Maximum cold ischemia duration for a kidney allograft: a prediction model for allograft failure at the time of organ allocation

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Summary

Background Many determinants of kidney allograft failure are established at the time of allocation by organ distribution agencies. At this point, the main modifiable factor is the duration of cold ischemia (CIT). Currently, no practical tool exists to determine the maximum permissible cold ischemia time for a specific recipient at allocation.

Methods We analyzed two prospective cohorts of kidney transplant recipients from European centers: a derivation cohort of 7040 patients from 10 centers (Barcelona; Leuven; Oslo; Paris Necker, Lyon, Nantes, Nancy, Montpellier, Nice, Paris Saint Louis) with data collected between 2005 and 2020, and a validation cohort of 6131 patients from 6 French centers (Paris Necker, Lyon, Nantes, Nancy, Montpellier, Nice) with data collected between 2008 and 2019. The main outcome was allograft failure (return to dialysis or pre-emptive retransplantation). We assessed 26 determinants of allograft failure available at the time of allograft allocation including cold ischemia time as a modifiable factor. Prediction models were developed using a classical survival analysis and a competing risk framework.

Findings Allograft failure occurred in 16% (1113) of the derivation cohort and 14% (832) of the validation cohort. Independent determinants of allograft failure were donor age (HR 2.2 [1.9–2.6] for donors above 65 years old), previous allografts (HR 1.5 [1.3–1.6]), dialysis history (HR 1.7 [1.3–2] for Hemodialysis), diabetes (HR 1.4 [1.2–1.6]), vascular disease (HR 1.3 [1.1–1.5]), HLA-DR incompatibility (HR 1.2 [1.1–1.3]), donor serum creatinine (HR 1 [1–1]),

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and cold ischemia time (HR 1 [1–1]). Donor age was the strongest contributor, while cold ischemia was the only modifiable factor. These factors were combined into two predictive models of kidney allograft failure (Cox regression and Fine Gray) showing accurate calibration, and discrimination with a C-Index of 0.66 (95% CI: 0.63–0.70 at year one) on the validation cohort for the Fine Gray model. The Fine–Gray model, which accounts for the competing risks between allograft failure and patient death, was used to develop a practical tool for predicting allograft failure based on cold ischemia.

Interpretation Prediction model at the time of allocation provides a simple and practical tool which may guide organ distribution agencies and medico-surgical teams by customizing cold ischemia time for a kidney allograft transplantation.

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Keywords: Predictive model; Allograft allocation; Cold ischemia; Kidney transplantation

Research in context

Evidence before this study

Cold ischemia duration is a key modifiable factor influencing kidney allograft failure, but its impact depends on donor and recipient characteristics.

In clinical practice, ischemia time is often prolonged due to logistical, geographical, or immunological constraints.

No existing tool helps determine acceptable cold ischemia duration based on donor-recipient profiles at the time of allocation.

Added value of this study

We developed a predictive model for allograft failure at the time of kidney allocation, integrating cold ischemia as a modifiable factor.

The model was derived from a large European cohort and validated.

It accounts for competing risks and is implemented as a practical tool for individualized risk estimation.

Implications of all the available evidence

Efforts should focus on anticipating and minimizing cold ischemia duration during kidney allocation.

When ischemia is prolonged, our tool supports risk-based decision-making tailored to each donor-recipient pair.

This may improve allocation strategies and long-term transplant outcomes.

Introduction

Organ distribution agencies face the complex task of allocating suitable allografts from deceased donors to the appropriate recipients on the waiting list.[1–4]

The specific combination of donor and recipient characteristics determines allograft recovery and its long-term failure. Once the kidney allograft is removed from the donor and allocated to its recipient, many determinants of allograft failure become non-modifiable, such as donor and recipient age, comorbidities, or HLA compatibility.[5,6]

From this point, the primary pretransplant modifiable factor influencing long-term allograft failure is the duration of cold ischemia (CIT)–the period in which the allograft is maintained at a low temperature without receiving blood supply.[7]

CIT significantly impacts both allograft and recipient outcomes, and as such, should be kept as short as possible.[8,9]

In the context of organ scarcity, equitable allograft allocation necessitates accounting for the waiting duration of candidates. Over recent decades, both in Europe and the USA, waiting lists witnessed a notable rise a rise in highly HLA-immunized patients.[10,11] This trend reduces the pool of compatible allografts and may justify extending CIT for geographically distant matches. Logistical constraints, including transport, operating room availability, and medical-surgical team schedules, further contribute to CIT extensions.

The effects of prolonged CIT on transplant outcomes vary by donor and recipient characteristics, with older or comorbid donors being particularly vulnerable.[12–16]

Currently, no practical tool exists to predict kidney allograft failure for a given donor-recipient pair based on cold ischemia time.

To address this gap, we developed a predictive model capable of estimating the risk of allograft failure for a

specific kidney allocated to an individual recipient at the time of organ offer, using data available to organ allocation agencies. Cold ischemia time was incorporated into the model as a modifiable factor.

The ultimate aim of this study was to develop a practical, intuitive tool that could assist organ allocation agencies and transplant teams in guiding clinical decision-making and optimizing kidney allograft allocation.

Methods

Derivation and validation cohorts

The derivation cohort (EKITE, European Cohort for Kidney Transplantation Epidemiology) included 7040 adult recipients of deceased-donor kidney transplants from 10 European centers (Spain: Barcelona, Belgium: Leuven, Norway: Oslo, and France: Paris Necker, Lyon, Nantes, Nancy, Montpellier, Nice, Paris Saint Louis) between January 1, 2005, and December 31, 2020.

The validation cohort (DIVAT, Données Informatisées et VAlidées en Transplantation) included 6131 adult recipients of deceased-donor kidney transplants from 6 French centers (Paris Necker, Lyon, Nantes, Nancy, Montpellier, Nice) between January 1, 2008, and June 30, 2019.

Both datasets included only heart-beating donations (neurological death).

Data were anonymized and prospectively collected as part of routine clinical practice, entered in the centres'databases in compliance with local and national regulatory requirements.

Data for DIVAT were extracted from the French multicentric, observational, and prospective DIVAT cohort (www.divat.fr, CNIL no. 914184, ClinicalTrials.gov: NCT02900040).

EKITE had a larger sample size and broader geographic coverage, making it more suitable as the derivation cohort. Due to partial overlap in time and centers, matching entries were excluded from EKITE (see Supplementary Table S1).

European centers outside France followed the allocation rules of Eurotransplant (Leuven), Scandiatransplant (Oslo), and the National Transplant Organization (Barcelona). In France, kidney allocation adhered to the French National Agency for Organ Procurement (Agence de la Biomédecine).

Candidate predictors of kidney allograft failure and outcome

We considered the parameters known to organ distribution agencies at the time of allograft allocation, thus focusing only on the pre-transplant period. CIT was included as the primary modifiable factor influencing allograft failure.

We considered 26 variables including demographic characteristics (recipients' age, height, weight, gender, comorbidities, donors' age, gender, cause of death), transplant characteristics (time in waiting list, number of previous allografts, time and type of dialysis), biological parameters (such as HLA-A, -B, -DR matching, PRA class I and II antibodies, blood type, donors'serum creatinine) and cold ischemia time (Table 1).

Entries with missing CIT and missing donor age were excluded. Missing values for the other variables were imputed as described in the statistical analysis.

The outcome of interest was allograft failure defined as a patient's definitive return to dialysis or pre-emptive kidney retransplantation.

Statistics

We followed the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statement for reporting the development and validation of a multivariable prediction model.

All analyses were performed using R Statistical Software (v4.2.1); R Core Team.[17]

Continuous variables were described using means, standard deviations/IQR (interquartile range) and categorical variables by frequencies and percentages.

