Association of Predicted HLA T-Cell Epitope Targets and T-Cell–Mediated Rejection After Kidney Transplantation

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Rationale & Objective: The relationship between human leukocyte antigen (HLA) molecular mismatches and T-cell–mediated rejection (TCMR) is unknown. We investigated the associations between the different donor HLA–derived T-cell targets and the occurrence of TCMR and borderline histologic changes suggestive of TCMR after kidney transplantation.

Study Design: Retrospective cohort study.

Setting & Participants: All kidney transplant recipients at a single center between 2004 and 2013 with available biopsy data and a DNA sample for high-resolution HLA donor/recipient typing (N = 893).

Exposure: Scores calculated by the HLA matching algorithm PIRCHE-II and HLA eplet mismatches.

Outcome: TCMR, borderline changes suggestive of TCMR, and allograft failure.

Analytical Approach: Multivariable cause-specific hazards models were fit to characterize the association between HLA epitopes targets and study outcomes.

Results: We found 277 patients developed TCMR, and 134 developed only borderline changes suggestive of TCMR on at least 1 biopsy. In multivariable analyses, only the PIRCHE-II scores for HLA-DRB1 and HLA-DQB1 were independently associated with the occurrence of TCMR and with allograft failure; this was not the case for HLA class I molecules. If restricted to rejection episodes within the first 3 months after transplantation, only the T-cell epitope targets originating from the donor's HLA-DRB1 and HLA-DQB1, but not class I molecules, were associated with the early acute TCMR. Also, the median PIRCHE-II score for HLA class II was statistically different between the patients with TCMR compared to the patients without TCMR (129 [IQR, 60-240] vs 201 [IQR, 96-298], respectively; $P < 0.0001$). These differences were not observed for class I PIRCHE-II scores.

Limitations: Observational clinical data and residual confounding.

Conclusions: In the absence of HLA-DSA, HLA class II but not class I mismatches are associated with early episodes of acute TCMR and allograft failure. This suggests that current immunosuppressive therapies are largely able to abort the most deleterious HLA class I–directed alloimmune processes; however, alloresponses against HLA-DRB1 and HLA-DQB1 molecular mismatches remain insufficiently suppressed.

Visual Abstract online

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Am J Kidney Dis. 80(6):718-729. Published online June 9, 2022.

doi: 10.1053/j.ajkd.2022.04.009

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The disparity in the human leukocyte antigen (HLA) system between the donor and recipient transplant pair plays a central role in both Banff-defined rejection phenotypes, T-cell–mediated rejection (TCMR) and antibody-mediated rejection (ABMR), primarily related to the presence of donor-specific antibodies to HLA (HLA-DSA).[1-4] Serologic or low-resolution molecular typing methods and kidney allocation strategies based on antigen level for "classic" HLA loci (A, B, and DRB1) oversimplify the complexity of the HLA system and do not accurately predict the actual risk of allograft rejection and anti-HLA antibody formation after kidney transplantation.[5,6] These 3 loci represent only part of the HLA system and other highly polymorphic HLA loci exist, like HLA-C, DRB3/4/5, DQA1, DQB1, DPA1, and DPB1, which are not taken into account in most of the current allocation strategies and pretransplant risk assessment.[7]

Editorial, p. 704

A more detailed evaluation of the HLA complex at the molecular mismatch (epitope) level with use of high-resolution HLA molecular typing methods has the potential for more precise prediction of posttransplant donor-specific alloimmune responses.[8,9] In terms of predicting de novo HLA-DSA formation and subsequently developing ABMR after transplantation, there are several tools available to predict the HLA epitopes that can be recognized by B cells (Fig 1).[10-12] We and others have shown that HLA class II molecular mismatches, specifically DRB1/3/4/5 and DQA1B1, are particularly harmful given their capability of inducing HLA-DSA and causing ABMR.[5,13] However, defining the real immunogenic B-cell HLA epitopes that induce de novo HLA-DSA formation remains challenging in the transplant field and is still a work in progress.[14,15]

Beyond the estimation of the HLA epitopes recognized by B cells and anti-HLA antibodies, the PIRCHE-II (Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules) algorithm evaluates and quantifies the T-cell epitope targets, linear peptides of the mismatched donor HLA molecules (Fig 1). This tool estimates the number of potential immunogenic T-cell linear peptide targets derived from the mismatched donor HLA molecules

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PLAIN-LANGUAGE SUMMARY

Genetic differences in the human leukocyte antigen (HLA) complex between kidney transplant donors and recipients play a central role in T-cell–mediated rejection (TCMR), which can lead to failure of the transplanted kidney. Evaluating this genetic disparity (mismatch) in the HLA complex at the molecular (epitope) level could contribute to better prediction of the immune response to the donor organ post-transplantation. We investigated the associations of the different donor HLA–derived T-cell epitope targets and scores obtained from virtual crossmatch algorithms with the occurrence of TCMR, borderline TCMR, and graft failure after kidney transplantation after taking into account the influence of donor-specific anti-HLA antibodies. This study illustrates the greater importance of the molecular mismatches in class II molecules compared to class I HLA molecules.

and presented to the recipient's T cells.[16] The PIRCHE-II score is suggested to help identify immunogenic HLA mismatches at high risk for T-cell allorecognition and consequently also for de novo HLA-DSA formation, as T-cell help is required in B-cell activation.[17] We and others recently demonstrated that HLA molecular mismatches are the main driver for the development of TCMR but mainly in the presence of HLA-DSA.[5,13] However, until now, most of the studies using the PIRCHE tool have limited their analyses to only the HLA-DRB1 locus for peptide presentation and neglected the other HLA class II molecules HLA-DRB3/4/5, DQA1B1, and DPA1B1.[14–17]

Inducing alloimmune tolerance to prevent allograft rejection and minimizing generalized immunosuppression has been a major focus of transplant research. In contrast to the well-defined relation between HLA molecular mismatches and the risk for HLA antibody formation and ABMR, our understanding of the relation between the HLA molecular mismatches and the risk for TCMR remains vague. Specifically, it is unknown to what degree the different HLA molecules and mismatched HLA donor epitope targets contribute to the development of antibody-independent rejection phenotypes, which still occurs despite the use of immunosuppressive therapies that primarily target T-cell activation pathways.[18]

We investigated the associations of the different donor HLA-derived T-cell epitope targets, PIRCHE-II scores, and the occurrence of TCMR, borderline changes suggestive of TCMR, and graft failure after kidney transplantation, correcting for the influence of HLA-DSA.

