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A Retrospective Study on Human Leukocyte Antigen Types and Haplotypes in a South African Population

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• ***Context.***—**Human Leukocyte Antigen (HLA) is a polymorphic protein of the immune system with a central role in organ transplantation. Organ recipients can be sensitized against HLA from previous exposure, which increases the likelihood of antidonor immune responses and subsequently organ rejection. HLA matching represents an attractive option to improve graft function, reduce sensitization of recipients in first transplantations, and improve organ allocation.**

Objective.—**To examine the feasibility of the reintroduction of HLA matching into the criteria in the Johannesburg program, we retrospectively assessed HLA types in our donor population.**

Design.—**HLA types of 782 deceased and related living donors from 2015 until 2019 were recorded and analyzed to identify the most common HLA types and haplotypes. A virtual crossmatch was also done to examine the anti-HLA antibodies in the recipient population compared with the common HLA types identified in this study.**

Results.—**Of the commonest HLA types identified, at least 1 was present in 732 (93.6%) of the renal donors assessed. The virtual crossmatch confirmed that most recipients are sensitized against most donors, and this greatly impacts the number of recipients who can receive organ transplants.**

Conclusions.—**This study determined the most common HLA types and haplotypes in a South African organ donor population. This information, combined with the evidence suggesting the immunogenic potential of these common types, the high number of recipients with antibodies against common HLA types, and the ethnic distribution of the donor and recipient populations, informs the recommendation that the pretransplantation workup should not reinclude HLA matching.**

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Kidney transplantation is a cost-effective intervention for patients with end-stage kidney disease.[1,2] The South African transplant waiting list for deceased kidney transplants has more than 2500 people, and currently 5000 people in South Africa have a diagnosis of end-stage kidney disease.[3] This organ shortage is compounded by the diseases prevalent in South Africa that can directly impact kidney function.[4] These include a high burden of infectious diseases (including human immunodeficiency virus and tuberculosis) and noncommunicable diseases, such as hypertension and diabetes.[4] Although end-stage kidney disease can be managed with dialysis, kidney transplants are more cost-effective.[1] There are currently 7 centers in South Africa where kidney transplantations are performed.[5] The Johannesburg transplant program includes 1 state hospital and 3 private centers that can perform kidney transplantations in adults and children. Organ allocation from deceased donors (also called cadaveric donors) is managed using a waiting list. Several factors are considered in the Johannesburg transplant program when allocating organs to recipients on the waiting list: time on the waiting list, age, previous transplantations, and panel-reactive antibodies.[6] Panel-reactive antibody is a surrogate measure of sensitization and predicts the proportion of 100 hypothetical donors against which potential recipients will react.[7] Although antibodies can be directed toward several different antigens, including MIC-A, anti–Human Leukocyte Antigen (anti-HLA) antibodies are the most commonly identified donor-specific antibodies.[7,8] These antibodies can predict more than 90% of acute renal rejections and therefore contribute substantially to the risk assessment of transplantation, and subsequently transplantation outcomes.[7–9] Previously, patients who were HLA matched to the donor were also allocated additional points, but the significant HLA heterogeneity in the ethnically diverse population made HLA matching difficult, and this criterion was removed to rectify any potential bias.[10,11]

HLA is an integral part of the immune system and is primarily responsible for presenting pathogenic peptide antigens and self-antigens to the adaptive immune system.[12] The genes encoding HLA are located on chromosome 6 in the p21.1 to p21.3 region.[13,14] Class I includes classical HLA-

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A, HLA-B, and HLA-C, and nonclassical HLA-E, HLA-G, and HLA-F.[15] HLA-DR, HLA-DQ, HLA-DM, and HLA-DP are classified as class II.[15] These genes are closely linked and are inherited as 1 HLA haplotype comprising different combinations of HLA loci.[16] This region is considered the most polymorphic in the human genome.[17] This diversity can be problematic for organ transplantation.[13] Foreign HLA may be recognized by the recipient's immune system, resulting in donor-specific anti-HLA T-cell and B-cell responses.[18] The role of natural killer cells in solid organ transplantations is debated, but they may mediate rejection, especially chronic rejection.[19] Previous exposure to HLA antigens, such as pregnancies, blood transfusions, and transplants, may cause sensitization and the production of anti-HLA antibodies.[18] Antidonor responses impact graft function and may lead to rejection. HLA-matched transplants typically have better graft outcomes, and therefore better posttransplantation outcomes.[20] Partial mismatching is defined as the difference of 1 locus between the donor and recipient, whereas a complete mismatch consists of more than 2 HLA allele differences.[21] HLA-matching protocols for hematopoietic and solid organ transplantations commonly prioritize matching at HLA-A, HLA-B, and HLA-DRB1.[21,22] Renal cells are more likely to express class I HLA molecules (with the exception of HLA-C, which often shows low-level expression) compared with class II HLA molecules (which are typically found on professional antigen-presenting cells).[13] Renal cells may upregulate the expression of class II antigens as a stress response, however, with HLA-DRB1 as the most highly expressed.[13,23] HLA matching at class II was previously controversial for solid organs but is increasingly recognized to predict graft survival.[9,13,23,24]

