



Regional Disparities in Kidney Transplant Allocation in Brazil. A retrospective cohort study.

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Abstract:	Background: Brazil has a large public transplant program, but it remains unclear if the kidney waitlist criteria effectively allocate organs. This study aimed to investigate whether gender, ethnicity, clinical characteristics, and Brazilian regions affect the chance of deceased donor kidney transplant (DDKT). Methods: We conducted a retrospective cohort study using the National Transplant System/Brazil database, which included all patients on the kidney transplant waitlist from January 2012 to December 2022, followed until May 2023. The primary outcome assessed was the chance of DDKT, measured using subdistribution hazard and cause-specific hazard models. Results: We analyzed 118,617 waitlisted patients over a 10-year study period. Male patients had a sHR of 1.07 [95% CI: 1.05 – 1.10], $p < 0.001$, indicating a higher chance of DDKT. Patients of mixed race and Yellow/Indigenous ethnicity had lower rates of receiving a transplant compared to Caucasian patients, with sHR of 0.97 [95% CI: 0.95 – 1] and 0.89 [95% CI: 0.95 – 1], respectively. Patients from the South region had the highest chance of DDKT, followed by those from the Midwest and Northeast, compared to patients from the Southeast, with sHR of 2.53 [95% CI: 2.47 – 2.61], 1.21 [95% CI: 1.16 – 1.27], and 1.10 [95% CI: 1.07 – 1.13], respectively. The North region

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	had the lowest chance of DDTK, sHR of 0.29 [95% CI: 0.27 – 0.31]. Conclusion: We found that women and racial minorities faced disadvantages in kidney transplantation. Additionally, we observed regional disparities, with the North region having the lowest chance of DDKT and longer times on dialysis before being waitlisted. In contrast, patients in the South regions had a chance of DDKT and shorter times on dialysis before being waitlisted. It is urgent to implement approaches to enhance transplant capacity in the North region and address race and gender disparities in transplantation.

Regional Disparities in Kidney Transplant Allocation in Brazil. A retrospective cohort study.

Running title: Disparities in Kidney Transplant Allocation in Brazil

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3 **Abbreviations**

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- 7 CI: Confidence Interval
- 8 CIF: cumulative incidence function
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- 10 cPRA: calculated Panel Reactive Antibodies
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- 12 DATASUS: Department of Informatics of the Unified Health System
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- 14 DDKT: deceased donor kidney transplant
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- 16 HLA: Human Leukocyte Antigen
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- 18 HR: hazard ratio
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- 20 IBGE: Brazilian Institute of Geography and Statistics
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- 22 IQR: Interquartile Range
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- 24 KAS: Kidney Allocation System
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- 26 KDRI: Kidney Donor Risk Index
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- 28 OPTN: Organ Procurement and Transplantation Network
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- 30 PRA: Panel Reactive Antibodies
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- 32 SIG-SNT: Brazilian Transplant National System
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- 34 SUS: Brazilian Unified Health System
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- 36 sHR: subdistribution hazard ratios
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Abstract

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Regional Disparities in Kidney Transplant Allocation in Brazil. A retrospective cohort study.

Background: Brazil has a large public transplant program, but it remains unclear if the kidney waitlist criteria effectively allocate organs. This study aimed to investigate whether gender, ethnicity, clinical characteristics, and Brazilian regions affect the chance of deceased donor kidney transplant (DDKT).

Methods: We conducted a retrospective cohort study using the National Transplant System/Brazil database, which included all patients on the kidney transplant waitlist from January 2012 to December 2022, followed until May 2023. The primary outcome assessed was the chance of DDKT, measured using subdistribution hazard and cause-specific hazard models.

Results: We analyzed 118,617 waitlisted patients over a 10-year study period. Male patients had a sHR of 1.07 [95% CI: 1.05 – 1.10], $p < 0.001$, indicating a higher chance of DDTK. Patients of mixed race and Yellow/Indigenous ethnicity had lower rates of receiving a transplant compared to Caucasian patients, with sHR of 0.97 [95% CI: 0.95 – 1] and 0.89 [95% CI: 0.95 – 1], respectively. Patients from the South region had the highest chance of DDKT, followed by those from the Midwest and Northeast, compared to patients from the Southeast, with sHR of 2.53 [95% CI: 2.47 – 2.61], 1.21 [95% CI: 1.16 – 1.27], and 1.10 [95% CI: 1.07 – 1.13], respectively. The North region had the lowest chance of DDTK, sHR of 0.29 [95% CI: 0.27 – 0.31].

Conclusion: We found that women and racial minorities faced disadvantages in kidney transplantation. Additionally, we observed regional disparities, with the North region having the lowest chance of DDKT and longer times on dialysis before being waitlisted. In contrast, patients in the South regions had a chance of DDKT and shorter times on dialysis before being waitlisted. It is urgent to implement approaches to enhance transplant capacity in the North region and address race and gender disparities in transplantation.

Keywords: Organ Transplantation; waiting list; racial groups; gender bias; disparities, healthcare; Kidney Transplantation

Introduction

The Brazilian national organ transplant system is the world's largest for performing transplantations through the public health system.¹ It is responsible for conducting 95% of all solid organ transplants, as well as purchasing immunosuppressants.¹ The rules for allocating donor kidneys in Brazil are governed by the Brazilian Transplant National System (SIG-SNT), which manages the donation and transplantation process.²

In the allocation process for deceased donor kidneys, blood type identity is used as a criterion for selecting possible transplant candidates.² The allocation prioritizes candidates with a blood type identical to that of the donor, followed by Human Leukocyte Antigen (HLA) compatibility. HLA compatibility carries the highest score among other criteria given to the recipient. This scoring system in Brazil was designed to prioritize HLA compatibility, as it leads to better graft survival.³ Another objective of the Brazilian scoring system was to allocate additional points to vulnerable groups, such as children, highly sensitized individuals, diabetics, and patients with longer waitlist times.

Patients on a transplant waitlist may have competing outcomes, such as receiving a living donor transplant, a deceased donor transplant, death on waitlist or removal from the list. Conventional Cox regression models may struggle to account for changes in the patient status on the waitlist overtime. Consequently, individuals removed from the list are unable to receive organ offers and are thus unable to compete for a deceased donor transplant. To address this issue, a competing risk approach aims to accurately estimate the probability of an event occurring, considering the presence of competing events. The subdistribution hazard ratios (sHR) obtained from the Fine-Gray model describe the relative impact of covariates on the subdistribution hazard function.⁴ In our study, we utilized competing risk analysis, similar to previous studies on kidney transplant allocation, to properly address the transplant probability.⁵

To date is not clear if the Brazilian kidney waitlist selection criteria have been effective in their allocation strategy, such as prioritizing recipients under 18 years of age or sensitized recipients. Previous studies in Brazilian state of Sao Paulo have shown that despite the additional scores given to recipients with a high Panel Reactive Antibodies (PRA), they had a reduced chance of transplantation, indicating that the current allocation system does not favor these recipients.^{6,7} Despite this allocation

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3 system being available nationwide since October 2009, studies have not been
4 conducted to date to confirm whether the allocation system followed the initial proposal
5 and whether there was a balance among groups. Thus, the allocation criteria for the
6 Brazilian kidney transplant system were designed to prioritize the most effective
7 distribution of kidneys based on HLA compatibility, with the aim of ensuring fairness
8 across genders, social statuses, and ethnicities. This study aimed to investigate
9 whether gender, ethnicity, clinical characteristics, and Brazilian regions affect the odds
10 of receiving a transplant within the Brazilian kidney transplant system.
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For Review Only

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3 **Methods**

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7 **Population**

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10 A retrospective cohort study based on a database from the National Transplant
11 System/Brazil (SIG-SNT) regarding all patients on waitlist for deceased donor kidney
12 transplant (DDKT) from January 2012 to December 2022 and followed until May 2023.
13 The study was approved by the research ethics committee of the Botucatu Medical
14 School – UNESP (approval number: 49318921.4.0000.5411, approval date: August
15 2021). Informed consent was waived as the data were analyzed anonymously.
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18 **Inclusion and Exclusion Criteria**

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20 All patients enrolled in the national kidney transplant list between January 2022
21 and December 2022 was included. Patients who underwent kidney transplants with
22 living donors and those prioritized were excluded from the study. In Brazil there are two
23 main reasons from prioritized: patients without vascular access for kidney
24 transplantation and kidney donors that development end stage kidney disease.
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28 **Brazilian kidney allocation system**

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30 The waitlist criteria adhere to the guidelines of the National Transplant System.²
31 Selection is primarily based on blood group matching, with scores assigned for HLA
32 compatibility. These scores vary depending on the degree of compatibility at the
33 Human leucocyte antigen DR, B, and A loci.
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- 36 For the DR locus:
- 37 - 0 MM compatibility receives 10 points
 - 38 - 1 MM compatibility receives 5 points
 - 39 - 2 MM compatibility receives 0 points
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- 44 For the B locus:
- 45 - 0 MM compatibility receives 4 points
 - 46 - 1 MM compatibility receives 2 points
 - 47 - 2 MM compatibility receives 0 points
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- 50 For the A locus:
- 51 - 0 MM compatibility receives 1 point
 - 52 - 1 MM compatibility receives 0.5 points
 - 53 - 2 MM compatibility receives 0 points
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56 In the case of tied scores, recipients are reclassified based on the following
57 criteria:

- 58 1. Waitlist time:
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- 0 points for up to the first year of waiting
 - 1 point for the first complete year
 - 0.5 points for each subsequent year, up to a maximum of 5 points
2. Potentially hypersensitized recipients:
 - 4 points for potential recipients with a panel-reactive antibody (PRA) of 80% or higher
 - 2 points for potential recipients with a PRA between 50% and 79%
 3. Children and adolescents:
 - 4 points for recipients under 18 years of age
 4. Diabetic recipients (type I or type II):
 - 3 points

Furthermore, donors under 18 years old are prioritized for recipients under 18 years old. Therefore, recipient classification was based on several factors: HLA and blood type compatibility, prioritization, donor age compared to potential recipient age, and geographical distance. Organs procured were offered to potential recipients registered in the same geographical region as the donor, except in cases where there were potential recipients with zero HLA mismatches.

Clinical Variables

The recipient variables studied included: age at onset of the waiting list, gender, ethnicity, Brazilian geographical region, underlying kidney disease, time from dialysis initiation to waitlisting, blood type, panel reactive antibody, number of blood transfusions, previous kidney transplants, and serology for Chagas disease, Hepatitis B, and Hepatitis C.

Gender-related data: The gender data was collected based on physician reporting at the time the patient was waitlisted and refers to the sex assigned at birth.

Ethnicity was classified as follows: Caucasian (White), Pardo/Black (Mixed race), Yellow (Asian), and Indigenous.

The geographical regions of Brazil were classified according to the Brazilian Institute of Geography and Statistics (IBGE)⁸ into five regions: North Region, Northeast Region, Central-West Region, Southeast Region, and South Region.

Patients placed on the waiting list between March 2020 and December 2022 were considered to have been on the waiting list during the COVID-19 pandemic.

Human leukocyte antigen typing was performed for antigens A, B, and DR, and the calculated panel reactive antibody (cPRA) was performed and updated every six months. We retrieved the last available cPRA for the analysis.

Brazilian Data

To obtain data about total Brazilian population, population per geographical region, ethnicity, and gender distribution we used data from Brazilian Institute of Geography and Statistics (IBGE) related to census of 2022.⁸

Outcome

The primary outcome assessed was the odds of kidney transplantation with a deceased donor, measured using the subdistribution hazard ratio (sHR). A hazard ratio greater than 1 suggests a higher chance of DDKT, while a HR less than 1 indicates a lower chance of DDKT.

There were three outcomes in the Brazilian national system: death on the waitlist, transplantation, and removal from the waitlist. Patients were removed from the waitlist if they did not submit blood samples to the Brazilian transplant system for more than one year.

