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Contents

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EDITORIAL

3791 Targeting both ferroptosis and pyroptosis may represent potential therapies for acute liver failure

Xing ZY, Zhang CJ, Liu LJ

3799 Lipid metabolism-related long noncoding RNAs: A potential prognostic biomarker for hepatocellular carcinoma

Zhang RN, Fan JG

3803 Linear endoscopic ultrasound: Current uses and future perspectives in mediastinal examination

Gadour E, Al Ghamdi S, Miutescu B, Shaaban HE, Hassan Z, Almuhaidb A, Okasha HH

3810 Colorectal cancer cell dormancy: An insight into pathways

Kumar A, Saha L

3818 Early diagnostic strategies for colorectal cancer

Liu SC, Zhang H

ORIGINAL ARTICLE

Retrospective Cohort Study

3823 Pan-immune-inflammation value as a prognostic biomarker for colon cancer and its variation by primary tumor location

Wang QY, Zhong WT, Xiao Y, Lin GL, Lu JY, Xu L, Zhang GN, Du JF, Wu B

Observational Study

3837 Human leukocyte antigen compatibility and incidence of donor-specific antibodies in pediatric liver transplant recipients

Melere MU, Feier FH, Neumann J, Kalil AN, Montagner JM, Nader LS, da Silva CS, Junior MAF, Coral GP, Bobsin GP, Ferreira CT

LETTER TO THE EDITOR

3846 Depression weights in patients with gastric cancer: Bibliometric analysis as a weapon to chart the future of research

Pellegrino R, Gravina AG

ABOUT COVER

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ORIGINAL ARTICLE

Observational Study

Human leukocyte antigen compatibility and incidence of donor-specific antibodies in pediatric liver transplant recipients

Melina U Melere, Flavia H Feier, Jorge Neumann, Antônio N Kalil, Juliana de M Montagner, Luiza S Nader, Carolina S da Silva, Marco Aurélio F Junior, Gabriela P Coral, Guilherme P Bobsin, Cristina T Ferreira

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Abstract

BACKGROUND

Antibody-mediated rejection following liver transplantation (LT) has been increasingly recognized, particularly with respect to the emergence of *de novo* donor-specific antibodies (DSAs) and their impact on graft longevity. While substantial evidence for adult populations exists, research focusing on pediatric LT outcomes remains limited.

AIM

To investigate the prevalence of human leukocyte antigen (HLA) mismatches and DSA and evaluate their association with rejection episodes after pediatric LT.

METHODS

A cohort of pediatric LT recipients underwent HLA testing at Santa Casa de Porto Alegre, Brazil, between December 2013 and December 2023. Only patients who survived for > 30 days after LT with at least one DSA analysis were included.

DSA classes I and II and cross-matches were analyzed. The presence of *de novo* DSA (dnDSA) was evaluated at least 3 months after LT using the Luminex® single antigen bead method, with a positive reaction threshold set at 1000 MFI. Rejection episodes were confirmed by liver biopsy.

RESULTS

Overall, 67 transplanted children were analyzed; 61 received grafts from living donors, 85% of whom were related to recipients. Pre-transplant DSA (class I or II) was detected in 28.3% of patients, and dnDSA was detected in 48.4%. The median time to DSA detection after LT was 19.7 [interquartile range (IQR): 4.3-35.6] months. Biopsy-proven rejection occurred in 13 patients at follow-up, with C4d positivity observed in 5/13 Liver biopsies. The median time to rejection was 7.8 (IQR: 5.7-12.8) months. The presence of dnDSA was significantly associated with rejection (36% *vs* 3%, $P < 0.001$). The rejection-free survival rates at 12 and 24 months were 76% *vs* 100% and 58% *vs* 95% for patients with dnDSA anti-DQ *vs* those without, respectively.

CONCLUSION

Our findings highlight the importance of incorporating DSA assessment into pre- and post-transplantation protocols for pediatric LT recipients. Future implications may include immunosuppression minimization strategies based on this analysis in pediatric LT recipients.

