Original Article

Calculated Panel Reactive Antibody for an Organ-Sharing Zone: Concept and Execution Based on Data from North Kerala

Abstract

Background: Calculated-PRA (CPRA) is derived by virtually matching a recipient's antibody profile against HLA antigens of a representative donor pool of a geographical region. **Materials and Methods:** An android application–based CPRA calculator was created from HLA typing data (A/B/DR loci) of 712 consecutive living donors spanning over last 10 years from an organ-sharing region in Kerala. Only an open-source software was used. **Results:** Our HLA data, compared with the National Marrow Donor Program (NMDP) 2011 database, show that the most common haplotype frequencies show comparable positions in order of prevalence. Available online PRA calculators like OPTN and Canadian CPRA show significant differences in PRA estimation when used in our population. This calculator provides a more accurate and realistic estimate of sensitization against the representative donor pool. **Conclusion:** This CPRA tool can be customized for any allocation region using portable open-source software. The donor pool can be updated continually by populating data from multiple regional centers.

Keywords: *Calculated panel reactive antibody, Sensitisation, Renal transplant, Organ allocation*

Sooraj Sasindran[1], Feroz Aziz[2,3], Sajith Narayanan[3], Melemadathil Sreelatha[4], Benil Hafeeq[2], Ismail N Aboobacker[3], Sunil George[5], Vinugopal Sreekumar[6], Sreejesh Balakrishnan[3], Ranjit Narayanan[2,7], Ginil Benny[8]

[1]Department of Nephrology, Dr. Moopen's Medical College, Wayanad, [2]Department of Nephrology, Iqraa International Hospital and Research Center, [3]Department of Nephrology, ASTER MIMS Hospital, [4]Department of Nephrology, Government Medical College, [5]Department of Nephrology, Baby Memorial Hospital, Calicut, [6]Department of Nephrology, Meitra Hospital, Calicut, [7]Department of Nephrology, ASTER MIMS Hospital, Kottakkal, [8]Immunology Lab, ASTER MIMS Hospital, Calicut, Kerala, India

Corresponding author: *Sooraj Sasindran, Department of Nephrology, Dr. Moopen's Medical College, Wayanad, Kerala, India. E-mail: sooraj87@gmail.com*

DOI: 10.25259/ijn_493_23

Received: 17-01-2024
Accepted: 23-07-2024
Online First: 18-09-2024
Published: ***

Introduction

An allograft recipient harboring donor-specific antibodies causing positive cross-match is an unambiguous contraindication for renal transplantation. Immunologically sensitizing events like blood transfusion, pregnancy, and prior transplantation remain the most common triggers for allosensitzation. Though the utility of cross-match as the final gatekeeper was established by Terasaki in 1969, the concept of allosensitization has evolved over the years.[1] Reactivity of the recipient's sera against a panel of HLA antigens representative of the potential donor pool has been the central theme of defining the index of sensitization and is expressed as a percentage (PRA–panel reactive antibodies).[2] Higher PRA means the chance of getting an immunologically compatible donor is less than the one with lower PRA. Sensitized patients are getting accrued and account for more than 10% of any transplant wait list (TWL).[3,4] With the advent of single antigen bead (SAB) assay, the concept of PRA has evolved from cell-based panels to computed calculated-PRA (CPRA), which is derived by virtually matching a recipient's antibody profile against HLA antigens of the representative donor pool of a region. Sensitized patients are prioritized for organ allocation as per CPRA values in countries with a structured deceased donor program.[5] In India, the deceased donor program is only evolving with no centralized organ sharing. Health in India remains a state subject, with each of the 28 states of the Indian Union having its policies for organ allocation. In India, we have not compiled or analyzed the HLA data about an organ-sharing region, and the size and diversity of the country add to the complexity of identifying a representative donor pool.

The study aims to construct a portable software-based CPRA tool for an organ-sharing geographical zone from the most updated and representative HLA data freely accessible to transplant professionals of the region that can give a fair idea of the degree of sensitization with respect to the representative donor region. The CPRA readout can be used as a reliable guide to plan desensitization or paired kidney exchange (PKE) or for proceeding with a deceased donor organ program.

