

Article

Clinical Impact of De Novo Donor-Specific HLA Antibodies on Early Kidney Allograft Outcomes: A Prospective Single-Center Cohort Study

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Abstract

Background: De novo donor-specific antibodies (dnDSA) are associated with impaired allograft outcomes and the development of acute and chronic antibody-mediated rejection. However, their clinical impact during the early post-transplant period remains incompletely characterized. **Methods:** In this prospective single-center cohort study, we analyzed 218 kidney transplant recipients between 2006 and 2013. All patients underwent serial screening for the development of de novo donor-specific antibodies at different time points (1, 3, 6, 12 months) after kidney transplantation using contemporaneously available ELISA- or Luminex-based solid-phase assays. The data were correlated with clinical parameters and histopathological results from indication biopsies and analyzed in relation to clinical outcomes and histopathological findings. All data were analyzed to assess the impact on 1-year kidney function, patient and graft survival. **Results:** One year after renal transplantation, 7% of patients (n = 37) developed de novo donor-specific antibodies (dnDSA). Among dnDSA-positive patients, 22% developed class I dnDSA, 67% class II dnDSA, and 11% both. In univariate analysis, markers of increased immunologic risk—such as previous transplantation, greater HLA mismatch, and reductions in immunosuppressive therapy—were associated with an increased risk of de novo donor-specific antibody (dnDSA) development. However, in multivariate analysis, only a panel-reactive antibody (PRA) level greater than 20% emerged as an independent predictor of dnDSA formation. Patients who developed dnDSA experienced a significant decline in graft function, with an approximately fourfold increased risk of overall graft failure within the first year. DnDSA-positive patients showed significantly reduced graft survival and impaired renal function at one year. Rejection rates were significantly higher in this group, with 48.6% experiencing histologically confirmed rejection, compared to 13.3% among dnDSA-negative patients. **Conclusions:** Monitoring for de novo DSA after kidney transplantation helps to identify patients at high risk for rejection, declining graft function, and poorer long-term outcomes. Routine post-transplant dnDSA monitoring may support early risk stratification and individualized clinical management.



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Keywords: donor-specific HLA antibodies; rejection; kidney function; graft survival; renal transplantation

1. Introduction

Kidney transplantation remains the treatment of choice for eligible patients with end-stage kidney disease [1,2]. Over the past decades, major immunological barriers to successful kidney transplantation have been substantially reduced. Hyperacute rejection due to preformed donor-specific antibodies has become uncommon owing to modern compatibility testing and crossmatch strategies [3], and acute T cell-mediated injury has been markedly reduced by the effective multimodal use of immunosuppressive agents [4].

Despite these advances, long-term graft survival remains limited. Acute and chronic antibody-mediated rejection (ABMR) have emerged as dominant causes of kidney allograft failure and are now considered among the most important barriers to durable transplant outcomes [4–6]. In this context, the development of de novo donor-specific antibodies (dnDSA) has become one of the most relevant immunological challenges after transplantation.

DnDSA are antibodies directed against donor-specific human leukocyte antigen (HLA) molecules and are a key driver of ABMR [7]. They arise when the recipient's immune system recognizes donor HLA antigens as foreign, triggering a complex adaptive immune response that involves B-cell activation, T-helper cell support, and immunoglobulin class switching to IgG antibodies [8]. Once formed, dnDSA can bind to the allograft endothelium, activate the complement cascade, and induce inflammatory injury, ultimately leading to antibody-mediated rejection [7,9]. Consequently, Antibody-mediated rejection is widely recognized as a major contributor to late allograft dysfunction and graft loss [1,2].

Clinically, donor-specific antibodies identified before transplantation (preformed DSA) are associated with early graft injury, including hyperacute rejection, accelerated acute rejection, early acute antibody-mediated rejection, and graft loss [1]. In contrast, dnDSA developing after transplantation are mainly linked to late acute antibody-mediated rejection, chronic antibody-mediated rejection, and transplant glomerulopathy [6]. Importantly, not all DSAs are necessarily harmful: so-called “benign” DSA may not be associated with antibody-mediated rejection or graft failure [3], highlighting the biological and clinical heterogeneity of these antibodies.

Despite extensive research, the true clinical impact of dnDSA—particularly with respect to renal function, graft survival, and patient survival—remains controversial and incompletely understood. In this study, we prospectively assessed the occurrence of dnDSA and correlated these findings with detailed clinical and histological outcomes. We evaluated the occurrence of dnDSA during the first post-transplant year and examined its association with renal function, rejection, graft survival, and patient survival. These findings may help refine post-transplant immunologic risk assessment and inform individualized monitoring strategies.

