

D 2024



Evaluation of deceased donors' kidney allocation systems on transplantation

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TESE DE DOUTORAMENTO APRESENTADA

À FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO EM

CIÊNCIA DE DADOS DE SAÚDE

Dissertação de candidatura ao grau de Doutor apresentada à Faculdade de Medicina da Universidade do Porto, no âmbito do Programa Doutoral em Ciência de Dados de Saúde.

This PhD thesis has been submitted in fulfilment of the requirements for the PhD degree in Health Data Science at the Faculty of Medicine of the University of Porto.

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Evaluation of deceased donors' kidney allocation systems on transplantation

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Artigo 48º, parágrafo 3º:

A Faculdade não responde pelas doutrinas expendidas na dissertação

(Regulamento da Faculdade de Medicina do Porto. Decreto-Lei nº 19337, de 29 de Janeiro de 1931)

Acknowledgements

Primarily, I would like to express my deeply gratitude towards my adviser, Professor Teresa Henriques, for her support, advice, encouragement and guidance.

I also wish to thank my co-adviser, Professor Andreia Teixeira. Although she only joined us in the final part of this project, she was of outmost value, helping me reaching a successful conclusion.

To my co-authors, Helena Alves and Filipe Reis, also many thanks. It was a privilege to have their contributions as co-authors and I'm certain we will still work together in future research endeavours.

To my family, for all their support, their care, and their patience, especially when I have been absent or when I have been overwhelmed by this work.

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List of publications

This dissertation is based on the following 9 publications which will be referred to throughout the document.

Manuscripts

The manuscripts are listed here chronologically:

- **Portuguese calculated panel reactive antibodies online estimator.**
Lima BA, Alves H. *HLA* 2019; 93(6):445-450. DOI: 10.1111/tan.13516
Scimago Journal & Country Rank in 2019 (Q3)
- **Access to kidney transplantation: a bioethical perspective.**
Lima BA, Alves H. *Port J Nephrol Hypert* 2020; 34(1): 107-109. DOI: 10.32932/pjnh.2020.07.070
- **Kidney allocation rules simulator.**
Lima BA, Henriques TS, Alves H. *Transplant Immunology* 2022; Volume 72, 101578. DOI: 10.1016/j.trim.2022.101578
Scimago Journal & Country Rank in 2022 (Q3)
- **Transplant Open Registry Initiative.**
Lima BA, Henriques TS, Reis FP, Alves H. *Port J Nephrol Hypert* 2022; 36(4): 201-206, DOI: 10.32932/pjnh.2022.10.204
- **histoc: Histocompatibility analysis performed by kidney allocation systems.**
Lima BA, Reis FP. *JOSS* 2022 7(80), 4807. DOI: 10.21105/joss.04807
- **Equity matrix for kidney transplant allocation.**
Lima BA, Reis FP, Alves H, Henriques TS. *Transplant Immunology* 2023; Available online, 101917. DOI: 10.1016/j.trim.2023.101917
Scimago Journal & Country Rank in 2023 (Q3)

- **simK: Synthetic Data on Kidney Transplantation.**

Lima BA. *JOSS* 2023 (submitted for publication in December 2023)

- **Calculated Human Leucocyte Antigens Evolutionary Divergence (cHED).**

Lima BA. *OBM Transplantation* 2024, volume 8, issue 1. DOI:

10.21926/obm.transplant.2401208

- **Revision of the Portuguese Rules for the Selection of the Donor-Recipient Pair in Kidney Transplantation**

Bruno A Lima, Helena Alves. *Port Kidney Journal* 2024; 38(1): 54-57

Original publications are made available according to the permissions of the respective journals holding the publication rights.

Some of the articles were first presented as oral or poster communications in national and international conferences.

Oral communications

HLA evolutionary divergence (HED) calculator

Bruno A Lima

36th European Immunogenetics and Histocompatibility Conference

EFI2023 «Big Data In Immunogenetics At The Crossroad Of Care, Tools, And Research »

26-29th April 2023, Nantes, France

Kidney Allocation Rules Simulator

Bruno A Lima, Filipe Reis, Teresa Henriques, Helena Alves

XVI Congresso Português de Transplantação, 1st-3rd December, 2022, Cascais, Portugal

Poster communications

Kidney Allocation Rules Simulator

Bruno A Lima, Teresa Henriques, Helena Alves

20th Congress of the European Society for Organ Transplantation, 29th August-1st September 2021, Milan, Italy

Comparing Scores for Predicting Kidney Transplantation Outcomes.

Bruno A Lima, Teresa Henriques, Helena Alves

20th Congress of the European Society for Organ Transplantation, 29th August-1st September 2021, Milan, Italy

Abbreviations

cHED	calculated HLA Evolutionary Divergence
cPRA	calculated Panel Reactive Antibodies
DSA	Donor Specific Antibodies
EPTS	Estimated Post Transplant Survival
EQM	Equity Matrix
ESRD	End-stage renal disease
ET	Eurotransplant
ETKAS	Eurotransplant Kidney Allocation system
HLA	Human Leucocyte Antigens
IPST	Instituto Português do Sangue e da Transplantação
KARS	Kidney Allocation Rules Simulator
KAS	Kidney Allocation System
KDPI	Kidney Donor Percentual Index
mmHLA	HLA mismatches
pmp	Per million population
PT	Portugal
TxOR	Transplant Open Registry
UK	United Kingdom
vXM	virtual CrossMatch

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Abstract

Allocation rules of scarce healthcare resources should balance fairness, medical utility, and efficiency. Similarly, a deceased donor kidney allocation system must be periodically assessed, allowing possible modifications to ensure it remains equitable, transparent, and justifiable according to medical criteria.

Particularly, current Portuguese rules for deceased donors' kidney allocation on transplantation have more than sixteen years and there is a need to reassess them, which has been requested for some time.

This thesis aims to present a way to evaluate and assess different kidney allocation models using only open-source means.

During this journey, we developed and deployed some freely and openly available web applications to aid the analysis of donor recipients' pairs in kidney transplantation.

With Kidney Allocation Rules Simulator (KARS) application, any researcher can test their data, changing punctuation values on allocation systems. The R package *histoc* was developed to encapsulate all the functions used in the KARS application. To account for possible selection bias (both in selected patients and donors input files), *histoc* functions can be used to simulate an allocation process several times with the same set of allocation rules and determine outcomes on average. Data on transplant candidates and organ donors used in these works are simulated, through the R package *simK*, in order to mimic both the actual Portuguese waiting list and Portuguese organ donors.

Discussion regarding kidney allocation rules should rely on data and strive for data-driven decision making. The findings presented here contribute to the aforementioned goal.

Resumo

A distribuição dos recursos escassos da saúde deve ser feita de forma a procurar um equilíbrio entre equidade, utilidade médica e eficiência. Analogamente, um sistema de alocação de rins de dador cadáver para transplantação deve ser avaliado periodicamente, permitindo que seja alterado para garantir que se mantem equitativo, transparente e justificável de acordo com critérios médicos. Em particular, as regras portuguesas para a selecção do par dador receptor em homo-transplantação com rim de dador cadáver têm já mais de dezasseis anos e a necessidade para a sua reavaliação tem sido pedida há algum tempo a esta parte.

Esta tese tem como objectivo apresentar uma forma de avaliar e aferir diferentes modelos de alocação de rins para transplantação, usando apenas recursos *open-source*.

Durante esta travessia desenvolvemos e disponibilizamos de forma aberta e gratuita algumas aplicações *web* que podem ajudar na análise dos pares dador-receptor em transplantação renal. Com a aplicação *Kidney Allocation Rules Simulator* (KARS) qualquer investigador pode testar os seus próprios dados mudando as pontuações definidas nos sistemas de alocação renal. Para isto, desenvolvemos o pacote *histoc* (em linguagem R) que compila todas as funções usadas pela aplicação KARS. Tendo em conta um possível viés de selecção (tanto para os dados de *input* dos doentes como dos dadores), as funções do *histoc* que simulam o processo de alocação, podem ser executadas várias vezes com o mesmo conjunto de regras mas com diferentes grupos de dadores e consequentemente, podemos obter distribuições dos *outcomes* do par dador-receptor. Os dados aqui usados, quer sejam de candidatos a transplante ou dos dadores cadáver de órgãos, foram simulados com o pacote *simK*, de forma a replicar a lista de espera portuguesa para transplante renal bem como um grupo de dadores portugueses.

A discussão relativa às regras de alocação de rins de dador cadáver para transplantação deve ser feita com base em evidências, tendo em vista a tomada de decisão com base em dados. Acima de tudo, esperamos que os resultados aqui apresentados possam contribuir para este desiderato.

INTRODUCTION

1. Introduction

The *Introduction* chapter provides justification for the work carried out within the scope of this thesis.

In the *Outline*, the motivation for this endeavour is given from a more personal point of view. It also refers to the main chapters of this document. The *Rationale*, on the other hand, presents the foundation that justifies the research question posed.

In addition, the *Background* section presents the approach taken to find the most appropriate solution to the research question.

1.1. Outline

This thesis is the culmination of several years of research that I have been privileged to carry out in the field of kidney transplantation in Portugal. My Master's thesis, defended at the University of Porto in 2008 [1], having as scope 'Access to kidney transplantation', marks the beginning of this journey in which I have published the results of my studies.

My work has mainly focused on measuring kidney transplantation activity in Portugal [2] [3] and the need to establish and apply practical and systematic measures of clinical significance. These metrics would allow informed decision making in evaluating and analysing health policies [4].

In 2013, we presented a new approach suitable for a kidney allocation system in transplantation [5], which could be compared with the Portuguese rules in place since 2007. Based on a colour-based priority framework, this proposal was designed to be simple, transparent, and intuitive. It could also be used for future evaluations against alternative allocation systems.

When we published our first results comparing our colour priority system with the Portuguese regulation for the selection of donor-recipient pairs in renal transplantation [6], our paper had the editorial's focus on that particular issue of *Acta Médica Portuguesa* [7]. Moreover, when we compared the Portuguese allocation system with those of the United Kingdom or Eurotransplant [8], we were more certain that a "change is needed", as stated by the (at the time) President of the Portuguese Society of Transplantation [9].

However, my main concern has always been, and still is, the need for accessible open data regarding renal transplantation in Portugal. When I published '*A call for open data of renal transplantation in Portugal*' [10], I argued the need for such data, as it can improve healthcare quality, increase health literacy and community involvement in defining new public policies. Moreover, in the next issue of the same journal, a letter to

the editor supported my call [11], while pointing out that the regular publication of such data is the responsibility of the *Instituto Português do Sangue e da Transplantação* (IPST), which is in charge of organising, maintaining, and disclosing transplant data.

The first edition of the Health Data Science doctoral programme was my next logical step. It would allow me to develop my skills, experiment with my ideas and evaluate them. It would also enable me to explore the optimal allocation of deceased donor kidneys for transplantation, considering their limited and valuable availability.

It was time for me to get involved not only in simulation tasks to test proposed solutions but also in creating open-source software that could be used and evaluated by others.

This dissertation is structured into four main chapters in the subsequent manner:

1. **Introduction** that includes:

- a. **Rationale** – a description of the rationale for the research question and the aim of this thesis, including the need to define equitable rules for deceased donor kidney allocation and the role that health data science can play in this endeavour;
- b. **Research question** – synthesizes the aim and specific objectives of this thesis;
- c. **Background** – a brief background on renal transplantation as the best treatment for end-stage renal disease (ESRD) patients, when it is an option. Moreover, a justification for the work that has been done.

2. **Transplant Open Registry** – the Transplant Open Registry (TxOR) initiative, born out of the need for a platform to collect and make accessible the work developed for this thesis:

- a. **Web Applications** – a description of the applications available from TxOR as open-source software and as proof of concepts that can be freely used.

3. **Equity Matrix Model** – The equity matrix algorithm as a new proposal for a simpler and more equitable distribution of deceased donor kidneys for transplantation.

4. **Discussion** – Some final remarks, where I try to summarise all the work presented. Within each of these chapters, available published papers are presented, detailing the work achieved.

1.2. Rationale

The biggest challenge for any kidney transplant programme is to find enough donors (in terms of number and quality) for all transplant candidates on the waiting list. While we wait for the future to bring us transplantable artificial kidneys or the ability to prolong organ preservation, allowing us to substantially increase the number of quality organs from marginal donors [12], we must resign ourselves to a manifestly insufficient supply of organs for the current demand.

In Portugal, there is a growing consensus on the need to change the current kidney allocation rules for transplantation [9]. The Portuguese rules have been in place since 2007, and more than sixteen years later, it is time to evaluate their outcomes and propose improvements, taking into account the *Leges Artis* [7].

One way to evaluate the implementation of a new deceased donor kidney allocation system (KAS) would be to compare two waiting lists of transplant candidates. On one list, organs would be allocated by the rules in force; on the other, organs would be allocated, applying new rules in evaluation. However, this type of study design is not feasible due to the deontological questions it raises. Alternatively, we can simulate different candidates' waiting lists subject to different organs' allocation rules.

The discussion on new proposals for the allocation of kidneys cannot be conducted only in a rhetorical plan, hoping that the moment a new solution is implemented, everything will work out for the best. Before implementing new rules, it is necessary to test them in order to remove, as far as possible, any doubts about their success.

Any new scientific research hypothesis can be raised either through a deductive process, which is based on established knowledge and generates a hypothesis applicable to the problem at hand, or through an inductive process, in which, by observation and experimentation with available data combined with gained knowledge, we can postulate new hypothesis [13]. Nevertheless, a new proposal for a new KAS needs to be empirically tested. If the rules that have been in place since 2007 for the

selection of donor-recipient pair in transplantation with deceased donors, emerged from a consensus of an experts' group, we now have data science tools that allow us to do more and better.

Based on the ethical principles of beneficence, non-maleficence, and respect for the autonomy of the individual, evidence-based medicine is the integration of clinical expertise with the most reliable evidence from high-quality clinical research, taking into account the values, preferences, and situation of the patient [14]. Similarly, evidence-based decision making is critical in distributing public health resources (such as allocating deceased donor's kidneys). Grounded on both egalitarian and utilitarian goals, it ensures that the available scientific evidence supports decisions.

1.3. Research question

How do the clinical, demographic, and immunological characteristics of donor-recipient pairs compare between groups selected using different kidney allocation rules?

1.3.1. Aims

1. Development of a Kidney Allocation Rules Simulator (KARS) application to simulate the distribution of deceased donor's kidneys on different waiting lists:
 - a. An application that will be freely accessible and available to all interested parties (researchers, health professionals, patient groups) without any restrictions;
 - b. The KARS application will allow not only the evaluation of current kidney allocation models but also the assessment of changes to existing models, so that we can understand how these may affect the distribution of organs;
 - c. With KARS, it will be possible to simulate not only the Portuguese model from Decree n°6537/2007 [15] but also allocation models such as the one proposed by Lima *et al.* [5], the Eurotransplant (ET) KAS [16] and the United Kingdom (UK) transplant model [17]. All these models use clinical, immunological, and demographic information from donors and transplant candidates while assigning different weights to these characteristics in prioritising patients for access to transplantation.
2. Propose a new kidney allocation system based on an equity matrix. In managing access to deceased donor kidney transplantation, a balance is sought between optimising the clinical outcome of the transplant (principle of utility) and giving all patients a reasonable chance of receiving a transplant (principle of justice) [18]:

- a. The aim is to find a form of distribution that is equitable, both in terms of horizontal equity (treating equals equally) and vertical equity (treating differently what is different).

1.4. Background

When possible, kidney transplantation is the best treatment for ESRD patients [19]. Transplanted patients have a lower mortality rate, fewer cardiovascular complications, and a better quality of life than patients who remain on dialysis [20]. Kidney transplantation with a living donor before starting dialysis would probably be the optimal treatment for this type of patient, but most patients cannot opt for a living donor transplant and the only way to receive a transplant is to be placed on a waiting list for a kidney from a deceased donor. The success of this type of treatment and the increase of ESRD patients has resulted in ever-longer waiting lists for the limited number of deceased donor kidneys available for transplantation [21].

In 2021, with 243 new patients per million population (pmp), Portugal was one of the European countries with the highest incidence of patients on renal replacement treatment (surpassed only by Greece and Cyprus) and by far the European country with the highest prevalence of patients on renal replacement therapy (2003 patients pmp) [22], of whom a total of 1944 were on the waiting list for a kidney transplant at the end of that year [23].

Usually, the distribution of scarce health resources seeks a balance between criteria of justice (fair access for all who need it), medical utility (optimising the function of the resource), and efficiency (including time, cost, waste, and geography) [24]. Regarding the management of waiting lists for organ transplantation, the Council of Europe recommends that member states should ensure that a system is in place to provide patients with equitable access to transplantation services and to ensure that organs and tissues are allocated according to fair and transparent rules, taking into account medical criteria. It also states that allocation rules should be changed when necessary to ensure similar waiting times for similar groups of patients [25].

Therefore, the definition of rules for the allocation of deceased donor kidneys for transplantation should be based on sound clinical criteria, should seek to make the

best use of available organs by minimising their waste and must ensure fair access to all patients. The availability of dialysis treatment for ESRD patients means that transplantation should only be considered in exceptional circumstances as an urgent treatment on which a patient's life depends.

The success of a kidney transplant depends not only on ABO blood group compatibility but also on genetic and immunological compatibility between donor and recipient. Human Leukocyte Antigens (HLA) are highly polymorphic proteins that play a key role in transplantation. HLA-A, -B, and -C (class I) are present in virtually all our cells (except red blood cells), while HLA-DR, HLA-DQ, and HLA-DP (class II) are mainly in immune cells. Although HLA polymorphism may help diversify humanity, it is a major obstacle to successful transplantation, and it is recommended that the HLA types of recipient and donor be matched as closely as possible [26].

In addition, HLA sensitisation of transplant candidates to donor's HLA is usually a contraindication to transplantation. The most common sensitisation events are blood transfusions, pregnancies, and organ transplants, with the latter having the greatest potential for sensitisation [27]. After losing an organ, the patient's risk of developing HLA antibodies increases exponentially [28].

Donor specific antibodies (DSAs), both those present at the time of transplantation and those arising *de novo*, are a risk factor for rejection and potential organ loss [29]. Identifying DSAs and, consequently defining unacceptable donor's HLA antigens for transplant candidates, has allowed the development of the concepts of calculated Panel Reactive Antibodies (cPRA) and virtual CrossMatch (vXM). The cPRA value of a given transplant candidate serves as an estimate of the likelihood that the next available transplant donor will be incompatible with that candidate. This value depends not only on the identification of HLA antigens that are not acceptable to the patient but also on the HLA frequencies of the population to which the organ donors belong [30]. The way in which these non-acceptable antigens are defined can restrict the chances

of finding a potential donor for the patient [27]. Therefore, the cPRA value and the vXM result must be seen as two sides of the same coin [31].

A system for allocating deceased donor kidneys for transplantation should be reviewed periodically so that it can be modified based on evolving data and its association with recorded outcomes. Such a system should be transparent and understandable to both healthcare professionals and transplant candidates and must allow for the best use of available organs [32].

The discussion around the allocation of kidneys for transplantation is based on the importance that each person attaches to a more utilitarian distribution of this scarce resource (the best organ should be given to the patients who can best use it) or to a fairer distribution (giving relatively equal access to all patients, without taking into account the possible outcomes of each transplant) [33].

Patients vary in their expected longevity and organs vary in their quality. Deceased donor kidneys that are expected to last longer should not be allocated to patients with a shorter expected survival [32]. Allocating kidneys with a longer expected survival to patients with a longer post-transplant life expectancy would reduce the number of patients candidates for re-transplantation [33]. While using utilitarian criteria in allocating kidneys for transplantation would minimise the difference between the life expectancy of an organ and its recipient, it could undermine public confidence in a kidney allocation system [34].

A detailed description of kidney allocation rules from the UK, EuroTransplant or Portugal can be found in the KARS application's users' manual [35]. In these examples, different weights are given to utilitarian and justice criteria.

In 2022, Portugal was the second country (after Spain) with the highest relative number of deceased donors for organ transplantation (31.5 pmp) and the fourth country with the highest relative number of deceased donor kidney transplants performed (43.3 pmp) [36].

However, the current Portuguese rules for selecting donor-recipient pairs in kidney transplantation, implemented in 2007, lack transparency, equity, and simplicity [6][37]. These rules are based on a scoring system that is difficult to decipher, the weight given to time on dialysis does not compensate for hyper-sensitised patients, and candidates on the waiting list have no idea how far they are from being transplanted. Therefore, it is necessary to evaluate these rules objectively and analytically and to propose valid alternatives that can be tested.

A recent working group, under the national transplant programme, finally recognizes the need to revise the current Portuguese KAS [38].

Whether a new research hypothesis emerges from a deductive or an inductive process [13] it needs to be tested. Similarly, any new proposal for an allocation system of deceased donor kidneys for transplantation should be subject to public scrutiny. In addition, these rules should be periodically reviewed so that they can be updated and adapted to the clinical, ethical, social, and technological advances that affect organ transplantation [39].

TxOR INITIATIVE

2. TxOR initiative

The Transplant Open Registry (TxOR) initiative [40] was born out of the need to provide a single point of access to the work we are developing. These projects are in some way related to transplantation activities, with a particular focus on kidney transplantation. The vision of this initiative is to provide information on transplantation using only open-source resources. Its goals are:

- Assemble open data on transplantation (patients and donors) and make it available, in a transparent and accessible way, to all possible stakeholders;
- Carry out statistical and epidemiological analyses with open data on transplantation to generate knowledge;
- Defining organ allocation algorithms that guarantee equity of access to a scarce resource such as organs for transplantation;
- Providing accurate, clear, and transparent information on transplantation activities in Portugal;
- Enabling decision making based on evidence of data.

As an interdisciplinary concept, Health Data Science seeks to extract knowledge from data, using ideas and techniques from fields as diverse as computer science, statistics, epidemiology, and knowledge domains such as medical specialties [41]. Data science solutions for patient management and monitoring are becoming more widespread, either as an adjunct to diagnosis or as a means of defining prognosis and predicting disease progression. Likewise, it is possible to attempt to predict the outcome of a particular transplant with efficiency gains in organ allocation [42], while seeking to maximise fair access for all patients on the transplant waiting list.

Several open-source applications are currently available through TxOR that can potentially be used at different stages of some of the activities that make up the entire transplantation process.

Transplant Open Registry Initiative

Bruno A Lima, Teresa S Henriques, Filipe Pinto Reis, Helena Alves. *Port J Nephrol Hypert* 2022; 36(4): 201-206. DOI: 10.32932/pjnh.2022.10.204

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Transplant Open Registry Initiative

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Contributorship Statement:

■ BAL, FPR: Conceptualization, drafting, review and editing of the manuscript and approval of the final version of the manuscript.

■ TSH, HDA: Supervision, review and editing of the manuscript and approval of the final version of the manuscript.

ABSTRACT

Health data science aims to extract knowledge from data allowing better decision-making, using multidisciplinary approaches from fields such as computation, statistics, epidemiology, and several medical knowledge domains. We live in the 'big data' era, with a growing availability of health data, in volume, variety, and velocity, also for tasks such as kidney transplantation. Hereby, secondary use of this health data must be encouraged to improve patient care planning, disease research, and policymaking around transplantation.

This article presents the Transplant Open Registry (TxOR) website where some health data science applications on kidney transplantation are available. With it, we try to answer, some of the remaining questions on kidney transplantation in Portugal, with a new approach.

Keywords: Information Systems; Kidney Transplantation; Machine Learning; Process Assessment, Health Care; Tissue and Organ Procurement

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BACKGROUND

Kidney transplant success as kidney replacement treatment for end-stage renal disease patients has evolved over several decades, with both scientific advances and some incidents, and it should be viewed as a work-in-progress.¹ Renal transplantation, when possible, is the preferential treatment for patients with end-stage kidney disease. It is associated with a long-term reduction in risk of death when compared to patients on dialysis waiting for a transplant.² As donor-recipient incompatibilities are a major cause for rejection, improving the match between donors and recipients could minimize the rejection rates and optimize the utilization of such valuable resource.³

In 2018, with 256 cases per million population (p.m.p.), Portugal was the second European country with the highest incidence of patients starting renal replacement therapy, barely surpassed by Greece.⁴ In Portugal, the prevalence of patients in renal replacement therapy was 2011 p.m.p., the highest number in all of Europe. A much higher value than those from countries like Spain, Belgium, or Greece with less than 1500 patients p.m.p.⁴

The implementation of new measures to improve activities related to renal transplantation in Portugal requires the definition of systematic metrics for these activities. We not only need to know how kidney transplantation has evolved in our country over the years, but we also

need tools that allow us to assess established practices. Thus, we seek to make available several open access applications that can be an adjuvant to evaluate transplantation activities as well as some implemented policies, in Portugal. Some of these applications include: predicting transplant's outcomes; count the percentage of potential histocompatible donors that may be available for a given patient; simulating kidney allocation rules; or simple visualizations of the evolution of kidney transplantation compared to other European Union countries.

Health data science is a multidisciplinary concept rendered into the extraction of knowledge from data using theories and techniques from fields as diverse as computation, statistics, epidemiology, and knowledge domains such as medical specialties.⁵ Although there is evidence that these computational and statistical techniques could be an asset to the field of transplantation, the best way to implement them in the clinical management of renal patients is still questionable.⁶

Data science solutions applied to patients' managing and monitoring are increasingly frequent, either as an aid in determining diagnoses or for prognosis and prediction of disease evolution. Machine learning can be used to develop models that predict transplant outcomes, allowing efficiency gains in organ allocation by determining the ideal candidate to receive a specific organ, maximizing the survival of both

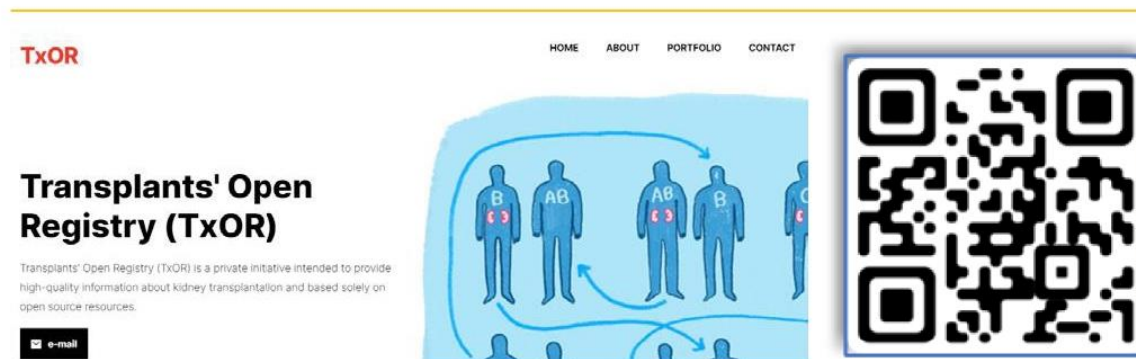


Figure 1

QR code for TxOR website.

patient and graft.⁶ Likewise, these models can be a clinical prognostic tool that maximizes the best matching between donor and recipient while ensuring equity in kidney allocation systems.