Key Words: Human leukocyte antigens; Donor-specific antibodies; Liver transplantation; Pediatric; Rejection

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Core Tip: The assessment of human leucocyte antigens and donor-specific antibodies (DSAs) is becoming crucial in pediatric liver transplantation (LT). This cohort study demonstrates the association of DSAs with rejection episodes after LT.

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INTRODUCTION

The role of human leukocyte antigens (HLA) in determining the outcomes of solid organ transplantation has been the subject of extensive debate[1]. In the last decade, antibody-mediated rejection, detection of circulating anti-HLA donor-specific antibodies (DSA), and their influence on the outcomes of pediatric liver transplantation (LT) have been extensively studied[2-6]. Few single-center studies have been conducted, and their impact on long-term graft and recipient survival and immunosuppression protocols has been controversial[4,5,7,8].

Rejection remains one of the most common complications of LT[6]; nonetheless, our understanding of antibody-mediated rejection remains limited. Some centers have adopted protocols for liver biopsies to detect early signs of rejection despite normal liver function test results. In antibody-mediated rejection, B lymphocytes and C4d deposits dominate in the periportal vessels. However, C4d staining is not routinely performed in liver biopsy, and how this detection could affect patient care remains unclear[9,10].

Children exhibit a more vigorous immunological response than adults. A meta-analysis showed a higher prevalence of circulating DSAs in pediatric LT recipients than in adults[8]. Furthermore, a previous study reported that the presence of circulating DSAs was linked to rejection and long-term liver fibrosis development[5]. HLA typing and circulating DSA analysis may facilitate early rejection diagnosis, guide personalized treatment approaches, and help select more compatible donors. Therefore, the current study aimed to investigate the prevalence of class I and II HLA mismatches and DSA and evaluate their association with rejection episodes after pediatric LT.

MATERIALS AND METHODS

A cohort of pediatric LT recipients aged < 18 years underwent pre- and post-LT HLA testing and DSA detection at Santa Casa de Porto Alegre, Brazil, between December 2013 and December 2023. Only patients who survived for > 30 days after LT with at least one DSA analysis were included. DSA classes I (A/B/C) and II (DQ/DR) and cross-matches were analyzed before and after LT. The presence of *de novo* DSA (dnDSA) was evaluated at least 3 months after LT using the Luminex® single antigen bead method, with a positive reaction threshold set at 1000 MFI. Rejection episodes were confirmed by liver biopsy.

HLA collection and analysis

HLA typing of the donor and recipient, collection of reactivity against the panel of class I and II antigens, and cross-match testing were performed through systematic serum collection screening prior to LT. After transplantation, DSAs were collected at various time points according to clinical events in each patient, starting from 3 months after LT. Such collection was performed during routine patient visits at the central laboratory of the Hospital da Criança Santo Antônio (Porto Alegre, Brazil) under the supervision of an outpatient clinic nurse. Donor samples were collected at the immunology laboratory under the supervision of the same technician.

HLA class I and II antibody tests were performed on sera. The presence of recipient HLA antibodies was detected using the Luminex® Mixed single antigen bead technology by One Lambda, with MFI > 1000 being considered positive for anti-HLA antibodies.

DSAs were classified as "preformed" if they were present before LT, "dnDSAs" if they developed after LT, or "persistent" if preformed DSAs remained after LT. For patients with more than one DSA, the highest MFI value was used (or the cumulative value for each class was calculated). All anti-HLA antibody assays were conducted at the Transplant Immunology Laboratory located at Hospital Dom Vicente Scherer, within the Santa Casa de Misericórdia de Porto Alegre Complex, RS, Brazil.

Liver biopsy

All rejections were confirmed by liver biopsy following the Banff classification criteria. The decision to perform biopsy was made based on laboratory abnormalities indicative of hepatic dysfunction such as elevated aminotransferase levels. Normal aminotransferase values were based on our laboratory's reference values, as follows: Serum aspartate aminotransferase with a reference value below 79 U/L, alanine aminotransferase with a reference value below 35 U/L, total bilirubin with a reference value of 0.2-1 mg/dL, and glutamyl transpeptidase with a reference value below 38 U/L. Infectious causes such as cytomegalovirus infection during outpatient follow-up were excluded, and all biopsies were interpreted by the same pathologist. C4d staining was performed retrospectively after confirmation of rejection; thus, this was only searched for patients with biopsy-proven rejection.