2. Materials and Methods

2.1. Study Design and Population

This study represents a retrospective analysis of prospectively collected data from a single-center kidney transplant cohort at the University Hospital Augsburg, Germany. The study included all consecutive adult patients who underwent kidney transplantation between 2006 and 2013 and were enrolled in the institutional dnDSA surveillance program. All participants provided written informed consent for prospective data collection and subsequent retrospective analysis. Ethical approval was obtained from the Ethics Committee of Ludwig Maximilians University (LMU), Munich (reference number 25-0697). Patients were followed for 12 months after transplantation and were seen regularly in the outpatient clinic during this period. Inclusion required complete dnDSA measurements

at all predefined follow-up time points. Patients with incomplete immunologic follow-up were excluded. Based on these measurements, patients were categorized into two groups:

1. dnDSA-positive group: dnDSA positivity was defined as the detection of at least one donor-specific anti-HLA antibody not present prior to transplantation, identified at any predefined post-transplant assessment.
2. dnDSA-negative group: patients without detectable donor-specific antibodies at any time point during the screening period (Figure 1).

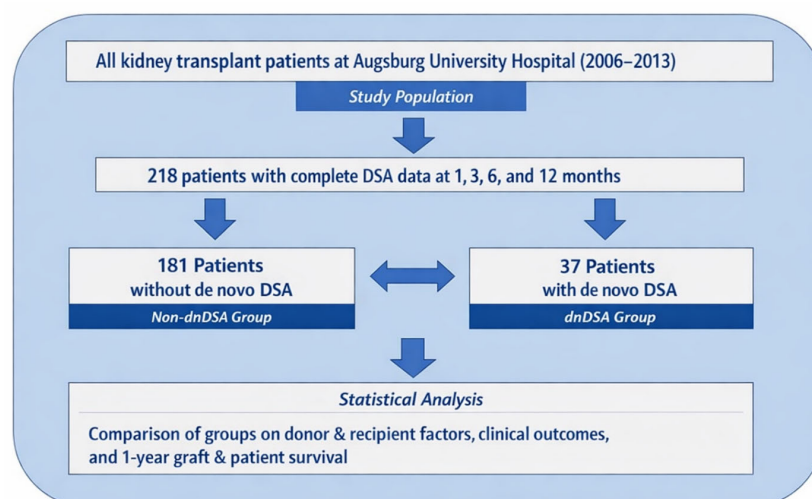


Figure 1. Study design.

2.2. Antibody Testing

Serum samples were collected at 1, 3, 6, and 12 months after transplantation as part of routine post-transplant monitoring. All sera were analyzed for HLA class I and class II antibodies by the Laboratory for Immunogenetics and Molecular Diagnostics, Ludwig-Maximilians-University Munich.

Because institutional antibody testing methodology evolved during the study period, HLA antibody detection was performed using ELISA between 2006 and 2010 and Luminex single-antigen bead assays thereafter. For Luminex-based analyses, an MFI threshold >1000 was considered positive. ELISA positivity was interpreted according to manufacturer-defined criteria. In total, more than 870 serum samples were analyzed for the presence of DSA.

2.3. Clinical and Histological Assessment

All clinical, laboratory, and pathological parameters were collected at the same predefined follow-up time points (1, 3, 6, and 12 months) to ensure comparability between patients. When clinical deterioration or rising serum creatinine levels suggested possible graft rejection, a diagnostic kidney allograft biopsy was performed. Kidney allograft biopsies were performed on clinical indication only; protocol surveillance biopsies were not routinely conducted. Histological evaluation was carried out by the Institute of Pathology at the University of Erlangen. Histopathological evaluation was performed according to the contemporaneously applicable Banff classification criteria. More than 100 kidney biopsies were analyzed during the study period.

2.4. Data Sources

Clinical and perioperative data were obtained from surgical reports, inpatient medical records, and follow-up documentation of the Department of General, Visceral and Transplant Surgery, University Hospital Augsburg.

2.5. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean $\pm$ standard deviation or median with interquartile range, depending on data distribution, and were compared using Student's *t* test or the Mann–Whitney U test, as appropriate. Categorical variables are reported as absolute numbers and percentages and were compared using the chi-square test or Fisher's exact test.

Predictors of de novo donor-specific antibody (dnDSA) development were identified using multivariable binary logistic regression. Covariates were selected based on clinical relevance, prior literature, and biological plausibility, while limiting the number of predictors to maintain an appropriate events-per-variable ratio in accordance with the recommendations of Vittinghoff and McCulloch. Results are reported as odds ratios (OR) with 95% confidence intervals (CI).

Time-to-event analyses were performed for biopsy-proven acute rejection, overall graft survival and patient survival within the first post-transplant year. Survival was estimated using the Kaplan–Meier method, and differences between dnDSA-positive and dnDSA-negative patients were compared using the log-rank test. Multivariable Cox proportional hazards regression was used to estimate adjusted hazard ratios (HR) with 95% CI, including dnDSA status, number of HLA mismatches, panel reactive antibodies (PRA) $\geq$ 20%, and patients with previous transplantations as covariates.

All tests were two-sided, and a *p*-value < 0.05 was considered statistically significant.

3. Results

3.1. Detection of De Novo DSA

De novo donor-specific antibodies (dnDSA) were detected in 37 of 218 evaluable patients (17%) during the first post-transplant year. The highest number of first dnDSA detections occurred within the first month after transplantation, when 10 patients (27% of all dnDSA-positive cases) developed detectable antibodies (Figure 2). The incidence of dnDSA was elevated during the first six months after transplantation and subsequently declined steadily over the remainder of the observation period.

