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# Probability of deceased donor kidney transplantation based on % PRA ☆☆

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ABSTRACT

Sensitization to HLA antigens creates an obstacle for the accessibility and success of kidney transplantation (KT). Highly sensitized patients have longer waiting times and some may never receive a KT.

*Aim:* To determine the probability of patients on the deceased donor (DD) waiting list to receive a KT based on the panel reactive antibody percentage (% PRA) in our center.

*Methods:* The DD waiting list from our institution was analyzed from 01/05 to 08/12 documenting the clinical variables from donor and potential recipients (ABO blood group), lymphocyte cross-match [CxM (CDC-AHG)] results, highest % PRA determination, and time on the waiting list. The patients were classified into 4 groups based on the % PRA: 0%, 1–19%, 20–79% and 80–100%. The data was analyzed using odds ratio and logistic regression (significant $p < 0.05$).

*Results:* 58 DD (F:M 34:24, ABO group O = 35, A = 13, B = 10) and 179 potential recipients were analyzed (F:M 98:81, ABO group O = 127, A = 33, B = 19, participating 4.2 ± 3.8 times with different donors to receive KT). The mean PRA for the whole group was 22 ± 32%, median [md] 0 (0–98). A total of 100 patients received KT (mean waiting time 2.2 ± 1.7 years, 12 days–7 years) and their mean % PRA was 11.6 ± 24, md 0 (0–94) vs. 31.4 ± 37 md 8.5 (0–98) in those who have not received a KT. An association between the % PRA group and KT ($p < 0.003$) was observed. The probability of receiving KT with a 0% PRA vs. >0% was higher (OR 2.12, 1.17–3.84). There was no difference between the 0% vs. 1–19% group (OR 1); differences were observed between 0% vs. 20–79% (OR 2.5, 1.18–5.3) and 0% vs. 80–100% (OR 5, 1.67–14.9). For every percent increase in the PRA above 20%, the risk of not receiving a KT increased by 5% (1–9, $p < 0.01$).

*Conclusions:* The probability of receiving a DD kidney transplant is inversely related to the % PRA although a higher risk for not receiving a KT becomes evident with a PRA >20%.



## 1. Introduction

Kidney transplantation is the preferred treatment modality for patients with ESRD because of improved patient survival and quality-of-life over dialysis [1–4]. Several groups have analyzed transplantation in highly HLA-sensitized patients recently. The risks for transplantation can be assessed using currently available standard assays. Today, the techniques that are used to detect anti-HLA antibody include cytotoxicity (CDC) with/without anti-human globulin, ELISA, and flow cytommetry (using cells and antigen-coated beads). The development of newer, more sensitive assays has led to an increased ability to define highly sensitized patients and identify donor-specific antibody [2]. Several risk factors have been described regarding sensitization to HLA antigens including blood transfusions, pregnancy and previous organ transplantation. The degree of sensitization creates an obstacle for the accessibility and success of kidney transplantation [1].

In patients with high panel-reactive antibodies (% PRA) defined as having a % PRA >30, transplant rates are dramatically reduced because of the additional immunologic barrier with increased rejection risk [2]. In 2003, only 6.5% of all kidney transplants that were performed in the United States were in patients with PRA >80%, despite representing approximately 14% of the waiting list [5,7]. When these patients receive a transplant, they experience an increased number of rejection episodes and have poorer graft survival [6]. According to Marfo et al., 35% of the patients on the waiting list are sensitized with PRA levels >0%, and 15% are highly sensitized with PRA levels >80% [1].

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In some regions of the United States, the waiting time on the transplant list can exceed five years and due to organ shortage, this scenario is not changing in the near future. It has been thoroughly described that highly sensitized patients have longer waiting times and some may never receive a transplant [1]. In Mexico, roughly 75% of renal transplants are from living donors and approximately 2300 kidney transplants per year have been performed during the last 3 years [8].