Missing data in the original dataset were handled using the Multivariate Imputation by Chained Equations (MICE) procedure in R,[18] employing the Classification and Regression Trees (CART) method. This approach is suitable for both continuous and categorical variables, as it builds decision trees to predict missing values based on observed data. We performed 10 multiple imputations (m = 10) with 5 iterations each (maxit = 5), separately for the derivation and validation cohorts. All variables from Table 1 were included in the imputation model, covering donor, recipient, and transplant characteristics. We assumed that missing values are missing at random (MAR), as it was likely related to observed pre-transplant characteristics and not to unobserved or post-transplant outcomes. Entries with missing donor age or cold ischemia time were excluded prior to imputation. A summary of missing data is reported in Table 1.

To assess the associations between allograft failure and predictors, and subsequently build a prediction model, we used two different approaches: classical survival analysis using Cox regression and the Fine Gray model for competing risks (using survival and cmprsk packages[19,20]). Competing risks models were chosen to account for the interplay between allograft failure and death, as Cox regression alone may overestimate event rates, particularly in high-risk populations.

We used both Kaplan–Meier and Aalen-Johansen methods to estimate allograft failure. For the KM the duration of follow-up was from the patient's transplant date to the date of kidney allograft failure or the end of the follow-up. Kidney allograft failure was censored at the time of death for patients who died with a

	Ekite		Divat	
	N	Overall, N = 7040	N	Overall N = 6131
Recipient characteristics				
Recipient age	7040		6131	
		54.43 (13.81)		53.28 (13.97)
<50		2528/7040 (36%)		2379/6131 (39%)
50–65		2830/7040 (40%)		2515/6131 (41%)
≥65		1682/7040 (24%)		1237/6131 (20%)
Recipient gender	7040		6131	
Female		2597/7040 (37%)		2285/6131 (37%)
Male		4443/7040 (63%)		3846/6131 (63%)
Recipient height (cm)	6793		6103	
		169.93 (10.06)		168.32 (9.55)
Missing		247		28
Recipient weight (kg)	5726		6113	
		73.00 (15.73)		70.67 (14.86)
Missing		1314		18
Number of previous grafts	7040		6131	
		1.21 (0.50)		1.26 (0.54)
1		5829/7040 (83%)		4830/6131 (79%)
2		1008/7040 (14%)		1075/6131 (18%)
3		164/7040 (2.3%)		196/6131 (3.2%)
4		33/7040 (0.5%)		24/6131 (0.4%)
5		6/7040 (<0.1%)		4/6131 (<0.1%)
6				2/6131 (<0.1%)
Type of dialysis	7007		6115	
No dialysis		999/7007 (14%)		611/6115 (10.0%)
Hemodialysis		5064/7007 (72%)		4952/6115 (81%)
Peritoneal dialysis		944/7007 (13%)		552/6115 (9.0%)
Missing		33		16
Initial disease type	7013		6131	
Unknown		759/7013 (11%)		998/6131 (16%)
Glomerulonephritis		2117/7013 (30%)		1595/6131 (26%)
Tubulo interstitial disease		907/7013 (13%)		2302/6131 (38%)
Reno-vascular disease		1995/7013 (28%)		589/6131 (9.6%)
Diabetes		1235/7013 (18%)		647/6131 (11%)
Missing		27		
Time in dialysis (days)	6820		6103	
		1236.44 (1556.72)		1230.61 (1306.85)
Missing		220		28
Time in waiting list (days)	6437		5889	
		801.88 (805.42)		844.74 (781.33)
Missing		603		242
Recipient blood ABO type	6982		6099	
A		3086/6982 (44%)		2748/6099 (45%)
AB		355/6982 (5.1%)		280/6099 (4.6%)
B		753/6982 (11%)		658/6099 (11%)
O		2788/6982 (40%)		2413/6099 (40%)
Missing		58		32
History of vascular diseases	7017		6131	
No		5769/7017 (82%)		4898/6131 (80%)
Yes		1248/7017 (18%)		1233/6131 (20%)
Missing		23		
History of cardiac diseases	6959		6131	
No		4784/6959 (69%)		4280/6131 (70%)
Yes		2175/6959 (31%)		1851/6131 (30%)
Missing		81		

(Table 1 continues on next page)

functioning kidney allograft. Proportionality of predictors was tested graphically and statistically (cox.zph function from the failure package in R).

We performed an initial step of variable selection to arrive at a sparse predictive model. For the non-competing risks Cox regression, we used a penalized regression implementation (glmnet package[21]). Survival penalized regression uses linear models with penalties to avoid extreme parameters that may cause overfitting, while simultaneously addressing the issue of multi-multicollinearity (correlation) and performing variable selection. The two most common forms of penalization are L1 (LASSO) or an L2 (Ridge) penalty constraints, and we performed cross-validation to optimize this penalization parameter. We could not find a stable implementation of penalized regression for the competing risks framework and performed variable selection using the usual threshold of 0.05 p-value albeit on pooled estimators from 10 multiple imputations and 100 bootstraps (poolr package[22]).

We used the Cox penalized regression to identify the most important factors for prediction of kidney allograft failure in the derivation cohort. In the penalized regression setting we used a variable inclusion probability (VIP) threshold of 0.75 to select variables. The VIP is the percentage of times each variable was kept in the model out of the resampled models (100 bootstraps in 10 multiple imputed datasets). The VIP can be interpreted as the posterior probability of including a variable in the model, and is used as a measure of the stability of the association.[23]

We have also implemented survival random forests as a comparative method for variable selection. This nonparametric approach for censored survival data combines results from multiple decision trees, effectively handling complex, nonlinear relationships and multiple covariates without prior specification.

We evaluated the validity of the final model in the validation cohort DIVAT by computing calibration and discrimination metrics (rms and riskRegression packages[24,25]). Calibration was assessed using calibration plots (rms package) and by computing the ratio of observed and expected outcomes (O/E ratio) that summarises overall calibration. We evaluated discrimination by using Harrell's concordance index (C-Index).

We used the final sparse Cox and Fine Gray models to predict the risk of allograft failure for each individual in the DIVAT validation cohort, for a range of cold ischemia times (0–40 h, replacing the observed CIT) at different time points after transplant (one, three, five, and ten years). We present the results by 3 donor age categories: under 50 years-old, between 50 and 65 years-old and above 65 years-old.

A Beta version of the online application is available at the following link: https://nephrology-nice.

shinyapps.io/CIT-failure-predictor (Supplementary Fig. S1).

Ethics

The research protocol was reviewed and approved by the relevant local institutional review boards (IRBs) in accordance with national and international ethical standards. All data were fully anonymized prior to analysis, and a secure coding system was used to ensure strict donor and recipient confidentiality. As the study involved only retrospective analysis of registry data, informed consent was not required, in accordance with applicable data protection regulations and IRB guidelines.

Role of funding source

The DIVAT cohort is supported by the CENTAURE Foundation (SIREN 499,947,398–http://www.fondation-centaure.org) and receives funding from Roche Pharma, Novartis, Astellas, Chiesi, Sandoz, and Sanofi. None of these funding sources had any role in study design, data collection, data analyses, interpretation, or writing of report.

Results

Characteristics of derivation and validation cohorts

The derivation cohort (EKITE) included 7040 kidney transplant recipients (2005–2020), with a mean follow-up of 5.4 years [IQR 1.1–8.9]. Recipients had a mean age of 54.4 years, 63% were male, and the average waiting time was 2.2 years. Vascular and cardiac disease histories were reported in 18% and 31% of patients, respectively. Donors had a mean age of 52.5 years and an average blood creatinine level of 80.6 μmol/mL at donation.

The validation cohort (DIVAT) comprised 6131 recipients of kidney allografts between 2008 and 2019. Detailed comparisons of recipient, donor, and transplant characteristics between the cohorts are presented in Table 1.