This article presents the Transplant Open Registry (TxOR) initiative.⁷ TxOR (Fig. 1) compiles health data science applications on kidney transplantation, available as free open source.

TXOR

TxOR is a private initiative based on open-source means to provide high-quality information on kidney transplantation in Portugal. The fame-motivated open-source community grants a savory opportunity to make TxOR evolve at a higher pace than it would as proprietary software.⁸

Health data science has the potential to generate knowledge by extracting information from data, and getting answers to clinical research questions otherwise unsolvable through more traditional research approaches. With this in mind, the TxOR initiative's mission is to:

- Assemble open data from both kidney transplant donors and recipients and make it available, in a transparent and accessible format, for all interested parties;
- Provide clear and transparent information on kidney transplantation activities in Portugal allowing informed data-driven decision-making;
- Perform data and epidemiological analysis with open data on transplantation;
- Look for the best kidney allocation algorithms for kidney transplantation, using simulations to find an equitable way to distribute this valuable and scarce resource.

We lived in a so-called big data era and collections of data are generated constantly. Big data is usually characterized by 3 dimensions:

Volume, with more data-collecting devices, used every day, the volume of data increases dramatically; Variety, data can have different formats and different levels of completeness; and Velocity, as the volume of data increases, the rate of data generation (from the internet of things, social media, etc.) is increasing as well. Big data use has the potential to revolute medical practice as we know it.

In Portugal, the Portuguese Institute of Blood and Transplantation (IPST) is responsible for maintaining and running an information system to manage the candidates' kidney transplant waiting list and the selection of donor-recipient pairs in renal transplantation. Moreover, according to the Council of Europe, member states' entities responsible for transplant's waiting list management must provide information, to the general public, at least on an annual basis. Comparing the information provided by Portugal with the information from other European Union countries, it can be quickly concluded that IPST has very limited performance in this concern. Unfortunately, neither a characterization of the transplant candidates' waiting list over the years nor a clear description of transplanted patients could be found.⁹

APPLICATIONS

At TxOR we found two applications: **Renal Transplant activity in Portugal** and **Portugal within the EU** (Fig. 2); that use data from the Global Observatory on Donation and Transplantation.¹⁰ These applications analyze the evolution of renal transplantation activity in Portugal¹¹ and compare some of the information with that from other European Union countries.¹² Annual rates of kidney transplants by type of donor and the number of deceased donors for organ transplantation are presented since 2003.

In 2020, while Portugal was the fourth country with the higher rate p.m.p. of renal transplants performed from deceased donors in the European Union, it only occupies the 14th position for kidney transplants from living donors.¹⁰ In 2009, Portugal, reached the higher number of performed transplants from deceased donors' kidneys, with 50 transplants p.m.p., whilst between 2015 and 2019

barely surpasses 40 transplants p.m.p, even with a similar number of registered deceased donors (between 31 and 34 p.m.p.). The exception was 2020 with a reduced number of deceased donors (24.8 p.m.p.) and also a reduced number of performed transplants both from deceased and living donors (34.6 and 4 p.m.p., respectively), explainable by the effects of the COVID pandemic. Moreover, we also can observe that the number of patients actively listed for transplantation has been constantly around two thousand, for the last decade. For both applications, we have a left panel from which the user can select the indicators and a specific year to be displayed, while on the right we can visualize the data. These applications versions are intended to be used in a personal computer rather than a smartphone.

Human leukocyte antigens (HLA) are very polymorphic proteins that play a pivotal role in transplantation. HLA-A, -B, and -C (class I) are present on virtually all our cells (except red blood cells) while HLA-DR, -DQ, and HLA-DP (class II) are mainly on immune cells. While HLA polymorphism may help diversify humanity, it is a huge barrier to successful transplantation, which requires matching, as closely as possible, the HLA types of the recipient and donor.¹³ Sensitized patients have alloantibodies reactive to HLA alleles. Renal transplant candidates with HLA sensitization tend to be disregarded in kidney transplant allocation and even when transplanted they have a higher risk of graft rejection and long-term complications.¹⁴ For each transplant candidate, the calculated Panel Reactive Antibody (cPRA) value estimates the percentage of potential deceased donors having HLA alleles for which the candidate is reactive and consequently not an option for transplantation. Patients on the waiting list for renal transplantation from a deceased donor with higher cPRA values are less likely to found a suitable donor and must be informed about other alternatives (as could be transplantation with a living donor). The reliability of cPRA values depends on the pool of potential donors from which it is estimated and as such those donors' HLA allelic and haplotypic frequencies must be known and scrutinized. The application **Portuguese cPRA calculator**¹⁵ available from TxOR, computes cPRA values from identified HLA antibodies and is based on HLA frequencies from Portuguese voluntary bone marrow donors¹⁶ and therefore comparable to potential deceased kidney donors in Portugal. With transplant candidates' HLA alloantibodies as input, the cPRA calculator returns a percentage estimate of potential donors not available for transplantation.

When allocating a scarce commodity such as deceased donor kidneys for transplantation, it is crucial maximizing transplant outcome in order to guarantee efficient use of that organ. The application **ScoreTx**¹⁷ compiles some risk scores to predict kidney transplants outcome using only data known at the time of transplantation for the donor-recipient pair. The Organ Procurement and Transplantation Network (OPTN) uses two different scores: an Estimated Post Transplant Survival (EPTS) score (based on patients characteristics) to summarize the fitness of the patient; and a Kidney Donor Percentual Index (KDPI), that combines factors from donors and from the transplant, to summarize the risk of graft failure. Also, we make available the TRANSPLANTSCORE proposed by Molnar *et al*¹⁸ to predict posttransplant outcomes (for mortality or graft failure as a combined outcome) using pretransplant

information, computing the estimated 5-year event probability. Moreover, the Nyberg score¹⁹ can be computed from ScoreTx¹⁷ using only variables from the donor and the number of HLA mismatches with the recipient. In particular, this score is a quantitative approach to assessing kidneys from expanded criteria donors. The development of risk scores that can predict the outcome inherent to the data-recipient pair at transplantation has allowed for better decision-making either in allocating organs and patients' clinical management.

According to the Council of Europe, organ transplantation allocation rules must be changed whenever necessary to ensure that similar groups of patients have similar waiting times. The evaluation of new kidney allocation rules should depend on simulations that will allow, as far as possible, to predict future results and outcomes. The **Kidney Allocation Rules Simulator (KARS)** application²⁰ allows simulating different sets of rules changing the respective parameters and using different data.²¹ Having as inputs files with transplant candidates' demographic and immunological data, with KARS we can run simulations on kidney allocation systems and compare final results. In this application, it is possible to simulate allocation rules implemented in Portugal, in countries within Eurotransplant, in the United Kingdom, and an allocation system previously suggested by Lima *et al*.²²

Portuguese kidney allocation system on transplantation (implemented in 2007) is based on a points system that takes in consideration: HLA mismatches between donor and transplant candidate, level of immunization of the candidate, time on dialysis, and age difference between donor and transplant candidate. Additionally, hypersensitized candidates (cPRA >85%) are prioritized and after that all candidates are ordered by their corresponding punctuation. Also, the KARS app allows changing the original punctuation used by the aforementioned allocation systems, to simulate how these changes are translated into the type of candidates selected for transplantation. For each one of the models, transplant candidates are excluded considering ABO compatibility and virtual crossmatch, and the remaining are ordered for each donor according to the model's rules. For the option 'One donor', the top 10 candidates are displayed regarding the donor characteristics; for the option 'Multiple donors' each donor is attributed to the 2 best classified candidates and at the end, we will have a dataset with the number of candidates equal to the double of the number of donors. Finally, a resume of the characteristics of the selected candidates is displayed allowing for the comparison between models. Currently, fifteen years after its enforcement, there are a scientific consensus on the need to revise and upgrade the Portuguese kidney allocation system on transplantation.²³ Our KARS app is a tool available to researchers interested on simulating different scoring systems and comparing it with allocation systems implemented in other countries.

We also developed the R package²⁴ that allows generating synthetic data on donors and transplant candidates particularly useful on the KARS app.²⁰ The availability of synthetic data plays an increasingly important role in the development cycle of any data science project, allowing the development and preparation of the project before the use of real data without having to depend on it.²⁵

needed to implement these new approaches. The main objective of health data science is to allow both clinicians and researchers to make better decisions⁵ and cannot be seen as something esoteric or distant.

Defining key performance indicators, which permit systematically and objectively measuring access to kidney transplantation and its outcomes, is essential for making informed decisions in health policies' assessment. Only with a detailed description of candidates on the transplant waiting list, both at a socio-demographic level and their immunological characteristics, it is possible to know what type of interventions can be taken to guarantee equitable access to kidney transplants.²⁷ Unfortunately, the IPST has not been able to provide this kind of data, much less the processed information that could help make better decisions in the field. Furthermore, survival rates of kidney transplantation are not known for the current Portuguese deceased donor allocation model, not allow comparing this model with the ones implemented in other countries.²⁷

A kidney transplanted patient undergoes several stages of clinical follow-ups, such as diagnosis of chronic kidney disease, the assessment of end-stage renal disease, pre-transplantation follow-up, and post-transplantation follow-up. Providing these patients with quality health care is ensured when clinicians have access to reliable patient health data that allows critical decisions to be taken⁵ and equally with posterior processing of patients' compiled data. This secondary use of health data is an enhancement to improve personal care planning, research, or policymaking and must be encouraged and stimulated.²⁸

There is a growing movement calling for the availability of open health data allowing its analysis and processing with data science technologies, facilitating access to information and knowledge. The current COVID-19 pandemic also served to enhance and demonstrate the merits of this movement. Similarly, within the scope of kidney transplantation in Portugal, we appeal to the responsibility of public entities to make this kind of data available as a way of stimulating the transparency required to public administrations; even more when these entities have shown themselves incapable of using it.²⁹

Principal applications available at TxOR (scoreTx, cPRA, KARS) can be seen as calculators and one of their main advantages rely on the fact that at no time individual data are stored or processed neither can be accessed by anyone other than the user itself. As we do not manage users' data neither meta-data, we do not jeopardize any rule imposed by the European General Data Protection Regulation.

Although we need data to develop new policies or to evaluate existing ones, we cannot disregard concerns about individual privacy issues. With this in mind, we also made available an R package to generate synthetic data, this kind of data simulates real data and was used to develop KARS app. We do not ask for individual data to be made public, but we need to have access to a clear and good characterization of patients and donors (as legally required) to generate more accurate synthetic data. On Renal Transplant activity in Portugal and Portugal within the EU applications, we used public available aggregated data that, by its nature, it is not possible to identify any individual person from.

LIMITATIONS

Applications presented at TxOR are not medical devices and do not have a commercial purpose. Likewise, each of them must be seen as a proof of concept, i.e., as realizations of its feasibility. Moreover, we expect to still build on them, making them more user-friendly and with more functionalities. Also, as open source software, TxOR's applications are intentionally generic and not intended to be specific. Hence they can be used and adapted by anyone without any cost. We also must emphasize that algorithms on scoreTX were developed by others and do not used data from Portuguese patients. In future versions of these applications, we expect to make them more user-friendly with a better interface if accessed through smartphones.

CONCLUSION

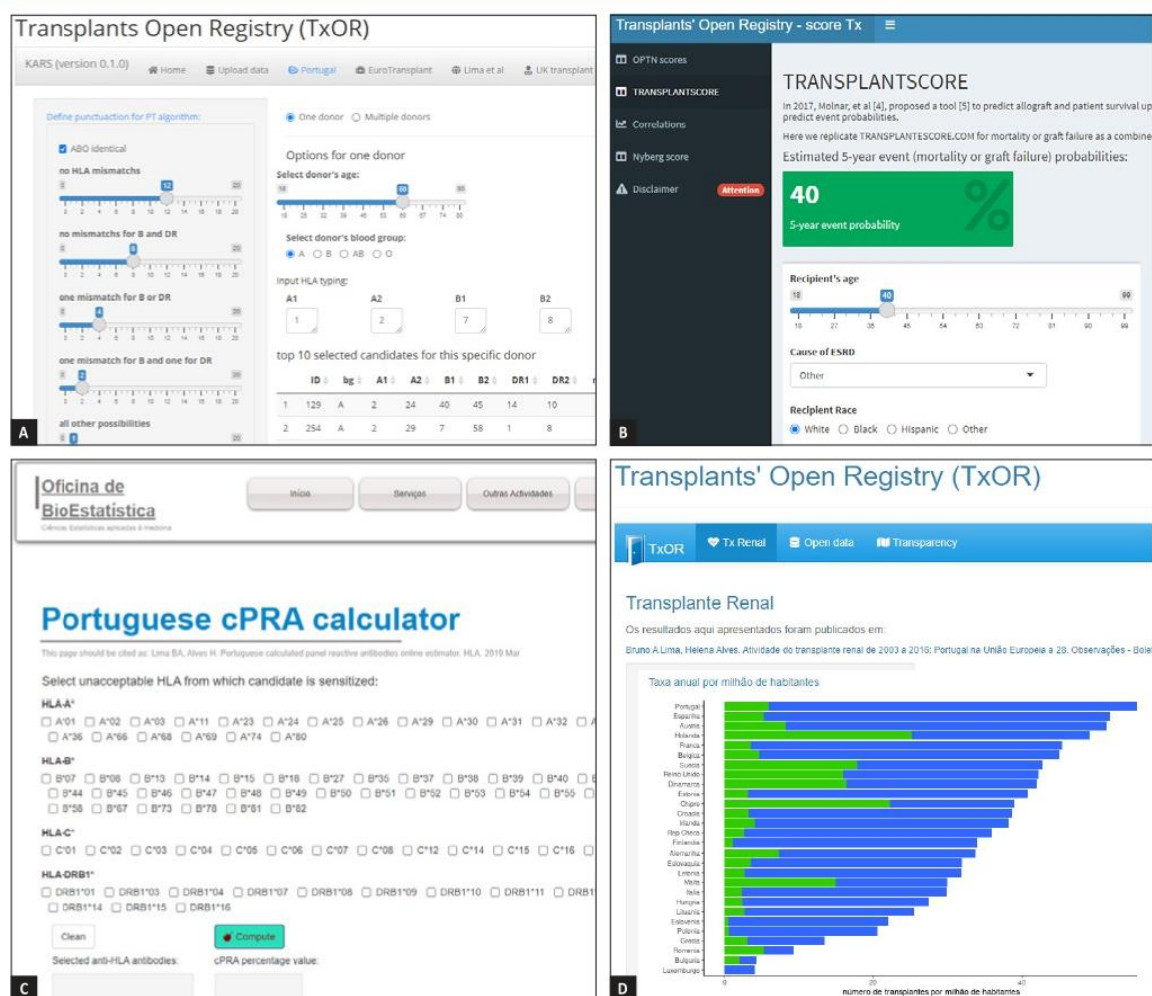
Machine learning techniques alone are not a panacea that will solve everything, and they are also subject to biases. Nevertheless, the potential of Real World Data to generate quality scientific evidence cannot be squandered by its custodians' failure to make data available.²⁶

Neither data alone nor only complex algorithms can answer complex clinical questions. This is the era of 'big data' but there is still a large gap between the amount of accumulated health data and medical domain knowledge. The gap can only be bridged by multidisciplinary teams that should include clinicians, data scientists, epidemiologists, and informaticians.⁵

TxOR initiative is built on health data science and tries to answer, some of the enduring questions on kidney transplantation in Portugal, with a new approach. It hopes to contribute to a fruitful discussion that allows clarifications on some hot topics such as the constant need for a better kidney allocation system.

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From left to right, top to bottom: A -The Kidney Allocation Rules Simulator (KARS); B -the Score Tx application; C - the cPRA calculator; D - Portugal within the EU.

Figure 2

Available applications from TxOR.

DISCUSSION

Data science technologies apply to several fields and have the ability to transform them. Health care is no exception and, here too, data science plays an increasingly relevant role.

The growing availability of health data in high volume, variety, and velocity, when reachable for data science, presents an opportunity to respond to those problems postured by precision medicine.⁵ Also, the concept of Real World Evidence applies to evidence in healthcare

obtained through so-called Real World Data and can be used to achieve better data-driven decision-making.²⁶

In order to implement algorithms that can transform data into information or build predictive models that can be used in production, interventions are often necessary both in collecting patients' data and analyzing institutions' needs. In kidney transplantation, machine-learning prediction models based on information from donor-recipient pairs can autonomously learn those donor-recipient relationships to predict transplant outcomes.³ However, upstream changes are still

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■ Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financial Support: This project received the “Antonio Morais Sarmento” research grant from the Portuguese Society of Transplantation. This funding had no role in: study design; collection, analysis or interpretation of data; in the writing of the report; neither in the decision to submit the article for publication.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

Consent for Publication: Not applicable.

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2.1. Web applications

During the course of this project, the need arose to create software tools that could aid us achieve the objectives delineated in this thesis. The solutions available to us did not respond to the specificity of the problems we had to solve.

In order to simulate the implementation of different allocation models, we developed software specific to each model. In addition, we also had the opportunity to craft tools that had a broader applicability across multiple models. In other words, by deconstructing the models we studied, we identified numerous tasks that are common to the implementation of these models.

While we had the option of creating these tools in a closed, restricted manner, we consistently chose to create open-source software. This approach not only allows for wider reuse by others, but also serves as a means to showcase our work to a wider audience.

The solutions we have created can be divided into two main groups: R packages [43]; and *shiny* [44] applications. In the first case, packages *histoc* [45] and *simk* [46] are primarily intended for people with experience in R programming. These packages include all the functionalities required to execute the tasks described in this thesis and are flexible enough to be generalised for future research endeavours.

The *shiny* applications, that have been developed, use these packages as their backend, making them accessible to a wide range of people, including those without any programming background. Essentially, these applications act as calculators, generating specific outputs based on user's input. In the cPRA calculator [30], the user enters the anti-HLA antibodies of a potential transplant candidate and the tool returns a value between 0% and 100%. For scoreTx [47], users provide clinical and demographic information for a potential donor-recipient pair at the time of transplantation and in return they have access to predictive measures regarding of transplant outcomes. The calculated HLA Evolutionary Divergence (cHED) application [48] calculates the HLA

Evolutionary Divergence (HED) score for allele pairs within each HLA *locus* of a potential patient. Finally, the KARS application [49] uses demographic, clinical, and other relevant data from potential transplant candidates and organ donors, together with specific parameters from those kidney allocation models that we wish to test.

2.1.1. {histoc}

The R package *histoc* [45] compiles a set of functions with which it is possible to perform some histocompatibility tests between donor and recipient in the context of transplantation. The main functions of this package allow the simulation of some kidney allocation systems for kidney transplantation. Currently, it is possible to simulate the rules for the distribution of deceased donor kidneys for transplantation used in Portugal [50] (PT model), the United Kingdom [17] (UK model), the EuroTransplant countries [51] (ET model), a previously presented model based on a colour prioritisation system [5] (Lima's model), and a model developed within the framework of this thesis based on an Equity Matrix (EQM).

For each of these models, the available functions have as arguments: a dataset containing the clinical and demographic information of kidney transplant candidates; another dataset containing the identification of anti-HLA antibodies of each candidate; and finally, the information of a potential donor. Each of these functions sorts the transplant candidates according to the donor information that is given as input, after excluding those candidates with a positive virtual crossmatch and without ABO compatibility.

histoc: Histocompatibility analysis performed by kidney allocation systems

Bruno A lima, Filipe P Reis. *JOSS* 2022 7(80), 4807. DOI: 10.21105/joss.04807

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histoc: Histocompatibility analysis performed by kidney allocation systems

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DOI: [10.21105/joss.04807](https://doi.org/10.21105/joss.04807)

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Submitted: 12 August 2022

Published: 05 December 2022

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Summary

The distribution of a scarce commodity such as deceased donor's kidneys for transplantation should be as equitable as possible. Different countries try to implement kidney allocation systems (KAS) in transplantation that balance principles of justice and utility in the distribution of such scarce resource ([Lima & Alves, 2020](#)). That is, a KAS should optimize the transplant clinical outcome (principle of utility) while giving a reasonable opportunity to all wait list candidates to be transplanted (principle of justice) ([Geddes et al., 2005](#)).

The selection of a donor-recipient pair in kidney transplantation is based on histocompatibility tests that can eliminate specific transplant candidates from opting for a kidney from a given deceased donor. These histocompatibility tests are used in several KAS and can be specific to each of them.

The goal of this package is to aid the evaluation and assessment of KAS in transplantation.

Statement of need

histoc is an R ([R Core Team, 2021](#)) package that assembles tools for histocompatibility testing in the context of kidney transplantation. The package's main functions allow simulating several KAS on the distribution of deceased donors' grafts for transplantation. Moreover, it is possible to redefine arguments for each one of the KAS as a way to test different approaches.

Currently, it is possible to simulate allocation rules implemented in Portugal [PT model; Ministry of Health ([2007](#))], in countries within Eurotransplant [ET model; EuroTransplant ([2020](#))], in the United Kingdom [UK model; National Health Service Blood and Transplant ([2017](#))], and a system suggested by [Lima et al. ([2013](#)); Lima's model].

Each one of these models have as arguments a data frame with transplant candidates' clinical and demographic characteristics, a data frame with candidates' Human Leukocyte Antigens (HLA) antibodies and potential donor's information. By default two candidates are selected for each donor, although we can define the number of candidates to be selected.

For all the models a virtual crossmatch between the donor and transplant candidates is performed (`xmatch()`). And, only those candidates with a negative crossmatch and ABO compatible can opt to a donor's kidney.

Results are presented as `data.table` ([Dowle & Srinivasan, 2021](#)) objects due to its high computation performance.

To get started, a vignette is available that describes [how to use](#) each one of the algorithms.

New kidney allocation systems should be assessed using simulations that, to the greatest extent possible, can predict outcomes. histoc is designed mainly for researchers working on organ

transplantation, assisting with data-driven decision making for the establishment of allocation policies.

While the R package `transplantr` (Asher, 2020) makes available a set of functions for audit and clinical research in transplantation, the package presented here enables the simulation of various sets of rules by adjusting relevant allocation parameters. Additionally, the Kidney-Pancreas Simulated Allocation Model [KPSAM; Scientific Registry of Transplant Recipients (2015)] is a proprietary software that the Scientific Registry of Transplant Recipients makes available to support studies on alternative allocations policies in transplantation. In contrast, `histoc`, coupled with being open source, needs less data to run in comparison to KPSAM software. Likewise, it can be used as a preliminary technique for developing new hypotheses that can then be tested on KPSAM.

Kidney Allocation Systems

Portuguese Model

Portuguese rules on allocation of kidneys from deceased donor [PT model; Ministry of Health (2007)] are based on a scoring system that takes in consideration:

1. HLA mismatches between donor and transplant candidate;
2. Level of immunization of the candidate;
3. Time on dialysis;
4. Age difference between donor and transplant candidate (`pts()`).

Total scores for donor-recipient pairs are given by the column `ptsPT`. Also, hypersensitized candidates (`HI`; `hiper()`; calculated Panel Reactive Antibody `cPRA > 85%`) are prioritized and all subsequent candidates are ordered by their corresponding score.

Euro Transplant Model

A simplified version of EuroTransplant Kidney Allocation System [ETKAS; EuroTransplant (2020)] can be simulated through `et()`. This applies to first time kidney only candidates with more than 18 years old and that haven't donated one of their own kidneys.

In this simulation for each donor, transplant candidates are sorted as :

1. Senior Program (SP; 65+ years old candidates when the donor has 65+ years old);
2. Acceptable Mismatch Program (AM; candidates with a `cPRA > 85%` and without HLA antibodies against HLA's donor);
3. 000 HLA mismatches (`mmHLA`; candidates without HLA mismatches with the donor);
4. ETKAS points (`pointsET`).

Final points for each eligible candidate are obtained from the sum of HLA points (`et_mmHLA()`), dialysis (`et_dialysis()`) points and MMP points (`et_mmp()`).

United Kingdom Model

United Kingdom deceased donor kidney allocation for transplantation [UK model; National Health Service Blood and Transplant (2017)] is firstly based on the definition of two ranked tiers of candidates eligible for the donor (Tier):

1. Tier A – patients with match score = 10 or `cPRA = 100%` or time on dialysis > 7 years;
2. Tier B – all other eligible patients.

Within Tier A, transplant candidates are ordered by matchability and time on dialysis. Transplant candidates within Tier B are prioritized according to a point-based system computed with 7 elements:

1. Matchability (`matchability`)
2. Time on dialysis (`dialysis`)
3. Donor-recipient risk index combinations (`ric()`)
4. HLA match and age combined (`age` and `mmHLA`)
5. Donor-recipient age difference (`age` and `donor_age`)
6. Total HLA mismatch (`mmHLA`)
7. Blood group match (`abo_uk()`)

The `uk()` function simulates the allocation of kidneys to a candidates' waiting list for kidney-only transplants and do not take in consideration geographical criteria.

Lima's Model

And lastly, within Lima's model ([Lima et al., 2013](#)), a color prioritization (`cp()`) of all waiting list transplant candidates is established.

Transplant candidates are classified according to their clinical urgency (red color), with regard to their time on dialysis and cPRA value cPRA. Orange is used to mark patients with a cPRA > 85% or with a time on dialysis higher than the waiting time for the 3rd quartile. Yellow is used to classify patients with a cPRA > 50% or with a time on dialysis higher than waiting time median. Green is used to specify all other candidates.

Within each color group candidates are ordered by mmHLA (ascendant) and time on dialysis (descendant).

Also, candidates are allocated to donors within the same age group (SP; old to old program), mimicking EuroTransplant senior program (`sp()`).

Candidates' selection for a pool of donors

We can also simulate the selection of wait list candidates for a pool of donors, according to a given model (or algorithm). The function `donor_recipient_pairs()` allow us to compute all possible donor-recipient pairs according to any of the previously described kidney allocation algorithms.

We provide example datasets within `histoc` for 500 wait list transplant candidates and a pool of 70 donors both of which are described in our [candidates' selection vignette](#).

Moreover, an additional column in the output can be generated to calculate the estimated 5-year event probability for mortality or graft failure described by Molnar et al. (2018). This is available from the application `TxScore` and can be computed using the `txscore()` function.

Input data

User provided input data used by this package regarding either candidate or donor information should match the exact format of the provided example data. Furthermore, the `simK` ([Lima, 2022](#)) package allows users to generate synthetic data both for candidates and donors that can be used with `histoc`.

Bug reports and contributions

Any bug reporting, feature requests, or other feedback will be welcomed by [submitting an issue](#) in our repository. When reporting a bug, please ensure that a reproducible example of your code is included so that we may respond to your issue promptly.

Funding

This project received the “Antonio Morais Sarmiento” research grant from the Portuguese Society of Transplantation. This funding had no role in: study design; software development; the writing of the report; neither in the decision to submit the article for publication.

