Changing Kidney Allocation Policy in France: the Value of Simulation

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Abstract

This paper advocates the value of simulation to promote changes in kidney allocation. Due to the scarcity of organs and to the competition between transplantation centers to obtain the best organs for their patients, any change in organ allocation policy remains a sensitive issue in public health decision-making. Organ allocation is not easily available for prospective experimental study. Observational studies only support limited changes. A simulation tool in this context permits the comparison of observed results against simulated ones. In our experience in France, it has shown to be a helpful tool during the allocation design phase providing objective facts for the debates and increasing the potential for change.

Keywords: *organ allocation, transplantation, public health, simulation model.*

Introduction

Progress in surgical procedures and immunosuppressive therapies in the mid-eighties brought about an increased need for organs to transplant (Tx) [1]. Although organ retrieval has been reinforced in many countries, it still fails to cover an always-increasing demand [2]. In such a context, organ allocation is an essential interface between organ retrieval and transplantation [3]. Allocation systems have to take into account specific conditions such as emergency or low access to Tx [4]. They usually strike an empirical compromise between equity, efficacy and practicability, with significant variations from one country to another and no definitive evidence-based solution.

Allocation in France falls under the responsibility of the *Agence de la biomédecine* (Abm). It includes general rules such as: donor-recipient ABO blood group identity, unique registration on the national waiting list (WL) and definition of some organ specific nation-wide allocation priorities.

For each kidney recipient, minimal HLA matching and forbidden antigens can be specified. Pediatric recipients get a priority for pediatric donors. Kidneys are proposed by order of priority to (1) urgent patients, (2) patients with panel reactive antibodies level ≥ 80% included in a specific acceptable antigen protocol or ≤1 HLA mismatch (MM) with the donor, then (3) zero MM patients, and (4) patients with low Tx accessibility. Abm's coordination offices make the organ offer. When a retrieved kidney triggers no allocation priority, it is proposed at the local Tx center.

Until now, the French kidney allocation system was thus a mixture of nationwide patient-based allocation priorities combined with center-based allocation procedures, that represent the main - and transplant physicians' favorite allocation modality. The evaluation of our allocation system demonstrated inter-regional and inter-center discrepancies in terms of Tx accessibility and waiting time. HLA matching was pinpointed as much prominent in many regional and local allocation procedures, leading to the exclusion of rare HLA patients awaiting a kidney. In a context of significant increase of organ donation in France (1629 Kidney Tx in 1997 vs. 2572 in 2005), such results prompt us to study the feasibility and magnitude of a potential optimization of kidney allocation with the introduction of a scoring function whose capability to improve simultaneously efficiency through donor-recipient matching in HLA and age, equity through waiting time and matched donors potential has been previously reported [5-7].

The need to compare various allocation schemes, to evaluate the impact of scoring function tuning and to assess the acceptability of a patient-based scoring system prior to its implementation prompt us to build a simulation tool. This paper describes the core functions used in the allocation model, reports on some evaluation end-points and discusses the value of a simulation in such a context.

Materials and Methods

Dynamic Historical Data Based Simulation Model

The input of the allocation model comprises: (i) an historical chronicle of donors compiled during a given period of time where at least one kidney was transplanted to a patient in a given allocation region; (ii) all the patients waiting for a kidney at the beginning of the period and all patients actually registered on the WL by one of the Tx team of the allocation region during the observation period. The output is a chronicle of pairs of recipient and allocated kidney. The chronicle of donors triggers the simulation loop. The WL is actualized according to real WL registrations and withdrawals since the last donor retrieval. The simulation model (SM) combines a Distribution Model (DM) and an Allocation Model (AM). The SM preserves existing allocation priorities. It also preserves general allocation principles: blood group identity, absence of forbidden antigens. In the absence of prioritized patient, various distribution models can be simulated. The two kidneys can be first proposed to local recipients and next, when there is no suitable local recipient, to other regional recipients. One kidney can be allocated within the local WL and the other within the regional WL, resulting in a local-regional distribution model, which may or may not lead to double Tx in the same center. Last, both kidneys can be distributed at the regional level.
The SM is implemented in Visual Basic. The SM is limited to allocation-reallocation of kidneys.