Donor-specific antibodies in sensitized patients are the primary cause of hyperacute and acute organ rejection, which has a high mortality rate for the recipient and can therefore be used to predict hyperacute and acute rejection episodes.[25] In South Africa, the panel-reactive antibody levels among recipients are high and directly proportional to their time spent waiting for an organ.[11] HLA matching is an attractive option to improve graft function, reduce sensitization of recipients in first transplantations, and improve organ allocation.[10] To examine the feasibility of the reintroduction of HLA matching into the criteria in the Johannesburg transplant program, we retrospectively assessed HLA types in our donor population.

METHODS AND MATERIALS

Ethical Clearance

Ethical clearance was given by the Human Research Ethics Committee at the University of Witwatersrand (Johannesburg, South Africa), Clearance certificate No. M190655, to collect and record the HLA types of deceased and related living kidney donors (RLDs) and to use the data collected for analysis in this study.

Study Population and Data Capturing

This study recorded the HLA types of 782 deceased and RLDs from 2015 until 2019 to identify the most common HLA types and haplotypes. The HLA types in these records were determined using a Luminex SSO technique with the One Lambda kit (Thermo Fisher Scientific Inc, Waltham, Massachusetts), performed routinely during donor evaluation. The typing provided low-resolution results for the following loci: A, B, C, DRB1, and DQB1. Results were analyzed for common allele frequencies. The data were collected from the laboratory information system with National Health Laboratory Service approval and recorded on a Microsoft Excel (Redmond, Washington) spreadsheet. Limited demographic information, including age, blood group, and donor type (deceased donor or RLD), was also collected.

Statistical Analysis of HLA Types and Haplotypes

The frequency of each HLA type and haplotype was determined using the statistical analysis software R and RStudio (RStudio Inc, Boston, Massachusetts). Each locus could be filtered individually and with other loci to determine the frequency of donors with a particular HLA type or a 2- or 3-allele haplotype. The percentage that each of these contributed to the population was then calculated to establish the most common types. The most common 2-allele and 3-allele haplotypes were similarly analyzed. The common HLA types identified in this population were compared to the findings of other studies examining HLA types in populations from different countries.

Virtual Crossmatch

A virtual crossmatch was undertaken with anti-HLA antibodies identified in potential organ recipients, using 50 patients (prioritized by the transplant division according to set criteria, including waiting time, age, and panel-reactive antibody levels) in each blood group from the September 2019 waiting list. A virtual crossmatch uses retrospective serologic analysis for donor-specific antibodies on recipients and matches them against a potential donor's HLA type.[26–29] The virtual crossmatch prevents high-risk patients from receiving an organ against which they have antibodies to minimize the risk of acute antibody-mediated rejection and to further optimize the use of this limited resource.[26,30] The antibody specificities of potential kidney recipients are analyzed using a Lifecodes kit (Immucore, Abingdon, United Kingdom), with an mean fluorescent intensity of greater than 750 considered positive. The specificities were compared with the most frequent antigens expressed at each locus found in this study, and a percentage of recipients with antibodies against the frequent antigens was calculated for each blood group. This would provide insight into the levels of sensitization against common HLA alleles in the recipient population and further inform if HLA matching could be reincluded in the Johannesburg transplant program criteria.

RESULTS

The members of the donor population (n = 782) were mainly between the ages of 31 and 40 years (186; 23.79%), and 41 to 50 years (195; 24.94%). Of the donors, 167 (21.36%) were deceased and 615 (78.64%) were potential RLDs undergoing pretransplantation testing. The frequency of the HLA types in the South African population was calculated to determine the most common HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 types.

