Received: 7 August 2023 | Revised: 8 September 2023 | Accepted: 11 September 2023

DOI: 10.1111/tan.15229

ORIGINAL ARTICLE

HLA Immune Response Genetics WILEY

ABO-adjusted cPRA metric for kidney allocation in an Asian-predominant population

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Recent studies showed that ABO-adjusted calculated panel reactive antibody (ABO-cPRA) may better reflect the histocompatibility level in a multi-ethnic population, but such data in Asians is not available. We developed an ABO-adjusted cPRA metric on a cohort of waitlist kidney transplant patients ($n = 647$, 99% Chinese) in Hong Kong, based on HLA alleles and ABO frequencies of local donors. The concordance between the web-based ABO-cPRA calculator and the impact on kidney allocation were evaluated. The blood group distribution for A, B, O and AB among waitlist kidney candidates were 26.2%, 27.5%, 40.1%, and 6.1%, and their chances of encountering incompatible blood group donors were 32.6%, 32.4%, 57.6%, and 0%, respectively. There is poor agreement between web-based ABO-cPRA calculator and our locally developed metrics. Over 90% of patients showed an increase in cPRA after ABO adjustment, most notably in those with cPRA between 70% and 79%. Blood group O patients had a much greater increase in cPRA scores after adjustment while patients of blood group A and B had similar increment. 10.6% of non-AB blood group waitlist patients had ABO-cPRA elevated to ≥80%. A local ABO-adjusted cPRA metric is required for Asian populations and may improve equity in kidney distribution for patients with disadvantageous blood groups. The result from the current study potentially helps other countries/localities in establishing their own unified ABO-cPRA metrics and predict the impact on kidney allocation.

KEYWORDS

ABO incompatibility, cPRA, HLA sensitization, kidney transplantation, organ allocation, virtual crossmatch

1 | INTRODUCTION

Kidney transplantation is the therapy of choice for patients with end-stage renal disease (ESRD), and is associated with improved life expectancy and quality of life.[1–3] Due to the scarcity of the organ pool, donor compatibility and multiple factors are taken into consideration when allocating deceased kidneys to optimize the organ utility and transplant outcomes.[4,5] The patients' access to transplantation is strongly affected by parameters such as HLA sensitization

and ABO blood type incompatibility.[6–8] The concept of panel reactive antibody (PRA) was first introduced by Patel and Terasaki in their seminal work published in 1969 to evaluate the risk of hyperacute rejection in transplant. The percentage of positive crossmatch within the testing panel, known as the PRA, can be used to estimate the likelihood of finding crossmatch-incompatible donors.[9,10] With the advancement in more sensitive and specific solid phase immunoassays, identification of low-level allele-specific HLA antibodies in patient's serum became feasible,[11,12] which led to the transition to calculated PRA value (cPRA) and hence a more consistent and comparable evaluation of the degree of sensitization. The cPRA estimates the percentage of potential donors having HLA antigens that are unacceptable to the candidates by comparing the HLA antibodies with the HLA allele frequencies among a donor population.[13] Many organ allocation organizations, including the United Network for Organ Sharing (UNOS) in the USA, Eurotransplant in the EU countries, the National Health Service Blood and Transplant program in the United Kingdom and Canadian Blood Services, have included prioritization for broadly sensitized candidates with high PRA to reduce the access disparity based on HLA incompatibility.[11,14] Historically, the UNOS gave those patients with a PRA greater or equal to 80% an extra four points during allocation. In USA, the kidney allocation system (KAS) was implemented where candidates receive allocation points on a sliding scale based on their cPRA value.[15–17]

