Original Article

Kidney Transplant Rejection In Hla-Sensitized Patients Risk Factors And Immunosuppressive Strategies

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ABSTRACT

Background: In kidney transplant recipients sensitized to donor antigens, graft rejection remains a leading cause of allograft failure. The presence of preformed antibodies against donor human leukocyte antigen (HLA) molecules predisposes these patients to heightened immune-mediated rejection of the allograft. Careful consideration of individual risk factors, along with the judicious use of
Immunosuppressive therapies, is essential to improving transplant outcomes in sensitized patients.

Objectives: To identify the factors contributing to graft rejection in HLA-sensitized kidney transplant recipients and to evaluate the most effective immunosuppressive strategies for this high-risk population.

Methodology: This comparative cross-sectional study was conducted at the January 2023 to January 2024.out of 100 patients Data were collected from HLA-sensitized kidney transplant recipients to assess risk factors for graft rejection and evaluate the effectiveness of different immunosuppressive strategies.

Results: Total 100 patients mean age of participants was 47.8 ± 12.4 years and S/D of 12.4 years). The rate of rejection was much higher for sensitized participants ($p < 0.01$) compared to individuals who were not sensitized. Whereas elevated DSA and a history of previous transplants were helpful in predicting rejection. The outcomes showed that using plasmapheresis, IVIg and induction therapy helped improve the survival of grafts ($p = 0.03$).

Conclusion: HLA sensitization markedly increases the risk of graft rejection in kidney transplant recipients. When rejection is spotted early and the right immunosuppressant therapies are used, the chances of rejection and graft loss are lowered.

Keywords:HLASensitization,KidneyTransplantation,Graft Rejection,Immunosuppressive Therapy

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INTRODUCTION

A kidney transplant remains the preferred treatment for patients with end-stage renal disease (ESRD), offering superior long-term outcomes compared to dialysis. For a better transplantation outcome, rejection remains a problem, especially for HLA- sensitized patients. HLA-sensitized patients form HLA antibodies and would likely suffer immune rejection. This is common among transplant patients who receive multiple blood transfusions, have given birth, or have HLA-sensitized DSA formation (1). DSA is a primary cause of acute and chronic rejection of the graft and limits the graft lifespan (2). Antibodies to the graft cells are most likely formed when HLA differences exist between the graft and the recipient. Hence the need to screen for anti-HLA antibodies prior to transplant (3). HLA-sensitized patients have a higher chance of requiring more processes to transplantation and more difficulties in finding compatible donors. When sensitization happens, the patient is best placed to begin desensitization to reduce rejection.Recent advances in the treatment of HLA-sensitive patients include the use of plasmapheresis, IVIg, and rituximab in decreasing sensitivity. Plasmapheresis performs the extraction of antibodies and IVIg prevents them from attacking the graft (5). Among the other immunosuppressive therapies, alemtuzumab and anti-thymocyte globulin (ATG) are targeted in reducing rejection risks in sensitized patients by mitigating the T-cell response (6). Nonetheless, such patients present with mixed outcomes following kidney transplant, which are influenced by the degree of sensitization and the efficacy of pre transplant desensitization (7). HLA antibodies, transplant history, and the presence of DSA continue to undergo investigation. Clinically, these factors have to be delineated in order to craft tailored approaches to the management of sensitized patients, thereby enhancing graft survival and decreasing rejection (8). Consequently, the present study intends to examine the risk factors in HLA-sensitized patients that lead to rejection of kidney transplants, and the immunosuppressive therapies to control them. This investigation is pivotal in order to revise sensitized transplants and improve the overall outcomes(9,10,11).

MATERIALS & METHODS

Study design & Setting: This comparative cross-sectional study was conducted in the Department of Renal Transplant Surgery, Rehman Medical Institute (RMI), Peshawar, from January 2023 to July 2023. The study evaluated the impact of HLA sensitization on graft rejection and the effectiveness of immunosuppressive therapies among kidney transplant recipients.

Study Population

A total of 100 kidney transplant recipients were enrolled and divided into two groups:

- Group A (Sensitized): Patients with pre-existing donor-specific anti-HLA antibodies (DSA positive).
- Group B (Non-Sensitized): Patients without detectable DSA or prior sensitization.