Statistics

The categorical variables were described in number and percentage. The numeric variables were reported in median and Interquartile Range (IQR: 25 and 75%). To evaluate the differences in baseline characteristics between Brazilian regions, we employed the Kruskal-Wallis test. For multiple comparisons between groups, we utilized the Dunn Test with Holm adjustment (post-hoc test). We used the chi-square test for categorical variables adjusted by Holm for multiple comparisons. For this study, a missing data rate of less than 1% is estimated because all analyzed variables are mandatory in the computerized transplant system (SIG-SNT).

Chance of Deceased Donor Kidney Transplantation

A regression analysis was conducted employing the competing risk approach described by Fine & Gray.⁹ Competing risk analysis aims to correctly estimate marginal probability of an event in the presence of competing events. This method accounts for simultaneous occurrences death on waitlist and removal from the waitlist as competing events alongside the primary outcome of transplantation. A Competing risk analysis models were fitted with transplantation as the outcome in univariate analysis. For

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3 multivariate regression, variables with p-values less than 0.15 from the univariate
4 analysis were considered as predictors in the multivariate model. We stratified the
5 competitive risk analysis by years of transplantation to account for the varying chance
6 of transplantation over time.
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10 Competing Risks Cumulative Incidence plots were used to visualize the
11 cumulative incidence. The cumulative incidence function (CIF) describes the incidence
12 of the occurrence of an event while taking competing risks into account. The p-values
13 reported are from Gray's test, as described by Gray RJ, for comparing the cumulative
14 incidence of a competing risk.¹⁰ We used R version 4.1.1. and packages survival,
15 mediator, and cmprsk.
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Results

During the 10-year study period, there were 120,975 patients on the Brazilian kidney waiting list for deceased donor. After excluding 2,358 prioritized patients, there were 118,617 remaining. The median age at waitlist entry was 48 years (IQR: 37-58), with 60% being male. The majority were Caucasian (51%), followed by mixed race (48%). Most patients were from the Southeast region (54%), while the minority were from the North region (5.2%). The majority had blood type O (50%) and a cPRA of zero (67%). During the period, 41,111 patients were transplanted (35%), with a median time to transplantation of 17 months (IQR: 9-33), and 11,911 (10%) were death on waitlist (Table 01).

The cumulative incidence (CIF) analysis revealed a higher chance of DDKT in patients younger than 18 years and a lower chance of DDKT in those older than 60 years (Figure 01A), $p < 0.001$. Male patients exhibited a higher chance of transplantation, $p < 0.001$ (Figure 01B). Patients of Yellow/Indigenous and mixed-race ethnicity showed a lower chance of DDKT compared to Caucasian patients, $p < 0.001$ (Figure 01C). The AB blood group had a higher chance of DDKT compared to the O group, $p < 0.001$ (Figure 01D). Patients with glomerulonephritis had the highest chance of DDKT, whereas those with other diseases had a lower chance, $p < 0.001$ (Figure 02A). The South region showed the highest chance of transplantation, while the Midwest Region had the lowest, $p < 0.001$ (Figure 02B).

Competing risk analysis revealed that male patients had a sHR of 1.07 [95% CI: 1.05 – 1.10], $p < 0.001$, indicating a higher chance of receiving a transplant compared to female patients. Patients of mixed race and Yellow/Indigenous ethnicity had lower rates of receiving a transplant compared to Caucasian patients, with sHR of 0.97 [95% CI: 0.95 – 1] and 0.89 [95% CI: 0.95 – 1], respectively. Patients from the South region had the highest rates of receiving a transplant, followed by those from the Midwest and Northeast, compared to patients from the Southeast, with hazard ratios of 2.53 [95% CI: 2.47 – 2.61], 1.21 [95% CI: 1.16 – 1.27], and 1.10 [95% CI: 1.07 – 1.13], respectively. The North region had the lowest sHR of receiving a transplant, at 0.29 [95% CI: 0.27 – 0.31] (Table 2).

There were no missing data for the analyzed variables in the Cox regression and competing risk analysis (supplementary 1).

Regional Differences

The highest number of patients on the waitlist were concentrated in the Southeast (n=63,855, 53.8%), followed by the South (n=18,057, 15.2%) and Northeast regions (n=23,733, 20%). The regions with a low number of patients on the waitlist were the Midwest (n=6861, 5.7%) and North regions (n=6111, 5.1%) (Supplementary Figure01). The highest chance of being transplanted is in the South region, while the North region has the lowest chance (Table 02).

Patients in the South and Southeast had a higher age at onset on the waitlist, while patients in the Northeast had a lower age. Patients in the South were more likely to be Caucasian, while mixed-race patients were more frequently found in the North and Northeast regions. Patients in the South region had higher values of cPRA and a higher number of patients with prior kidney transplants (supplementary Figure02). Patients in the South and Southeast regions had a shorter time on dialysis before being placed on the waitlist compared to patients in other regions. (Table 03).

Discussion

In this study, we evaluated the National Transplant System in Brazil over a 10-year period to assess the chance of kidney transplantation with a deceased donor. Male patients had a higher chance of transplantation, while racial minorities had a lower assess of DDKT. We showed that there were regional disparities, with the North region presenting the worst asses of DDKT and the South presenting the highest asses of DDKT. In the South and Southeast regions, patients had a higher age at onset on the waitlist and a shorter time on dialysis before being waitlisted. In contrast, more mixed-race patients were on the waitlist in the North and Northeast regions. A higher percentage of Caucasian patients were found in the South, as well as a higher percentage of patients on the waitlist with cPRA greater than zero.

Brazil has a large universal public health system constitutionally mandated as a state duty, is embodied in the creation of Brazilian Unified Health System (SUS). Established under principles of universality and decentralization, SUS aims to provide healthcare regardless of individual contribution capacity, and thereby avoiding inequalities.¹¹ Brazil has the largest world public organ transplant program with solid allocation criteria aimed at achieving optimal survival rates and ensuring fairness regardless of gender, social status, or ethnicity.¹² The National Transplant System, established in 1997, regulates organ donation and transplantation activities, including living donor transplantation criteria and organ allocation protocols.¹ Despite having the largest transplant service and a robust database server, DATASUS,¹³ to store data from the Brazilian Unified Health System (SUS), there are few studies that have analyzed the transplant likelihood in Brazilian healthcare to evaluate fairness of allocation.^{6,7,14}

Patients in American Transplant System (OPTN data)¹⁵ patients were older compared to Brazilian patients, with median ages of 55 [18-89] versus 48 [37-58] years, respectively. The percentage of male patients was similar at 62.4% and 60% for OPTN and Brazilian patients, respectively. White and Black patients accounted for 43.3% and 27.8% of OPTN patients, respectively, compared to 51% and 48% of Brazilian patients. The OPTN had more patients with a calculated panel-reactive antibody (cPRA) of zero, at 90.7% versus 67% in Brazil. Blood group distribution was similar between the two-allocation system. The OPTN had a higher percentage of patients with diabetes, at 36.6% versus 14% in Brazil.

We identified several findings that are consistent with other transplant allocation systems, such as the American¹⁶ and French¹⁷ systems. Specifically, patients with

blood types B and O, older patients, and patients with higher levels of PRA had a reduced chance of transplantation^{16,17}. One possible explanation for the impact of blood type is that kidneys from blood group O donors are often transplanted into recipients with different blood groups. This can lead to longer waiting times, a higher death rate, and an accumulation of blood group O patients on the waiting list¹⁸. The chance of DDKT was also reduced in sensitized patients, despite their higher allocation scores, due to a positive crossmatch, which explains their reduced chance of transplantation⁷.

Patients who tested positive for anti-HBs and anti-HCV had a higher chance of DDKT, possibly due to the Brazilian allocation strategy, which reserves kidneys from hepatitis B donors for recipients who are anti-HBs positive and from hepatitis C donors for recipients who are anti-HCV positive.² We also found that patients who were waitlisted during the COVID-19 pandemic had a trend towards a reduced rate of receiving a transplant, with a sHR of 0.92 (95% CI: 0.85-1.00, $p = 0.057$). Previously, we demonstrated a significant reduction in kidney transplantations performed in Brazil during the pandemic.¹⁴

Fewer women are referred for transplantation, placed on the waitlist, or receive a deceased donor kidney transplant compared to men¹⁹. Overall, women are estimated to be 10%–20% less likely to receive kidney transplantation compared to men.^{20,21} We show 7% higher chance (sHR: 1.07 [1.05-1.10, $p < 0.001$]) of men to be transplanted in current study. The reasons behind gender inequality in kidney transplantation are not clear, but nephrologists noted women often prioritize caregiving and family over their health, delaying or refusing transplants. They also face social disadvantages, limited decision-making power, and health literacy. Immigrant women encounter language barriers hindering transplant discussions with clinicians.²¹

Race inequality also exists in access to the waitlist and chance of DDKT. Non-Hispanic black patients have a lower probability of being waitlisted compared to non-Hispanic white patients.²² White patients had a higher probability of transplantation than Hispanic and Black patients among those with a calculated panel-reactive antibody (cPRA) over 80%.¹⁵ White patients were more likely than Hispanic or Black patients to resolve issues leading to waitlist inactivity.¹⁵ Unlike the North American binary system, Brazilians identify their skin color in a more nuanced, contextual manner, using multiple categories.²³ The official classification of race/skin color in Brazil is composed by five categories - White [Branco], Brown [Pardo], Black [Preto], Yellow and Indigenous.²³ We found that mixed-race patients (Pardo/Black) had 3% reduced rates of being transplanted, with an sHR of 0.97 (95% CI 0.95-1.0, $p = 0.016$),

while Yellow/Indigenous race patients had an 11% reduction, with an sHR of 0.89 (95% CI 0.81-0.99, $p = 0.025$). The distribution of ethnicity among Brazilian people according IBGE census 2022 was as follows: mixed-race (Pardo/Black) 55.5%, Caucasian (White) 43.5%, and Yellow/Indigenous 1%.²⁴ In the Brazilian waitlist, we found a similar percentage of Yellow/Indigenous patients (1.1%). However, we had more Caucasian waitlisted patients (51%) and less mixed-race patients (48%).

Regional Differences

Providing healthcare in Brazil, a country of 203 million people spread over 8,200,000 km² and divided into 27 states across five administrative regions poses several challenges.²⁵ There are significant regional disparities in access to dialysis and kidney transplantation in Brazil. The North, Northeast, and Midwest regions perform poorly compared to the South, which has a donor rate similar to Spain. These differences may stem from historical income disparities, impacting healthcare infrastructure and access to services.¹ We observed in the present study significant disparities across regions in the likelihood of transplantation. The South region had a 2.5 fold higher of transplantation compared to the Southeast, with sHR of 2.53 (95% CI: 2.47-2.61, $p < 0.001$). In contrast, the North regions had a 62% lower rate compared to the Southeast, with an sHR of 0.38 (95% CI: 0.36-0.41, $p < 0.001$). The Midwest and Northeast had 21% and 10% higher hazard ratio, respectively, compared to the Southeast. The South and Southeast regions had a higher median age at onset on the waitlist compared to the other regions. This is consistent with the 2022 Brazilian census population, which also showed a higher median age in the South and Southeast regions.⁸ The Brazilian census showed that the proportion of mixed-race individuals varies across regions, with the North, Northeast, Midwest, Southeast, and South regions having proportions of 78.4%, 73.9%, 62.6%, 48.5%, and 26.3%, respectively.⁸ In comparison, the proportion of waitlist patients in the same regions was 75%, 84%, 55%, 40%, and 17%, respectively. This indicates that there was a lower representation of mixed-race individuals in the Southeast and South regions. There were also differences in the time spent on dialysis before being placed on the waitlist. Patients in the South and Southeast regions had a median time of 12 months, compared to 21 to 25 months in the other regions. This suggests that patients in the South and Southeast regions spent half the time on dialysis before being placed on the waiting list, compared to patients in other regions. Patients in the South region had higher levels of cPRA and a higher frequency of patients who had a previous transplant. This suggests that patients in the South region may be facing more complicated medical conditions with patients more challenging for transplantation.