Description of the primary outcome: kidney allograft failure

Kidney allograft failure in the derivation and the validation cohort

Respectively 1113 (16%) and 832 (14%) patients experienced allograft failure in the derivation cohort EKITE and the validation cohort DIVAT.

Fig. 1 shows cumulative incidence curves for allograft failure with death censored, using the Kaplan–Meier estimator (Panel A) in EKITE. At one year post-transplant, 352 patients experienced failure, rising to 983 at ten years.

Panel B shows the cumulative incidence with death as a competing risk, calculated using the Aalen-Johansen

	Ekite		Divat	
	N	Overall, N = 7040	N	Overall N = 6131
(Continued from previous page)				
History of neoplasy	7035		6131	
No		6318/7035 (90%)		5306/6131 (87%)
Yes		717/7035 (10%)		825/6131 (13%)
Missing		5		
History of diabetes	7032		6131	
No		5025/7032 (71%)		4911/6131 (80%)
Yes		2007/7032 (29%)		1220/6131 (20%)
Missing		8		
Detectable anticlass I PRA	5866		5558	
No		4325/5866 (74%)		3056/5558 (55%)
Yes		1541/5866 (26%)		2502/5558 (45%)
Missing		1174		573
Detectable anticlass II PRA	4996		5520	
No		3643/4996 (73%)		3129/5520 (57%)
Yes		1353/4996 (27%)		2391/5520 (43%)
Missing		2044		611
Donor characteristics				
Donor gender	7016		6124	
Female		2968/7016 (42%)		2628/6124 (43%)
Male		4048/7016 (58%)		3496/6124 (57%)
Missing		24		7
Donor age (years)	7003		6105	
		52.52 (16.71)		54.78 (16.87)
<50		2799/7003 (40%)		2194/6105 (36%)
50–65		2568/7003 (37%)		2162/6105 (35%)
≥65		1636/7003 (23%)		1749/6105 (29%)
Missing		37		26
Age gap (years)	7003		6105	
		10.00 (9.55)		7.50 (7.51)
Missing		37		26
Donor cause of death	7037		6131	
Other		4028/7037 (57%)		2769/6131 (45%)
Cerebrovascular		3009/7037 (43%)		3362/6131 (55%)
Missing		3		
Donor serum creatinine (μMol/L)	6513		6121	
		80.58 (47.15)		89.83 (60.06)
Missing		527		10
Donor blood ABO type	7016		6119	
A		3123/7016 (45%)		2682/6119 (44%)
AB		269/7016 (3.8%)		229/6119 (3.7%)
B		643/7016 (9.2%)		579/6119 (9.5%)
O		2981/7016 (42%)		2629/6119 (43%)
Missing		24		12
Transplant characteristics				
HLA incompatibility A	6444		6073	
		1.04 (0.69)		1.07 (0.68)
Missing		596		58
HLA incompatibility B	6443		6077	
		1.30 (0.68)		1.38 (0.66)
Missing		597		54
HLA incompatibility DR	6443		6074	
		0.78 (0.65)		0.76 (0.67)
Missing		597		57
Cold ischemia time (hours)	7040		6131	
		16.31 (6.53)		17.79 (6.66)

(Table 1 continues on next page)

	Ekite		Divat	
	N	Overall, N = 7040	N	Overall N = 6131
(Continued from previous page)				
Outcome				
Time to allograft failure or to last follow up (days)	7040		6131	
		1975.64 (1685.11)		1404.50 (1117.05)
Allograft failure		1113 (15.81)		832 (13.57)
Death with functioning graft		1257 (17.86)		606 (9.88)
Censored		4670 (66.34)		4693 (76.55)

Continuous variables are described using means and standard deviations, categorical variables using frequency and percentages.

Table 1: **Patients' characteristics in the derivation cohort (EKITE) and the validation cohort (DIVAT).**

estimator. In the first five years post-transplant, the risk of allograft failure was higher than the risk of death with a functioning allograft. After five years, these risks reversed.

Kidney allograft failure according to donor age

In EKITE, kidney allografts from donors aged 65 or older had a 5-year cumulative failure incidence of 0.18 (CI 0.16–0.21), higher than those from donors aged 50–64 (0.13, CI 0.12–0.15) or under 50 (0.08, CI 0.07–0.09; $p < 0.0001$). Panel C in Fig. 1 shows competing risks of failure and death with a functioning allograft by donor age. In the under-50 group, the risk of failure was similar to the risk of death with a functioning allograft. For the 50–65-year-old donor group, the curves intersected after 5.5 years, while for donors over 65, the risk of death exceeded the risk of failure after three years.

Description of the modifiable parameter: Cold Ischemia time duration

Distribution of cold ischemia time in the derivation and validation cohorts

The mean cold ischemia time was 16.3 h (SD 6.53) in the derivation cohort EKITE and 17.8 h (SD 6.66) in the validation cohort DIVAT. The distribution of CIT in both cohorts is shown in Fig. 2, Panel A.

Kidney allograft failure according to cold ischemia time

In the derivation cohort, five-year allograft survival was similar for allografts with CIT above 30 h (0.84, CI 0.79–0.89) and those between 20 and 30 h (0.85, CI 0.83–0.88), but lower than for those with CIT between 10 and 20 h (0.89, CI 0.87–0.90) and under 10 h (0.90, CI 0.88–0.92). In the validation cohort, survival trends overlapped except for those with CIT under 10 h, which showed a lower incidence of failure.

Fig. 2B and C illustrates kidney allograft survival stratified by CIT in both cohorts.

Identification of determinants of kidney allograft failure at the time of the transplantation

We considered 26 potential determinants of allograft failure, including recipient and donor characteristics, HLA compatibility, and CIT, the modifiable factor during allocation.

Table 2 shows the association of candidate predictors with kidney allograft failure in the EKITE derivation cohort, using multivariate penalized Cox regression and Fine Gray competing risks models. Seven independent variables were identified with Cox penalized regression: number of previous allografts (VIP 1.0), type of dialysis (VIP 0.95), history of vascular disease (VIP 0.85), history of diabetes (VIP 0.95), donor age (VIP 1), HLA-DR incompatibility (VIP 0.76), and cold ischemia time (VIP 0.84).

In the Fine Gray competing risks regression, the predictors with a pooled p-value < 0.05 were number of previous allografts, type of dialysis, history of diabetes, donor age, and donor serum creatinine.

Relative contribution of the determinants of kidney allograft failure: major impact of donor age

Among the determinants identified in the penalized regression analysis, the random forest algorithm identified donor age as the most important factor for allograft survival in the EKITE derivation cohort (Fig. 3). Other determinants from the penalized regression were also considered important by the random forest algorithm, but never negatively impactful for predicting allograft survival.

Regarding cold ischemia time, the key modifiable factor, its relative contribution was limited at the population level.

Kidney allograft failure prediction models

Table 2 includes the results of a sparse predictive multivariable Cox regression using the seven variables highlighted by the Cox penalized regression. The estimates are pooled results from 1000 models (10 MI, 100 bootstraps). All variables were statistically significant at the 5% level: number of previous allografts Pooled HR of 1.5 [1.3–1.6] $p < 0.0001$; type of dialysis: hemodialysis (Pooled HR of 1.7 [1.3–2] $p < 0.0001$), peritoneal dialysis (Pooled HR of 1.3 [1.0–1.7] $p = 0.03$); history of vascular diseases (Pooled HR 1.3 [1.1–1.5] $p = 0.006$); history of diabetes (Pooled HR of 1.4 [1.2–1.6] $p < 0.0001$); donor age: 50–65 (Pooled HR 1.5 [1.3–1.8] $p < 0.0001$), ≥65 (Pooled HR 2.2 [1.9–2.6] $p < 0.0001$); HLA incompatibility DR (Pooled HR of 1.2 [1–1.3 $p < 0.0001$), and cold ischemia time (Pooled HR of 1 [1–1] $p = 0.004$).