Allocation Model

When a potential donor is detected, an allocation score is computed for each patient waiting for a kidney. Recipients are then ranked according to the score value. Kidneys are offered to the patients with the highest score. To facilitate discussion with transplant teams, we use a scoring system that is a weighted sum of parametric functions f_i that vary between 0 and 1. Each function can take a donor and/or a recipient characteristic as variables:

Score$(R_t ; D_t) = \sum [\mathbf{w}_i.\mathbf{f}_i(Rc_i; Dc_i; P_{ik})]$ with:
- R_t a recipient on the WL at time t,
- D_t a retrieved donor at time t,
- $\mathbf{w}_i$: weight given to function f_i ,
- $\mathbf{f}_i$: discrete or continuous function on [0 ; 1]
- Rc_i : recipient characteristic considered in f_i
- Dc_i : donor characteristic considered in f_i
- P_{ik} : the k parameters of function f_i

Each function f_i has a particular objective, a practical definition and a computational specification. For kidney allocation, we proposed five functions. The functions $\mathbf{f}_1$ and $\mathbf{f}_2$ are donor independent (no Dc_i).

• Recipient time on the waiting list: f_1

Function $\mathbf{f}_1$ aims at avoiding the selection of long waiting patients in giving an increasing amount of points to patients according to their time on the WL (T_{WL}): $Rc_1 = T_{WL}$. $\mathbf{f}_1$ has two parameters P_{11} and P_{12}, which are durations (months). From a practical point of view, a patient with $T_{WL} < P_{11}$ is assigned 0% of the points $\mathbf{w}_1$ given to the function; a patient with $T_{WL} > P_{12}$ receives 100% of $\mathbf{w}_1$. Between P_{11} and P_{12}, patients get a linear increasing percentage of the points (Fig.1).

$\mathbf{f}_1(T_{WL}; P_{11} ; P_{12})$:

$T_{WL} \in [0, P_{11}[\quad \rightarrow \mathbf{f}_1(T_{WL})=0,$

$T_{WL} \in [P_{11}, P_{12}] \quad \rightarrow \mathbf{f}_1(T_{WL}) = (T_{WL} - P_{11})/(P_{12} - P_{11}),$

$T_{WL} \in]P_{11}, +\infty] \quad \rightarrow \mathbf{f}_1(T_{WL})=1$

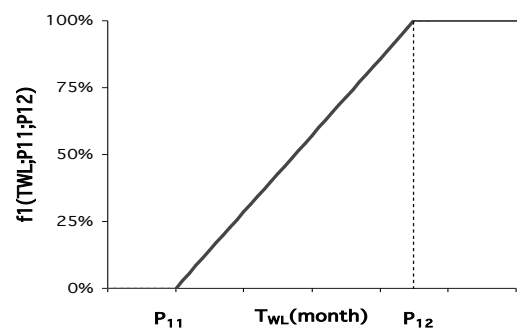

Figure 1 - A sigmoid-like function of T_{WL} with inflection points at P_{11} and P_{12}

• Recipient's well-Matched Donors Potential: f_2

Function $\mathbf{f}_2$ aims at improving Tx accessibility for patients with low potential for a well-matched donor. This function balances points given to the quality of Donor-Recipient HLA-matching (see $\mathbf{f}_3$ below). Using an appropriate weight factor, such a function should provide improved matched kidneys and reduced waiting times to those difficult patients. Previous works showed us that it is possible to compute for each recipient the number of donors (1) matching his blood group, (2) retrieved during *the past 5 years* within his allocation region, (3) with *less than 3 HLA* A, B, DR MM and (4) without unacceptable HLA. This metric, referred to as *Matched Donors Potential* (P_{MD}), is especially relevant to identify patients with a low Tx accessibility. Because P_{MD} takes into account the frequencies of HLA phenotypes and blood groups within the *real* allocation region, together with the impact of registered unacceptable antigens, it is a more accurate measure than the panel reactive antibody (PRA) rate. Patients with high PRA, but a very frequent HLA phenotype with unacceptable antigens that are not frequent among donors, can have a good access to transplantation whereas patients with rare HLA or frequent unacceptable antigens may have low PRA, but a poor access to Tx.

Function $\mathbf{f}_2$ considers the recipient's Potential of

Matched Donors: $Rc_2 = P_{MD}$ (donors≤3MM.5years). $\mathbf{f}_2$ has one parameter P_{21} which is the highest P_{MD} among the recipients with an identical blood group: $\max_i(P_{MDi})$. From a practical point of view, a patient with no donor less than 3 MM receives 100% of the points $\mathbf{w}_2$ given to the function; the patient with the highest P_{MD} receives 0% of the points $\mathbf{w}_2$. Between 0 and P_{21}, patients get a linear decreasing percentage of points (Fig.2).