Graft fibrosis

The degree of graft fibrosis was recorded. The METAVIR histological scoring system was utilized for staging, and sinusoidal fibrosis around the central veins was assessed using the modified Dixon criteria.

Statistical analysis

Quantitative variables were expressed as means and standard deviations, whereas categorical variables were presented as absolute and relative frequencies. Mean comparisons were conducted using student's *t*-test. Proportional comparisons were performed using Pearson's χ^2 test or Fisher's exact test. Statistical analyses were performed using the SPSS version 21.0 (IBM Corp., Armonk, NY, United States), with the significance level set at 5% (P value < 0.05). The study was reviewed by our expert Biostatistic Alvaro Rosler.

RESULTS

During the study period, 91 LTs were performed at the Santa Casa de Porto Alegre Hospital Complex; of these, 73 were from living donors, whereas three were re-transplants. Fifteen patients died at < 30 days after LT, and six patients were excluded because they did not reach the minimum follow-up. Finally, a total of 67 patients were analyzed in this study (Figure 1).

With respect to the general characteristics of the analyzed patients, there was a nearly equal distribution of sex, with 37 (55%) being male. Furthermore, the median age at transplantation was 11.9 [interquartile range (IQR): 7.7-24.6] months, and the median weight was 7.4 (IQR: 6.4-11.5) kg. LT from living donors was the most prevalent modality, accounting for 90% (n = 60). Biliary atresia was the primary etiology of the disease, leading to an indication for LT in 38 patients (57%) (Table 1). As for the donors, 40 (59.7%) were male, with fathers, mothers, unrelated persons, and other grades of relationships being the donors in 30 (45%), 17 (25%), 10 (15%), and 10 (15%) cases, respectively. The mean donor age was 30 ± 11.5 years.

In 60 patients, HLA typing was performed prior to LT: DSA was directed against HLA class I in 9 (15%) patients, HLA class II in 11 (18.3%) patients (Figure 2), and classes I and II in 3 (5%) patients. In 66 patients, HLA typing was performed after LT at a median of 19.7 (IQR: 4.3–35.6) months: DSA was directed against HLA class I in eight (12%) patients, HLA class II in 28 (43%) patients (Figure 2), and classes I and II in four (6%) patients.

Overall, 33 (50%) patients had dnDSA. The predominant distribution was at the DQ locus (dnDSA/DQ), which was present in 26 (39%) patients (Figure 3). Figure 4 illustrates DQ and DR locus distributions. A total of 12 (17.9%) patients exhibited biopsy-proven rejection; of these, five (41.6%) tested positive for C4d.

The rejection-free survival rates after dnDSA/DQ detection were 76% at 12 months and 58% at 24 months. In comparison, for the group that did not develop dnDSA/DQ, the rejection-free survival rates were 100% at 12 months and 95% at 24 months (P value < 0.001) (Figure 5).

The persistence of positive antibody levels for DAS/DQ after LT was associated with a graft rejection rate of 60%, indicating that this population had a more unfavorable outcome than others (Figure 6).