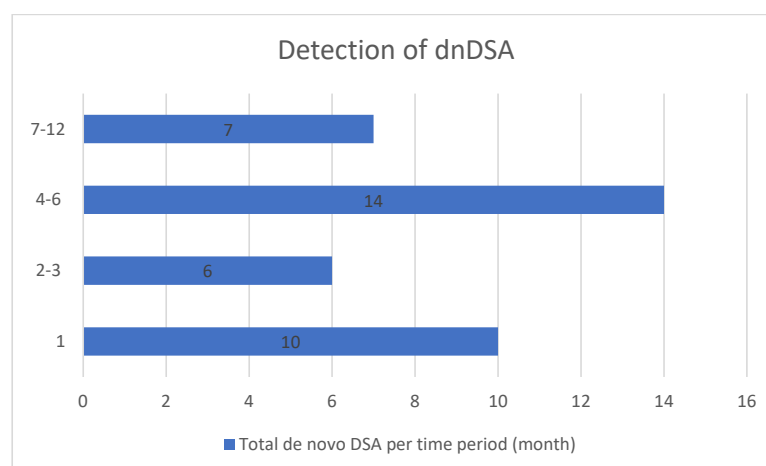


Figure 2. Patients with DSA during the observation period. Total numbers of patients with dnDSA are shown per month (*n* = 37). Labeling: x-axis: absolute number of dnDSA, Y-axis: months.

Among the 37 dnDSA-positive patients, 22% (8/37) had antibodies against HLA class I, 67% (25/37) had antibodies against HLA class II, and 11% (4/37) had antibodies against both HLA class I and class II. A total of 55 serum samples tested positive for donor-specific antibodies, reflecting repeated dnDSA detection in some recipients. As shown in Figure 3,

HLA-DQ antibodies constituted the largest subgroup of class II dnDSA, followed by HLA-DR antibodies. Within class I, antibodies directed against HLA-B were most frequent, closely followed by antibodies against HLA-A.

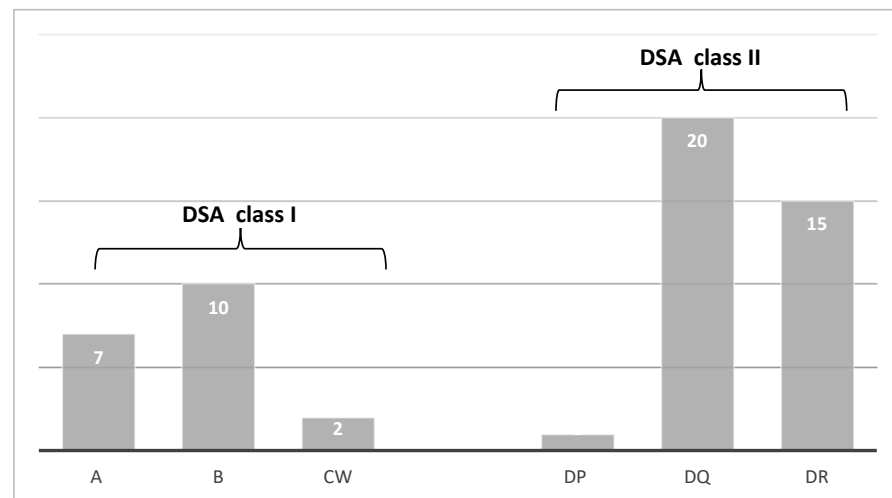


Figure 3. DnDSA subgroup analysis. Figure shows total numbers of antibodies. Labeling: X-axis: DnDSA subtype. Y-axis: Total number.

3.2. Demographics Recipient

No statistically significant differences were observed in recipient age, sex, or waiting time (Table 1). Patients who developed dnDSA demonstrated a significantly higher baseline immunologic risk profile, including greater HLA mismatch burden, higher pretransplant PRA levels, and more frequent prior transplantation. With regard to pretransplant immunologic sensitization, patients who developed dnDSA were significantly more likely to have a panel-reactive antibody (PRA) level greater than 20%.

Table 1. Demographics Recipient.

Variable	Total (n = 218)	dnDSA+ (n = 37)	dnDSA− (n = 181)	p-Value
Recipient age (years)	53.2 (±13.4)	51.9 (±12.1)	53.4 (±13.7)	n.s.
Sex				
Male	136 (62.4%)	20 (54.1%)	116 (64.1%)	
Female	82 (37.6%)	17 (45.9%)	65 (35.9%)	n.s.
Time on waiting list (months)	59.0 (±32.9)	60.6 (±33.5)	58.6 (±32.9)	n.s.
HLA mismatch	3.19 (±1.73)	3.67 (±1.33)	3.09 (±1.78)	0.031
Panel reactive antibodies (PRA)				
0–20%	192 (88.1%)	27 (73.0%)	165 (91.2%)	
≥20%	26 (11.9%)	10 (27.0%)	16 (8.8%)	0.002
Previous transplantation	29 (13.3%)	9 (24.3%)	20 (11.0%)	0.038

Numbers show mean ± SD or n (%); HLA = human leukocyte antigen; PRA = panel reactive antibody; n.s. = not significant.

