Dynamic prediction of renal survival among deeply phenotyped kidney transplant recipients using artificial intelligence: an observational, international, multicohort study

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Summary

Background Kidney allograft failure is a common cause of end-stage renal disease. We aimed to develop a dynamic artificial intelligence approach to enhance risk stratification for kidney transplant recipients by generating continuously refined predictions of survival using updates of clinical data.

Methods In this observational study, we used data from adult recipients of kidney transplants from 18 academic transplant centres in Europe, the USA, and South America, and a cohort of patients from six randomised controlled trials. The development cohort comprised patients from four centres in France, with all other patients included in external validation cohorts. To build deeply phenotyped cohorts of transplant recipients, the following data were collected in the development cohort: clinical, histological, immunological variables, and repeated measurements of estimated glomerular filtration rate (eGFR) and proteinuria (measured using the proteinuria to creatininuria ratio). To develop a dynamic prediction system based on these clinical assessments and repeated measurements, we used a Bayesian joint models—an artificial intelligence approach. The prediction performances of the model were assessed via discrimination, through calculation of the area under the receiver operator curve (AUC), and calibration. This study is registered with ClinicalTrials.gov, NCT04258891.

Findings 13 608 patients were included (3774 in the development cohort and 9834 in the external validation cohorts) and contributed 89 328 patient-years of data, and 416 510 eGFR and proteinuria measurements. Bayesian joint models showed that recipient immunological profile, allograft interstitial fibrosis and tubular atrophy, allograft inflammation, and repeated measurements of eGFR and proteinuria were independent risk factors for allograft survival. The final model showed accurate calibration and very high discrimination in the development cohort (overall dynamic AUC 0·857 [95% CI 0·847–0·866]) with a persistent improvement in AUCs for each new repeated measurement (from 0·780 [0·768–0·794] to 0·926 [0·917–0·932]; p<0·0001). The predictive performance was confirmed in the external validation cohorts from Europe (overall AUC 0·845 [0·837–0·854]), the USA (overall AUC 0·820 [0·808–0·831]), South America (overall AUC 0·868 [0·856–0·880]), and the cohort of patients from randomised controlled trials (overall AUC 0·857 [0·840–0·875]).

Interpretation Because of its dynamic design, this model can be continuously updated and holds value as a bedside tool that could refine the prognostic judgements of clinicians in everyday practice, hence enhancing precision medicine in the transplant setting.

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Introduction

Kidney allograft failure is an important burden in kidney disease and contributes to the increasing number of people with end-stage renal disease, now exceeding 7 million worldwide as of 2020.[1] Health agencies and medical societies have emphasised the need for a prediction model for kidney allograft survival adapted to routine clinical practice that would enhance decision making and patient management.[2]

Multiple factors—from clinical to histological and immunological—drive the deterioration of a kidney allograft, leading to allograft failure.[3] Additionally, several

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Research in context

Evidence before this study

Predicting the failure of kidney allograft requires the integration of multidimensional data and is a complex yet crucial task in clinical practice. In the past 20 years, many kidney allograft survival prediction models have been developed. We searched PubMed for publications in English between Jan 1, 2000, and Jan 1, 2021, using the terms ("prognosis" OR "prediction") AND ("kidney transplantation") AND ("graft failure" OR "graft loss" OR "graft survival"). The search yielded 1690 articles, of which 35 reported the development of a kidney allograft survival prediction system. Among these, five systems were externally validated and none dynamically integrated clinical, histological, and immunological data and repeated measurements of kidney function at the same time.

Added value of this study

Based on a joint modelling approach, we developed a dynamic, multidimensional kidney allograft survival prediction system (called dynamic, integrative system for predicting outcome [DISPO]), using four French cohorts of kidney transplant recipients for development and 14 international cohorts for external validation and six randomised controlled trials. Our system showed good prediction performance across countries, and in a series of clinical scenarios and subpopulations (eg, patients with a graft from a living donor, or patients with anti-IL2 receptor induction). It also captured response to therapeutic interventions and outperformed existing prediction models for kidney allograft survival.

Implications of all the available evidence

We adapted the model into an online interface devoted to patient risk stratification, enabling real-time prognostication. Therefore, our model could help to refine the prognostic evaluation of kidney transplant recipients in routine clinical practice, enhancing precision medicine and individualised patient management. To assess the effect of DISPO in clinical practice, we plan to conduct a randomised controlled trial.

studies have found that repeated measurements of allograft function can add value when predicting clinical outcomes.[4,5] Hence, capturing a comprehensive set of risk factors for allograft failure requires not only large, well annotated, deeply phenotyped cohorts[6] of kidney transplant recipients but also a dynamic and integrative method that uses repeated and diverse measures recorded throughout patient follow-up.

Although some kidney allograft survival prediction models hold promise as surrogate endpoints for clinical trials—such as the iBox score, a prediction system we previously developed focusing on an early timepoint after transplantation,[3] which was derived using standard Cox analysis—none has been designed to constantly refine individual patient predictions.[7] For this reason, the current models have not translated into an implementable strategy for routine patient monitoring and care.

Therefore, we aimed to develop and validate a dynamic, integrative allograft survival prediction system using information gathered by protocol-driven, repeated estimated glomerular filtration rate (eGFR) and proteinuria assessments done alongside clinical, biological, histological, and immunological testing in large prospective cohorts of kidney transplant recipients from Europe, North America, and South America, and six randomised controlled trials. We used a Bayesian joint modelling contemporary approach,[8] which is optimal for integrating longitudinal parameters recorded at any time intervals, and prognostic factors that do not vary over time. This approach has already been found to have clinical relevance in several health domains, such as oncology,[9] cardiovascular disease,[10] and hypertension.[11]

Methods

Study design and participating cohorts

In this multinational observational study, we used data from 18 cohorts of adult kidney recipients (aged ≥18 years) from seven countries. For the development cohort, we collected data from patients ourselves, and for the external validation cohorts, we sourced data from these studies using existing data collection systems.