How to cite this article: Sasindran S, Aziz F, Narayanan S, Sreelatha M, Hafeeq B, Aboobacker IN, *et al*. Calculated Panel Reactive Antibody for an Organ-Sharing Zone: Concept and Execution Based on Data from North Kerala. Indian J Nephrol. doi: 10.25259/ijn_493_23

We aimed to create a mobile device platform–based application that works with offline as well as online databases, as the existing web-based calculators, such as the organ procurement and transplantation network (OPTN) and the Canadian Calculator and Eurotransplant Calculator, need a full-sized web browser window with internet connectivity for proper operation.[6-8]

Materials and Methods

HLA typing data (A/B/DR loci) of 712 living donors spanning over the last 10 years from December 2011 to December 2021 were retrospectively collected from the central transplant immunology lab after informed consent ensuring de-identification. Only inhabitants of North Kerala were included. Ethical approval was not obtained as dataset has no identifying information. All HLA typing was performed at the transplant immunology laboratory at ASTER MIMS Hospital, Kozhikode, using polymerase chain reaction (PCR) sequence-specific oligonucleotide probe (SSOP) and sequence-specific primer (SSP) methods. Four-digit typing was converted to serological equivalents. Typing data were compiled in a worksheet. CPRA calculation was done by the donor filtering method, which was comparable to the allele frequency method according to Chan *et al.*[9] Python code was used to filter out unacceptable donors from the pool.[10] A graphical user interface was designed using the Kivy framework.[11] An android app was compiled using python-for-android build tools.[12] Only an open-source software was used. Apps can also be tweaked to read HLA typing data from a cloud-based live database contributed by multiple transplant centers in concert.

Results

HLA typing data of 712 living donors retrospectively collected over the past 10 years were analyzed. Our donor pool was representative of a population of around 14.65 million from five districts of North Kerala.[13] This ratio was comparable to 12,000 donor data used by the OPTN calculator for a population of 310 million of the United States; 10,000 donor data used by the Eurotransplant calculator for a population of 740 million of Europe, and 2,696 donor data used by the Canadian calculator for a population of 38.2 million of Canada.[7,14,15] Haplotype frequencies of A, B, and DR loci were compared to those downloaded from the National Marrow Donor Program (NMDP) 2011 database.[16] The most prevalent haplotype was A*33:03, B*44:03, and DRB1*07:01 closely followed by A*01:01, B*57:01, and DRB1*07:01 in our data as well as in the South Asian subset of NMDP 2011 database. Incorporation of CPRA as a weightage in an organ allocation algorithm mandates the calculation to be based on a representative donor pool. As our data were convincingly derived from a representative population, the same was used to write an algorithm to filter out unacceptable donors for sensitized patients in the TWL. This algorithm was packaged into an android app for portable use.

App download link: https://play.google.com/store/apps/details?id=org.prac.pracalc

Database link: https://docs.google.com/spreadsheets/d/1SE2QyYSMlTBxzeBk9yDpjr9cbT9BDhSg/edit?usp=sharing&ouid=114052726801807561841&rtpof=true&sd=true

App source code link: https://drive.google.com/file/d/1NfxgVxI7NOgy7oQXohzCjJUmE46BwuqR/view?usp=sharing

Inside the application input window, A, B, and DR unacceptable antigens can be entered in any order separated by comma, as shown in the screenshot [Figure 1]. Then, tap on "Click here to calculate PRA" to get the report in the same window. We have found a significant difference in PRA values for some common HLA antigens across different available calculators [Table 1].