Although there has been a decrease in the mortality rate of patients on dialysis, approximately 15 to 20% still die each year, which emphasizes the importance of early transplantation [4,9]. There is an evident financial cost and emotional burden secondary to maintaining a highly sensitized patient on dialysis in comparison to early transplantation. The impact of kidney transplantation on morbidity, mortality, quality of life and medical expenses is undeniable.

The main objective of this study was to determine the probability of patients in the deceased donor (DD) waiting list at the National Institute of Medical Sciences and Nutrition (INCMNSZ) in Mexico City to receive a kidney transplant (KT), based on the degree of sensitization determined by % PRA. Acute rejection rate, graft function, patient and graft survival, and causes for patient death/graft loss were also analyzed.

This protocol was approved by the Institutional Committee of Medical Ethics and performed in accordance with the revised Declaration of Helsinki content and Good Clinical Practice Guidelines.

## 2. Patients and methods

The renal transplant DD waiting list database was reviewed from January 2005 to August 2012 at the Histocompatibility Laboratory at INCMNSZ. For each DD event, we documented the donor's demographic characteristics (age and gender), donor's blood group (ABO group), the number and ABO group of all the potential recipients considered, the results of the lymphocyte cross-match test [CxM (AHG-CDC)] for each potential recipient considered, the % PRA of each potential recipient (highest % PRA documented in the last three determinations) and which patients consequentially received a DD kidney transplant.

Anti-HLA antibodies were tested by the Luminex technique using test kits purchased from One Lambda, Inc., Canoga Park, CA. In the patients on the waiting list, a LabScreen Mixed Classes I & II and a LabScreen PRA Classes I & II were simultaneously performed. Only those with positive results in either test received a Labscreen Single Antigen test. When available, the result of pre-transplant DSA assessment using the LABScreen Single Antigen Classes I & II was gathered for the analysis. Crossmatches were performed just prior to transplantation with the standard AHG enhanced complement-dependent cytotoxicity test (AHG-CDC-CXM) for T and B cells. Renal transplants were performed only when AHG-CDC CXMs were negative.

The potential recipients considered during the DD events were classified into 5 groups according to their % PRA: Group 1 (0%), group 2 (1–19%), group 3 (20–79%), group 4 (80–100%) and group 5 (unknown PRA). The patients in group 5 (unknown) were included in the deceased donor waiting list in a time period when the % PRA assay was not part of the regular practice in our setting.

In our institution, kidney allocation to patients on the waiting list has been based exclusively on a negative T and B cells AHG-CDC cross-match, the time on waiting list and blood group (equal ABO group with the donor). Patients without vascular and peritoneal access for dialysis are considered emergencies and always have had priority in our setting. All of the patients that undergo a DD KT at out institution receive some modality of induction therapy, whether anti-CD25 monoclonal antibodies or thymoglobulin, and is mostly defined by the immunological patient risk. During this time period, the immunosuppression regimen for this group of patients consisted of tacrolimus, mycophenolate mofetil, and prednisone.

Clinical information regarding 1-year post-KT graft function and/or the last graft function evaluation was gathered from the corresponding patient records. Causes of graft loss and patient death were documented.

The graft biopsy registry was analyzed to obtain the information regarding the total number of graft dysfunction biopsies performed, and acute rejection events documented whether cellular, humoral or both. The histological analysis and diagnosis were performed using the current BANFF criteria at the time of the graft biopsy [11–17]. Graft dysfunction was defined as SCr increase of $\geq$25% from baseline in the absence of an identified cause.

The statistical analysis was performed using odds ratio with prior group stratification, logistic regression analysis, Kaplan Meier method and Log Rank. A p value $<0.05$ was considered statistically significant with a confidence interval of 95%. For categorical variables, an analysis to determine frequencies, proportions, Chi2, and Spearman correlation coefficient was also performed.