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2.1.2. {simK}

The R package *simK* [46] allows to synthesize data on both the waiting list of patients who are candidates for kidney transplantation and on potential kidney donors for transplantation. The data generated by this package are particularly useful with the kidney allocation systems of the *histoc* package. Limited access to real data on transplant waiting lists and donors for kidney transplantation cannot be an excuse for not thoroughly reviewing public policies on the distribution of scarce resource such as deceased donor kidneys for transplantation.

With public information on the clinical, immunological, and demographic characteristics of both transplant candidates and potential organ donors, it is possible to generate synthetic data representing these individuals.

In the case of potential donors, we only need to know their HLA typing, their blood group, and age to use them in one of the kidney allocation algorithms available in the *histoc* package. With *simK*, we only need to define the population origin (Portuguese [52] or one from the National Marrow Donor Program [53]) to generate a dataset with HLA genotyping for a group of potential donors. To define the ABO group of each donor, we only need to specify the frequencies to be taken into account for each of the phenotypes (A, B, AB, and O), and for the respective ages, in addition to the maximum and minimum age's limits, we only need to specify the mean and the standard deviation to be used in generating numbers of a normal distribution. All this can be done with just one function.

To generate data from a waiting list of kidney transplant candidates, in addition to HLA, blood group and age, we also need to assign a cPRA value, and a time on dialysis, as well as a file with the anti-HLA antibodies of each candidate for input to the functions in the *histoc* package. The cPRA values are generated from a vector of probabilities for the groups 0%, 1%-50%, 51%-84%, and 85%-100% (in that order). The time on dialysis is generated taking into account whether the candidate is hypersensitised

(cPRA > 85%) and/or from group O, as they tend to have a longer time on dialysis. All this can be done with just one function.

It is also possible to generate a dataset of the anti-HLA antibodies for each candidate with a cPRA value > 0%, where antibodies are randomly assigned until the candidate's cPRA value is reached, these anti-HLA antibodies differ from the respective HLA typing, again in a single function of the *simK* package. This type of synthetic data is also particularly useful in preliminary analyses and when we want to develop and test code.

simK: Synthetic Data on Kidney Transplantation

Bruno A lima. *JOSS* 2023 (submitted for publication in December 2023)

JOSS The Journal of Open Source Software

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1 simK: Synthetic Data on Kidney Transplantation

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DOI: [10.xxxxxx/draft](https://doi.org/10.xxxxxx/draft)

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Reviewers:

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Submitted: 01 January 1970

Published: unpublished

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4 Summary

5 Synthetic data can be used to validate mathematical models and to train machine learning
6 algorithms. Furthermore, distinct subject-specific investigations would necessitate different
7 data. Privacy issues, data sensitivity, copyrights, and legal constraints, on the other hand,
8 are frequently substantial impediments to accessing the necessary data. In the case of kidney
9 transplantation, different countries have their own kidney allocation systems (KAS) in place, to
10 balance the concepts of fairness and utility in the distribution of such scarce resource ([B. Lima](#)
11 [& Alves, 2020](#)). Access to health data is becoming increasingly restricted, however synthetic
12 data can always be used to evaluate alternative KAS and its modifications.

13 The goal of this package is to allow generate synthetic data that can be used on the evaluation
14 and assessment of KAS in transplantation.

Statement of need

16 simK is an R ([R Core Team, 2021](#)) package that assembles functions that allow to generate
17 synthetic data sets with demographic, clinical and immunologic characteristics of wait listed
18 candidates for kidney transplantation and a pool of deceased donors. Data generated with simK
19 are particularly useful with the package histoc ([B. Lima & Reis, 2022](#)) and the application
20 Kidney Allocation Rules Simulator (KARS) ([B. Lima et al., 2022](#)). With this two packages it
21 is possible to simulate allocation rules implemented in Portugal ([Ministry of Health, 2007](#)),
22 in countries within Eurotransplant ([EuroTransplant, 2020](#)), in the United Kingdom ([National](#)
23 [Health Service Blood and Transplant, 2017](#)), and a system suggested by ([B. Lima et al., 2013](#)).

24 Access to health data is generally limited by issues of confidentiality of individuals' information.
25 Researchers' access to this type of data is usually dependent on consents for use, protocol
26 approval, ethical review approval, bureaucracies for data requests, and financial costs ([Gonzales](#)
27 [et al., 2023](#)). Nevertheless, sometimes, when it is not possible to have access to real data for
28 proprietary or even logistical reasons, there is the alternative of using synthetic data. This
29 type of data can be created, used, shared and discarded without major associated costs and is
30 useful for researchers, innovators and data entrepreneurs alike, however different their purposes
31 may be. Moreover, this data can be made available and used, publicly and free of charge, by
32 industry, innovators, researchers, education and without legal, privacy, security, financial, and
33 intellectual property limitations ([Walonoski et al., 2018](#)).

34 The US Census Bureau defines synthetic data as: "microdata records created by statistically
35 modeling original data and then using those models to generate new data values that reproduce
36 the original data's statistical properties" ([Philpott, 2017](#)). Likewise, synthetic data can thus be
37 a substitute for real records, useful for secondary uses that require realistic but not necessarily
38 real data ([Chen et al., 2019](#)).

39 Synthetic data generation is increasingly used in research to test and evaluate the applicability
40 of new statistical methods or new algorithms. In such cases, data synthesis seeks to provide
41 test data that can reflect as accurately as possible the complexity of the real-world data

where an algorithm under evaluation is to be applied. Moreover, synthetic data sets can also complement real data allowing researchers to increase their sample size or add variables that are not present in an original data set, enabling new levels of validation and comparison to test and develop new machine learning methods and algorithms (Gonzales et al., 2023).

Several R (R Core Team, 2021) packages are already available to synthesize different types of data (B. Lima, 2021). Although, none of these can be used in the specific case of KAS simulation without having as input your own data.

The simK outcomes are easily verifiable, modifiable, and redefined, which is a clear benefit as a facilitator of transparency and a desired continuous improvement.

Synthetic data sets

Donors' pool

A data frame with information for a pool of simulated donors can be generated with the function `donors_df()`.

For a given number of n rows, a data frame is generated with columns:

- *ID* unique identifier with the prefix 'D';
- *bg* with the blood group generated from the parameter `probs` a vector with the probabilities for groups A, AB, B and O, respectively;
- *A1, A2, B1, B2, DR1, DR2* HLA typing obtained according to origin option (with `replace = TRUE` we can generate a data frame without limitations on the number of rows);
- *age* generated from a Normal distribution with mean and sd given by the user, values truncated by lower and upper boundaries;
- *DR1* when option `uk = TRUE`, Donor Risk Index is computed as described by transplant (Asher, 2020)

HLA population origin has currently as valid options 'PT' for Portuguese (B. Lima & Alves, 2013), and populations available from US National Marrow Donor Program (NMDP, 2023):

- 'API' - Asian / Pacific Islander
- 'AFA' - African American / Black
- 'CAU' - White / Caucasian
- 'HIS' - Hispanic

Defining `seed.number` allows for reproducibility.

Kidney transplant candidates

A simulated waiting list for kidney transplant candidates, can be generated with `candidates_df()`.

For a given number of n rows, a data frame is generated with columns:

- *ID* unique identifier with the prefix 'K';
- *bg* with the blood group generated from the parameter `probs.abo` a vector with the probabilities for groups A, AB, B and O, respectively (here by default, we assumed group O patients are more frequent);
- *A1, A2, B1, B2, DR1, DR2* HLA typing obtained according to origin option (with `replace = TRUE` we can generate a data frame without limitations on the number of rows);
- *age* generated from a Normal distribution with mean and sd given by the user, values truncated by lower and upper boundaries;
- *dialysis* time on dialysis in months, values computed according to patients' blood group and hypersensitisation status ($cPRA > 85$): for patients with blood group O and

88 Hypersensitized time on dialysis obtained from $N(85, 20)$; for those patients blood O
 89 or Hypersensitized $N(70, 20)$; remaining patients have time on dialysis obtained from
 90 $N(35, 20)$;
 91 ▪ *cPRA* patients are classified in groups with probabilities given by `probs.cpra` for 0%,
 92 1%-50%, 51%-85% and 86%-100%, respectively. Within the groups $> 0\%$, *cPRA* are
 93 computed as random values from distributions $P(\lambda = 30)$, $P(\lambda = 70)$ and $P(\lambda = 90)$;
 94 ▪ *Tier* patients are classified in two Tiers as described on POL186/11 – Kidney Transplan-
 95 tation: Deceased Donor Organ Allocation from UK transplant ([National Health Service](#)
 96 [Blood and Transplant, 2017](#)). In Tier A are patients with $MS = 10$ or $cPRA = 100$ or
 97 $timeondialysis > 7years$, all remaining patients are classified as Tier B;
 98 ▪ *MS* matchability score are the deciles obtained from the number of donors on dataset
 99 D10K that are a match to each transplant candidate. This score takes into account a
 100 patient's blood type, HLA type and *cPRA* value. A patient with a $MS = 1$ is defined as
 101 easy to match and a $MS = 10$ as difficult to match ([National Health Service Blood and](#)
 102 [Transplant, 2017](#)).
 103 ▪ *RRI* when `option uk = TRUE`, Recipient Risk Index is computed as described by
 104 transplantr ([Asher, 2020](#)). To compute *RRI*, variables *age*, time on *dialysis* (in
 105 days) and the probability of being *diabetic* (obtained from `prob.dm`) are used. Also, we
 106 assumed all patients were on dialysis at time of listing.
 107 ▪ *urgent* a dicotomic variable that assumes 1 for clinical urgent patients. It's generated
 108 from `prob.urgent`.
 109 HLA population origin can be defined from options: 'PT', 'API', 'AFA', 'CAU' and 'HIS', as
 110 reported for `donors_df()` data frame.
 111 Defining `seed.number` allows for reproducibility.

112 Input data

113 The package presented here (`simK`), returns only fully synthetic data because it only requires
 114 common summary statistics (that can be found for different populations) as inputs to generate
 115 the new microdata.

116 Bug reports and contributions

117 Any bug reporting, feature requests, or other feedback will be welcomed by [submitting an issue](#)
 118 in our repository. When reporting a bug, please ensure that a reproducible example of your
 119 code is included so that we may respond to your issue promptly.

120 Funding

121 This project received the "Antonio Morais Sarmiento" research grant from the Portuguese
 122 Society of Transplantation. This funding had no role in: study design; software development;
 123 the writing of the report; neither in the decision to submit the article for publication.

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2.1.3. KARS

The Kidney Allocation Rules Simulator (KARS) application can be used with data generated by *simK*. This application allows the simulation of the different deceased donor kidney allocation systems provided by the *histoc* package. The KARS application has a simple interface so that anyone interested can try it out, even if they do not have any knowledge of programming in R. A user's manual [35] is provided with the application, which describes simply and clearly all the steps necessary to use this application. The main objective of the KARS application is to allow the comparison between different systems for the allocation of deceased donor kidneys for transplantation. By using different data sets (both for donors and for transplant candidates) and by adjusting the parameters of each kidney allocation system according to the user's preferences, it is possible to obtain different results for comparison. This application doesn't aim to provide a single solution to the problem of kidney allocation. However, it can be used not only to define new rules to be implemented but also to evaluate the implemented rules, as the waiting list of transplant candidates and potential donors also changes.

Awarded for scientific publication in 2023, attributed by the Portuguese Society of Transplantation

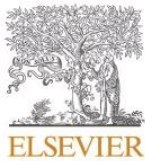
Kidney allocation rules simulator

Bruno A. Lima, Teresa S. Henriques, Helena Alves. *Transplant Immunology* 2022; Volume 72, 101578. DOI: 10.1016/j.trim.2022.101578

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Research article

Kidney allocation rules simulator

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ARTICLE INFO

Keywords:

Kidney transplantation
Clinical decision-making
Allocation system

ABSTRACT

The greatest challenge of any kidney transplant program lies in finding enough organ donors (in number and quality) for all waitlisted transplant candidates. Unfortunately, we must resign ourselves to a manifestly insufficient supply of organs for the current demand. Furthermore we must be able to predict kidney transplant success at organ allocation if we want to minimize the number of patients who return to an already overcrowded waiting list for transplantation. Therefore, the definition of deceased donors' kidney allocation rules on transplantation must be supported by simulations that allow foreseeing, as much as possible, the consequences of these rules.

Here we present the Kidney Allocation Rules Simulator (KARS) application that enables testing different kidney transplant allocation systems with different donors and transplant candidates' datasets. In this application, it is possible to simulate allocation rules implemented in Portugal, in the United Kingdom, in countries within Eurotransplant, and a previously suggested color priority system. As inputs, this application needs three data files: a file with transplant candidates' information, a file with candidates' anti-HLA antibodies, and a file with donors' information. As output, we will have a file with donor-recipient pairs selected according to the kidney allocation system simulated.

When seeking waste reduction while ensuring a fair distribution of organs from deceased donors, the definition of rules selecting donor-recipient pairs in renal transplantation must be based on evidence supported by data. On the continuously changing process for a better distribution of an increasingly scarce resource must, we must be able to predict transplant outcomes when defining the best allocation rules.

1. Introduction

Renal transplantation, when possible, is the most effective treatment for end-stage renal disease (ESRD) patients. Renal transplantation with a living donor before the patient initiates a dialysis treatment would probably be the optimal therapy for these patients. However, many ESRD patients do not have a potential living donor and consequently can only opt for a transplant from a deceased donor. The increasing success of this type of treatment and the growing number of chronic kidney disease patients have resulted in a large number of renal transplant candidates on the waiting list for a limited number of available kidneys

from deceased donors [1].

The philosophy that traditionally supports allocation rules of scarce resources lies on balance between equity (fairness in access for all who need it), medical utility (optimal exploitation of available organ function), and efficiency (including time, cost, organ waste, and geography) [2].

The Council of Europe stated: 'Member states should guarantee that a system exists to provide equitable access to transplantation services for patients which ensures that organs and tissues are allocated in conformity with transparent and duly justifiable rules according to medical criteria.' Moreover: 'The allocation rules should be changed when

Abbreviations: AI, artificial intelligence; cPRA, Calculated Panel Reactive Antibody; EBM, Evidence-based medicine; ESRD, end-stage renal disease; ET, Eurotransplant; ETKAS, EuroTransplant Kidney Allocation System; HLA, Human Leucocyte Antigens; KAS, Kidneys allocation system; KARS, Kidney Allocation Rules Simulator application; KPSAM, Kidney-Pancreas Simulated Allocation Model; MMP, Mismatch Probability; PT, Portugal; txScore, Transplant score; UK, United Kingdom.

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<https://doi.org/10.1016/j.trim.2022.101578>

Received 13 November 2021; Received in revised form 5 March 2022; Accepted 5 March 2022

Available online 9 March 2022

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necessary to ensure similar waiting times for all groups of similar patients on the waiting list' [3].

The greatest challenge of any kidney transplant program lies in finding enough organ donors (in number and quality) for all waitlisted transplant candidates. While we wait for the future that will bring us transplantable artificial kidneys or the possibility to extend organ preservation, allowing us to substantially increase the number of quality organs from marginal donors [4], we must resign ourselves to a manifestly insufficient supply of organs for the current demand.

One way to evaluate the implementation of a new deceased donor kidneys' allocation system (KAS) would be by comparing two transplant candidates' waiting lists. To one list, organs would be allocated by the rules in force, and on the other list, organs would be allocated, applying new rules in evaluation. However, this kind of study design is not feasible due to the deontological questions it raises. Alternatively, we can simulate different candidates waiting lists subjected to different organs' allocation rules.

We live in a so-called data revolution, where better data and statistics can help us make evidence-based decisions. Every day in our lives, we hear people talking about concepts such as big data analytics, artificial intelligence (AI), and its technologies such as machine learning, deep learning or artificial neural networks. Additionally, in the health field, these concepts are increasingly becoming common in research and increasingly being used in decision making. Nevertheless, it is not enough to make data analytics available to health systems; it is also necessary to look for behavioral changes in health professionals and in patients themselves. Through AI, it is possible to make predictions for health outcomes, but final decisions belong to clinicians who depend on their habits and behaviors and will not change just because they are presented with a new source of information often seen as a black box that is difficult to interpret [5].

2. Objective

This paper aims to present a Kidney Allocation Rules Simulator application (KARS app) [6] that allows simulations on deceased donor kidney distributions in different waiting lists. When compared to other well-known computer programs on Simulated Allocation Models [7], KARS app is open-source, user friendly and requires little previous information to be used. This application is free to access and available to any interested (researchers, health professionals, patients groups) without any restrictions. Also, the KARS app allows not only testing current kidney allocation models, as well as testing changes in existing models so that we can understand how this can influence organs' distribution.

3. Material and methods

The ability to predict kidney transplant success at the time of organ allocation is an essential advantage if we want to minimize the number of patients who return to an already overcrowded waiting list for transplantation.

Kidney Allocation Rules Simulator (KARS) application [6] allows testing different kidney transplant allocation systems with different donors and transplant candidates' datasets.

In this application, it is possible to simulate allocation rules implemented in Portugal (PT model), in countries within Eurotransplant (ET model), in the United Kingdom (UK model), and a system previously suggested by Lima et al. [8] (Lima's model). Also, the KARS application allows changing the original rating scores used by the mentioned allocation systems to simulate how these changes are translated into the type of candidates selected for transplantation.

In brief, Portuguese rules on allocation of kidneys from deceased donor (PT model) are in force since 2007 and based on a scoring system that takes in consideration: HLA mismatches between donor and transplant candidate, level of immunization of the candidate, time on

dialysis, and age difference between donor and transplant candidate. Also, hypersensitized candidates (cPRA >85%) are prioritized and after that ordered by their corresponding score.

From KARS app we can simulate a simplified version of EuroTransplant Kidney Allocation System (ETKAS) for first time kidney only candidates with more than 18 years old, no high clinical urgency and not having donated one of their own kidneys. In this simulation for each donor, transplant candidates are sorted as:

1. Senior Program (65+ years of old candidates when the donor has 65+ years);
2. Acceptable Mismatch Program (candidates with a cPRA >85% and without HLA antibodies against HLA's donor);
3. 000 HLA mismatches (candidates without HLA mismatches with the donor);
4. ETKAS points.

Candidates on Senior Program are ordered only based on their time on dialysis. Patients on Acceptable Mismatch Program do not need to have the same blood group as the donor, those ABO compatible also opt to the donor and are ordered according to ETKAS points. All remaining candidates need to have a negative virtual crossmatch with the donor regarding their HLA antibodies and must be ABO identical before ordering by their ETKAS points. When entering in waiting list candidates' Mismatch Probability (MMP) is computed as the probability of receiving a kidney offer with 0 or 1 HLA-A, -B, -DR mismatch based on 1000 kidneys offered. This MMP can be calculated based on Dutch or Portuguese HLA antigen frequencies (this is a KARS app option). Final points for each eligible candidate are obtained from the sum of HLA points, dialysis points and MMP points.

In 2003, a KAS based on a color prioritization of candidates in waiting list for kidney transplantation (Lima's model) [8] was proposed. The aim of this proposal was to define a simple and transparent set of rules that could be used as a baseline in comparison to others KAS. With this model, patients are classified according to their clinical urgency (red color), and regarding their time on dialysis and cPRA value. With an orange color are marked those patients with a cPRA >85% or with a time on dialysis higher than waiting time 3rd quartile. As yellow are classified the patients with a cPRA >50% or with a time on dialysis higher than waiting time median. And, as green are classified all the rest. Also, patients are allocated to donors within the same age group (old to old program), mimicking EuroTransplant senior program.

United Kingdom (UK) deceased donor kidney allocation for transplantation is firstly based on the definition of two ranked Tiers of candidates eligible for the donor:

1. Tier A – patients with match score = 10 or cPRA = 100% or time on dialysis >7 years;
2. Tier B – all other eligible patients.

Within Tier A, transplant candidates are ordered by matchability and time on dialysis. Transplant candidates within Tier B are prioritized according to a point-based system computed with 7 elements:

1. Matchability
2. Time on dialysis
3. Donor-recipient risk index combinations
4. HLA match and age combined
5. Donor-recipient age difference
6. Total HLA mismatch
7. Blood group match

Donor – recipient blood group compatibility is defined as ABO identical, with exceptions:

- B candidates can opt to O donors;

- AB candidates can opt to A donors;
- within Tier A, candidates A and AB can opt to O donors.

The UK transplant module on KARS app simulates the allocation of kidneys to a candidates' waiting list for kidney-only transplants and do not take in consideration geographical criteria.

A more detailed description of the applicability of each model can be found on a detailed user manual [9].

As inputs, this application has three data files: a file with transplant candidates' information, a file with candidates' anti-HLA antibodies, and a file with donors' characteristics. As output, it returns a file with donor-recipient pairs selected according to the kidney allocation system simulated.

For each of the models (PT, ET, UK, and Lima), transplant candidates are excluded considering ABO compatibility and Virtual Crossmatch, and the remaining are ordered for each donor according to the model's rules.

The option 'One donor' displays the top 10 candidates regarding the donor characteristics; for the option 'Multiple donors' each donor is attributed to de 2 best classified candidates, creating a dataset where the number of candidates equals double donors.

From the KARS app [6], we can simulate the rules from each model, setting the scores as we pleased. On the sidebar panel, default punctuation is presented, but users can modify it and apply a new set of scores to reorder candidates on the waiting list for a given donor.

The application is built with *shiny* [10] in R [11].

To test KARS app we also developed the R package `{simK}` [12] that allows to generate synthetic data for a pool of donors and a set of transplant candidates. With this package we generated 280 donors and 2000 transplant candidates using the default parameters from the functions of `{simK}` package as described at its website [12].

In short, a virtual pool of 280 donors was generated using HLA allelic and haplotypic frequencies from Portuguese bone marrow voluntary donors [13]. Donor's age was generated from a normal distribution with mean 55 and standard deviation 15 (trimmed between 18 and 75), blood groups were obtained sampling from options A, AB, B and O with probabilities 0.47, 0.03, 0.08 and 0.42 respectively. Donor risk index was computed considering independent random heights with a normal distribution with mean 165 and standard deviation 20, donors were considered hypertensive with a probability of 0.43, male sex with a probability of 0.55, CMV positive with a probability of 0.9, days of hospital stays with an independent random Poisson distribution with lambda of 4 and estimated glomerular filtration rate was deduced according to donor's age. Likewise, the simulated 2000 candidates' waitlist was generated with HLA typing from Portuguese bone marrow donors [13] and non-HLA characteristics age ($N(45, 15)$), blood group and cPRA were considered independent and randomly distributed while time on dialysis was obtained conditionally to blood group and cPRA higher than 85%. Candidates are classified by Tier A or B, as previously described. Matchability Score are the deciles obtained from the number of donors on a dataset of 10,000 simulated donors that are a match to each transplant candidate. Recipient Risk Index was computed according to age, time on dialysis and a probability of being diabetic of 0.12.

Also, a dataset with HLA antibodies for each sensitized candidate was generated according to their respective cPRA value. Antibodies are randomly withdraw from all possible HLA antibodies that are not self-HLA typing, at each draw a virtual PRA is computed and when we reach candidates' cPRA value, we stop drawing.

Results are presented as mean ($\pm$ standard deviation) for continuous variables or as frequencies (percentages) for categorical one, p -values lower than 0.05 were considered statistically significant.

4. Results

A simulated waiting list of 2000 kidney transplant candidates have a mean age ($\pm$ standard deviation) of 45.5 (± 12.8) years old. Also, 924

(46.2%) candidates are blood group O, 870 (43.5%) are group A, 157 (7.8%) group B and 49 (2.4%) are AB blood group. This group of candidates has a mean time on dialysis of 53.5 (± 27.3) months, and 203 (10.2%) have a cPRA value higher or equal to 85%.

Likewise, a pool of 280 simulated potential deceased donors was generated. This group has a mean age of 57.8 (± 10) years old, and 122 (43.6%) are blood group O, 138 (49.3%) blood group A, 15 (5.4%) blood group B, and 5 (1.8%) are blood group AB.

For both groups (candidates and donors datasets), HLA genotype frequencies were derived from previously published Portuguese bone marrow voluntary donors HLA frequencies [13].

For each output ('One donor' or 'Multiple donors'), we have a resume for the selected donor-recipient pairs as: recipients' blood groups frequencies, mean age, mean time on dialysis, cPRA frequencies, HLA mismatches, and median transplant score as a measure of good transplant outcome. The characteristics' resume of the presented selected candidates allows for the comparison between models. With the same candidates' and donors' files, we will have different outputs for each simulation we run.

On the 'One donor' option, we present, as default, a possible donor with 60 years old, blood group A and with HLA-A1,2-B7,8-DR1,3. For this example donor, the app returns the first 10 candidates from simulated candidates' data (candidates and candidates' antibodies) uploaded in KARS app. Using default parameters per model, candidates' uploaded data and for our default donor, in models PT, ET and Lima the first candidate selected has the ID K694: an hiper immunized candidate with 2 HLA mismatches and 100 months on dialysis. Also candidates with ID K641 and K1517 appear in both top 5 of PT and ET models, these candidates having a cPRA $> 85\%$ and the former also having only 3 HLA mismatches. Candidate with ID K641 is also selected in the top 5 from Lima model due to its number of mismatches. The top 5 candidates from UK model all belong to Tier A. This Tier includes patients with a match score = 10 (which corresponds to a matchability value = 1745.9, the highest possible value), or patients with a cPRA = 100% or patients with at least 7 years (84 months) of waiting time on dialysis. Candidates K641 and K1517, also appear in the top 5 candidates from UK model.

By way of example, if we use the simulated data and the default parameters per model from KARS app, on the 'Multiple donors' option, we will obtain 4 different datasets with 560 selected donor-recipient pairs per models PT, ET and Lima, while for UK model only 555 pairs are selected. For this simulation, as reported in Table 1, the set of recipients selected through UK model have an higher percentage of AB and B blood groups while the higher percentage of O recipients are selected through Lima and PT models. Also, recipients' median ages are close between the models, although UK model is the one with a lower median receptor's age. On the other hand, Lima model is the one that selects a lower number of hiper immunized candidates (116).

Using Lima's model as reference (Table 1), candidates selected by ET and UK models have statistically significant lower median time on dialysis ($p = 0.007$ and $p = 0.004$, respectively). Also, median receptors age selected by UK model is statistically significant lower than median age from candidates selected by Lima's model. In contrast, when compared txScore from receptors selected with Lima's model with those selected by the remaining tree models, Lima is the one with an higher value being the differences statistically significant.

Conversely, with KAS from EuroTransplant and with the one by Lima et al. [8], selected donor-recipient pairs have the higher frequencies for 0 to 3 HLA mismatches (60.7% and 73.9%, respectively) while, UK model frequency is way lower with only 42.7% (Fig. 1). Additionally, median time on dialysis from candidates selected by UK transplant is statistically significant lower when compared with candidates select by Lima and PT models (Fig. 2).