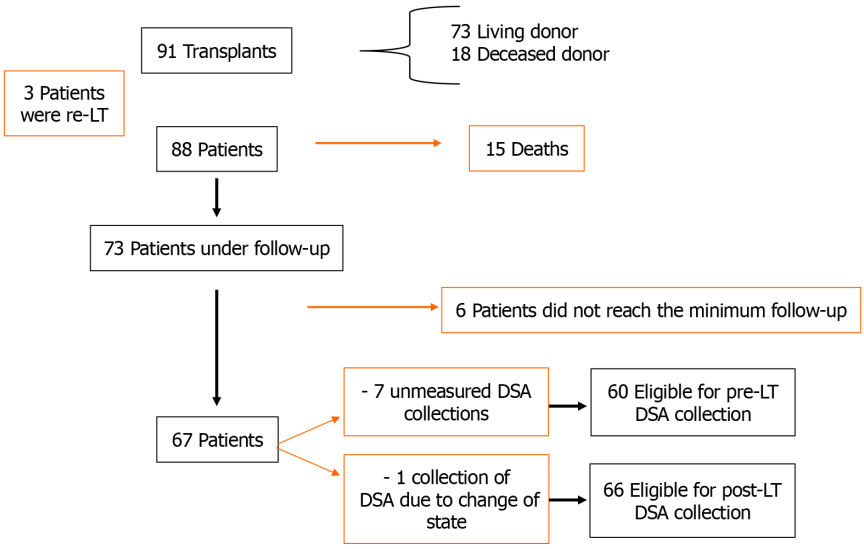

Figure 1 Study design and patient inclusion and exclusion criteria. LT: Liver transplantation; DSA: Donor-specific antibody.

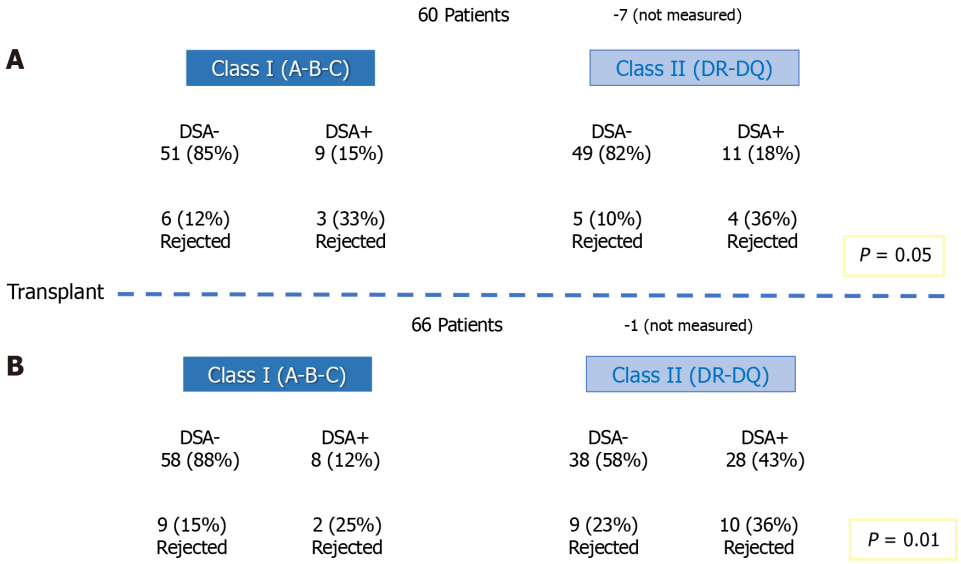

Figure 2 Prevalence of class I and II donor-specific antibodies pre-transplant and post-transplant correlated with the prevalence of rejection. A: Pre-transplant; B: Post-transplant. DSA: Donor-specific antibody.

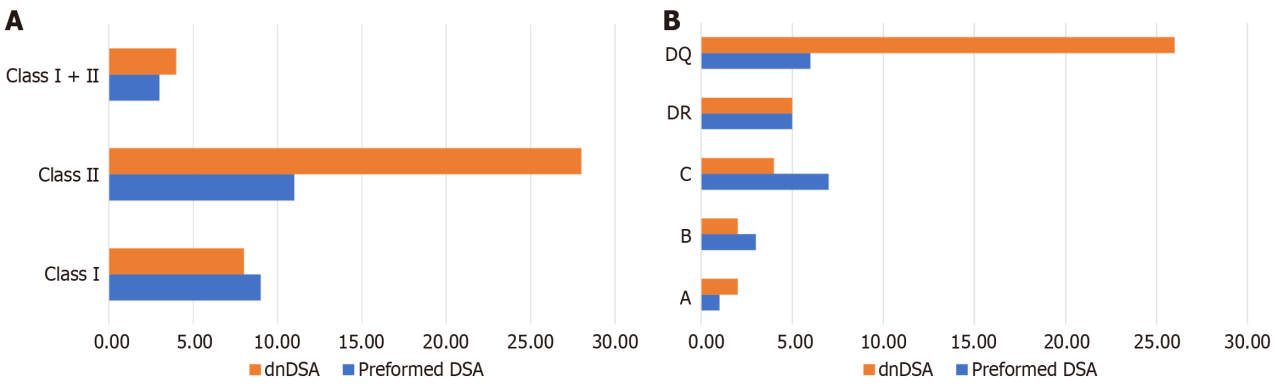

Figure 3 Human leucocyte antigens typing in patients with preformed and *de novo* donor-specific antibodies. X-axis represents number of