Discussion

The transplant scenario of the Indian subcontinent had been handicapped in the past with a lack of panels representative of the donor population to do PRA calculation based on cytotoxicity or flow-cytometer

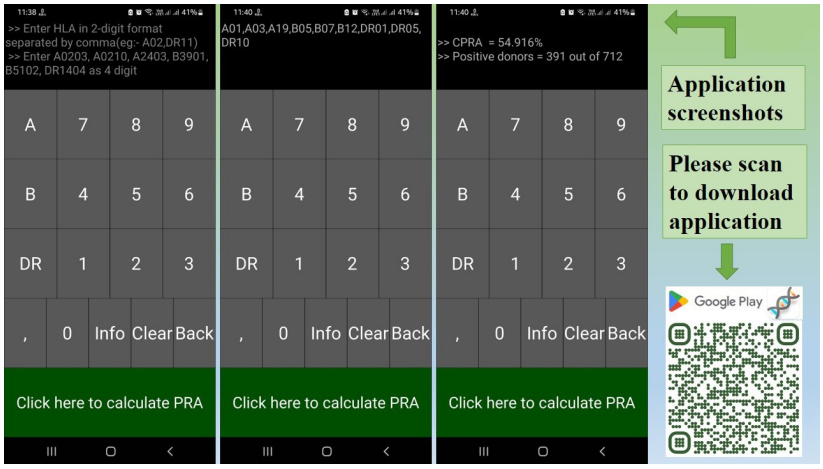

Figure 1: Application screenshots. HLA: Human Leukocyte Antigen, CPRA: Calculated Panel Reactive Antibodies, PRA: Panel Reactive Antibodies.

Table 1: Comparison of Our CPRA Frequencies with the OPTN Calculator, Canadian Calculator, and Eurotransplant Virtual PRA Calculator

HLA	OPTN CPRA	Canadian CPRA	Eurotransplant Virtual PRA	Our CPRA
A2	47.9	47.28	50.68	28.65
A24	17.42	19.21	17.75	37.07
A33	5.34	3.38	2.82	24.86
B7	21.43	23.26	21.65	21.62
B44	23.74	25.22	22.57	15.16
B58	4.38	3.08	1.93	14.04
DR7	21.81	24.52	22.41	31.03
DR15	25.67	26.41	23.03	34.12

All CPRA values are in percentage (%). HLA: Human Leukocyte Antigen, OPTN: Organ Procurement and Transplantation Network, CPRA: Calculated Panel Reactive Antibodies, PRA: Panel Reactive Antibodies

platforms. Multibead technology using the Luminex platform has revolutionized the concept of PRA with the introduction CPRA. The challenge of setting up a CPRA is to have HLA data which are updated and representative of the potential donor pool. In India, due to a lack of centralized organ-sharing policy and organized deceased donor program, there had never been a quest to seek a PRA tool that could be useful for routine transplant practice. During the last decade, transplant centers have been established in majority of the states of the Indian union. Each state has its organ-sharing program run by local rules and policies. Our center, where the retrospective study has been done, is situated in the northern region of Kerala, which has three distinct zones (North, Central, and South) for organ sharing. We assimilated the HLA data of 712 consecutive donors in the North Kerala region, spread over the last 10 years, to create an easy-to-use app-based CPRA which is representative of the subpopulation.

Our CPRA has the following advantages:

1. The calculator is representative of the local subpopulation. There is no other Indian calculator available due to a lack of pooled and updated HLA data in the public domain.
2. Available calculators like OPTN and Canadian CPRA show significant difference in PRA estimation when used in our population [Table 1].
3. The HLA data, when compared with the NMDP 2011 database, show that the most common haplotype frequencies are showing comparable positions in the order of prevalence.[16]
4. The tool can help to provide a more accurate and realistic estimate of sensitization against the representative donor pool.
5. The calculator helps to provide a road map to discuss the transplant prospects with an individual recipient with options of desensitization or PKE. Renal transplantation in India is primarily driven by living kidney donation. The utility of the concept of PRA can pave the way for the identification of patients who would benefit by PKE and can stimulate networking of transplant centers to populate a registry of pairs who can mutually benefit from the PKE program. This can serve as an objective tool for a transplant physician to recommend desensitization and transplantation for patients with high CPRA if they have a relatively acceptable living donor from an immunological standpoint, as we do not have a dependable deceased donor program.
6. Once the deceased donor program gains momentum, this tool can be the backbone for organ sharing and allocation.
7. The tool can be easily updated when designed to read HLA data from a cloud-based live database that is continually updated from a number of desired transplant centers.
8. It can be adopted by any state or region provided they can accrue the HLA data.

