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Positive Long-Term Outcome of Kidney Allocation via Acceptable Mismatch Program in Highly Sensitized Patients

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Keywords

Kidney transplantation · Human leukocyte antigen epitope matching · Induction therapy · Highly sensitized · De novo donor-specific antibody

Abstract

Introduction: Eurotransplant established the acceptable mismatch (AM) program to facilitate timely kidney transplantations of highly sensitized patients, but long-term granular clinical and immunological outcomes regarding overall graft survival and de novo DSA (dnDSA) formation are still intensively researched. The right choice of induction therapy in patients with differing immunological risk is not conclusively determined, as well as the impact of human leukocyte antigen (HLA) epitope matching on dnDSA formation. ***Methods:*** This monocentric, retrospective study analyzed 94 patients transplanted within the AM program between 2000 and 2019 compared to case-control matched cohorts of non- (PRA 0–5%; PRA-0) and intermediately sensitized (PRA 6–84%; PRA-6/84) patients transplanted through Eurotransplant Kidney Allocation System. ***Results:*** Estimated 10-year overall graft survival between the PRA-0 and AM cohorts was similar, whereas PRA-6/84 was significantly disadvantageous compared to PRA-0. Estimated 10-year incidence of antibody-mediated rejection rates was significantly lower in the PRA-0 group compared to AM and PRA-6/84 groups. Compared to the AM group, estimated incidence of de novo donor-specific antibody (dnDSA) was significantly lower in PRA-0 patients, with no differences between the AM and PRA-6/84 cohorts. The PRA-6/84 cohort was the only subgroup in which interleukin-2 receptor antagonist (IL2RA) induction was associated with longer overall graft survival, patient survival, and graft survival compared to depleting induction (ATG or OKT3). Broad HLA-A, -B, -DR mismatches (mmABDR) and HLA epitope mismatches determined by Eplets and PIRCHE-II were predictive for dnDSA formation in the total cohort, and the AM subgroup. ***Discussion:*** The high efforts expended on AM patients are justified to allow timely organ transplantation with acceptable risk profile and non-inferior outcomes. IL2RA induction in intermediately sensitized patients is associated with superior overall graft survival, patient survival, and graft survival compared to ATG/OKT3 induction, without negative effects on rejection episodes or dnDSA formation. In silico epitope matching might further help reduce dnDSA formation, particularly in high-risk AM patients.

Introduction

Kidney Transplantation in Highly Sensitized Patients

For end-stage renal disease (ESRD) patients, kidney transplantation is the best treatment option with highest long-term survival [1]. The Eurotransplant (ET) Kidney

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Allocation System (ETKAS) balances between various factors, such as histocompatibility, patients' waiting time, and country balance between imported and exported organ donors (ET Manual Chapter 4) [2], but not all patients have the same chance of receiving a compatible kidney [3]. The presence of preformed donor-specific antibodies (DSAs) prior to transplantation constitutes a risk factor for transplant outcome, and represents a major challenge in transplantation today [4]. The proportion of patients in the ET region with antibodies against >85% of a representative donor pool (PRA) increased from 2% in 2011 to 5.6% in 2019 [5]. To facilitate the timely transplantation of these highly sensitized patients, ET established the acceptable mismatch (AM) program. It identifies human leukocyte antigen (HLA) mismatches that likely will not cause a positive complement dependent cytotoxicity (CDC) crossmatch. HLA antigens the patient has never formed any relevant antibody against are classified as acceptable and can be tolerated on potential donor organs [6]. Various ET-initiated studies proved that AM patients have a similar short- and long-term graft survival to less-sensitized patients, while the graft survival of highly sensitized ET patients transplanted outside the AM program shown to be inferior [7, 8]. However, granular clinical and immunological long-term data are rare on this question and need further investigation.

Immunosuppressive Therapy

The aim of an effective immunosuppressive regimen was to avoid acute and chronic rejections as well as the development of dnDSA that are associated with late acute antibody-mediated rejection (ABMR), chronic ABMR, and transplant glomerulopathy [9–11]. The most important components are the maintenance immunosuppression that is initiated at the time of surgery and typically constitutes a lifelong therapy, and the induction therapy that attempts to reduce acute rejection periods early after organ transplantation. The 2009 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline recommends the use of a calcineurin inhibitor (preferably tacrolimus) combined with an antiproliferative agent (preferably mycophenolate) with or without corticosteroids as the first-line maintenance regimen. The recommended induction therapy depends on the immunological risk, with an interleukin-2 receptor antagonist (IL2RA) that prevents T cells from replicating (first-line) or a lymphocyte-depleting agent (immunologically high-risk patients) such as antithymocyte globulin (ATG) and Muromonab-CD3 (OKT3) [12]. Whereas the benefit of induction therapy compared to no induction is widely recognized, the right choice of induction agent is subject of controversial debate [13–15] and hence mainly dependent on patients' personal risk factors and local practice. Moreover, few studies address their possible impact on dnDSA formation. Given their substantial role on short- and long-term outcome in transplantation, further research is required to assess the role of induction therapy on the formation of dnDSA.

HLA Epitope Matching

HLA mismatches between donor and recipient may trigger the formation of dnDSA and constitute a major risk factor for graft rejection and late graft failure [16–18]. The most effective strategy to minimize the alloreactive humoral response is to limit the number of broad HLA mismatches between organ donor and recipient [19], but it brings limitations. Not all mismatches contribute equally to the risk of alloreactivity since the recipient's alloimmune response is directed exclusively toward those HLA mismatches, whose epitopes are specific for the donor and absent in the recipient [20–22]. Several in silico epitope matching algorithms such as HLAMatchmaker, EMS3D, EMMA, Snowflake, and PIRCHE-II have been developed to predict the underlying HLA epitopes triggering an immune response [22–25]. Conformational epitope-based algorithms calculate a mismatch load based on differing amino acid configurations at antibody-accessible regions that are present on the HLA molecular surface and function as targets for DSA [26]. HLAMatchmaker aggregates up to three amino acids in structural proximity, so-called Eplets, whereas EMS3D, EMMA, and Snowflake consider single amino acids. The PIRCHE-II algorithm aims on predicting the indirect pathway of allorecognition estimating the number of linear donor HLA-derived peptides that can be presented by the recipient's HLA Class II molecules [27]. Indirect recognition of such donor antigen promotes CD4+ T-cell help antibody-producing cells, a process termed linked recognition [28]. Although the established algorithms are well-known to correlate with dnDSA, rejection, and graft survival [29–31], it is currently an insufficiently addressed question to what extent in silico matching is predictive in highly sensitized patients.