For the development cohort, consecutive patients were prospectively included on the day of transplantation (living or deceased donation) at the Necker and Saint-Louis hospitals in Paris, France, the CHU Rangueil and Purpan hospital in Toulouse, France, and the Foch hospital in Suresnes, France, between Jan 1, 2005, and Jan 1, 2014. These cohorts were part of the Paris Transplant Group study. We anonymised and continuously entered the clinical data into the Paris Transplant Group unified dataset using a standardised, shared protocol to ensure harmonisation. More information on this process is available in the appendix (p 2).

For external validation of our system, we used data from six registered and published phase 2 and 3 clinical trials[12–17] in addition to 14 cohorts that contained adult patients (aged ≥18 years) who received transplants (living or deceased donation) between Jan 1, 2000, and Jan 1, 2016: five cohorts from Europe (Montpellier Hospital, Montpellier, France; Bretonneau Hospital, Tours, France; University Hospital Centre Zagreb, Zagreb, Croatia; Nancy Hospital, Nancy, France; and Hospital del Mar, Barcelona, Spain), five from the USA (Johns Hopkins University School of Medicine, Baltimore, MD, USA; Northwestern University Feinberg School of Medicine, Chicago, IL, USA; William J von Liebig Center for Transplantation and Clinical Regeneration, Mayo Clinic,

Rochester, MN, USA; Comprehensive Transplant Center, Cedars Sinai Medical Center, Los Angeles, CA, USA; and Renal Division Montefiore Medical Center, Bronx, NY, USA), and four from South America (Hospital do Rim and Hospital das Clinicas da Universidade de São Paulo, São Paulo, Brazil; Centro de Educacion Medica e Investigaciones Clinicas Buenos Aires, Argentina; Kidney Transplantation Department, Clinica Alemana de Santiago, Santiago, Chile; appendix p 2). Details about the kidney allograft allocation system and data collection for each cohort are provided in the appendix (pp 14–15).

We used the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines (appendix pp 16–17)[18] for reporting the development and validation of the prediction model.

All data from the Necker, Saint Louis, Foch, and Toulouse hospitals were extracted from the prospective Paris Transplant Group Cohort (Commission nationale de l'informatique et des libertés, known as CNIL, registration number 363505; protocol was validated on June 8, 2004). The database networks were approved by the CNIL and codes were used to ensure strict donor and recipient anonymity and blinded access. Written informed consent was obtained from participants at the time of transplantation. The validation cohorts followed the legal and ethical rules applied in each country (for more information see appendix p 2). As part of research collaborations, the institutional review boards with oversight for patients at each centre and in each trial agreed to send the anonymised data to the Paris Transplant Group. In each cohort, patients gave written informed consent on the day of transplantation.

Data collection and procedures

The following data collection methods were only applied to the development cohort. The selection and acquisition of data was based on the expertise of the transplant nephrologists, pathologists, and methodologists in the Paris Transplant Group (MR, OA, GD, PPR, DY, J-PE, XJ, CLeg, CLef, AL), and on the evidence and findings in the scientific literature. Initial risk assessment of each patient was performed at the time of allograft biopsy after transplantation for a clinical indication or per protocol (which was usually performed around 1 year after transplantation) to build deeply phenotyped cohorts of transplant recipients. The following information was collected: recipient and donor age, sex, and comorbidities; transplant characteristics (ie, previous kidney transplant, cold ischaemia time, and HLA mismatch number); functional parameters (ie, eGFR and proteinuria); immunological profile (ie, circulating anti-HLA donor-specific antibody specificities and mean fluorescence intensity specificities and levels); and allograft histopathology data, including lesion scores and diagnoses.

The following assessments were done for the development cohort, even though similar strategies were used for all external validation cohorts. Circulating anti-HLA donor-specific antibodies were assessed using single-antigen flow-bead using the One Lambda strategy (appendix pp 2–3).[19] Histopathological data were assessed according to the Banff international classification (the list of all prognostic parameters assessed from the development cohort is in the appendix [pp 3–5]).[20]

In the development cohort, all study centres performed the protocol biopsies and all patients had at least one biopsy. For patients with several biopsy samples from the development or external validation cohorts, initial assessment was done using the date of and data from the first biopsy. For patients without a biopsy sample from the external validation cohorts, one of the timepoints of eGFR and proteinuria measurement in the first year after transplantation was randomly chosen as the time of initial assessment was.

In the development cohort, repeated eGFR and proteinuria measurements were done at the time of initial evaluation after transplantation and every 6 months thereafter according to a predefined protocol, and at the time of any clinically indicated allograft biopsies. eGFR was calculated using the Modification of Diet in Renal Disease Study equation, which has been shown to have good accuracy compared with other estimating equations in kidney transplant recipients.[21,22] Proteinuria was assessed using the proteinuria to creatininuria ratio.[23,24] For the external validation cohorts and randomised controlled trial data, eGFR and proteinuria measurements were recorded per centre protocol for all patients after transplantation.

Statistical analysis

We aimed to predict the outcome of death-censored allograft survival using a dynamic prediction system. The failure of the allograft was defined as a patient's definitive return to dialysis or pre-emptive kidney re-transplantation.

We describe continuous variables using mean (SD) or median (IQR), as appropriate. We compared means and proportions between groups using Student's *t* test, ANOVA (Mann-Whitney *U* test for donor-specific antibodies mean fluorescence intensity), or χ^2 test (or Fisher's exact test if appropriate). Follow-up started from the patient's initial risk assessment up to the date of allograft failure or the end of follow-up (Dec 31, 2019), and the outcome was assessed at the end of follow-up. For patients who died with a functioning allograft, allograft survival was censored at the time of death as a functional allograft.