The frequency graphs of the HLA types in this study population (Figures 1 and 2) established the most common HLA type at each locus and the 2-allele and 3-allele haplotypes, summarized in Table 1. At least 1 of these most common HLA types (Table 1) was found in 732 (93.6%) of the renal donors assessed.

The common HLA types identified in this study population were compared with common HLA types found in populations of different nationalities (Table 2).[31–35] Common HLA frequencies at the A allele in our study corresponded to those found in a British, French, Chinese, and African American population.[31–35] B and DRB1 loci, common in British and French populations, were also well represented in our population. A number of commonly reported alleles in these populations were found in our study as high-frequency alleles.

The most common frequencies in this population were then used in a virtual crossmatch with anti-HLA antibodies

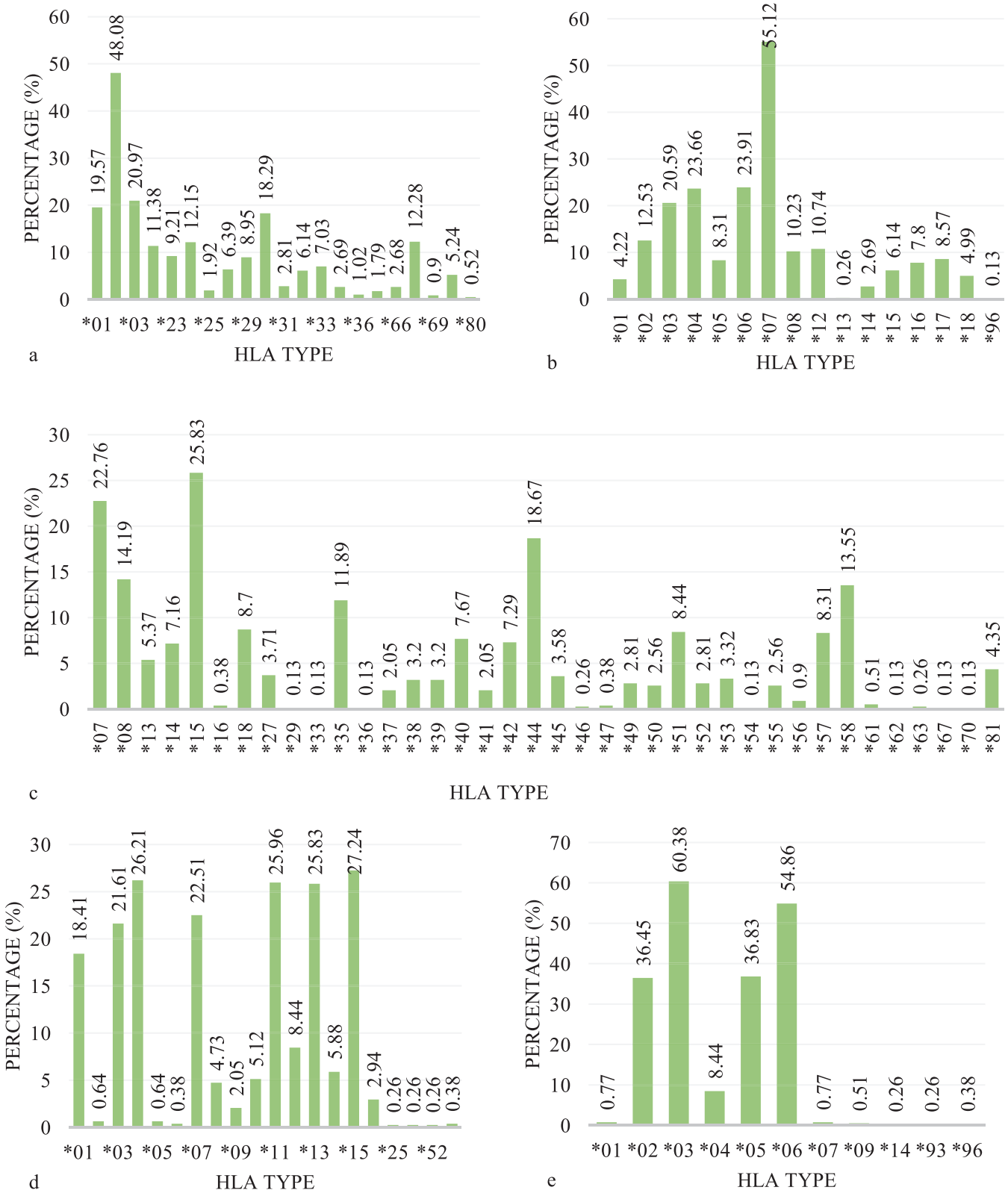

Figure 1. *Human Leukocyte Antigen (HLA) type frequency graphs. a, HLA-A. b, HLA-C. c, HLA-B. d, HLA-DRB1. e, HLA-DQB1.*

identified in the 50 potential recipients from each ABO blood type in September 2019 (Table 3). The antibodies identified were directed against HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1. This determined that 75 of the 105 total recipients (71.43%) had antibodies against at least 1 of the frequent HLA class I antigens in our donor population (A*02, B*15, and C*07), and 60 (57.14%) had them against at least 1 of the frequent class II antigens