Materials and Methods

Analytic Cohort

This retrospective study has been conducted as a single-center study, allowing consistency in antibody detection and consequential organ allocation. Antibodies considered for organ allocation have consistently been assessed for the loci HLA-A, -B, -C, -DR, and DQ and deemed positive if mean fluorescence intensity in single antigen beads assay resulted in more than 1,000 in at least two screenings or if detected by ELISA at least twice. In case DP antibodies were known to be present in the recipient's serum, donors have been typed for HLA-DP prior to the

acceptance of an organ offer to avoid transplantation across a DP-DSA. Repeated mismatches have never been accepted irrespective if antibodies have been detected. Patients who received a kidney transplantation via the AM program between January 01, 2000, and December 31, 2019, at Charité Berlin were examined (n = 107). Thirteen patients were excluded due to missing follow-up data. Renal patients transplanted within the same period via ETKAS were categorized by PRA value, creating three subgroups: (i) low-sensitized with PRA ≤5% (PRA-0, n = 1,911), (ii) intermediately sensitized with PRA 6–84% (PRA-6/84, n = 203), and (iii) highly sensitized with PRA ≥85% transplanted outside the AM program that were for various reasons not accepted for AM program (PRA-85, n = 34). The small sample size of the latter did not allow for a sophisticated matched case-control group, hence PRA-85 was not considered for analysis. Re-transplants and simultaneous pancreas-kidney transplantations were included, other multiorgan transplants and patients with missing data for cold ischemia (CI) time were excluded. Two case-control groups were created, matched for known important confounders (i) year of transplantation, (ii) recipient age at transplantation, (iii) donor age at transplantation, (iv) CI time, and (v) total mismatches of HLA-A and -B loci (mmAB) [32]. Mismatches of HLA-DR locus (mmDR) have not been applied for matching purposes due to the adherence of minimal match criteria in the AM program resulting in less mmDR compared to patients allocated via ETKAS (minimum matching of two HLA-DR or one HLA-DR and one HLA-B [split level], abandoned in 2020 [Eurotransplant Manual© –version 4.6; February 10, 2020]). The resulting three cohorts (AM n = 94; PRA-0 n = 92; PRA-6/84 n = 87) were used for analyses. All data on the identified patients-donor pairs have been obtained from Eurotransplant Network Information System (ENIS), Eurotransplant Donor Database, T-Base electronic health record [33], and hardcopy files of patients transplanted before January 01, 2005.

Rejections have been defined as follows: (i) biopsy-proven ABMR, (ii) biopsy-proven T-cell-mediated rejection (TCMR), (iii) biopsy-proven borderline rejection (BL) according to Banff criteria available at the respective time, and (iv) clinical rejection as per judgment of treating physician (CR). Rejections after graft failure or documented discontinuation of immunosuppressive medication have been excluded. Date of graft failure was either the date determined and documented by the treating physician or date of dialysis readmission.

Detection and Definition of DSA

Antibodies against loci HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 were included into the analysis. Before transplantation, all waitlisted patients have been screened for HLA antibodies at least quarterly. Following transplantation, all patients have been monitored for dnDSA in regular intervals stratified by their immunological risk. Patients with PRA <5% have been screened for DSA on an annual basis, whereas patients with PRA >5% have been screened at least twice a year. Post-transplant, patients typically are hospitalized for approximately 3 weeks average; during this period, all patients are routinely screened on a weekly basis. The DSA detection throughout the study period was performed at the Charité Tissue Typing Laboratory according to the latest standards at the respective time. The historically used CDC method was complemented by the solid phase ELISA technique in 1996. Over the year 2007, the more sensitive single antigen bead assay (Luminex) was introduced as standard DSA screening method. Typically, the methods have been used in combination to minimize their respective limitations. A small number of samples analyzed before the introduction of Luminex technique have later been re-analyzed by single antigen bead assay to retrospectively clarify ambiguous results. A subgroup analysis was conducted to assess the potential impact of the Luminex introduction on our endpoints by comparing patients transplanted between 2000 and 2007 to those transplanted from 2008 onward (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000536533). The year 2008 was selected as separation date to ensure that all patients had at least two screenings with single antigen beads assay before transplantation. In assigning DSA while the donor's DQ-typing was unknown, the most likely combination was assumed according to the most frequent haplotypes present in Europe (n = 2) [34, 35].

Epitope Matching

The PIRCHE-II score (www.pirche.com, version 3.47) was calculated for the prediction of indirect T-cell epitopes. The number of interlocus-mismatched antibody-verified eplets as defined by the HLA Epitope Registry (www.epregistry.com.br, version 3.0) was determined as a representative score for the epitope matching concept. The two matching approaches were shown to be statistically independent and representative for both indirect T-cell recognition (PIRCHE-II) and antibody recognition (Eplet score) [29, 36, 37]. HLA typing of the recipient was obtained by serological (HLA class I) and DNA-based techniques (HLA class I and II), details as described in Lachmann et al. [29]. The highest resolution HLA typing available for all patient-donor pairs was used and low/intermediate typings were imputed via multiple imputation to generate 2-field-typings. The resulting variety of high-resolution typings were weighted according to 2011 NMDP haplotype frequencies for European Caucasians and re-aggregated into one PIRCHE-II and Eplet score, respectively [38, 39].

Statistics

Continuous variables are summarized as means with standard deviation or as median with interquartile range, where applicable. ANOVA global F test or Kruskal-Wallis test was used to evaluate differences between continuous variables. Categorical and ordinal variables were compared by Pearson's χ^2 test. Time-to-event outcome data on death-censored allograft survival, patient survival, incidence of rejection episodes and formation of dnDSA were assessed by Kaplan-Meier plots and log-rank test. For PRA-6/84 subgroup analysis, we fitted multivariable Cox proportional hazards regression models to evaluate the associations between induction regimen and outcome while adjusting for mmABDR, re-transplants (first vs. repeated transplant) and PRA levels (peak and at transplantation).

The correlation between PIRCHE-II, Eplet score, and mmABDR was investigated by Spearman's rank-correlation coefficient. To account for the logarithmic correlation of PIRCHE-II score and the predicted incidence of dnDSA as shown by Lachmann et al. [29], the natural logarithm of PIRCHE-II score was applied. Mann-Whitney U test was used to compare the incidence of dnDSA depending on Eplet and PIRCHE-II scores, Kruskal-Wallis test for the distribution of the respective scores between the three cohorts. Univariate Cox proportional hazards regression models were created to investigate the hazards of mmABDR, PIRCHE-II, and Eplet score on posttransplant dnDSA formation. SPSS Version 26 and 27 (IBM Corp., Armonk, NY, USA) were used to conduct case-control matching and all statistical analyses. Two-tailed p values of <0.05 were considered significant.