While the current cPRA calculation considers only the sensitization of HLA antibodies, ABO incompatibility also constitutes a key determinant that limits the chance of a patient receiving a transplant. The ABO blood groups are not uniformly distributed across different ethnic categories.[18] Owing to a significant discrepancy in the size of the donor pool among different blood groups, candidates of some blood groups have less chance of encountering compatible donor and thus have disadvantage in deceased kidney allocation. Indeed, previous studies have shown persistent disparity in organ allocation due to ABO incompatibility. In this context, blood group B and O kidney transplant candidates face additional barriers to transplantation than those with blood types A and AB, resulting in a longer waitlist time and accumulation of candidates on the waitlist.[19–23] Blood group O candidates are only biologically compatible with blood group O donor, whereas blood group O donors are compatible with candidates of all blood group. Zero HLA-A, B, DR mismatch donors' kidney might be allocated to potential recipients who belong to other compatible blood groups.[24] The OPTN policy in the USA permits alternative transplantation option, which enables blood group A2 and A2B deceased donor kidney to be allocated to group B or O candidates who have consistently low levels of A isoagglutinin. These practices aim to increase minority transplantation and partially address the imbalance in the organ sharing system.[11,23,25] A more efficient allocation system is required to achieve equity in transplant opportunities by reducing the biological disadvantage based on ABO incompatibility. Gragert et al. recently published a unified metric for immunologic compatibility in kidney transplantation, incorporating both HLA sensitization and ABO blood group incompatibility in cPRA calculation.[26] One should appreciate that ABO frequencies varies with the ethnic composition of a population, and a unified HLA-ABO metrics derived from a multi-ethnic population such as the USA may not be fully applicable to localities where a single ethnic group is highly predominant (e.g., Asia-Pacific regions). In Hong Kong and various Asia-Pacific countries, ABO disparity is observed in the current organ allocation system and hence an ABO-adjusted cPRA metrics developed from local ABO and HLA frequency data is eagerly awaited. Furthermore, the impact of adjusting ABO incompatibility during cPRA calculation on organ allocation remains unclear. Based on these backgrounds, we developed a unified ABO-cPRA metric using local ABO frequency/compatibility data and evaluated the effect on allocation priority of renal allografts. The results from this study will potentially help other countries/localities to develop their own unified ABO-cPRA metrics and predict the impact on organ allocation.

2 | MATERIALS AND METHODS

2.1 | HLA antibody detection of renal patients

Unacceptable antigens profiles of waitlist kidney patients ($n = 2306$) were retrieved from the Hospital Authority Organ Registry and Transplant System (ORTS) database. The ORTS is a centralized Renal Registry database implemented by the Central Renal Committee of the Hospital Authority of Hong Kong since 1995. It contains data on HLA mapping and is used for organ allocation in deceased donor kidney transplantation.[27] HLA antibodies were detected by Lifecodes Class I and Class II ID kit, Lifecodes Class I and Class II LSA kit (Immucor, Stamford, CT, USA), and LABScreen Class I and Class II Single Antigen kit (One Lambda, West Hills, CA, USA).

2.2 | Data collection of donor pool

This study included HLA typing of HLA-A, B, DR for all deceased donors ($n = 821$) registered under the ORTS database from September 1994 to August 2022. HLA typing by serological micro-lymphocytotoxicity method was performed for these donors before 5 December 2014, PCR sequence-specific oligonucleotide probe method

(PCR-SSO) and/or PCR sequence-specific primer (PCR-SSP) method were used after that date. The HLA 11 loci (HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, and -DPB1 alleles) genotype of Hong Kong Bone Marrow Donor Registry (HKBMDR) donors ($n = 18{,}297$) were performed using next generation sequencing (AllType NGS; One Lambda, Canoga Park, California) on the Illumina MiSeq system platform. For the calculation of cPRA, the HLA genotypes were then resolved to single serologic equivalence for each allele.

Previous study demonstrated that cPRA calculation using stem cell donors HLA data could potentially improve equity in kidney transplant allocation.[28] Besides, using the stem cell donor provides a more accurate estimation of the population frequency of HLA antigens since the stem cell donor pool is much larger than the deceased donor pool. We utilized HKBMDR donors ($n = 18{,}297$) as the HLA haplotype reference panel for cPRA calculation in this study. The cPRA values (cPRA (filter)) collected using deceased donors were compared with those using HKBMDR donors (cPRA (freq)) using Lin's concordance correlation to ensure the accuracy of using stem cell donors as the reference panel (Figure S1). The Lin's coefficient was 0.9993 for cPRA (filter) against cPRA (freq), indicating an almost perfect agreement.