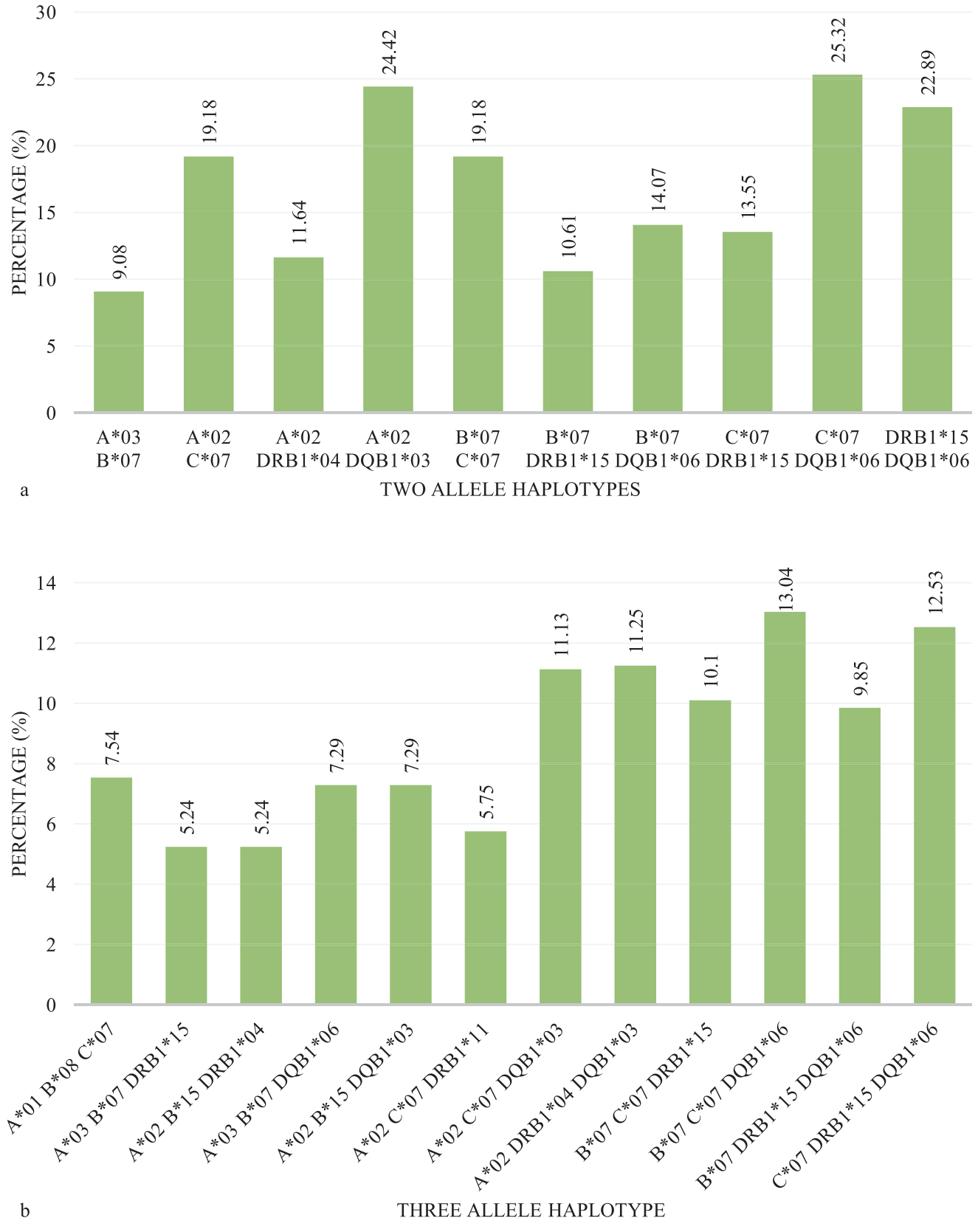

Figure 2. *The most common 2-allele (a) and 3-allele (b) haplotypes in our study population.*