Methods

Study Population

This is a retrospective observational cohort study. Between March 1, 2004, and February 6, 2013, consecutive patients undergoing single kidney transplantation at the University Hospitals Leuven were eligible for this retrospective observational cohort study (n = 1,137) (Fig 2). The transplantations were performed with compatible T- and B-cell complement-dependent cytotoxicity tests and compatible ABO blood groups. Prospective collection of clinical data was performed by systematically storing the data in electronic formats; the clinical data for this study were extracted from these electronic files. Tacrolimus, mycophenolic acid, and corticosteroids were used as a basic immunosuppressive regimen in the large majority of patients, with additional induction therapy in higher-risk patients. No desensitization therapies for HLA antibodies were used. The Ethics Committee of the University Hospitals Leuven approved and waived the requirement for obtaining informed consent from the patients for this retrospective study (approval no. S64006).

HLA Genotyping of the Cohort

All recipients and donors of this cohort with available DNA samples were genotyped retrospectively at the high-resolution (2-field) HLA level using next-generation sequencing (NGS) technology, and for all 11 HLA loci: HLA-A, B, C, DRB1, DRB3, DRB4, DRB5, QA1, DQB1, DPA1, and DPB1. We used 2 HLA genotyping approaches: the MIA FORA NGS FLEX 11 HLA Typing Kit (Immucor Inc) on the MiSeq sequencing instrument (Illumina Inc) and the Histogenetics HLA genotyping approach on the HiSeq sequencing system (Illumina Inc). We have described this retyping strategy in detail elsewhere.[5]

Calculation of the HLA PIRCHE-II Scores and HLA Eplet Mismatches

To calculate the different donor-recipient HLA molecular mismatches, the high-resolution (2-field) HLA genotyping data for all 11 loci were uploaded to the PIRCHE-II tool (v3.1.148) available at the www.pirche.org. Using the this tool, we calculated the number of donor mismatched HLA-derived peptides that can be presented by the recipient's HLA class II molecules, HLA-DRB1/3/4/5, DQA1/B1, DPA1/B1, both total and for each HLA molecule separately. Additionally, we also used the HLAMatchmaker program (v3.1, downloaded August 2020 from www.epitopes.net) to calculate HLA eplet mismatches for this cohort. The same HLA data were used in the HLAMatchmaker program to calculate the different HLA eplet mismatches.

Detection and Identification of Circulating Anti-HLA Antibodies

We screened all recipients for the presence of pretransplant (pre-existing) and posttransplant (de novo) anti-HLA antibodies with the LIFECODES LifeScreen Deluxe kit (Immucor). When positive or when a false-negative screening result was suspected (for instance, in patients with historical, pretransplant, or previously positive sample; retransplant patients; patients with rejection episodes;

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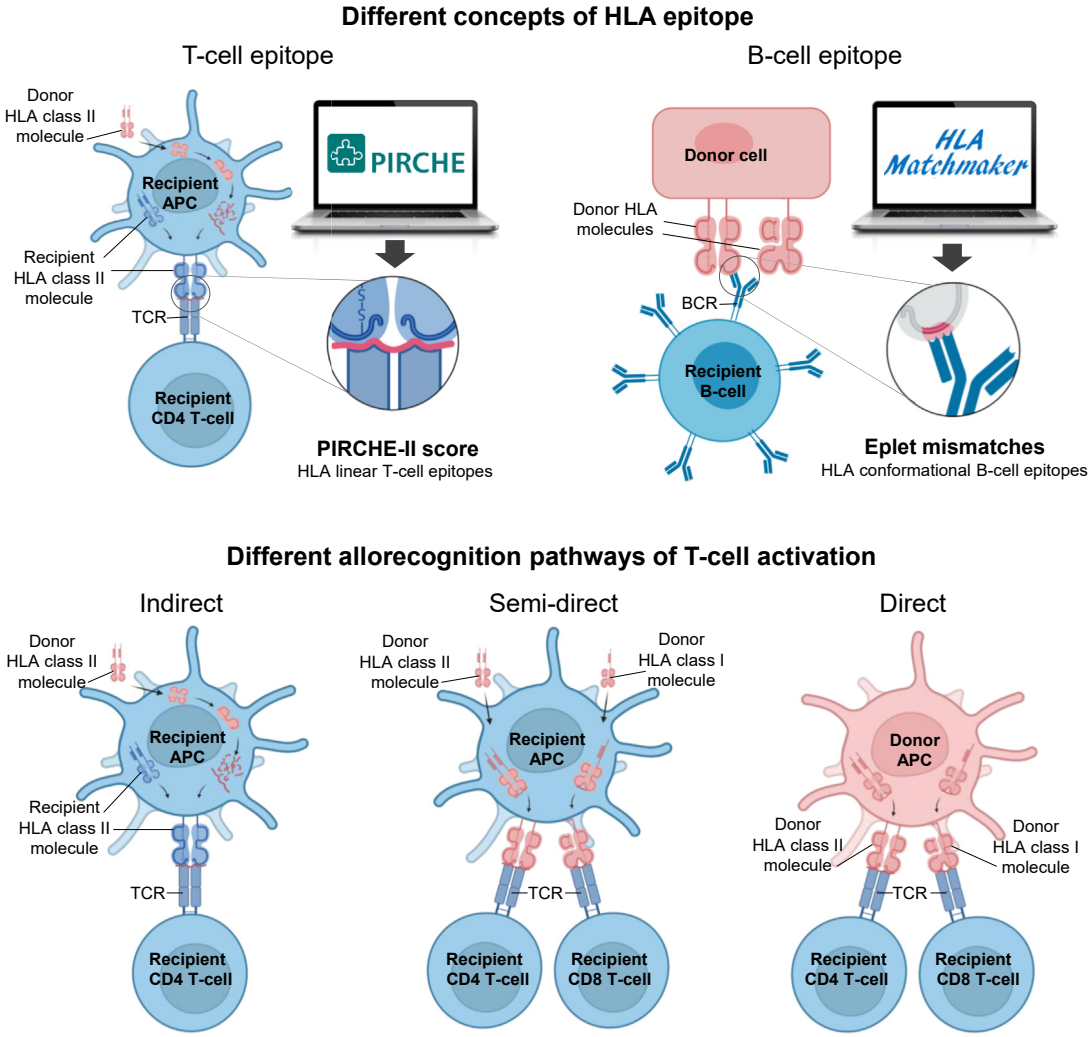