2.3 | ABO blood group frequencies

The ABO blood group frequencies of our local population were assessed by direct counting. The reference group consists of the deceased donors ($n = 821$) registered under the ORTS database from September 1994 to August 2022. In this study, donors of blood group O were considered compatible to candidates with any blood type. Blood group AB donors were only compatible to candidates of the same blood group. Blood group A donors were compatible to blood group A or AB candidates, while blood group B donors were compatible to candidates with blood type B or AB.

2.4 | cPRA calculation by HLA allele frequencies

The cPRA by allele frequencies method (cPRA (freq)) was calculated using the formula presented by the OPTN online calculator. According to our previous studies,[29] the PHASE computer program was used to estimate the three-loci (A, B, DRB1) haplotype frequencies from observed phenotypes using the Markov Chain Monte Carlo (MCMC) simulation algorithm.[30] The simulation algorithm entails recursively sampling haplotypes from all theoretical haplotypes based on phenotypes observed in a population of unrelated individuals. Single- and two-locus haplotype frequencies were derived from these estimated three-locus haplotype frequencies by marginalizing on the corresponding locus. The equation used for the cPRA calculation is:

$$cPRA = 1 - (1 - S1 + S2 - S3)^2,$$

S1 is the sum of allele frequencies of each of the unacceptable antigen of a patient. S2 is the sum of all two- loci haplotype combinations frequencies. S3 represents the frequencies of all three-loci haplotype combinations. According to the definitions of S1, S2, and S3, we listed all possible haplotype combinations for each patients' unacceptable antigens. Then, using the donor pool, we extracted the corresponding frequencies from the marginalized haplotype frequencies. S1, S2, and S3 values from each patient were then entered into the OPTN equation to calculate the final cPRA.

2.5 | cPRA calculation by donor filtering

The cPRA (filter) of waitlist patients were generated based on donor filtering principle. With the use of an in-house computer script reported in Chan et al. 2017, the unacceptable antigens of each waitlist patient were compared with the donors' HLA typing.[29] Patients were filtered out when they had at least one unacceptable antigen against donor HLA antigen during the mapping process. cPRA (filter) was presented as the percentage of filter out count over the total number of historical deceased donors, estimating the possibility of a patient encountering incompatible donors.

2.6 | ABO-adjusted cPRA calculation

The calculation of ABO-adjusted cPRA (HK ABO-cPRA) involved the frequencies of incompatible donor HLA antigens (conventional cPRA) and the frequency of incompatible donor ABO phenotype ($\text{Freq}_{\text{ABOi}}$). The ABO-adjusted cPRA was computed according to the method reported previously,[26] the equation is:

$$ABO\ \text{adjusted cPRA} = \text{conventional cPRA} + \left[(100\% - \text{conventional cPRA}) \times \text{Freq}_{\text{ABOi}}\right].$$

2.7 | Comparison with web ABO-cPRA calculator

Antibodies data against HLA-A, B and DR from 647 kidney patients were selected for the trial to assess the

validity of using an ABO-adjusted cPRA web calculator (http://transplanttoolbox.org/abo_hla_cpra)[31] for Hong Kong patients. The ABO-cPRA values generated from the web calculators were compared to HK ABO-cPRA values calculated in-house.

2.8 | Methods agreement analysis

Lin's concordance coefficient (Rc) was used to examine agreement between cPRA values generated using various methods. Lin's coefficient was a reproducibility index which assessed the correlation between two readings that fall on a 45-degree line going through the origin.[32] A coefficient of 0.95–0.99 shows a significant level of agreement between two models, whereas a value of 0.99 or higher illustrates almost perfect agreement.

2.9 | Ethics approval

This study was performed under the approval of The University of Hong Kong/ Hospital Authority Hong Kong West Cluster Institutional Review Board (Reference number: UW22-660).

3 | RESULTS

3.1 | ABO blood group phenotypic frequencies in Hong Kong

The ABO blood group frequencies were determined using the 821 deceased donors registered in Hong Kong (99% were Chinese). Blood group A, B, O, and AB each had a phenotypic frequency of 25.0%, 25.2%, 42.4%, and 7.4%, respectively which was in line with blood group frequencies in Hong Kong population.[33] The blood group distribution for A, B, O and AB among waitlist kidney candidates in Hong Kong were 26.2%, 27.5%, 40.1%, and 6.1%, respectively (Table 1), and their corresponding chances of encountering incompatible blood group donors were 32.6%, 32.4%, 57.6%, and 0%, respectively (Table 2).