To derive a dynamic, integrative, prediction system including patients' longitudinal assessments, we used Bayesian, shared-parameter, multivariable joint models, which is an artificial intelligence approach and optimal to assess the associations between longitudinal markers and survival data. The principle of this approach is to join a Cox model that correlates features measured at

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one timepoint with survival data to mixed models that estimate the trajectories of eGFR and proteinuria based on the repeated measurements.[25,26] With this method, we included clinical, immunological, functional, and histopathological data measured at the initial risk assessment in a Cox model, while the continuously recorded eGFR and proteinuria measurements were included in two mixed models. To assess the effect of repeated eGFR and proteinuria measurements up to a specific timepoint, we considered in turn the updated measurement only, the slope with all measurements observed, and the cumulative effect with the area under all measurements observed (appendix pp 6–8). According to these different parameterisations, we selected the model presenting the best prediction performance.

The performance of the dynamic prediction model was based on its discrimination and calibration. We assessed the discrimination of the final model using dynamic area under the receiver operator curves (AUCs).[8,27] For each cohort, the prediction horizon for the calculation of AUCs was set at the median follow-up time after initial risk evaluation (appendix pp 8–9). We assessed the calibration (ie, the similarity between the predicted risk and the actual outcome) using calibration plots and the calibration intercept and slope from the linear regression of the observed outcomes versus the predicted risk.[28]

We assessed the internal validity of the final multivariable model by bootstrapping 50 samples from the development cohort, which allowed us to repeat the calculation of hazard ratios, allowing us to generate bias-corrected hazard ratios, and repeat the discrimination and the calibration. Thereafter, we assessed the external validity of the model in the 14 independent observational cohorts and one cohort comprising the six randomised controlled trial datasets, and included dynamic AUC calculation and calibration.

We built a dynamic, integrative system for predicting outcome (hereafter called DISPO) from the final multivariable joint model and created an interface for online use (appendix pp 6–8). This dynamic system provides a personalised prediction of long-term allograft survival on the basis of observed repeated measures of eGFR and proteinuria and parameters assessed at the time of initial risk assessment. A table summarising the population, data, outcome, and model development and validation is presented in the appendix (pp 6–8). Details regarding the calculation of prediction performance and data imputation are provided in the appendix (pp 6–8).

We investigated whether the system could capture treatment response in three distinct clinical scenarios: antibody-mediated rejection, T-cell mediated rejection, and calcineurin inhibitor minimisation. We calculated the change in predicted allograft survival based on patient evaluation after and before therapeutic interventions and defined patients with a favourable response as those with a change greater than 0.

To confirm the prediction performance of our system, we applied the system to subpopulations of the development cohort were: recipients who had a biopsy per protocol; recipients who had a biopsy by clinical indication; recipients who had an initial risk evaluation before 1 year after transplant; recipients who had an initial risk evaluation more than 1 year after transplant; recipients of living donor kidneys; recipients of deceased donor kidneys; recipients who received induction with an anti-IL-2 receptor; and recipients who received induction with anti-thymocyte globulin. Additionally, we adapted the system to centres that do not grade the biopsy sample using the Banff classification, by using histological diagnoses instead. We also added to the system the transplant baseline characteristics to assess whether it added predictive value. Finally, we adapted the system to centres that do not perform biopsy or immunological assessment by removing these data from the system, and assessing the prediction performances.

To compare our system with the prediction models previously developed in kidney transplantation, we did a literature review. The details of this literature review are presented in the appendix (p 13). We compared the prediction performances of our system with the iBox system using eGFR slopes—a standard measure to assess the risk of allograft loss.

To assess the robustness of the model, we did several sensitivity analyses in the development cohort. We assessed the effect of the study site in the model, to ensure that the model was not centre dependent. We added parameters assessed at the time of transplantation to investigate whether this could enhance prediction performance. We implemented different timing of the risk assessment (ie, timing of biopsy) to ensure that the model can be applied at different times. We also stratified donor-specific antibody data by different loci becasue they can be differently associated with allograft survival.

We used R (version 3.2.1) and STATA (version 14) for the descriptive and survival analyses. We considered p values of less than 0·05 to be significant, and all tests were two-tailed. This study is registered with ClinicalTrials.gov, NCT04258891.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The development cohort (n=3774), European validation cohort (n=5506), US validation cohort (n=2944), South American validation cohort (n=858), and six randomised controlled trials (n=526) contained a total of 13 608 kidney recipients from 18 centres in seven countries, corresponding to 89 328 patient-years (table 1). The median time from kidney transplantation to initial risk assessment