These findings from the univariate analysis were further evaluated in a multivariate model. The analysis confirmed that a PRA ≥ 20% remained independently associated with dnDSA development. HLA Mismatch was nearly significant (Table 2).

Table 2. Multivariable logistic regression of predictors of dnDSA development.

Variable	OR	95% CI	p-Value
HLA mismatch (per mismatch)	1.25	1.00–1.58	0.054
PRA $\geq$ 20%	3.27	1.09–9.84	0.035
Previous transplantation	1.52	0.49–4.68	0.470

(n = 216; 2 cases excluded due to missing HLA-MM data). OR = odds ratio; CI = confidence interval. PRA and retransplantation.

3.3. Demographics Donor

Donor characteristics were comparable between the two groups with respect to donor age and sex.

The European Senior Program (ESP) is a special allocation scheme within the Eurotransplant network in which HLA matching is not taken into account. We examined whether allocation through the ESP was associated with the development of dnDSA. Among patients who developed dnDSA, 16.2% were transplanted through the ESP, compared with 24.9% in the dnDSA-negative group. This difference was not statistically significant (Table 3).

Table 3. Demographics of the Donor.

Variable	Total (n = 218)	dnDSA+ (n = 37)	dnDSA– (n = 181)	p-Value
Donor age (years)	57.2 ($\pm$ 14.1)	55.1 ($\pm$ 13.7)	57.7 ($\pm$ 14.2)	n.s.
Donor sex				
Male	120 (55.0%)	19 (51.4%)	101 (55.8%)	
Female	97 (44.5%)	17 (45.9%)	80 (44.2%)	n.s.
ESP allocation	51 (23.4%)	6 (16.2%)	45 (24.9%)	n.s.
Donor creatinine > 3 mg/dL	15 (6.9%)	4 (10.8%)	11 (6.1%)	n.s.
Cold ischemia time (min) *	797 ($\pm$ 381)	841 ($\pm$ 403)	789 ($\pm$ 377)	n.s.
Living kidney donation	21 (9.6%)	2 (5.4%)	19 (10.5%)	n.s.

Numbers show mean $\pm$ SD or n (%). * Cold ischemia time was calculated for deceased-donor kidneys only (n = 197). ESP = European Senior Program; n.s. = not significant.

To assess the impact of donor organ quality on dnDSA formation, donor serum creatinine > 3 mg/dL was used as a pragmatic surrogate marker of impaired donor renal function. Recipients of kidneys with impaired function showed a numerically higher frequency of developing dnDSA, although this association did not reach statistical significance.

Cold ischemia time (CIT) was also evaluated, excluding living kidney donations (LKD). Mean cold ischemia time was numerically longer by 26 min than that of the dnDSA-negative group; however, this difference was not statistically significant. As expected, CIT was substantially shorter in LKD recipients (135 min) compared with recipients of deceased-donor kidneys (797 min). Although dnDSA incidence was numerically lower after living kidney donation, this difference did not reach statistical significance, likely reflecting limited sample size. (Table 3).

3.4. Factors Associated with the Development of De Novo DSA: Post-Transplant Monitoring

3.4.1. Renal Function

Patients who developed dnDSA exhibited impaired renal function at one year, reflected by significantly lower eGFR. Although serum creatinine levels were numerically higher, this difference did not reach statistical significance. (Table 4).

Table 4. Summary of the results after one year.

Variable	dnDSA+ Patients (n = 37)	dnDSA– Patients (n = 181)	p-Value
Renal function			
Creatinine 1Y (mg/dL, mean $\pm$ SD)	2.46 $\pm$ 1.92	1.82 $\pm$ 0.88	0.084
eGFR 1Y (MDRD, mL/min)	36	45	0.012
Graft outcomes at 1 year			
Stable graft function	25 (69.4%)	154 (88.5%)	0.003
Nephrectomy	6 (16.2%)	3 (1.7%)	<0.001
Histologically confirmed rejection	18 (48.6%)	24 (13.3%)	<0.001
Humoral	5 (29%)	2 (8.3%)	
Cellular	13 (71%)	22 (91.7%)	
Immunosuppression protocol			
1—Cyclosporine-based	19 (51.4%)	85 (47.0%)	
2—Tacrolimus-based	10 (27.0%)	67 (37.0%)	
3—ATG/Thymoglobulin	8 (21.6%)	29 (16.0%)	n.s.
Patient survival			
Alive at 1 year	36 (97.3%)	178 (98.3%)	n.s.

Numbers show n (%) or mean $\pm$ SD as indicated. Rejection refers to histologically confirmed acute rejection on biopsy. Graft loss = transplant nephrectomy within 1 year. eGFR = estimated glomerular filtration rate (MDRD formula). n.s. = not significant.

Among patients with stable graft function (serum creatinine < 3 mg/dL), 88.5% of dnDSA-negative patients maintained stable renal function at one year, compared with only 69.4% of dnDSA-positive patients ($p = 0.003$), highlighting the negative impact of dnDSA on graft stability (Table 4).