The Fine Gray competing risks regression estimates for variables with a pooled p-value < 0.05: number of previous allografts (Pooled HR of 1.3 [1.2–1.5] $p = 0.001$); hemodialysis (Pooled HR of 1.6 [1.3–1.9] $p = 0.018$); history of diabetes (Pooled HR of 1.5

[1.2–1.7] p = 0.003); donor age: 50–65 (Pooled HR 1.5 [1.3–1.8] p < 0.0001), ≥65 (Pooled HR 1.9 [1.6–2.3] p < 0.0001); and donor serum creatinine (Pooled HR of 1.0 [1.0–1.0] p = 0.021).

Models prediction performance in the validation cohort

Table 3 shows the calibration (O/E) and discrimination (C-index) metrics at one, three, five, and ten years post-transplantation, for the Cox and Fine Gray models in the validation cohort. The total O:E ratio indicates overall model calibration across predicted risks. At years one, three, and five post-transplant, the Fine Gray model had better calibration (O/E 1.06 [0.94; 1.20], 1.13 [1.02, 1.24], and 1.19 [1.09, 1.29]) than the Cox model (1.22 [1.10, 1.36], 1.24 [1.13, 1.35], and 1.26 [1.17, 1.37]) (ratio >1 indicates underprediction). Discrimination of the Fine Gray model is higher in the first year but decreases from 0.66 to 0.60 at 10 years, while the Cox model's discrimination remains constant at 0.64 across time horizons.

Supplementary Fig. S2 shows the calibration plots for the Cox (A) and Fine Gray models (B). Given these parameters, the Fine Gray prediction model was favored in the following analysis.

Kidney allograft failure prediction

Fig. 4 shows the prediction of allograft failure using the Fine Gray predictive model aggregated by donor age group and based on CIT (Supplementary Fig. S3 shows Cox regression model using the same visual presentation).

Young donors: impact of CIT from 10 years post-transplantation

For recipients of kidney allografts from donors under 50 years, CIT had a negligible effect on allograft failure at one, three, and five years post-transplantation. However, at ten years, the effects of CIT became noticeable: the proportion of allografts failing after 8, 16, 24, and 32 h of CIT were 12%, 25%, 31%, and 36%, respectively.

Donors aged 50–65: significant impact of CIT from three years post-transplantation

For donors aged 50–65, the impact of CIT became noticeable after three years post-transplant. At five years, the failure rates for CIT of 8, 16, 24, and 32 h were 4%, 6%, 8%, and 12%. At ten years, the failure rate increased substantially, with a projected failure rate above 50% for CIT over 11 h.

Older donors: major impact of CIT on allograft failure

The older allografts exhibited slightly lower risk of failure for extreme CIT at year one.

Three years after transplantation, the impact of prolonged CIT was significant with a risk of failure of 3% with a CIT of 8 h; and 11% with a CIT of 32 h.

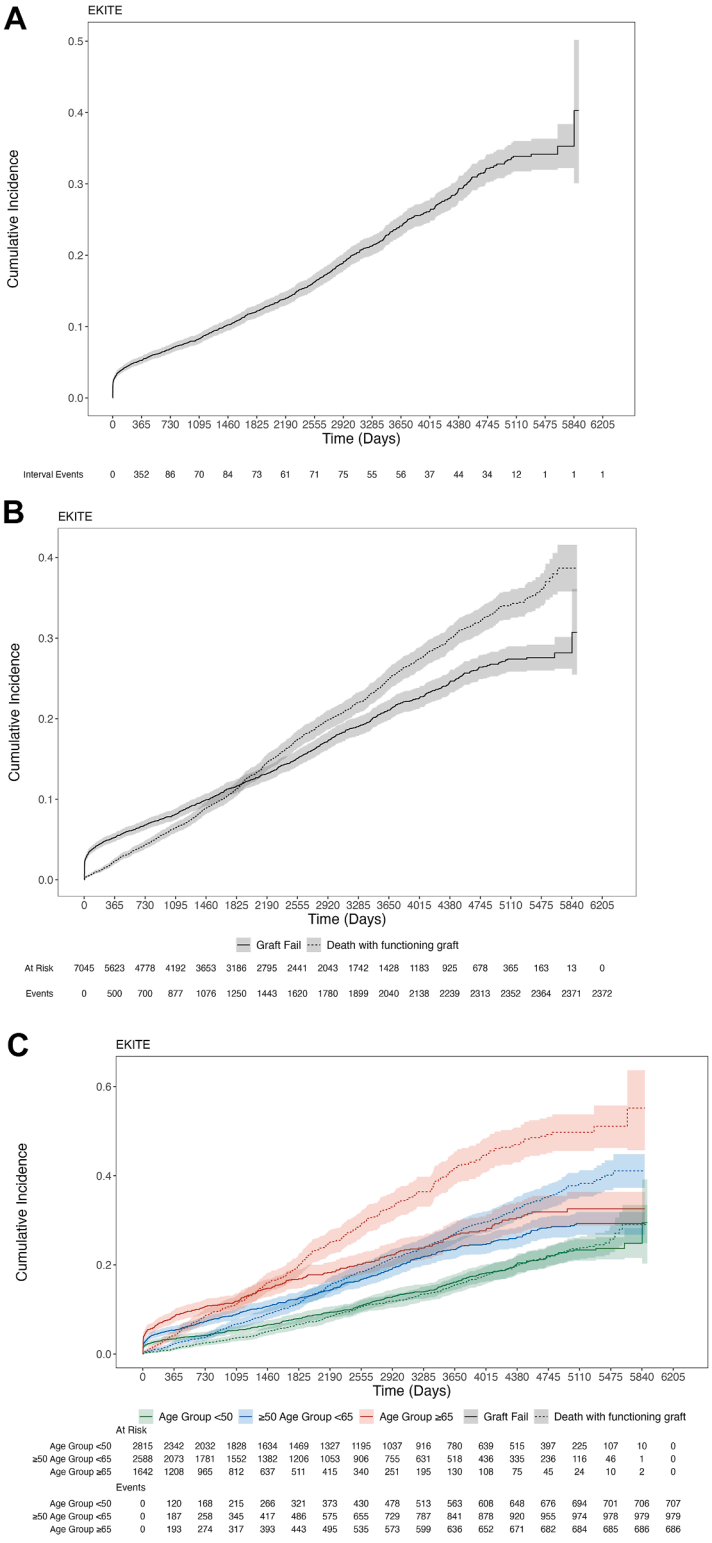

Fig. 1: Cumulative incidence curves for allograft failure in the derivation cohort EKITE. A. Kaplan–Meier estimates of time to kidney allograft failure with censoring for death. B. Aalen-Johansen estimates of time to kidney allograft failure or death with functioning allograft as a competing event. C. Aalen-Johansen estimates of time to kidney allograft failure or death with functioning allograft as a competing event according to the donor group of age (<50 years old; 50–64 years old; ≥65 years old).