Results

Study Population

The case-control matching resulted in three groups (total n = 273) undergoing kidney or combined kidney-pancreas transplantation: The AM patients (AM, n = 94),

Table 1. Basic characteristics patient population (n = 273)

	AM, N = 94	PRA-0, N = 92	PRA-6/84, N = 87	p value
Year of Tx	2011 (±5)	2010 (±5)	2010 (±5)	0.260[a]
R-age @ Tx, years	46 (±12)	47 (±11)	48 (±12)	0.307[a]
D-age @ Tx, years	45 (±13)	47 (±13)	48 (±13)	0.531[a]
Waiting time, months	58 (±37)	53 (±38)	54 (±38)	0.667[a]
CI-time, h	16 (±4)	15 (±5)	14 (±5)	0.051[a]
PRA @ Tx, %	64 (±36)	0 (±0)	37 (±21)	<0.001[a]
Peak PRA, %	95 (±12)	0 (±0)	55 (±26)	<0.001[a]
Delayed graft function, *n* (%)	58 (61.7)	41 (44.6)	49 (56.3)	0.057[b]
R-sex male, *n* (%)	48 (51.1)	60 (65.2)	37 (42.5)	0.009[b]
D-sex male, *n* (%)	46 (48.9)	50 (54.3)	48 (55.2)	0.655[b]
Re-transplant, *n* (%)	69 (73.4)	7 (7.6)	39 (44.8)	<0.001[b]
mmA (broad), *n* (%)				
0 mmA	54 (57.4)	51 (55.4)	36 (41.4)	0.198[b]
1 mmA	35 (37.2)	38 (41.3)	46 (52.9)	
2 mmA	5 (5.3)	3 (3.3)	5 (5.7)	
mmB (broad), *n* (%)				
0 mmB	41 (43.6)	43 (46.7)	35 (40.2)	0.314[b]
1 mmB	47 (50.0)	42 (45.7)	39 (44.8)	
2 mm B	6 (6.4)	7 (7.6)	13 (14.9)	
mmDR (broad), *n* (%)				
0 mmDR	52 (55.3)	43 (46.7)	32 (36.8)	0.003[b]
1 mmDR	40 (42.6)	37 (40.2)	38 (43.7)	
2 mmDR	2 (2.1)	12 (13.0)	17 (19.5)	
mmABDR (broad), *n* (%)				
0 mmABDR	16 (17.0)	29 (31.5)	20 (23.0)	<0.001[b]
1 mmABDR	26 (27.7)	10 (10.9)	5 (5.7)	
2 mmABDR	35 (37.2)	19 (20.7)	19 (21.8)	
3 mmABDR	16 (17.0)	25 (27.2)	24 (27.6)	
4 mmABDR	1 (1.1)	7 (7.6)	17 (19.5)	
5 mmABDR	0 (0.0)	2 (2.2)	2 (2.3)	
6 mmABDR	0 (0.0)	0 (0.0)	0 (0.0)	
dnDSA, *n* (%)				
None	64 (68.1)	71 (77.2)	57 (65.5)	0.772[b]
Class I	8 (8.5)	4 (4.3)	7 (8.0)	
Class II	13 (13.8)	10 (10.9)	12 (13.8)	
Class I + II	6 (6.4)	6 (6.5)	9 (10.3)	
Unknown	3 (3.2)	1 (1.1)	2 (2.3)	
Immunosuppression 1-year posttransplant, *n* (%)				
Tac-based	70 (74.5)	58 (63.0)	71 (81.6)	<0.001[b]
CyA-based	4 (4.3)	18 (19.6)	5 (5.7)	
Other/inconsistent[d]	20 (21.3)	16 (17.4)	11 (12.6)	
PIRCHE-II score	35 (±31)	50 (±40)	62 (±46)	<0.001[a]
Eplet score	7 (±5)	10 (±8)	12 (±8)	<0.001[a]
IL2RA induction, *n* (%)	57 (65.5)	76 (90.5)	52 (65.8)	<0.001[b]
ATG/OKT3 induction, *n* (%)	30 (31.9)	8 (8.7)	27 (31.0)	<0.001[b]
Death, *n* (%)	15 (16.0)	17 (18.5)	17 (19.5)	0.810[b]
Graft loss, *n* (%)	21 (22.3)	12 (13.0)	28 (32.2)	0.009[b]
Time to dnDSA, years	2.93 (0.12–8.01)	5.31 (2.69–10.34)	4.99 (0.51–7.74)	<0.001[c]
Time to 1st rejection, years	2.31 (0.05–7.72)	3.70 (0.25–8.11)	2.98 (0.04–7.02)	0.300[c]
Follow-up period, years	6.81 (2.25–9.65)	7.04 (3.54–10.64)	6.08 (3.38–8.16)	0.270[c]

Tx, transplantation; R, recipient; D, donor; mm, mismatch; DSA, donor-specific HLA antibodies; CI, cold ischemia; IL2RA, interleukin-2 receptor antagonist; Tac, tacrolimus; CyA, cyclosporine A. [a]ANOVA global F test. [b]Pearson's χ^2 test. [c]Kruskal-Wallis test. [d]Excluded in test for significance.

the non-sensitized patients with PRA 0–5% (PRA-0, n = 92) and the intermediately sensitized patients with PRA 6–84% (PRA-6/84, n = 87). Basic characteristics of recipients, donors, and transplantation are detailed in Table 1; details on applied maintenance therapy agents are summarized in online supplementary Table 1. No significant differences were detected between the groups regarding donor and recipient age, donor sex, waiting time, CI time and delayed graft function, mmA and mmB. Expectedly, the recipient sex slightly differs between the groups as they are stratified according to immunization level and women are more likely to be immunized due to pregnancies. As mentioned before, the differences in mmDR can be explained by the minimal match criteria applied until 2020 for the AM patients.

Long-Term Outcome, Incidence of dnDSA, and Rejections

During the total follow-up time, 110 of 273 (40.3%) patients experienced death or graft loss (AM = 36 [38.3%], PRA-0 = 29 [31.5%], PRA-6/84 = 45 [51.7%]). Figure 1a illustrates the estimated 10-year overall graft survival defined as time to death or allograft failure. PRA-0, AM, and PRA-6/84 cohorts show an estimated 10-year overall graft survival of 69.1%, 62.0%, and 47.8%, respectively (p = 0.054). Kaplan-Meier plot shows an advantage of PRA-0 versus PRA-6/84 (p = 0.020), but no significant difference between PRA-0 and AM (p = 0.384). Separate analysis of 10-year estimated death-censored allograft survival (Fig. 1b) confirmed this observation (PRA-0 = 82.2%, AM = 72.2%, PRA-6/84 = 65.4%; p = 0.042). A similar pattern emerged for estimated 10-year patient survival (PRA-0 = 84.1%, AM = 85.9%, PRA-6/84 = 73.1%; p = 0.601), although not statistically significant. A subgroup analysis of the aforementioned endpoints indicates that the inferior overall graft survival and graft survival observed in the PRA-6/84 cohort appear to be predominantly driven by transplants performed in the early period from 2000 to 2007 (online suppl. Fig. 1, confirmed with Cox regression [data not shown]), prior to the introduction of the Luminex technique.

