Jul 12, 2021

Eurotransplant Kidney Allocation Simulations

Matthias Niemann[1], Nils Lachmann[2], Kirsten Geneugelijk[3], Eric Spierings[3]

[1]PIRCHE AG; [2]Charité Universitätsmedizin Berlin; [3]University Medical Center Utrecht

1 *Works for me* Share dx.doi.org/10.17504/protocols.io.bqrtmv6n

PIRCHE AG

Matthias Niemann

ABSTRACT

Background:

The EuroTransplant Kidney Allocation System (ETKAS) aims at allocating organs to patients on the waiting list fairly whilst optimizing HLA match grades. ETKAS currently considers the number of HLA-A/-B/-DR mismatches. Evidently, epitope matching is biologically and clinically more relevant. We here executed ETKAS-based computer simulations to evaluate the impact of epitope matching on allocation and compared the strategies.

Methods:

A virtual population of 400,000 individuals was generated using the National Marrow Donor Program (NMDP) haplotype frequency dataset of 2011. Using this population, a waiting list of 10,400 patients was constructed and maintained during simulation, matching the 2015 Eurotransplant Annual Report characteristics. Unacceptable antigens were assigned randomly relative to their frequency using HLAMatchmaker. Over 22,600 kidneys were allocated in 10 years in triplicate using Markov Chain Monte Carlo simulations on 32-CPU-core cloud-computing instances. T-cell epitopes were calculated using the www.pirche.com portal. Waiting list effects were evaluated against ETKAS for five epitope matching scenarios.

Results:

Baseline simulations of ETKAS slightly overestimated reported average HLA match grades. The best-balanced scenario maintained prioritisation of HLA A-B-DR fully matched donors while replacing the HLA match grade by PIRCHE-II score and exchanging the HLA mismatch probability (MMP) by epitope MMP. This setup showed no considerable impact on kidney exchange rates and waiting time. PIRCHE-II scores improved, whereas the average HLA match grade diminishes slightly, yet leading to an improved estimated graft survival.

Conclusions:

We conclude that epitope-based matching in deceased donor kidney allocation is feasible while maintaining equal balances on the waiting list.

DOI

dx.doi.org/10.17504/protocols.io.bqrtmv6n

PROTOCOL CITATION

Matthias Niemann, Nils Lachmann, Kirsten Geneugelijk, Eric Spierings 2021. Eurotransplant Kidney Allocation Simulations. **protocols.io** https://dx.doi.org/10.17504/protocols.io.bqrtmv6n

KEYWORDS

kidney transplantation, organ allocation, simulation, epitope matching

CREATED

Dec 15, 2020

LAST MODIFIED

Jul 12, 2021

PROTOCOL INTEGER ID

45587

GUIDELINES

NA

MATERIALS TEXT

Computer with internet access. Depending on allocation, compute clusters or cloud computing instances may be required. Implement via any scripting language like python 3.6

Computer or calculator or equivalent NA
Computer software (e.g. Excel) with the mean and standard deviation functions

SAFETY WARNINGS

NA

Data aquisition 1d

1 Collect demographic data from Eurotransplant Annual Report page

- age distribution per country
- donor blood group distribution per country
- recipient blood group distribution per country on the initial waiting list
- number of DBD donors per country
- number of DCD donors per country
- DBD/DCD acceptance matrix, i.e. which country accepts which donor types
- number of organ donors involved in later transplantation
- number of used donor kidneys per donor per country
- PRA group distribution per country
- probability of transplant center rejecting an organ offer per HLA match grade, in our case 0.1 for all situations
- patients removed from the waiting list per country, subtracted by the ETKAS transplanted patients per country
- urgency distribution per country
- country distribution of patients on the waiting list, for bootstrapping only
- country distribution of patients registered to the waiting list
- waiting time distribution of patients on the waiting list per country, for bootstrapping only
- waiting time distribution of patients registered to the waiting list per country

2 Download NMDP haplotype frequency dataset

3 Download HLA Matchmaker, extract eplet definitions as CSV

4 Download rel-dna-ser file containing serological equivalents for alleles WMDA

Data preprocessing 1d

5 Create virtual phenotypes by randomly picking two haplotypes

- Select population, 2011 EURCAU in our case
- considering weight in random selection
- exclude phenotypes with identical haplotype
- add translation into serological equivalents