Figure 1. Methods for HLA molecular mismatch analysis and relation to the current insights in allorecognition after kidney transplantation. *Upper panel:* Two different concepts of HLA molecular mismatch (epitope) analysis. The PIRCHE tool aims to assess T-cell epitopes and predict the total number of different donor-derived HLA linear peptides (PIRCHE-II score) that are presented by recipient-type HLA class II molecules on APCs to the TCR of the recipient CD4-positive T cells. The HLAMatchmaker tool aims to evaluate B-cell epitopes and quantify the different conformational eplets (protein surface residues within a 3-angstrom radius) that can bind to the BCR of recipient B cells or antibodies. *Lower panel:* Three mechanisms of allorecognition for T-cell activation. In indirect allorecognition, recipient CD4-positive T cells are "indirectly" activated when the recipient HLA class II molecules of the recipient APCs present donor-derived allopeptides. Semidirect allorecognition occurs when the recipient APCs acquire full donor HLA molecules and bind donor-derived allopeptides, thus activating recipient T cells. Finally, in direct allorecognition, donor APCs with intact donor-type HLA molecules on their surface directly activate the recipient T cells. Created with BioRender.com. Abbreviations: APC, antigen-presenting cell; BCR, B-cell receptor; HLA, human leukocyte antigen; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules; TCR, T-cell receptor.

samples with high background; etc), antibody identification for donor-specificity against HLA-A, B, C, DRB1/3/4/5, DQA1B1, and DPA1B1 molecules was done with the LIFECODES Single Antigen Bead kits (Immucor) on the day of transplantation, at 3 months after transplant, and then yearly after transplantation. Anti-HLA antibody evaluations were also performed at the time of indication biopsies. We systematically used EDTA to avoid the prozone effect. We considered background-corrected median fluorescence intensity values of ≥500 as an indication of a possible presence of HLA-DSA. More details on the final assignment of HLA-DSA in this cohort were described recently.[19,20]

Histologic Grading and Treatment of Acute TCMR Rejections

We included all protocol and indication kidney allograft biopsies performed during posttransplant follow-up in this cohort until September 1, 2019 (Fig 2). The baseline biopsies performed at the time of implantation were not included in this study. One pathologist (E.V.) reviewed all

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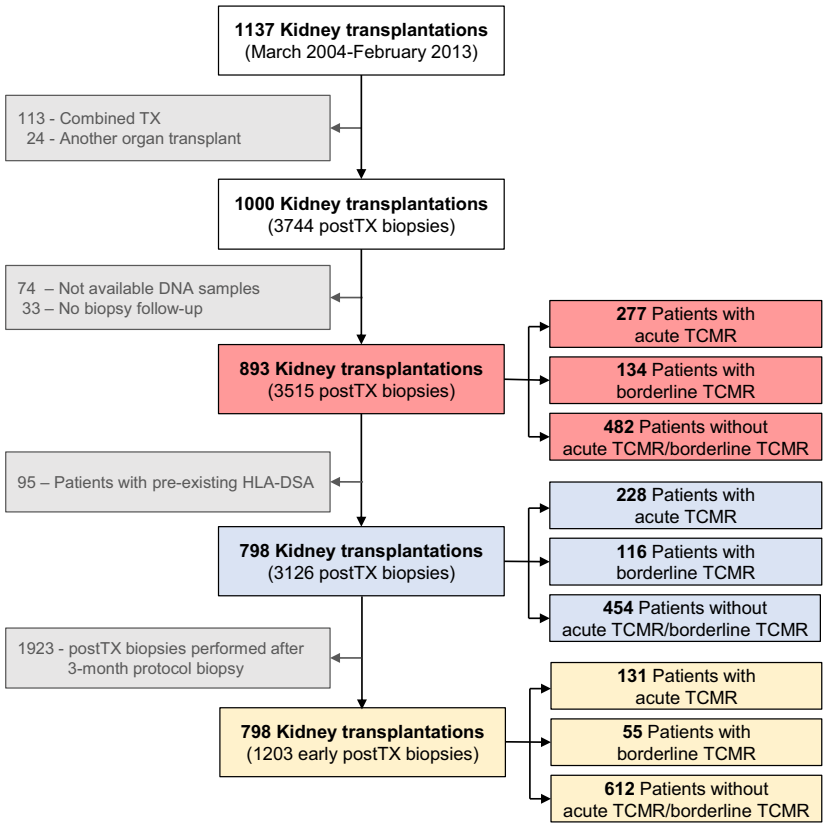

Figure 2. Flow diagram for patient enrollment and study design. Of the total 3,515 posttransplant biopsies available for the final cohort of 893 patients, 2,611 were protocol kidney transplant biopsies performed at 3 (n = 775), 12 (n = 722), 24 (n = 621), 36 (n = 190) or 48 (n = 18), and 60 (n = 208) months after transplant, and 904 were for-cause or clinically indicated biopsies. The red boxes represent the patients included in the analyses of PIRCHE-II scores and the risk for acute TCMR or the combined outcome of acute TCMR/borderline TCMR. The blue boxes indicate the analyses of PIRCHE II scores and the risk for acute TCMR or acute TCMR/borderline TCMR in the absence of any HLA-DSA (12 patients who developed de novo DSA were censored at the time of de novo HLA-DSA occurrence). The yellow boxes show analyses of PIRCHE-II scores and the risk for early acute TCMR or acute TCMR/borderline TCMR in patients with neither pre-existing or de novo HLA-DSA. Abbreviations: HLA, human leukocyte antigen; HLA-DSA, donor-specific anti-HLA antibodies; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules; TCMR, T-cell–mediated rejection; TX, transplantation.

biopsies. Indication biopsies were performed at the time of graft dysfunction, as evaluated by the treating physician based on the evolution of estimated glomerular filtration rate and/or proteinuria. There were no strict mathematical rules that were used to trigger these decisions. Protocol biopsies were defined as prescheduled biopsies at time of stable graft function. The individual histological lesion scores were semiquantitatively assessed in concordance with the latest Banff guidelines.[21,22]

The primary end point of this study was acute TCMR and development of borderline changes suggestive for rejection (borderline TCMR) was a competing event. The diagnosis of acute TCMR was based on the criteria defined by the Banff 2019 consensus.[23] Borderline TCMR was diagnosed as foci of tubulitis ($t > 0$) with minor interstitial inflammation (i1) or moderate-severe interstitial inflammation (i2 or i3) with mild (t1) tubulitis, also in concordance with the Banff 2019 consensus. We did not separately consider chronic active TCMR. All acute TCMR episodes were treated with high-dose steroids, both in indication and protocol biopsy settings, with subsequent second-line therapy using antithymocyte globulin in steroid-resistant cases. Although borderline TCMR was not considered acute TCMR, it was treated with the same therapy as acute TCMR when diagnosed at the time of graft dysfunction (indication biopsy setting) but not treated when present in the context of stable graft function (protocol biopsy setting).