75 patients (27.5%) across the total cohort developed dnDSA after transplantation during total follow-up time; for 6 patients (2.0%; AM: n = 3, PRA-0: n = 1, PRA-6/84: n = 2) no consecutive posttransplant HLA antibody monitoring data were available. The dnDSA occurred in 20 (22.0%) of the PRA-0 patients, 27 (29.7%) of the AM patients, and 28 (32.9%) of the PRA-6/84 patients. The estimated 10-year incidence of dnDSA (Fig. 1c) is significantly lower in the non-sensitized PRA-0 group (23.6%) compared to the AM (34.2%; p = 0.022) and PRA-6/84 (45.5%; p = 0.011), no relevant difference could be shown between the PRA-6/84 and the AM group (p = 0.861); all results have been confirmed by univariate Cox regression, hazard ratios summarized in online supplementary Table 2. The highest risk for the development of dnDSA manifests within the first weeks posttransplant.

A total of 114 (41.8%) patients experienced at least one rejection episode over the total observation period, thereof 35 (37.2%) of the AM, 36 (39.1%) of the PRA-0, and 43 (49.4%) of the PRA-6/84. The estimated 10-year incidence of rejections in the PRA-6/84 group (61.1%) appears to be higher than in the PRA-0 (44.9%) and AM cohort (40.3%), although not significant (p = 0.195, online suppl. Fig. 2A). Of note, this effect appears particularly prominent in the early phase (100 days) after transplantation: 6 months posttransplant, PRA-0 and AM show no relevant differences in estimated incidence of rejection episodes (23.9% and 28.3%, p = 0.532), while PRA-6/84 patients show a significantly higher rate (39.4%, p = 0.044). Among the different types of rejections, TCMR was the most prevalent, followed by BL, ABMR, and CR (number and type of rejections per cohort in online suppl. Table 3). While Kaplan-Meier plots in online supplementary Figure 2B–D show no significant difference in TCMR, CR, and BL between the cohorts, a clear distinction was observed in ABMR (Fig. 1d, p = 0.008). Consistent with the findings for dnDSA incidence, the estimated 10-year incidence of ABMR was significantly lower in the non-sensitized PRA-0 group (3.1%) as compared to the AM (8.6%; p = 0.047) and PRA-6/84 (35.3%; p = 0.001). No meaningful difference was observed between the PRA-6/84 and AM groups (p = 0.168).

Induction Therapy

Out of the total 273 patients, 185 (67.8%) received an IL2RA, and 65 (23.8%) a lymphocyte-depleting (ATG or OKT3) induction (n = 65). The remaining 23 (8.4%) patients received other combinations of induction therapies (n = 13), or no induction at all (n = 10). The cohorts were examined individually for the effect of IL2RA versus ATG/OKT3 induction therapy on overall graft survival, death-censored allograft survival, patient survival, dnDSA formation and incidence of rejection episodes. Whereas in the AM and PRA-0 cohorts we observed no correlation with any of the above-mentioned endpoints (online suppl. Fig. 3–7), IL2RA induction was associated with a statistically significant improvement in the PRA-6/84 group. In this subgroup (n = 79), 52 patients (59.8%) received IL2RA induction, 27 (31.0%) received ATG/OKT3 induction. During the total follow-up time, 40 of 79 (50.6%) patients experienced death or graft loss. Similarly, IL2RA induction correlated with superior estimated 10-year overall graft survival compared to the ATG/OKT3 group (56.4% vs. 30.0%, p = 0.001; Fig. 2a). This beneficial association manifests also in an estimated 10-year death-censored