Our CPRA tool has certain limitations. Our data currently cover only A, B, and DR loci, but can be designed to include C, DP, and DQ as and when required. The tool is based on serological equivalents. Current day antibody profile using SAB is more identified at a four-digit allele level and hence can result in overestimation of the CPRA. The App is being updated to confer this ability using prospective high-resolution data.

Updated app download link: https://play.google.com/store/apps/details?id=org.prac.pracalc4

The application is currently limited to Android devices (Android version 9 and above), but the source code is written in a cross-platform programming language. All the limitations are technical and can be rectified in future updates.

Conclusion

Current day assessment of allosensitization is based on CPRA. The CPRA calculator has to be based on a representative donor pool for meaningful utilization. In India, we could develop an easy-to-use portable CPRA calculator based on the donor population of an organ-sharing zone, which could be emulated in the rest of the country. There is more than 10% difference in CPRA values across many common HLA antigens when compared to already available calculators of North America and Europe. Based on the breadth of sensitization, the clinician can discuss the option of desensitization, PKE, or probability of getting a deceased donor organ.

Conflicts of interest

There are no conflicts of interest.

References

1. Patel R, Terasaki PI. Significance of the positive crossmatch test in kidney transplantation. N Engl J Med 1969;280:735-9.
2. Cecka JM. Calculated PRA (CPRA): The new measure of sensitization for transplant candidates: Special feature. Am J Transplant 2010;10:26–9.
3. National data - OPTN. Available from: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/# [Last accessed on 2023 Jan 16].
4. Parsons RF, Locke JE, Redfield RR, Roll GR, Levine MH. Kidney transplantation of highly sensitized recipients under the new kidney allocation system: A reflection from five different transplant centers across the United States. Hum Immunol 2017;78:30-6.
5. Policies - OPTN. Available from: https://optn.transplant.hrsa.gov/policies-bylaws/policies/ [Last accessed on 2023 Jan 16].
6. CPRA calculator - OPTN. Available from: https://optn.transplant.hrsa.gov/data/allocation-calculators/cpra-calculator/ [Last accessed on 2023 Jan 6].
7. Canadian cPRA Calculator. Available from: https://ctr2.transplantregistry.ca/otd-cpra-client/ctr2.jsp [Last accessed on 2023 Jan 6].
8. Virtual PRA calculator. Available from: https://www.etrl.org/vPRA.aspx [Last accessed on 2023 Jan 16].
9. Chan YP, Wong MWK, Tang LWM, Guo M, Yang W, Ip P, *et al*. A simplified method of calculating cPRA for kidney allocation application in Hong Kong: A retrospective study. Transpl Int 2017;30:1234-42.
10. Python.org. Available from: https://www.python.org/ [Last accessed on 2023 Jan 6].
11. Kivy: Cross-platform Python Framework for GUI apps Development. Available from: https://kivy.org/ [Last accessed on 2023 Jan 6].
12. Python-for-android 0.1 documentation. Available from: https://python-for-android.readthedocs.io/en/latest/ [Last accessed on 2023 Jan 6].
13. Population finder | Government of India. Available from: https://censusindia.gov.in/census.website/data/population-finder [Last accessed on 2023 Jan 16].
14. Organ Procurement and Transplantation Network. About CPRA. Available from: https://optn.transplant.hrsa.gov/data/allocation-calculators/about-cpra/ [Last accessed on 2023 Jan 6].
15. Information about Virtual PRA Calculator. Available from: https://www.etrl.org/InformationVPRA.aspx [Last accessed on 2023 Jan 16].
16. HaploStats. Available from: https://www.haplostats.org/haplostats?execution=e1s1 [Last accessed on 2023 Jan 15].