The Southeast region accounted for 53.8% of the total patients on the waitlist, followed by the Northeast (20%), South (15.2%), Midwest (5.7%), and North (5.1%) regions, respectively. According to the IBGE, the Brazilian population was higher in the Southeast, Northeast, South, North, and Midwest regions, respectively: 42%, 25.7%, 14.6%, 8.5%, and 7.9%.⁸ The distribution between the Brazilian population and waitlisted patients was similar in the South and Northeast regions, although there was a higher frequency of waitlisted patients in the Southeast and lower in the Midwest and North regions. This could be explained by the lower availability of transplant services in the Midwest and North regions, leading some patients from those regions to be waitlisted and transplanted in the Southeast region.²⁶

Implication of study

We have identified some inequities in the Brazilian kidney transplant allocation system. Women and racial minorities were found to have a lower chance of DDKT. To address these disparities, we need to understand the reasons behind them and work to fix the problem. There are also regional inequities that disadvantage patients in the North region, who experience longer times on dialysis before being waitlisted and have lower chance of DDKT. In contrast to the challenges faced by the North region, the South region of Brazil has a higher chance of DDKT but is simultaneously managing a more sensitized patient population on the waiting list. This underscores the complexity of transplant allocation, where different regions face distinct challenges. Given these disparities, it is urgent to implement approaches to enhance transplant capacity in the North region. One potential solution could involve collaboration between regions, where the South region could support the North in increasing its transplant capacities through shared resources, expertise, and strategies. In the United States, studies have shown that patients listed at non-local transplant centers have increased access to DDKT, which suggests that expanding listing options beyond local regions can improve outcomes²⁷. Although our study did not have specific data on the feasibility of this approach in Brazil, exploring similar strategies could be a valuable avenue for future research and policy development.

Limitations

Although we employed several analytical approaches, our study remains a retrospective cohort study, making it challenging to establish robust causal inference. We lacked data to analyze socioeconomic factors that could be associated with the chance of DDKT. We only had data about gender assigned at birth, which made it impossible to evaluate other potential gender inequalities related to gender minority

health, such as those experienced by transgender people. We did not retrieve data from patients who underwent living kidney donation. Although this information was mandatory in the Brazilian Transplant System, not all transplant services provided it, and many patients in that category were classified as removed from the list. We had no data in the Brazilian Transplant System regarding Human Immunodeficiency Virus status.

Conclusion

We evaluated the Brazilian Transplant program waitlist over a 10-year period to assess the fairness of the allocation process based on the chance of receiving a deceased donor kidney transplant. We found that women and racial minorities faced disadvantages in kidney transplantation. Additionally, we observed regional disparities, with the North region having the lowest chance of DDKT and longer times on dialysis before being waitlisted. In contrast, patients in the South regions had a higher chance of DDKT and shorter times on dialysis before being waitlisted. It is urgent to implement approaches to enhance transplant capacity in the North region and address race and gender disparities in transplantation.

Declarations

Authors' contributions

Daniela Ferreira Salomão Pontes, design of the work and acquisition analysis; Gustavo Fernandes Ferreira, acquisition analysis; Dorry Segev, interpretation of data; Allan B Massie, interpretation of data; Macey Levan, interpretation of data; Abner Macola Pacheco: formal analysis; Naila Camila da Rocha: formal analysis; Luis Gustavo Modelli de Andrade, interpretation of data and drafted the work.

Data Sharing

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of interests statment

The authors declare that they have no competing interests.

References

- 1 Cristelli MP, Ferreira GF, Medina-Pestana J. Global Perspective on Kidney Transplantation: Brazil. *Kidney360* 2021; **2**: 2016–8.
- 2 Minist rio da Sa de.
https://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prc0004_03_10_2017.html
(accessed Feb 14, 2024).
- 3 Shi X, Lv J, Han W, *et al.* What is the impact of human leukocyte antigen mismatching on graft survival and mortality in renal transplantation? A meta-analysis of 23 cohort studies involving 486,608 recipients. *BMC Nephrology* 2018; **19**: 116.
- 4 Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med* 2017; **36**: 4391–400.
- 5 Hart A, Salkowski N, Snyder JJ, Israni AK, Kasiske BL. Beyond ‘Median Waiting Time’: Development and Validation of a Competing Risk Model to Predict Outcomes on the Kidney Transplant Waiting List. *Transplantation* 2016; **100**: 1564–70.
- 6 Sapiertein Silva JF, Ferreira GF, Perosa M, Nga HS, de Andrade LGM. A machine learning prediction model for waiting time to kidney transplant. *PLoS One* 2021; **16**: e0252069.
- 7 Perosa M, Ferreira GF, Modelli LG, *et al.* Disparity in the access to kidney transplantation for sensitized patients in the state of Sao Paulo-Brazil. *Transpl Immunol* 2021; **68**: 101441.
- 8 2022 Census | IBGE. <https://www.ibge.gov.br/en/statistics/social/labor/22836-2022-census-3.html> (accessed Feb 17, 2024).
- 9 Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association* 1999; **94**: 496–509.
- 10 Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *The Annals of Statistics* 1988; **16**: 1141–54.
- 11 Cobo B, Cruz C, Dick PC. Gender and racial inequalities in the access to and the use of Brazilian health services. *Cien Saude Colet* 2021; **26**: 4021–32.
- 12 Bittencourt PL, Codes L, Hyppolito EB, Cesar HF, Moura-Neto JA, Gomes Ferraz ML. Attitudes of the Brazilian Population Toward Organ Donation. *Kidney Int Rep* 2022; **7**: 2737–40.
- 13 DATASUS – Minist rio da Sa de. <https://datasus.saude.gov.br/> (accessed July 21, 2022).
- 14 de Andrade LGM, Barbosa AMP, da Rocha NC, *et al.* Impact of the COVID-19 Pandemic on Solid Organ Transplant and Rejection Episodes in Brazil's Unified Healthcare System. *J Clin Med* 2022; **11**: 6581.

- 15 Kulkarni S, Ladin K, Haakinson D, Greene E, Li L, Deng Y. Association of Racial Disparities With Access to Kidney Transplant After the Implementation of the New Kidney Allocation System. *JAMA Surg* 2019; **154**: 618–25.
- 16 Sanfilippo FP, Vaughn WK, Peters TG, *et al.* Factors affecting the waiting time of cadaveric kidney transplant candidates in the United States. *JAMA* 1992; **267**: 247–52.
- 17 Trébern-Launay K, Kessler M, Bayat-Makoei S, *et al.* Horizontal mixture model for competing risks: a method used in waitlisted renal transplant candidates. *Eur J Epidemiol* 2018; **33**: 275–86.
- 18 Glander P, Budde K, Schmidt D, *et al.* The ‘blood group O problem’ in kidney transplantation--time to change? *Nephrol Dial Transplant* 2010; **25**: 1998–2004.
- 19 Smothers L, Patzer RE, Pastan SO, DuBay D, Harding JL. Gender Disparities in Kidney Transplantation Referral Vary by Age and Race: A Multiregional Cohort Study in the Southeast United States. *Kidney Int Rep* 2022; **7**: 1248–57.
- 20 Vinson AJ. Gender Disparities in Access to Kidney Transplant: Inequities in the Inequity. *Kidney Int Rep* 2022; **7**: 1145–8.
- 21 Natale P, Hecking M, Kurnikowski A, *et al.* Perspectives of Nephrologists on Gender Disparities in Access to Kidney Transplantation. *Clin J Am Soc Nephrol* 2023; **18**: 1333–42.
- 22 Buford J, Retzliff S, Wilk AS, *et al.* Race, Age, and Kidney Transplant Waitlisting Among Patients Receiving Incident Dialysis in the United States. *Kidney Med* 2023; **5**: 100706.
- 23 Travassos C, Laguardia J, Marques PM, Mota JC, Szwarcwald CL. Comparison between two race/skin color classifications in relation to health-related outcomes in Brazil. *Int J Equity Health* 2011; **10**: 35.
- 24 Ethno-Racial Characteristics of the Population | IBGE.
<https://www.ibge.gov.br/en/statistics/social/population/17590-ethno-racial-characteristics-of-the-population.html> (accessed Feb 17, 2024).
- 25 Quarterly National Accounts | IBGE.
<https://www.ibge.gov.br/en/statistics/economic/national-accounts/17262-quarterly-national-accounts.html?=&t=publicacoes> (accessed Feb 17, 2024).
- 26 Gómez EJ, Jungmann S, Lima AS. Resource allocations and disparities in the Brazilian health care system: insights from organ transplantation services. *BMC Health Serv Res* 2018; **18**: 90.
- 27 Ross-Driscoll K, Gunasti J, Lynch RJ, *et al.* Listing at non-local transplant centers is associated with increased access to deceased donor kidney transplantation. *Am J Transplant* 2022; **22**: 1813–22.

Table 01. Baseline Characteristics of Patients on the Waitlist in the Brazilian Kidney Transplant System

Characteristic	N = 118,617
Age at baseline (years)	48 (37, 58)
Age group (years)	
between 18 and 60	88,766 (75%)
below 18	4,322 (3.6%)
Higher than 60	25,529 (22%)
Gender	
Female	47,428 (40%)
Male	71,189 (60%)
Ethnicity	
Caucasian (white)	60,163 (51%)
Yellow/Indigenous	1,273 (1.1%)
Mixed race (Pardo/Black)	57,181 (48%)
Time from dialysis initiation to waitlisting (months)	15 (7, 35)
Underline Kidney Disease	
Indeterminate	28,319 (24%)
Diabetes	17,158 (14%)
Hypertension	21,561 (18%)
Glomerulonephritis	9,997 (8.4%)
Other	41,582 (35%)
Brazilian Region	
Southeast	63,855 (54%)
South	18,057 (15%)
Midwest	6,861 (5.8%)
North	6,111 (5.2%)
Northeast	23,733 (20%)
Blood Type	
A	41,364 (35%)
AB	4,175 (3.5%)
B	14,118 (12%)
O	58,960 (50%)
Previous Transplant	
No	112,026 (94%)
Yes	6,591 (5.6%)
Panel Reactive Antibody	
0%	79,706 (67%)
1-79%	26,737 (23%)

Characteristic	N = 118,617
80-89%	3,075 (2.6%)
90-100%	9,099 (7.7%)
Number of blood transfusions	
0	74,029 (62%)
1	38,951 (33%)
2	3,738 (3.2%)
3	1,899 (1.6%)
Chagas serology	
Negative	117,682 (99%)
Positive	935 (0.8%)
anti-HBs serology	
Negative	81,865 (69%)
Positive	36,752 (31%)
anti-HBc serology	
Negative	110,942 (94%)
Positive	7,675 (6.5%)
HBsAg serology	
Negative	117,370 (99%)
Positive	1,247 (1.1%)
anti-HCV serology	
Negative	117,418 (99%)
Positive	1,199 (1.0%)
Outcome	
Remain on waiting list	65,595 (55%)
Death on waiting list	11,911 (10%)
Deceased donor transplant	41,111 (35%)
Time to transplant (months)	17 (9, 33)

The categorical variables were described in number and percentage. The numeric variables were reported in median and percentiles (25 and 75%)

Table 02. Competing risk analysis of the Probability of Receiving a Deceased Donor Kidney Transplant in the Brazilian Kidney Transplant System