Early post-transplant dialysis requirement was significantly different between groups, with 4 of 181 dnDSA-negative patients and 5 of 37 dnDSA-positive patients requiring dialysis at one month. By 12 months, 24.3% of dnDSA-positive patients remained dialysis-dependent, compared with only 3.9% of dnDSA-negative patients, demonstrating a significant association between dnDSA development and dialysis dependency ($p < 0.001$).

3.4.2. Rejection

Within the first month after transplantation, patients in the dnDSA-positive group exhibited a significantly higher incidence of histologically confirmed cellular and antibody-mediated rejection compared with dnDSA-negative patients. By 12 months, both cellular and humoral rejection rates further increased in the dnDSA group, reinforcing the strong association between dnDSA development and allograft injury.

In the dnDSA-negative cohort, rejection was diagnosed in 24 of 181 patients (13.3%) within the first year post-transplantation. A total of 24 rejection episodes were recorded, of which 22 (91.7%) were T-cell-mediated and 2 (8.3%) antibody-mediated.

In contrast, among dnDSA-positive patients, 18 of 37 (48.6%) experienced rejection within the first year. A total of 18 rejection episodes occurred in this group, including 13 T-cell-mediated rejections (71%) and 5 antibody-mediated rejections (29%). This difference between groups was highly statistically significant (Table 4).

Stratification by dnDSA class revealed that rejection (cellular or humoral) occurred in 26.3% of patients with isolated class I dnDSA and 44% of patients with isolated

class II dnDSA. 29.7% of patients with rejection exhibited combined class I and class II dnDSA. Of 7 antibody-mediated rejection episodes with C4d positivity, five were associated with class II dnDSA and two with class I dnDSA at one year post-transplantation (Supplemental Data).

3.4.3. Nephrectomy

The incidence of graft loss within the first year after transplantation was analyzed. The nephrectomy rate was significantly higher in patients with dnDSA (16.2%) than in patients without detectable DSA (1.7%). This difference was highly statistically significant ($p < 0.001$).

3.4.4. Immunosuppression and Panel-Reactive Antibodies (PRA)

At Augsburg University Hospital, kidney transplant recipients are managed according to three standardized immunosuppressive protocols based on pretransplant immunologic risk, as determined by panel-reactive antibody (PRA) levels.

Protocol I is assigned to patients with low immunologic risk (PRA $< 10\%$) and consists of basiliximab induction, corticosteroids, mycophenolate mofetil (MMF), and cyclosporine A. Protocol II is used for patients with intermediate immunologic risk (PRA 10–30%) and includes basiliximab, corticosteroids, MMF, and tacrolimus. Protocol III is reserved for patients with high immunologic risk (PRA $> 30\%$) and comprises thymoglobulin induction, corticosteroids, MMF, and tacrolimus.

Within the study cohort, 47.7% of patients ($n = 104$) received Protocol I, 35.3% ($n = 77$) Protocol II, and 17% ($n = 37$) Protocol III. The distribution of immunosuppressive regimens did not differ significantly between dnDSA-positive and dnDSA-negative patients (Table 4).

Despite risk-adapted intensification of immunosuppression in patients with higher immunologic risk, including higher target calcineurin inhibitor exposure and more potent antibody-based induction therapy, no significant difference in the incidence of dnDSA development was observed between the immunosuppressive protocol groups.

3.4.5. Patient Survival One Year After Transplantation

No statistically significant difference in one-year patient survival was observed. One-year patient survival was 97.3% in the dnDSA group and 98.3% in the dnDSA-negative group (Table 4, Figure 4c).

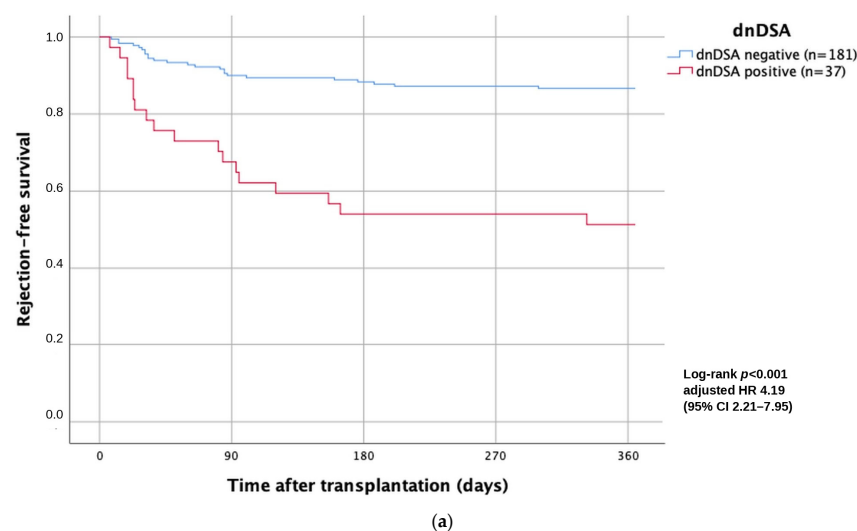


Figure 4. Cont.