## 3. Results

### 3.1. Transplant characteristics and organ assignment

Fifty-eight DD events with a female to male ratio of 34:24 and a mean age of 35.4 $\pm$ 13.3 were identified. The ABO group distribution among these donors was of 35 donors for group "O", 13 donors for group "A" and 10 donors for group "B". A group of 179 potential kidney transplant recipients was included in the analysis all of whom were older than 18 years of age, with a female to male ratio of 98:81 and a ABO group distribution of 127 patients for group "O", 33 patients for group "A" and 19 patients for group "B". The mean PRA for all the potential recipients was 22 $\pm$ 32%, median [md] 0 (0–98). Males had a mean % PRA of 11.7 $\pm$ 26 md 0 (0–97) vs. females with a mean % PRA of 30.9 $\pm$ 35 md 13.5 (0–98).

Overall, potential kidney transplant recipients participated in a mean of 4.2 $\pm$ 3.8 cross-matches with potential donors for kidney allocation. The mean number of patients included for cross-match testing per donation event was 21 for ABO group "O", 8 for group "A", and 5 for group "B".

A total of 100 patients received a KT with a mean time on the DD waiting list of 2.2 $\pm$ 1.7 years (12 days–7 years) vs. 5.2 $\pm$ 3.7 years (119 days–18.5 years) in the patients (n = 79) that remain in the waiting list for the period of time of this analysis. The mean % PRA of the KT recipients was 11.6 $\pm$ 24 md 0 (0–94) vs. 31.4 $\pm$ 37 md 8.5 (0–98) in those who have not received a KT. Regarding the administration of induction therapy, in the period of January 2005 to August 2012, 57% received anti-CD25 monoclonal antibodies (Daclizumab or Simulect) and 43% thymoglobulin. None of these patients were involved in any sort of desensitization protocol prior to KT.

### 3.2. Risk assessment

A statistically significant association between a lower % PRA group and receiving a KT was observed ($p < 0.003$). A Kaplan Meier curve depicting the percentage of patients without a KT among the different % PRA groups adjusted for time on the waiting list (years) is presented in Fig. 1. The probability of receiving KT with a 0% PRA vs. >0% was higher (OR 2.12, 1.17–3.84). There was no difference in the probability of receiving a KT between the 0% vs. 1-–19% group (OR 1). In the probability analysis of the group with 0% vs. 20–79% and 0% vs. 80–100% the odds ratio was 2.5 (1.18–5.3) and 5 (1.67–14.9), respectively. For every percent increase in the PRA above 20%, the risk of not receiving a KT increased by 5% (1–9, $p < 0.01$). The probability analysis is presented in Table 1. This analysis was performed on a population level and not by calculating individual patient probabilities using HLA typing and HLA specific antibodies towards possible organ donors.

There was no association observed between the recipient's ABO group and receiving a KT (p .126). A Spearman correlation coefficient of .135 was determined between the % PRA and the number of times potential recipients were considered for DD renal transplantation.

In Fig. 2, the proportion of DD renal transplants performed at the INCMNSZ based on the % PRA for the period analyzed is presented. As observed, the number of patients receiving a KT in this period of time for group 1 (PRA0%) conformed the 50% of the KT procedures performed.

### 3.3. Graft biopsies and acute rejection rates

In this group of KT recipients, a mean number of 2.1 $\pm$ 1.6 graft biopsies (protocol first year biopsies and graft dysfunction biopsies) were performed in their follow-up period by the time of this study. The mean number of biopsies performed for indication (dysfunction) was 1.13 $\pm$ 1.26. Overall, acute rejection (cellular, humoral, or both) was diagnosed in 20%. Further analysis of the acute rejection rates by % PRA group is presented in Table 2 and the distribution of acute cellular rejection and acute humoral rejection by % PRA group is presented in Fig. 3.