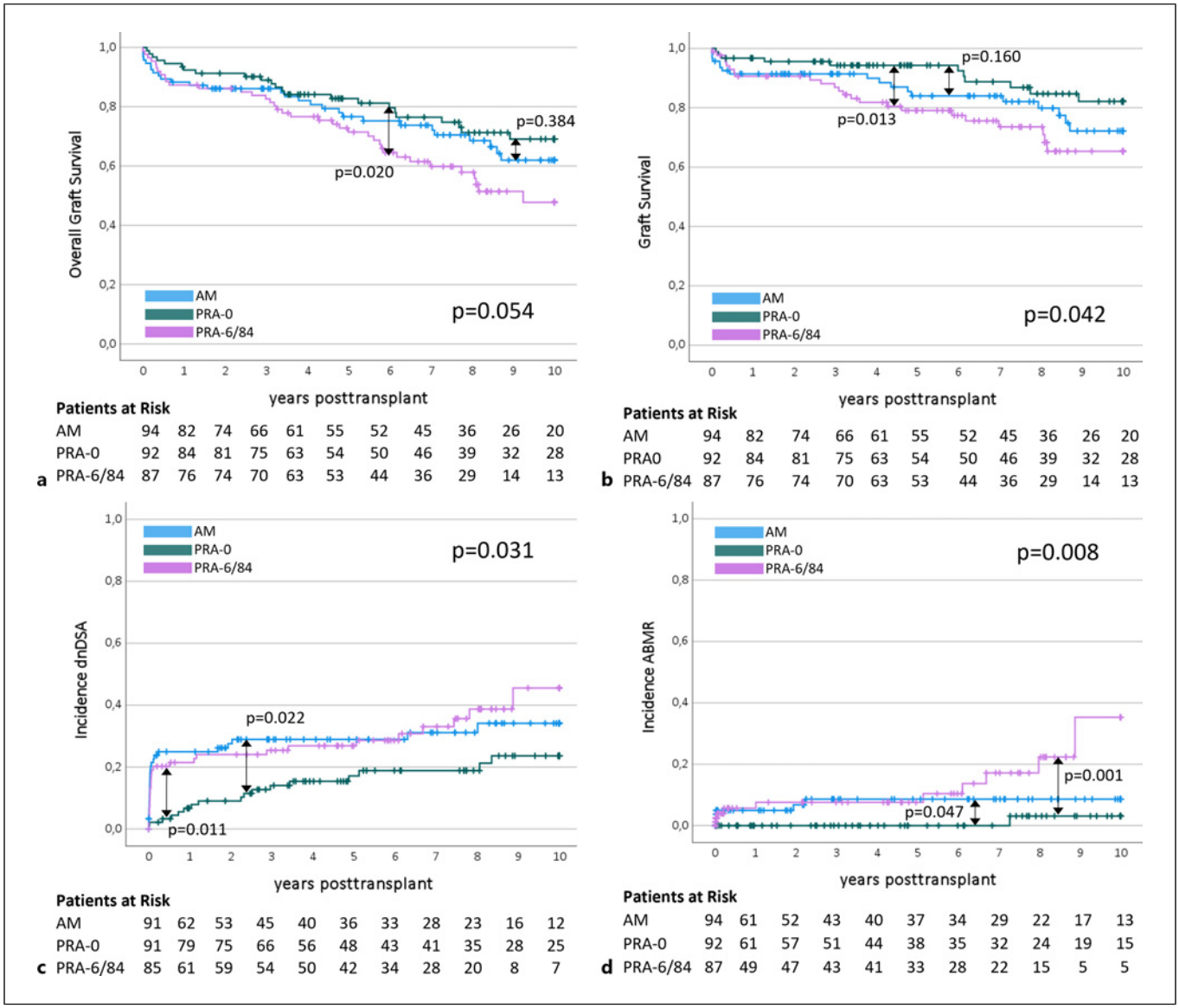

Fig. 1. Comparison of 10-year overall graft survival (**a**), 10-year death-censored graft survival (**b**), 10-year incidence dnDSA (**c**), and 10-year incidence of ABMR (**d**) between the acceptable mismatch (AM) patients, the non-sensitized patients with PRA 0–5% (PRA-0) and the intermediately sensitized patients with PRA 6–84% (PRA-6/84). *p* values calculated with log-rank test; PRA, panel reactive antibody; dnDSA, de novo donor-specific HLA antibodies; ABMR, antibody-mediated rejection.

allograft survival of 71.9% versus 49.1% ($p = 0.014$). The 10-year patient survival also favors the IL2RA induction with rates of 78.4% versus 61.1% ($p = 0.029$). 24 of the 79 patients (30.4%) developed dnDSA, 53 (67.1%) did not, and for 2 patients (2.5%) no information on posttransplant DSA was available. The estimated incidences of dnDSA after one, five, and 10 years were 9.8%, 16.1%, and 40.9% in the IL2RA group and thus considerably lower than in the ATG/OKT3 induction group with 40.1%, 40.1%, and 55.7% ($p = 0.002$, $p = 0.008$, $p = 0.008$; Fig. 2d). No significant difference was observed in time to first rejection episode 6 months, 5 years and 10 years posttransplant (28.8%, 34.7%, and 59.5% in IL2RA induction group vs. 50.0%, 54.5%, and 61.1% in ATG/OKT3 induction group; $p = 0.082$, $p = 0.093$, $p = 0.144$; online suppl. Fig. 7D). Basic characteristics of the PRA-6/84 cohort stratified by induction therapy shown to be comparable as detailed in online supplementary Table 4, except ATG/OKT group show a higher median peak PRA (66 (±24) versus 50 (±25), $p = 0.008$) and more re-transplants (70.4% vs. 30.8%, $p < 0.001$). To identify potential confounders, multivariable analyses were performed, and hazard ratios (HR) summarized in Table 2. After adjusting for immunological parameters mmABDR (selected as predominant factor for organ allocation