$\mathbf{f}_2(P_{MD}; P_{21})$:

$P_{MD} \in [0, P_{21}] \rightarrow \mathbf{f}_2(P_{MD}; P_{21}) = 1 - (P_{MD}/P_{21})$

$P_{21} = \max_i(P_{MDi})$

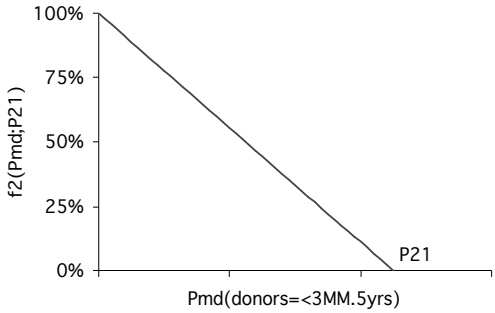

Figure 2 - Recipient's well-matched Donors Potential function

• Donor-Recipient HLA Matching: f_3

Function $\mathbf{f}_3$ aims at improving post-Tx results by favoring a good HLA A, B, DR matching. It is a discrete decreasing function giving a percentage of $\mathbf{w}_3$ depending on the number of HLA MM. For a given donor, recipients with 0-MM will get P_{31}=100% of $\mathbf{w}_3$ whereas 6-MM recipients get P_{37} = 0% of $\mathbf{w}_3$.

The 5 other parameters P_{32} to P_{36} (Fig.3) are scaled according to the relative risk of graft loss calculated in a multivariate analysis.

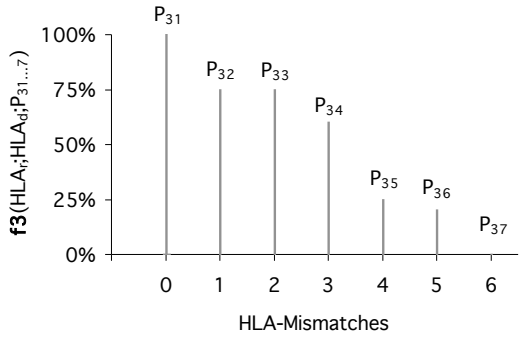

Figure 3 - Donor-Recipient HLA mismatches function

Donor-Recipient age matching: f_4

Function $\mathbf{f}_4$ aims at improving post-Tx results in dealing with nephronic reduction. It favors an appropriate donor-recipient age matching. The solution we show here is a function giving a percentage of points $\mathbf{w}_4$ decreasing with an increasing differential of age classes (Fig.4). Classes and their related values are the parameters of $\mathbf{f}_4$.

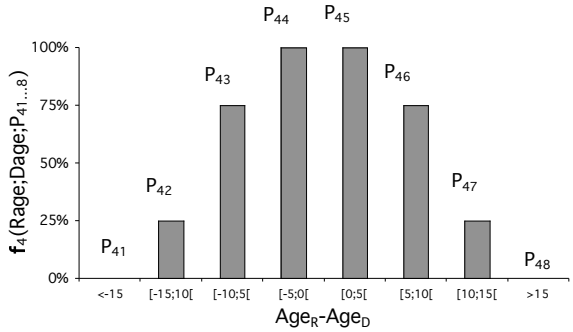

Figure 4 - Donor-Recipient age matching function

Results

To illustrate our approach, we present here some results obtained in one of our 6 allocation districts. During the selected period, 2,956 new patients were added to the 568 patients registered on the WL at the beginning of the period; 2,421 Kidney Tx were performed. The former allocation system was based on a dual-local distribution model (LLDM). One challenge was to implement a cultural change by introducing a local-regional distribution model (LRDM). National allocation priorities were kept unchanged in both models, accounting for 18% of kidney Tx during the period. In the observed LLDM, Tx were performed at the local level in 61% and at regional level in 21% versus 48% and 35%, respectively, with the simulated LRDM. Patients' characteristics are in table 1.

	Patients on WL on 01/01/1998	Registered patients 1998-2003	Transplanted 1998-2003	Patients on WL on 1/01/2003
n	568	2956	2461	770
Sex				
male	342 *60%*	1846 *62%*	1573 *64%*	473 *61%*
female	226 *40%*	1110 *38%*	888 *36%*	297 *39%*
Blood Group				
A	191 *34%*	1274 *43%*	1100 *45%*	233 *30%*
AB	29 *5%*	106 *4%*	93 *4%*	16 *2%*
B	33 *6%*	303 *10%*	199 *8%*	106 *14%*
O	315 *55%*	1273 *43%*	1069 *43%*	415 *54%*
Age				
years (m±ds)	44,6 ±13,1	45,8 ±14,2	46,0 ±14,4	48,4 ±13,0
PRA				
>=80%	128 *99%*	175 *6%*	162 *7%*	92 *12%*
>=5%	183 *32%*	475 *16%*	394 *16%*	198 *26%*
<5%	257 *45%*	2306 *78%*	1905 *77%*	480 *62%*

Table 1 - Patients characteristics

Characteristics of transplanted patients

The simulated allocation model significantly increases the number of transplantations for long-waiting patients (Fig.5) and for patients with low well-matched donors potential (Fig.6) during the 3 first years and after reaches a steady state.