5. Discussion

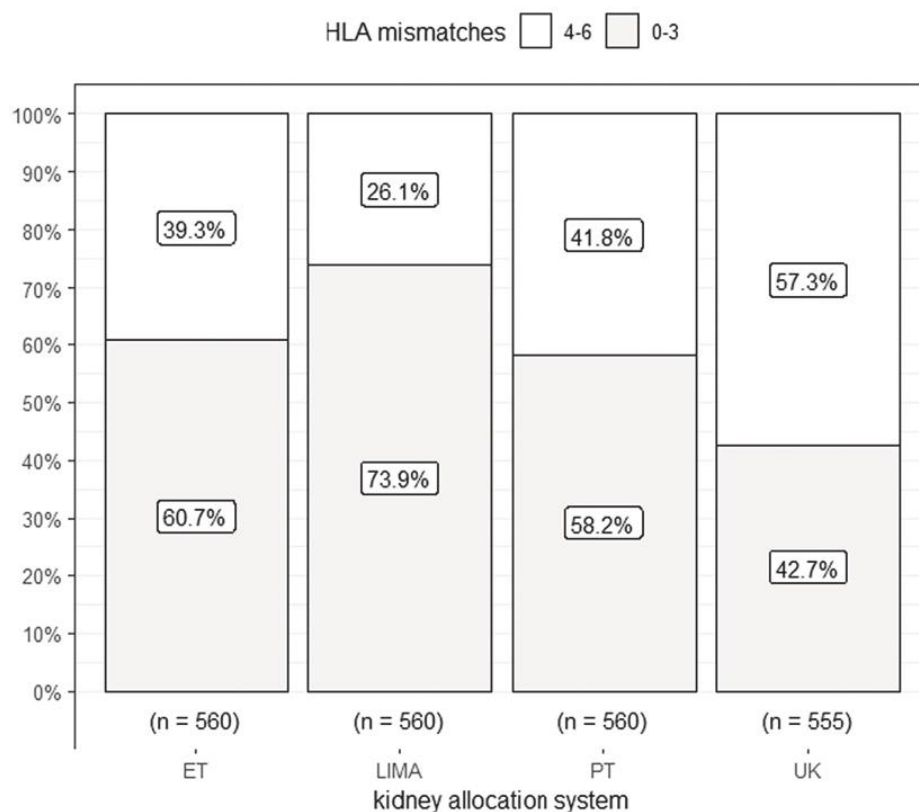
The discussion on new kidneys allocations proposals cannot be made

Table 1

Descriptive results for 140 donor-recipient pairs selected according to each one of the 4 models. And comparison with model Lima et al.

	Lima et al.	EuroTransplant	Lima vs ET	Portugal	Lima vs PT	UK transplant	Lima vs UK
Blood group			0.12 ¹		>0.9 ¹		<0.001 ¹
A	276 (49%)	297 (53%)		276 (49%)		252 (45%)	
AB	10 (1.8%)	11 (2.0%)		10 (1.8%)		49 (8.8%)	
B	30 (5.4%)	43 (7.7%)		30 (5.4%)		60 (11%)	
O	244 (44%)	209 (37%)		244 (44%)		194 (35%)	
receptores' age (years)	50 (39, 65)	50 (39, 65)	0.8 ²	48 (38, 59)	0.001 ²	47 (36, 57)	<0.001 ²
time on dialysis (months)	70 (56, 86)	66 (48, 84)	0.007 ²	71 (53, 88)	0.6 ²	65 (36, 89)	0.004 ²
Hiper Immunized	116 (21%)	196 (35%)	<0.001 ¹	189 (34%)	<0.001 ¹	175 (32%)	<0.001 ¹
HLA miss matches			<0.001 ¹		<0.001 ¹		<0.001 ¹
0	42 (7.5%)	59 (11%)		91 (16%)		26 (4.7%)	
1	58 (10%)	29 (5.2%)		34 (6.1%)		17 (3.1%)	
2	168 (30%)	124 (22%)		76 (14%)		72 (13%)	
3	146 (26%)	128 (23%)		125 (22%)		122 (22%)	
4	104 (19%)	101 (18%)		109 (19%)		119 (21%)	
5	32 (5.7%)	83 (15%)		93 (17%)		122 (22%)	
6	10 (1.8%)	36 (6.4%)		32 (5.7%)		77 (14%)	
TxScore	62 (59, 67)	61 (57, 67)	0.042 ²	60 (56, 64)	<0.001 ²	61 (58, 65)	0.002 ²

Statistics presented: n (%); median (IQR);

¹ p-value for Chi-square test.² p-value for Mann-Whitney test.**Fig. 1.** HLA mismatches' proportions for each Kidney allocation system.

ET EuroTransplant model; LIMA Lima et al. Model; PT Portuguese model; UK UK transplant model;

0-3 zero to 3 HLA mismatches; 4-6 four to six HLA mismatches.

only in a rhetorical plan, hoping that at the moment a new solution is implemented, everything will run for the best. Before implementing new rules, it is necessary to test them in order to dissipate, as much as possible, doubts questioning implementation's success.

Thus, the definition of rules for allocating deceased donors' organs

must be based on solid clinical criteria. They should seek the best use of the available organs, avoiding their waste while promoting access to transplants [14]. In addition, the possibility of dialysis as a treatment for ESRD patients implies that only in exceptional cases can a transplant be seen as an urgent treatment on which a patient's life may depend [15].

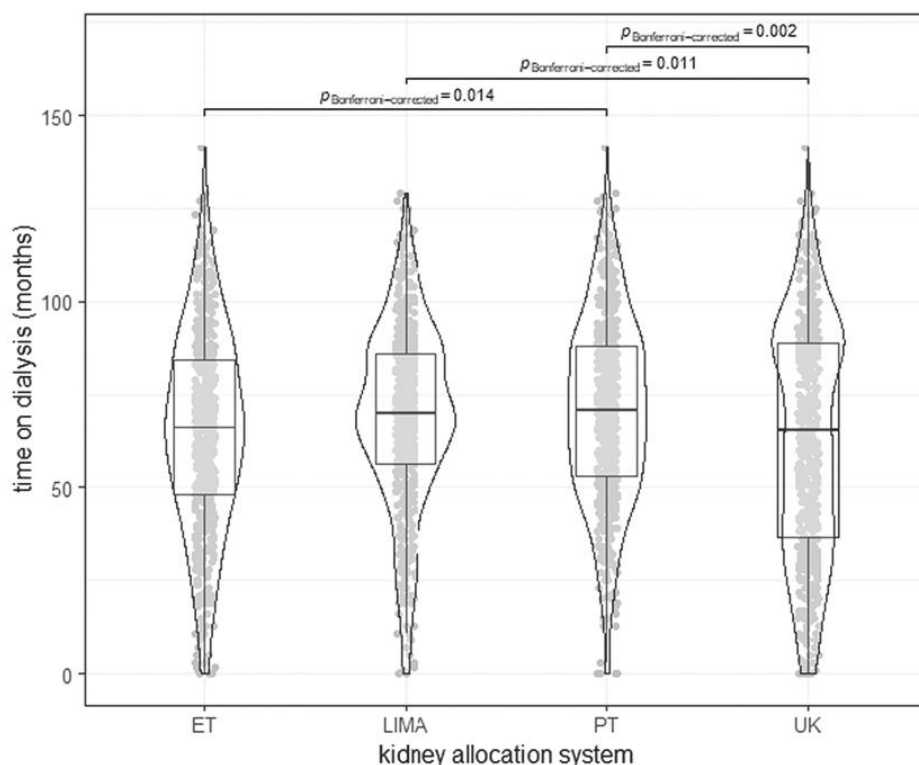


Fig. 2. Time on dialysis (months) distribution by kidney allocation system. Non-parametric pairwise test. ET EuroTransplant model; LIMA Lima et al. Model; PT Portuguese model; UK UK transplant model;

With this application, we seek to provide a tool that allows us to compare different organ allocation systems with different rules rather than presenting a proposal for the best KAS [16].

A deceased donor KAS should be periodically assessed, allowing possible modifications based on data evolution and correlation with recorded outcomes. In addition, this system should be transparent and understandable for both health professionals and transplant candidates, allowing the best use of available organs [17].

We used Lima's model as baseline and we compared the characteristics of select donor-recipient pairs from other models to the latter. Although, in the simulation presented here, Lima's model is the one with a higher percentage of pairs with up to 3 HLA mismatches it is also the one with a lower percentage of hypersensitized patients and with a higher median age for the selected candidates.

Our app allows the use of different HLA typing resolution both for donors and candidates input datasets. Although, HLA typing resolution for HLA-A, -B and -DRB1 loci must be consistent not only for donors and candidates but also for HLA-antibodies identified in the second dataset. For instance, if HLA typing for candidates is in serological resolution so donor's typing and identified HLA antibodies must be in serological resolution too. In like manner, for a genotyping resolution all HLA must be consistent. When alleles have a 0 on the left (meaning A01 or DR04) it can be omitted only if this is always the case, as we do in our example data. By the same token, on our example data, if donors have the values 1 and 4 for columns DR1 and DR2, so the correspondent HLA antibodies will be DR1 and DR4, respectively.

Discussion on deceased donor kidneys allocation tends to be based on the importance that each person gives to a more utilitarian distribution of this scarce good (the best organs should be assigned to those patients who better will use them) or a fairer distribution of it (giving

relatively equal access to all patients without taking into account possible outcomes of each transplant) [15].

Patients vary in their life expectancy as organs vary in their quality. Organs with higher expected longevity should not be transplanted into candidates with a short-expected survival time [17]. Allocating kidneys with a long-expected survival time in candidates with an expected long survival after transplantation may be a response to the lack of organs for transplantation since it would reduce the number of candidates for a re-transplant [15]. Utilitarian criteria for kidney donation from deceased donors minimize the differences between life expectancy for a kidney and life expectancy for its recipient. However, they may jeopardize reliance on the allocation system [18].

There is no consensus on addressing policies that conflict with fairness and efficiency objectives, i.e., those that can improve efficiency while increasing health inequalities or those that improve justice while decreasing care efficiency [19]. For example, regulations based on the principles of fairness require that patients have similar waiting times or that 'the sickest' be prioritized to receive a transplant. However, both organ and patient survival depend on age, sex, histocompatibility, immune response, body habits, causes of disease, causes of death, and other characteristics of the patients and donors [20]. A compromise between fairness and utility in transplantation is more likely achieved through sophisticated and careful donor-recipient matching [21].

Artificial Intelligence is a promising tool for clinical practice. However, the quality of the data on which it is based and the best way to integrate it into the clinical process still need to be clarified [22]. In machine learning, mathematical models are designed to perform generalizations from input data and identify patterns contained in that data. For instance, machine learning models developed for the prediction of graft rejection and graft failure following kidney transplantation have

been increasingly used [23,24]. Notwithstanding, the selection and application of those models will always depend on human judgment to take into account eventual cultural, political, legal and ethical constraints [25]. Data science, as an extension of statistical sciences powered with advances in computational data analysis, allows designing computer simulation models as a reliable way to test different equity criteria when defining organ allocation rules. Yet the final choice of any KAS requires a judgment of value on what is equitably acceptable. Additionally, for any simulation model, the quality of the data to be tested is a key factor for the accuracy of the results [26,27].

On 2011, Nielman *et al* [28] presented a computer simulation to evaluate the impact of epitope matching and compare it with current ETKAS. For this purposed they generated a simulated population of 400,000 individuals and from it a waiting list of 10,400 patients. Our approach is quite different, KARS app is intended to be used by anyone, with data that could represent a current waiting list and test how different kidney allocation models and their modifications can affect that waiting list. Here, we present results for a simulated waiting list of 2000 transplant candidates a number nearby to the Portuguese waiting list. Kidney transplant waiting lists are modelled by the allocation systems enforced to them, so with our app we can also fine-tune the applied allocation system, slightly changing their parameters and observe the changes on the selected donor-recipient pairs.

KARS app was designed to be user friendly and each allocation run must be as simple as possible in order to be useful for any clinician or researcher even those who are not computer experts. When compared to Kidney-Pancreas Simulated Allocation Model (KPSAM) [7] from the Scientific Registry of Transplant Recipients, our application requires less information to run and so, can be used as a first approach to define hypothesis that afterwards can be tested on KPSAM.

Evidence-based medicine (EBM) [29] aims to combine clinicians' experience with the best evidence from quality clinical research, and considering the patient's values, expectations and context. Since EBM is increasingly used as the standard to define good practices in healthcare, there is a need to develop prognostic tools that can be used in decision-making. Therefore, the definition of deceased donors' kidneys allocation rules on transplantation must be supported by simulation exercises that allow foreseeing, as much as possible, the consequences of these rules. Even so, the process of legitimizing a new and equitable organ allocation system must be founded on the definition of clear and transparent procedures that can allow not only a continuous evaluation of the new system, but even its eventual reversion [30].

When seeking waste reduction while ensuring a fair distribution of organs from deceased donors, the definition of rules selecting donor-recipient pairs in renal transplantation must be based on evidence supported by data. With this purpose, we also need to be able to predict transplant outcomes to define the best allocation rules [31]. As a measure of predicting the outcome of a transplant, we used the score defined by Molnar *et al* [32] for mortality or graft failure as a combined outcome, computing the estimated 5-year event probability. This score is based on data collected at the time of transplantation rather than posttransplant data.

6. Conclusions

Implementing a new deceased donor's kidney allocation system intended to be equitable, transparent, and intelligible must be based on simulations of multiple scenarios. The application presented here allows simulating different allocation rules on different candidates' waiting lists and, with it, we hope to contribute to the continuously changing process for a better distribution of an increasingly scarce resource.

Authors' contributions

Conception and design: BL

Analysis and interpretation of data: BL, TH.

Drafting the article and revising it: BL, TH, HA.

Providing intellectual content: BL, TH, HA.

Approval of final version: BL, TH, HA.

Conflict of interest statement

The authors declare that they have no conflicts of interest to disclose.

Funding

This project received the "Antonio Morais Sarmiento" research grant from the Portuguese Society of Transplantation. This funding had no role in: study design; collection, analysis or interpretation of data; in the writing of the report; neither in the decision to submit the article for publication.

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2.1.4. Score Tx

The development of risk scores that can predict the outcome of the donor-recipient pair in transplantation has enabled better decision making, either in organ allocation or in the clinical management of patients. The KAS from the United States uses two different scores: an Estimated Post Transplant Survival (EPTS) score (based on the patient's characteristics) to summarise the fitness of the patient; and a Kidney Donor Percentual Index (KDPI), which combines donor and transplant characteristics, to summarise the risk of graft failure. Molnar *et al.* [54] also proposed the TRANSPLANTSCORE to predict posttransplant outcomes using only pretransplant information. Furthermore, in 2003, Nyberg *et al.* [54] developed and presented a scoring system to grade deceased donors' kidneys based on the success of renal transplantation. In particular, this score is a quantitative approach to assessing kidneys from expanded criteria donors. We have therefore developed the Score Tx application [55], which compiles some risk scores that can be used to predict the outcome of the donor-recipient pair in transplantation.

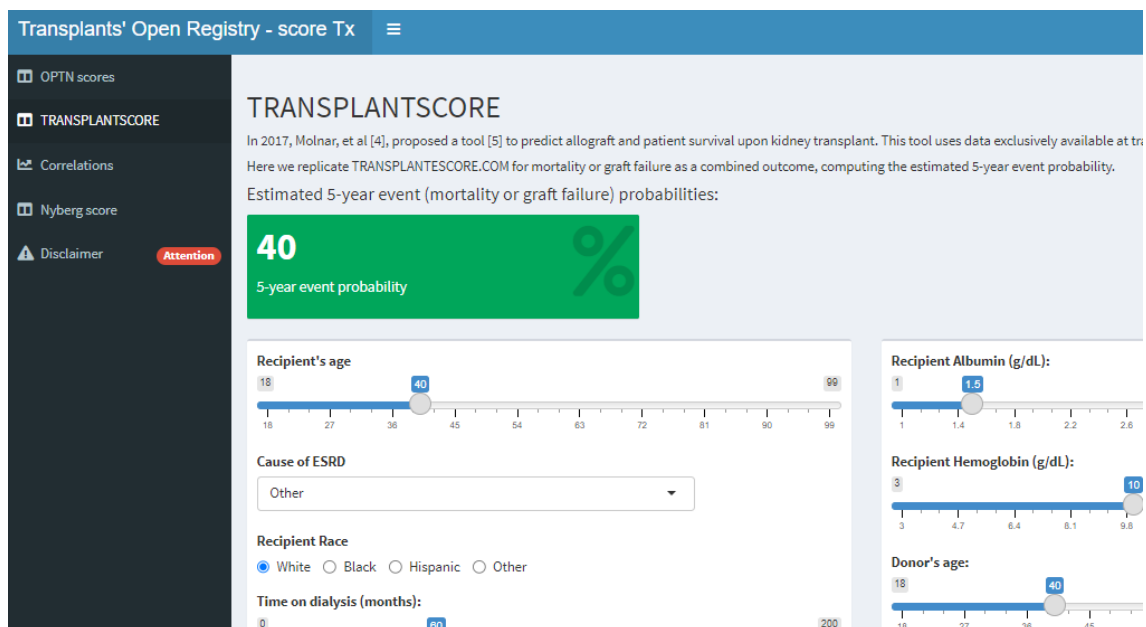


Figure 1. scoreTx application [55] with the computation of TRANSPLANTSCORE probability.

The TRANSPLANTSCORE, which estimates the 5-year event (probability of mortality or graft loss) (Figure 1), is used in the KARS application because it requires only data available at the time of transplantation for its calculation. Clinical and demographic characteristics of both the donor and the kidney recipient are used to calculate this probability.

If we could have a crystal ball at transplantation, we would like to be able to predict the time to graft failure or patient survival. Of course, the scores presented here are not a crystal ball, but they can help us compare potential donor-recipient pairs and make evidence-based decisions.

2.1.5. cPRA calculator

The calculated PRA (cPRA) value is an estimate of the probability that the next available donor for a given transplant candidate will have a positive virtual crossmatch. This value is calculated not only from the anti-HLA antibodies of the transplant candidate but also from the allele and haplotype frequencies of the population from which the donors come. In the case of the Portuguese cPRA calculator application [30], cPRA values are obtained using the allelic and haplotypic HLA distributions [52] previously published for Portuguese volunteer bone marrow donors [56]. In this application, which functions as a simple calculator, the user selects the unacceptable HLA antigens for a given patient and obtains the cPRA value (Figure 2).

Portuguese cPRA calculator

This page should be cited as: Lima BA, Alves H. Portuguese calculated panel reactive antibodies online estimator. HLA.

Select unacceptable HLA from which candidate is sensitized:

HLA-A*

☐ A*01 ☐ A*02 ☐ A*03 ☐ A*11 ☐ A*23 ☐ A*24 ☐ A*25 ☐ A*26 ☐ A*29 ☐ A*30
☐ A*36 ☐ A*66 ☐ A*68 ☐ A*69 ☐ A*74 ☐ A*80

HLA-B*

☐ B*07 ☐ B*08 ☐ B*13 ☐ B*14 ☐ B*15 ☐ B*18 ☐ B*27 ☐ B*35 ☐ B*37 ☐ B*38
☐ B*44 ☐ B*45 ☐ B*46 ☐ B*47 ☐ B*48 ☐ B*49 ☐ B*50 ☐ B*51 ☐ B*52 ☐ B*53
☐ B*58 ☐ B*67 ☐ B*73 ☐ B*78 ☐ B*81 ☐ B*82

HLA-C*

☐ C*01 ☐ C*02 ☐ C*03 ☐ C*04 ☐ C*05 ☐ C*06 ☐ C*07 ☐ C*08 ☐ C*12 ☐ C*14

HLA-DRB1*

☐ DRB1*01 ☐ DRB1*03 ☐ DRB1*04 ☐ DRB1*07 ☐ DRB1*08 ☐ DRB1*09 ☐ DRB1*10
☐ DRB1*14 ☐ DRB1*15 ☐ DRB1*16

Clean

Compute

Selected anti-HLA antibodies:

cPRA percentage value:

Figure 2. Computation of cPRA given HLA alleles as inputs [57].

The R package *simK* [46] also has a function to obtain a virtual PRA value from a patient's vector of anti-HLA antibodies and a user-defined dataset of HLA genotyping from a pool of potential donors.

Awarded for scientific publication in 2019, attributed by the Portuguese Society of Transplantation

Portuguese calculated panel reactive antibodies online estimator.

Bruno A. Lima, Helena Alves. *HLA* 2019; 93(6):445-450. DOI: 10.1111/tan.13516

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ORIGINAL ARTICLE

Portuguese calculated panel reactive antibodies online estimator

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Calculated panel reactive antibodies (CPRA) is a sensitization measure used to classify and prioritize transplant candidates in different kidney transplant allocation systems. CPRA is based on identification of HLA unacceptable on potential organ donors making a transplant candidate ineligible for transplantation. Here, we present a CPRA online estimator based on HLA allelic and haplotypic frequencies from Portuguese donors. We also compare the values we obtained from our CPRA estimator (Portuguese [PT]-CPRA) against CPRA values obtained from: Eurotransplant virtual PRA calculator (ET-CPRA); Canadian CPRA calculator (Canadian [CN]-CPRA) and Organ Procurement and Transplantation Network CPRA calculator (United States [US]-CPRA). When we analyzed correlations between CPRA values obtained from pairs of calculators, we observed that they are significantly and highly correlated. Bland-Altman plots for the comparison between PT-CPRA calculator against the other calculators, show higher differences between PT and CN than between PT and ET and PT and US. Also, the lowest value for Lin's concordance coefficient was obtained for the comparison between PT and CN calculators. CPRA values reliability depend on donors' pool from which it is calculated and it is crucial for classify correctly highly sensitized patients. A CPRA calculator must use donors' HLA frequencies similar from those who would be actual organ donors.

KEYWORDS

anti-HLA antibodies, calculated panel reactive antibodies, highly sensitized patients, kidney transplantation

1 | INTRODUCTION

Exposures to HLAs occur in blood transfusions, previous pregnancies and transplants and are the reasons for patients' sensitization.¹ We classified as sensitized patients, those who have alloantibodies reactive against different HLA alleles. This HLA sensitization is a barrier that rises in candidates' access to transplantation, being a challenge for any renal transplantation program. Specifically, patients with anti-HLA antibodies have an increased risk of hyperacute rejection, acute accelerated rejection, antibody-mediated rejection, delayed graft function, and long-term complications when transplanted from donors with HLA corresponding to those antibodies.²

Traditionally, histocompatibility laboratories measured transplant candidates' sensitization through panel reactive antibodies (PRA) aiming to estimate the percentage of possible donors with whom a patient will have a positive crossmatch. PRA complement-dependent cytotoxicity (CDC) tests a patient's serum against a panel of donors' cells (generally about 50 donors arbitrarily chosen) allowing percentage calculation of positive reactions against tested donors' antigens, that is, an 80% PRA means that the patient's serum reacted against 80% of the total donor's antigens. In other words, the higher the PRA value, the lower the transplantability rate of a given patient.³ Thus, sensitized candidates have limited access to transplantation, and this limitation is proportional to their degree of sensitization.²

As an alternative to the dated PRA test, the calculated PRA (CPRA) value uses HLA antigens for which a patient is sensitized (and are listed as unacceptable) and estimates the percentage of potential donors on the population with these antigens.² This CPRA value can be calculated with known HLA frequencies from a representative population's sample of potential kidney donors for transplantation. Likewise, transplant candidate's CPRA gives us the percentage of potential organ donors having at least one HLA antigen to which the candidate is sensitized and consequently is not available for transplantation to this specific candidate.

2 | AIM

The aim of this study is to compare CPRA values obtained from an online estimator based on allelic and haplotypic HLA frequencies from a Portuguese (PT) population with CPRA values obtained from well-established CPRA calculators openly and widely available.

3 | METHODS

We simulated a cohort of 100 patients with HLA typing frequencies similar to those previously published for PT bone marrow donors.⁴ To each one of these patients, we randomly attributed HLA-A, -B and -DR unacceptable antigens different from their own HLA typing. With these attributed antibodies per patient, we were able to compute their respective CPRA values for HLA class I and II combined. For each patient, we computed four CPRA values. The first CPRA value was calculated according to the formula previously published by others⁵ and using HLA allelic and haplotypic frequencies of 37.993 unrelated PT bone marrow donors.⁴ We deployed an R package⁶ to calculate this CPRA values from PT HLA frequencies (PT-CPRA), and with this package we developed an online estimator⁷ available to anyone interested in its use. In this online calculator, only low-resolution HLA unacceptable alleles are allowed, once donors' HLA frequencies used for calculation are available on low resolution. With the same patients' data, we also aimed to obtain CPRA values from: Eurotransplant (ET) virtual PRA calculator (ET-CPRA)⁸; Canadian CPRA calculator (CN-CPRA)⁹; and Organ Procurement and Transplantation Network (OPTN) CPRA calculator (United States [US]-CPRA).¹⁰ With this intention, we contacted ET, Canadian Blood Services (CBS), and OPTN to know their availability to compute their CPRA values for each one of our simulated patients if we send them our data. Both ET as CBS kindly agreed to return to us their results from our patients' data. The answer from OPTN requested a fee of \$250 to \$1000 that we could not support, so we decided to compute CPRA values directly

from OPTN CPRA calculator.¹⁰ Values obtained for each one of the four CPRA calculators (PT, ET, CN, and US—C values) were used to classify patients as low sensitized (CPRA < 20%), as sensitized (CPRA between 20% and 79%), and as highly sensitized (CPRA ≥ 80%) within each calculator.

Pearson's rho and correlation test were used to compare results from each calculator and to assess correlation between them; agreement between CPRA calculation methods was analyzed by Bland-Altman plot. Concordance correlation was assessed by Lin's concordance coefficient (LCC). Cohen's kappa coefficient was used to access agreement for grouped CPRA values (CPRA < 20%; CPRA between 20% and 79%; and CPRA ≥ 80%).

All statistical analysis and graphical representations were performed through RStudio an environment to R programming language.