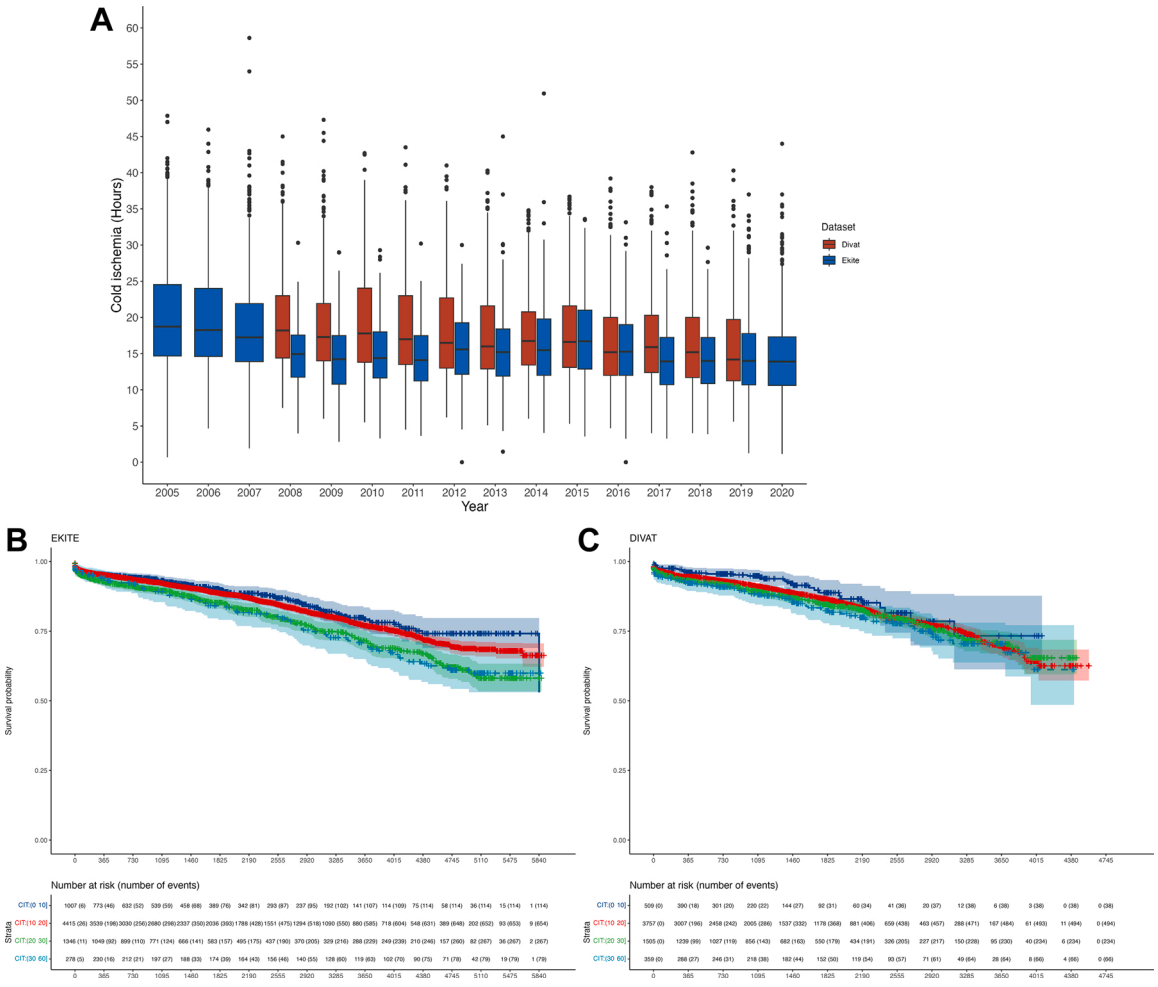

Fig. 2: Cold ischemia in the derivation and the validation cohorts. A. Distribution of cold ischemia time in the derivation cohort EKITE and on the validation cohort DIVAT. B. Kaplan–Meier estimates of time to kidney allograft failure in the derivation cohort EKITE stratified by cold ischemia time (hours). C. Kaplan–Meier estimates of time to kidney allograft failure in the validation cohort DIVAT stratified by cold ischemia time (hours).

At year five, risk of allograft failure was respectively of 11%; 21%; 37%; and 47% for CIT of 8; 16; 24; and 32 h.

To achieve a risk of failure below 15% at 5 years post-transplant in this category of donor age, CIT should be under than 11 h.

The risk of kidney allograft failure from older donors was high at 10 years, independently of CIT.

Practical application of the model

Fig. 5 illustrates the application of the allograft failure prediction model to six individual cases. The model predicts the expected risk of failure at one, three, five, and ten years based on cold ischemia time. The patients' parameters at the time of allograft allocation and their predicted allograft failure at five years post-transplant are detailed in the figure legend.

Patients 1 and 4 have low predicted allograft failure risk profiles, with long-term failure risk below 10% for cold ischemia times (CIT) under 40 h. These patients have similar profiles, though patient 4 had an older donor with better creatinine levels and no history of dialysis.

Similarly, patients 2 and 3, despite differing at allocation, are predicted to have a high risk of allograft failure, with a failure risk close to 10% at 1 year for CITs exceeding 24 h.

Patients 5 and 6 have intermediate, comparable failure risk profiles, despite different presentations at allocation. Patient 6 received a younger allograft with

	EKITE Cox Penalized regression		EKITE Cox regression on subset of variables		EKITE fine gray model competing risks	
	Median Hazard ratio [95% CI]	VIP	Pooled Hazard ratio [95% CI]	Pooled p-value		p-value
Recipient age						
<50	1.052 [1.027, 1.083]	0.007				
50–65	0.962 [0.901, 0.997]	0.306			0.79 [0.676, 0.911]	1.000
≥65	1.043 [1.002, 1.196]	0.205			0.76 [0.621, 0.925]	1.000
Recipient gender						
Female	1.051 [1.001, 1.153]	0.171				
Male	1 [0.998, 1]	0.092			0.94 [0.795, 1.102]	1.000
Recipient height (cm)	0.998 [0.992, 1]	0.498			0.99 [0.985, 1.002]	1.000
Recipient weight (kg)	0.999 [0.997, 1.003]	0.055			1.00 [0.996, 1.005]	1.000
Number of previous allografts	1.212 [1.061, 1.36]	**0.996**	**1.476 [1.329, 1.632]**	**0.000**	1.33 [1.182, 1.502]	**0.001**
Type of dialysis						
Hemodialysis	1.162 [1.042, 1.411]	**0.951**	**1.655 [1.349, 2.049]**	**0.000**	1.56 [1.262, 1.919]	**0.018**
No dialysis	0.913 [0.749, 0.993]	0.495				
Peritoneal dialysis	0.996 [0.99, 0.997]	0.003	**1.319 [1.023, 1.746]**	**0.030**	1.35 [1.043, 1.751]	1.000
Initial disease type						
Unknown	0.936 [0.829, 1.011]	0.033				
Glomerulonephritis	1.046 [1.001, 1.144]	0.058			1.15 [0.861, 1.524]	1.000
Tubulo interstitial disease	0.937 [0.895, 0.994]	0.023			1.50 [1.149, 1.953]	1.000
Reno-vascular disease	0.955 [0.822, 0.997]	0.401			1.24 [0.955, 1.611]	1.000
Diabetes	1.071 [1.003, 1.209]	0.33			1.42 [1.101, 1.832]	1.000
Time in dialysis (days)	1 [1, 1]	0.311			1.00 [1, 1]	1.000
Time in waiting list (days)	1 [1, 1]	0.095			1.00 [1, 1]	1.000
Recipient blood ABO type						
A	1.039 [1.001, 1.12]	0.044				
AB	1.078 [1.004, 1.173]	0.064			0.92 [0.545, 1.542]	1.000
B	0.968 [0.825, 0.998]	0.087			0.80 [0.377, 1.716]	1.000
O	0.994 [0.978, 1]	0.005			1.09 [0.603, 1.978]	1.000
History of vascular diseases						
No	0.887 [0.78, 0.99]	**0.852**				
Yes	1 [1, 1.003]	0.682	**1.280 [1.088, 1.478]**	**0.006**	1.20 [1.036, 1.399]	1.000
History of cardiac diseases						
No	0.918 [0.833, 0.992]	0.75				
Yes	1 [1, 1.001]	0.534			1.11 [0.974, 1.268]	1.000
History of neoplasy						
No	0.944 [0.865, 0.997]	0.219				
Yes	1 [1, 1]	0.18			1.11 [0.908, 1.346]	1.000
History of diabetes						
No	0.858 [0.72, 0.98]	**0.949**				
Yes	1 [1, 1]	0.609	**1.421 [1.232, 1.629]**	**0.000**	1.46 [1.237, 1.717]	**0.003**
Detectable anticlass I PRA						
No	0.916 [0.804, 0.997]	0.682				
Yes	1 [1, 1.001]	0.417			1.11 [0.94, 1.301]	1.000
Detectable anticlass II PRA						
No	0.919 [0.775, 0.996]	0.585				
Yes	1 [1, 1]	0.406			1.12 [0.938, 1.332]	1.000
Donor gender						
Female	1.057 [1.003, 1.151]	0.395				
Male	1 [1, 1]	0.277			0.88 [0.776, 0.995]	1.000
Donor age (years)						
<50	0.74 [0.64, 0.84]	**1**				
50–65		0	**1.549 [1.346, 1.783]**	**0.000**	1.52 [1.307, 1.764]	**0.000**
≥65	1.277 [1.07, 1.485]	**0.991**	**2.222 [1.909, 2.615]**	**0.000**	1.94 [1.613, 2.341]	**0.000**
Age gap (years)	1 [0.998, 1.004]	0.055				
Donor cause of death						
Other	1.048 [1.002, 1.154]	0.333			0.93 [0.812, 1.054]	1.000
Cerebrovascular	1 [1, 1]	0.277				