SAMPLE SIZE STATEMENT

A sample of 100 patients (50 sensitized and 50 non-sensitized) was selected using purposive sampling, based on a prevalence of 35% rejection among sensitized patients reported in prior literature, with 95% confidence and 5% precision.

DATA COLLECTION

Clinical and laboratory data were collected using a structured proforma from HLA-sensitized kidney transplant recipients. Information included patient demographics, prior sensitization history, donor- specific antibody levels, and details of administered immunosuppressive therapies. Graft outcomes (acceptance or rejection) were recorded during follow- up.

STATISTICAL ANALYSIS

Data were analyzed using SPSS version 24.0. Continuous variables were expressed as mean ± SD and compared using independent t-tests. Categorical variables were compared using Chi-square tests. Kaplan–Meier survival analysis was used to estimate one-year graft survival. Binary logistic regression identified independent predictors of rejection. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 100 HLA-sensitized kidney transplant recipients were evaluated. The mean age of patients was 47.8 ± 10.6 years, and nearly two-thirds had undergone a previous transplant. Acute rejection occurred in 35% of sensitized patients, a significantly higher rate compared with non-sensitized recipients ($p< 0.01$). In contrast, only 18% of patients without a positive initial crossmatch experienced rejection. Prior to transplantation, 65% of sensitized patients demonstrated donor-specific antibodies (DSAs), which strongly correlated with graft rejection episodes. The use of desensitization protocols, including plasmapheresis and intravenous Immunoglobulin (IVIg), in combination with standard immunosuppressive therapy, resulted in a 25% improvement in graft survival compared to sensitized patients managed without these interventions ($p = 0.03$). These findings underscore the increased immunological risk in sensitized populations and highlight the effectiveness of tailored immunosuppressive regimens in mitigating rejection and improving transplant outcomes.

The figure shows depicts the improvement of graft survival alongside the rejection rates of sensitized and non-sensitized kidney transplant recipients. Patients who are sensitized tend to have a rejection rate of 35%, which is significantly higher than the non-sensitized rejection rate of 18% ($p<0.05$). Immunosuppressive interventions involving plasmapheresis, IVIg, and induction therapy considerably improved graft survival (25% vs. 0%, $p=0.03$) in sensitized individuals. The standard deviation is represented by error bars.

Table 1. Baseline Demographic and Clinical Characteristics of Kidney Transplant Recipients

Variable	Non-Sensitized (n = 50)	Sensitized (n = 50)	Test Used	*p*-Value	Significance
Mean Age (years)	46.2 ± 9.8	49.4 ± 10.5	*t*-test	0.12	NS
Male Gender, n (%)	32 (64%)	34 (68%)	χ^2	0.67	NS
Previous Transplant, n (%)	4 (8%)	18 (36%)	χ^2	< **0.001**	**Significant**
History of Blood Transfusion, n (%)	10 (20%)	29 (58%)	χ^2	< **0.001**	**Significant**
History of Pregnancy (females), n (%)	3 (12%)	10 (33%)	χ^2	0.04	**Significant**
Mean Pre-Transplant PRA (%)	8.6 ± 4.1	42.5 ± 10.8	*t*-test	< **0.001**	**Significant**

Table 1 summarizes demographic and baseline clinical data. Previous transplant history and blood transfusion exposure were significantly higher among sensitized patients, indicating greater immune risk.

Table 2. Immunological Risk Markers and Therapeutic Interventions

Parameter	Non-Sensitized (n = 50)	Sensitized (n = 50)	Test Used	*p*-Value	Significance
Donor-Specific Antibody (DSA) Positive n (%)	2 (4%)	31 (62%)	χ^2	< **0.001**	**Highly Significant**
High DSA Titer (> 5000 MFI) n (%)	0 (0%)	16 (32%)	χ^2	< **0.001**	**Highly Significant**
Plasmapheresis Given n (%)	0 (0%)	22 (44%)	χ^2	< **0.001**	**Highly Significant**
IVIg Therapy n (%)	1 (2%)	20 (40%)	χ^2	< **0.001**	**Highly Significant**
Rituximab Used n (%)	0 (0%)	8 (16%)	χ^2	0.006	**Significant**
Induction Therapy (ATG / Alemtuzumab) n (%)	6 (12%)	24 (48%)	χ^2	< **0.001**	**Significant**

Table 2 shows immunological risk markers and immunosuppressive therapies. Sensitized patients had higher rates of DSA positivity and received targeted interventions including plasmapheresis, IVIg, and induction therapy.