patients. A: Distribution by Class; B: Distribution by locus. DSA: Donor-specific antibody; dnDSA: *De novo* donor-specific antibody.

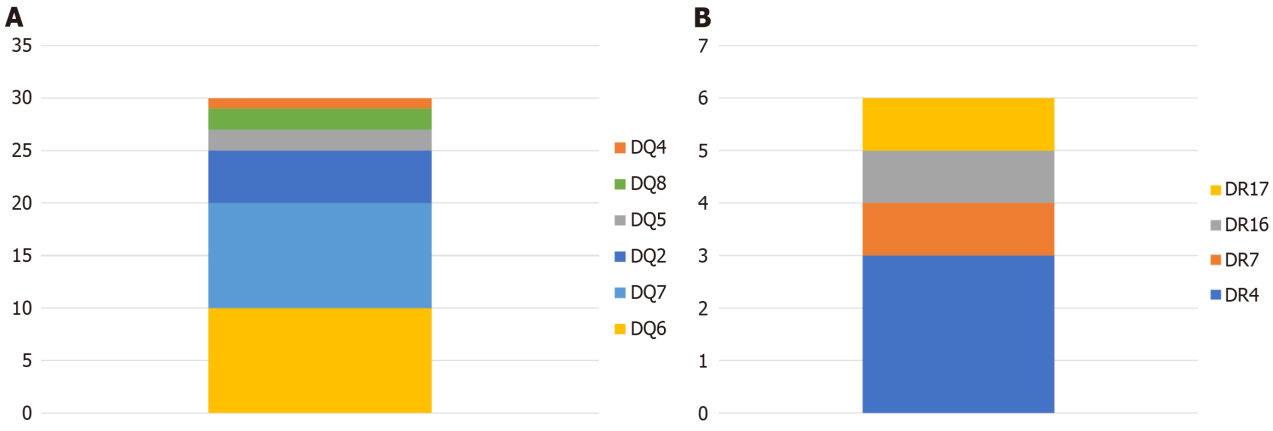

Figure 4 Pre and post liver transplant donor-specific antibodies frequencies-locus distribution. A: DQ allele; B: DR allele.