In the observed situation, the median P_{MD} was around 105 donors≤3MM (Fig.6); in contrast, patients remaining on the WL had median P_{MD} around 80 donors≤3MM (Fig.9).

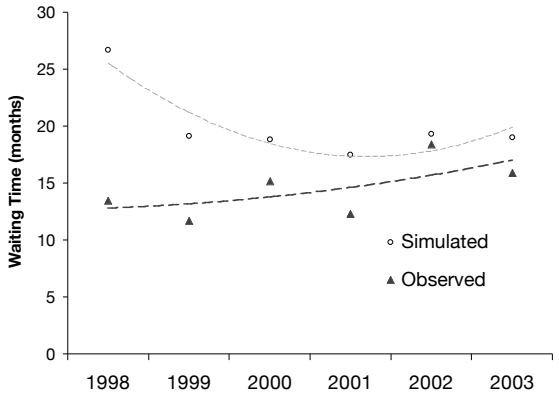

Figure 5 - Median Waiting Time at kidney Tx

With the simulated allocation model, the median P_{MD} of Tx patients at steady state (Fig.6) becomes similar to the median P_{MD} in the WL (Fig.9), suggesting that there is no more segregation of patients, excluded from Tx due to a rare HLA phenotype.

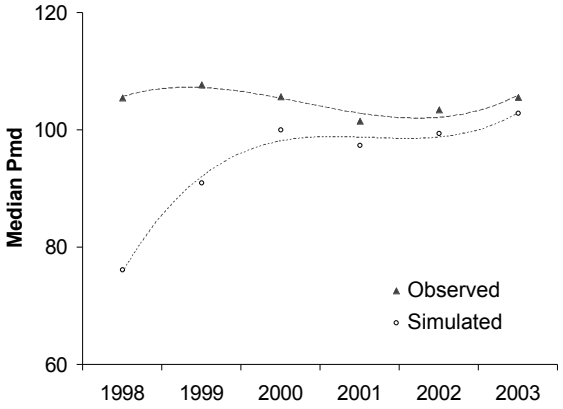

Figure 6 - Median P_{MD} of transplanted patients

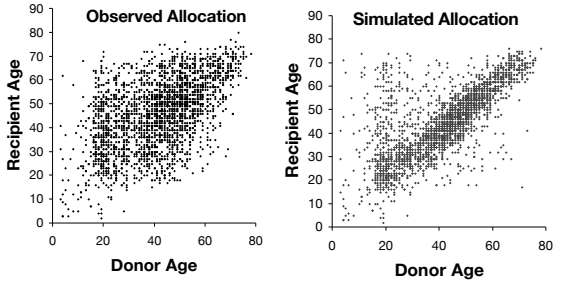

Figure 7 - Donor-Recipient age matching transplanted patients

In the observed situation, kidneys retrieved in young donors were frequently allocated to old recipients, and kidneys retrieved in old donors were frequently allocated to young recipients. The switch to a LRDM and the use of a scoring function significantly improves the age matching between donor and recipients (Fig.7). The regional distribution indeed enlarges the diversity of recipients screened for a given donor. The simulated scheme minimizes 5 and 6 MM Tx that were a side effect of the local distribution (Fig.8).

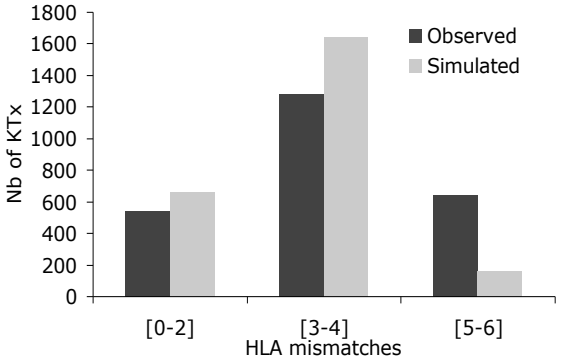

Figure 8 - Donor-Recipient HLA matching

Characteristics of patients waiting for a kidney

The simulated allocation model significantly changes the content of the WL in terms of median P_{MD} as shown in Figure 9. The same holds for median waiting time (data not shown).