Characteristic		all	sHR (competing risks multivariable*+)
Age at baseline (years)	Between 18 and 60	88766 (74.8)	Ref
	Below 18	4322 (3.6)	3.66 (3.50-3.83, p<0.001)
	Higher than 60	25529 (21.5)	0.77 (0.75-0.79, p < 0.001)
Gender	Female	47428 (40.0)	Ref
	Male	71189 (60.0)	1.07 (1.05-1.10, p < 0.001)
Ethnicity	Caucasian	60163 (50.7)	Ref
	Mixed Race (Pardo/Black)	57181 (48.2)	0.97 (0.95-1.0, p = 0.016)
	Yellow/Indigenous	1273 (1.1)	0.89 (0.81-0.99, p = 0.025)
Time on dialysis (years)	Mean (SD)	2.4 (3.2)	0.97 (0.97-0.98, p < 0.001)
Underline Kidney Disease	Indeterminate	28319 (23.9)	Ref
	Diabetes	17158 (14.5)	1.02 (0.98-1.06, p = 0.33)
	Hypertension	21561 (18.2)	1.12 (1.09-1.16, p < 0.001)
	Glomerulonephritis	9997 (8.4)	1.25 (1.21-1.30, p < 0.001)
	Other	41582 (35.1)	1.09 (1.06-1.12, p < 0.001)
Blood Type	A	41364 (34.9)	Ref
	AB	4175 (3.5)	1.16 (1.10-1.22, p < 0.001)
	B	14118 (11.9)	0.93 (0.90-0.96, p < 0.001)
	O	58960 (49.7)	0.77 (0.75-0.79, p < 0.001)
Previous Transplant	No	112026 (94.4)	Ref
	Yes	6591 (5.6)	0.87 (0.82-0.91, p < 0.001)

Characteristic		all	sHR (competing risks multivariable*+)
Panel Reactive Antibody (cPRA)	0%	79706 (67.2)	Ref
	1-79%	26737 (22.5)	0.88 (0.86-0.90, p < 0.001)
	80-89%	3075 (2.6)	0.58 (0.54-0.62, p < 0.001)
	90-100%	9099 (7.7)	0.29 (0.27-0.31, p < 0.001)
Brazilian Region	Southeast	63855 (53.8)	Ref
	South	18057 (15.2)	2.53 (2.47-2.61, p < 0.001)
	Midwest	6861 (5.8)	1.21 (1.16-1.27, p < 0.001)
	North	6111 (5.2)	0.38 (0.36-0.41, p < 0.001)
	Northeast	23733 (20.0)	1.10 (1.07-1.13, p < 0.001)
anti-HBs serology	No	81865 (69.0)	Ref
	Yes	36752 (31.0)	1.45 (1.42-1.48, p < 0.001)
anti-HCV serology	No	117418 (99.0)	Ref
	Yes	1199 (1.0)	1.24 (1.13-1.37, p < 0.001)
Waiting list within COVID-19 pandemic	No	87264 (73.6)	Ref
	Yes	31353 (26.4)	0.92 (0.85-1.00, p = 0.057)

* The analysis was stratified by year of performed transplant; + competing events were death on waitlist and removal from waitlist.

sHR (competing risks multivariable*+) was calculated using a sub-distribution hazard model to conduct Hazard Ratio (HR) analysis, accounting for competing risks and multiple variables.

Table 03. Baseline Characteristics of Patients on the Waitlist in the Brazilian Kidney Transplant System stratified by Brazilian regions.

Characteristic	Southeast, N = 63,855	South, N = 18,057	Midwest, N = 6,861	North, N = 6,111	Northeast, N = 23,733	p- value
Age at baseline (years)	50 (39, 60)	49 (37, 58)	45 (34, 55)*	46 (34, 56)*	44 (33, 55)	<0.001
Age group (years)						<0.001
between 18 and 60	45,832 (72%)	13,415 (74%)	5,377 (78%)	4,834 (79%)	19,308 (81%)	
below 18	1,952 (3.1%)	729 (4.0%)	368 (5.4%)	291 (4.8%)	982 (4.1%)	
Higher than 60	16,071 (25%)	3,913 (22%)	1,116 (16%)	986 (16%)	3,443 (15%)	
Gender						0.027
Female	25,564 (40%)	7,271 (40%)	2,783 (41%)	2,510 (41%)	9,300 (39%)	
Male	38,291 (60%)	10,786 (60%)	4,078 (59%)	3,601 (59%)	14,433 (61%)	
Ethnicity						<0.001
Caucasian (white)	37,242 (58%)	14,745 (82%)	3,061 (45%)	1,443 (24%)	3,672 (15%)	
Yellow/Indigenous	859 (1.3%)	185 (1.0%)	60 (0.9%)	81 (1.3%)	88 (0.4%)	
Mixed race (Pardo/Black)	25,754 (40%)	3,127 (17%)	3,740 (55%)	4,587 (75%)	19,973 (84%)	
Time on dialysis (months)	12 (6, 27)+	12 (5, 28)+	21 (10, 46)	25 (10, 54)	25 (12, 56)	<0.001
Underline Kidney Disease						<0.001
Indeterminate	6,484 (10%)	7,096 (39%)	1,163 (17%)	1,794 (29%)	11,782 (50%)	
Diabetes	11,297 (18%)	2,362 (13%)	779 (11%)	1,051 (17%)	1,669 (7.0%)	
Hypertension	13,802 (22%)	2,645 (15%)	1,058 (15%)	1,014 (17%)	3,042 (13%)	
Glomerulonephritis	5,781 (9.1%)	1,395 (7.7%)	823 (12%)	439 (7.2%)	1,559 (6.6%)	

Characteristic	Southeast, N = 63,855	South, N = 18,057	Midwest, N = 6,861	North, N = 6,111	Northeast, N = 23,733	p-value
Other	26,491 (41%)	4,559 (25%)	3,038 (44%)	1,813 (30%)	5,681 (24%)	<0.001
Blood Type						
A	22,484 (35%)	6,762 (37%)	2,305 (34%)	1,760 (29%)	8,053 (34%)	
AB	2,414 (3.8%)	627 (3.5%)	242 (3.5%)	132 (2.2%)	760 (3.2%)	
B	7,917 (12%)	1,873 (10%)	800 (12%)	614 (10%)	2,914 (12%)	
O	31,040 (49%)	8,795 (49%)	3,514 (51%)	3,605 (59%)	12,006 (51%)	<0.001
Panel Reactive Antibody						
0%	46,245 (72%)	9,773 (54%)	4,593 (67%)	4,454 (73%)	14,641 (62%)	
1-79%	12,019 (19%)	5,400 (30%)	1,538 (22%)	1,200 (20%)	6,580 (28%)	
80-89%	1,548 (2.4%)	623 (3.5%)	177 (2.6%)	117 (1.9%)	610 (2.6%)	
90-100%	4,043 (6.3%)	2,261 (13%)	553 (8.1%)	340 (5.6%)	1,902 (8.0%)	<0.001
Previous Transplant						
No	60,306 (94%)	16,459 (91%)	6,560 (96%)	5,956 (97%)	22,745 (96%)	
Yes	3,549 (5.6%)	1,598 (8.8%)	301 (4.4%)	155 (2.5%)	988 (4.2%)	

The categorical variables were described in number and percentage. The numeric variables were reported in median and percentiles (25 and 75%)

The Kruskal-Wallis test, followed by the Dunn Test, was employed for multiple comparisons of continuous variables. Furthermore, chi-squared tests with Holm correction were employed for categorical variables.

*Patients from Midwest and North were not statistical different

+ Southeast and South were not statistical different.

Figure Legend

Figure 01. Cumulative Incidence Function (CIF) of the likelihood of being transplanted in the Brazilian Kidney Transplant System. 1A: stratified by gender (male and female); 1B: stratified by ethnicity (Caucasian, Mixed-Race, and Yellow/Indigenous); 1C: stratified by age group (under 18 years, between 18 and 69 years, and over 60 years); 1D: stratified by blood group (A, B, AB, and O).

Figure 02. Cumulative Incidence Function (CIF) of the likelihood of being transplanted in the Brazilian Kidney Transplant System. 2A: stratified by baseline disease (diabetes, glomerulonephritis, hypertension, indeterminate, and other). 2B: stratified by Brazilian region (North, Midwest, Northeast, Southeast, and South).

Regional Disparities in Kidney Transplant Allocation in Brazil. A retrospective cohort study.

Running title: Disparities in Kidney Transplant Allocation in Brazil

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Abbreviations

CI: Confidence Interval

CIF: cumulative incidence function

cPRA: calculated Panel Reactive Antibodies

DATASUS: Department of Informatics of the Unified Health System

DDKT: deceased donor kidney transplant

HLA: Human Leukocyte Antigen

HR: hazard ratio

IBGE: Brazilian Institute of Geography and Statistics

IQR: Interquartile Range

KAS: Kidney Allocation System

KDRI: Kidney Donor Risk Index

OPTN: Organ Procurement and Transplantation Network

PRA: Panel Reactive Antibodies

SIG-SNT: Brazilian Transplant National System

SUS: Brazilian Unified Health System

SHR: subdistribution hazard ratios

Abstract

Salomão Pontes DF; Ferreira GF; Segev D; Massie AB; Barbosa AMP, Rocha N; Modelli de Andrade LG.

Regional Disparities in Kidney Transplant Allocation in Brazil. A retrospective cohort study.

Background: Brazil has a large public transplant program, but it remains unclear if the kidney waitlist criteria effectively allocate organs. This study aimed to investigate whether gender, ethnicity, clinical characteristics, and Brazilian regions affect the chance of deceased donor kidney transplant (DDKT).

Methods: We conducted a retrospective cohort study using the National Transplant System/Brazil database, which included all patients on the kidney transplant waitlist from January 2012 to December 2022, followed until May 2023. The primary outcome assessed was the chance of DDKT, measured using subdistribution hazard and cause-specific hazard models.

Results: We analyzed 118,617 waitlisted patients over a 10-year study period. Male patients had a sHR of 1.07 [95% CI: 1.05 – 1.10], $p < 0.001$, indicating a higher chance of DDTK. Patients of mixed race and Yellow/Indigenous ethnicity had lower rates of receiving a transplant compared to Caucasian patients, with sHR of 0.97 [95% CI: 0.95 – 1] and 0.89 [95% CI: 0.95 – 1], respectively. Patients from the South region had the highest chance of DDKT, followed by those from the Midwest and Northeast, compared to patients from the Southeast, with sHR of 2.53 [95% CI: 2.47 – 2.61], 1.21 [95% CI: 1.16 – 1.27], and 1.10 [95% CI: 1.07 – 1.13], respectively. The North region had the lowest chance of DDTK, sHR of 0.29 [95% CI: 0.27 – 0.31].

Conclusion: We found that women and racial minorities faced disadvantages in kidney transplantation. Additionally, we observed regional disparities, with the North region having the lowest chance of DDKT and longer times on dialysis before being waitlisted. In contrast, patients in the South regions had a chance of DDKT and shorter times on dialysis before being waitlisted. It is urgent to implement approaches to enhance transplant capacity in the North region and address race and gender disparities in transplantation.

Keywords: Organ Transplantation; waiting list; racial groups; gender bias; disparities, healthcare; Kidney Transplantation

Introduction

The Brazilian national organ transplant system is the world's largest for performing transplantations through the public health system.¹ It is responsible for conducting 95% of all solid organ transplants, as well as purchasing immunosuppressants.¹ The rules for allocating donor kidneys in Brazil are governed by the Brazilian Transplant National System (SIG-SNT), which manages the donation and transplantation process.²

In the allocation process for deceased donor kidneys, blood type identity is used as a criterion for selecting possible transplant candidates.² The allocation prioritizes candidates with a blood type identical to that of the donor, followed by Human Leukocyte Antigen (HLA) compatibility. HLA compatibility carries the highest score among other criteria given to the recipient. This scoring system in Brazil was designed to prioritize HLA compatibility, as it leads to better graft survival.³ Another objective of the Brazilian scoring system was to allocate additional points to vulnerable groups, such as children, highly sensitized individuals, diabetics, and patients with longer waitlist times.