TABLE 1 The ABO blood group frequencies of waitlist kidney candidates in Hong Kong.

Candidate blood group	ABO blood group frequency
A	26.2%
B	27.5%
O	40.1%
AB	6.1%

TABLE 2 The probability of encountering incompatible donor blood group.

Candidate blood group	Incompatible donor blood group	Probability of incompatible donor ABO blood group
A	B + AB	32.6%
B	A + AB	32.4%
O	A + B + AB	57.6%
AB	N/A	0.0%

3.2 | Determination of conventional and ABO-adjusted cPRA

We calculated the conventional cPRA values for 2306 waitlist kidney patients from ORTS system. Of those, there were 647 patients with at least one unacceptable antigen, which we included in the calculation and analysis of ABO-adjusted cPRA. The ABO-adjusted cPRA were computed by two methods using a web calculator and the equation described, and the values were correlated using the Lin's concordance coefficient (Figure 1). Lin's coefficients for blood groups A, B, O, and AB were 0.8907, 0.9064, 0.8935, and 0.8590, respectively. In view of the significant disagreement between the two approaches, we further performed a calculation based on local HLA typing and ABO blood group phenotypic frequencies and assessed the relationship between ABO-adjusted cPRA and conventional cPRA. Figure 2 compared the proportion of donors with incompatible blood types and HLA phenotypes (ABO-cPRA) to the proportion based on donors with incompatible HLA antigens only. After ABO adjustment, the cPRA values of patients with blood types A, B, or O were all elevated. Patients with blood type O (purple line) showed the largest increment after ABO adjustment, while patients with blood type A (blue line), and B (red line) showed similar degree of increase in cPRA scores. Patients with blood type AB (green line) showed no change in the ABO-cPRA value as they were compatible with donors of any blood group.

3.3 | Change of cPRA in different cPRA point group after ABO adjustment

The overall distribution of conventional cPRA and ABO-adjusted cPRA of waitlist patients was depicted in Figure 3A. In general, the majority of the candidates