	French development cohort (four centres; n=3774)	European validation cohort (five centres; n=5506)	US validation cohort (five centres; n=2944)	South America validation cohort (four centres; n=858)	p value*
Recipient characteristics					
Age, years	49·8 (13·7)	50·8 (14·0)	52·1 (14·1)	44·5 (14·1)	<0·0001
Sex					
Female	1455 (38·6%)	2090 (38·0%)	1335 (45·3%)	378 (44·1%)	0·0006
Male	2319 (61·4%)	3416 (62·0%)	1609 (54·7%)	480 (55·9%)	..
Causes of end-stage renal disease					
Glomerulonephritis	1018 (27·0%)	1557 (28·3%)	574 (19·5%)	224 (26·1%)	<0·0001
Any diabetes	411 (10·9%)	546 (9·9%)	400 (13·6%)	104 (12·1%)	..
Vascular	274 (7·3%)	447 (8·1%)	170 (5·8%)	123 (14·3%)	..
Other	2071 (54·9%)	2956 (53·7%)	1800 (61·1%)	407 (47·4%)	..
Preformed anti-HLA donor-specific antibodies	532 (14·1%)	215 (3·9%)	339 (11·5%)	NA†	<0·0001
Calculated PRA >85%	520 (13·8%)	496 (9·0%)	218 (7·4%)	NA†	<0·0001
Donor characteristics					
Age, years	51·6 (16·4)	50·9 (15·8)	41·3 (14·3)	44·9 (13·6)	0·0009
Sex					
Female	1749 (46·3%)	2344/5498 (42·6%)	1458/2943 (50·0%)	424/854 (49·6%)	<0·0001
Male	2025 (53·7%)	3154/5498 (57·4%)	1485/2943 (50·5%)	430/854 (50·4%)	..
Hypertension	944/3688 (25·6%)	1564/5024 (31·1%)	379/2166 (17·5%)	22/97 (22·7%)	<0·0001
Any diabetes	220/3648 (6·0%)	294/4085 (7·2%)	53/2191 (2·4%)	4/113 (3·5%)	<0·0001
Creatinine >1·5mg/dL	393/3741 (10·5%)	1129/5245 (21·5%)	197/1298 (15·2%)	102/152 (67·1%)	<0·0001
Donor type					
Deceased donor	3137 (83·1%)	4508/5089 (88·6%)	1348 (45·8%)	538/856 (62·9%)	<0·0001
Death from cerebrovascular disease	1751/3137 (55·8%)	2777/4461 (62·3%)	215/498 (43·2%)	NA†	<0·0001
Expanded criteria donor	1317/3769 (34·9%)	1622/4175 (38·9%)	235/2345 (10·0%)	180/816 (22·1%)	<0·0001
Transplant baseline characteristics					
Previous kidney transplant	564/3774 (14·9%)	530/5028 (10·5%)	411/2070 (19·9%)	55/848 (6·5%)	<0·0001
Cold ischaemia time in deceased donors, h					
n	3118	3319	1270	519	..
Mean	19·0 (7·2)	17·4 (6·7)	18·6 (10·5)	22·1 (7·9)	<0·0001
HLA-A, HLA-B, and HLA-DR mismatch					
n	3770	5431	2014	850	..
Mean (SD)	3·8 (1·4)	3·3 (1·4)	3·7 (1·7)	2·7 (1·4)	0·0005

Data are mean (SD), n (%), or n/N (%). Unless otherwise stated, the denominators for proportions and the populations for mean data are the totals at the top of the columns. DSA=donor-specific antibodies. HLA=human leucocyte antigen. NA=not available. PRA=panel reactive antibody. *p values were calculated for means and proportions between groups using Student's *t* test, ANOVA (Mann-Whitney *U* test for donor-specific antibody mean fluorescent intensity) or the χ^2 test (or Fisher's exact test if appropriate). †These data were not available for the South American cohort.

Table 1: **Baseline characteristics of the development and validation cohorts (n=13 082)**

was 1·0 years (IQR 0·3–1·1) in the development cohort and 0·3 years (0·2–1·0) in the validation cohorts overall. The median follow-up after transplantation was 8·1 years (5·6–10·9) in the development cohort and 6·0 years (3·9–8·9) in the validation cohorts overall. Overall, 416 510 eGFR and proteinuria measurements were assessed (mean of 27·4 [SD 10·3] measurements per patient in the development cohort, 39·1 [12·1] in the European validation cohort, 22·8 [12·9] in the US validation cohort, and 35·5 [11·9] in the South American validation cohort), and 1893 patients lost their allograft during study follow-up. In the development cohort, 287 (7·6%) of 3774 patients had de-novo donor-specific antibodies. This number should be put in the context of the early timepoint of the risk assessment in our study design: 94 (32·8%) 287 of donor-specific antibodies were class I, and 193 (67·2%) were class II. Baseline characteristics of the development and validation cohorts are shown in table 1. Baseline data for participants in the randomised controlled trials have been published elsewhere.[12–17] Follow-up characteristics for each cohort, by centre, are shown in table 2 and the appendix (p 18). Additional characteristics, which include the distinct programmes of transplantation in the development cohorts, and the clinical scenarios and interventions in the clinical trials, are shown in the appendix (pp 14–15).

	N	Follow-up after transplantation, years	Time from transplantation to initial evaluation, years	eGFR at initial assessment, mL/min per 1·73m²	Proteinuria at initial assessment, g/g
Development cohort					
Necker hospital, Paris, France	1416	8·39 (6·04–11·06)	0·98 (0·27–1·06)	50·82 (19·84)	0·17 (0·09–0·35)
Saint-Louis hospital, Paris, France	872	7·35 (4·82–10·10)	1·00 (0·29–1·13)	47·88 (19·66)	0·20 (0·10–0·42)
CHU Rangueil and Purpan hospital, Toulouse, France	835	8·46 (5·83–11·01)	0·99 (0·42–1·05)	48·47 (16·69)	0·18 (0·05–0·34)
Foch hospital, Suresnes, France	651	7·96 (5·49–11·08)	0·87 (0·25–1·03)	54·32 (19·43)	0·22 (0·15–0·40)
Development cohort overall	3774	8·06 (5·60–10·9)	0·98 (0·27–1·07)	50·22 (19·20)	0·19 (0·10–0·38)
Validation cohorts					
Europe					
Montpellier hospital, Montpellier, France	1586	6·16 (4·19–8·29)	0·25 (0·25–0·34)	50·12 (18·66)	0·21 (0·12–0·36)
Bretonneau Hospital, Tours, France	1399	7·30 (4·97–10·58)	0·45 (0·24–1·09)	50·83 (20·31)	0·29 (0·18–0·54)
University Hospital Centre Zagreb, Zagreb, Croatia	1206	5·65 (3·54–7·94)	0·25 (0·25–0·25)	55·61 (14·16)	0·25 (0·15–0·38)
Nancy hospital, Nancy, France	1136	10·28 (8·14–12·41)	0·25 (0·25–0·25)	51·29 (16·93)	0·23 (0·14–0·40)
Hospital del Mar, Barcelona, Spain	179	7·54 (5·66–10·29)	1·25 (0·97–3·67)	48·19 (23·45)	0·29 (0·14–0·72)
Europe overall	5506	7·15 (4·56–10·11)	0·25 (0·25–0·77)	51·68 (18·18)	0·24 (0·14–0·42)
USA					
Johns Hopkins Univerisity School of Medicine, Balitmore, MD	1017	4·25 (2·39–6·72)	0·16 (0·16–0·16)	59·68 (19·96)	0·08 (0·05–0·22)
Northwestern University Feinberg School of Medicine, Chicago, IL	872	4·73 (3·35–6·61)	1·03 (1·00–1·10)	55·93 (25·55)	0·05 (0·05–0·43)
Mayo Clinic, Rochester, MN	552	11·04 (9·03–12·76)	1·01 (0·99–1·06)	56·36 (15·25)	0·11 (0·07–0·23)
Cedars Sinai Medical Center, Los Angeles CA	380	2·80 (1·54–4·25)	0·47 (0·23–1·02)	45·35 (23·23)	0·31 (0·21–0·51)
Montefiore hospital, Bronx, NY	123	6·85 (5·83–7·84)	0·29 (0·11–1·35)	38·65 (19·35)	0·31 (0·14–1·00)
USA overall	2944	5·07 (3·00–7·78)	0·96 (0·16–1·03)	55·22 (22·15)	0·11 (0·05–0·33)
South America					
Hospital do Rim, São Paulo, Brazil	481	4·61 (3·91–5·70)	2·60 (1·25–3·67)	33·89 (13·51)	0·38 (0·11–0·90)
Centro de Educacion Medica e Investigaciones Clinicas, Buenos Aires, Argentina	140	5·01 (3·73–6·23)	0·86 (0·42–1·10)	56·41 (21·15)	0·10 (0·05–0·23)
Hospital das Clinicas da Universidade de São Paulo, São Paulo, Brazil	121	4·30 (3·05–5·14)	1·00 (1·00–1·00)	68·26 (17·45)	0·13 (0·09–0·23)
Clinica Alemana de Santiago, Santiago, Chile	116	6·33 (3·00–9·21)	1·44 (0·44–4·84)	36·44 (18·77)	0·11 (0·05–0·59)
South America overall	858	4·73 (3·78–5·85)	1·27 (1·00–3·21)	42·74 (20·89)	0·23 (0·06–0·63)