4 | RESULTS

For our simulated cohort of 100 patients, we obtain a mean (±SD) of 54.85% (±24.99) for PT-CPRA, the highest mean value, when compared to 50.70% (±22.53), 46.94% (±22.29), and 49.99% (±22.35), respectively, for ET-CPRA, CN-CPRA, and US-CPRA calculators. As shown in Figure 1, PT-CPRA values also have the highest median value and wider values' range when compared to the values obtained from the others calculators. When we analyzed correlations between CPRA values obtained from calculators' pairs (Figure 2), we observed that calculators are significantly and highly correlated with the lower correlation coefficient of 0.934 obtained for the correlation between PT and CN calculators. Bland-Altman plots for the comparison

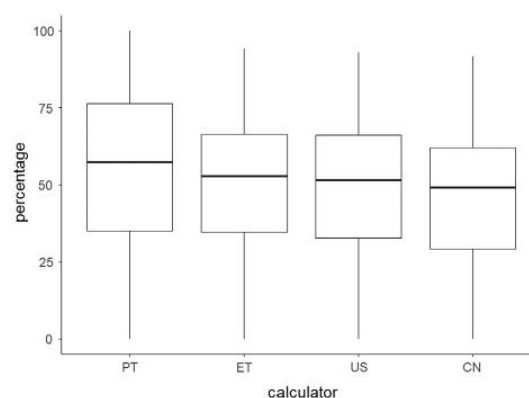


FIGURE 1 Boxplots with CPRA values' distributions for each one of the analyzed calculators. In each box are represented median (darker line), upper and lower quartiles (respectively, 75 and 25 percentiles); whiskers show minimum and maximum values. Values from PT calculator have an higher median CPRA value and also higher maximum value. CN, Canadian; ET, Eurotransplant; PT, Portuguese; US, United States

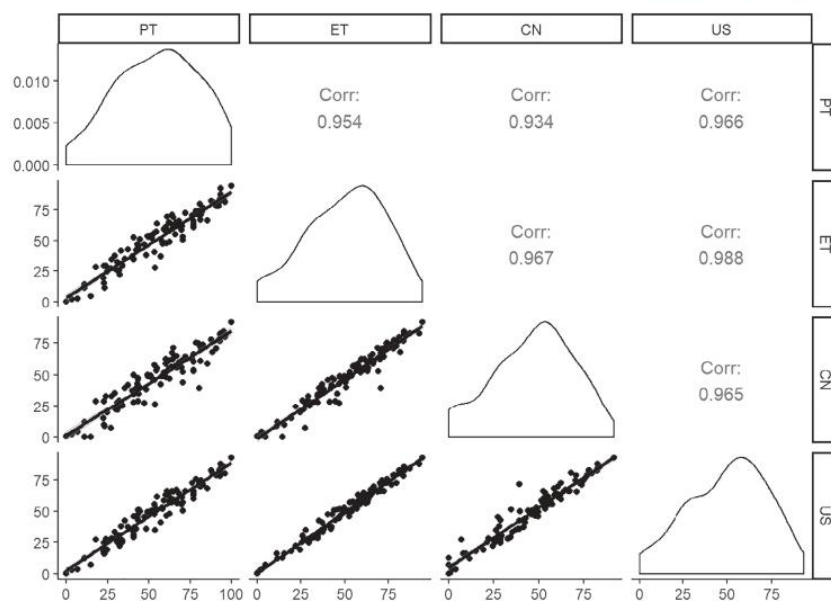


FIGURE 2 Correlation matrix with correlations between pairs of calculators and density plots for CPRA values obtained from each one of the calculators. CN, Canadian; Corr, Pearson correlation coefficient between calculators; CPRA, calculated panel reactive antibodies; ET, Eurotransplant; PT, Portuguese; US, United States;

between PT-CPRA calculator against the other calculators (Figure 3), show higher differences between PT and CN than between PT and ET and PT and US. Also, the lowest value for LCC was obtained for the comparison between PT and CN calculators.

CPRA values obtained from each one of the calculators were grouped in three sensitization classes: low sensitized (CPRA < 20%), sensitized (CPRA between 20% and 79%)

and as highly sensitized (CPRA > 79%). When compared sensitization classes' frequencies between PT calculator and the others calculators, we obtained the highest Cohen's kappa for the comparison against ET calculator (0.67) and the lowest against CN calculator (Table 1). Also, as shown in the agreements' plots (Figure 4), the highest agreement between calculators within three sensitization classes is seen for PT against ET calculator.

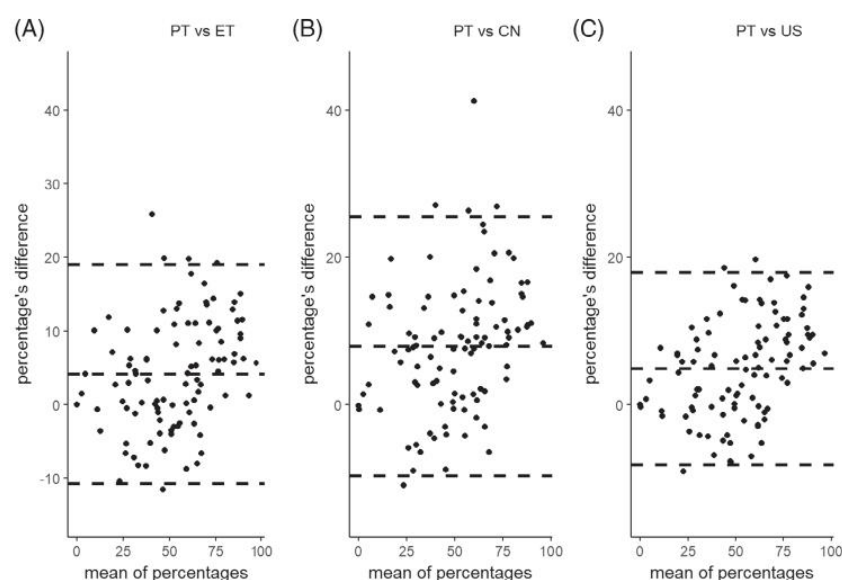


FIGURE 3 Bland-Altman plots of: [A] PT-CPRA against ET-CPRA, LCC = 0.94 (95% CI = 0.91-0.96); [B] PT-CPRA against CN-CPRA, LCC = 0.88 (95% CI = 0.83-0.91); [C] PT-CPRA against US-CPRA, LCC = 0.94 (95% CI = 0.92-0.96). CI, confidence interval; CN, Canadian; CPRA, calculated panel reactive antibodies; ET, Eurotransplant; LCC, Lin's concordance coefficient; PT, Portuguese; US, United States

TABLE 1 CPRA values distributed by sensitization classes. Estimate Cohen's kappa statistics and test for the null hypothesis that the extent of agreement is the same as random ($\kappa = 0$) between PT-CPRA values and each one of the other calculators

Calculators	Sensitization classes			Cohen's kappa	Kappa 95% confident interval
	0%-19%	20%-79%	80%-100%		
PT	8	73	19	1 ^a	
Eurotransplant	10	80	10	0.67	0.5-0.84
Canadian	12	83	5	0.47	0.26-0.68
United States	11	80	9	0.62	0.44-0.8

Abbreviations: CPRA, calculated panel reactive antibodies; PT Portuguese.
^aReference.

5 | DISCUSSION

Unlike PRA, CPRA is a more accurate candidate's transplantability measure, because we calculate it from unacceptable HLA antigens that will make donors unprofitable because of a predicted positive crossmatch (virtual crossmatch).² Replacing PRA with CPRA as a sensitization measure for renal transplant candidates gives us a more uniform and more consistent indicator between different laboratories, additionally, it reflects better the chances of finding a compatible donor.¹¹

In 2009, OPTN/United Network Organ Sharing (UNOS) adopted CPRA as a transplant candidate's sensitization measure to assign extra points in their deceased donor kidney allocation system. After its application, there was a decrease in the number of kidney refusals because of positive crossmatches; and further, an increasing efficiency in the distribution of deceased donor kidneys for transplantation in the US.¹² When implemented by OPTN/UNOS in their kidney transplant allocation system, there was also an increase in the number of transplanted sensitized candidates, although there was a decrease in kidney offers to these candidates proportional to their CPRA.¹³ The use of CPRA as a standardized measure of sensitization in deceased donors' kidney allocation, in addition to promoting an effort to compensate

disadvantages of broadly sensitized patients,³ allows a more efficient organ allocation by reducing the number of positive crossmatches in donor-recipient pairs selection. Once we estimate CPRA from unacceptable antigens, the candidates only opt for donors who do not have these antigens, so an offer to a transplant candidate with a high CPRA value will have a high probability of having an actual negative crossmatch.²

Transplantation success of highly sensitized candidates depends on histocompatibility results reliability for both HLA typing of donors and candidates and in antibodies' identification that permits applying virtual crossmatch and estimating CPRA values.¹⁴ Using Luminex recombinant single antigens essays permits the identification of antibodies HLA-specific with high acuity and sensitivity³; moreover, the presence of anti-donor antibodies detected by single antigen beads even with a negative CDC crossmatch is associated with a higher incidence of acute antibody-mediated rejection in the first year after transplantation.¹⁵ Nevertheless, the high sensitivity of solid phase tests used to determine anti-HLA antibodies implies that not all antibodies detected have clinical relevance for transplantation.² Antibodies detected only by more sensitive methods such as single antigen bead in serum from CDC and enzyme-linked immunosorbent assay negative patients and without a history

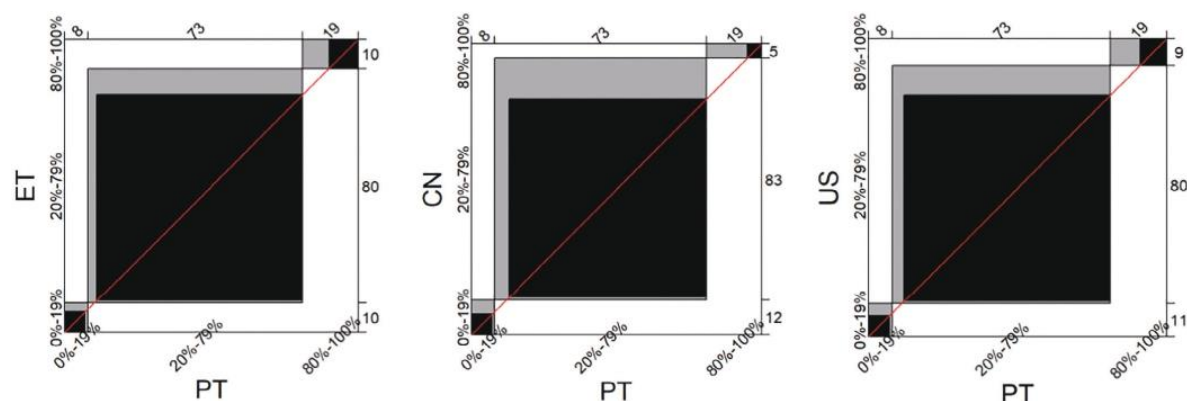


FIGURE 4 Agreement plots between PT-CPRA calculator and the others calculators for within three sensitization classes. In black are represented agreement areas between PT calculator and the other calculators by sensitization classes; gray areas represent disagreements. Agreement plot between PT and ET calculators has small gray areas reflecting higher agreement. CN, Canadian; CPRA, calculated panel reactive antibodies; ET, Eurotransplant; PT, Portuguese; US, United States

of sensitization may translate only false positive results and as such we should not consider it as nonacceptable for CPRA estimation.¹⁶ Concerning retransplant candidates, antigens from previous transplants' HLA mismatches may also be considered in CPRA estimation, even if they have not been identified in the laboratory. In these previous transplants, natural reaction of receptors cells' contacts leads to the creation of memory cells that if stimulated can result in the appearance of donor specific antibodies at a future transplant.

We must distribute deceased donor kidneys for transplantation as equitably and fairly as possible to optimize the use of such a scarce resource.¹ With this goal in mind, CPRA values will be a measure as accurate as reliable are HLA (allelic and haplotype) frequencies of the donors used for its estimation, because we can estimate them from haplotypes' reconstruction based on Hardy-Weinberg equilibrium assumptions.¹⁴ Indeed, the use of data from local donors' representative of future potential organ donors is essential to ensure CPRA estimation accuracy. Furthermore, because we can estimate CPRA from HLA allele and haplotype distributions in the population, this is the most consistent measure to define a patient's sensitization.¹³ As far as we know, HLA frequencies⁴ used in our online CPRA estimator are from the more extensive and comprehensive publicly available group of HLA-typed PT donors. Although these HLA allelic and haplotypic frequencies are only available on low resolution typing and consequently unacceptable HLA listed on our calculator⁷ are only those identified on our PT donors.

The differences we found between the CPRA values of different calculators are due to differences in the genotypic frequencies of the respective populations from which they are originated. Besides, an accurate measure of the value of CPRA is fundamental for a better characterization of hypersensitized patients on transplant waiting lists.¹⁷ Discrepancies between CPRA values result in a poor classification of transplant candidates on their degree of sensitization and consequently, affects their prioritization in the waiting list for transplantation, so it is essential to use a donor pool from the same region of transplant candidates.¹⁴ As we expected, CPRA values obtained from our calculator are more similar to those we obtained from ET calculator, mainly because HLA frequencies from PT donors are more alike with other European donors than North American (CN and from the US) donors.

CPRA value and virtual crossmatch are two sides of the same coin, and their application in deceased donors' kidney allocation requires the establishment of clear and objective rules in the definition of unacceptable antigens both on defined cutoff values and which HLA loci to consider.¹ As a matter of fact, in the distribution of organs for transplantation, donors' HLA typing resolution should be equivalent to the resolution achieved by the techniques used in the determination and identification of unacceptable specificities of

HLA antibodies on the transplant candidates.¹¹ Nonetheless, identification of nonacceptable HLA mismatches in donor-recipient pair selection for transplantation depends on the rules defined by each transplantation center and is not dependent on a single and universal criterion.¹⁸ Actually, usage of unacceptable antigens from HLA loci others than classic HLA-A, HLA-B, and HLA-DR depends on the importance kidney transplant programs give to it. Although using HLA-C nonacceptable antigens in CPRA estimation should have a small impact on sensitization levels because nonacceptable C antigens are primarily observed in patients already with higher CPRA values determined from HLA-A, -B, and -DR.¹¹ Even though the use of the HLA-C, HLA-DQ, and HLA-DP donors' typing will allow an even more accurate transplant candidates' CPRA value.¹³ When estimating CPRA, using others unacceptable HLA loci in addition to the classic HLA-A, -B, and -DR is more relevant in candidates for retransplantation, mainly in organ allocation programs that give more weight to time on dialysis than to the number of HLA mismatches in transplant candidates prioritization. The use of the unacceptable antigens of all these loci will also increase virtual crossmatch predictions accuracy.¹⁹ Here, we only presented CPRA values for the classic HLA loci, although our calculator allows for CPRA estimation also with HLA-C antigens. Furthermore, our R package can be modified by anyone, not only to use HLA frequencies from other donors' samples but also to consider more HLA loci on CPRA calculation. In a near future, we expect to have different groups of donors typed at different resolution levels (serological and high resolution) and even to other HLA locus (for instance, *HLA-DQB1**) in order to compute new CPRA values and compare them with the results obtained with our current CPRA estimator.

In conclusion, reliability of CPRA values depends on donors' pool from which it is calculated and it is crucial for highly sensitized patients to be classified as so. The genotypic frequencies used for CPRA computation should be known and scrutinized to assure a correct measure of candidates' sensitization and must correspond, as far as possible, to those from future organ donors.

ACKNOWLEDGEMENT

We would like to acknowledge Mr. Geert Haasnoot from Leiden University Medical Centre for his help computing CPRA values from Eurotransplant Reference Laboratory Virtual PRA Calculator (www.etrl.org). Also, we are pleased to acknowledge Mr. Anthony Murphy, Canadian Blood Services Program Coordinator for his help computing values from Canadian cPRA calculator.

CONFLICT OF INTEREST

The authors have declared no conflicting interests.

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How to cite this article: Lima BA, Alves H. Portuguese calculated panel reactive antibodies online estimator. *HLA*. 2019;93:445-450. <https://doi.org/10.1111/tan.13516>

2.1.6. cHED

Heterozygous individuals at HLA *loci* are assumed to present a broader range of pathogen-derived peptides than homozygotes, thereby increasing the probability of triggering a specific immune response. This heterozygote advantage hypothesis has been further extended by considering the sequence level, leading to the idea of a divergent allele advantage [58]. This mechanism may explain the diversity of highly polymorphic HLA genes.

HLA evolutionary divergence (HED) is a quantifiable measure of the Grantham distance [59] between the peptide-binding domains of the two alleles of each HLA *loci*. The HED is a simple proxy for the size of the repertoire of peptides presented by the HLA molecules of a given individual. By definition, the HED is zero in the case of homozygosity.

Looking at it from a clinical perspective, HED has been associated with better control of HIV, with the response to checkpoint inhibitors in certain cancers, with patients' survival after haematopoietic stem cell transplantation, and also with the occurrence of rejection after liver transplantation.

Calculated HED (cHED) [48] is an application that allows the computation of HED scores for the 5 classical HLA genes (HLA-A, -B, -C, -DRB1, and -DQB1) when defined at two-field resolution for alleles annotated as 'commons' [60].

The cHED application has been developed using the shiny framework [44] within the R programming language [43] and uses the *histoc* package [45] for HED computation.

This application functions as a basic calculator and one of its main advantages is that no personal information is ever stored or analysed; only the user has access to it and no one else can retrieve it.

Calculated Human Leucoyte Antigens Evolutionary Divergence

Bruno A Lima. *OBM Transplantation* 2024, volume 8, issue 1

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Communication

Calculated Human Leucocyte Antigens Evolutionary Divergence (cHED)

Bruno A Lima *

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2024, volume 8, issue 1

doi:10.21926/obm.transplant.2401208

Received: December 15, 2023**Accepted:** March 05, 2024**Published:** March 11, 2024**Abstract**

Human Leucocyte Antigens (HLA) constitute a highly polymorphic set of genes pivotal to the immune response. The HLA heterozygous advantage hypothesis assumes that heterozygous individuals at the HLA level have a wider range of peptides for T cell recognition than homozygous individuals. Consequently, they possess an enhanced capacity to trigger a targeted immune reaction. The divergent allele advantage hypothesis is an extension of heterozygous advantage, considering the excessive sequence divergence between alleles of the same HLA locus. The HLA Evolutionary Divergence (HED) score has been proposed to quantify this divergence between alleles of the same HLA locus. Presented here is the calculated HED (cHED), an open-source web application designed for the computation of HED scores about the 5 classical HLA genes (HLA-A, -B, -C, -DRB1, and -DQB1) when delineated at two-field resolution.

Keywords

HLA; evolutionary divergence; heterozygote advantage; Grantham's distance



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1. Introduction

The two classes of proteins with the highest degree of polymorphism in the human genome are Human Leucocyte Antigens (HLA) class I and II. HLA-A, -B, and -C molecules are found in nearly all cells except red blood cells, whereas class II HLA-DR and -DQ molecules are primarily found in immune cells [1]. The polymorphism of HLA is not only one of the main contributors to humanity's diversity, but with a genetically predetermined history, HLA has a crucial role in the immune response [2].

The HLA heterozygous advantage hypothesis postulated by Doherty and Zinkernagel [3] states that heterozygous genotypes for HLA *loci* are more likely to trigger an immune response in the presence of an infection. Also, according to this hypothesis, heterozygous HLA genotypes promote the presentation of more diverse tumor antigens to T cells [4].

Heterozygous individuals at the HLA level are assumed to possess a broader array of peptides for T cell recognition compared to homozygous individuals, thereby potentially enhancing their capacity to elicit a specific immune response. Since heterozygous individuals have shown greater resistance to pathogens, this may also explain the population's persistent increase of different HLA alleles.

This hypothesis of heterozygous advantage has been expanded to encompass the sequence level, leading to the emergence of the concept known as divergent allele advantage [5, 6]. The divergent allele advantage hypothesis [7] is a consequence of heterozygous advantage and results from excessive sequence divergence between alleles of the same HLA *locus* [8].

In other words, the divergent allele advantage hypothesis stipulates that diversity between HLA alleles of the same locus (i.e., with a greater number of amino acid differences between the peptide binding domains of two alleles of the same HLA locus) may increase the functional capacity of peptide antigen presentation and as such increase protection against pathogens and tumors through the ability to activate the protective immunity of T cells [9].

The HLA Evolutionary Divergence (HED) score has been proposed to quantify this divergence between alleles of the same HLA locus. An individual with a higher HED value between HLA alleles may allow the presentation of a more diverse immunopeptidome, as the different set of peptides from each allele within the highly polymorphic HLA collectively constitutes the immunopeptidome [10].

2. Objective

This paper aims to present a simple web application that allows the calculation of HED scores.

3. Methods

The calculated HED (cHED) is an application that allows the computation of HED scores for the 5 classical HLA genes (HLA-A, -B, -C, -DRB1, and -DQB1) when defined at two-field resolution for alleles annotated as 'commons.' This web application is available online as open-source software (<https://txor.shinyapps.io/ched/>).

The HED value is obtained from the Grantham distance [11] that calculates the difference of paired chains of polymorphic amino acids for different HLA alleles of the same *locus* and predicts the range of the immunopeptidome presented by the molecules encoded by that HLA locus. The Grantham distance [11] is a classical metric that allows quantifying the differences between

sequences of amino acids of proteins, considering their physiochemical properties: composition, polarity, and volume. The sum of the distances of the amino acids is normalized by the sequence length [12]. As per the definition, the value of HED is zero in instances of homozygosity.

The respective protein sequences of the peptide binding domain (exon 2 and 3 for HLA class I, exon 2 for HLA class II) were obtained from the international immunogenetics project's HLA database [13]; exon annotation was performed with the Ensembl database [14].

This application was built with shiny [15] in R [16] and using the package {histoc} [17] for HED computation. The entire code is accessible via its dedicated GitHub repository [18], and any reporting of bugs, requests for new features, or other forms of feedback are encouraged by submitting an issue through that platform.

4. Results

The cHED web application returns the HED values for each of the 5 main HLA's loci: HLA-A, -B, and -C of class I and HLA-DRB1 and -DQB1 of class II. It allows two forms of input: picking the alleles or uploading a data file.

Therefore, it is feasible to choose a pair of common alleles from the specific locus for which an outcome is required (Figure 1).

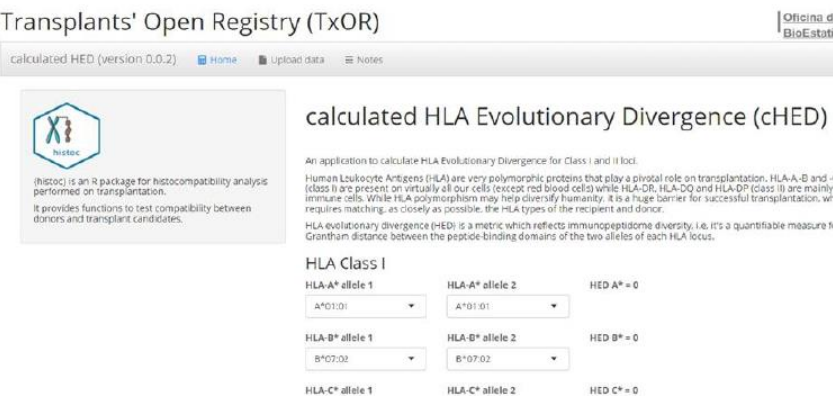


Figure 1 Calculated HED given as input a pair of alleles for each loci.

Alternatively, we can provide a text file containing HLA genotypes for multiple individuals as input (Figure 2). When using a text file as input, this should have 11 columns; the first corresponds to an identifier, and the remaining 10 to the 5 pairs of alleles for HLA genotypes. These columns should be named as: 'ID', 'A_1', 'A_2', 'B_1', 'B_2', 'C_1', 'C_2', 'DRB1_1', 'DRB1_2', 'DQB1_1' and 'DQB1_2'.

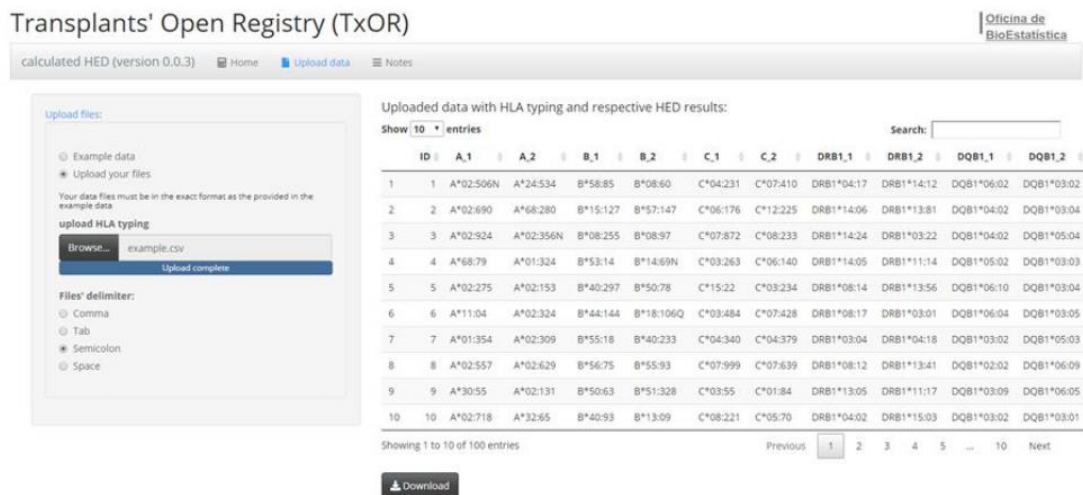


Figure 2 Inputing a file with HLA genotypes an.

For each *loci*, the valid alleles must be on two-field resolution. As shown in the example data, each allele must begin with its locus' name followed by an asterisk, the first two digits of the first field, a colon, and the digits of the second field. In the output, 5 additional columns are generated alongside the uploaded data, providing the HED results for each HLA *loci*. Moreover, the tabled results can be downloaded locally.

This web application is a straightforward calculator, offering the key advantage that individual data is neither stored nor processed, ensuring it remains inaccessible to anyone other than the user.

5. Discussion

A previously documented correlation between the genetic divergence of two alleles within the same *locus* and the combined number of peptides they are linked to has confirmed the divergent alleles advantage for the genes located within the classical HLA *loci* [6].

Likewise, higher HED values may permit the presentation of a greater variety of the immunopeptidome and, as such, facilitate the recognition of T cells and a more adapted immune response [2]. Employing the notion of allelic divergence permits a continuous and functionally oriented strategy for delineating HLA variability, in contrast to the binary classification intrinsic to basic pathogenic zygotes [8].

We can already find in the literature several studies that describe the association of HED values with some forms of cancer and their treatment. The effectiveness of T-cell-based immunotherapy approaches, for instance, is significantly influenced by HED values, which serve as a gauge of immunopeptidome variety [10]. Additionally, it was found that HED values (as a measure of sequence divergence between HLA alleles) are associated with checkpoint blockade immunotherapy response in patients treated for cancer [4]. The association between HED class I and outcome after kidney cancer treatment has also been described [12]. Similarly, an association between HED values and the effectiveness of immunotherapy for gastrointestinal cancer was established [2].

Furthermore, it has been described that HED values for both classes I and class II are associated with the survival of patients with Acute Myeloid Leukemia after hematopoietic stem cell

transplantation (HSCT) [19]. Likewise, higher HED values were associated with a better outcome after HSCT in pediatric patients [9].

In the case of infectious diseases, the functional basis of a protective association between HLA heterozygosity and HIV control has already been demonstrated [8]. While higher HED values for HLA-B could be associated with COVID-19 outcomes [20].

When HLA genotyping is conducted with a two-field resolution, the HED value can be calculated without incurring any extra expenses. Notably, this value can be computed on donors and recipients in transplantation. Suppose a link between donor HED levels and liver transplant outcome is described [21] in the future. In that case, there is potential to study the potential HED associations in kidney transplantation when the widespread utilization of HLA genotyping at a two-field resolution becomes a reality.

We can find other open-source software that allows us to calculate HED values, whether a Perl package [22] or an application that calculates HED for HLA class I loci [4, 6]. The application presented here (cHED) also allows us to calculate HED for class II loci.