Statistical Analysis

Patient and donor characteristics are described by frequency and percentage for categorical variables and by mean and standard deviation or median and interquartile range for continuous variables. PIRCHE-II scores and HLA eplet mismatches were the exposures of interest. The Wilcoxon rank-sum test was used for comparing medians between the patients with and without TCMR. Unadjusted cumulative incidence curves were used to estimate incidence rates of TCMR after transplantation according to

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PIRCHE-II score tertiles. Multivariable cause-specific hazards models were applied to quantify the hazard ratios of the different PIRCHE-II scores and eplet mismatches for developing acute TCMR/borderline TCMR (respectively excluding and including borderline TCMR in the definition as a competing event).

Biopsies showing mixed rejection were considered as acute TCMR, while biopsies with only ABMR rejection were not considered a histological end point in any of our analyses. These survival models were censored at the time of the last performed biopsy for each patient. All models were adjusted for donor and recipient age, cold ischemia time, repeat transplantation, donor type (brain death, circulatory death, living), panel-reactive antibody (%), and induction therapy (no induction vs basiliximab vs other treatment). Sensitivity analyses in HLA-DSA–negative patients were performed in the subpopulation of patients without pretransplant (pre-existing) HLA-DSA, with censoring of the survival models at time of de novo HLA-DSA occurrence.

The PIRCHE-II scores and HLA eplet mismatches were included as continuous variables in the models. Multivariable cause-specific hazards models were used to investigate the association between different PIRCHE-II scores and graft failure, including covariates as detailed above. We defined graft failure as the loss of kidney transplant function (return to dialysis or re-transplantation). In case of death of the recipient with a functioning graft, graft failure was censored at this time of death for death-censored graft failure analysis. For the calculation of all-cause graft failure, recipient death was considered as an event. We administratively censored patients who did not experience graft failure and were still in follow-up on September 1, 2019, at the time of data extraction. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS (v9.4; SAS Institute), and graphs were produced using GraphPad Prism software (v9.3; GraphPad Software).

Results

Demographics and Clinical Characteristics of the Study Population

Of all single kidney transplantations performed at the University Hospitals Leuven between March 2004 and February 2013, we included all with available DNA samples of the transplant pairs and biopsy follow-up (N = 893) (Fig 2). Pretransplant HLA antibodies were present in 233 patients, and 95 (40.8%) patients had pretransplant HLA-DSA, which were mainly directed against HLA class II molecules (61/95 [64%]) (Table S1). De novo HLA-DSA occurred in 43 (4.8%) patients, and they were also mainly against the donor HLA class II molecules (34/43 [79%]). Median follow-up was 8.0 (IQR, 5.2-10.5) years. For most patients (85.3%), standard maintenance immunosuppression consisted of tacrolimus, mycophenolic acid, and corticosteroids. Of the 893 patients, 369 (41.3%) of the patients received induction therapy, primarily basiliximab (317/369 [85.9%]).

The median total, HLA class I, and HLA class II PIRCHE-II scores were 310 (IQR, 205-452), 140 (IQR, 82-207), and 177 (IQR, 81-289), respectively (Table S1). Of all HLA molecules, HLA-DQA1/B1 had the highest median PIRCHE-II score at 75 (IQR, 7-161). The distribution of the total PIRCHE-II scores per HLA allele (0-17) mismatches and per HLA antigen (0-10) mismatches is depicted in Figure S1.

PIRCHE II Scores and the Risk for TCMR

After the baseline biopsy for this cohort, histologic follow-up comprised 3,515 posttransplant biopsies (2,611 protocol and 904 indication biopsies). Acute TCMR (not including borderline TCMR) was detected in 277 (31.0%) recipients (per 6,944.4 total patient-years) in at least 1 posttransplant biopsy. According to the Banff classification, 119 (43.0%), 153 (55.2%), and 5 (1.8%) patients had grades I-III acute TCMR, respectively. Unadjusted cumulative incidence curves showed significantly increased incidence rates of acute TCMR after transplantation only when stratified by PIRCHE-II score tertile for HLA class II but not for HLA class I (Fig 3). In multivariable cause-specific hazards analysis, adjusted for donor age, recipient age, donor type, cold ischemia time, repeat transplantation, panel-reactive antibody, and induction therapy, each 10-point greater total PIRCHE-II score was associated with an increased risk of developing TCMR (hazard ratio [HR], 1.01 [95% CI, 1.00-1.02]; $P = 0.009$) (Table 1). Analyses on each HLA molecule separately revealed that this association was mainly related to the PIRCHE-II score for HLA class II molecules (HR, 1.01 [95% CI, 1.01-1.02]; $P = 0.002$), more specifically HLA-DRB1 (HR, 1.08 [95% CI, 1.03-1.12]; $P < 0.001$) and HLA-DQA1/B1 (HR, 1.02 [95% CI, 1.00-1.03]; $P = 0.01$). Interestingly, the PIRCHE-II score for HLA class I did not show any trend toward association with the occurrence of acute TCMR.

In addition to the 277 patients with Banff-grade TCMR, 134 patients showed only borderline changes suggestive of TCMR in at least 1 posttransplant biopsy during histologic follow-up (thus never meeting the criteria for acute TCMR by the Banff classification). Similar to findings in patients who had acute TCMR alone, the adjusted cause-specific hazards model showed the PIRCHE-II score for HLA-DRB1 (HR, 1.07 [95% CI, 1.04-1.10]; $P < 0.001$) and HLA-DQA1/B1 (HR, 1.02 [95% CI, 1.01-1.03]; $P = 0.002$) independently contributed to the combined outcome of acute TCMR and borderline TCMR (Table 1). Again, in these analyses, there was no association between the PIRCHE-II score for HLA class I molecules and the combined acute TCMR/borderline TCMR outcome.

PIRCHE-II Scores and the Risk for TCMR in the Absence of HLA-DSA

Because most pretransplant and de novo HLA-DSA were against HLA class II molecules, and because this could

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confound the association between PIRCHE-II scores and TCMR, we investigated the association between PIRCHE-II scores and TCMR in the absence of any detectable HLA-DSA. This analysis was restricted to patients without pre-transplant HLA-DSA (N = 798) and censored at the time of de novo HLA-DSA occurrence (Fig 4). Of these 798 patients, 228 had acute TCMR, and 116 showed only borderline changes suggestive of TCMR on at least 1 biopsy after transplantation. Patients with acute TCMR or borderline TCMR and concomitant de novo HLA-DSA (n = 12) were censored in this analysis. In the absence of any HLA-DSA, only the T-cell epitope targets originating from the mismatched donor's HLA-DRB1 (HR, 1.08 [95% CI, 1.03-1.13]; P = 0.001) and HLA-DQA1/B1 (HR, 1.01 [95% CI 1.00-1.03]; P = 0.04) molecules were independently associated with an increased rate of acute TCMR. The same associations with PIRCHE-II scores for HLA-DRB1 and DQA1B1 were found in the combined acute TCMR/borderline TCMR outcome (Fig 4). These associations were not dependent on concomitant C4d-positive ABMR in the absence of HLA-DSA (Table S2). No relationship between rejection and HLA class I PIRCHE-II scores was observed.