In a successive outcome analysis regarding the presence of pre-transplant donor specific antibodies (DSA, mean fluorescence index >500), 76% (38/50) of renal transplant recipients were evaluated and 13% (n = 5) had positive pre-transplant DSA (PRA

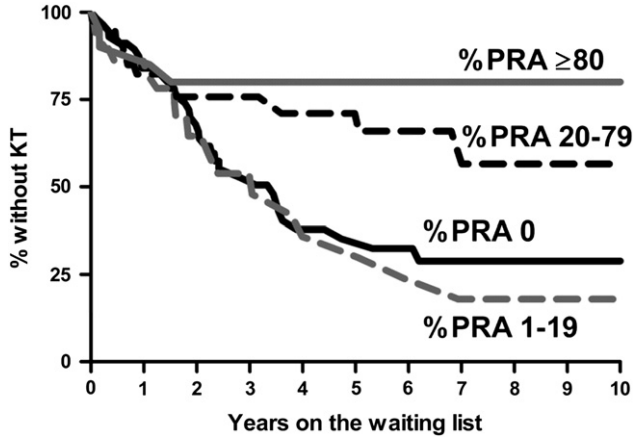


**Fig. 1.** Kaplan Meier curve depicting the percentage of patients without a KT among the different % PRA groups adjusted for time on the waiting list (years).

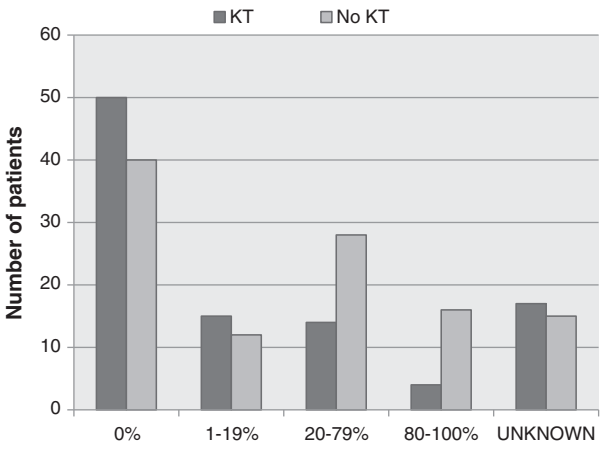


**Fig. 2.** Proportion of patients receiving a KT in each % PRA group from 2005 to 2012.

20–79% n = 3, 1–19% n = 1, and unknown n = 1). A statistically significant association between the % PRA and the presence of pre-transplant DSA was observed (p .025). Of those patients with pre-transplant DSA, histological evidence of humoral rejection was observed in 60% of cases.

### 3.4. Graft function

Overall, at a mean follow up posttransplant period of 3.3 ± 2.2 years 95 of the 100 KT recipients included in this study continued to have a functioning graft (estimated glomerular filtration rate, eGFR >15 ml/min). The latest mean serum creatinine (SCr) for the whole group is 1.5 ± 1.2 mg/dl, and the corresponding eGFR by MDRD at year 1 post-KT, and in their most current determination was 62.1 ± 19.6 ml/min and 60.3 ± 22 ml/min, respectively. The graft function analysis by % PRA groups is presented in Table 2. In the patients that had an episode of acute rejection, the latest mean eGFR was 43 ± 22.9 ml/min vs. 67.7 ± 17.9 ml/min in those patients that never have had an episode of acute rejection. One patient included in this patient population endured acute graft loss secondary to primary graft nonfunction, hyperacute rejection with necrotizing arteritis, 0% PRA, negative anti-HLA and negative anti-MICA antibodies [10]. This patient was subsequently transplanted in a second occasion with an adequate outcome and current functioning graft. Five additional patients had lost their graft at the time of this analysis, with a mean time to return to dialysis of 2.3 ± 2 years and a distribution among the % PRA groups of 3 patients in group 5 (unknown), 1 in group 2 (1–19 %PRA) and 1 in group 3 (20–79% PRA). The cause of graft loss in these patients, determined by tissue biopsy was interstitial fibrosis/tubular atrophy (n = 4) and chronic cellular rejection (n = 1). One patient with graft loss died during this time period, having return to hemodialysis prior to the event.

## 4. Discussion

Even though the probability of receiving a KT from a DD is inversely related to the % PRA, during the time period analyzed in this study we observed that in the past 7 years there has been a number of highly sensitized patients that receive a DD renal transplant (~10% with % PRA >80). The risk of not receiving a KT based on the % PRA in this analysis, only became evident with a PRA >20%. For every percent increase in the PRA above 20%, the risk of not receiving a KT increased by 5% (1–9, p < 0.01).