In conclusion, the cHED web application is simple and freely available for anyone interested in calculating HED values. It is a part of the Transplant Open Registry (TxOR) initiative [23], which assembles several histocompatibility and transplantation-related open-source software applications and tools.

Hopefully, cHED will be a valuable instrument for researchers exploring the connection between allele advantage and the immune response to particular diseases or conditions.

Abbreviations

HED	HLA Evolutionary Divergence
HLA	Human Leucocyte Antigens
HSCT	Haematopoietic stem cell transplantation
TxOR	Transplant Open Registry

Author Contributions

Conception and design: Bruno A Lima. Drafting the article and revising it: Bruno A Lima. Providing intellectual content: Bruno A Lima. Approval of final version: Bruno A Lima.

Competing Interests

The author declares that he has no conflicts of interest to disclose.

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EQUITY MATRIX

3. Equity Matrix

Decree no. 6537, of April 3rd, 2007, of the Portuguese Republic revoked Decree no. 10507, of May 23rd, 2000, and approved the current rules for the selection of the donor-recipient pair in deceased donor kidney transplantation. The current regulation, in its wording, has inherited from its predecessor the paragraph: *"Organs for transplantation are a public good intended for patients who will be able to improve their survival and quality of life through this gesture. Therefore, the selection of the donor-recipient pair should always be based on the criteria best suited to achieve these objectives updated whenever recommended by the Leges Artis, thus respecting the principles of equity and medical ethics."*

It took seven years to repeal the 2000 rules, but sixteen years of technical and scientific evolution have not yet been enough to define better selection criteria than those remaining in force since 2007. While the criteria of Decree nº 10507/2000 were based on ABO compatibility, a negative crossmatch, and the search for the highest number of HLA matches between donor and recipient, the 2007 rules impose the prioritisation of an identical ABO distribution and scoring criteria encompassing the number of HLA mismatches, PRA values, time on dialysis, and the ages of donor and transplant candidate. This scoring system was questioned shortly after its introduction because it led to an increase in the number of transplanted patients with episodes of acute rejection and a consequent increase in costs [61]. One could ask whether these results were expected and, if so, what was done to minimise these effects, but unfortunately we are not aware of any published study supporting the implementation of this scoring system.

In recent years, many voices have been raised about the need to change the rules for the distribution of deceased donor kidneys for transplantation, as established by Decree nº 6537/2007, in particular those from the Portuguese Society of

Transplantation [9]. One of the main objectives of the scoring system introduced in 2007 was to mitigate the disadvantage of longer waiting times faced by hypersensitised patients [7]. However, sufficient time has now elapsed to evaluate the results of this system and, consequently, to make improvements taking into account the new data available.

The evaluation of any allocation system for a scarce resource such as organs for transplantation depends on the quality of the data available and the ability to analyse them. In the specific case of kidney transplantation in Portugal, there are no public data available for analysis and the information provided by the IPST is clearly insufficient, even more so when discussing the possibility of implementing a new allocation system [11].

The availability of open data in the field of transplantation would not only be a way to promote innovation but would also allow scrutiny of public policies in this area of health. The availability of this type of data can improve the health care provided and reduce its costs [10]. The role of the IPST is not only to provide information on the management of the transplant waiting list but also to provide the data to process and analyse it.

3.1. Bioethical Considerations

The definition and public dissemination of periodic indicators to assess transplantation activity in Portugal would be essential to ensure better decision making regarding the implementation of new health policies. A detailed characterisation of patients on the transplant waiting list, but also of transplanted patients, and of the factors that may affect both patient and graft survival, must be taken into account when defining rules for the distribution of a scarce commodity such as organs for transplantation [4].

However, the lack of open data and public key performance indicators on transplantation in Portugal cannot be an excuse for accepting a set of rules for the distribution of deceased donor kidneys for transplantation that have long been questioned but for which there are few alternatives available [62]. The use of synthetic data is an alternative to explore and evaluate new organ allocation rules against the existing ones [6]. The search for a simpler, more transparent, and more equitable system for allocating deceased donor kidneys for transplantation should be an ongoing process that allows the best decision to be made at any given time [63].

Finding a balance between fairness and utility in the allocation of a limited resource such as deceased donor kidneys for transplantation is a major obstacle for entities overseeing organ allocation systems [63]. The aim is to find a method of allocation that is equitable both in terms of treating identical cases equally and recognising differences appropriately.

Given the limitations of health resources and the need to redistribute them equitably, Daniels and Sabin proposed, in 1998, the concept of “*accountability for reasonableness*” [64], based on four conditions:

- Publicity condition – Decisions about the implementation of new health policies and the reasons for these decisions should be made public.
- Relevance condition – The rationale for these decisions must be supported by sound evidence and principles on which all stakeholders (managers, health

professionals, and patients) can reach consensus, taking into account the needs of their target populations and the inevitable need for cost containment in a context of scarce resources.

- Appeals condition – A mechanism should be established for challenging decisions taken and for revising them if new evidence or arguments justify doing so.
- Regulative condition – This process should be regulated to ensure that the three previous conditions are met.

Furthermore, a fair distribution of health resources must take into account a hierarchy of needs and the financial constraints of public health systems [65]. In this way, it is possible to prioritise health care according to a society's financial means at a given time and to guarantee a minimum level of health care for the entire population. In the case of kidney transplantation, the scarcity of organs can be equated with a financial constraint, so it is necessary to prioritise candidates on the waiting list for their access to transplantation.

Combining the conditions of "*accountability for reasonableness*" with distributive justice, which takes into account not only individual needs but also the needs of the group, makes it possible to define better criteria for allocating deceased donor kidneys for transplantation, fairly and transparently [66].

Awarded for scientific publication in 2020, attributed by the Portuguese Society of Transplantation

Access to kidney transplantation: a bioethical perspective.

Bruno A Lima, Helena Alves. *Port J Nephrol Hypert* 2020; 34(1): 107-109. . DOI: 10.32932/pjnh.2020.07.070

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Access to kidney transplantation: a bioethical perspective

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■ BACKGROUND

When possible, kidney transplantation is the best renal replacement treatment for end stage renal disease patients. Indeed, compared to dialysis, kidney transplantation has better survival outcomes, its costs are lower, and patients' quality of life increases substantially¹. Unfortunately, kidneys from deceased donors for transplantation are scarce, and their availability falls far short of the needs of wait-list patients.

Striking a balance between fairness and utility in the distribution of a scarce good such as deceased donors' kidneys (DDK) for transplantation has long been a challenge and a goal for many organizations that bear responsibility for defining organ allocation systems². Moreover, when managing access to kidney transplantation from deceased donors, a balance is sought between optimizing the transplant's clinical outcome (principle of utility) and giving all patients a reasonable opportunity to receive a transplant (principle of justice)³. The aim is to find a form of distribution that is equitable, in terms of both horizontal equity (treating equals equally) and vertical equity (treating differently what is different).

For the occasion of the 10th anniversary of the adoption by the General Conference of the United Nations Educational, Scientific and Cultural Organisation (UNESCO) of the "Universal Declaration on Bioethics and Human Rights"⁴, Petrini addressed the necessity for considering the principles in the Declaration on policies concerning the allocation of organs⁵. The author highlighted, among the principles laid down in the declaration: benefit and harm (Article 4), equality, justice and equity (Article 10), nondiscrimination and nonstigmatization (Article 11), solidarity and cooperation (Article 13), social responsibility and health (including access to quality healthcare; Article 14), and sharing of benefits (Article 15); as those most relevant for the allocation of organs⁵.

When donation is not expressed and directed to someone in particular, organs for transplantation can be seen as property of wait-list patients as a whole. Further, the State, as regulator, has the obligation to ensure, for each available organ for transplantation, an impartial choice of organ receptor⁶. Under the ethical principle of fairness, equals should be treated equally so that all patients have an equal opportunity to access transplantation. Conversely, given utilitarian values, some inequalities may be allowed if doing so gives society – as a group – the greatest benefit through maximizing the utility of resources. Therefore, kidneys from deceased donors may be directed to those patients who can best use them and are less likely to return to waiting lists due to graft rejection.

■ EQUAL OPPORTUNITY MATRIX

Given the limitations on health resources and the consequent need for them to be distributed equitably, in 1998, Daniels and Sabin proposed the concept of "accountability for reasonableness"⁷, whereby decisions about the allocation of limited and scarce resources must not only be made publicly but should seek to satisfy people's perceptions of appropriate healthcare. To accomplish this goal, verification of "accountability for reasonableness" relies on 4 conditions:

- Publicity condition – Decisions on the implementation of new health policies and the reasons behind these decisions should be made public.
- Relevance condition – The rationale behind these decisions must be supported by solid evidence and principles whereby all stakeholders (managers, health professionals and patients) can reach consensus, considering the needs of their target populations and the inevitable need for cost containment given scarce assets.
- Appeals condition – A mechanism should be established for challenging decisions made and for revising those decisions whenever there is new evidence or argumentation that justifies doing so.
- Regulatory condition – This process should be regulated assuring that the three previous conditions are fulfilled.

Daniels' distributive proposal⁷ assumes the need to make a binary choice between acceptable and superfluous healthcare, discerning between health needs (i.e., healthcare required for typical functioning) and health preferences (where convenience is prioritized beyond what is reasonably normal). Additionally, Nunes and Rego⁸ proposed a form of healthcare distributive justice designated as the Equal Opportunity Function ((EO)F) – a complementary approach to Daniels's proposal. In (EO)F, authors consider both a hierarchy of needs, in agreement with Maslow's pyramid⁹, and the financial constraints imposed by the public health system. With this proposal, it is possible to adjust the available healthcare resources to the financial means of a society at a given time, always ensuring a minimum of healthcare for the entire population. Furthermore, as the authors reported, an iniquity (treating two people unfairly) may be ethically acceptable if this treatment is due to restrictions imposed by the system as stated by (EO)F, if and only if this inequality does not undermine the basic rights of the people and the decision that gave rise to it has been taken according to Daniels' 4 conditions for "accountability for reasonableness". In fact, those four conditions legitimize health choices made through the application of (EO)F⁸. In a linear way, we can transpose (EO)F to an equal opportunity matrix ((EO)M) as described in Table 1. In this (EO)M, for each row we

Table 1

Equal opportunity matrix (EOM).

According to the financial capability, Maslow's needs are ranked in the upper half of the matrix

	\$	\$\$	\$\$\$	\$\$\$\$	\$\$\$\$\$	\$\$\$\$\$\$
Physiological needs	1 st	1 st	1 st	1 st	1 st	1 st
Safety needs	–	2 nd	2 nd	2 nd	2 nd	2 nd
Love and belonging	–	–	3 rd	3 rd	3 rd	3 rd
Esteem	–	–	–	4 th	4 th	4 th
Self-actualization	–	–	–	–	5 th	5 th
Self-transcendence	–	–	–	–	–	6 th

Each \$ represents an amount of money in a healthcare system.

have Maslow's hierarchy of needs and in each column we have different levels of available resources represented by the financial capability of the health system. The upper half of (EOM) have the rank of mandatory Maslow needs for the public service according to the financial availability of the system (i.e. by column). The dilemma health systems face is to articulate, in a fair and impartial manner, the right of access to healthcare, using the available resources in society.

The previously proposed kidney allocation color system^{10,11}, can be seen from the point of view of justice as a practical example of the application of (EOM): patients on the waiting list are prioritized by the criteria of clinical urgency (red group) and then by waiting time or because they are less likely to be transplanted (those who remain on dialysis the longest are in the poorest health). However, all listed patients are always considered for transplantation, achieving a systematic and fair solution for the distribution of DDK (Table 2).

Table 2Kidney allocation color system¹⁰

	Not ECD		ECD	
Recipients ≤ 65 years old	Clinically Urgent	RED	Clinically Urgent	Recipients > 65 years old
	cPRA ≥ 85% or ToD ≥ 3rd Quartile *	ORANGE	cPRA ≥ 85% or ToD ≥ 3rd Quartile *	
	cPRA ≥ 50% or ToD ≥ Median *	YELLOW	cPRA ≥ 50% or ToD ≥ Median *	
	cPRA < 50% and ToD < Median *	GREEN	cPRA < 50% and ToD < Median *	

ECD – Extended Criteria Donor; cPRA – calculated PRA;

ToD – Time on dialysis

* – wait-list patients' time from first dialysis to transplantation

The right of access to healthcare is crucial to provide effective equal opportunities in a free and inclusive society¹². Further, this right must be interpreted from the point of view of egalitarian theories (i.e., equally fair opportunities for all) but also from a utilitarian point of view, once the benefit, utility and effectiveness associated with healthcare costs must be analysed. Similarly, scarce health resources, such as organs for transplantation, should be used to ensure the effectiveness of treatments and the least possible waste. As noted by Nunes *et al.*¹², a universal right of access to healthcare must be based

on three principles: equal opportunity; solidarity; and evidence-based practice. By the same token, in the case of access to DDK for transplantation, an organ allocation system should ensure that all wait-list patients have a real opportunity of being transplanted; fair access to organs is ensured; and that organ distribution rules take into consideration the best available scientific evidence.

EVIDENCE BASED DECISION MAKING

As Sackett put it¹³: "Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients". Indeed, evidence based medicine (EBM) practice translates into combining the clinician's experience with the best evidence from quality clinical research and considering the patient's values, expectations and context. Through EBM, it is possible to identify and apply not only the most effective but also the most efficient treatments to maximize the amount and quality of patient health. Thus, EBM can and should also be used to allocate health resources¹⁴.

The use of EBM in clinical practice is based on the ethical principles of beneficence, nonmaleficence and respect for the autonomy of the person as part of the clinical process. Notwithstanding those principles, EBM can be extended to include healthcare policy decision making, public health and population-based decision making. This extension of EBM we call Evidence Based Decision Making (EBDM). Likewise, EBDM is a key tool in the distribution of public health resources (such as the allocation of DDK) that, based on both egalitarian and utilitarian values, can ensure that decisions are supported by the best available scientific evidence. Using EBDM in the distribution of scarce resources at a macro level also implies the application of Daniels' four conditions for the "accountability for reasonableness"⁷. Thus, the application of EBDM in the definition of kidney transplant allocation rules also safeguards that the rules defined for the allocation of deceased organ donors must guarantee the best predictable results based on existing scientific evidence.

In addition, if EBM's primary goal is to increase scientific knowledge and consequently to increase the quality of the healthcare provided, a second goal will be to ensure that scarce health resources are allocated fairly in treatments of proven clinical value¹⁴. In accordance with the EBM paradigm, an objective application of distributive justice requires that scarce health resources must be used in treatments of proven effectiveness. Therefore, EBM allows the prioritization of healthcare based on effectiveness, ensuring fair access to that healthcare. Furthermore, as stated by Nunes *et al.*¹², efficiency in health resource allocation should be seen as an ethical imperative. The combination of Daniels' "accountability for reasonableness" and Nunes' (EO)F principles will allow us to define, in a fair and transparent manner, the best criteria to take into account when allocating a scarce good such as DDK for transplantation¹².

CONCLUSION

To substitute current Portuguese rules for donor-recipient selection in kidney transplantation, in force since 2007, we should try to find a simpler, more transparent and fairer kidney allocation system¹¹. The

need to define new rules to replace current ones has been recognized for a long time^{10,15,16}. In conclusion, the application of (EO)M principles, with the four conditions of “accountability for reasonableness” will guarantee the process legitimacy in defining the necessary new rules; it will also guarantee the fairness of the obtained results.

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3.2. Utility / Justice matrix

An equitable kidney allocation system for transplantation must balance criteria of utility and justice, and somehow tolerate adjustments and tuning of parameters according to the population in which it will be applied. To achieve this, we have proposed an Equity Matrix (EQM) model [67], which allows the definition of a punctuation system for the selection of donor-recipient pairs in kidney transplantation.

In this EQM model, the criteria for allocating organs for transplantation are divided between:

- Utility criteria:
 - Longevity match – given by age difference (AgeDiff) between donor and candidate;
 - Number of HLA mismatches (mmHLA);
- Justice criteria:
 - Medical urgency;
 - Time on dialysis (TmDial);
 - HLA sensitization – given by candidates' cPRA values.

The EQM model is based on a utility/justice matrix (Figure 3) in which both utility and justice criteria are weighted.

Thus, from a maximum initial value, the ratio assigned to the utility weight is subtracted by row and the ratio assigned to the justice weight is subtracted by column.

		Utility					
		AgeDiff < 9 mmHLA 0-2	AgeDiff < 9 mmHLA 3-4	AgeDiff >= 9 mmHLA 0-2	AgeDiff < 9 mmHLA 5-6	AgeDiff >= 9 mmHLA 3-4	AgeDiff >= 9 mmHLA 5-6
Justice	TmDial > q3 cPRA >50	Max	Max (1 - ratio.util)	Max (1 - 2 x ratio.util)	Max (1 - 3 x ratio.util)	Max (1 - 4 x ratio.util)	Max (1 - 5 x ratio.util)
	TmDial > q3 cPRA <=50	Max (1 - ratio.just)	-	-	-	-	-
	TmDial > q2 cPRA >50	Max (1 - 2 x ratio.just)	-	-	-	-	-
	TmDial > q2 cPRA <=50	Max (1 - 3 x ratio.just)	-	-	-	-	-
	TmDial <= q2 cPRA >50	Max (1 - 4 x ratio.just)	-	-	-	-	-
	TmDial <= q2 cPRA <=50	Max (1 - 5 x ratio.just)	-	-	-	-	-

Figure 3. Utility / Justice matrix computation [67].

As with other allocation models, prior to applying the EQM model, some groups of patients are usually prioritised, according to:

1. Clinical urgency;
2. Paediatric status;
3. Multiorgan candidates;
4. Hipersensited candidates.

And for each potential donor, there are always some candidate exclusion criteria that are common to almost all allocation models, such as:

- ABO incompatibility (or not identical, as appropriate);
- Positive crossmatch (virtual or otherwise);
- Virology results.

To compare the outcome of different kidney allocation systems, we can start with a waiting list of kidney transplant candidates. From a pool of potential deceased donors,

we select the best recipients (on the waiting list) for each one of the donors, until we run out of donors. So, if we do this for two different allocation models, we will end up with two sets of donor-recipient pairs (about twice the total number of donors) and we can now compare the demographic, clinical and immunological characteristics of these two sets of donor-recipient pairs. However, the order in which we pick the donors to find the best matching recipients could affect our final results because for each donor we take the best recipients without reposition. So we need to repeat this process many times, shuffling the donors each time. In the end, we can compare the distributions of the characteristics we want to analyse.

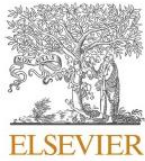
Equity matrix for kidney transplant allocation

Bruno A. Lima, Filipe Reis, Helena Alves, Teresa S. Henriques. *Transplant Immunology* 2023; Volume 81, December 2023, 101917. DOI: 10.1016/j.trim.2023.101917

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Equity matrix for kidney transplant allocation

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ARTICLE INFO

Keywords:

Kidney allocation system
Renal transplantation
Equity and utility
Wait-list

ABSTRACT

There is a general agreement that the distribution of kidneys for transplantation should balance utility criteria with justice. Moreover, a kidney allocation system must be based on transparent policies and seen as an ongoing process.

This study aims to present an allocation system grounded on an equity matrix that balances the criteria of utility and justice.

Synthetic data for a waiting list with 2000 transplant candidates and a pool of 280 donors were generated. A color priority system, the Eurotransplant (ET) kidney allocation system, and the proposed Equity Matrix (EQM) allocation system were compared after 1000 iterations of kidney allocations. Distributions of variables like the age difference, Human Leukocyte Antigens (HLA) mismatches (mmHLA), recipients' time on dialysis, cPRA, and a transplant score obtained by different allocation models were compared graphically and with Cohen's d effect size.

For the analyzed variables, when we compare only the selected recipients from ET with the selected recipients from the EQM neutral model, we can conclude that the former model selects more hypersensitized recipients, a higher number of 65+ years' old recipients with 65+ years' old donors and higher number of recipients with 0 mmHLA. While recipients from EQM neutral are slightly older, have a lower age difference with their donors, have a lower number of mmHLA, are less likely to have 6 mmHLA with their donors, and have more time on dialysis.

The proposed EQM model attempts to provide a simple, transparent, and equitable response to a complex question with results that outperform established practices.

1. Introduction

Kidney transplantation is the preferred treatment for patients with renal insufficiency once it allows for a better quality of life and prolonged survival compared to patients on dialysis [1,2].

Transplantation is one of the most publicized fields of medicine and, as a result, is constantly exposed to public scrutiny [3]. Organs from deceased donors are the 'gift of life' for patients on the waiting list and can save many lives [4].

Due to demographic changes, the age of patients on dialysis has been

constantly increasing, and with the lack of organs for transplant, the waiting time on dialysis has also increased dramatically, decreasing the relative number of patients who can be transplanted [5]. Furthermore, time on dialysis has a negative impact on both wait-list mortality and transplant survival [6].

Besides time on dialysis, age, heart failure, and diabetes are comorbidities of end-stage renal disease (ESRD) patients associated with poor post-transplant survival. Further, increased donor age is associated with reduced graft survival. Alloantigens expressed on the surface of peripheral blood leukocytes called Human Leukocyte Antigens (HLA) and

Abbreviations: AM, Acceptable mismatch; cPRA, Calculated Panel Reactive Antibodies; DSA, donor-specific antibodies; ECD, Extended criteria donors; EQM, Equity matrix; EPTS, Estimated Post Transplant Survival; ESRD, End-stage renal disease; ET, Eurotransplant; ETKAS, Eurotransplant Kidney Allocation system; HLA, Human Leukocyte Antigens; KARS, Kidney Allocation Rules Simulator; KAS, Kidney Allocation system; KDPI, Kidney Donor Profile Index; MMP, Mismatch Probability; mmHLA, HLA mismatches; Q2, Median; Q3, 3rd quartile; SCD, standard criteria donors; SP, Senior Program; TmDial, time on dialysis; TxOR, Transplant Open Registry; txScore, Transplant score; UNOS, United Network Organ Sharing.

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<https://doi.org/10.1016/j.trim.2023.101917>

Received 26 July 2023; Accepted 8 August 2023

Available online 9 August 2023

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the number of HLA mismatches between donor and recipient are also a factor that influences graft survival and disease [5].

A kidney allocation system should be based on transparent policies and consider the relationship between supply and demand. Thereby, the search for the most suitable system should be seen as an ongoing process [7].

There is a consensus that the distribution of a rare and life-saving treatment, such as organ transplantation, should be fair (principle of justice) and provide value (principle of utility) [8]. Thus, the rules for allocating scarce resources should balance utility (better use of organs) with justice (providing equal access to transplantation) [6,9]. Under the principle of justice, patients on the waiting list should have an equal opportunity to access kidney transplantation. However, by the principle of utility, the distribution of available organs must maximize the benefit of the recipients and efficiently reduce waste [3,10].

In longevity matching, the kidneys of younger donors are prioritized for younger candidates, while the organs of older donors are restricted to the groups of older patients to pair the longevity of the organ with that of the recipient [11]. Kidneys with a more limited expected survival are not likely to work throughout the life of a younger, healthier recipient, so they will have to return to the transplant waiting list [12].

Matching HLA is another utilitarian criterion used in several allocation programs. Despite advances in current immunosuppression, each additional HLA-A, -B, -DR mismatch is associated with decreased graft survival [13].

HLA sensitization can occur due to pregnancy, blood transfusion, or a previous transplant [14]. Although the percent panel reactive antibody (PRA) obtained by Complement-Dependent Cytotoxicity is not a precise way to define the degree of sensitization, a cut-off of 85% is generally used to classify highly sensitized patients [15]. On the other hand, the calculated PRA (cPRA) value [16] reflects the probability of a patient having HLA antibodies reactive to a donor from the donor's population. So, those patients with higher values of cPRA are less likely to find a suitable donor for transplantation.

Waiting time in dialysis can be seen as a utilitarian criterion, and it is also the most globally accepted justice factor in kidney allocation. The time of pre-transplant dialysis is a strong predictor of mortality both in the post-transplant period and in patients on the waiting list. Therefore, a fair allocation system will prioritize candidates with higher dialysis time to prevent further development of complications [13].

2. Objective

This study aims to present an allocation system based on an equity matrix that balances the criteria of utility and justice.

3. Materials and methods

3.1. Data

A simulated waiting list comprising 2000 kidney transplant candidates was generated. The age of these candidates has an $N(45, 15^2)$ distribution trimmed between 18 and 75 years old. Their ABO blood groups were randomly attributed with probabilities 0.44, 0.022, 0.042, and 0.496 for A, AB, B, and O groups, respectively. Sensitization to HLA was randomly assigned with 70% of the candidates having a cPRA of 0%, 10% with cPRA between 1% and 50% (with a distribution $P(\lambda = 30)$), other 10% with cPRA between 51% and 85% (with a distribution $P(\lambda = 70)$), and the last 10% having a cPRA between 86% and 100% (with a distribution $P(\lambda = 90)$). Candidates' HLA antibodies were randomly given according to their respective cPRA values and HLA genotyping. Also, we assume no candidate is clinically urgent. The number of months on dialysis was generated according to candidates' HLA sensitization and blood group O status, i.e., hypersensitized (cPRA >85%) candidates and blood group O have time on dialysis with

an $N(75, 20^2)$ distribution, those that have just one of these characteristics (hypersensitized or being group O) have time on dialysis with an $N(60, 20^2)$ distribution, all the remaining transplant candidates have the number of months from a $N(25, 20^2)$ distribution. Those distributions for clinical and demographic variables (Table 1) were described elsewhere by others [17].

For the simulated 280 deceased donors pool, their age was calculated from a $N(60, 20^2)$ distribution trimmed between 18 and 75 years old. Donors' ABO blood groups were randomly attributed with probabilities 0.4658, 0.0343, 0.077, and 0.4229 for A, AB, B, and O groups, respectively, as described by others [18] (Table 1).

Both for candidates and donors, HLA genotyping, was generated according to HLA allelic and haplotypic frequencies from Portuguese bone marrow voluntary donors [19].

All synthetic data on donors and transplant candidates were generated with {simK} [20], an R package developed to generate synthetic data on kidney transplant simulations.

3.2. Models

As a benchmark, we simulate deceased donors' kidney allocation with a system previously suggested by Lima et al. [22]. With this model, the patients are prioritized for each available organ according to their clinical urgency (red color) and regarding their time on dialysis and cPRA value. Those patients with a cPRA >85% or with a time on dialysis higher than the 3rd quartile (Q3) of all wait-listed candidates' time on dialysis are classified as orange. Yellow is attributed to patients with a cPRA >50% or with a time on dialysis higher than the median time on dialysis (Q2). Green is the color for all the rest. Also, patients are allocated to donors within the same age group (old to old program), mimicking the EuroTransplant senior program [23]. Within the same color groups, candidates are ordered by the number of HLA mismatches (increasing) and time on dialysis (decreasing).