PIRCHE-II Scores and Early TCMR in the Absence of HLA-DSA

A central theory is that recipient T cells can directly recognize non-self HLA molecules on the donor cells via "direct" allorecognition, especially in the early period after transplantation.[24] Therefore, we evaluated the associations between different PIRCHE-II scores and the risk of developing early TCMR in the absence of HLA-DSA, defined here as occurring within the first 3 months after transplant. Of 798 patients, 131 (16.4%) patients developed acute TCMR early after transplantation, until and including the 3-month protocol biopsy for each patient. Of this group, 48 (36.6%), 81 (61.8%), and 2 (1.6%) were diagnosed with grades I-III acute TCMR, respectively. Additionally, 55 patients showed borderline TCMR on at least 1 biopsy during the same period.

The median PIRCHE-II scores between patients with acute TCMR and those who did not develop acute TCMR by 3 months after transplant (Fig 5; Table S3) were 355 (IQR, 268-485) and 305 (IQR, 200-445), respectively (P = 0.01). This difference was solely due to the higher median PIRCHE-II score based on HLA class II molecules in the TCMR compared with the no-TCMR group (211 [IQR, 121-322] vs 161 [IQR, 74-276], respectively; P < 0.001). No statistically significant difference was noted in PIRCHE-II score for the HLA class I molecules between these groups (144 [IQR, 77-209] vs 139 [IQR, 79-206]; P = 0.6).

The multivariable cause-specific hazards analyses showed that even for early acute TCMR episodes we found independent associations for the T-cell epitope targets originating from the donor's HLA class II molecules, HLA-DRB1 (HR, 1.10 [95% CI, 1.04-1.16]; P = 0.001) and HLA-DQB1 (HR, 1.05 [95% CI, 1.02-1.09]; P = 0.002) (Table 2). Again, the PIRCHE-II score for HLA class I did not show an association with the occurrence of early acute TCMR alone or acute TCMR/borderline TCMR.

Next, we also used the HLAMatchmaker program to quantify the structural HLA molecular mismatch targets, which could be important in recognizing the intact non-self HLA donor's molecules in the direct allorecognition pathway. The multivariable cause-specific hazards models using the different HLA eplet mismatches also indicated that the occurrence of acute TCMR and borderline TCMR/acute TCMR was driven mainly by the eplet mismatches originating from the donors' HLA class II (HR, 1.03 [95% CI, 1.01-1.04]; P < 0.001), not from HLA class I (HR, 1.01 [95% CI, 0.98-1.03]; P = 0.7) (Table S4).

Kidney Allograft Failure According to the Different PIRCHE-II Scores

During the follow-up period, 351 of 893 grafts experienced graft failure, of which 139 were death-censored graft failures. In multivariable cause-specific hazards analysis, the PIRCHE-II scores for HLA-DRB1 and DQB1 were associated with death-censored graft failure (HRs of 1.07 [95% CI, 1.01-1.14; P = 0.03] and 1.04 [95% CI, 1.01-

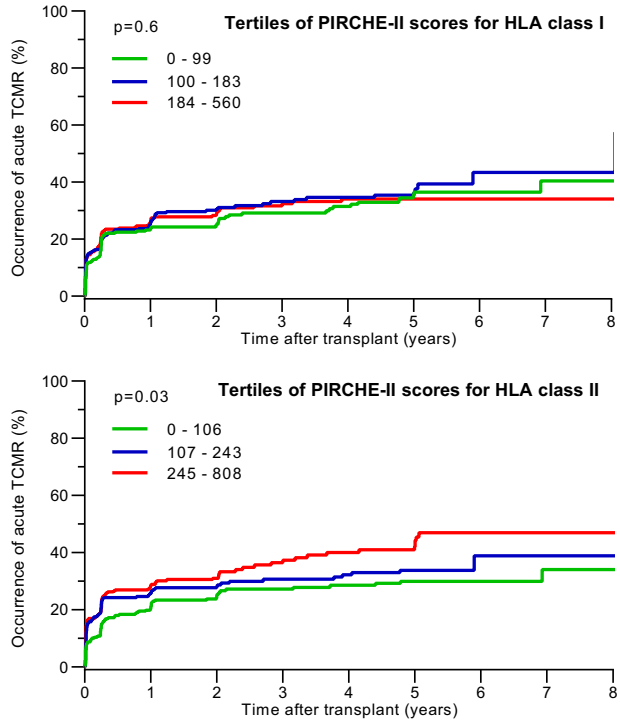

Figure 3. Cumulative incidence of occurrence of TCMR after transplantation according to PIRCHE-II score tertile (N = 893 transplantations). Score ranges of tertiles are 0-99, 100-183, 184-560 for HLA class I and 0-106, 107-243, 245-808 for HLA class II molecules. Abbrevations: HLA, human leukocyte antigen; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules; TCMR, T-cell–mediated rejection.

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Table 1. Adjusted Hazard Ratios for Acute TCMR Only or Acute/Borderline TCMR by PIRCHE-II Score

	Acute TCMR Only (277 Events)		Acute/Borderline TCMR (411 Events)	
	AHR (95% CI)	*P*	AHR (95% CI)	*P*
Total PIRCHE-II score	1.01 (1.00-1.02)	0.009[a]	1.01 (1.00-1.01)	0.007[a]
PIRCHE-II score for HLA class I	1.00 (0.99-1.02)	0.7	1.00 (0.99-1.01)	0.8
PIRCHE-II score for HLA-A	1.00 (0.98-1.03)	0.8	1.01 (0.99-1.03)	0.3
PIRCHE-II score for HLA-B	1.00 (0.97-1.03)	0.9	0.99 (0.97-1.02)	0.7
PIRCHE-II score for HLA-C	1.01 (0.98-1.03)	0.5	1.00 (0.98-1.02)	0.9
PIRCHE-II score for HLA class II	1.01 (1.01-1.02)	0.002[a]	1.01 (1.00-1.02)	0.001[a]
PIRCHE-II score for HLA-DRB1/3/4/5	1.02 (1.00-1.04)	0.03[a]	1.02 (1.00-1.04)	0.03[a]
PIRCHE-II score for HLA-DRB1	1.08 (1.03-1.12)	<0.001[a]	1.07 (1.04-1.10)	<0.001[a]
PIRCHE-II score for HLA-DRB3/4/5	1.01 (0.98-1.04)	0.4	1.01 (0.98-1.03)	0.7
PIRCHE-II score for HLA-DQA1/B1	1.02 (1.00-1.03)	0.01[a]	1.02 (1.01-1.03)	0.002[a]
PIRCHE-II score for HLA-DQA1	1.02 (1.00-1.04)	0.1	1.02 (1.00-1.04)	0.01[a]
PIRCHE-II score for HLA-DQB1	1.03 (1.01-1.06)	0.005[a]	1.03 (1.01-1.05)	0.001[a]
PIRCHE-II score for HLA-DPBA1/B1	1.03 (0.99-1.06)	0.1	1.02 (0.99-1.05)	0.2
PIRCHE-II score for HLA-DPA1	1.04 (0.99-1.08)	0.1	1.02 (0.98-1.06)	0.3
PIRCHE-II score for HLA-DPB1	1.05 (0.99-1.12)	0.1	1.03 (0.98-1.09)	0.2