Data are number of transplant recipients, median (IQR), or mean (SD). eGFR=estimated glomerular filtration rate.

Table 2: **Follow-up characteristics of transplant recipients in the development and validation cohorts (n=13 082)**

In the development cohort, functional, immunological, and histopathological features assessed at the initial risk assessment were combined with repeated eGFR and proteinuria measurements to develop a dynamic, integrative prediction model. In the multivariable analysis, all these features were independent predictors of long-term (ie, >7 years) allograft survival (figure 1; appendix p 19, 29). The different parameterisations implemented, and their discriminative performances are shown in the appendix (p 20).

Based on these results, we constructed the DISPO. In internal validation, the overall dynamic AUC of the final multivariable model was 0·857 (95% bootstrap percentile CI 0·847–0·866) at the prediction horizon of 7 years after initial assessment, with a persistent improvement in AUCs for each new repeated measurement (0·780 [0·768–0·794] to 0·926 [0·917–0·932]; p<0·0001; figure 2). How successful the calibration performance of the model was is shown using calibration plots (figure 2) and the robustness was ascertained through calculation of bias-corrected hazard ratios (appendix p 19).

We then tested the exportability of the system. Overall, we found very high discrimination performance with an overall dynamic AUC of 0·845 (95% bootstrap percentile CI 0·837–0·854) in the European cohort, 0·820 (0·808–0·831) in the US cohort, and 0·868 (0·856–0·880) in the South American cohort, and 0·857 (0·840–0·875) in the cohort comprising patients from six previously published phase 2 and 3 randomised clinical trials (figure 3). Via the calibration plots, we found strong agreement between the predicted allograft survival and observed allograft survival (appendix pp 22–25).

In the development cohort, 425 (11·3%) of 3774 transplant recipients were receiving standard of care treatment for antibody-mediated rejection, 305 (8·1%) were receiving standard of care treatment for T-cell mediated rejection, and 261 (6·9%) were weaned off of immunosuppression with calcineurin inhibitors due to toxicity and switched to

belatacept. In the antibody-mediated rejection group, the median change in predicted allograft survival was 1·5% (IQR 0·8 to 3·4) in patients with a favourable response and –3·4% (–8·0 to –1·5) in patients with an unfavourable response. In the T-cell mediated rejection group, the median change in predicted allograft survival was 1·5% (0·7 to 2·7) in patients with a favourable response and –2·1% (–4·7 to –0·9) in patients with an unfavourable response. In the calcineurin inhibitor minimisation group, the median change in predicted allograft survival was 5·3% (2·4 to 11·9) in patients with a favourable response and –2·8% (–6·6 to –1·2) in patients with an unfavourable response. Patients with favourable treatment responses had better allograft survival than those with unfavourable treatment responses (log-rank p=0·0005 for the antibody-mediated rejection group; log-rank p<0·0001 for the T-cell mediated rejection group; and log-rank p=0·011 for the calcineurin inhibitor minimisation group; appendix pp 26–27).

We confirmed the prediction performance of the system when applied in a series of distinct subpopulations in the development cohort (appendix p 22). Overall, we found very good prediction performances in all the subpopulations.

To adapt to distinct health system contexts in which there might be limited availability of kidney allograft biopsies or immunological data, we derived a series of variations of DISPO based on subsets of the full model parameters (appendix p 22). Additionally, we derived a dynamic integrative system on the basis of histological diagnoses (antibody-mediated rejection, T-cell mediated rejection, primary nephropathy recurrence, and BK virus nephropathy) instead of the Banff international classification. We found that the models performed well in all these scenarios in the development cohort (AUC range 0·848–0·857).

We found that our system had superior prediction performance compared with the other existing prediction systems (appendix p 11). We found that our system outperformed both the cross-sectional iBox system, which is actually designed for clinical trials,[3] and the eGFR slope[4] at any timepoint after initial risk assessment (mean difference in AUC of 0·053 [IQR 0·035–0·071] with the iBox, and of 0·126 [0·117–0·156] with the eGFR slope; appendix p 28).