6 Append PIRCHE Risk Profile median to virtual phenotypes

- top 50 haplotypes in 2011 EURCAU population

via REST API

Bootstrap 1d

7 Generate virtual initial waiting list

7.1 pick random phenotype from virtual population

7.2 randomly select patient country, considering country distributions on waiting list

7.3 randomly select patient age range based on country

7.4 randomly select waiting time range based on country with uniform distribution within waiting time range

7.5 randomly select urgency based on country

7.6 randomly select PRA range based on country with uniform distribution within PRA range, used as target PRA

7.7 Iteratively add unacceptable alleles randomly based on allele frequency
Translate current unacceptable alleles to eplets with respect to self-eplets
calculate current PRA based on eplets in virtual population
repeat steps until current cPRA is target PRA +- 4 %
discard random unacceptable alleles if PRA exceeds threshold or if eplets matching with self-eplets

7.8 translate unacceptable alleles to unacceptable antigens
allele-specific antibodies are not translated into an unacceptable but are kept for later crossmatching

Simulation 1w

8 Iterate over 3650 days, i.e. 10 years each having 365 days

Citation: Matthias Niemann, Nils Lachmann, Kirsten Geneugelijk, Eric Spierings (07/12/2021). Eurotransplant Kidney Allocation Simulations. https://dx.doi.org/10.17504/protocols.io.bqrtmv6n

9 Generate donor

9.1 Randomly select number of donors available "today"

9.2 Iterate over donors

9.3 Draw random phenotype from virtual population without replacement

9.4 Randomly select donor type based on distributions, i.e. DBD/DCD

9.5 Randomly select donor country based on distributions

9.6 Randomly select donor blood group based on distributions

9.7 Randomly decide number of kidneys harvested from this donor

10 Allocate donor to current waiting list

10.1 Filter waiting list by donor acceptance in country

10.2 Filter waiting list by blood group identity

10.3 Filter waiting list by unacceptable mismatches

10.4 Add *points* for waiting time, 0.091/d

10.5 Calculate PIRCHE scores for waiting list and donor, via REST API

10.6 Add *points* for country balance, 10 * [maxCountryBalance - countryBalance]

10.7 Add 100 pediatric bonus *points*, multiply match points by 2 for pediatric patients

10.8 Add 500 HU bonus *points*, match points are ignored in this case

10.9 Add 300 *points* if donor and recipient country match

10.10 ⚠

Add 100 mismatch probability *points*:

$$mmp = 100 \times \left(1 - \left[bloodgroupFrequency * (1 - relativePRA) \times \left[1 - min\left[1, \frac{PIRCHE{-}II{-}Risk{-}Profile{-}median}{200}\right]\right]\right]\right)^{20}$$

10.11 ⚠

Citation: Matthias Niemann, Nils Lachmann, Kirsten Geneugelijk, Eric Spierings (07/12/2021). Eurotransplant Kidney Allocation Simulations. https://dx.doi.org/10.17504/protocols.io.bqrtmv6n

Add 400 *points* based on matching:

$$matching = 400 * max\left(-0.0111 * \left[1 + PIRCHE - II - Score\right], 0\right)$$

10.12 ⚠

Priority if PIRCHE-II score is below 9

10.13 Evaluate homozygous loci, per homozygosity add 1 to *homozygosity score*

- HLA-A, -B, -DRB1

10.14 For fully homozygous donors: sort descending by *priority*, *homozygosity score* and *points*
For other donors: sort descending by *priority* and *points*

10.15 Crossmatch recipient and donor, i.e. exclude if recipient unacceptable alleles contain donor allele

10.16 Select patients from the top of the ordered waiting list for each harvested kidney of current donor, randomly reject patient based on rejection probability

11 Remove selected recipients from the waiting list

12 Update country balance according to selected patients' country of origin and donor country

13 Evolve waiting list by increasing waiting time for all patients

14 Randomly deregister patients from the waiting list according to conditional probability

15 Register new patients to the waiting list, see **step #7**

16 **go to step #8 , start next day**