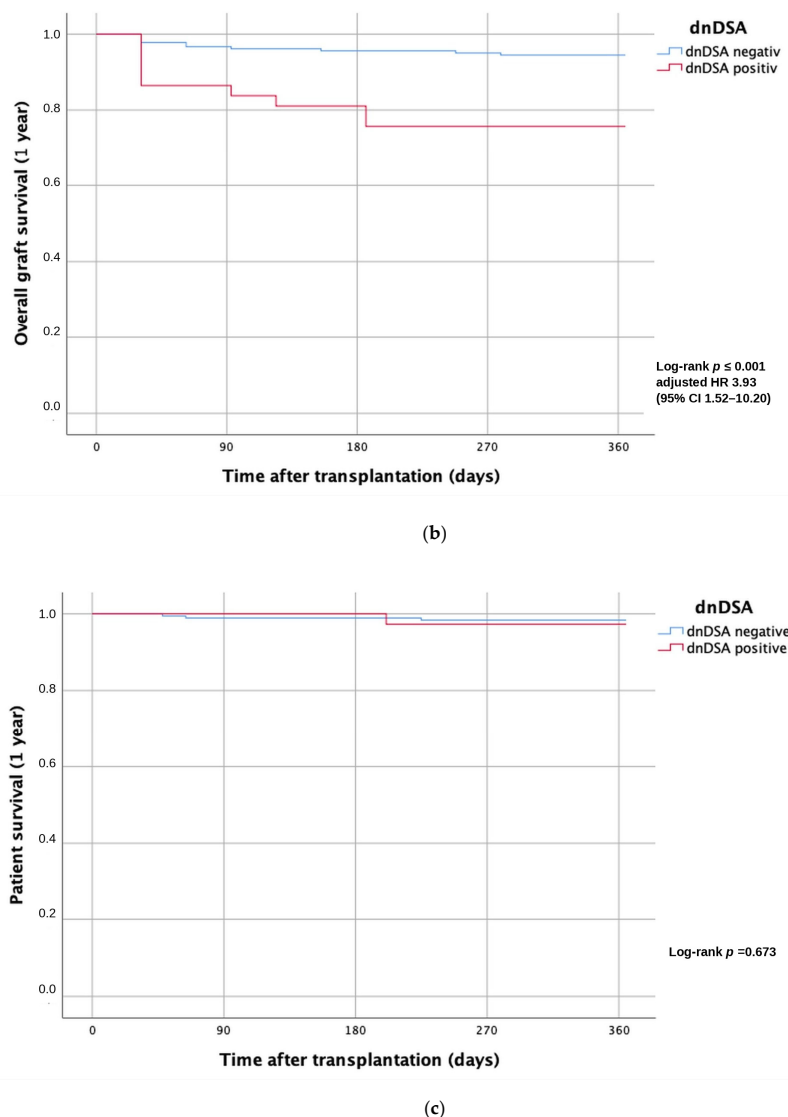


Figure 4. (a): Kaplan–Meier analysis of rejection-free survival stratified by dnDSA status. Patients with de novo donor-specific antibodies (dnDSA-positive) showed significantly lower rejection-free survival during the first year after kidney transplantation compared with dnDSA-negative recipients (adjusted HR 4.19, 95% CI 2.21–7.95; log-rank $p < 0.001$), indicating a strong association between dnDSA development and allograft. (b): Overall one-year graft survival according to dnDSA status after kidney transplantation. Kaplan–Meier analysis showing significantly lower graft survival in recipients who developed de novo donor-specific antibodies (dnDSA-positive) compared with dnDSA-negative patients during the first 12 months post-transplantation. dnDSA development was significantly associated with an increased risk of graft loss (adjusted HR 3.93, 95% CI 1.52–10.20; log-rank $p < 0.001$). Overall graft survival was defined as the time from transplantation to graft loss, retransplantation, or death. (c): Overall one-year patient survival according to dnDSA status after kidney transplantation. Kaplan–Meier analysis demonstrated comparable patient survival between dnDSA-positive and dnDSA-negative recipients during the first 12 months post-transplantation, with no statistically significant difference observed (log-rank $p = 0.673$).

3.5. Summary of the Results After One Year

Table 5 and Figure 4 summarize the clinical outcomes, graft function, rejection events, postoperative complications, immunosuppressive regimens, and patient survival at one year after kidney transplantation, comparing recipients who developed de novo donor-specific antibodies (dnDSA) with those without DSA.

Table 5. Multivariable Cox proportional hazards regression for acute rejection and graft loss within 1 year.