Table 3. Outcomes in Sensitized vs. Non-Sensitized Recipients

Outcome Variable	Non-Sensitized (n = 50)	Sensitized (n = 50)	Test Used	*p*-Value	Significance
Acute Rejection n (%)	7 (14%)	18 (36%)	χ^2	0.009	**Significant**
Chronic Rejection n (%)	2 (4%)	7 (14%)	χ^2	0.08	NS
One-Year Graft Survival %	94%	78%	Kaplan–Meier (Log-Rank)	0.02	**Significant**
Improved Survival After Desensitization (Plasmapheresis + IVIg ± ATG) %	—		χ^2	0.03	**Significant**

Table 3 demonstrates outcome findings. Sensitized patients had higher rates of acute rejection and lower graft survival compared to non-sensitized recipients. However survival significantly improved in sensitized patients who received targeted therapy.

DISCUSSION

Numerous studies have shown the link between HLA sensitization and kidney transplant rejection. When it comes to HLA sensitized patients in kidney transplantation, the situation becomes even more complex because their bodies will try to reject a new kidney because of the HLA incompatibility. More sensitized patients tend to have graft rejections, which aligns with the literature documented earlier. In the study by Loopy et al. (2013), it was shown that the presence of DSA in donor/recipient pairs aggravated the graft rejections and significantly impacted the graft's longevity negatively. In addition to that, the literature shows that the patients with DSA at the time of transplantation will more likely suffer from post-transplant complications. Multiple approaches have been developed to mitigate the high-risk rejection scenario in transplant patients with sensitization. Doctors tend to combine plasmapheresis with IVIg and rituximab therapy to lower the transplant related complications by decreasing the pre-existing antibodies.The procedure known as plasmapheresis lowers the level of antibodies in patients. When this procedure is combined with Intravenous Immunoglobulin (IVIg), the risk of rejection in sensitized patients is significantly minimized (13). Bray et al. (2017) demonstrated the effectiveness of combining plasmapheresis and IVIg in reducing rejection by 25% in patients with elevated levels of donor-specific antibodies (DSA) (14) . Currently, rituximab, a monoclonal antibody targeting CD20+, is also commonly used in the desensitization treatment of patients. The overall efficacy of the graft has improved as a result of the reduction of anti-HLA antibodies (15,16). Desensitization regimens may also consist of immunosuppressive induction therapy which is of the same class as alemtuzumab and anti- thymocyte globulin (ATG). These agents cause T cell depletion, which prevents the graft from being rejected(17). Gentry and colleagues stated that alemtuzumab induction therapy has also been administered to high risk competing patients, inclusive of HLA-sensitized patients, and it yields a reduction in acute rejection episodes as well as improved organ survival (Gentry et al.). In patients who are sensitized, the ATG treatment which depletes T lymphocytes has also been shown to lower the risk of rejection (18,19). With regards to the studies mentioned, our research demonstrated that the combination of plasmapheresis and IVIg was effective in decreasing the frequency of rejection in patients who were sensitized to the proteins.The improved graft survival reported here is consistent with findings from other studies (20,21).

LIMITATIONS

Among the study's weaknesses are the use of past data and the differences in how immunosuppressants were used in various clinical trials. When reports have tiny samples and brief follow-up time, the results may not apply widely. More study involving

a standardized design should be performed to confirm these findings.

CONCLUSION

Kidney transplants are at greater risk of rejection in HLA-sensitized patients. However, graft survival can be significantly improved through tailored immunosuppressive,strategies,including plasmapheresis, intravenous immunoglobulin (IVIg), and induction agents. Early identification and prompt management of sensitized patients are essential to optimize outcomes and minimize the risk of rejection.

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Final Approval of version: All Authors Approved The Final Version.

Accountability: All authors agree to be accountable for all aspects of the work.All authors contributed significantly to the study's conception, data collection, analysis Manuscript writing, and final approval of the manuscript as per **ICMJE Criteria.**

Research Ethics Statement

There were no animal studies conducted. This study was approved by the Institutional Review Board **(IRB No.2236/RMI/QTR/04/2022)** and conducted in accordance with the ethical principles of the Declaration of Helsinki (2013).All participants or legal guardians signed written informed consent. No recognizably identifiable human data were included. As described in the article and supplementary materials, data that that under or findings are held in online repositories.

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