Based on all these results, we developed a ready-to-use online application for clinicians that predicts the long-term, personalised allograft survival of a patient. This application adapts to the parameters available, although eGFR and proteinuria measurements need to be provided as a minimum to obtain predictions. An example of clinical use is presented in the appendix (p 13).

In our sensitivity analysis adjusting for study site, we found that prognostic parameters identified in the primary analysis remained independently associated with allograft survival and that study site did not add

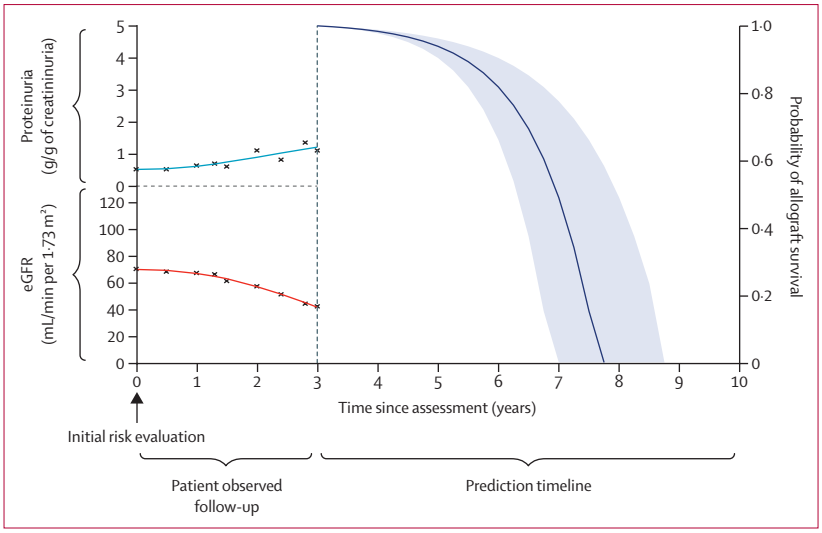

Figure 1: **Construction of the DISPO model to predict kidney allograft survival**
This figure presents the DISPO model we developed in kidney transplantation. Clinical parameters, histology, immunology, as well as changes in the patients' condition that were captured through repeated measurements of graft function were combined to build deeply phenotyped cohorts of kidney recipients. We then applied joint models to these datasets and developed a dynamic prediction system. DISPO=dynamic, integrative system for predicting outcome.

predictive value (appendix p 21). When we added parameters assessed at the time of transplantation (donor and recipient baseline characteristics), the parameters of the system remained independently associated with allograft survival, and the performance remained the same (appendix p 22). The system had high prediction performances. When we assessed the performance of the system when initial risk assessment was done using clinically indicated allograft biopsies at any time after transplantation (1449 [38·4%] of 3774 patients in the development cohort), and then when initial risk assessment used biopsies obtained per protocol (2324 [61·6%]; appendix p 22). The system had high prediction performances when initial risk assessment was done before 1 year after transplant (mean 0·51 years [SD 0·31]) and when done after 1 year after transplant (mean 1·42 years [0·77]; appendix p 22). Finally, when we accounted for the locus of anti-HLA donor-specific antibodies in our analyses, patients with HLA-DQ donor-specific antibodies had worse allograft survival than patients with other donor-specific antibodies, but this was not independently associated with allograft survival and was hence not included in our prediction system (data not shown).

For the **ready-to-use dynamic, integrative system for predicting outcomes** see https://transplant-prediction-system.shinyapps.io/AI-DISPO/

Discussion

In this multicountry, observational multicohort study, we developed and validated the DISPO model to predict outcomes after kidney transplantation. The system had good prediction performance, which remained very high in 14 external validation cohorts from Europe, the USA, and South America with heterogeneous

allocation systems,[29] patient characteristics, and clinical practices.[30] The performance of the model was also confirmed in a cohort comprising data from six randomised control trials and in various clinical scenarios and subpopulations. The system outperformed other allograft survival prediction systems that have been developed to date in kidney transplantation and is well suited for routine patient care and monitoring.