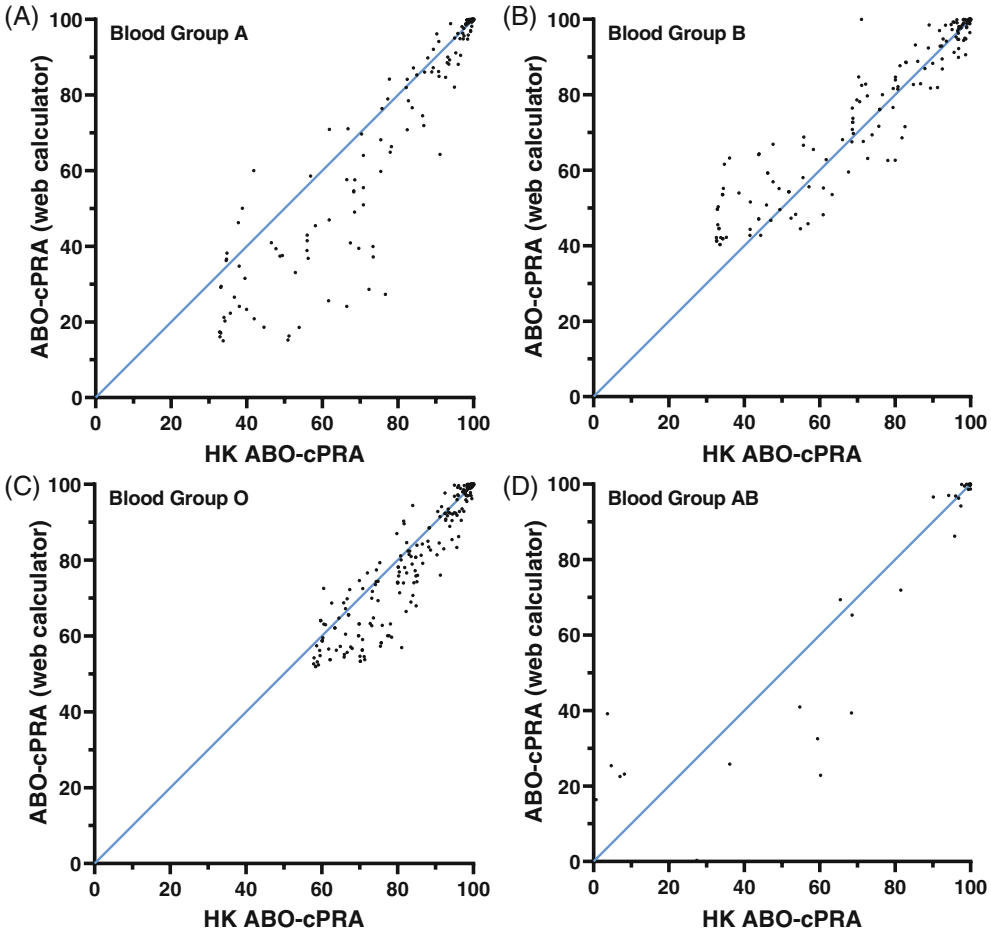

FIGURE 1 Correlation plot of HK ABO-cPRA against ABO-cPRA (web calculator) values for (A) blood group A, (B) blood group B, (C) blood group O, and (D) blood group AB candidates. Lin's correlation coefficients were 0.8907, 0.9064, 0.8935 and 0.8590 for blood groups A, B, O, and AB, respectively.

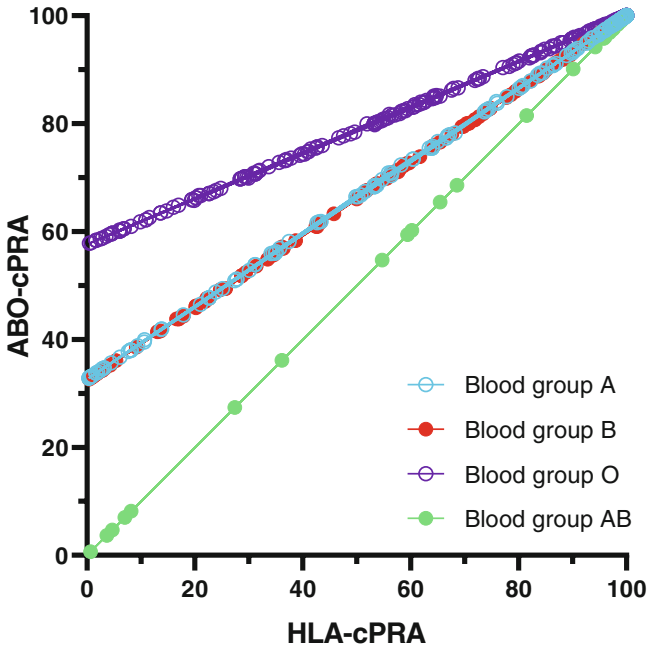

FIGURE 2 Scatterplot of cPRA against ABO-cPRA values of candidates of different blood groups. Each ABO blood group is indicated with different colors.

moved up to a higher cPRA point group following ABO adjustment. There was a significant reduction in number of waitlist patients in the lower point groups (0%–30%), accompanied by an increase in number of waitlist patients in other cPRA point groups (60%–100%). Figures 3B and 4 showed the percentage of waitlist patients who remained in the same point group or moved to a higher point group after ABO adjustment. Here we focused on patients whose cPRA moved up to higher than 80% because they will be given additional points for organ allocation in Hong Kong. Among the candidates ($n = 647$) included in our analysis, 10.6% of the patients with cPRA <80% had moved up to ABO-cPRA point groups of 80% or above after ABO adjustment. Figure 3B showed the proportion of candidates who increased to a specific point group, which could help to evaluate if the current cut-off for additional scores is appropriate if the ABO-cPRA is implemented. When stratified according to the original cPRA scores, waitlist patients with original cPRA scores of 40%–59% and 60%–79%, 26%, and 41% elevated to ABO-cPRA scores of 80%–84% respectively. 19% and 7% of waitlist patients having original cPRA of 60–79% moved up to 85–89% and 90%–94%,