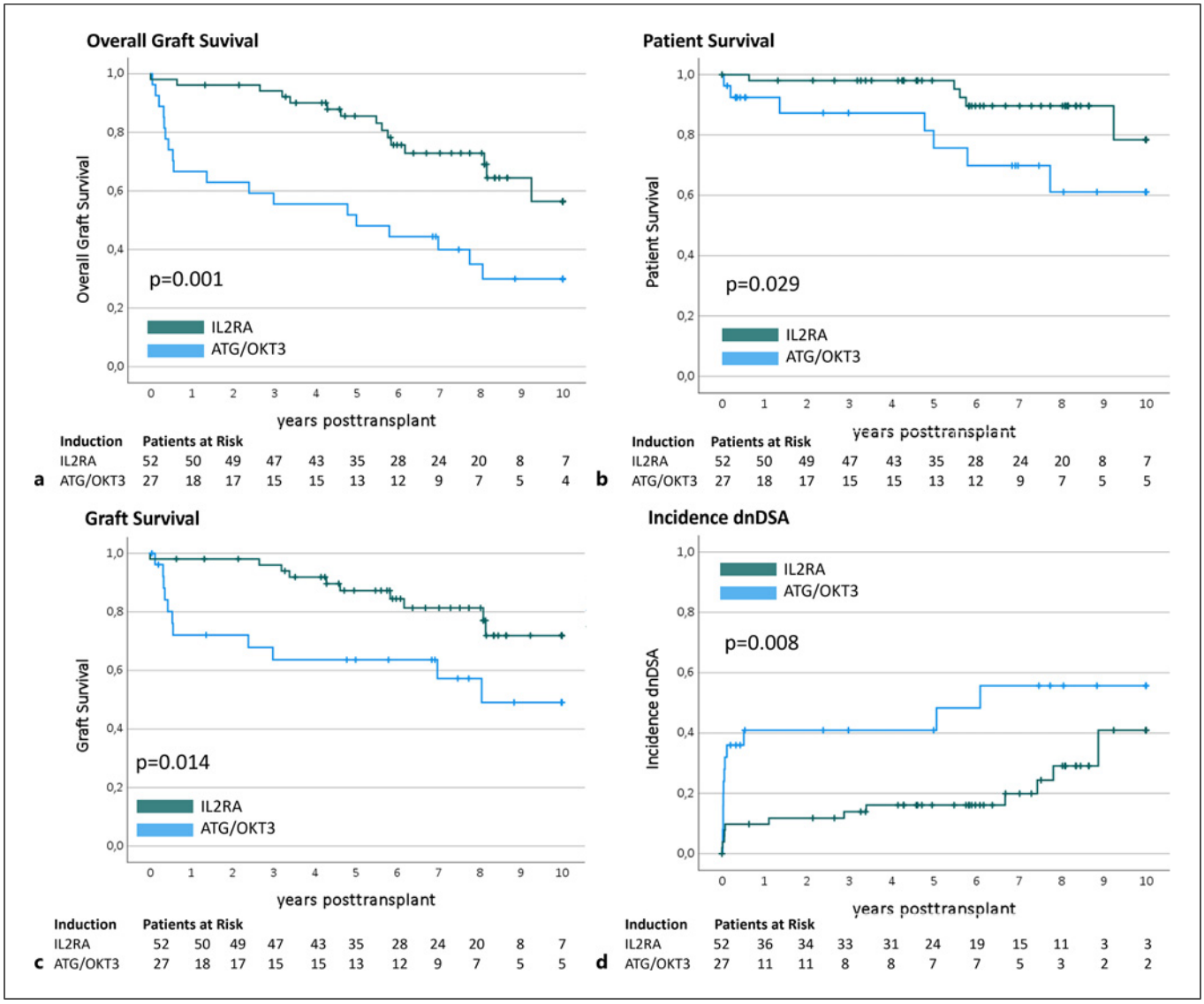

Fig. 2. Induction therapy in the intermediately sensitized cohort (PRA 6–84%; PRA-6/84). Kaplan-Meier plots comparing 10-year overall graft survival (**a**), 10-year patient survival (**b**), 10-year death-censored graft survival (**c**), and 10-year Incidence of dnDSA (**d**) between patients of the intermediately sensitized cohort (PRA-6/84) induced either IL2RA or ATG/OKT3. *p* values calculated with log-rank test. PRA, panel reactive antibody; dnDSA, de novo donor-specific antibody; IL2RA, interleukin-2 receptor antagonist.

and representative score for match grade) and PRA levels (peak and at transplantation), as well as for factor re-transplant as differing significantly between the groups, IL2RA induction remains associated with superior overall graft survival, patient survival, and death-censored allograft survival. Expectedly, high peak PRA levels showed to be a risk factor for overall graft survival, patient survival, and formation of dnDSA. mmABDR was identified as an additional independent risk factor for dnDSA formation. Interestingly, the suspected effect of IL2RA induction on the incidence dnDSA formation as per trend in Figure 2d could not be confirmed in adjusted multivariable analysis.

Impact of HLA Epitope Matching on dnDSA Development

The multiple imputation process to calculate a PIRCHE-II and an Eplet score succeeded for all but 1 of the 273 patients. In this PRA-0 patient, the typing resulted in an excessive amount of potential 2-field-typings obstructing the score calculation.

Confirming previous observations an overall association of dnDSA occurrence with higher levels of mmABDR, PIRCHE-II, and Eplet scores (Mann-Whitney U test, all $p < 0.0001$) was found. Due to adherence to minimal match criteria, the AM cohort expectedly shows less mmABDR than the other two cohorts (χ^2 test; both $p < 0.001$). Equally, PIRCHE-II and Eplet scores appear

Table 2. Sub-cohort PRA-6/84: multivariable Cox regression models of IL2RA induction, PRA at Tx, peak PRA, re-transplants and mmABDR on overall graft survival, patient survival, graft survival, incidence of rejection episodes, and dnDSA development

	Multivariable Cox regression	
	HR (95% CI)	*p* value
Overall graft survival		
IL2RA induction	0.270 (0.120–0.606)	0.002*
PRA at Tx	0.977 (0.960–0.995)	0.012*
PRA peak	1.022 (1.006–1.039)	0.006*
mmABDR	1.090 (0.835–1.423)	0.527
Re-transplant	0.898 (0.400–2.014)	0.794
Patient survival		
IL2RA induction	0.212 (0.055–0.813)	0.024*
PRA at Tx	0.976 (0.946–1.006)	0.113
PRA peak	1.027 (1.001–1.055)	0.044*
mmABDR	1.117 (0.706–1.766)	0.637
Re-transplant	0.634 (0.177–2.273)	0.484
Death-censored graft survival		
IL2RA induction	0.316 (0.114–0.877)	0.027*
PRA at Tx	0.978 (0.956–1.000)	0.049*
PRA peak	1.019 (1.000–1.040)	0.055
mmABDR	1.074 (0.773–1.492)	0.671
Re-transplant	1.137 (0.398–3.254)	0.810
Incidence rejection episodes		
IL2RA induction	0.835 (0.396–1.759)	0.636
PRA at Tx	0.998 (0.982–1.014)	0.766
PRA peak	1.010 (0.995–1.025)	0.179
mmABDR	1.205 (0.950–1.527)	0.124
Re-transplant	1.728 (0.799–3.736)	0.164
Incidence dnDSA development		
IL2RA induction	0.440 (0.175–1.103)	0.080
PRA at Tx	1.000 (0.981–1.019)	0.989
PRA peak	1.027 (1.005–1.050)	0.015*
mmABDR	1.455 (1.056–2.005)	0.022*
Re-transplant	0.882 (0.348–2.234)	0.790

HR, hazard ratio; CI, confidence interval; IL2RA, interleukin-2 receptor antagonist; PRA, panel reactive antibody; mm, mismatch; dnDSA, de novo donor-specific HLA antibodies. *Significant.

lower in the AM patients compared to PRA-0 (Kruskal-Wallis test; $p = 0.089$ and $p = 0.005$, respectively) and PRA-6/84 (Kruskal-Wallis test; both $p < 0.001$).

For the total, and the AM cohort, univariate Cox regression confirmed Eplet score, ln(PIRCHE-II) score, and mmABDR to be predictive factors for dnDSA formation (Table 3). In PRA-0 patients, an association was confirmed for Eplets and mmABDR ($p = 0.011$ and $p = 0.007$), in PRA-6/84 cohort for mmABDR only ($p = 0.014$).

To investigate the correlation between the 10-year formation rate of dnDSA and PIRCHE-II and/or Eplet score, we allocated all patients into four groups defined by the quartiles of the respective scores. Kaplan-Meier plots for the total cohort confirm the correlating estimated incidence of dnDSA with higher PIRCHE-II and Eplet scores (log-rank test $p = 0.001$ and $p < 0.001$, Fig. 3). Within the subgroups, this effect appears to be particularly prominent in the AM cohort for both PIRCHE-II ($p = 0.003$) and Eplet ($p = 0.004$) scores. This correlation could not be confirmed for PRA-0 or PRA-6/84 cohorts ($p = 0.463$ and $p = 0.194$, $p = 0.266$ and $p = 0.125$ for PIRCHE-II and Eplet scores, respectively). Interestingly, the lower quartile of the Eplet score seems to imply a particularly low incidence of dnDSA formation compared to the upper three quartiles with considerably higher incidences that barely differ between the groups. PIRCHE-II on the other hand, seems to increase the incidence stepwise from first to second to the upper two quartiles. Kaplan-Meier plots were unable to prove a correlation between overall graft survival of the total cohort and PIRCHE-II or Eplet score ($p = 0.796$ and $p = 0.836$), or time to first rejection ($p = 0.133$ and $p = 0.181$).