N = 893. Each row represents a separate multivariable analysis, and each hazard ratio is estimated per 10-point greater PIRCHE-II score. All multivariable models were adjusted for donor and recipient age, donor type, cold ischemia time, repeat transplantation, panel-reactive antibody (%), and induction therapy (no induction vs basiliximab vs other treatment). Abbreviations: AHR, adjusted hazard ratio; HLA, human leukocyte antigen; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules; TCMR, T-cell–mediated rejection.
[a]Statistically significant value.

1.08; $P = 0.02$], respectively) (Table 3). Also, the PIRCHE-II scores for the same class II molecules independently associated with an increased rate of all-cause graft failure. Again, there was no association with the PIRCHE-II score for HLA class I molecules in these analyses with graft failure. Similar associations were found in the sensitivity analysis restricted to patients without pre-existing HLA-DSA, censored for the occurrence of de novo HLA-DSA (Table S5).

Discussion

By studying the associations between TCMR and the predicted indirectly recognizable HLA epitopes by recipient HLA class II molecules (PIRCHE-II scores), this study illustrates the greater importance of molecular mismatches in class II (HLA-DRB1 and DQB1 molecules) compared with mismatches in HLA class I molecules (which did not associate with TCMR). Although the PIRCHE-II score for the complete HLA-DQ molecule (including alpha 1 and beta 1 chains) also showed an association with TCMR risk, this association was not observed in the analysis of death-censored graft failure. These associations were independent of donor-specific HLA humoral alloimmunity and were observed in the early months after transplantation. This study suggests that in current clinical practice the powerful immunosuppressive therapies can largely abort the most deleterious HLA class I–directed alloimmune processes, while allorecognition directed against HLA class II molecules remains insufficiently suppressed. This leads not only to an increased risk for HLA-DSA formation and ABMR but also to early episodes of acute TCMR, with an impact on graft failure.

Our current study showed that transplantation with a high degree of HLA class II molecular mismatch, assessed using PIRCHE-II scores for HLA-DRB1 and DQB1 molecules, increases the risk of acute TCMR and acute TCMR/borderline TCMR. This finding is in concordance with other recent studies reporting that HLA class II molecular mismatches, mainly HLA eplet mismatches, predict the development of TCMR after kidney transplantation.[5,13] However, in a large portion of these cases reported in the previous studies the occurrence of TCMR can be related to the presence of pretransplant or de novo HLA-DSA against these 2 HLA molecules. To our knowledge, our study is the first to demonstrate independent associations of HLA-DRB1 and DQB1 donor-derived T-cell epitope targets and the risk of de novo T-cell–mediated rejection after kidney transplantation in the absence of any serological evidence of humoral activation against the donor HLA molecules.

The HLAMatchmaker and PIRCHE-II algorithms use the same principle of estimating the amino acid differences between the donor and recipient HLA molecules that can induce an alloimmune response (Fig 1). Although there is an inherent and significant correlation between the HLA-Matchmaker eplet mismatch load and the PIRCHE-II scores, these tools are based on different immunological allorecognition pathways and therefore define different types of polymorphic epitope targets. HLAMatchmaker is based on the direct allorecognition paradigm by predicting conformational B-cell epitopes whereas the PIRCHE-II tool is based on the indirect allorecognition theory and predicts T helper cell epitopes, which represent linear peptides.[25-27]

Currently, PIRCHE-II is the only tool available designed to reflect the unique peptide-binding repertoires determined by the donor-derived amino acid variations

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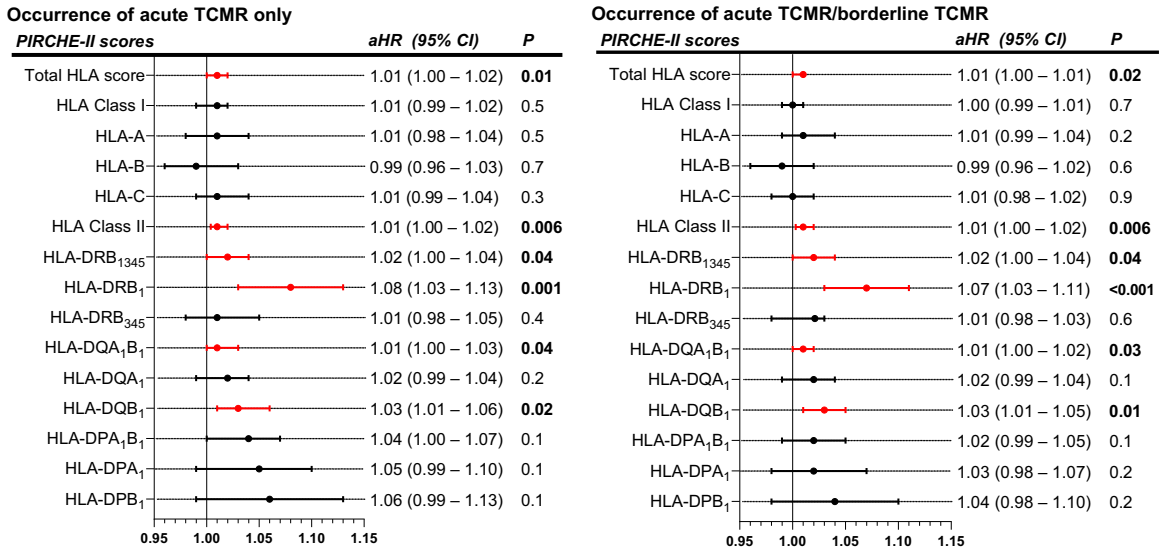

Figure 4. Forest plots with adjusted hazard ratios for the occurrence of acute TCMR only or acute TCMR/borderline TCMR according to the different PIRCHE-II scores in the cohort without pre-existing HLA-DSA, censored at the time of de novo HLA-DSA detection (N = 798 transplantations). Each PIRCHE-II score is included in a separate multivariable analysis, and each hazard ratio is estimated per increment of 10 in PIRCHE-II score. All multivariable models were adjusted for donor and recipient age, donor type, cold ischemia time, repeat transplantation, panel-reactive antibody (%), and induction therapy (no induction vs basiliximab vs other treatment). The red bars on the figure indicate statistical significance. Abbreviations: aHR, adjusted hazard ratio; HLA, human leukocyte antigen; HLA-DSA, donor-specific anti-HLA antibodies; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules; TCMR, T-cell–mediated rejection.