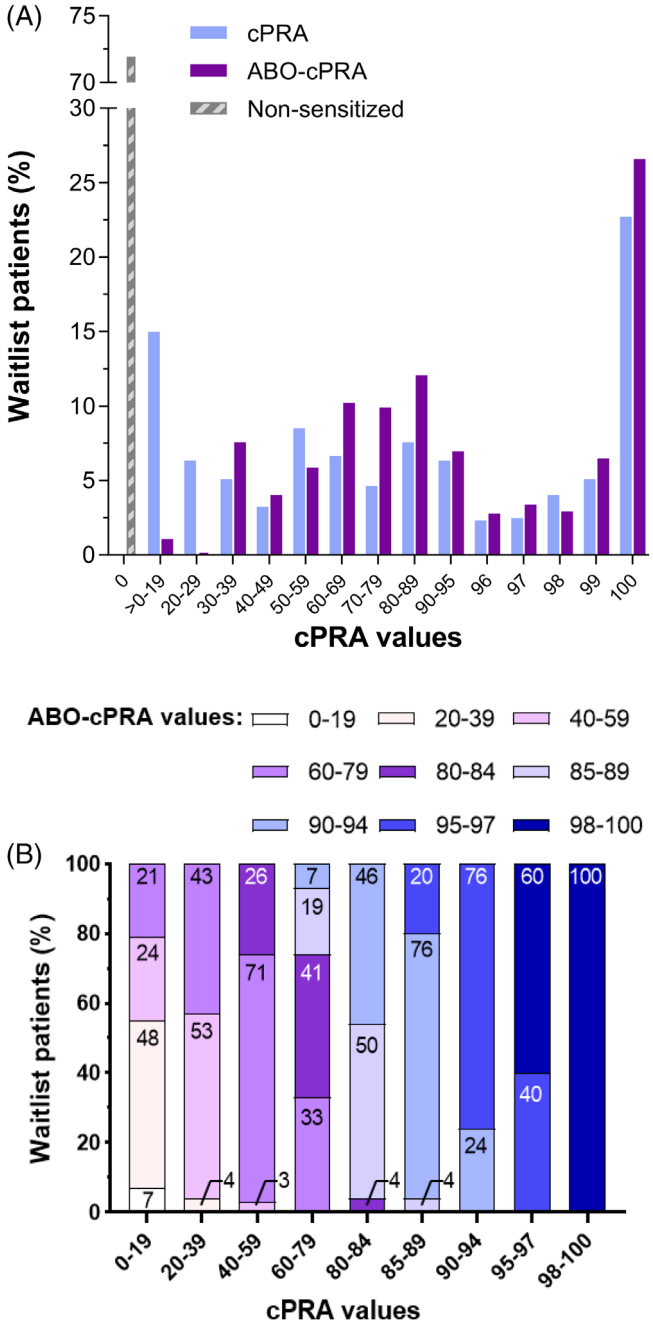

FIGURE 3 (A) Distribution of cPRA values of waitlist candidates in percentages. The distribution of cPRA and ABO-cPRA of candidates at different point groups were compared. (B) The proportion of waitlist patients at each HLA-cPRA point group moving up to a particular ABO-cPRA point group category after ABO adjustment. The *X*-axis represents the original cPRA values, and the Y-axis represents the percentage of waitlist patient of each ABO-cPRA point group after ABO adjustment. Each color indicates an ABO-cPRA point group category.

respectively. When stratified according to A, B, and O blood groups, 100%, 100%, and 50% of waitlist candidates with original cPRA 70–79% were moved up to have ABO-cPRA scores of 80%–89% (Figure S2).