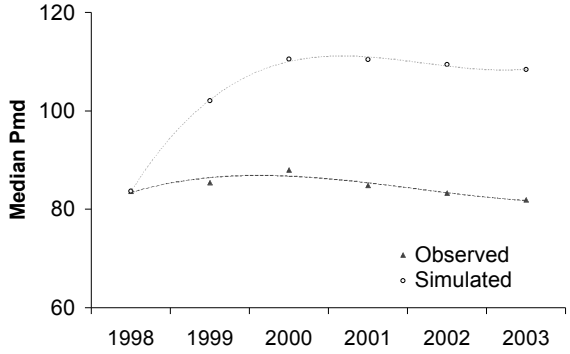

Figure 9 - Median P_{MD} among patients on WL at each 1st of January

Specific Transplantation Access Rates

Transplantation access rate is defined by the number of transplanted patients among the total number of Tx candidates for a given period. One can examine specific Tx access rates according to various patients characteristics: blood group, Tx centers, age or P_{MD} as shown in Figure 10, which suggests an over-correction of Tx access rate for patients with lowest P_{MD} in the simulated model. After tuning, the w_3 resulted in a more equitable allocation.

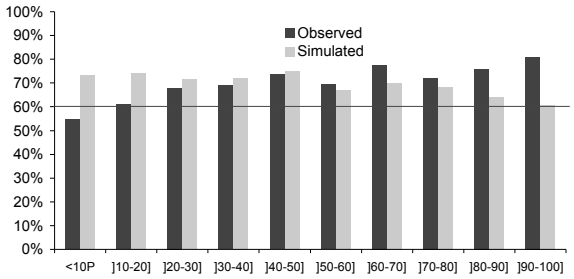

Figure 10 - Specific Tx Access rates per P_{MD} deciles

Discussion - Conclusion

Simulating the redistribution of kidneys according to new allocation schemes using historical data instead of generated ones has interesting advantages: computation is simple, it makes few assumptions and thus it is more credible for the transplant community. A main originality of our tool is its flexibility. Various allocation schemes depending on the setting of the score function and on the distribution model have easily been assessed. Comparing the results actually observed during a past period of time to results obtained by simulation also facilitated the debates. The question is not "is it the best?" but "is it better?". An important step was to define major allocation evaluation end-points, a key for an evidence-based debate; maybe the beginning of an answer to the absence of well-agreed optimization criteria. Simulation thus permits to tackle the allocation optimization issue.

Results obtained indicated that the objective to improve both equity and efficacy was feasible. The expected improvements in terms of the clearance of long waiting patients from the WL (Fig.5), age (Fig.7) and HLA matching (Fig.8) and the scalability of the scoring system appeared promising. The simulated allocation model also minimizes center differences in Tx accessibility, improving the equity between patients and centers at the price of slight - but highly sensitive variations in Tx activities for some centers. The magnitude of expected results facilitated the switch from local center-based to regional patient-based distribution in some regions. The new scoring system is in use since April 2004 in Paris allocation area. It has been extended to other regions. Simulations have been widely used to interact with Tx physicians and patients associations to promote evidence-based allocation [8] and to customize the allocation model to the regional specificity.

Simulation tools have been previously used to change allocation systems [5-7]. The simulation model can be extended to the outcome of patients on the WL or after Tx. It can also comprise the generation of donors or recipients when one need to assess the impact of future changes in donors or recipients populations. Such extensions can benefit from generic simulation environment [9].

The relevance of simulation is due to the fact that organ allocation is poorly accessible to experimental study. Observational studies permits to evaluate allocation policies. But they are of limited help to bring about deep changes in allocation policies due to the fear of adverse effects. Simulation facilitates the design of new allocation schemes and their acceptability among the Tx community as it focuses discussions on objective factors and gives an idea of expected results before the implementation of the new policy.

This work illustrates the interest of Information Technologies to deal with ethical and social issues. It underlines the value of simulation in the context of organ allocation that is in many aspects a matter for social economy. Our simulation tool is now used to change liver allocation. Abm coordinates a EC-FP6 ERA-NET project, Alliance-O, which aims to promote the coordination of National Research Programs on Organ Donation and Transplantation in Europe. This project comprises a work package devoted to the specification of a common simulation tool.

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