Discussion

The aim of our study was to provide a detailed comparison of kidney transplant patients of differing immunization status regarding their risks and long-term outcome while considering induction therapy and HLA compatibility. The comparison between the cohorts showed a distinct disadvantage of the PRA-6/84 versus AM and PRA-0 cohort in terms of overall graft survival, death-censored allograft survival, and incidence of rejection episodes, specifically ABMR. Confirming previously published data, the PRA-0 cohort performed best regarding death-censored allograft survival [8] and overall graft survival, although the gap to the AM patients was less pronounced than to the PRA-6/84. Notably, a subgroup analysis showed that this result appears predominantly driven by the transplants performed in the early period from 2000 to 2007, prior to the introduction of the Luminex technique. This interesting observation may be attributed partly to potentially missed DSA with less sensitive techniques in the early period, and further to the substantial developments in the field of kidney transplantation triggered by the introduction of the Luminex technique, a subsequently increased recognition of preformed DSAs as significant risk factor, and advancements in immunosuppressive strategies and surgical techniques. All these factors have contributed to a continuous enhancement of kidney transplant outcomes and appear to have been particularly beneficial for intermediately sensitized patients.

The PRA-0 cohort showed the lowest incidence of dnDSA compared to the equally appearing other two cohorts, which may be explained by their generally lower

Table 3. Univariate Cox regression models of Eplet score, ln(PIRCHE-II) score, and count of ABDR mismatches to predict the incidence of dnDSA

Cohort	Matching score	Univariate Cox regression analysis	
		HR (95% CI)	*p* value
Total, *N* = 267	Eplet score	1.060 (1.028–1.092)	<0.001*
	ln(PIRCHE-II) score	1.614 (1.270–2.052)	<0.001*
	mmABDR per MM	1.517 (1.268–1.815)	<0.001*
AM, *N* = 91	Eplet score	1.104 (1.036–1.176)	0.002*
	ln(PIRCHE-II) score	2.277 (1.385–3.743)	0.001*
	mmABDR per MM	1.808 (1.185–2.759)	0.006*
PRA-0, *N* = 91	Eplet score	1.080 (1.018–1.146)	0.011*
	ln(PIRCHE-II) score	1.420 (0.915–2.205)	0.118
	mmABDR per MM	1.572 (1.133–2.181)	0.007*
PRA-6/84, *N* = 84	Eplet score	1.047 (0.994–1.102)	0.082
	ln(PIRCHE-II) score	1.449 (0.994–2.111)	0.054
	mmABDR per MM	1.461 (1.081–1.975)	0.014*

dnDSA, de novo donor-specific HLA antibodies; HR, hazard ratio; CI, confidence interval; PIRCHE, predicted indirectly recognizable HLA epitopes.

immunological reactivity. Despite regular screenings, the possibility of preexisting DSA below the limit of detection can never be ruled out definitively and needs to be taken into consideration. Preformed antibodies may have existed (temporarily) below the limit of detection and then amplified by the transplantation, thus some of the recognized dnDSA may not be genuinely de novo. However, the total cumulative incidence of dnDSA we observed in the present study (27.5% in total, 16.8% in the first 12 months) is consistent with previously published data [40, 41]. In terms of rejection episodes, the highest incidence manifests in the PRA-6/84 cohort, whereas there were no relevant differences among the other groups. That confirms the findings of Heidt et al. [42], 2019, who detected no differences in rejection episodes within 6 months posttransplant between non-sensitized (PRA 0–5%) and AM patients, but a marked disadvantages of intermediately sensitized patients (PRA 6–84%). In concordance with the elevated incidence of dnDSA observed in the sensitized AM and PRA-6/84 patient groups, a higher frequency of ABMR was observed in these groups. Patient survival between the groups did not show any clear differences, which may be a result of the comparatively small sample size. As the immunosuppressive maintenance therapy has not explicitly been included in the analysis, a potential influence due to changes in dose levels must be taken into account when interpreting our findings. Given the prevalent use of tacrolimus in our patient cohort and the limited changes of prescribed immunosuppressive agents (online suppl. Table 1), it is not expected to be decisive, but a potential impact cannot entirely be disregarded.

We identified an association of IL2RA induction with superior outcome in the intermediately sensitized PRA-6/84 cohort: patients treated with IL2RA showed a superior overall survival, death-censored allograft survival, and patient survival compared to depleting induction. No significant correlation was observed with the incidence of rejection episodes, although that may be due to the low number of events. Notably, the major differences between the groups show early posttransplant, which is the assumed specific period of action of the induction therapy. This interesting observation in our small cohort could help answer the controversially discussed question [13, 14, 43] on the ideal induction therapy for intermediately sensitized patients. Depleting induction may result in more side effects within a well-matched Eurotransplant cohort not necessitating strong induction. While both cohorts appear comparable with regards to know risk factors (online suppl. Table 4), the possibility remains that IL2RA induction has been predominantly chosen for patients with an overall lower risk profile, suggesting that our observations may be a result of reverse causation. Thus, these results need further investigation and prospective studies to justify a treatment recommendation.

Across all endpoints, a trend of increasing event incidence was observed in the PRA-6/84 cohort commencing in the later posttransplant phases (e.g., overall graft survival and graft survival at year 3 onward, incidence dnDSA and ABMR at year 5) that we were unable to explain with the present data. Interestingly, while the risk of events appears to stabilize or remain consistent over time for AM and PRA-0 patients, PRA-6/84 patients exhibit a progressive decline in their posttransplant prognosis. Further investigations are warranted to elucidate the underlying mechanisms driving this trend. In the interim, heightened vigilance and meticulous monitoring may be considered for this specific patient population.