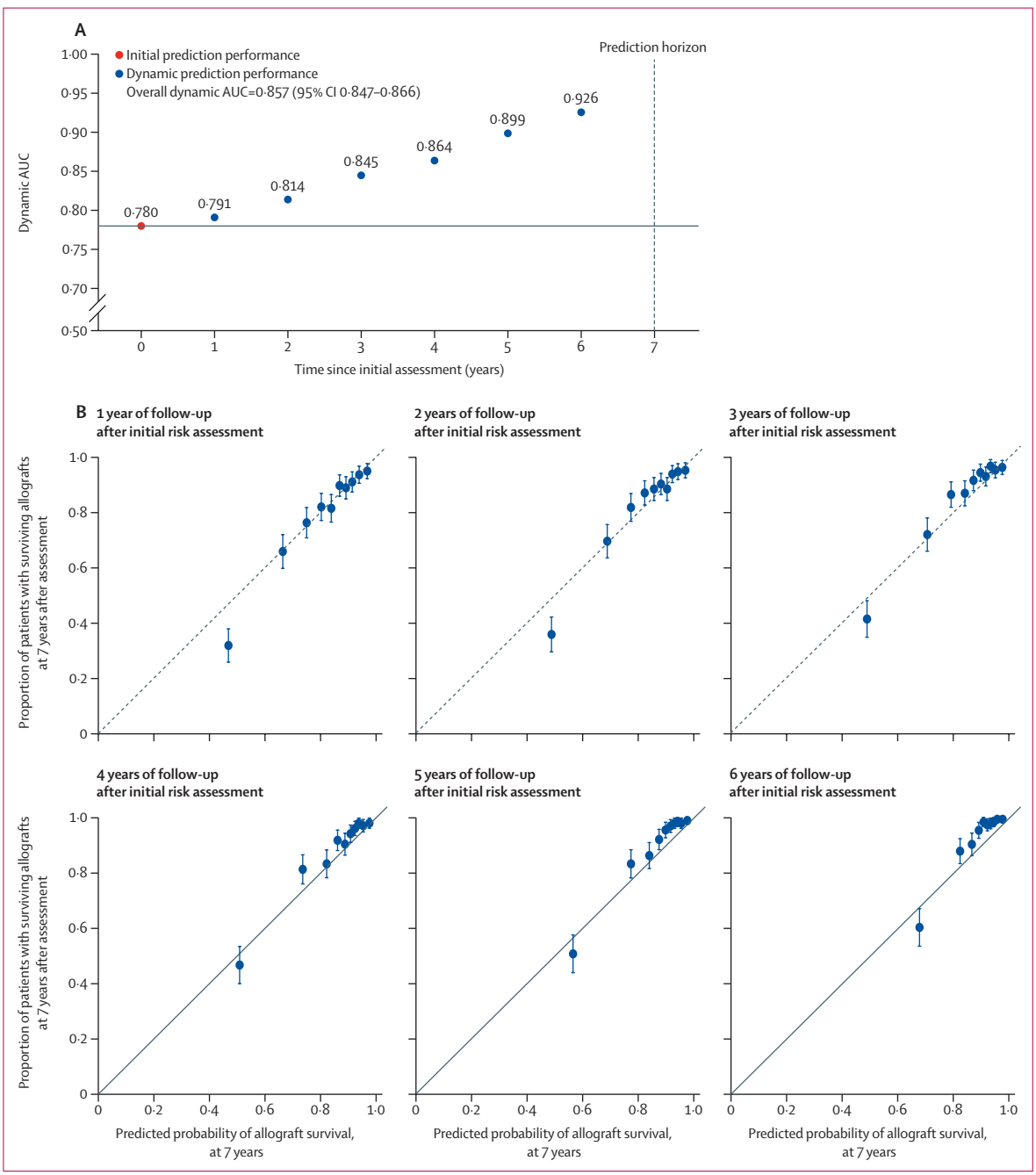

Figure 2: **Performance of DISPO in the development cohort**

(A) Discrimination—ie, ability to separate patients who lose their allografts from those who do not, according to patient follow-up ranging from 1 to 6 years after initial risk assessment, with a prediction horizon at 7 years after initial risk assessment. We calculated the overall dynamic AUC by averaging dynamic AUCs from 1 year of follow-up to 6 years of follow-up after assessment. (B) Calibration between the predicted risk and the observed number of allografts lost, according to patient follow-up. The diagonal line at the origin represents the perfectly calibrated model. Calibration plots are presented for each of the six assessments from 1 year to 6 years of serial eGFR and proteinuria measurements after initial assessment, with a fixed prediction horizon at 7 years after initial assessment. The initial prediction performance was calculated at the initial risk assessment, at the time of allograft biopsy after transplantation. AUC=area under the receiver operating characteristic curve. DISPO=dynamic, integrative system for predicting outcome. eGFR=estimated glomerular filtration rate.

We designed our dynamic integrative system to be generalisable in most transplant centres worldwide. This aim relied on the following hypothesis: if a prediction system derived from a deeply phenotyped dataset performs well in independent, external validation cohorts, then it is likely to be generalisable.

Although the system was developed in a cohort of patients who were closely followed up after transplantation and who were deeply phenotyped, its components are commonly assessed in most transplant centres worldwide, making the model convenient and well adapted to routine clinical practice. Nevertheless, to adapt this tool to patient populations without histological or immunological data, or with diagnoses instead of the Banff classification, we also developed a series of adapted systems for which performance remained high; these systems are available via our ready-to-use online tool. Additionally, some transplant centres use the Immucor strategy to assess donor-specific antibodies, rather than the One Lambda strategy, which was used in all cohorts of this study.[31] Although these two strategies sometimes provide different results, there is some correlation between them, and the interpretation remains the same.[31]

Our system provides a substantial advance in risk prediction for kidney transplantation. Typical kidney allograft survival prediction models rely on parameters assessed at a single timepoint;[3] however, these models do not include the individual-patient trajectory of allograft function and cannot be integrated during patient follow-up. Only a prediction model considering the trajectory of allograft function can capture the evolution of a patient's condition and ameliorate its prediction performance at each patient evaluation.

Using our model, we found that combining histological, immunological, and clinical parameters with repeated measurements of allograft function provides high prediction performance, with increasingly precise predictions with each new eGFR and proteinuria measurement. These findings support the idea that the family of risk factors that predict allograft survival are not only cross-sectional parameters, but also dynamic parameters that are present within the longitudinal component of the disease. Therefore, by incorporating all changes in allograft function, our dynamic prediction system improves upon traditional prediction models and holds potential value for patient monitoring and management.

We found that our prediction system outperforms the previous kidney allograft survival prediction systems.[32–35] In particular, the DISPO offers better prediction performance than the iBox,[3] a prediction system we previously developed and that constituted the first step in the long construction of DISPO but that was designed for clinical trials.

Importantly, we found that our new system can capture the effects of therapeutic interventions on allograft survival changes, which would allow clinicians to quantify how well a treatment has worked, thus enhancing treatment management.

