	Diabetes	Diabetes	Diabetes
DSA before transplantation	Cardiac rythm disorder	-	Cardiac rythm disorder	Cardiac rythm disorder
Left Ventricular Mass	COPD	-	COPD	COPD
Cardiac complication	Cardiac complication	Cardiac complication	Cardiac complication	Cardiac complication
Vascular complication	Vascular complication	Duration of first hospitalisation	Duration of first hospitalisation	Duration of first hospitalisation
Cancer	Cancer	-	-	Cancer
Anemia	Need for dialysis	-	-	Need for dialysis
UPCR	UPCR	UPCR	UPCR	UPCR
HbA1C	HbA1C	HbA1C	HbA1C	HbA1C
-	Albumin	Albumin	Albumin	Albumin
Uric acid	Uric acid	Uric acid	Uric acid	Uric acid
GGT	GGT	-	-	GGT
Neutrophils	Neutrophils	-	-	Neutrophils
Lymphocytes	CRP	-	-	-

Performances of ML models



Brier Score


Brier score
0.25
0.20
0.15
0.10
0.05
0.00
0
1
2
3
4
5
6
7
8
9
10
Time (years)
model
RSF
RSF-ERT
RSF-MaxStat
GBM-Cox
GBM-CoxTree
XGBoost-CoxTree
mBox score
Integrated Brier Scores:
RSF: 0.0781
RSF-ERT: 0.0793
RSF-MaxStat: 0.0751
GBM-Cox: 0.0715
GBM-CoxTree: 0.0763
XGBoost-CoxTree: 0.0733
mBox Y1: 0.0712

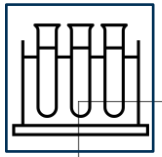
VARIABLES INCLUDED IN THE FINAL MULTIVARIABLE COX MODEL

Recipient's History

- Age (HR=1.07, CI: 1.06-1.08)
- Major CV events. (HR=1.71, CI:1.35-2.16)
- Psychiatric history (HR=2.62, CI:1.75-3.92)
- HCV status (HR=1.59, CI:1.11-2.29)
- Left Ventricular Mass (HR = 1.01, CI:1.001-1.008)
- DSA before transplantation (HR = 1.32, CI: 1.03-1.71)

Complications during the First Year

- Cardiac complication (HR=1.38, CI:1.11-1.72)
- Vascular complication (HR=1.29, CI: 1.03-1.61)
- Cancer (HR=1.94, CI: 1.32-2.84)
- Anemia. (HR=1.28, CI :1.03-1.61)



Biology M12

- UPCR (HR=1.22, CI:1.11-1.35)
- HbA1C (HR=1.13, CI: 1.03-1.25)
- Uric acid (HR=1.01, CI: 1.01-1.01)
- Gamma-gt (HR=1.18, CI:1.05-1.34)
- Lymphocytes (HR=0.85, CI:0.73-0.98)
- Neutrophils (HR=1.12, CI: 1.06-1.18)

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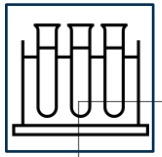

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Application of mortality algorithm: patient care

Improve knowledge of mortality predictors

Intervention when possible

HbA1C

Dialysis duration

HCV

Immunosuppression

Medical decision-making

Stratify patients into clinically meaningful risk groups

Patient monitoring

Personnalized follow-up

Application of mortality algorithm: clinical trials

Emerging surrogate end point

Reliable prediction of the long-term patients survival up to 10 years

A clinical decision support system

Help to design clinical trials

Facilitates faster drug development

THANK YOU !