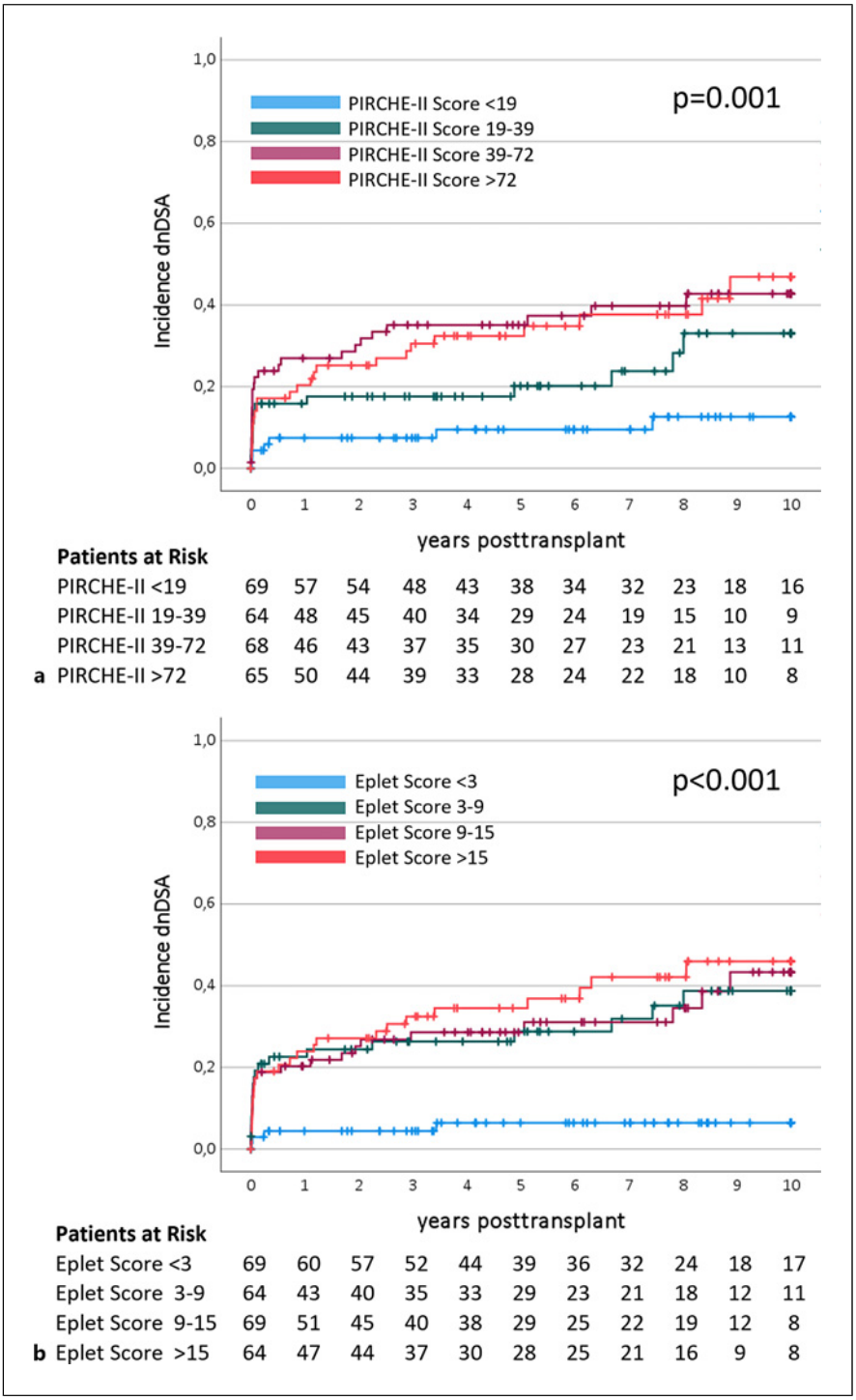

Fig. 3. Kaplan-Meier plots illustrating the incidence of dnDSA between groups defined by the quartiles of the PIRCHE-II score (i.e., <19, ≥19 to <39, ≥39 to <72, and ≥72) (**a**) and the Eplet score (<3, ≥3 to <9, ≥9 to <15, and ≥15) (**b**). dnDSA, de novo donor-specific HLA antibodies; PIRCHE, predicted indirectly recognizable HLA epitopes.

In line with previous findings [29, 44], our analysis confirmed the correlation between match grade (mmABDR, Eplets, and PIRCHE-II) and dnDSA formation. Our results manifest most prominently within the AM cohort, highlighting the importance of utmost matching efforts in order to prevent dnDSA formation and its known long-term disadvantages, particularly in the immunologically high-risk patients. Interestingly, the lower quartile of the Eplet score seems to suggest a particularly low risk for dnDSA formation compared to the barely differing upper three quartiles. This observation may indicate the existence of a cutoff threshold for the Eplet score, below which the incidence of dnDSA is low and by whose exceedance the risk appears invariably high. This result ties well with previous studies by Wiebe et al. [45], who defined an epitope mismatch threshold for HLA-DR and HLA-DQ at 10 and 17, respectively, resulting in dnDSA formation rates of 0% and 2.7%.

PIRCHE-II on the other hand seems to increase the estimated incidence stepwise from the first to the second to the upper two quartiles, suggesting a more continuous correlation between score and risk for dnDSA. This observation, however, needs to be addressed in future studies.

Other than Lachmann et al. [29], our study was unable to show a correlation between PIRCHE-II or Eplet scores and allograft survival, patient survival, overall graft survival, or rejection rates. Considering the small sample size compared to previously published data that appears according to expectations.

Limitations

Inherent with the retrospective study design, some relevant data points in the patients' files were ambiguous or missing and could not be clarified despite big efforts. Potential differences in patient compliance have not been taken into consideration, as well as drug doses and blood levels. These factors bring limitations to the present data, although sample size and case-control matching can reduce the influence of potential confounders.

Conclusion

In conclusion, the AM program of Eurotransplant is a valid and beneficial approach to allow timely kidney transplantation of highly sensitized patients with acceptable risk profile and good long-term outcome. The high effort expended to find suitable organs is justified in view of the considerable outcomes in terms of overall graft survival, death-censored allograft survival, incidence of rejection episodes, and dnDSA development.

Importantly, for intermediately sensitized patients, IL2RA induction resulted in better outcomes (overall graft survival, patient survival, and death-censored graft survival) compared to ATG/OKT3 induction. Finally, epitope matching via algorithms such as PIRCHE-II and Eplets provides additional information and may further help reduce the de novo formation of DSA and early rejection, particularly in high-risk AM patients.

Statement of Ethics

The study was approved by the Ethics Committee at Charité-Mitte, approval number EA1/263/21. Written informed consent from participants was not required in accordance with local/national guidelines.

Conflict of Interest Statement

M. Niemann works for PIRCHE AG, which develops and operates the PIRCHE web service. The remaining authors have no conflicts of interest to declare.

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Author Contributions

A. Pruß and N. Lachmann conceptualized the study. Y. Strehler was responsible for data collection, curation, formal analysis, visualization, and writing the original draft supervised by N. Lachmann. M. Niemann contributed the Eplet and PIRCHE-II score calculations and supported statistical analysis. K. Budde and F. Halleck supported clinical data analysis and interpretation. All authors reviewed and edited the manuscript.

Data Availability Statement

The data underlying this article cannot be shared publicly due to ethical restrictions and to protect the privacy of individuals that participated in the study. The data will be shared with qualified researchers on reasonable request to the corresponding author.

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