Patients on a transplant waitlist may have competing outcomes, such as receiving a living donor transplant, a deceased donor transplant, death on waitlist or removal from the list. Conventional Cox regression models may struggle to account for changes in the patient status on the waitlist overtime. Consequently, individuals removed from the list are unable to receive organ offers and are thus unable to compete for a deceased donor transplant. To address this issue, a competing risk approach aims to accurately estimate the probability of an event occurring, considering the presence of competing events. The subdistribution hazard ratios (sHR) obtained from the Fine-Gray model describe the relative impact of covariates on the subdistribution hazard function.⁴ In our study, we utilized competing risk analysis, similar to previous studies on kidney transplant allocation, to properly address the transplant probability.⁵

To date is not clear if the Brazilian kidney waitlist selection criteria have been effective in their allocation strategy, such as prioritizing recipients under 18 years of age or sensitized recipients. Previous studies in Brazilian state of Sao Paulo have shown that despite the additional scores given to recipients with a high Panel Reactive Antibodies (PRA), they had a reduced chance of transplantation, indicating that the current allocation system does not favor these recipients.^{6,7} Despite this allocation

system being available nationwide since October 2009, studies have not been conducted to date to confirm whether the allocation system followed the initial proposal and whether there was a balance among groups. Thus, the allocation criteria for the Brazilian kidney transplant system were designed to prioritize the most effective distribution of kidneys based on HLA compatibility, with the aim of ensuring fairness across genders, social statuses, and ethnicities. This study aimed to investigate whether gender, ethnicity, clinical characteristics, and Brazilian regions affect the odds of receiving a transplant within the Brazilian kidney transplant system.

For Review Only

Methods

Population

A retrospective cohort study based on a database from the National Transplant System/Brazil (SIG-SNT) regarding all patients on waitlist for deceased donor kidney transplant (DDKT) from January 2012 to December 2022 and followed until May 2023. The study was approved by the research ethics committee of the Botucatu Medical School – UNESP (approval number: 49318921.4.0000.5411, approval date: August 2021). Informed consent was waived as the data were analyzed anonymously.

Inclusion and Exclusion Criteria

All patients enrolled in the national kidney transplant list between January 2022 and December 2022 was included. Patients who underwent kidney transplants with living donors and those prioritized were excluded from the study. In Brazil there are two main reasons from prioritized: patients without vascular access for kidney transplantation and kidney donors that development end stage kidney disease.

Brazilian kidney allocation system

The waitlist criteria adhere to the guidelines of the National Transplant System.² Selection is primarily based on blood group matching, with scores assigned for HLA compatibility. These scores vary depending on the degree of compatibility at the Human leucocyte antigen DR, B, and A loci.

For the DR locus:

- 0 MM compatibility receives 10 points
- 1 MM compatibility receives 5 points
- 2 MM compatibility receives 0 points

For the B locus:

- 0 MM compatibility receives 4 points
- 1 MM compatibility receives 2 points
- 2 MM compatibility receives 0 points

For the A locus:

- 0 MM compatibility receives 1 point
- 1 MM compatibility receives 0.5 points
- 2 MM compatibility receives 0 points

In the case of tied scores, recipients are reclassified based on the following criteria:

1. Waitlist time:

- 0 points for up to the first year of waiting
 - 1 point for the first complete year
 - 0.5 points for each subsequent year, up to a maximum of 5 points
2. Potentially hypersensitized recipients:
 - 4 points for potential recipients with a panel-reactive antibody (PRA) of 80% or higher
 - 2 points for potential recipients with a PRA between 50% and 79%
 3. Children and adolescents:
 - 4 points for recipients under 18 years of age
 4. Diabetic recipients (type I or type II):
 - 3 points

Furthermore, donors under 18 years old are prioritized for recipients under 18 years old. Therefore, recipient classification was based on several factors: HLA and blood type compatibility, prioritization, donor age compared to potential recipient age, and geographical distance. Organs procured were offered to potential recipients registered in the same geographical region as the donor, except in cases where there were potential recipients with zero HLA mismatches.

Clinical Variables

The recipient variables studied included: age at onset of the waiting list, gender, ethnicity, Brazilian geographical region, underlying kidney disease, time from dialysis initiation to waitlisting, blood type, panel reactive antibody, number of blood transfusions, previous kidney transplants, and serology for Chagas disease, Hepatitis B, and Hepatitis C.

Gender-related data: The gender data was collected based on physician reporting at the time the patient was waitlisted and refers to the sex assigned at birth.

Ethnicity was classified as follows: Caucasian (White), Pardo/Black (Mixed race), Yellow (Asian), and Indigenous.

The geographical regions of Brazil were classified according to the Brazilian Institute of Geography and Statistics (IBGE)⁸ into five regions: North Region, Northeast Region, Central-West Region, Southeast Region, and South Region.

Patients placed on the waiting list between March 2020 and December 2022 were considered to have been on the waiting list during the COVID-19 pandemic.

Human leukocyte antigen typing was performed for antigens A, B, and DR, and the calculated panel reactive antibody (cPRA) was performed and updated every six months. We retrieved the last available cPRA for the analysis.

Brazilian Data

To obtain data about total Brazilian population, population per geographical region, ethnicity, and gender distribution we used data from Brazilian Institute of Geography and Statistics (IBGE) related to census of 2022.⁸

Outcome

The primary outcome assessed was the odds of kidney transplantation with a deceased donor, measured using the subdistribution hazard ratio (sHR). A hazard ratio greater than 1 suggests a higher chance of DDKT, while a HR less than 1 indicates a lower chance of DDKT.

There were three outcomes in the Brazilian national system: death on the waitlist, transplantation, and removal from the waitlist. Patients were removed from the waitlist if they did not submit blood samples to the Brazilian transplant system for more than one year.

Statistics

The categorical variables were described in number and percentage. The numeric variables were reported in median and Interquartile Range (IQR: 25 and 75%). To evaluate the differences in baseline characteristics between Brazilian regions, we employed the Kruskal-Wallis test. For multiple comparisons between groups, we utilized the Dunn Test with Holm adjustment (post-hoc test). We used the chi-square test for categorical variables adjusted by Holm for multiple comparisons. For this study, a missing data rate of less than 1% is estimated because all analyzed variables are mandatory in the computerized transplant system (SIG-SNT).

Chance of Deceased Donor Kidney Transplantation

A regression analysis was conducted employing the competing risk approach described by Fine & Gray.⁹ Competing risk analysis aims to correctly estimate marginal probability of an event in the presence of competing events. This method accounts for simultaneous occurrences death on waitlist and removal from the waitlist as competing events alongside the primary outcome of transplantation. A Competing risk analysis models were fitted with transplantation as the outcome in univariate analysis. For

multivariate regression, variables with p-values less than 0.15 from the univariate analysis were considered as predictors in the multivariate model. We stratified the competitive risk analysis by years of transplantation to account for the varying chance of transplantation over time.

We conducted a mediation analysis to examine the mediating role of ethnicity in the relationship between Brazilian region and DDKT. We hypothesized that Brazilian regions would influence DDKT both directly and indirectly through ethnicity. To test this hypothesis, we used counterfactual framework assuming interaction between the exposure and mediator to estimate the total, direct, and indirect effects in the mediation model.

Competing Risks Cumulative Incidence plots were used to visualize the cumulative incidence. The cumulative incidence function (CIF) describes the incidence of the occurrence of an event while taking competing risks into account. The p-values reported are from Gray's test, as described by Gray RJ, for comparing the cumulative incidence of a competing risk.¹⁰ We used R version 4.1.1. and packages survival, mediator, and cmprsk.

Results

During the 10-year study period, there were 120,975 patients on the Brazilian kidney waiting list for deceased donor. After excluding 2,358 prioritized patients, there were 118,617 remaining. The median age at waitlist entry was 48 years (IQR: 37-58), with 60% being male. The majority were Caucasian (51%), followed by mixed race (48%). Most patients were from the Southeast region (54%), while the minority were from the North region (5.2%). The majority had blood type O (50%) and a cPRA of zero (67%). During the period, 41,111 patients were transplanted (35%), with a median time to transplantation of 17 months (IQR: 9-33), and 11,911 (10%) were death on waitlist (Table 01).

The cumulative incidence (CIF) analysis revealed a higher chance of DDKT in patients younger than 18 years and a lower chance of DDKT in those older than 60 years (Figure 01A), $p < 0.001$. Male patients exhibited a higher chance of transplantation, $p < 0.001$ (Figure 01B). Patients of Yellow/Indigenous and mixed-race ethnicity showed a lower chance of DDKT compared to Caucasian patients, $p < 0.001$ (Figure 01C). The AB blood group had a higher chance of DDKT compared to the O group, $p < 0.001$ (Figure 01D). Patients with glomerulonephritis had the highest chance of DDKT, whereas those with other diseases had a lower chance, $p < 0.001$ (Figure 02A). The South region showed the highest chance of transplantation, while the Midwest Region had the lowest, $p < 0.001$ (Figure 02B).

In a multivariate Cox regression analysis, patients undergoing kidney transplantation were more likely to be young, male, and have blood type AB or A. Patients with a prior transplant, higher cPRA, longer time on dialysis, and of Yellow/Indigenous ethnicity had a lower chance of being transplanted. Patients with positive serology for anti-HBs and anti-HVC had a higher chance of being transplanted. Patients living in the South region had a higher chance of being transplanted, while those in the North region had a lower chance (Table 02).

Competing risk analysis revealed that male patients had a sHR of 1.07 [95% CI: 1.05 – 1.10], $p < 0.001$, indicating a higher chance of receiving a transplant compared to female patients. Patients of mixed race and Yellow/Indigenous ethnicity had lower rates of receiving a transplant compared to Caucasian patients, with sHR of 0.97 [95% CI: 0.95 – 1] and 0.89 [95% CI: 0.95 – 1], respectively. Patients from the South region had the highest rates of receiving a transplant, followed by those from the Midwest and Northeast, compared to patients from the Southeast, with hazard ratios of 2.53 [95%

CI: 2.47 – 2.61], 1.21 [95% CI: 1.16 – 1.27], and 1.10 [95% CI: 1.07 – 1.13], respectively. The North region had the lowest sHR of receiving a transplant, at 0.29 [95% CI: 0.27 – 0.31] (Table 2).

The mediation analysis indicated that the independent variable (Brazilian region) has both direct and indirect effects on the dependent variable (DDKT), with a small proportion of the total effect being mediated by ethnicity (supplementary 1).

There were no missing data for the analyzed variables in the Cox regression and competing risk analysis (supplementary 1).

Regional Differences

The highest number of patients on the waitlist were concentrated in the Southeast (n=63,855, 53.8%), followed by the South (n=18,057, 15.2%) and Northeast regions (n=23,733, 20%). The regions with a low number of patients on the waitlist were the Midwest (n=6861, 5.7%) and North regions (n=6111, 5.1%) (Supplementary Figure01). The highest chance of being transplanted is in the South region, while the North region has the lowest chance (Table 02).

Patients in the South and Southeast had a higher age at onset on the waitlist, while patients in the Northeast had a lower age. Patients in the South were more likely to be Caucasian, while mixed-race patients were more frequently found in the North and Northeast regions. Patients in the South region had higher values of cPRA and a higher number of patients with prior kidney transplants (supplementary Figure02). Patients in the South and Southeast regions had a shorter time on dialysis before being placed on the waitlist compared to patients in other regions. (Table 03).

Discussion

In this study, we evaluated the National Transplant System in Brazil over a 10-year period to assess the chance of kidney transplantation with a deceased donor. Male patients had a higher chance of transplantation, while racial minorities had a lower assess of DDKT. We showed that there were regional disparities, with the North region presenting the worst asses of DDKT and the South presenting the highest asses of DDKT. In the South and Southeast regions, patients had a higher age at onset on the waitlist and a shorter time on dialysis before being waitlisted. In contrast, more mixed-race patients were on the waitlist in the North and Northeast regions. A higher percentage of Caucasian patients were found in the South, as well as a higher percentage of patients on the waitlist with cPRA greater than zero.