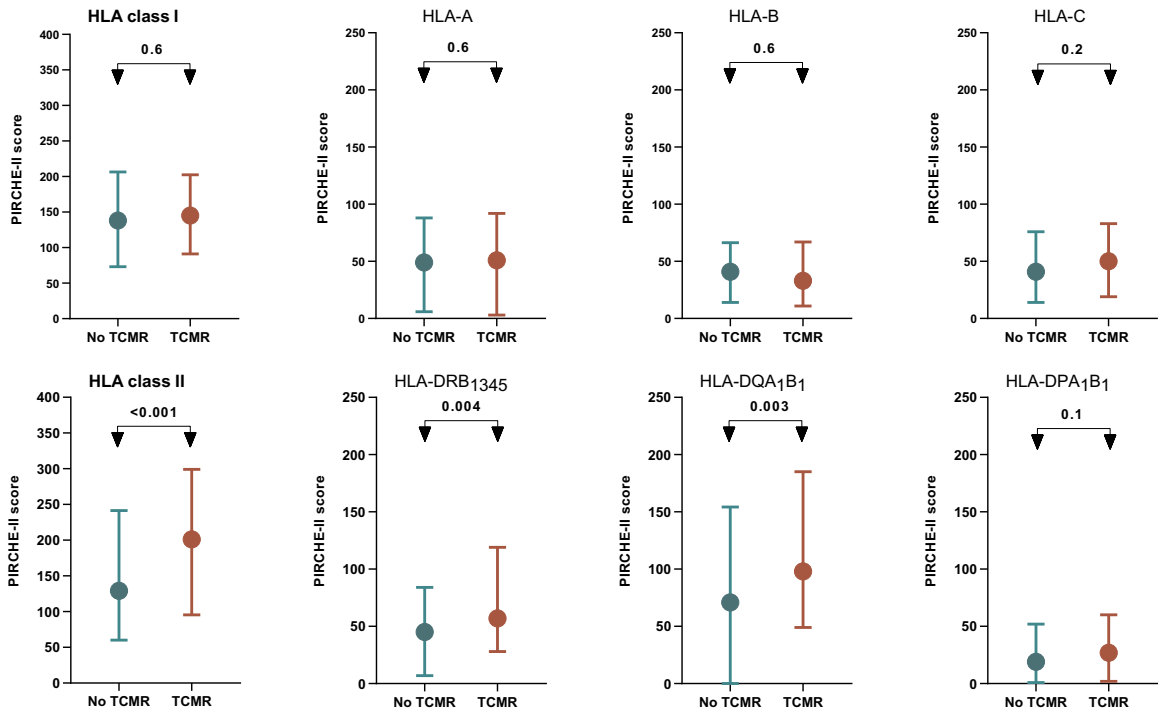

Figure 5. Comparison of the median PIRCHE-II scores between patients who developed TCMR and those without TCMR rejection within the first 3 months after transplantation in the absence of both pre-existing or de novo HLA-DSA (N = 781 transplantations). We excluded 17 patients from this analysis due to the short biopsy follow-up period (less than 1 month after transplant). The medians and the interquartile ranges are depicted on each graph, and the *P* values were obtained using the Wilcoxon rank-sum test. Abbreviations: HLA, human leukocyte antigen; HLA-DSA, donor-specific anti-HLA antibodies; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules; TCMR, T-cell–mediated rejection.

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Table 2. Adjusted Hazard Ratios for Early Acute TCMR Only or Acute/Borderline TCMR From Transplantation Through the 3-Month Protocol Biopsy, by PIRCHE-II Score in Patients Without Pre-existing HLA-DSA Censored at the Time of de Novo HLA-DSA Occurrence

	Acute TCMR Only (131 Events)		Acute/Borderline TCMR (186 Events)	
	AHR (95% CI)	*P*	AHR (95% CI)	*P*
Total PIRCHE-II score	1.01 (1.00-1.02)	0.01[a]	1.01 (1.00-1.02)	0.03[a]
PIRCHE-II score for HLA class I	1.00 (0.98-1.02)	0.8	0.99 (0.98-1.01)	0.9
PIRCHE-II score for HLA-A	1.02 (0.98-1.05)	0.4	1.02 (0.99-1.05)	0.3
PIRCHE-II score for HLA-B	0.98 (0.93-1.02)	0.3	0.98 (0.94-1.02)	0.2
PIRCHE-II score for HLA-C	1.01 (0.97-1.04)	0.8	0.99 (0.96-1.02)	0.5
PIRCHE-II score for HLA class II	1.02 (1.01-1.03)	0.002[a]	1.01 (1.01-1.02)	0.004[a]
PIRCHE-II score for HLA-DRB1/3/4/5	1.03 (1.01-1.06)	0.02[a]	1.03 (1.01-1.06)	0.02[a]
PIRCHE-II score for HLA-DRB1	1.10 (1.04-1.16)	0.001[a]	1.09 (1.04-1.14)	<0.001[a]
PIRCHE-II score for HLA-DRB3/4/5	1.03 (0.99-1.06)	0.2	1.01 (0.98-1.05)	0.4
PIRCHE-II score for HLA-DQA1/B1	1.02 (1.00-1.04)	0.01[a]	1.02 (1.00-1.03)	0.01[a]
PIRCHE-II score for HLA-DQA1	1.02 (0.99-1.05)	0.1	1.02 (0.99-1.05)	0.1
PIRCHE-II score for HLA-DQB1	1.05 (1.02-1.09)	0.002[a]	1.04 (1.01-1.07)	0.003[a]
PIRCHE-II score for HLA-DPBA1/B1	1.05 (1.00-1.10)	0.1	1.02 (0.99-1.07)	0.2
PIRCHE-II score for HLA-DPA1	1.07 (1.00-1.15)	0.04[a]	1.04 (0.98-1.10)	0.2
PIRCHE-II score for HLA-DPB1	1.05 (0.96-1.15)	0.3	1.02 (0.95-1.10)	0.6