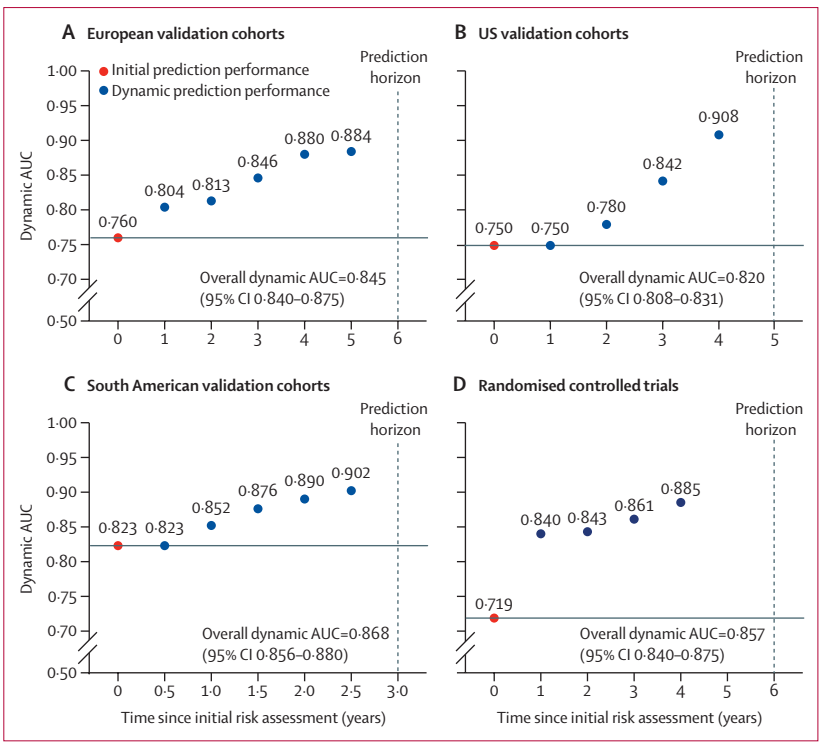

Figure 3: **Discrimination performance of DISPO in the external validation cohorts**
DISPO was applied in external validation cohorts from Europe (A), the USA (B), South America (C), and in a cohort of patients from six randomised controlled trials (D). For each validation cohort, the prediction horizon was defined according to the median follow-up of the cohorts. The calibration plots are presented in the appendix (pp 23–25). DISPO=dynamic, integrative system for predicting outcome.

Although we found that induction therapy was not an independent predictor of allograft failure and therefore did not include it in the final model, we did not assess the hypothesis that our prediction system might have captured the consequences of induction therapy. To investigate this hypothesis would require an additional study.

Taken together, these advantages make DISPO a promising new system for prediction of allograft survival. DISPO provides an accurate and detailed prediction of personalised risk of allograft failure, which can be continuously refined with additional patient assessments, and could allow improved and earlier detection of a treatable disease. Overall, it could improve or change clinicians' prognostic judgement and enable more rapid and informed clinical decisions, potentially leading to better patient outcomes. However, a randomised study specifically designed to assess the effect of the DISPO on patient management is needed.

Our study has several limitations. First, emerging kidney disease risk factors,[36,37] such as those based on donor genetics, are not included in our model. Nonetheless, the good performance of the existing model using convenient data suggests that the addition of new data

elements will not substantially improve prediction. Second, medication non-adherence can be an important risk factor for allograft survival, although methods of measuring medication adherence are often flawed.[38] High-quality information on adherence was not available for the included cohorts; however, because DISPO can be updated several times during a patient's follow-up, it might capture the consequences of non-adherence, such as the development of de-novo donor-specific antibodies, reduced eGFR, or allograft injury and inflammation on biopsy. Additionally, because French law does not permit use of parameters related to race or ethnicity, we could not use them in the development of the DISPO. Third, we could not conduct a competing risk of death analysis. We found that this method is not yet implemented in statistical software for joint models with two repeated parameters. When it is available, this would deserve an additional analysis. Fourth, a model that also integrates repeated biopsy and immunological data would probably be optimal. However, to our knowledge, due to variability in the timepoint that eGFR, proteinuria, histology, and immunology assessments are done, no model allows such integration so far. Additionally, our study was not specifically designed for assessment of the specificity and other effects of HLA and non-HLA antibodies, which deserve a study in themselves. Finally, although the prediction performance of the DISPO was high, its usefulness in clinical practice has yet to be determined and would require implementation in real-life settings. To assess the effect of DISPO in clinical practice, we plan to conduct a randomised controlled trial.

In summary, we constructed and validated a dynamic and integrative system to predict kidney allograft survival in deeply phenotyped cohorts from Europe, the USA, South America, and randomised controlled trials. The high prediction performance, large-scale validation, and dynamic component of the system distinguish it from other kidney-survival prediction models, and make it promising for clinical use. By continuously integrating all kidney function measurements assessed during patient follow-up, as well as clinical, histopathological, and immunological parameters, the DISPO model could be a useful bedside tool to guide clinicians in the routine monitoring and management of kidney transplant recipients.

Contributors

MR, OA, and AL contributed to study design and led the study. GD, NK, ÉB, MB, ML, MLQ, MD, IJ, NB-J, MC, HTS, KL, MCRdC, GSP, CU, EA, GB, EH, MDS, AJB, RAM, SCJ, RO, DLS, JJF, CLeg, CLef, and AL contributed to data collection. MR, OA, C-SC, CLef, and AL contributed to data analysis. MR, OA, GD, PPR, J-PE, XJ, and AL contributed to data interpretation. MR, OA, DY, and AL contributed to figure design. MR, OA, PPR, J-PE, and AL wrote the manuscript. MR, OA, GD, PPR, NK, DY, C-SC, ÉB, MB, ML, MLQ, MD, IJ, NB-J, MC, HTS, KL, MCRdC, GSP, J-PE, CU, EA, GB, EH, MDS, AJB, RAM, SCJ, RO, DLS, JJF, XJ, CLeg, CLef, and AL reviewed the manuscript. MR, OA, GD, and AL had access to and verified the underlying study data. All authors had access to the raw data and AL was responsible for the decision to submit the manuscript for publication.

Declaration of interests

AL holds shares in Cibiltech, a company that develops software and IT solutions. C-SC is affiliated with Deep Learning in Medicine and Genomics, DNAnexus. All other authors declare no competing interests.

Data sharing

Deidentified participant-level data from the development cohort will be made available on reasonable request. For access, please email the corresponding author. Requests will be assessed by the members of the Paris Transplant Group. For validation cohorts, data access is not covered by our data transfer agreements. The code used in the development of our model will not be shared because we present in detail the methods, model parameterisation, and development, and the associated R packages.

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