Brazil has a large universal public health system constitutionally mandated as a state duty, is embodied in the creation of Brazilian Unified Health System (SUS). Established under principles of universality and decentralization, SUS aims to provide healthcare regardless of individual contribution capacity, and thereby avoiding inequalities.¹¹ Brazil has the largest world public organ transplant program with solid allocation criteria aimed at achieving optimal survival rates and ensuring fairness regardless of gender, social status, or ethnicity.¹² The National Transplant System, established in 1997, regulates organ donation and transplantation activities, including living donor transplantation criteria and organ allocation protocols.¹ Despite having the largest transplant service and a robust database server, DATASUS,¹³ to store data from the Brazilian Unified Health System (SUS), there are few studies that have analyzed the transplant likelihood in Brazilian healthcare to evaluate fairness of allocation.^{6,7,14}

Patients in American Transplant System (OPTN data)¹⁵ patients were older compared to Brazilian patients, with median ages of 55 [18-89] versus 48 [37-58] years, respectively. The percentage of male patients was similar at 62.4% and 60% for OPTN and Brazilian patients, respectively. White and Black patients accounted for 43.3% and 27.8% of OPTN patients, respectively, compared to 51% and 48% of Brazilian patients. The OPTN had more patients with a calculated panel-reactive antibody (cPRA) of zero, at 90.7% versus 67% in Brazil. Blood group distribution was similar between the two-allocation system. The OPTN had a higher percentage of patients with diabetes, at 36.6% versus 14% in Brazil.

We identified several findings that are consistent with other transplant allocation systems, such as the American¹⁶ and French¹⁷ systems. Specifically, patients with

blood types B and O, older patients, and patients with higher levels of PRA had a reduced chance of transplantation^{16,17}. One possible explanation for the impact of blood type is that kidneys from blood group O donors are often transplanted into recipients with different blood groups. This can lead to longer waiting times, a higher death rate, and an accumulation of blood group O patients on the waiting list¹⁸. The chance of DDKT was also reduced in sensitized patients, despite their higher allocation scores, due to a positive crossmatch, which explains their reduced chance of transplantation⁷.

Patients who tested positive for anti-HBs and anti-HCV had a higher chance of DDTK, possibly due to the Brazilian allocation strategy, which reserves kidneys from hepatitis B donors for recipients who are anti-HBs positive and from hepatitis C donors for recipients who are anti-HCV positive.² We also found that patients who were waitlisted during the COVID-19 pandemic had a trend towards a reduced rate of receiving a transplant, with a sHR of 0.92 (95% CI: 0.85-1.00, p = 0.057). Previously, we demonstrated a significant reduction in kidney transplantations performed in Brazil during the pandemic.¹⁴

Fewer women are referred for transplantation, placed on the waitlist, or receive a deceased donor kidney transplant compared to men¹⁹. Overall, women are estimated to be 10%–20% less likely to receive kidney transplantation compared to men.^{20,21} We show 7% higher chance (sHR: 1.07 [1.05-1.10, p < 0.001]) of men to be transplanted in current study. The reasons behind gender inequality in kidney transplantation are not clear, but nephrologists noted women often prioritize caregiving and family over their health, delaying or refusing transplants. They also face social disadvantages, limited decision-making power, and health literacy. Immigrant women encounter language barriers hindering transplant discussions with clinicians.²¹

Race inequality also exists in access to the waitlist and chance of DDKT. Non-Hispanic black patients have a lower probability of being waitlisted compared to non-Hispanic white patients.²² White patients had a higher probability of transplantation than Hispanic and Black patients among those with a calculated panel-reactive antibody (cPRA) over 80%.¹⁵ White patients were more likely than Hispanic or Black patients to resolve issues leading to waitlist inactivity.¹⁵ Unlike the North American binary system, Brazilians identify their skin color in a more nuanced, contextual manner, using multiple categories.²³ The official classification of race/skin color in Brazil is composed by five categories - White [Branco], Brown [Pardo], Black [Preto], Yellow and Indigenous.²³ We found that mixed-race patients (Pardo/Black) had 3% reduced rates of being transplanted, with an sHR of 0.97 (95% CI 0.95-1.0, p = 0.016),

while Yellow/Indigenous race patients had an 11% reduction, with an sHR of 0.89 (95% CI 0.81-0.99, $p = 0.025$). The distribution of ethnicity among Brazilian people according IBGE census 2022 was as follows: mixed-race (Pardo/Black) 55.5%, Caucasian (White) 43.5%, and Yellow/Indigenous 1%.²⁴ In the Brazilian waitlist, we found a similar percentage of Yellow/Indigenous patients (1.1%). However, we had more Caucasian waitlisted patients (51%) and less mixed-race patients (48%).

Regional Differences

Providing healthcare in Brazil, a country of 203 million people spread over 8,200,000 km² and divided into 27 states across five administrative regions poses several challenges.²⁵ There are significant regional disparities in access to dialysis and kidney transplantation in Brazil. The North, Northeast, and Midwest regions perform poorly compared to the South, which has a donor rate similar to Spain. These differences may stem from historical income disparities, impacting healthcare infrastructure and access to services.¹ We observed in the present study significant disparities across regions in the likelihood of transplantation. The South region had a 2.5 fold higher of transplantation compared to the Southeast, with sHR of 2.53 (95% CI: 2.47-2.61, $p < 0.001$). In contrast, the North regions had a 62% lower rate compared to the Southeast, with an sHR of 0.38 (95% CI: 0.36-0.41, $p < 0.001$). The Midwest and Northeast had 21% and 10% higher hazard ratio, respectively, compared to the Southeast. The South and Southeast regions had a higher median age at onset on the waitlist compared to the other regions. This is consistent with the 2022 Brazilian census population, which also showed a higher median age in the South and Southeast regions.⁸ The Brazilian census showed that the proportion of mixed-race individuals varies across regions, with the North, Northeast, Midwest, Southeast, and South regions having proportions of 78.4%, 73.9%, 62.6%, 48.5%, and 26.3%, respectively.⁸ In comparison, the proportion of waitlist patients in the same regions was 75%, 84%, 55%, 40%, and 17%, respectively. This indicates that there was a lower representation of mixed-race individuals in the Southeast and South regions. There were also differences in the time spent on dialysis before being placed on the waitlist. Patients in the South and Southeast regions had a median time of 12 months, compared to 21 to 25 months in the other regions. This suggests that patients in the South and Southeast regions spent half the time on dialysis before being placed on the waiting list, compared to patients in other regions. Patients in the South region had higher levels of cPRA and a higher frequency of patients who had a previous transplant. This suggests that patients in the South region may be facing more complicated medical conditions with patients more challenging for transplantation.

The Southeast region accounted for 53.8% of the total patients on the waitlist, followed by the Northeast (20%), South (15.2%), Midwest (5.7%), and North (5.1%) regions, respectively. According to the IBGE, the Brazilian population was higher in the Southeast, Northeast, South, North, and Midwest regions, respectively: 42%, 25.7%, 14.6%, 8.5%, and 7.9%.⁸ The distribution between the Brazilian population and waitlisted patients was similar in the South and Northeast regions, although there was a higher frequency of waitlisted patients in the Southeast and lower in the Midwest and North regions. This could be explained by the lower availability of transplant services in the Midwest and North regions, leading some patients from those regions to be waitlisted and transplanted in the Southeast region.²⁶

Implication of study

We have identified some inequities in the Brazilian kidney transplant allocation system. Women and racial minorities were found to have a lower chance of DDKT. To address these disparities, we need to understand the reasons behind them and work to fix the problem. There are also regional inequities that disadvantage patients in the North region, who experience longer times on dialysis before being waitlisted and have lower chance of DDKT. In contrast to the challenges faced by the North region, the South region of Brazil has a higher chance of DDKT but is simultaneously managing a more sensitized patient population on the waiting list. This underscores the complexity of transplant allocation, where different regions face distinct challenges. Given these disparities, it is urgent to implement approaches to enhance transplant capacity in the North region. One potential solution could involve collaboration between regions, where the South region could support the North in increasing its transplant capacities through shared resources, expertise, and strategies. In the United States, studies have shown that patients listed at non-local transplant centers have increased access to DDKT, which suggests that expanding listing options beyond local regions can improve outcomes²⁷. Although our study did not have specific data on the feasibility of this approach in Brazil, exploring similar strategies could be a valuable avenue for future research and policy development.

Limitations

Although we employed several analytical approaches, our study remains a retrospective cohort study, making it challenging to establish robust causal inference. We lacked data to analyze socioeconomic factors that could be associated with the chance of DDKT. We only had data about gender assigned at birth, which made it impossible to evaluate other potential gender inequalities related to gender minority

health, such as those experienced by transgender people. We did not retrieve data from patients who underwent living kidney donation. Although this information was mandatory in the Brazilian Transplant System, not all transplant services provided it, and many patients in that category were classified as removed from the list. We had no data in the Brazilian Transplant System regarding Human Immunodeficiency Virus status.

Conclusion

We evaluated the Brazilian Transplant program waitlist over a 10-year period to assess the fairness of the allocation process based on the chance of receiving a deceased donor kidney transplant. We found that women and racial minorities faced disadvantages in kidney transplantation. Additionally, we observed regional disparities, with the North region having the lowest chance of DDKT and longer times on dialysis before being waitlisted. In contrast, patients in the South regions had a higher chance of DDKT and shorter times on dialysis before being waitlisted. It is urgent to implement approaches to enhance transplant capacity in the North region and address race and gender disparities in transplantation.

Declarations

Authors' contributions

Daniela Ferreira Salomão Pontes, design of the work and acquisition analysis; Gustavo Fernandes Ferreira, acquisition analysis; Dorry Segev, interpretation of data; Allan B Massie, interpretation of data; Macey Levan, interpretation of data; Abner Macola Pacheco: formal analysis; Naila Camila da Rocha: formal analysis; Luis Gustavo Modelli de Andrade, interpretation of data and drafted the work.

Data Sharing

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of interests statment

The authors declare that they have no competing interests.

References

1 Cristelli MP, Ferreira GF, Medina-Pestana J. Global Perspective on Kidney Transplantation: Brazil. *Kidney360* 2021; **2**: 2016–8.

2Ministrio da Saude.
https://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prc0004_03_10_2017.html (accessed Feb 14, 2024).

3Shi X, Lv J, Han W, *et al.* What is the impact of human leukocyte antigen mismatching on graft survival and mortality in renal transplantation? A meta-analysis of 23 cohort studies involving 486,608 recipients. *BMC Nephrology* 2018; **19**: 116.

4Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med* 2017; **36**: 4391–400.

5Hart A, Salkowski N, Snyder JJ, Israni AK, Kasiske BL. Beyond ‘Median Waiting Time’: Development and Validation of a Competing Risk Model to Predict Outcomes on the Kidney Transplant Waiting List. *Transplantation* 2016; **100**: 1564–70.

6Sapiertein Silva JF, Ferreira GF, Perosa M, Nga HS, de Andrade LGM. A machine learning prediction model for waiting time to kidney transplant. *PLoS One* 2021; **16**: e0252069.

7Perosa M, Ferreira GF, Modelli LG, *et al.* Disparity in the access to kidney transplantation for sensitized patients in the state of Sao Paulo-Brazil. *Transpl Immunol* 2021; **68**: 101441.

82022 Census | IBGE. <https://www.ibge.gov.br/en/statistics/social/labor/22836-2022-census-3.html> (accessed Feb 17, 2024).

9Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association* 1999; **94**: 496–509.

10 Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *The Annals of Statistics* 1988; **16**: 1141–54.

11 Cobo B, Cruz C, Dick PC. Gender and racial inequalities in the access to and the use of Brazilian health services. *Cien Saude Colet* 2021; **26**: 4021–32.