Variable	HR	95% CI	p-Value
Acute rejection within 1 year (n = 42 events)			
dnDSA-positive	4.19	2.21–7.95	<0.001
HLA mismatch (per mismatch)	1.14	0.93–1.39	0.206
PRA $\geq$ 20%	0.64	0.24–1.68	0.362
Previous transplantation	5.81	2.51–13.42	<0.001
Overall graft loss within 1 year (n = 9 events)			
dnDSA-positive	3.93	1.52–10.2	0.001
HLA mismatch (per mismatch)	1.54	1.06–2.25	0.025
PRA $\geq$ 20%	1.04	0.27–4.04	0.954
Previous transplantation	5.99	1.59–22.51	0.008

HR = hazard ratio; CI = confidence interval. The proportional hazards assumption was assessed by including a time-dependent covariate for dnDSA, which was non-significant ($p = 0.785$ for rejection; $p = 0.174$ for graft loss), supporting the validity of the proportional hazards model. Sensitivity analyses using multivariable logistic regression yielded consistent results: dnDSA was associated with rejection (OR 5.66, 95% CI 2.46–13.00, $p < 0.001$) and graft loss (OR 20.42, 95% CI 3.37–123.61, $p = 0.001$). Retransplantation was an independent risk factor for both rejection (OR 6.67, 95% CI 2.24–19.90, $p = 0.001$) and graft loss (OR 12.49, 95% CI 1.41–111.06, $p = 0.024$).

In multivariable Cox proportional hazards analysis, the development of dnDSA emerged as an independent predictor of acute rejection within the first year after transplantation (HR 4.19, 95% CI 2.21–7.95; $p < 0.001$). Previous transplantation was likewise identified as a strong independent risk factor for rejection (HR 5.81, 95% CI 2.51–13.42; $p < 0.001$), whereas HLA mismatch burden and pretransplant sensitization (PRA $\geq$ 20%) were not significantly associated with rejection risk (Table 5).

For overall graft loss within the first year, dnDSA positivity remained an independent predictor (HR 3.93, 95% CI 1.52–10.20; $p = 0.001$). In addition, a higher number of HLA mismatches was significantly associated with an increased risk of graft loss (HR 1.54 per mismatch, 95% CI 1.06–2.25; $p = 0.025$), as was previous transplantation (HR 5.99, 95% CI 1.59–22.51; $p = 0.008$). Pretransplant sensitization (PRA $\geq$ 20%) was not significantly associated with graft loss (Table 5).

The proportional hazards assumption was formally assessed by inclusion of a time-dependent covariate for dnDSA and was not violated for either rejection ($p = 0.785$) or graft loss ($p = 0.174$), supporting the validity of the Cox regression models.

Sensitivity analyses using multivariable logistic regression confirmed the robustness of these findings. dnDSA remained strongly associated with acute rejection (OR 5.66, 95% CI 2.46–13.00; $p < 0.001$) and graft loss (OR 20.42, 95% CI 3.37–123.61; $p = 0.001$). Retransplantation was also independently associated with both rejection (OR 6.67, 95% CI 2.24–19.90; $p = 0.001$) and graft loss (OR 12.49, 95% CI 1.41–111.06; $p = 0.024$).

4. Discussion

In this study, the development of de novo donor-specific antibodies (dnDSA) during the first year after kidney transplantation was associated with impaired graft function, higher rates of both cellular and antibody-mediated rejection, and reduced graft survival. Despite these adverse outcomes, dnDSA formation did not translate into reduced patient survival during the one-year follow-up period.

The incidence of dnDSA observed in our cohort (17%) aligns with previously reported rates of 10–30% among kidney transplant recipients [6,10–16]. Consistent with earlier work

showing that most dnDSA emerge within the first 6–12 months post-transplant [11,16], over 80% of first dnDSA detections occurred within the first six months, with a pronounced peak during the first postoperative month. This temporal pattern suggests a phase of increased immunologic vulnerability during the early post-transplant period.

Regarding antibody specificity, most dnDSA detected were directed against HLA class II antigens, consistent with prior analyses demonstrating the predominance and clinical relevance of class II responses [16,17]. Class I and class II DSAs contribute differently to graft injury: class I DSAs are associated with both acute and chronic rejection, particularly in sensitized patients [12,18–21], whereas class II donor-specific antibodies are generally considered to be particularly clinically relevant due to their strong association with antibody-mediated rejection (ABMR), accelerated graft dysfunction, and chronic allograft injury [22,23]. The predominance of class II dnDSA in our cohort therefore aligns with the observed clinical deterioration.

Multiple factors contribute to the development of de novo donor-specific antibodies (dnDSA), including pretransplant sensitization, HLA mismatch burden, and post-transplant immunologic events [24–27]. Consistent with previously published data, our univariate and multivariate analyses identified pretransplant panel-reactive antibodies (PRA), reflecting increased immunologic risk, as a factor associated with dnDSA development [28–30]. Although these recipients typically receive intensified immunosuppressive regimens, they may remain susceptible to episodes of alloimmune activation that promote antibody formation. Similarly, reduction of immunosuppressive therapy may contribute to dnDSA development, particularly in the context of fluctuating immunosuppressive exposure or delayed achievement of therapeutic drug levels [31,32].

Donor-derived factors may also contribute to dnDSA development. Acute kidney injury (AKI) in deceased donors has been associated with increased inflammatory signaling, complement activation, and upregulation of HLA expression, potentially enhancing alloimmune responses in transplant recipients [33–35]. However, in our cohort AKI was not significantly associated with dnDSA development. These findings suggest that, although donor-related inflammatory injury may theoretically promote alloimmune activation, AKI alone did not emerge as an independent determinant of dnDSA development in this population.