(Table 2 continues on next page)

	EKITE Cox Penalized regression		EKITE Cox regression on subset of variables		EKITE fine gray model competing risks	
	Median Hazard ratio [95% CI]	VIP	Pooled Hazard ratio [95% CI]	Pooled p-value		p-value
(Continued from previous page)						
Donor serum creatinine (μMol/L)	1.001 [1, 1.002]	0.482			1.00 [1.001, 1.003]	**0.021**
Donor blood ABO type						
A	1.043 [1.003, 1.115]	0.052				
AB	1.063 [0.992, 1.225]	0.055			1.15 [0.642, 2.076]	1.000
B	1.005 [0.941, 1.154]	0.013			1.10 [0.501, 2.392]	1.000
O	0.971 [0.916, 0.999]	0.07			0.86 [0.474, 1.551]	1.000
HLA incompatibility A	0.996 [0.967, 1.024]	0.033			0.99 [0.909, 1.089]	1.000
HLA incompatibility B	1.032 [1.001, 1.095]	0.184			1.04 [0.949, 1.14]	1.000
HLA incompatibility DR	1.063 [1.005, 1.168]	**0.76**	**1.160 [1.057, 1.267]**	**0.000**	1.17 [1.068, 1.287]	0.120
Cold ischemia time (hours)	1 [1, 1]	**0.838**	**1.000 [1, 1]**	**0.004**	1.00 [1, 1]	1.000

Multivariate Cox regression (middle panel) integrates the determinants identified by penalized regression with a VIP > 0.75. Pooled parameter estimates were derived from 1000 models (100 bootstraps in 10 multiple imputed datasets). For classical Cox regression (middle panel) and Fine–Gray regression (right panel), categorical variables are modeled relative to a reference category, which is omitted from the table and implicitly has a hazard ratio of 1. In contrast, in penalized regression (left panel), categorical variables are treated using one-hot encoding, meaning that all levels are included as separate variables rather than being compared to a single reference category. The values in bold correspond to statistically significant results ($p < 0.05$).

Table 2: **Independent determinants of kidney allograft failure in the derivation cohort EKiTE assessed using Cox penalized regression (left panel) and Fine–Gray model (right panel).**

poorer function, in the context of a second kidney transplant. For these patients, the predicted failure risk at 3 years remains below 10% for CITs under 24 h.

Supplementary Fig. S4 shows allograft failure prediction model to the same six individual cases.

Discussion

We assessed long-term kidney allograft failure using an epidemiological approach that integrated data from the recipient, donor, and transplant conditions. We focused on CIT as a modifiable factor influencing allograft failure at the time of organ allocation.

We developed two predictive models: a traditional Cox model and a Fine–Gray model, which accounts for the competing risks of allograft failure and patient death with a functioning allograft. This approach revealed that the risk of death with a functioning allograft surpasses the risk of allograft failure after five years, with the intersection occurring earlier in allografts from older donors.

Donor age was identified as the main determinant of allograft failure, and CIT had a limited impact at the population level, becoming significant for allografts from older donors or recipients with comorbidities.

The final model predicts the risk of failure at one, three, five, and ten years post-transplantation at the time of allocation.

We confirmed the replicability of our predictor tool by showing its validity in a large European validation cohort.

At the time of kidney allograft allocation, balancing efficiency and equity is often challenged by logistical constraints, such as transportation distance and cross-match results. Our predictive model can guide organ distribution agencies and medical teams in determining the maximum CIT, balancing failure risk with prolonged kidney disease or dialysis. For younger donors, extended CIT is acceptable but should be minimized, while for older donors, the CIT should ideally be under 10 h to achieve a risk of failure under 15% at five years. The model emphasizes the need for personalized evaluation of CIT based on donor and recipient characteristics.

A Beta version of the online application is available at the following link: https://nephrology-nice.shinyapps.io/CIT-failure-predictor.

We used established statistical methodologies to develop two predictive models, avoiding reliance solely on statistical significance for variable selection. Both models identified the same major determinants of allograft failure, reinforcing the robustness of our findings.

Given the high frequency of death as a competing event in kidney transplant recipients, we selected the Fine–Gray model, which estimates the cumulative incidence of allograft failure while accounting for death with a functional allograft as a competing risks. This approach provides clinically interpretable risk estimates, directly aligned with the objective of guiding allocation and acceptance decisions at the time of organ allocation.

Although Fine–Gray may slightly underestimate the effect of variables moderately associated with death, such as CIT, previous studies have shown minimal differences in predictive performance compared to Cox or cause-specific models.[26] Other studies strongly support the use of competing risk approaches: in a large-scale analysis of over 300,000 transplant recipients,