It is important to mention that although the % PRA is not entirely specific in regard to alloreactivity towards the donor, it does provide an indirect measure to estimate the probability of the presence of DSA and/or a positive crossmatch [1,2]. Furthermore, this is supported by the distribution of organ assignment among % PRA groups 1 and 2 in contrast with groups 3 and 4 (Fig. 3) in which it becomes clear that the patients with lower % PRA are receiving a kidney more often than those with higher percentages.

**Table 1**
Probability of receiving a KT among the different % PRA groups.

| %PRA | Probability of KT (OR) |
|---|---|
| 0% vs. >0% | 2.12 (1.17–3.84) |
| 0% vs. 1–19% | 1 |
| 0% vs. 20–79% | 2.5 (1.18–5.3) |
| 0% vs. 80–100% | 5 (1.67–14.9) |

Pre-transplant HLA highly sensitized patients portend a higher risk for acute rejection after transplantation. Interestingly, in this series the documented rate of acute rejection – whether cellular or humoral – across the groups 1 to 4 was similar. It is important to mention however, that the low number of patients who received a kidney transplant in groups 2 to 4 preclude to have statistical power to detect significant differences compared to unsensitized patients (group 1 = PRA 0%).

The humoral rejection rates were similar throughout the % PRA groups as well as in group 1 (0%), which implies that the rejection rate is not entirely dependent on the % PRA. In this scenario, risk factors for the occurrence of humoral rejection episodes could be linked to inadequate immunosuppression adherence and/or drug minimization, as recently demonstrated [18], however we did not search for patient's compliance to immunosuppressive therapy in this analysis, therefore the cause of the 8% acute humoral rejection episodes (alone or combined with cellular rejection) in the 0% PRA group remains elusive.

Overall, the current acute rejection rate reported by the OPTN/SRTR in DD KT is 11.6% in the first year post-KT with a tendency to increase thereafter to attain ~19% at 60 months post-KT [9]; our series showed similar numbers with an overall acute rejection rate of 20% at a mean follow up post-transplant period of 3.3 ± 2.2 years. It is worth mentioning that the 35% acute rejection episodes in the unknown pre-transplant PRA group suggest that a number of patients included in this group were highly sensitized. Regarding the pre-transplant sensitization status, it is important to mention that in those patients with a % PRA >0 or with the presence of pre-transplant DSA, induction therapy with thymoglobulin was administered.

It is important to highlight that 95% of the patients included in this analysis had a functioning allograft at the time of the database review. The graft function analysis by % PRA groups revealed very similar eGFR in the 0% and 1–19% PRA groups (65 ± 20.12 ml/min vs. 64.9 ± 22.5 ml/min, respectively). These similarities seem to support the statistical findings that were presented in the risk analysis, consequently implying that the sensitization characteristics and tendency towards immune mediated graft dysfunction are constant with a % PRA <20.

In a recent retrospective and single center study by Dunn et al., the authors concluded that the best short and long-term immunologic outcomes occur when donor sensitization is avoided, and that historically accepted risk factors such as % PRA, pre-transplant and DD grafts do not necessarily confer significant immunologic risk and probability of adequate outcomes. However, a probabilistic analysis focusing on the event of transplantation with these characteristics was not provided [19].