The clinical relevance of dnDSA formation is well established. DnDSA are a major predictor of graft failure and reduced long-term allograft survival [36]. In our study, dnDSA-positive recipients showed significantly poorer graft-related outcomes at one year, and Kaplan–Meier analysis showed significantly lower graft survival in recipients who developed de novo donor-specific antibodies. Rejection rates were significantly higher in this group, with 48.6% experiencing histologically confirmed rejection, compared to 13.3% among dnDSA-negative patients. These findings corroborate earlier work demonstrating worse renal function among dnDSA-positive patients [37] and the high prevalence of DSA in individuals with chronic graft failure [37]. Importantly, antibodies emerging within the first post-transplant year have been shown to predict graft loss within a relatively short timeframe [38], consistent with the rapid decline in graft survival observed here.

Rejection likely represents a central pathway associated with the relationship between dnDSA formation and graft injury. Acute rejection—whether antibody-mediated, T-cell-mediated, or mixed—continues to affect 10–30% of transplant recipients in the early years after transplantation [39]. Several studies, including those by Wiebe et al., demonstrate that rejection episodes often precede or accompany dnDSA formation, particularly within the first six months post-transplant [6,40]. Our data demonstrated higher rates of both cellular and antibody-mediated rejection among dnDSA-positive recipients, particularly during the early post-transplant period. Although T-cell-mediated rejection remains the predominant

acute rejection phenotype in the first year [41], the presence of dnDSA has been associated with capillaritis, C4d positivity, and antibody-mediated rejection—each well-established predictors of poor graft outcomes [42,43]. The increased rejection burden in dnDSA-positive patients observed in our cohort therefore likely represents both antibody-driven injury and a broader dysregulation of alloimmune control.

Suboptimal or reduced immunosuppression, non-adherence, and dose modifications due to infections or malignancy continue to play an important role in rejection and dnDSA formation [44,45]. Despite risk-adapted intensification of immunosuppression in recipients with higher baseline immunologic risk, for high-risk patients with PRA > 20% in our study, these individuals still exhibited increased dnDSA incidence, highlighting the limitations of current approaches in fully preventing alloantibody development in sensitized recipients.

This study has several limitations. A relevant limitation of this study is the change in the antibody detection platform over time. Between 2006 and 2010, donor-specific antibodies were assessed by ELISA, whereas from 2011 onward, testing was performed using the Luminex platform. As these assays differ substantially in analytic sensitivity and detection characteristics, longitudinal comparisons across both periods should be interpreted with caution. In particular, the transition to Luminex may have increased the detection of low-level antibodies that were not reliably captured by ELISA, thereby introducing a method-related bias that may partially confound temporal trends in donor-specific antibody prevalence. An additional limitation relates to the analytical treatment of dnDSA as a dichotomous exposure variable during follow-up. Because dnDSA develops over time after transplantation, temporal relationships between dnDSA detection and clinical events such as rejection cannot be fully resolved in this observational design, and time-dependent bias cannot be excluded. Furthermore, biopsy sampling was performed on clinical indication rather than according to a protocol surveillance strategy, which may have led to underdetection of subclinical rejection and potential ascertainment bias between groups. Inclusion required complete dnDSA surveillance at all predefined time points, which may have introduced selection bias by excluding patients with incomplete follow-up or early adverse events. Further, the sample size limited subgroup analyses, and epitope or eplet mismatch data—known to be associated with dnDSA development—were not available [46,47]. Additionally, the one-year observation period restricts conclusions regarding long-term graft survival. Follow-up analyses at 3 and 5 years are planned to validate the prognostic implications reported here.

5. Conclusions

Overall, our findings reinforce the critical role of immunomonitoring in kidney transplantation. Routine post-transplant dnDSA monitoring may facilitate early identification of recipients at increased immunologic risk of rejection and graft failure, potentially informing closer clinical surveillance and individualized management. Although dnDSA formation did not impact patient survival within the study period, it significantly compromised graft survival and function. Continued research is needed to refine preventive strategies, optimize immunosuppression, and improve treatment options for antibody-mediated injury to ensure long-term allograft success.

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Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Full term
ABMR	Antibody-mediated rejection
AKI	Acute kidney injury
ATG	Anti-thymocyte globulin
CI	Confidence interval
CIT	Cold ischemia time
C4d	Complement split product C4d
dnDSA	De novo donor-specific antibodies
DSA	Donor-specific antibodies
DGF	Delayed graft function
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ESP	European Senior Program
HLA	Human leukocyte antigen
HR	Hazard ratio
IgG	Immunoglobulin G
LMU	Ludwig Maximilians University
LKD	Living kidney donation
MDRD	Modification of Diet in Renal Disease
MFI	Mean fluorescence intensity
MMF	Mycophenolate mofetil
OR	Odds ratio
PRA	Panel-reactive antibody
SD	Standard deviation
TCMR	T-cell-mediated rejection

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