12 Bittencourt PL, Codes L, Hyppolito EB, Cesar HF, Moura-Neto JA, Gomes Ferraz ML. Attitudes of the Brazilian Population Toward Organ Donation. *Kidney Int Rep* 2022; **7**: 2737–40.

13 DATASUS – Ministério da Saúde. <https://datasus.saude.gov.br/> (accessed July 21, 2022).

14 de Andrade LGM, Barbosa AMP, da Rocha NC, *et al.* Impact of the COVID-19 Pandemic on Solid Organ Transplant and Rejection Episodes in Brazil's Unified Healthcare System. *J Clin Med* 2022; **11**: 6581.

- 15 Kulkarni S, Ladin K, Haakinson D, Greene E, Li L, Deng Y. Association of Racial Disparities With Access to Kidney Transplant After the Implementation of the New Kidney Allocation System. *JAMA Surg* 2019; **154**: 618–25.
- 16 Sanfilippo FP, Vaughn WK, Peters TG, *et al*. Factors affecting the waiting time of cadaveric kidney transplant candidates in the United States. *JAMA* 1992; **267**: 247–52.
- 17 Trébern-Launay K, Kessler M, Bayat-Makoei S, *et al*. Horizontal mixture model for competing risks: a method used in waitlisted renal transplant candidates. *Eur J Epidemiol* 2018; **33**: 275–86.
- 18 Glander P, Budde K, Schmidt D, *et al*. The ‘blood group O problem’ in kidney transplantation--time to change? *Nephrol Dial Transplant* 2010; **25**: 1998–2004.
- 19 Smothers L, Patzer RE, Pastan SO, DuBay D, Harding JL. Gender Disparities in Kidney Transplantation Referral Vary by Age and Race: A Multiregional Cohort Study in the Southeast United States. *Kidney Int Rep* 2022; **7**: 1248–57.
- 20 Vinson AJ. Gender Disparities in Access to Kidney Transplant: Inequities in the Inequity. *Kidney Int Rep* 2022; **7**: 1145–8.
- 21 Natale P, Hecking M, Kurnikowski A, *et al*. Perspectives of Nephrologists on Gender Disparities in Access to Kidney Transplantation. *Clin J Am Soc Nephrol* 2023; **18**: 1333–42.
- 22 Buford J, Retzliff S, Wilk AS, *et al*. Race, Age, and Kidney Transplant Waitlisting Among Patients Receiving Incident Dialysis in the United States. *Kidney Med* 2023; **5**: 100706.
- 23 Travassos C, Laguardia J, Marques PM, Mota JC, Szwarcwald CL. Comparison between two race/skin color classifications in relation to health-related outcomes in Brazil. *Int J Equity Health* 2011; **10**: 35.
- 24 Ethno-Racial Characteristics of the Population | IBGE.
<https://www.ibge.gov.br/en/statistics/social/population/17590-ethno-racial-characteristics-of-the-population.html> (accessed Feb 17, 2024).
- 25 Quarterly National Accounts | IBGE.
<https://www.ibge.gov.br/en/statistics/economic/national-accounts/17262-quarterly-national-accounts.html?=&t=publicacoes> (accessed Feb 17, 2024).
- 26 Gómez EJ, Jungmann S, Lima AS. Resource allocations and disparities in the Brazilian health care system: insights from organ transplantation services. *BMC Health Serv Res* 2018; **18**: 90.
- 27 Ross-Driscoll K, Gunasti J, Lynch RJ, *et al*. Listing at non-local transplant centers is associated with increased access to deceased donor kidney transplantation. *Am J Transplant* 2022; **22**: 1813–22.

Table 01. Baseline Characteristics of Patients on the Waitlist in the Brazilian Kidney Transplant System

Characteristic	N = 118,617
Age at baseline (years)	48 (37, 58)
Age group (years)	
between 18 and 60	88,766 (75%)
below18	4,322 (3.6%)
Higher than 60	25,529 (22%)
Gender	
Female	47,428 (40%)
Male	71,189 (60%)
Ethnicity	
Caucasian (white)	60,163 (51%)
Yellow/Indigenous	1,273 (1.1%)
Mixed race (Pardo/Black)	57,181 (48%)
Time from dialysis initiation to waitlisting (months)	15 (7, 35)
Underline Kidney Disease	
Indeterminate	28,319 (24%)
Diabetes	17,158 (14%)
Hypertension	21,561 (18%)
Glomerulonephritis	9,997 (8.4%)
Other	41,582 (35%)
Brazilian Region	
Southeast	63,855 (54%)
South	18,057 (15%)
Midwest	6,861 (5.8%)
North	6,111 (5.2%)
Northeast	23,733 (20%)
Blood Type	
A	41,364 (35%)
AB	4,175 (3.5%)
B	14,118 (12%)
O	58,960 (50%)
Previous Transplant	
No	112,026 (94%)
Yes	6,591 (5.6%)
Panel Reactive Antibody	
0%	79,706 (67%)
1-79%	26,737 (23%)

Characteristic	N = 118,617
80-89%	3,075 (2.6%)
90-100%	9,099 (7.7%)
Number of blood transfusions	
0	74,029 (62%)
1	38,951 (33%)
2	3,738 (3.2%)
3	1,899 (1.6%)
Chagas serology	
Negative	117,682 (99%)
Positive	935 (0.8%)
anti-HBs serology	
Negative	81,865 (69%)
Positive	36,752 (31%)
anti-HBc serology	
Negative	110,942 (94%)
Positive	7,675 (6.5%)
HBsAg serology	
Negative	117,370 (99%)
Positive	1,247 (1.1%)
anti-HCV serology	
Negative	117,418 (99%)
Positive	1,199 (1.0%)
Outcome	
Remain on waiting list	65,595 (55%)
Death on waiting list	11,911 (10%)
Deceased donor transplant	41,111 (35%)
Time to transplant (months)	17 (9, 33)

The categorical variables were described in number and percentage. The numeric variables were reported in median and percentiles (25 and 75%)

Table 02. Competing risk analysis of the Probability of Receiving a Deceased Donor Kidney Transplant in the Brazilian Kidney Transplant System

Characteristic			sHR (competing risks multivariable*+)
all			
Age at baseline (years)	Between 18 and 60	88766 (74.8)	Ref
	Below 18	4322 (3.6)	3.66 (3.50-3.83, p<0.001)
	Higher than 60	25529 (21.5)	0.77 (0.75-0.79, p < 0.001)
Gender	Female	47428 (40.0)	Ref
	Male	71189 (60.0)	1.07 (1.05-1.10, p < 0.001)
Ethnicity	Caucasian	60163 (50.7)	Ref
	Mixed Race (Pardo/Black)	57181 (48.2)	0.97 (0.95-1.0, p = 0.016)
	Yellow/Indigenous	1273 (1.1)	0.89 (0.81-0.99, p = 0.025)
Time on dialysis (years)	Mean (SD)	2.4 (3.2)	0.97 (0.97-0.98, p < 0.001)
Underline Kidney Disease	Indeterminate	28319 (23.9)	Ref
	Diabetes	17158 (14.5)	1.02 (0.98-1.06, p = 0.33)
	Hypertension	21561 (18.2)	1.12 (1.09-1.16, p < 0.001)
	Glomerulonephritis	9997 (8.4)	1.25 (1.21-1.30, p < 0.001)
	Other	41582 (35.1)	1.09 (1.06-1.12, p < 0.001)
Blood Type	A	41364 (34.9)	Ref
	AB	4175 (3.5)	1.16 (1.10-1.22, p < 0.001)
	B	14118 (11.9)	0.93 (0.90-0.96, p < 0.001)
	O	58960 (49.7)	0.77 (0.75-0.79, p < 0.001)
Previous Transplant	No	112026 (94.4)	Ref
	Yes	6591 (5.6)	0.87 (0.82-0.91, p < 0.001)

Characteristic		all	sHR (competing risks multivariable*+)
Panel Reactive Antibody (cPRA)	0%	79706 (67.2)	Ref
	1-79%	26737 (22.5)	0.88 (0.86-0.90, p < 0.001)
	80-89%	3075 (2.6)	0.58 (0.54-0.62, p < 0.001)
	90-100%	9099 (7.7)	0.29 (0.27-0.31, p < 0.001)
Brazilian Region	Southeast	63855 (53.8)	Ref
	South	18057 (15.2)	2.53 (2.47-2.61, p < 0.001)
	Midwest	6861 (5.8)	1.21 (1.16-1.27, p < 0.001)
	North	6111 (5.2)	0.38 (0.36-0.41, p < 0.001)
	Northeast	23733 (20.0)	1.10 (1.07-1.13, p < 0.001)
anti-HBs serology	No	81865 (69.0)	Ref
	Yes	36752 (31.0)	1.45 (1.42-1.48, p < 0.001)
anti-HCV serology	No	117418 (99.0)	Ref
	Yes	1199 (1.0)	1.24 (1.13-1.37, p < 0.001)
Waiting list within COVID-19 pandemic	No	87264 (73.6)	Ref
	Yes	31353 (26.4)	0.92 (0.85-1.00, p = 0.057)

* The analysis was stratified by year of performed transplant; + competing events were death on waitlist and removal from waitlist.

sHR (competing risks multivariable*+) was calculated using a sub-distribution hazard model to conduct Hazard Ratio (HR) analysis, accounting for competing risks and multiple variables.

Table 03. Baseline Characteristics of Patients on the Waitlist in the Brazilian Kidney Transplant System stratified by Brazilian regions.

Characteristic	Southeast, N = 63,855	South, N = 18,057	Midwest, N = 6,861	North, N = 6,111	Northeast, N = 23,733	p- value
Age at baseline (years)	50 (39, 60)	49 (37, 58)	45 (34, 55)*	46 (34, 56)*	44 (33, 55)	<0.001
Age group (years)						<0.001
between 18 and 60	45,832 (72%)	13,415 (74%)	5,377 (78%)	4,834 (79%)	19,308 (81%)	
below18	1,952 (3.1%)	729 (4.0%)	368 (5.4%)	291 (4.8%)	982 (4.1%)	
Higher than 60	16,071 (25%)	3,913 (22%)	1,116 (16%)	986 (16%)	3,443 (15%)	
Gender						0.027
Female	25,564 (40%)	7,271 (40%)	2,783 (41%)	2,510 (41%)	9,300 (39%)	
Male	38,291 (60%)	10,786 (60%)	4,078 (59%)	3,601 (59%)	14,433 (61%)	
Ethnicity						<0.001
Caucasian (white)	37,242 (58%)	14,745 (82%)	3,061 (45%)	1,443 (24%)	3,672 (15%)	
Yellow/Indigenous	859 (1.3%)	185 (1.0%)	60 (0.9%)	81 (1.3%)	88 (0.4%)	
Mixed race (Pardo/Black)	25,754 (40%)	3,127 (17%)	3,740 (55%)	4,587 (75%)	19,973 (84%)	
Time on dialysis (months)	12 (6, 27)+	12 (5, 28)+	21 (10, 46)	25 (10, 54)	25 (12, 56)	<0.001
Underline Kidney Disease						<0.001
Indeterminate	6,484 (10%)	7,096 (39%)	1,163 (17%)	1,794 (29%)	11,782 (50%)	
Diabetes	11,297 (18%)	2,362 (13%)	779 (11%)	1,051 (17%)	1,669 (7.0%)	
Hypertension	13,802 (22%)	2,645 (15%)	1,058 (15%)	1,014 (17%)	3,042 (13%)	
Glomerulonephritis	5,781 (9.1%)	1,395 (7.7%)	823 (12%)	439 (7.2%)	1,559 (6.6%)	

Characteristic	Southeast, N = 63,855	South, N = 18,057	Midwest, N = 6,861	North, N = 6,111	Northeast, N = 23,733	p- value
Other	26,491 (41%)	4,559 (25%)	3,038 (44%)	1,813 (30%)	5,681 (24%)	<0.001
Blood Type						
A	22,484 (35%)	6,762 (37%)	2,305 (34%)	1,760 (29%)	8,053 (34%)	
AB	2,414 (3.8%)	627 (3.5%)	242 (3.5%)	132 (2.2%)	760 (3.2%)	
B	7,917 (12%)	1,873 (10%)	800 (12%)	614 (10%)	2,914 (12%)	
O	31,040 (49%)	8,795 (49%)	3,514 (51%)	3,605 (59%)	12,006 (51%)	<0.001
Panel Reactive Antibody						
0%	46,245 (72%)	9,773 (54%)	4,593 (67%)	4,454 (73%)	14,641 (62%)	
1-79%	12,019 (19%)	5,400 (30%)	1,538 (22%)	1,200 (20%)	6,580 (28%)	
80-89%	1,548 (2.4%)	623 (3.5%)	177 (2.6%)	117 (1.9%)	610 (2.6%)	
90-100%	4,043 (6.3%)	2,261 (13%)	553 (8.1%)	340 (5.6%)	1,902 (8.0%)	<0.001
Previous Transplant						
No	60,306 (94%)	16,459 (91%)	6,560 (96%)	5,956 (97%)	22,745 (96%)	
Yes	3,549 (5.6%)	1,598 (8.8%)	301 (4.4%)	155 (2.5%)	988 (4.2%)	

The categorical variables were described in number and percentage. The numeric variables were reported in median and percentiles (25 and 75%)

The Kruskal-Wallis test, followed by the Dunn Test, was employed for multiple comparisons of continuous variables. Furthermore, chi-squared tests with Holm correction were employed for categorical variables.

