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Calculated panel reactive antibody with decimals: A refined metric of access to transplantation for highly sensitized candidates

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ABSTRACT

The use of the calculated panel reactive antibody (CPRA) value and the implementation of allocation points for sensitized candidates by the United Network for Organ Sharing (UNOS) have improved access to kidney transplantation for highly sensitized candidates (98% CPRA and above). Despite this, a large population of highly sensitized candidates remain awaiting transplantation. To better define this population, we propose the use of two refinements of the standard UNOS CPRA, the CPRA with decimals or CPRAd, and the likelihood of a compatible donor (LCD). These refined metrics of the standard UNOS CPRA will allow transplant programs to describe their patients' access to transplantation with increased granularity and will help in decisions regarding the use of desensitization.

1. Introduction

Anti-human leukocyte antigen (HLA) antibodies in the transplant recipient directed against the allograft were first shown to cause hyperacute graft failure in 1966 [1]. Since this time, multiple technologies have been developed to identify and exclude recipient antibodies to donor HLA antigens that will lead to graft failure. The first of these technologies was the crossmatch, in which a cytotoxic reaction between recipient serum and donor lymphocytes was found to strongly correlate with graft failure [2]. This technique was extended to transplant candidates on the waiting list in order to identify those sensitized patients with anti-HLA antibodies [3]. The level of sensitization was quantified by determining the panel-reactive antibody (PRA): the number of cytotoxic reactions using recipient serum and a panel of third-party lymphocytes that was representative of different HLA phenotypes in the population divided by the total number of reactions [4]. Patients with high levels of sensitization, as indicated by a higher PRA, were more likely to have a positive crossmatch at the time of transplantation.

In 1985 Zachary and Braun described a new method for calculating the probability of finding a compatible donor, which they termed P_C, based on the level of sensitization of the patient by using the gene frequency of the excluded HLA antigens in historic donors [5]. This method overcame the limitation that PRA values for recipients with similar levels of sensitization would vary between laboratories due to the different lymphocyte panels used. Rather than using P_C as a predictive metric, UNOS implemented its inverse – the probability of a positive crossmatch – based on HLA antigens which need to be excluded in 2009 [6].

Given a large number of sensitized patients on the waiting list [7] who experience a prolonged waiting time [8] and an increased risk of mortality [9], points are awarded for sensitization in the kidney allocation system. As a result of these policy changes, the overall number of sensitized kidney transplant candidates on the waiting list has decreased, but the number of very highly sensitized transplant candidates on the waiting list (CPRA greater than 98%) has increased substantially between 2003 and 2013 [7]. The CPRA as currently implemented in the OPTN kidney allocation system is an integer percentage between 0% and 100%. As such, the CPRA of candidates with a true CPRA of 99.5% or greater will round to CPRA of 100%. Given recent updates to kidney allocation policy that give a large priority for allocation to these very highly sensitized transplant candidates [10], measurement of the level of sensitization with increased granularity is necessary.

Abbreviations: CPRA, calculated panel reactive antibody; CPRAd, calculated panel reactive antibody with decimals; HLA, human leukocyte antigen; LCD, likelihood of finding a compatible donor; UNOS, United Network for Organ Sharing.

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In this study, we propose the use of a refined definition of the standard UNOS CPRA as a probability value expressed from 0 to 1, with as many decimal places as needed. We term this modification the CPRA with decimals (CPRAd). The use of the CPRAd also facilitates conversion of the CPRA value to the likelihood of finding a compatible donor (LCD), which is particularly useful for assessment of very highly sensitized transplant candidates.

2. Materials and methods

2.1. CPRA with decimals (CPRAd)

CPRAd is calculated the same way as the CPRA implemented by UNOS [11] with the difference that the CPRA is rounded to the nearest integer, whereas CPRAd is a decimal number between 0 and 1. We utilized the same HLA antigen and haplotype frequencies used by UNOS for calculation of the CPRA, which were obtained from the tables "Proposed CPRA frequencies (Excel) – implemented in 2013" available online from UNOS [12].

2.2. Likelihood of compatible donor (LCD)

For sensitized patients with CPRA greater than 50%, there will be a substantially reduced frequency of compatible donors in the population. For patients with CPRAd greater than 0.995 (100% CPRA), the CPRAd becomes cumbersome for the description of the level of sensitization given the large number of decimal places required. To better express the number of potential compatible donors within the population, we defined the likelihood of finding a compatible donor (LCD) as:

$$LCD = 1\ in \frac{1}{1 - CPRAd} \quad (1)$$

with rounding to the nearest integer. The relationship between CPRA and LCD is shown in Fig. 1A where a candidate with 50% CPRA will have an LCD of 1 in 2 (1:2) and another one with 99% CPRA will have an LCD of 1:100.