Table 1. Summary of the Most Common Human Leukocyte Antigen Types, 2-Allele and 3-Allele Haplotypes in Our Donor Population (n = 782)					
HLA Type	Frequency, No. (%)	2-Allele Haplotype	Frequency, No. (%)	3-Allele Haplotype	Frequency, No. (%)
A*02	376 (48.08)	C*07 DQB1*06	198 (25.32)	B*07 C*07 DQB1*06	102 (13.04)
B*15	202 (25.83)	A*02 DQB1*03	191 (24.42)	C*07 DRB1*15 DQB1*06	98 (12.53)
C*07	431 (55.12)	DRB1*15 DQB1*06	179 (22.89)	A*02 DRB1*04 DQB1*03	88 (11.25)
DRB1*15	213 (27.24)	A*02 C*07	150 (19.18)	A*02 C*07 DQB1*03	87 (11.13)
DQB1*03	471 (60.23)	B*07 C*07	150 (19.18)	B*07 C*07 DRB1*15	79 (10.1)

(DRB1*15 and DQB1*03). The frequencies of the individual antibodies against each of the most common loci are summarized in Table 4. Additionally, the HLA types with a frequency greater than 15% (Figure 2) contributed on average 42% of the antibodies in the recipient population (n = 105). Further analysis of the antibodies revealed that the most common HLA types identified in this study only partially match the most common antibody specificities found in each blood group (Table 5).

DISCUSSION

Transplantable organs are a scarce resource, and pretransplantation immunologic risk assessment is essential before organ allocation to prevent acute and hyperacute organ rejection.[6] It is necessary, however, to maximize access to this intervention even in highly sensitized populations. This study reviewed the HLA types and haplotypes of 782 organ donors in South Africa to establish the frequent HLA types and haplotypes in South Africa while considering the implications of these common frequencies in sensitization and the role of HLA matching in the transplantation process. This is the largest review of the common frequencies in the South African population.

A study undertaken in 2018 of 237 South African bone marrow donors reviewed the most common HLA types and haplotypes.[31] The most common alleles at the A, C, and DRB1 loci were A*02, C*07, and DRB1*15, which agrees with our findings. Although the most common B and DQB1 loci identified in this study were not identical to our findings, the B and DQB1 alleles were nonetheless characterized as high-frequency alleles. The top 3 most common HLA types and haplotypes were substantially similar to those identified in our study, and the HLA types from our study not in the top 3 were still identified as common in this study.[31] A study comparing HLA types in different ethnic populations in South Africa in 302 participants suggested that HLA types are substantially different in different populations.[36] The HLA types in our study match the white individual frequencies of this study more closely than participants from other ethnic groups.[36] This suggests a potentially high degree of mismatch in our donor and recipient populations, which may increase the risk of sensitization and anti-HLA antibody formation. A more extensive analysis of HLA types from all population groups is required to confirm whether the anticipated heterogeneity in the HLA types precludes reintroduction of HLA matching as a criterion for our transplantation program. Unfortunately, automated systems for HLA matching that are available in other countries have not been implemented in South Africa, and this may also limit the feasibility of widespread reintroduction of HLA matching for solid organ transplantation in large programs. Mitigation would include expanding donor recruitment programs to all ethnic populations in South Africa. Removing HLA matching as a requirement will potentially increase the number of recipients eligible for kidney transplants but may impact sensitization and graft survival because of HLA mismatches, as has been shown in other populations.[6,10,37,38] Long-term follow-up studies of renal transplant recipients in the Johannesburg program are awaited to see the consequences of removing HLA matching as a criterion.

The immunogenicity of different HLA molecules is another factor increasing the risk of donor-specific antibody formation.[25] A high immunogenic potential increases the stimulation of the immune system, which increases anti-HLA antibody production and is therefore a major challenge for transplants.[37,39] A study conducted in an American population in 2015 determined the immunogenic potential of HLA-A, HLA-B, HLA-DR, and HLA-DQ molecules and suggested that the magnitude of donor-specific antibody response may be higher in patients of black ethnicity.[40] Of the top 3 most common HLA types from our study, 3 (53%) of the common South African alleles in class I and 4 (70%) in class II were identified as highly immunogenic in this study.[37,39] Immunogenicity increases the likelihood of anti-