**Table 2**
Graft function analysis and acute rejection rates by % PRA groups.

| % PRA group | PRA 0% (n = 50) | 1–19% (n = 15) | 20–79% (n = 14) | 80–100% (n = 4) | Unknown (n = 17) |
|---|---|---|---|---|---|
| Donor gender (F/M) | 15/35 | 6/9 | 8/6 | 2/2 | 11/6 |
| Donor mean age (years) | 32.2 ± 12.5 | 36 ± 10.8 | 35.5 ± 12.4 | 32.5 ± 15.9 | 39.1 ± 14.8 |
| 1-year post-KT eGFR by MDRD (ml/min) | 67 ± 18.9 | 63.1 ± 19.4 | 57.7 ± 22.5 | 54.5 ± 17.4 | 55.6 ± 18.5 |
| Latest eGFR by MDRD (ml/min) | 65 ± 20.12 | 64.9 ± 22.5 | 55 ± 21.8 | 56 ± 17.5 | 50.25 ± 26.85 |
| Latest serum creatinine (mg/dl) | 1.3 ± 0.34 | 1.5 ± 1.03 | 1.5 ± 0.9 | 1.4 ± 0.5 | 2.2 ± 2.3 |
| Acute rejection rate (%) | 16% | 20% | 14% | 25% | 35% |
| Mean time to 1st acute rejection (days) | 165 ± 169 | 99 ± 96 | 240 ± 243 | 35 | 243 ± 187 |
| Mean time post-KT (years) | 2.8 ± 1.9 | 2.8 ± 2 | 2.7 ± 1.7 | 1.7 ± 1 | 5.8 ± 1.8 |

The impact of an episode of acute rejection on graft function seems undeniable [20–22]; in our series an eGFR of 43 ± 22.9 ml/min vs. 67.7 ± 17.9 ml/min was documented in the patients with an episode of AR vs. those patients without history of rejection.

In conclusion, this information suggests that excluding sensitized patients from the DD waiting list should not be favored, although a thorough explanation and preparation of the patients for a longer time period on the waiting list should be emphasized. Although this study was carried out in a limited population, when a patient with a high % PRA overcomes the immunological barriers for transplantation and receives a kidney, the functional graft outcomes seem to be very similar to the patients with lesser PRA percentages in the short run. However, long-term follow up is deserved to know the fate of graft and patient survival in this patient population with different pre-transplant % PRA. The tendency for the generalization of single antigen determination in the pre-transplant screening in our setting will most likely favor the organ assignment process and prioritize adequate outcomes. As was reported by Fuggle et al., the tendency for the generalization of single antigen determination in the pre-transplant screening in our setting will most likely favor the organ assignment process and prioritize adequate outcomes by increasing antibody specificity definition and the understanding of a patient's sensitization profile [23].

## Author contributions

Bostock IC: Concept/design, data analysis/interpretation, drafting article, critical revision of article, data collection.

Alberú J: Concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article, data collection.

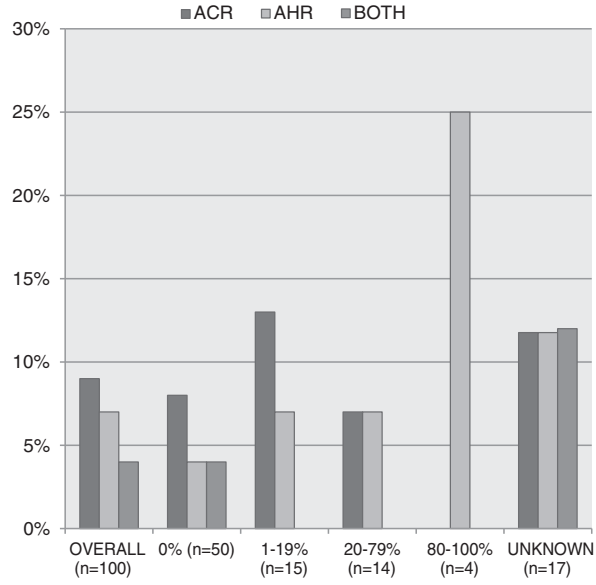


**Fig. 3.** Acute cellular and humoral rejection rates in each % PRA group from 2005 to 2012.

Arvizu A: Patient care, critical revision of article, data collection.

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Contreras AG: Patient care, critical revision of article, data collection.

Morales-Buenrostro LE: Data analysis/interpretation, drafting article, critical revision of article.

Gabilondo B: Data analysis/interpretation, drafting article, critical revision of article.

Vilatoba M: Concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article, data collection, senior author.

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