A simplified version of EuroTransplant (ET) Kidney Allocation System (ETKAS) [23] was also simulated. This version only applies to adults who were getting their first kidney, did not have an urgent medical condition, and had not previously donated one of their kidneys. In this simulation for each donor, transplant candidates are ordered as follows:

1. Senior Program (65+ years of old candidates when donor has 65+ years old);
2. Acceptable Mismatch Program (candidates with a cPRA >85% without HLA antibodies against donor's HLA);
3. 000 HLA mismatches (no donor-recipient HLA mismatches);
4. ETKAS points.

The Senior Program prioritizes candidates solely based on their time on dialysis. At the same time, the Acceptable Mismatch (AM) Program allows candidates with compatible blood groups (not only ABO identical) to receive a kidney offer, and then they are ordered according to ETKAS points. All candidates have their Mismatch Probability (MMP) calculated at registration, reflecting their chance of getting a kidney with low HLA mismatch (0 or 1 HLA-A, -B, -DR mismatch based on 1000 kidneys offered). The final points for each eligible candidate are the sum of HLA, dialysis, and MMP points. [24]

Here we present the Equity Matrix (EQM) model, applicable to kidney allocation for transplantation. As utility criteria, we consider longevity match and the number of their HLA mismatches (mmHLA), where longevity match is the absolute value between the donor's and recipient's age differences (ageDiff). Then, we built 6 levels of utility for donor-recipient pairs, ordered as ageDiff <9 and mmHLA between 0 and 2; ageDiff <9 and mmHLA 3 or 4; ageDiff ≥9 and mmHLA between 0 and 2; ageDiff <9 and mmHLA 5 or 6; ageDiff ≥9 and mmHLA between 3 or 4; ageDiff ≥9 and mmHLA between 5 or 6.

As criteria of justice, we consider candidates' time on dialysis

Table 1
Variables' distributions for the generation of candidates and donors' synthetic data.

Variable	Distribution	Reference
Recipients' age (years)	$\sim N(45, 15^2)$	Tafulo et al, 2016 [17]
Recipients' ABO blood group	$\begin{cases} Pr(A) = 0.44 \\ Pr(AB) = 0.022 \\ Pr(B) = 0.042 \\ Pr(O) = 0.496 \end{cases}$	Tafulo et al, 2016 [17]
cPRA values (%)	$\begin{cases} Pr(cPRA = 0\%) = 0.7 \\ Pr(1\% < cPRA \leq 50\%) = 0.1 \\ Pr(51\% < cPRA \leq 85\%) = 0.1 \\ Pr(cPRA > 85\%) = 0.1 \end{cases}$	Tafulo et al, 2016 [17]
Recipients' time on dialysis in months (according to blood group and cPRA value)	$\begin{cases} O & \text{and } cPRA > 85\% \sim N(75, 20^2) \\ O & \text{or } cPRA > 85\% \sim N(60, 20^2) \\ \text{all the rest} \sim N(25, 20^2) \end{cases}$	Tafulo et al, 2016 [17]
Donors' age (years)	$\sim N(60, 20^2)$	IPST, 2022 [21]
Donors' ABO blood group	$\begin{cases} Pr(A) = 0.4658 \\ Pr(AB) = 0.0343 \\ Pr(B) = 0.077 \\ Pr(O) = 0.4229 \end{cases}$	Duran et al., 2007 [18]

cPRA calculated the Panel Reactive Antibody percentage.

(TmDial) and their cPRA values. Likewise, for each candidate, we define 6 levels of justice, ordered as TmDial > Q3 and cPRA > 50%; TmDial > Q3 and cPRA ≤ 50%; TmDial between Q2 - Q3 and cPRA > 50%; TmDial between Q2 - Q3 cPRA ≤ 50%; TmDial ≤ Q2 and cPRA > 50%; TmDial ≤ Q2 cPRA ≤ 50% (where Q2 and Q3 are proxies for the second and third quartile of wait-listed candidates' time on dialysis, respectively).

With those levels, we make a utility/justice matrix with 36 cells (a_{ij}).

Given $a_{1,1}$ = maximum value:

$$\begin{cases} a_{i,1} = a_{i-1,1} - a_{1,1} \times \text{ratio.just}, & i > 1 \\ a_{i,j} = a_{i,j-1} - a_{1,1} \times \text{ratio.util}, & i, j > 1 \end{cases}$$

Where

- *ratio.util* – is a value between 0.1 and 0.5 corresponding to the relative weight given to utility criteria.
- *ratio.just* – is a value between 0.1 and 0.5 corresponding to the relative weight given to justice criteria;

For instance, when we assign more weight to the utility ratio (a utility ratio of 0.5 and a justice ratio of 0.1, for example), candidates that fall in the first two columns of the matrix are more likely to be selected for transplantation (Fig. 1 A). On the other hand, when we give more weight to the justice ratio (a utility ratio of 0.1 and a justice ratio of 0.5), those candidates within the first two rows will be more likely the chosen ones (Fig. 1 B).

Within each matrix cell, candidates are ordered by the number of

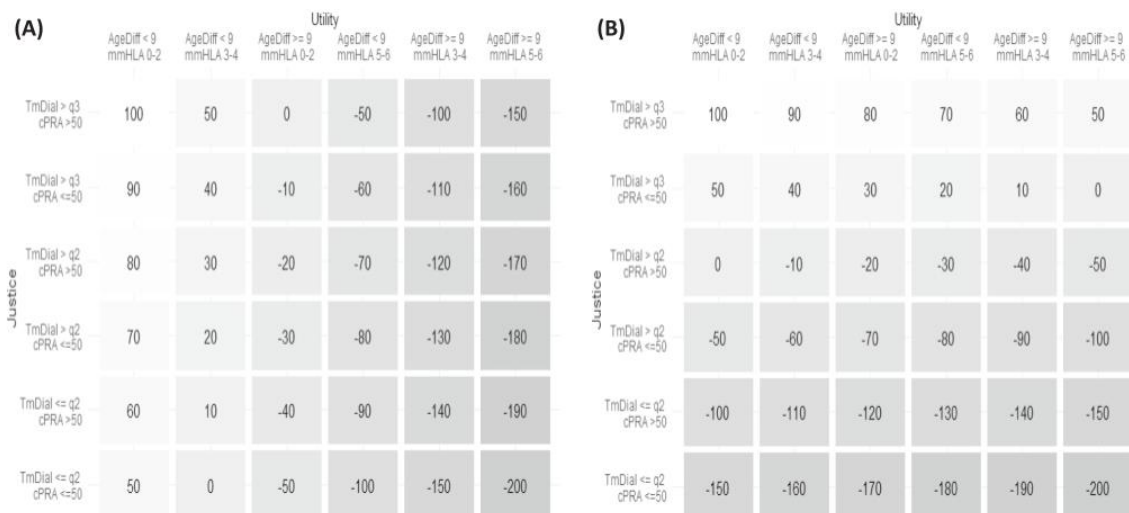


Fig. 1. Examples of Utility / Justice matrixes.

(A) maximum value = 100; *ratio.util* = 0.5; *ratio.just* = 0.1.

(B) maximum value = 100; *ratio.util* = 0.1; *ratio.just* = 0.5.

HLA mismatches (increasing) and time on dialysis (decreasing).

For this study, we built multiple matrices for different combinations of utility and justice ratios, and with it, we tested different EQM models for kidney allocation. We defined the neutral EQM model (EQM_0.1–0.1), where both ratios have the same value (0.1). In addition, we built some imbalance models where we give more weight to utility than justice (EQM_0.2–0.1, EQM_0.3–0.1, EQM_0.4–0.1, EQM_0.5–0.1) or more weight to justice than utility (EQM_0.1–0.2, EQM_0.1–0.5, EQM_0.1–0.4, EQM_0.1–0.5).

Besides, we also tested EQM models combined with rules similar to the priorities applied to the ET system (EQM_ET), i.e., SP, AM program, and 000 HLA mismatches having priority before applying the utility/justice matrix.

Both for Lima's and EQM's models, we assumed Q2 = 50 months and Q3 = 70 months on dialysis.

For each tested model (Lima, ETKAS, and models derived from EQM), the allocation of the 280 donors selects the two best candidates for the donor without candidate repetition. That is, in each iteration, the two best candidates (according to each allocation model) are assigned to the first donor, to the second donor are assigned the 2 best remaining candidates (i.e., without candidates assigned to previous donors), and so on until a maximum of 560 (2×280) candidates are assigned for a poll of donors.

In all the models, eligible candidates for each donor must have a negative virtual crossmatch and must be ABO identical to the donor to be considered for transplantation.

3.3. Analysis

To ensure that the ordering of donors does not influence the results of the models, up to 1000 iterations per model have been performed. Further, the order of the donors to which candidates were assigned was randomly defined at each iteration.

Consequently, for each iteration of each model, it was possible to compute summary statistics of the selected recipients' variables (age, age difference for donor-recipients pairs, number of HLA mismatches, time on dialysis, cPRA value and TxScore a predictive score for transplant outcome [25]). The distributions of this summary statistics were plotted and analyzed. We compared mean values between models with Cohen's d-effect size statistic.

Allocation models analyzed here can be simulated using the application KARS [24] from Transplant Open Registry (TxOR) initiative [26]. The KARS user manual [27] contains a more detailed overview of the applicability of each model.

All analysis and simulations were done in R with {histoc} [28], a package for histocompatibility on kidney transplant allocation systems. A GitHub repository with all the data and R code used in this analysis [29] is also available.

4. Results

The EQM neutral model (EQM_0.1–0.1) selects slightly older recipients than ET and EQM_ET_0.1–0.1 (EQM_0.1–0.1 applied after SP, AM, and 000 mmHLA) models (Table 2). As the pool of donors has an age distribution with a higher mean than the wait list candidates and the age differences between donors and recipients are one of the criteria used by EQM models, these models chose donor recipients pairs with lower age differences (Fig. 2).

By the same token, TxScores are to some extent higher for EQM models than ET alone (Fig. 3). The TxScore measures transplant outcome efficacy and computes a 5-year probability of death or graft failure [25]. Here, and due to the limitations of our synthetic data, for each recipient, TxScore was calculated taking into account the donor's age, recipient's age, time on dialysis, and mmHLA, for all other variables used to calculate the TxScore constant values were assumed. So, this probability is influenced by the recipients' age. Then, being the recipients selected by ET younger than those selected by EQM models and with more recipients with 0 mmHLA, we observe that the former have slightly lower TxScore values than the latter (Fig. 3).

From the comparison between ET and EQM_ET_0.1–0.1, the higher size effect (with Cohen's $d = -17.04$) is for the mean age difference between donors and recipients (Table 3). As for the ET model also for EQM_ET_0.1–0.1 allocation is done after the application of SP and AM program. Consequently, we found smaller differences for cPRA and Hypersensitized recipients (with Cohen's d of 0.18 and -2.26 , respectively) as for the comparison of ET vs. Lima (with Cohen's d of -18.9 and -34.3 , respectively) and ET vs EQM_0.1–0.1 (with Cohen's d of -26.5 and -39.3 , respectively).

Regarding the number of HLA mismatches (mmHLA) for selected donor-recipients pairs and comparing to the other models (Fig. 4), EQM_0.1–0.1 presents a lower mean for the total number of mmHLA (EQM_0.1–0.1 = 2.87; ET = 3.34; Lima = 3.04), a lower number of pairs with 6 mmHLA (EQM_0.1–0.1 = 4.98; ET = 43.4; Lima = 17.36) and a higher number of pairs with until 2 mmHLA (EQM = 229.78; ET = 178.44; Lima = 192.73) as reported in Table 2. Both ET and EQM_ET_0.1–0.1 models select a higher number of donor-recipient pairs with 0 mmHLA (14.49 and 13.21, respectively) once these models prioritize 0 mmHLA on candidates' selection.

Table 2
Descriptive statistics for each allocation model and effect size between models after 1000 iterations.

Variable	EQM_0.1–0.1	EQM_ET_0.1–0.1	ET	Lima	Lima vs. ET	Cohen's d	
						EQM_0.1–0.1 vs. ET	EQM_ET_0.1–0.1 vs. ET
recipients' age	49.48 (± 0.21)	50.72 (± 0.21)	49.21 (± 0.18)	48.58 (± 0.14)	−1.895	2.653	7.618
age differences	6.49 (± 0.22)	7.69 (± 0.23)	11.96 (± 0.26)	11.84 (± 0.24)	−0.841	−23.744	−17.044
number of HLA mm	2.87 (± 0.03)	3.35 (± 0.03)	3.34 (± 0.03)	3.04 (± 0.02)	−9.967	−14.771	1.842
pairs' with 0 HLA mm	3.30 (± 0.88)	14.49 (± 2.63)	13.21 (± 2.69)	9.27 (± 1.54)	−3.750	−7.012	−0.219
pairs with 0 to 2 HLA mm	229.78 (± 7.38)	152.06 (± 6.70)	178.44 (± 6.28)	192.73 (± 6.72)	2.468	5.986	−5.873
pairs' with 6 HLA mm	4.98 (± 1.93)	31.31 (± 4.01)	43.40 (± 5.26)	17.36 (± 3.39)	−5.488	−8.678	−2.599
time on dialysis	59.65 (± 0.28)	57.80 (± 0.27)	58.11 (± 0.36)	59.98 (± 0.21)	5.523	6.018	−1.122
cPRA	23.09 (± 0.64)	38.27 (± 0.53)	37.35 (± 0.46)	29.21 (± 0.37)	−18.887	−26.529	0.177
Hypersensitized recipients	75.52 (± 3.25)	184.08 (± 2.24)	189.16 (± 2.12)	100.53 (± 2.26)	−34.317	−39.310	−2.259
transplants with Senior Program	54.70 (± 3.10)	108.96 (± 0.20)	108.38 (± 0.67)	108.70 (± 0.49)	1.148	−20.845	1.886
TxScore (%)	60.17 (± 0.09)	59.96 (± 0.09)	59.56 (± 0.09)	60.32 (± 0.06)	12.855	8.261	8.010

Summary statistics: mean ($\pm$ sd).

cPRA calculated the Panel Reactive Antibody percentage.

TxScore predictive score for transplant outcome.

HLA mm mismatches HLA.

age differences given by |donor's age – recipient's age|.

ET EuroTransplant.

EQM Equity Matrix.

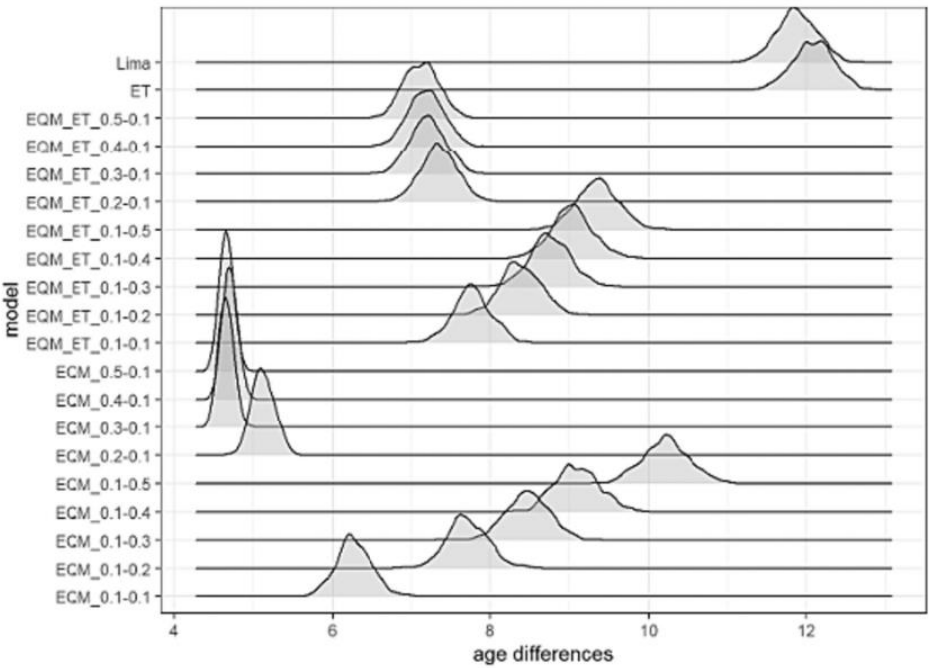


Fig. 2. Age differences distribution from donor-recipient pairs obtained from 1000 iterations.

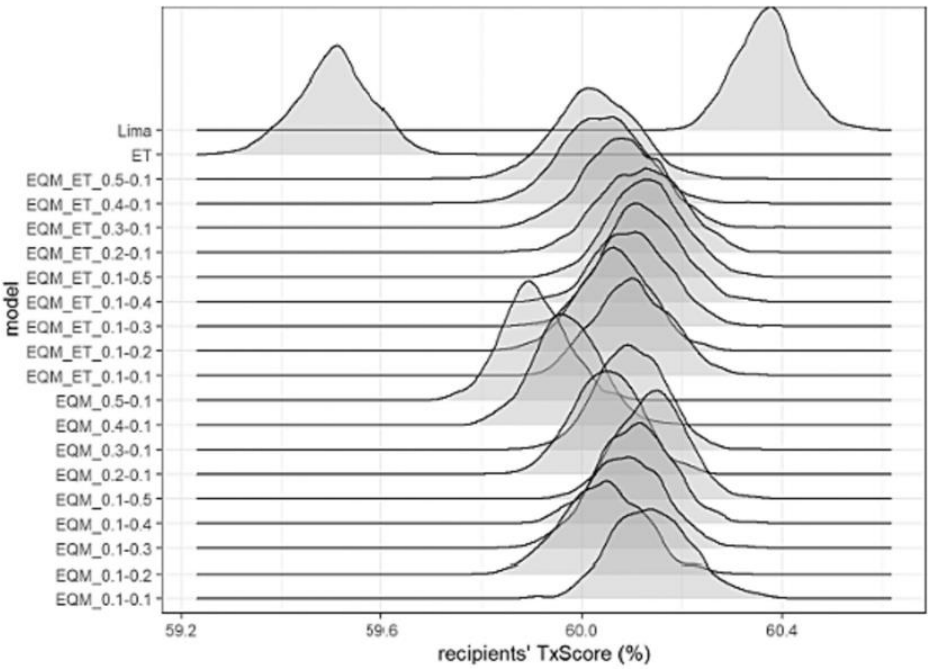


Fig. 3. TxScore % (predictive score for transplant outcome) distribution obtained from 1000 iterations.

Table 3

Ranked models for best performance by variable.

Variable	Lima	ET	EQM_0.1–0.1	EQM_ET_0.1–0.1	Best model
age differences	3rd	4th	1st	2nd	EQM_0.5–0.1
number of HLA mm	2nd	3rd	1st	3rd	EQM_0.5–0.1
pairs' with 0 HLA mm	3rd	1st	4th	1st	EQM_ET_
pairs with 0 to 2 HLA mm	2nd	4th	1st	3rd	EQM_0.5–0.1
pairs' with 6 HLA mm	2nd	4th	1st	3rd	EQM_0.5–0.1
time on dialysis	2nd	3rd	1st	4th	EQM_0.1–0.5
cPRA	4th	1st	3rd	1st	EQM_ET_0.1–0.5
Hypersensitized recipients	3rd	1st	4th	2nd	ET
transplants with Senior Program	1st	1st	4th	1st	ET
TxScore (%)	4th	1st	2nd	2nd	ET

cPRA calculated the Panel Reactive Antibody percentage.

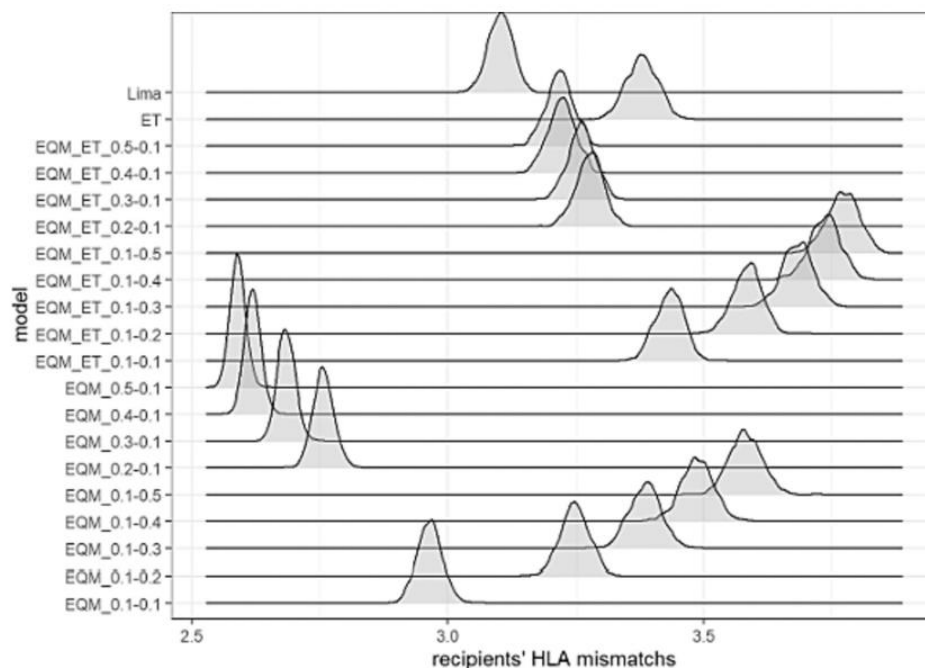
TxScore predictive score for transplant outcome.

HLA mm mismatches HLA.

age differences given by |donor's age – recipient's age|.

ET EuroTransplant.

EQM Equity Matrix.

**Fig. 4.** Number of HLA mismatches for donor-recipient pair; distribution obtained from 1000 iterations.

The EQM models that give a higher weight to justice (EQM_0.1–0.2 to EQM_0.1–0.5) are those that select recipients with higher time on dialysis (Fig. 5). Recipients' time on dialysis from the ET model and from the EQM model, even with higher weight for justice but with ET prioritization (EQM_ET_0.1–0.2 to EQM_ET_0.1–0.5) are lower than those of selected recipients both by the neutral EQM model and Lima's model.

Models that apply the AM program (ET and EQM_ET) (Table 3) select a higher number of hyperimmunized recipients (ET = 189.16; EQM_ET_0.1–0.1 = 184.08; EQM_0.1–0.1 = 75.52; Lima = 100.53) and have higher means of cPRA values than Lima and the neutral EQM (ET = 37.35; EQM_ET_0.1–0.1 = 38.27; EQM_0.1–0.1 = 23.09; Lima = 29.21). Only the EQM with the higher weight to justice (EQM_0.1–0.5) has a higher mean cPRA value than ET but fewer hyperimmunized recipients (Fig. 6A).

Similarly, for the models that apply the Senior Program (Lima, ET, and EQM_ET), the number of 65+ recipients transplanted with 65+

years old donors is way higher than for the remaining models.

Suppose we apply the Senior program, the AM program, and the priority of 0 mmHLA to a neutral EQM (results given by EQM_ET_0.1–0.1 model). In that case, we obtain similar results to the ET allocation regarding the number of hypersensitized recipients (Fig. 6A), the number of 65+ recipients with a 65+ donor (Fig. 6B), the number of pairs with 0 mmHLA (Cohen's $d = -0.22$), the number of total mmHLA (Fig. 4) and mean time on dialysis (Fig. 5). In contrast, recipients selected from the EQM_ET_0.1–0.1 model have a lower age difference with their donor (Fig. 2), lower mean for the total number of HLA mismatches (Fig. 4), and are less likely to have 6 mmHLA than the recipients selected from the ET model (31.31 and 43.4, respectively) (Table 3).

When we compare the performance of the models Lima, ET, EQM_0.1–0.1, and EQM_ET_0.1–0.1 and rank them for the obtained results by each of the analyzed variables (table 4), both ET and

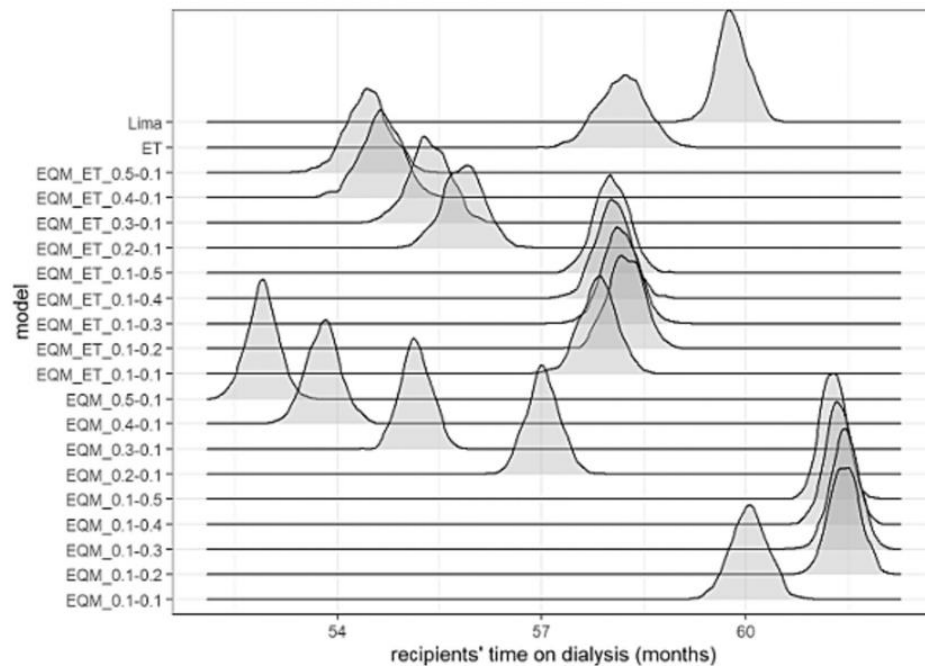


Fig. 5. Mean recipients' time on dialysis distribution from 1000 iterations.

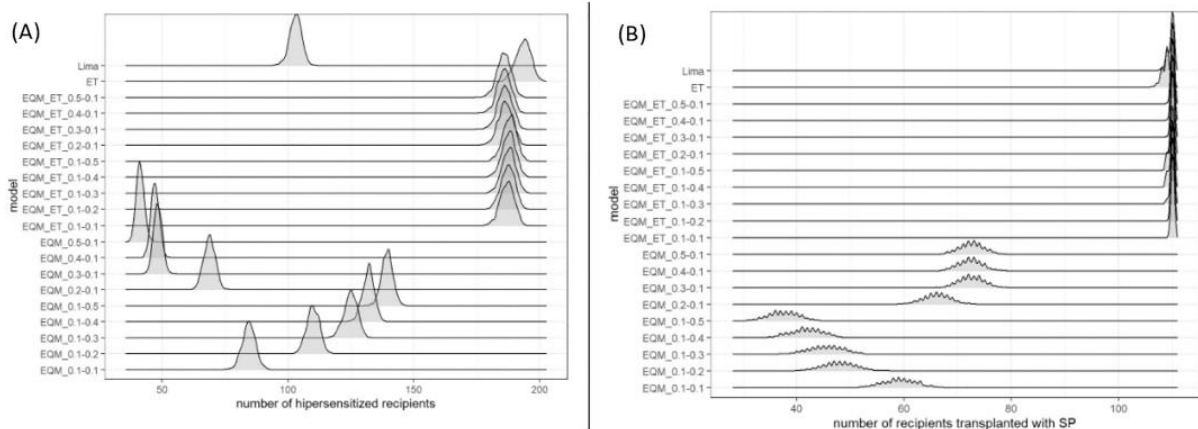


Fig. 6. Results from Senior Program and acceptable Mismatch program (distributions from 1000 iterations).