Table 2. A Comparison Between the Common Human Leukocyte Antigen Types and Haplotypes Identified in This Study and Those Identified in Other Populations					
	Population				
Allele Loci	South African	White British	French	Chinese	African American
A	*02	*02:01	*02	*02	*02:01
B	*15	*08:01	*44	*40	*53:01
C	*07	*07:01	*07	—	*04:01
DRB1	*15	*07:01	*13	*09	*15:03
DQB1	*03	*03:01	*03	—	—

Table 3. Virtual Crossmatch Between Anti–Human Leukocyte Antigen (HLA) Antibodies Identified in Potential Organ Recipients and the Most Common HLA Types Observed in This Study		
	Percentage of Recipients With Anti-HLA Antibodies, No. (%)	
Blood Group	Class I	Class II
A (n = 30)	23 (76.67)	19 (63.33)
B (n = 34)	23 (67.65)	19 (55.88)
O (n = 24)	18 (75)	15 (62.5)
AB (n = 17)	11 (64.71)	7 (41.18)
Total (n = 105)	**75** (71.43)	**60** (57.14)

Table 4. The Number of Patients in Each Blood Group With Antibodies Against the Most Common Human Leukocyte Antigen (HLA) Types Identified in This Study

	Antibodies Against the Most Common HLA Loci, No. (%)				
Blood Group	**A*02**	**B*15**	**C*07**	**DRB1*15**	**DQB1*03**
A (n = 30)	10 (33.33)	17 (56.67)	11 (36.67)	9 (30)	18 (60)
B (n = 34)	9 (26.47)	16 (47.06)	14 (41.18)	10 (29.41)	17 (50)
O (n = 24)	12 (50)	16 (66.67)	13 (54.17)	8 (33.33)	12 (50)
AB (n = 17)	8 (47.06)	9 (52.94)	3 (17.65)	5 (29.41)	5 (29.41)
Total (n = 105)	**39** (37.14)	**58** (55.24)	**41** (39.05)	**32** (30.48)	**52** (49.52)

Table 5. The Most Common Anti–Human Leukocyte Antigen (HLA) Antibody Specificities From Each Locus Found in Each Blood Group

	Blood Group			
HLA Loci	**A (30) (n [%])**	**B (34) (n [%])**	**O (24) (n [%])**	**AB (17) (n [%])**
A	*11 (14 [47])	*24 (13 [38])	*11 (13 [54])	*02 (8 [47])
B	*15 (18 [60])	*37 (17 [50])	*15 (16 [67])	*15 (9 [53])
C	*07 (11 [37])	*07 (14 [41])	*17 (13 [54])	*04 (5 [29])
DRB1	*15 (9 [30])	*01 and *04 (11 [32])	*15 (11 [46])	*13 (6 [35])
DQB1	*03 (16 [53])	*02 and *03 (14 [41])	*03 (12 [50])	*06 (7 [41])

HLA antibody formation and may account for the high levels of sensitization in our recipient population.

We show in this study that 75 (71.43%) and 60 (57.14%) potential recipients possess antibodies against 1 or more of the common donor alleles in class I and class II, respectively. Although it was not possible to confirm the HLA type in several recipients retrospectively, the high levels of sensitization suggest a mismatch between donor and recipient HLA type. A potential strategy under consideration is desensitization. The immune system can be desensitized by combination intravenous immunoglobulin therapy; monoclonal antibodies and cytokine inhibitors to block various immune pathways; plasmapheresis or immunoabsorption; and a splenectomy if other measures fail.[41,42] The desensitization protocol has the potential to further expand the list of people eligible for a transplant.

A limitation of this study was that the ethnicity information of the donor population was not available, which could have indicated how well the study population reflected the general South African population. Because this was a retrospective study, the transplant outcomes of the patients were also unavailable. Furthermore, this study was limited to HLA typing results with only low to intermediate resolution provided in the patient records. This study does, however, provide some guidance on including HLA matching in the criteria in a highly diverse, low-resource setting.

CONCLUSIONS

In conclusion, this study determined the most common HLA types and haplotypes in a South African organ donor population. This information, combined with the evidence suggesting the immunogenic potential of these common types, the high number of recipients with antibodies against common HLA types, and the ethnic distribution of the donor and recipient population, suggests that HLA matching in an ethnically heterogenous population may not be feasible. The donor population should be widened across ethnic populations to increase the number of people who are eligible for transplantation and improve posttransplantation outcomes.

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