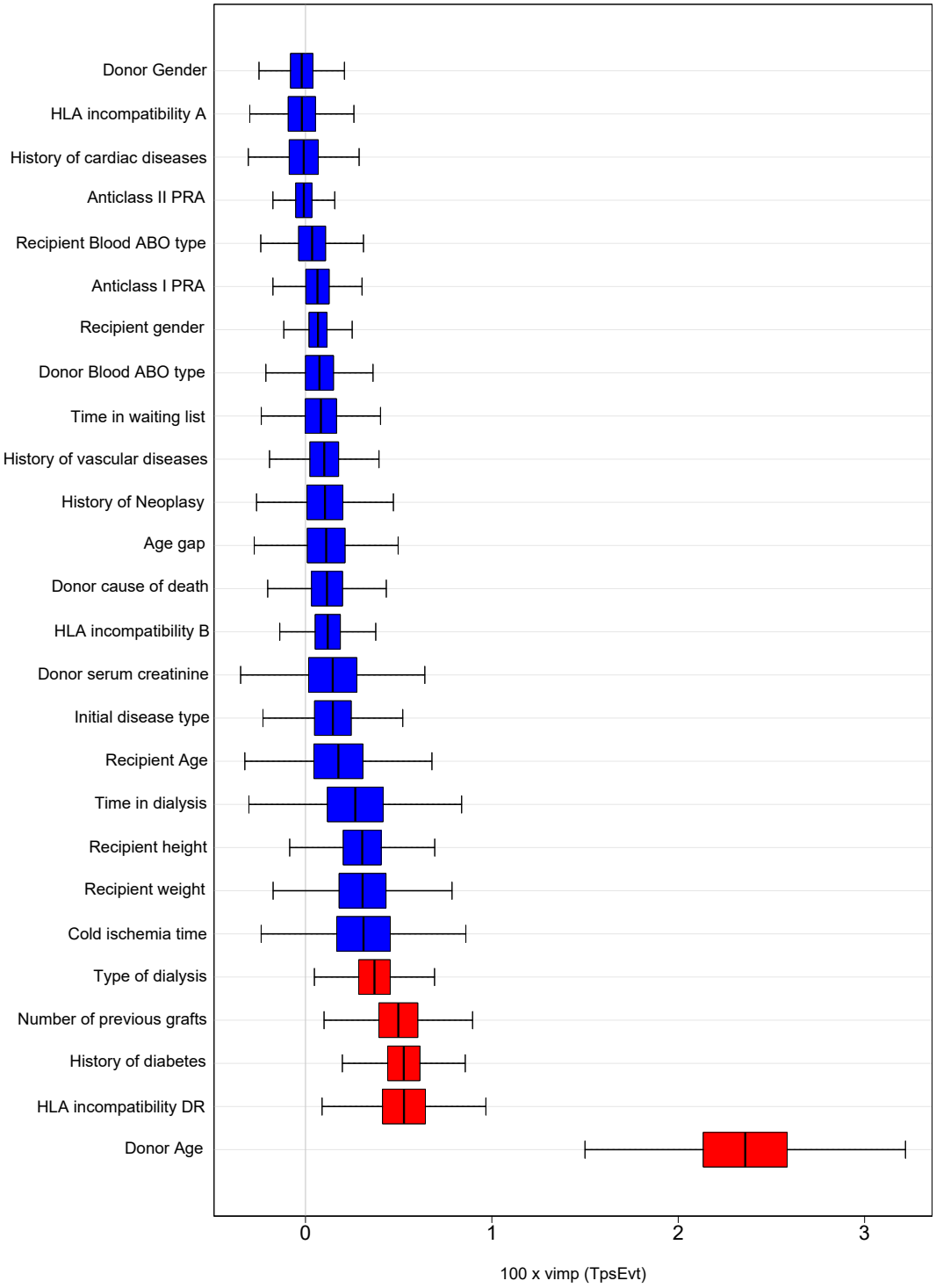

Fig. 3: Out of bag (OOB) variable importance (VIMP) results from the prediction of kidney allograft failure using survival random forests on the derivation cohort EKITE.

Coemans et al. demonstrated that failure to account for death as a competing event led to significant overestimation of allograft failure risk, particularly in older donor-recipient pairs.[27] In our context, Fine Gray offered the best balance between predictive performance, interpretability, and practical application.

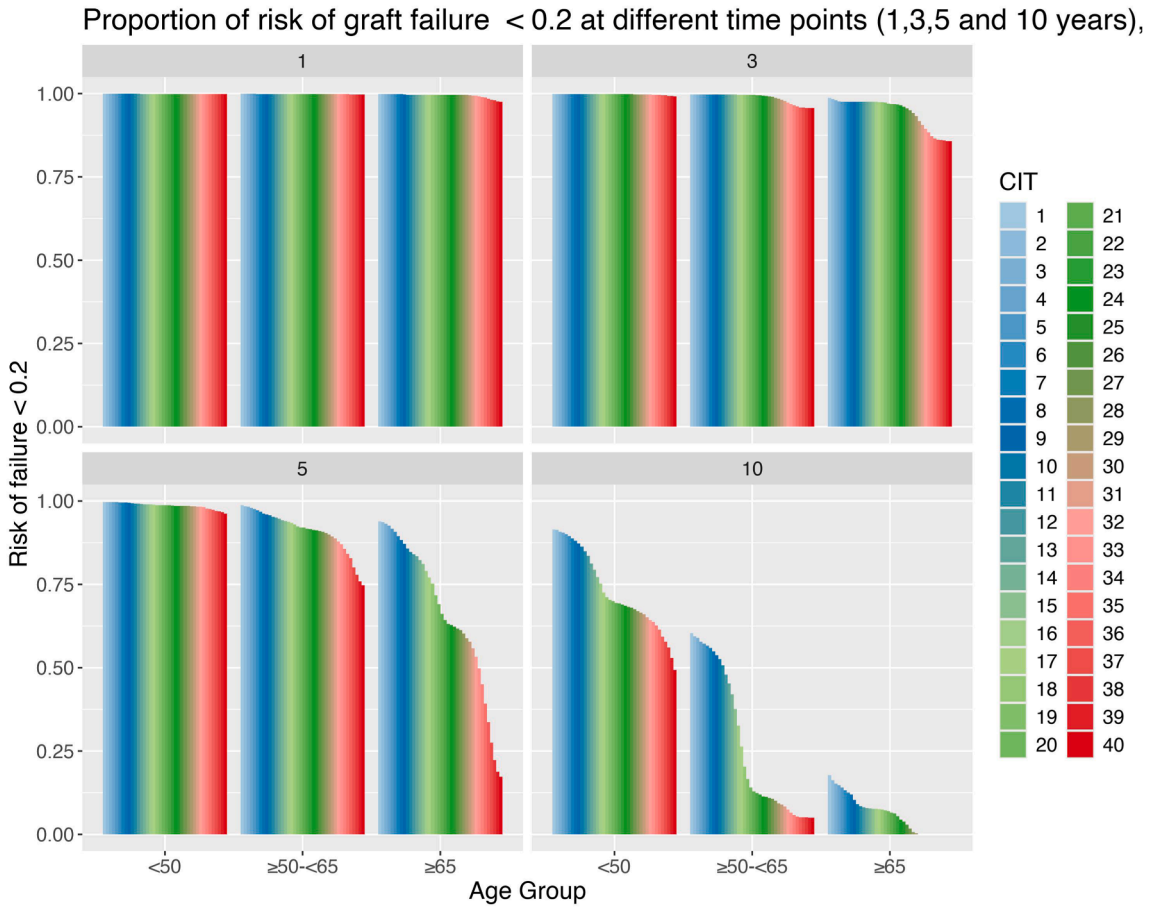

Fig. 4: Proportion of individuals with a risk of failure under 0.2 predicted using the Fine Gray model. Predictions were computed for cold ischemia time ranging from 0 to 40 h at 1, 3, 5 and 10 years post-transplant in each panel. Presenting individual risk of failure for the different CIT and time points would result in saturated plots, hence, we decided to present the proportion of individuals in the dataset with a predicted risk of failure smaller than 0.2.

One of the major strengths of our study lies in the diversity and representativeness of the cohorts included. The dataset encompasses 10 transplant centers across Europe, ensuring broad applicability. Moreover, the demographics of our population (age, sex, dialysis exposure, comorbidities) are consistent with recent registry reports from the Agence de la Biomédecine,[28] EuroTransplant,[29] and OPTN,[30] supporting the generalizability of our findings.

Although direct comparison with other predictive models is not possible, our model demonstrated good discriminative performance, with a C-index comparable to those used in validated oncology prognostic systems.[31]

However, some limitations should be acknowledged. First, our model excludes perioperative and post-transplant variables (e.g., rejection episodes, infections, drug toxicity), as well as post-transplant events. While these factors are known to influence long-term graft outcomes, their inclusion was not compatible with the goal of our model–namely, to support decision-making at the time of allograft allocation using only pre-allocation data.