(A) number of hypersensitized recipients.

(B) number of recipients transplanted according to the Senior Program.

EQM_0.1–0.1 ranked 1st for 5 different variables. The models' ET and EQM_ET_0.1–0.1 ranked 1st on variables that measure the number of recipients with 0 mmHLA, mean cPRA, number of hypersensitive recipients, and recipients transplanted with SP. Obviously, this is a clear result of the priorities inherent to the ET allocation program.

So, for the analyzed variables, when we compare only the selected recipients from ET with the selected recipients from the EQM neutral model (EQM_0.1–0.1), we can conclude that the former model selects more hypersensitized recipients, a higher number of 65+ recipients with a 65+ donor and higher number of recipients with 0 mmHLA. While recipients from EQM neutral are slightly older, have a lower age difference with their donors, have a lower number of mmHLA, are less

likely to have 6 mmHLA with their donor, and have more time on dialysis.

5. Discussion

The presented Equity Matrix neutral model (EQM_0.1–0.1) can outperform not only the Lima model (used as a benchmark) but also the EuroTransplant kidney allocation algorithm in some of the measured variables. The EQM model not only selects recipients with more time on dialysis but also donor-recipient pairs with a lower number of HLA mismatches and lower age differences.

There is a significant longevity mismatch with consequent loss of

graft years when kidneys from young donors are transplanted into older recipients who die with functioning kidneys and when younger candidates receive older kidneys and consequently need a re-transplant [6]. The EQM model prioritized transplants that minimize age differences between donors and their recipients as a proxy for a longevity match.

If it has proven challenging to increase the number of available donors for transplantation, then the few available organs should be optimized to ensure their best utilization. In other words, efforts should be made to allocate the right kidney to the right patient. Nevertheless, there is evidence that virtually all renal transplant recipients live longer than similar patients on dialysis; there are also clear differences in survival rates among groups of transplanted patients based on their underlying disease, comorbidities, race, gender, and age. So, to ensure that the maximum amount of renal function is recovered from a deceased donor kidney, this should be allocated to the recipient who would benefit the most from it [3].

The shortage of organs for transplantation is increasing with the growing number of ESRD patients in aging societies, resulting in longer waiting times for transplantation. Theoretically, a more efficient program for kidney allocation would avoid assigning kidneys with a high expected survival rate to patients with a low post-transplant life expectancy. Similarly, kidneys with limited expected survival should not be allocated to younger patients or those with a longer life expectancy who would require a re-transplant [12].

In EuroTransplant, most kidneys are allocated according to the ETKAS score based on HLA mismatches, the probability of matching, the waiting time, the distance between recipient and donor, and the trade-off between the participating countries [12]. Whereas the EuroTransplant Senior Program (ESP) is applied to candidates and donors over 65 years of age to use the organs of older donors [5]. With ESP, organ allocation is done locally based on ABO compatibility and waiting time without necessarily considering the donor's HLA. The rejection rates of the ESP program are higher than those of transplants from elderly patients with young donors. However, it should be noted that despite the risk factors for this increased mortality after transplantation, ESP transplantation results in increased life expectancy and better quality of life compared to 65+ patients who remain on dialysis [5]. While by ESP, a 64 years old candidate will not be an option for a 65+ donor, by the EQM model, this transplant candidate will have more points for all donors aged between 56 and 72 (age difference < 9).

In contrast to standard criteria donors (SCD), extended criteria donors (ECD) are those aged 60 years or older or over 50 with 2 or more of the following criteria: death from stroke, history of hypertension, and terminal creatinine >1.5 mg/dL. The Kidney Donor Risk Index (KDRI) was developed as an alternative to the dichotomous classification of donors between SCD vs ECD. Constructed from 10 variables, KDRI expresses a hazard ratio on a gradual, continuous scale that reflects the risk of graft failure. Proposed by Rao et al. [30], this score is based on some donors' characteristics associated with graft survival: age, height, weight, ethnicity, history of hypertension and/or diabetes, cause of death, serum creatinine, HCV, and donation after cardiac death. Based on the KDRI, the Kidney Donor Profile Index (KDPI) is calculated, which expresses the quality of a donor relative to other kidney donors. The Estimated Post Transplant Survival (EPTS) score was proposed to predict how long a patient will survive after kidney transplantation and is based on only 4 variables: age, time on dialysis, number of previous transplants, and diabetes status [6,31]. So, in the Kidney Allocation System (KAS) from United Network Organ Sharing (UNOS), patients with EPTS <20% are prioritized for donors with KDPI <20% as a longevity matching criterion, i.e., pairing kidneys that are expected to last longer (top 20% KDPI) with patients with a longer life expectancy (top 20% EPTS). The 20% cut-off could be reasonable when KAS was initially implemented, although it probably should be revisited now. Thus, a continuous distribution based on a scoring system has been suggested to replace the current KAS, which is based on a classification.

In this study, we could not test a longevity match based on KDPI and

EPTS values as done by UNOS' KAS, mainly due to the limitations of our simulated data. Although, we believe that age difference between donor and recipient is a good proxy for the mentioned longevity match. Nevertheless, using KDPI in the decision-making process for organ acceptance from deceased donors could also help increase transplant rates and outcomes [32].

With the identification of the different HLA antigen groups, it was quickly concluded that the peaceful acceptance of grafts in humans depended on the HLA identity between the donor and the recipient [33]. Despite the relevance of HLA matching in kidney transplantation being questioned in favor of other non-immunological factors, HLA factors are still important in many kidney allocation systems. Since it is considered that HLA mismatches influence transplant outcomes, as proven by the results of large patient registries [33]. Another utilitarian criterion utilized in various allocation methods is HLA matching, including ET and our proposed EQM. There is no consensus on its use, although prioritizing kidneys with zero-mismatches is a common practice [13].

Highly sensitized transplant recipients may have worse outcomes than non-sensitized recipients due to a higher risk of delayed graft function, acute rejection, and graft failure [34]. The presence of anti-HLA antibodies in the circulation of a candidate for kidney transplantation negatively impacts their access to transplantation and graft survival, especially if the antibody is specific to their donor [35]. Besides, the calculated PRA (cPRA) value [16] indicates the likelihood that a patient may have HLA antibodies reactive to the next donor available. Moreover, since the reliability of cPRA values depend on the donor pool from which they are calculated, it is very important that this pool represents those who are potential organ donors [36].

With more sensitive techniques for anti-HLA antibody detection and the identification of hypersensitized patients through cPRA, the number of these patients on the waiting list for kidney transplantation has increased. With the careful immunological characterization of transplant candidates, it is possible to implement a virtual crossmatch in organ allocation systems with the identification of donor-specific antibodies (DSA) and thus increase the pool of available donors for hypersensitized patients [37]. Despite this, not all DSA are equally harmful, nor does the absence of DSA detected at the time of transplantation mean that the patient cannot develop a humoral memory cell response against the graft [35].

The success of kidney transplantation depends on the genetic and immunological compatibility between donor-recipient pairs, and HLA sensitization is a barrier to possible transplantation. The combined use of sensitization measures such as cPRA and virtual crossmatch is crucial in managing hypersensitized patients for their access to kidney transplantation [38]. The EQM algorithm also depends on candidates' cPRA and the application of a virtual crossmatch, although it does not prioritize hypersensitized (cPRA >85%) patients.

The Acceptable Mismatch (AM) program of EuroTransplant has been proven to be an efficient way to increase the transplantation of highly sensitized patients with great outcomes [39]. Although hypersensitized patients have a lower graft survival than others, justice for these patients competes with the principle of utility.

It is well known that kidney transplantation in highly sensitized patients through regular allocation rules is associated with a high risk of graft rejection. In contrast, patients transplanted through the AM program of ET have significantly lower rejection rates [14] due to three factors: the absence of HLA specificity is determined for patients in the AM program both in current serum and historical serum; there is evidence that neonatal tolerance explains a portion of acceptable antigens, as acceptable antigens often include non-inherited maternal antigens; both antigens may include low-level epitope mismatches, or the present epitope mismatch is of low immunogenicity [14].

In KAS from UNOS, candidates with cPRA ≥99% are allocated at a national level with a large increase in their priority points. Therefore, these patients also receive organs from donors with lower KDPI values (better organs), reducing access to these kidneys for less sensitized

candidates [6]. The increased use of kidneys with lower KDPI values in hypersensitized patients reduces the availability of these organs for the remaining candidates on the waiting list, many of whom have a much higher expected post-transplant survival than hypersensitized patients [40].

The use of a program like AM in combination with the EQM model can be considered depending on a detailed characterization and analysis of the patients on the waiting list for transplantation. Furthermore, there is a survival advantage for patients transplanted as HLA incompatible compared to those who remain on dialysis. So, deceased donors' kidney allocation programs should also consider the additional waiting time to which hypersensitized patients are subject.

Other factors may be considered for some candidates on the waiting list to achieve fairness in allocation. For instance, candidates who have donated a kidney in the past may get priority, as their current condition may be related to their donation. Similarly, children are prioritized due to the negative impact of dialysis and the unique benefits of transplantation on growth and development. In addition, kidney transplantation becomes an urgent life-saving treatment for patients for whom it is impossible to obtain adequate access to dialysis. Thus, most allocation programs define medical urgency as eligible for prioritization [13]. Additionally, it is customary to allocate the kidneys to identical ABO candidates instead of compatible ABO to prevent candidates from group O of increasing waiting times [41].

We must be able to look for different answers to the necessary distribution of deceased donor kidneys, compare them and evaluate the best measures to improve that distribution [42]. In order to measure the desired evolution and improvements in kidney transplantation, systematic metrics, and tools must be defined to evaluate established practices [26]. The definition of such objective and systematic measures for analyzing and evaluating the activities inherent to kidney transplantation is even more necessary when it is intended to make informed decisions to suggest new health policies [43].

Allocation systems that are assumed to work well may fail to do so due to changes in the donor pool, the demographics of transplant candidates, or due to societal changes in perceptions about the allocation of scarce goods [8].

In the search for a more straightforward, more transparent, and more equitable allocation system, the principles of Equal Opportunity Matrix [10], previously proposed, as well as the 4 conditions of 'accountability for reasonableness' [44] can and should be observed. The suggested EQM model tries to be a simple, transparent, and equitable answer to a complex question. Thus, any new proposal for a new kidney allocation system must be subject to the public scrutiny of its merits and should be assessed with data from different sources [45].

Authors' contributions

Conception and design: BL.
Analysis and interpretation of data: BL, TH.
Drafting the article and revising it: BL, FR, HA, TH.
Providing intellectual content: BL, FR, HA, TH.
Approval of final version: BL, FR, HA, TH.

Funding

This project received the "António Morais Samento" research grant from the Portuguese Society of Transplantation. This funding had no role in: the study design; collection, analysis, or interpretation of data; in the writing of the report; neither in the decision to submit the article for publication.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest to disclose.

Data availability

Data will be made available on request.

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DISCUSSION

4. Discussion and final remarks

When possible, and compared with dialysis treatments, kidney transplantation increases patients' survival, improves their quality of life, has a lower long-term cost, and has a much lower environmental impact [68]. Defining a new set of rules for kidney allocation in transplantation is not just a matter of shouting in the dark and hoping that, for some unknown reason, we will somehow magically get there.

Any decision on a new KAS must be transparent, accountable, evidence-based, able to anticipate the needs of patients, and take into account the potential harm to patients caused by the system. With this thesis and our findings, we hope to contribute to the debate on this issue.

4.1. Limitations / Exclusions

In Portugal, we do not have meaningful open data on waitlisted transplant candidates and organ donors [10], nor a detailed immunological and demographic characterisation of patients and donors. This lack of data and information is a limitation when we want to simulate models that use data such as those needed to calculate the KDPI and the EPTS scores [69]. Therefore, one of the factors leading to the exclusion of the United States KAS from the KARS application, at least in its initial version, is the lack of accessible data. Furthermore, due to the aforementioned data limitations, the models included in this version of the KARS application do not include paediatric patients, regional allocation, candidates requiring multiple organs, or individuals requiring retransplantation.

Here, we have introduced and validated an approach to evaluate and compare allocation models in renal transplantation. We intend to incorporate additional models to be evaluated. Our package *histoc* [45] will grow to include other allocation models and consequently, future versions of the KARS application will also allow anyone to test these models.

4.2. The Portuguese case

Discussing the best rules for the distribution of deceased donor kidneys for transplantation is currently an urgent matter within the Portuguese transplant community. The current Portuguese rules are more than sixteen years old and we need to re-evaluate them in the light of our best knowledge [9]. A recent decree of the Portuguese Ministry of Health [70] establishes a working group to analyse and revise the rules for the selection of donor-recipient pairs in kidney transplantation. It is advisable that the recommendations made by this working group should be based on simulations, and we hope that the solutions presented here may have an impact on the work that will be carried out within the framework of that decree [71].

Furthermore, the definition of kidney allocation rules cannot be seen as a one-off exercise at a particular point in time. Any type of new KAS that may result from this effort will have to be followed up by analysing its impact both on the outcome of new transplants and on the evolution of the waiting list of transplant candidates. It is expected that the working group now formed will have regular access to indicators and systematic information based on reliable (and preferably public) data, which will allow the group to formulate insights on the evolution of kidney transplantation in Portugal.

In any case, we intend to continue our work, including the evaluation of the future Portuguese kidney allocation system, wherever it may be. We believe that the framework presented in this thesis (which was also used to propose our EQM model) would apply to the upcoming allocation model. Furthermore, we intend to enrich our KARS application with any new allocation model that emerges from the revision of Portuguese rules, so that other researchers can test their data.

**Revision of the Portuguese Rules for the Selecion of the Donor-Recipient Pair in
Kidney Transplantation**

Bruno A Lima, Helena Alves. *Port Kidney Journal* 2024; 38(1): 54-57

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Revision of the Portuguese Rules for the Selection of the Donor-Recipient Pair in Kidney Transplantation

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<https://doi.org/>

Abstract

The process of reviewing and updating the rules for the selection of donor-recipient pairs in transplantation is underway, 16 years after the implementation of the current rules. Shortly after the implementation of the 2007 rules, some voices questioned the effectiveness of their results. Therefore, in addition to technical and scientific advances, the errors identified in the past should also serve as lessons learned for this new process underway.

We hope that the current review will lead to simpler, more transparent and fairer allocation rules for such a precious commodity as deceased donor kidneys for transplantation.

Keywords: Donor Selection; Kidney Transplantation; Portugal; Resource Allocation; Tissue and Organ Procurement

INTRODUCTION

The current rules for selecting the donor-recipient pair in transplantation with kidneys from deceased donors were approved by Order No. 6537/2007.¹ These rules repealed those implemented in 2000,² maintaining the text: “Organs for transplantation are a community asset, destined for patients who, with this gesture, will be able to improve their survival and quality of life. For this reason, the choice of donor-recipient pair should always follow the criteria that can best fulfill these objectives, being updated whenever the state of the art recommends it, thus respecting the principles of equity and medical ethics.”

While the current rules were updated seven years after the implementation of the 2000 rules, we had to wait more than 16 years for the Portuguese Ministry of Health, through Order no. 5908/2023 of 25 May,³ to create a working group with the power to analyze and review the rules for selecting the donor-recipient pair in transplantation with deceased donor. This Order from May now states, in relation to Order no. 6537/2007, that “the experience acquired in the meantime with its application and technical scientific progresses demonstrate the need to revise it, in order to updating the clinical and laboratory criteria and the donor eligibility criteria”. But in fact, shortly after they came into force, several voices questioned the results of implementing the 2007 standards.⁴ Furthermore, to date

there is no published evidence to justify the implementation of the 2007 rules from a technical-scientific point of view.

Now that a new process is underway to update the rules for selecting the donor-recipient pair in kidney transplantation, we can only hope that the mistakes of the past are not repeated and that the criteria used to define the new standards are in fact transparent, respecting the principles of fairness and medical ethics.

ASSESSMENT OF PATIENTS AND DONORS

The assessment of the rules for allocating deceased donor kidneys for transplantation must be based on a continuous process adaptable to the evolution of both the patients on the transplant waiting list and the organ donors themselves.⁵ This assessment should be as objective as possible, based on the most up-to-date data and systematic information that can describe both the evolution of the waiting list and the kidney transplants carried out over the last few decades.⁶

Data on end stage renal disease patients who have been or are still on the waiting list for transplantation can come from various sources, such as histocompatibility laboratories, nephrology consultants, hemodialysis centres or transplant units. The definition of objective and systematic

Received: 01/11/2023 Accepted: 22/12/2023 Published Online: 08/01/2024 Published: 11/03/2024

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metrics that can be obtained from this data would allow for better decision-making, also in the evaluation of health policies applicable to the distribution of deceased donor kidneys for transplantation.⁷

In Portugal, there are many entities involved in transplantation activities, namely: the Instituto Português do Sangue e da Transplantação (IPST) with its three *Centros de Sangue e Transplantação*; the five *Gabinetes Coordenadores de Colheita e da Transplantação*, whose focal point is the Hospital Donation Coordinator; and the seven Transplant Centres spread across the country. Each patient on the waiting list can also be registered at two transplant centres, so the process of assessing the candidate for a kidney transplant (and generating all the data that needs to be analyzed) is not simple for either the patients or the medical teams dedicated to this activity.⁸

Currently, the data available on kidney transplantation in Portugal is clearly insufficient. In particular, and because transplantation activities are sponsored by the National Health System, it would be expected that the IPST, as the entity responsible for managing the transplant waiting list, would be able to make data and public information available that would benefit individual patients and could promote research in this area.⁹ Making this type of data available would also be a way of increasing health literacy and community involvement in defining new health policies.¹⁰ It is not intended that individual data be made available, but with the correct characterization of both patients and donors it would be possible to generate more accurate synthetic data and apply data science technologies with which we could obtain new answers to old questions.¹¹ Nevertheless, there are also great examples of efficient data collection and management for kidney transplant recipients and donors. For instance, the CRISTAL application, initiated in 1996 and overseen by the Agence de la Biomédecine, is a nationwide database that systematically gathers information on organ transplants in France. Similarly, the Scientific Registry of Transplant Recipients in the United States is a noteworthy model that Portugal might contemplate adopting.

EQUITABLE DISTRIBUTION

A system for allocating deceased donor kidneys for transplantation must take into account not only the relationship between supply and demand, but also a balance between the net survival benefit that can be attributed to an organ and the waiting time for candidates, along with their likelihood of having access to a transplant.⁶ In other words, any kidney allocation system in transplantation has to take into account the scarcity of available organs, in the search for a fair distribution that can maximize efficiency and allow equitable access, while respecting *Leges Artis*. Unfortunately, the rules of Order No. 6537/2007, which are still in force, have long failed to fulfill this conjecture.¹²

From a utilitarian point of view, the aim of a kidney allocation system is to maximize the total benefit that can be obtained from an organ, while from an egalitarian point of view, all transplant candidates should have the same probability of being transplanted.⁶ According to the ethical principle of justice, equals should be treated equally so that all patients have a similar chance of access to transplantation. On the other hand, considering utilitarian values, some inequalities can be allowed if this gives society- as a group- the greatest benefit by maximizing the utility of resources. Thus, deceased donor kidneys can be directed to patients who can put them to better use and who are less likely to return to the waiting list due to graft rejection.¹³

HISTOCOMPATIBILITY

The success of kidney transplantation depends (to a large extent) on the genetic and immunological compatibility between donor and recipient. Human leucocyte antigens (HLA) are highly polymorphic proteins that play a key role in transplantation. An important barrier to transplantation is HLA sensitization of transplant candidates. The most common sensitization events are blood transfusions, pregnancies and organ transplants, the latter having the greatest potential for sensitization.¹⁴ After the loss of an organ, the risk of a patient developing HLA antibodies *de novo* increases exponentially.¹⁵ Donor-specific antibodies (DSAs), both those present at the time of transplantation and those that arise *de novo*, are a risk factor for rejection and potential organ loss.¹⁶

The identification of HLA antibodies and consequently the definition of non-acceptable HLA antigens for transplant candidates have made it possible to develop concepts of calculated panel reactive antibody (cPRA) and virtual crossmatch (vXM). The cPRA value of a given transplant candidate serves as an estimate of the likelihood that the next available transplant donor will be incompatible with that candidate. This value depends not only on the identification of HLA antigens that are not acceptable for the patient, but also on the HLA frequencies of the population to which the organ donors belong.¹⁷ The way in which these non-acceptable antigens are defined can restrict the chances of finding a possible donor for the patient.¹⁴ Therefore, the cPRA value and the vXM result have to be read as two sides of the same coin.¹⁸

The number of patients on the waiting list for re-transplantation has increased progressively in recent years. Re-transplantation also offers these patients a survival benefit when compared to those who remain on dialysis.¹⁴ This group of patients represents the largest portion of all hypersensitized patients on the waiting list. HLA sensitization compromises access to subsequent transplantation¹⁵ and the difficulty of transplanting these patients means that they remain on the waiting list forever.¹⁴

Kidney transplantation requires a careful immunological study of the donor-recipient pair. Although a positive vXM is a contraindication for transplantation, it can be seen only as an increased risk factor, depending on the patient's history and level of sensitization.¹⁶ Stratifying a transplant candidate's risk of DSAs is fundamental for a clinical assessment of the implications they may represent.¹⁶ Hypersensitized patients have a clear disadvantage in access to kidney transplantation¹⁵ and the current allocation system does not compensate for this disadvantage in an efficient way. The characterization of hypersensitized patients using a measure such as the cPRA is essential for clinicians to be able to inform patients about their real chances of being transplanted.¹⁵ One way of preventing sensitization in re-transplant candidates is to improve the HLA match at the first transplant.¹⁴ In addition, allocation programs aimed at hypersensitized candidates have been proposed as a way of mitigating the disadvantage to which they are subjected in terms of access to transplantation.¹⁴

TRANSPARENT RULES

When possible and compared to dialysis treatments, kidney transplantation increases patient survival, increases their quality of life, has a lower long-term cost and has a much lower environmental impact.⁸ However, the current rules for selecting the donor-recipient pair in kidney transplantation, which have been in force since 2007, are unnecessarily complex, non-transparent and inequitable.⁵ More than enough time has passed to justify an evaluation of the results of these rules and the introduction of improvements in the light of new clinical data available.¹⁹ Given the limitations of healthcare resources, decisions on how best to distribute these scarce goods (such as deceased donor kidneys for transplantation) should be based on the conditions: of publicity (decisions to implement new health policies must be publicized), of relevance (the rationale for decisions must be supported by data), of appeal (a mechanism for challenging decisions taken must be guaranteed) and of regulation (the decision-making process must be regulated to ensure that the previous conditions are met).¹³ Only by applying these four conditions can the legitimacy of the process for defining new rules for selecting the donor-recipient pair in kidney transplantation be guaranteed. A change is needed, but first it is necessary to carry out simulations that allow us to understand the implications they may have on the waiting list and to anticipate other repercussions that may arise.¹² This type of simulation

must be carried out transparently and based on methods that have been previously tested and evaluated.²⁰ While simplicity alone should not dictate the choice of new rules, it is essential to consistently evaluate them against straightforward and comprehensible rules that act as a reference point for transparency.

The definition of new standards can result from the evaluation of existing models, or from a systematic review of the literature, or from an idea based on empirical knowledge, or even from the consensus of a group of experts. In any case, it would always be desirable for these new rules to first be published in a scientific journal before being published in the Portuguese Republic Official Journal (*Diário da República*).²¹

CONCLUSION

Order no. 5908/2023 defines a working group, which lists some names of indisputable professional and technical-scientific competences for the task assigned to them. Even so, it was given to the IPST's *Coordenação Nacional da Transplantação* (CNT) the task of coordinating the work of this group (with a casting vote). Unfortunately, we do not know of any published scientific work on access to transplantation from CNT, so our expectations can not be very high.

The politician who signed Order 5908/2023 did not have the foresight to give this working group the task of monitoring the implementation of the solutions it was asked to find. The definition of rules for the selection of the donor-recipient pair in deceased donor kidney transplantation cannot be seen as a one-off task at a given moment in time. Any type of rules that may emanate from this endeavor, in addition to a systematic evaluation, must be followed up with an analysis of their impact, both on the outcome of new transplants and on the evolution of the waiting list of transplant candidates.

It would be desirable for the working group now formed to have access to indicators and systematic information every six months, based on reliable (and preferably public) data, which would allow it to draw conclusions about the evolution of kidney transplantation in Portugal. Moreover, considering that it has been over 15 years since the reassessment of rules that have been questioned almost since their introduction, legislators should now seize the opportunity to prescribe a specific timeframe for their revision. Whatever new rules are implemented, we can only hope that they will be the result of a transparent, verifiable and auditable process, unlike the one that took place in 2007.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

Contributorship Statement

BAL: Writing the original draft, Study conception. Read and approved the final manuscript

HA: Conceptualization and supervision. Read and approved the final manuscript

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4.3. More open-source solutions

Even in the absence of real data, we have developed an R package (*simK* [46]) that allows the generation of synthetic data for the evaluation of our models. In addition, this package is now available for anyone to use for testing our applications or for other research purposes. We plan to extend this package with additional functionalities to broaden its use. We want to be able to simulate new variables for both patients and donors and to use other models to generate synthetic data.

To evaluate and test the allocation models, we have had to create new functionalities and adopt new approaches. We have also made a point of creating open-source web applications that are accessible to anyone interested, regardless of their knowledge of advanced programming languages, and whenever possible. However, we believe that our applications can be improved in terms of usability, so in future work we want to directly contact a group of researchers and get their feedback on the available software.

Therefore, the creation of the TxOR initiative [40] was designed as a central hub where all our work is accessible and from which we can anticipate further expansion to incorporate new solutions. The TxOR website catalogues all the open-source software that has been created and serves as an optimal point of contact for those who may be interested in it.

4.4. Conclusion

Finally, we presented a proposal for a new KAS based on an equity matrix (EQM) [67]. The aim was to formulate a straightforward and clear-cut model that balances the criteria of utility and justice in the allocation of deceased donor kidneys for transplantation. At the very least, the EQM can be used as a benchmark against which any proposed new KAS can be compared.

Wrapping up this thesis, in addition to proposing the EQM model as a potential candidate for a new KAS, we have mainly introduced an approach to evaluate and compare the implementation of different KAS in transplantation.

To create this framework, we have also developed software that can generate synthetic data for transplant candidates and organ donors, as well as replicate histocompatibility tests and allocation criteria. All of this software is available in an open-source format, along with comprehensive instructions for its potential users.

Since searching for optimal rules for the allocation of deceased donors' kidneys in transplantation requires a continuous effort, we cannot blindly follow the first set of rules established by any authority. Especially in the Portuguese context, where the journey of developing a new KAS is just beginning, the framework we have implemented can serve as a guide for those in charge, helping them to make the most informed decision based on available data.

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