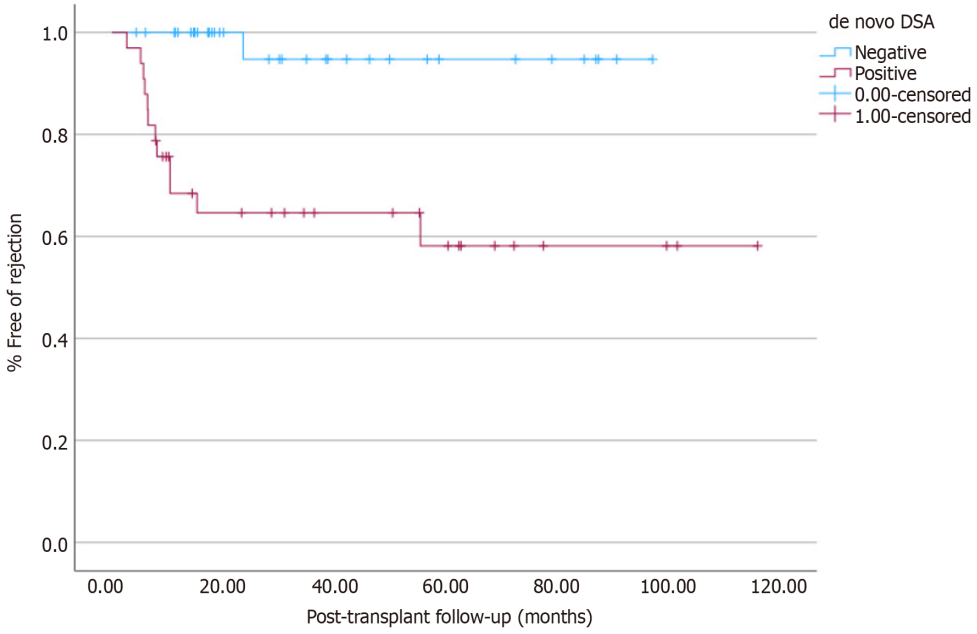

Figure 5 Rejection-free survival according to *de novo* donor-specific antibodies. DSA: Donor-specific antibody.

Table 2 shows the HLA mismatch value (MM) analysis in patients who developed rejection *vs* those who did not. Higher MM values were observed in the rejection group, particularly at locus A. However, these differences were not statistically significant.

DISCUSSION

Donor selection for LT has traditionally prioritized clinical urgency, blood group compatibility, and donor size, with HLA compatibility and the presence of DSAs being often overlooked. Nonetheless, recent studies have highlighted the significance of DSA in liver graft outcomes. Since DSA is a major contributor to allograft dysfunction and loss, monitoring patients positive for antibodies is crucial for improved post-transplant rejection and fibrosis-free survival[11,12].

In the present study, the prevalence of preformed DSAs was low (15% for class I and 18% for class II). In contrast, previous studies found dnDSAs in 50% of recipients[13-16]. Most dnDSAs were directed against HLA class II, with the predominance of dnDSA/DQ present in 39% of patients evaluated after transplantation. The predominance of the DQ locus has been described in previous studies[16].

Table 1 Patients' characteristics, *n* (%)

Number of patients included	67
Gender, male	37 (55)
Age at transplant (months), median (IQR)	11.9 (7.7 to 24.6)
Weight at transplant (kg), median (IQR)	7.4 (6.4 to 11.5)
Z-score BMI, median (IQR)	-0.4 (-1.3 to -1.0)
PELD score, median (IQR)	14 (6 to 22)
GRWR (%), median (IQR)	3.2 (2.5 to 4.0)
Transplant modality	
Living donor	60 (90)
Deceased donor	7 (10)
Baseline disease	
Biliary atresia	38 (57)
Acute liver failure	3 (4.4)
Alagille syndrome	6 (9)
Primary liver tumor	4 (6)
Other	16 (24)

IQR: Interquartile range; BMI: Body mass index; GRWR: Graft-to-recipient weight ratio.

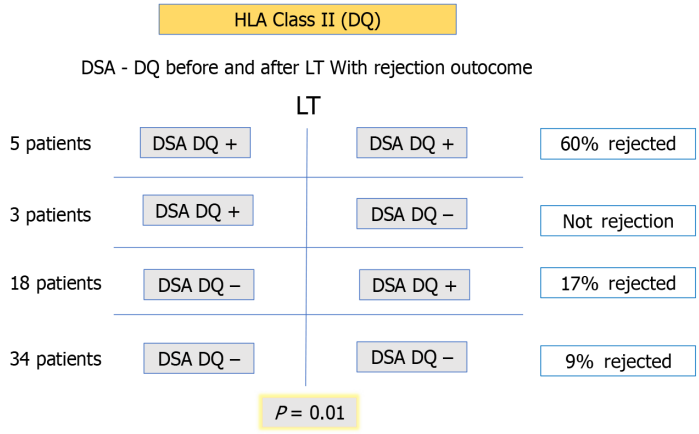

Figure 6 Pre-transplant donor-specific antibodies, donor-specific antibody persistence, *de novo* donor-specific antibodies-DQ, and graft rejection. DSA: Donor-specific antibodies; LT: Liver transplantation; HLA: Human leukocyte antigen.

However, it is difficult to determine when dnDSA could be detected after LT. Most studies on pediatric recipients are small series, collected without a specific protocol, and no evaluation of preformed DSA was conducted. There are also clues from renal transplantation that the prevalence of dnDSAs tends to increase over time[17]. Variations from 50 months to 10 years following LT have been described in studies on children[18,19].