	Cox regression				Fine gray competing risks			
	Year 1	Year 3	Year 5	Year 10	Year 1	Year 3	Year 5	Year 10
OE	1.22 [1.10–1.36]	1.24 [1.13–1.35]	1.26 [1.17.1.37]	1.28 [1.18–1.39]	1.06 [0.94–1.120]	1.13 [1.02–1.24]	1.19 [1.09–1.29]	1.35 [1.23–1.47]
C_index	0.64 [0.64–0.64]	0.64 [0.64–0.64]	0.64 [0.64–0.64]	0.64 [0.64–0.64]	0.66 [0.66–0.66]	0.63 [0.63–0.63]	0.62 [0.62–0.62]	0.60 [0.60–0.60]

Table 3: **Calibration (O/E) and discrimination (C-index) metrics at 1, 3, 5 and 10 years post-transplantation, for the Cox and Fine Gray predictive models in the validation cohort.**

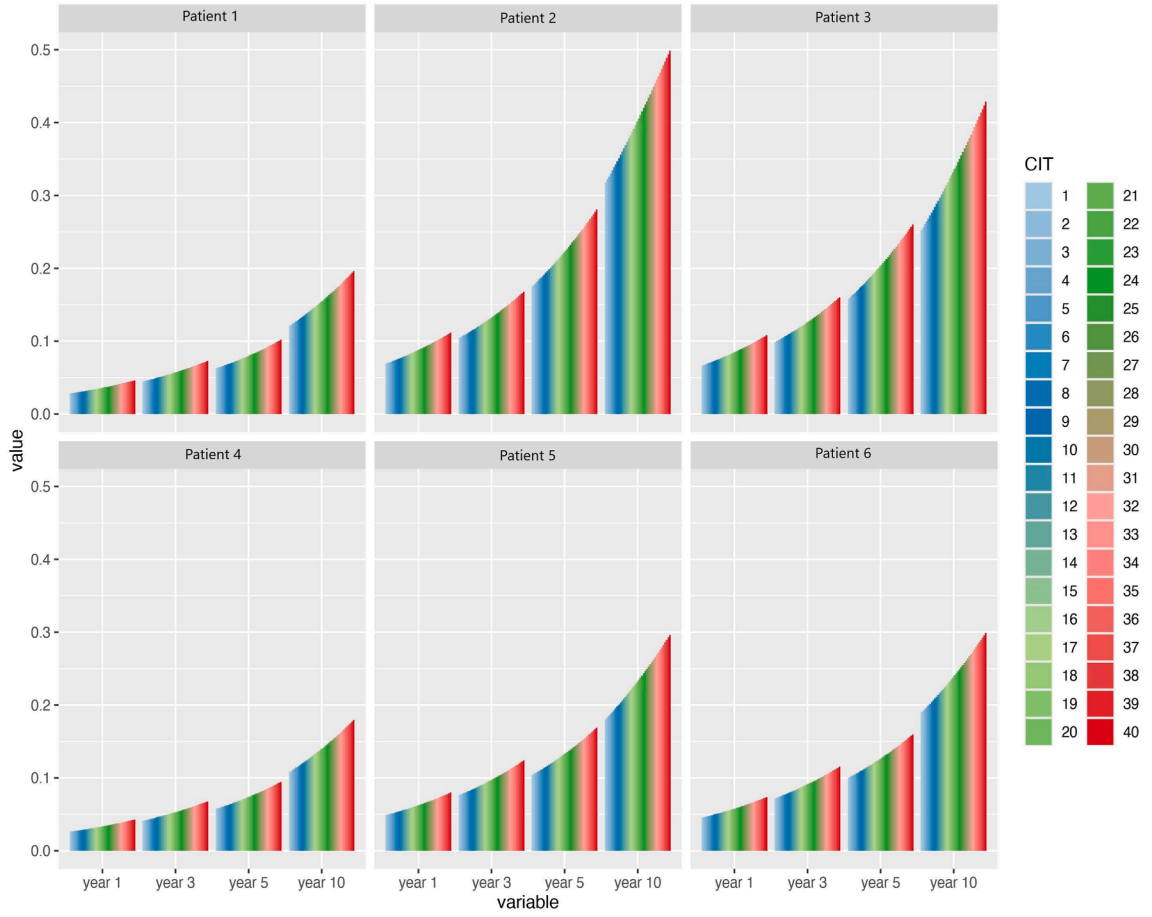

Fig. 5: Practical application of Fine Gray model: Individual prediction of kidney allograft risk of failure at time points post-transplant: one, three, five, and ten years based on cold ischemia time. *Patient 1:* 36-year-old donor, creatinin 77 µmol/L, Transplant #1, Diabetes: No, Hemodialysis: Yes. *Patient 2*: 54-year-old donor, creatinin 104 µmol/L, Transplant #2, Diabetes: Yes, Hemodialysis: Yes. *Patient 3*: 77-year-old donor, creatinin 64 µmol/L, Transplant #1, Diabetes: Yes, Hemodialysis: Yes. *Patient 4*: 59-year-old donor, creatinin 68 µmol/L, Transplant #1, Diabetes: No, Hemodialysis: No. *Patient 5*: 68-year-old donor, creatinin 57 µmol/L, Transplant #1, Diabetes: No, Peritoneal Dialysis: Yes. *Patient 6*: 48-year-old donor, creatinin 144 µmol/L, Transplant #2, Diabetes: No, Hemodialysis: Yes.

Second, our model does not incorporate machine perfusion, another modifiable factor. Its use varies significantly between centers and countries, and was not consistently recorded across datasets. Although incorporating machine perfusion could potentially improve predictive performance, our approach intentionally focuses on cold ischemia time–a widely available and actionable parameter–to provide a simple and effective tool for improving allocation decisions.

Several models predict kidney allograft failure, with those considering post-transplantation determinants offering better performance[32] but not addressing our goal of guiding CIT.

Our model has the particular feature of accounting for the competing risk between patient death and allograft failure, which is not the case for most pre-transplant models.[27,33,34]

Moreover, some predictive models for kidney allograft failure at the time of allocation are already in use, particularly the KDRI in the United States.[6] These models mainly focus on donor characteristics, whereas our model enables the prediction of allograft failure by considering data from a specific allograft allocated to a specific recipient.

For a given donor, the recipient's characteristics at the time of transplantation will influence the risk of allograft failure, and the impact of cold ischemia time will vary accordingly.

Our approach provides a flexible tool for estimating the risk of allograft failure across different CIT for a given donor-recipient pair.

As a result, organ allocation agencies can easily issue recommendations regarding the maximum acceptable CIT for a specific match. For transplant teams, our tool

offers valuable support in deciding whether to accept a given allograft for a particular recipient, based on real-world logistical considerations such as operating room availability or estimated transport time.

In summary, we developed and validated a predictive model for kidney allograft failure at the time of organ allocation. The model offers a simple and practical tool for organ distribution agencies and medical teams to select recipients and plan logistical organization based on permissible cold ischemia time.

Contributors

All authors read and approved the final version of the manuscript.
AS, CG and SB had access to and verified the underlying data.
AS, CG, and SB designed the study.
Data analysis was performed by SB, CG, AD, NG, DK, MC, MN and AS.
CG, SB and AS wrote the original draft and the final report.
CG, SB, SC, LA, EM, XC, MLQ, JEL, MaL, SG, CM, DA, CL, GD, EG, MD, DK, OBM, AA, MG, MN, AS collected the data and reviewed the manuscript.

Data sharing statement

The data underlying this study are derived from the EKITE and DIVAT cohorts. Due to ethical and legal restrictions related to patient confidentiality and data protection regulations, these datasets are not publicly available. However, access to the data may be granted upon reasonable request to the corresponding authors and with prior approval from the relevant institutional review boards and data custodians. No proprietary software was used; all analyses were performed using standard statistical packages (R Statistical Software (v4.2.1); R Core Team).

Declaration of interests

All authors have completed the Unified Competing Interest form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. Emmanuel Morelon reports having received personal payment from Sanofi for lectures or presentations. Dirk Kuypers reports having received consulting fees, honoraria for lectures or presentations, and support for attending meetings or travel from Astellas. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103322.

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