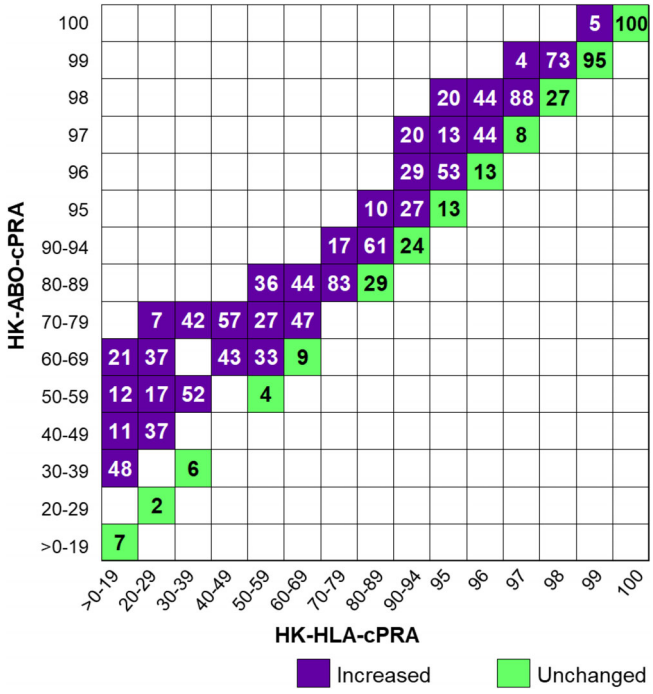

FIGURE 4 The percentage of waitlist candidates at each cPRA point group moving up to higher ABO-cPRA point group categories after ABO adjustment. Purple boxes represent the percentage of candidates whose cPRA value increased to higher point groups after ABO adjustment. The percentage of candidates who remained in the same point group following ABO adjustment is shown in green boxes on the diagonal.

4 | DISCUSSION

ABO incompatibility is a major immunologic barrier in kidney transplantation. Whilst attempts such as desensitization treatment and paired kidney exchange can help overcome such hurdle in live kidney transplantation, major blood group compatibility remains an important issue in the allocation of deceased donor kidneys. Our current findings suggest that a unified ABO-HLA metric using local ABO frequency data is required and has significant impact on kidney allograft allocation.

There is limited data regarding the HLA and blood group distribution among kidney donors in Asians. The OPTN in the USA includes only around 3% of Asian donors from unspecified countries of origin, while the Eurotransplant kidney donors are predominantly from Austria, Belgium, Germany, Hungary, Croatia, Luxembourg, the Netherlands, and Slovenia.[34,35] With a population of 7.3 million (91.6% were Chinese), over 95% of the kidney donor pool in the ORTS of Hong Kong are of Chinese ethnicity, and due to such ethnic predominance the HLA allele/haplotype frequencies differ significantly from other populations and transplant programs.[29,36–40] Add to that, the phenotypic frequency

TABLE 3 ABO blood group frequencies (%) across Asia-Pacific regions.

Blood Group	Hong Kong	Mainland China	Taiwan	India	Malaysia	Thailand	Japan
A	26.0	30.5	26.6	23.2	30.5	20.5	38.7
B	26.0	29.4	23.7	34.1	27.5	30.5	22.1
O	40.0	30.4	43.8	34.6	34.5	40.5	29.2
AB	7.0	9.7	5.9	8.2	7.5	8.5	10.0

of each blood group also varies considerably between different localities and ethnic groups.[18,26] Contrast to the USA where blood groups A and B accounts for 37% and 12% in the donor pool, our local data showed that blood groups A and B each accounts for approximately 25% of the donors. Another difference is the higher percentage of blood group AB in Hong Kong than in the USA (7% vs. 3.5%). These differences in HLA allele/haplotype and blood group distribution call for a different ABO-adjusted cPRA metric may be needed for Hong Kong. Our data showed that waitlist patients with blood group O in Hong Kong had the highest odds while blood groups A and B had similar chances of encountering ABO incompatible donors. This contrasts with the data in the USA where blood group O and B patients had the highest chance of having ABO incompatible donors, and such disparity is mostly explained by the difference in ABO blood group distribution.

While online calculators are convenient in generating the ABO-cPRA metrics, our results demonstrated a marked discordance between the scores determined by web-based calculator and our locally developed metrics. Again, such discrepancy is related to the difference in blood group distribution. The application of web calculator for our local patient could result in more than 20% over- or under-estimation of the value, leading to inaccurate estimation of patients' level of sensitization and hence their ranking on the waiting list. Along the same rationale, local waitlist patients of blood group O had a much greater increase in cPRA scores after major blood group adjustment while patients of blood group A and B had similar increment in the cPRA scores. This was in stark contrast to the observations in the USA where both blood group O and B patients both showed significant elevation in cPRA scores after ABO adjustment.