*Patients from Midwest and North were not statistical different

+ Southeast and South were not statistical different.

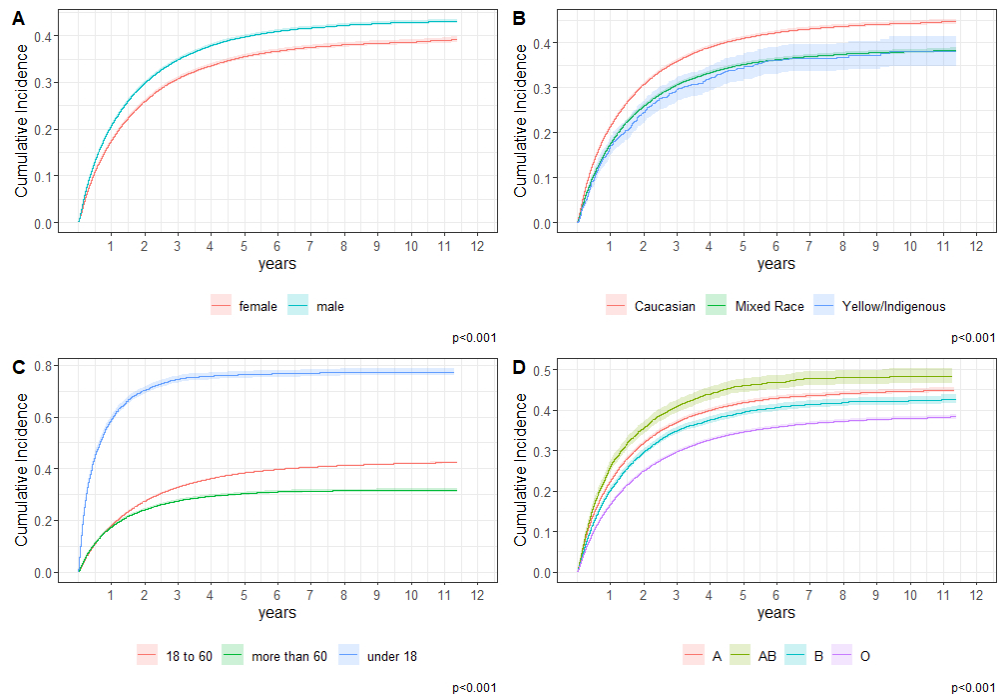
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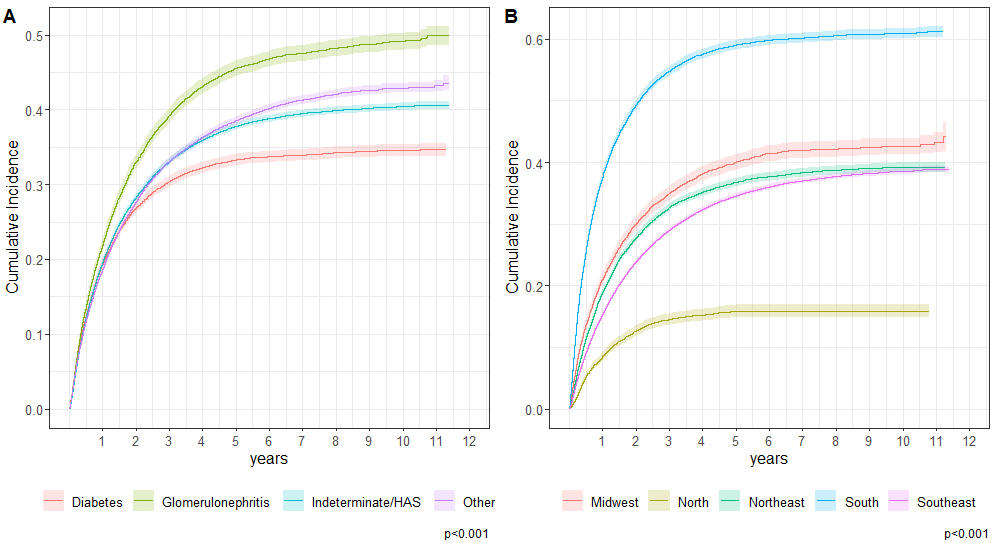
Figure 01. Cumulative Incidence Function (CIF) of the likelihood of being transplanted in the Brazilian Kidney Transplant System. 1A: stratified by gender (male and female); 1B: stratified by ethnicity (Caucasian, Mixed-Race, and Yellow/Indigenous); 1C: stratified by age group (under 18 years, between 18 and 69 years, and over 60 years); 1D: stratified by blood group (A, B, AB, and O).

Figure 02. Cumulative Incidence Function (CIF) of the likelihood of being transplanted in the Brazilian Kidney Transplant System. 2A: stratified by baseline disease (diabetes, glomerulonephritis, hypertension, indeterminate, and other). 2B: stratified by Brazilian region (North, Midwest, Northeast, Southeast, and South).

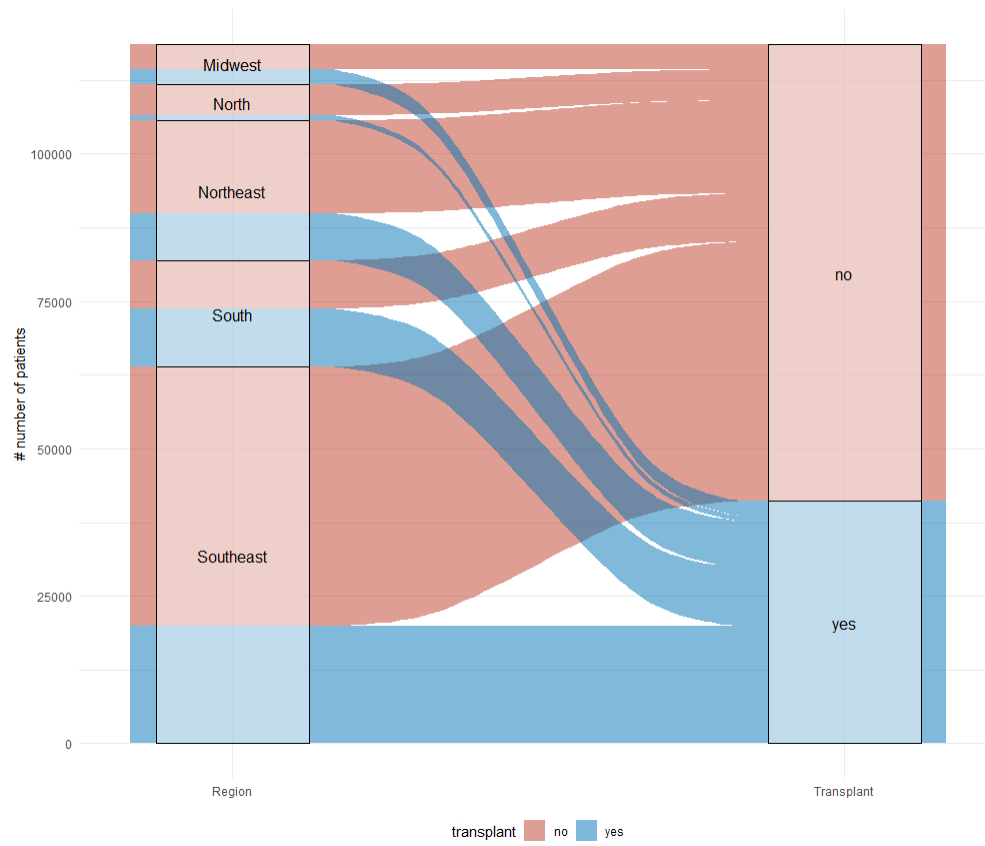
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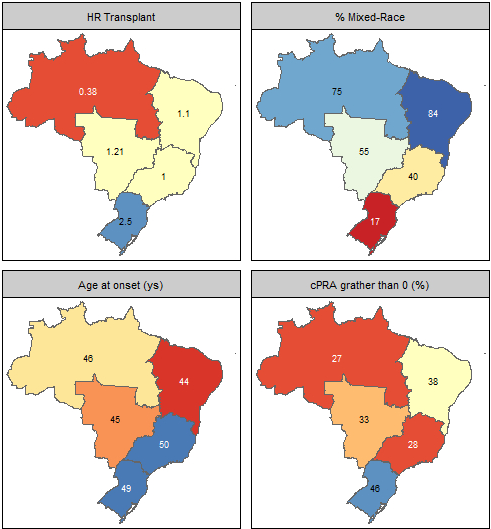
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Regional Disparities in Kidney Transplant Allocation in Brazil. A retrospective cohort study.

Supplementary

01. Missing Data

	Number	Missing number	Missing percentage
Age at baseline (years)	118617	0	0.0
Gender	118617	0	0.0
Ethnicity	118617	0	0.0
Time on dialysis (years)	118617	0	0.0
Underline Kidney Disease	118617	0	0.0
Brazilian Region	118617	0	0.0
Blood Type	118617	0	0.0
Number of Blood Transfusions	118617	0	0.0
Pregnancy	118617	0	0.0
Previous Transplant	118617	0	0.0
Number of Previous Transplant	118617	0	0.0
Panel Reactive Antibody (cPRA)	118617	0	0.0
Chagas serology	118617	0	0.0
anti-HBs serology	118617	0	0.0

	Number	Missing number	Missing percentage
Anti-Hbc serology	118617	0	0.0
Ag-HBs serology	118617	0	0.0
anti-HCV serology	118617	0	0.0
Time to transplantation (months)	118617	0	0.0
Deceased Donor Kidney Transplant	118617	0	0.0

Supplementary Figure 01. Alluvial plot showing the absolute number of patients on the waiting list in the Brazilian Kidney Transplant System, stratified by region in the first column. The second column represents a stratification between those who remain on the waitlist (red) and those who have been transplanted (blue).

Supplementary Figure 02. Plot showing the distribution of Brazilian regions (North, Midwest, Northeast, Southeast, and South) in the Brazilian Kidney Transplant System. Hazard Ratio for Transplantation: shows the HR of being transplanted, stratified by region (with Southeast as the reference HR = 1). Percentage of Mixed Race: shows the percentage of patients on the waitlist who are of mixed race, by region. Age at Onset: shows the median age at onset on the waitlist, stratified by region (in years). Percentage of cPRA Greater than Zero: shows the percentage of patients with cPRA greater than zero, stratified by region.