The prevalence of DSA has been consistently reported to be higher in children[20]. Several hypotheses in the literature explain the higher prevalence of DSA in pediatric patients. These include a heightened immune response in the developing immune system, susceptibility to viral illnesses inducing non-specific HLA antibodies, and frequent blood transfusions leading to sensitization[1].

The occurrence of dnDSA in LT recipients was lower than that in kidney transplant recipients, possibly because of the ability of the liver to absorb anti-HLA antibodies. Although this study did not analyze the immunosuppression levels, it is hypothesized that inadequate immunosuppression results in the emergence of dnDSA and T-cell-mediated rejection. Given the significant association between CD4 + T cells and B cell immunity, inadequate immunosuppression may result in insufficient blockade of CD4 + T cell helper activity against B cells, thereby facilitating DSA development[13].

The development of dnDSA could serve as a biomarker for the risk of T-cell-mediated rejection, potentially informing treatment decisions. dnDSA directed toward HLA class II was previously related to the development of rejection[4,20]. In

Table 2 Analysis of human leucocyte antigen A, B, and DR mismatch and the presence of rejection, *n* (%)

	With rejection, *n* = 12	Without rejection, *n* = 53	*P* value
HLA A MM			0.08
0	1 (8.3)	3 (5.7)	
1	7 (58.3)	45 (84.9)	
2	4 (33.3)	5 (9.4)	
HLA B MM			0.12
0	0	5 (9.4)	
1	7 (58.3)	39 (73.6)	
2	5 (41.7)	9 (17)	
HLA DR MM			0.9
0	1 (8.3)	4 (7.5)	
1	9 (75)	41 (77.4)	
2	2 (16.7)	8 (15.1)	
Class I MM			
1	1 (8.3)	8 (15.1)	0.16
2	6 (50)	37 (69.8)	
3	1 (8.3)	3 (5.7)	
4	4 (33.3)	5 (9.4)	
Total MM			0.52
2	2 (16.7)	11 (20.8)	
3	5 (41.7)	32 (60.4)	
4	1 (8.3)	3 (5.7)	
5	2 (16.7)	3 (5.7)	
6	2 (16.7)	4 (7.5)	

HLA: Human leucocyte antigen; MM: Mismatch value.

the present study, the DQ locus played a major role in the development of rejection and was associated with lower rejection-free survival. In the group with persistent DSA/DQ, 60% developed rejection. The DQ locus antibody has been described as a risk factor for decreased survival in solid organ transplant recipients[17]. Patient survival was not analyzed in our study because all mortalities occurred at < 30 days after LT and these patients were not included in the study.

Recent studies have shown that dnDSAs are associated with rejection, fibrosis, inflammation, and shorter survival after LT. Clinical factors, such as immunosuppression, infection, degree of ischemia-reperfusion injury, and level of HLA expression, contribute to the development, affinity for DSA, and persistence of the antibody after transplantation, leading to graft dysfunction[13].

Despite these insights, this study had several limitations. Pretransplant DSA samples were not collected from all patients, and posttransplant DSA measurements were not uniform. Liver biopsies were performed based on clinical suspicion, potentially leading to undiagnosed fibrosis. The C4d review was limited to patients with rejection, and HLA anti-DQ MM analysis was not feasible.

CONCLUSION

The presence of DSA significantly increases the risk of rejection, with the highest incidence observed in patients with persistent DAS/DQ. The predominance of class II DSA targeting the DQ locus underscores its significance. DSA detection can guide personalized immunosuppressive therapy and influence living-donor selection, highlighting the need for continuous surveillance and personalized management to optimize LT outcomes. Further studies are required to externally validate these results.

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FOOTNOTES

Author contributions: Melere MU, Feier FH, and Neumann J designed the research study and wrote the manuscript; Nader LS, Junior MAF, da Silva CS, Montagner JM, Coral GP, and Bobsin GP collected and evaluated the data; Ferreira CT and Kalil AN wrote the manuscript and critically evaluated the final version. All authors have read and approved the final manuscript.

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STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Corresponding Author's Membership in Professional Societies: International Liver Transplantation Society, No. 18973.

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