The LCD is particularly useful for very highly sensitized patients as shown in Fig. 1B. We use the term "very highly sensitized" to refer to patients with CPRA of 98% or greater (CPRAd of 0.98 or greater, LCD of less than 1:50) and "extremely sensitized" to refer to patients with CPRA of 100% (CPRAd of 0.995 or greater, LCD of less than 1:200).

2.3. Patient selection

Data from the UNOS kidney transplant waiting list as of 7/24/2015 were used. This included kidney transplant candidates added to the waiting list between 1/1/2010 and 4/30/2015. We excluded candidates (1) with CPRAd greater than 0.9999967 due to inconsistencies of unacceptable HLA antigens (n = 14) and (2) candidates with data entry errors for the date of waiting list removal (n = 2). HLA antigen inconsistencies included the exclusion of all HLA-DQ or DR antigens. The final data set contained 195,321 kidney transplant candidates. Calibration between the UNOS CPRA and the CPRAd was assessed using a subset of kidney transplant candidates removed from the waiting list after 2/1/2015 (n = 17,415).

For kidney transplant candidates with a CPRA of 100% at our institution, antibody mean fluorescence intensity (MFI) was determined via single-antigen Luminex assay (Luminex, One Lambda Inc., Canoga, Park, CA). The MFI cutoff for considering positive antibodies was 2,000.

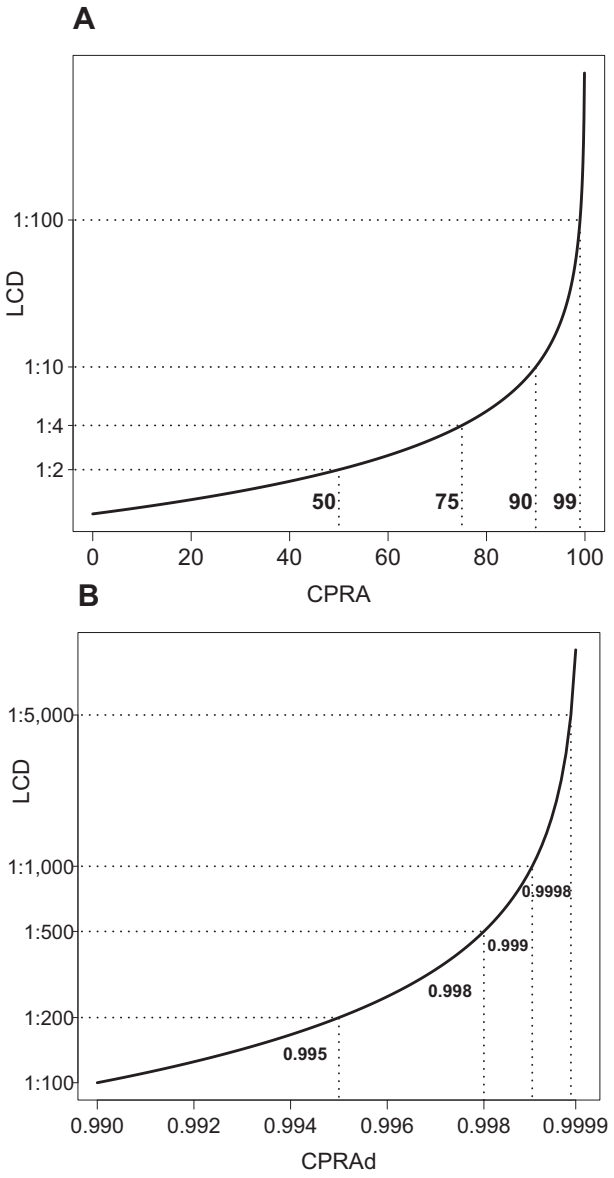

Fig. 1. A. The relationship between the CPRA and the likelihood of finding a compatible donor (LCD). The LCD is shown for a CPRA 50%, 75%, 90% and 99%. A transplant candidate with a CPRA of 50% will have a LCD of 1 in 2 (1:2), a CPRA of 75% will have a LCD of 1:4, a CPRA of 90% will have a LCD of 1:10, and a CPRA of 99% will have a LCD of 1:100. B. The relationship between the CPRA with decimals (CPRAd) and the likelihood of finding a compatible donor (LCD) for very highly sensitized candidates. As the reverse of the CPRAd, the LCD facilitates recognition of the degree of sensitization by expressing the number of compatible donors in the population for a transplant candidate.

2.4. CPRAd and LCD calculator

CPRAd and LCD were calculated with a Visual Basic program developed by M.J.P. To facilitate calculation of the CPRAd and LCD, E.P.K. developed the "cprad" package within the R program [13] that can be downloaded and installed for local use at https://www.github.com/evanpk/cprad. In addition, the calculator is available on the internet at https://txp-toolbox.shinyapps.io/cprad.

In the Supplementary Materials we have also provided R code that can be used to calculate CPRA or LCD for a single (Supplementary Document 1) or multiple candidates (Supplementary Document 2).