While the adjustment for ABO blood groups may appear to improve fairness of organ allocation in certain blood group phenotypes, it is also important to assess the overall impact on kidney allograft allocation in the transplant program. In line with the USA's data, the adjustment of ABO blood groups generally increases the cPRA scores in most waitlist patients. Of note, patients whose original cPRA scores between 70% and 79% showed the highest percentage of moving up to >80% (a cut-off which additional points were given during organ allocation) while those with high cPRA scores originally (90%–94%) had relatively little change in their degree of sensitization. Again, substantial percentages of non-AB blood group patients had upshifted to have ABO-cPRA scores of >80%. Currently, candidates with cPRA ≥80% receive an additional 15 points, increasing their chance of accessing transplantation. If ABO-adjustment is applied, majority of the candidates show an increase in ABO-cPRA, hence the policy of receiving additional points should be discussed for revision. Considering the UNOS Kidney Allocation System, candidates could receive 0–202 points on a sliding scale system based on their cPRA, with additional points awarded beginning at cPRA 20% and increasing exponentially as the value approaches 100%.[16,17] The sliding scale system allows the majority of non-AB candidates to compensate for the biological disadvantages due to ABO incompatibility by receiving some level of priority regardless of their level of HLA sensitization, which is not always achievable with the fixed threshold that we are using currently. However, one should appreciate that the allocation score includes various parameters other than the candidates' cPRA, and hence the local transplantation committees should decide on the cPRA cut-off at which additional scores should be awarded and also the appropriate score range to be awarded on the sliding scale. One should appreciate that the current data are largely theoretical and the exact impact on kidney allocation can also be assessed when ABO-cPRA has been implemented in the local transplant program.

One limitation of this study is the relatively small number of patients used to develop the ABO-cPRA metrics compared to that in the USA. Notwithstanding, our laboratory is the sole center performing tissue typing/allocation scores for all transplant hospitals within the entire territory, and thus the methods/results are highly consistent and represent the real-world situation. Our model, with very high Asian predominance, may also serve as a framework for Asia-Pacific countries which have varied ethnic compositions (Table 3) and wish to develop their own ABO-cPRA algorithms.[33,41–46] Indeed, systematic framework and allocation policies are necessary for ensuring efficiency and equity in distribution of

deceased organs as well as safe transplantation. Different transplant program adopts distinct policies; for instance, the OPTN assigns an allocation score based on multiple factors while the EuroTransplant program and Hong Kong filter patients by ABO blood groups.[47] It is recognized that the restrictions on ABO blood groups may affect the transplant rates and hence the accumulation of waitlist patients in certain blood group phenotypes. In Hong Kong, deceased kidneys are primarily allocated to candidates with the identical blood group, followed by compatible blood groups. Except for zero mismatch candidates, who have a higher priority in receiving the kidney even when their blood types are compatible but not identical. With the ABO-cPRA data available, allocation among non-identical, compatible blood groups can be considered, and this would need to be reviewed for adjustment if the ABO-cPRA metrics are implemented. Nevertheless, whether the adjustment of ABO blood groups in cPRA calculation may improve fairness in kidney allocation remains speculative, and this can only be answered when such modified metrics are fully implemented in the local transplant program. Taking one step further, ABO-adjusted cPRA approach could also be extended to candidates on the waitlist for other organs such as lung or heart recipients to enhance equity in organ distribution.

AUTHOR CONTRIBUTIONS

Janette S. Y. Kwok designed the study. Kei Man Lau, Patrick W. K. Chu, Lydia W. M. Tang, Bryan P. Y. Chen and Nicholas K. M. Yeung collected the data. Kei Man Lau, Patrick W. K. Chu and Bryan P. Y. Chen performed data analysis. Kei Man Lau wrote the manuscript. Janette S. Y. Kwok, Patrick Ip, Pamela Lee, Desmond Y. H. Yap, and Patrick W. K. Chu reviewed and edited the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data described in this article will be made available by the authors, without undue reservation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lau KM, Chu PWK, Tang LWM, et al. ABO-adjusted cPRA metric for kidney allocation in an Asian-predominant population. *HLA*. 2024;103(1):e15229. doi:10.1111/tan.15229