N = 798. Each row represents a separate multivariable analysis, and each hazard ratio is estimated per 10-point greater PIRCHE-II score. All multivariable models were adjusted for donor and recipient age, donor type, cold ischemia time, repeat transplantation, panel-reactive antibody (%), and induction therapy (no induction vs basiliximab vs other treatment). Abbreviations: AHR, Adjusted hazard ratio; HLA, human leukocyte antigen; HLA-DSA, donor-specific anti-HLA antibodies; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules; TCMR, T-cell–mediated rejection.
[a]Statistically significant value.

presented in the HLA binding grooves of recipient class II molecules, according to the indirect allorecognition paradigm. Using this in silico analysis tool, our study indicates that TCMR is predicted by a high PIRCHE-II score, suggesting possible involvement of the indirect allorecognition pathway in the T-cell recognition of alloantigens. Preclinical studies have demonstrated that CD4-positive cells alone are sufficient to induce allograft rejection.[28] In line with this finding, another recent study has shown that kidney transplant recipients can develop de novo donor-specific T cells with high frequencies of donor-reactive CD4-positive T cells primed by the indirect antigen presentation pathway, which ultimately predicts the occurrence of de novo HLA-DSA.[29]

Importantly, the associations between the HLA class II PIRCHE-II scores and acute TCMR were not restricted to a later time after transplantation. As we observed that TCMR early after transplantation primarily related to HLA class II mismatches, we conclude that the relationship between the different models of allorecognition and the timing of TCMR occurrence is likely not valid clinically, at least in the context of standard immunosuppression.[24] Moreover, our study illustrates that HLA class II mismatches and TCMR are associated with graft failure independently of other covariates, including HLA-DSA.

Due to the favourable response to corticosteroids or lymphocyte-depleting agents, acute TCMR is currently believed to have a lesser impact on allograft survival and to be a more favorable form of kidney transplant rejection.[30,31] Our study indicates that this is not entirely true and that HLA class II genetic differences between donors and recipients remain a primary target for improvement of outcome after transplantation, independent of the role in HLA-DSA formation. The complete understanding of the exact role of this donor-recipient genetic differences on the occurrence and progression of the T-cell–mediated allograft injury from acute to chronic phase and ultimate to graft failure is still limited.[32]

Surprisingly, we did not observe any trend for associations between HLA class I molecular mismatches and TCMR, either by the PIRCHE-II indirect presentation approach or through the HLAMatchmaker eplet mismatch calculations of conformational HLA targets. In both direct and semidirect allorecognition, alloreactive recipient T cells recognize *intact* donor HLA molecules on the graft cells and induce tissue injury. Therefore, HLA class I molecular mismatches are expected to play a central role in the occurrence of these alloimmune responses as they are expressed on every donor cell.[24,33]

Although it cannot be tested in our observational clinical data analysis, a possible explanation for the lack of importance of HLA class I mismatches in the risk for rejection is the use of strong immunosuppression that primarily targets T cells. It could be hypothesized that the currently used immunosuppressive combination regimens are most efficient at suppressing HLA class I–directed immune responses, while the capacity to generate alloimmune responses against HLA class II mismatches could be less suppressed. This is also supported in the literature by the higher incidence of de novo anti-HLA antibodies against these 2 HLA molecules and the occurrence of ABMR and TCMR later after kidney transplantation.[13,34,35]

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Table 3. Adjusted Hazard Ratios for Graft Failure by PIRCHE-II Score Censored at the Time of de Novo HLA-DSA Occurrence

	Death-Censored Graft Failure (139 Events)		All-Cause Graft Failure (351 Events)	
	AHR (95% CI)	*P*	AHR (95% CI)	*P*
Total PIRCHE-II score	1.01 (1.00-1.02)	0.1	1.01 (1.00-1.01)	0.006[a]
PIRCHE-II score for HLA class I	1.01 (0.99-1.03)	0.3	1.01 (0.99-1.02)	0.2
PIRCHE-II score for HLA-A	1.01 (0.98-1.05)	0.5	1.01 (0.99-1.04)	0.3
PIRCHE-II score for HLA-B	1.04 (0.99-1.09)	0.1	1.02 (0.99-1.05)	0.1
PIRCHE-II score for HLA-C	1.00 (0.97-1.04)	0.9	1.00 (0.98-1.03)	0.9
PIRCHE-II score for HLA class II	1.01 (1.00-1.02)	0.1	1.01 (1.00-1.02)	0.006[a]
PIRCHE-II score for HLA-DRB1/3/4/5	1.02 (0.99-1.05)	0.2	1.02 (1.00-1.03)	0.1
PIRCHE-II score for HLA-DRB1	1.07 (1.01-1.14)	0.03[a]	1.05 (1.01-1.09)	0.008[a]
PIRCHE-II score for HLA-DRB3/4/5	1.01 (0.97-1.05)	0.6	1.02 (0.99-1.04)	0.2
PIRCHE-II score for HLA-DQA1/B1	1.02 (1.00-1.03)	0.1	1.02 (1.01-1.03)	0.002[a]
PIRCHE-II score for HLA-DQA1	1.02 (0.99-1.05)	0.2	1.02 (1.01-1.04)	0.01[a]
PIRCHE-II score for HLA-DQB1	1.04 (1.01-1.08)	0.02[a]	1.03 (1.01-1.06)	0.002[a]
PIRCHE-II score for HLA-DPBA1/B1	0.98 (0.93-1.03)	0.4	0.99 (0.96-1.02)	0.5
PIRCHE-II score for HLA-DPA1	0.96 (0.90-1.04)	0.3	0.98 (0.94-1.03)	0.4
PIRCHE-II score for HLA-DPB1	0.98 (0.90-1.07)	0.6	0.99 (0.94-1.05)	0.9

N = 893. Each row represents a separate multivariable analysis, and each hazard ratio is estimated per 10-point greater PIRCHE-II score. All multivariable models were adjusted for donor and recipient age, donor type, cold ischemia time, repeat transplantation, pretransplant HLA-DSA, panel-reactive antibody (%), and induction therapy (no induction vs basiliximab vs other treatment). Abbreviations: AHR, adjusted hazard ratio; HLA, human leukocyte antigen; HLA-DSA, donor-specific anti-HLA antibodies; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes by Recipient HLA Class II Molecules.
[a]Statistically significant value.

There is surprisingly little literature on the differential effects of currently used immunosuppressive agents on CD4- and CD8-positive lymphocytes to explain these observations in preclinical models. Although it has been suggested that priming of CD4-positive T cells via the indirect allorecognition pathway is resistant to the conventional immunosuppression used in kidney transplantation, further research is necessary to confirm these findings.[36]

This single-center study was performed in a predominantly White European population with general and continued access to immunosuppression, contributing to the specific alloimmune risk of this population. Thus, our results may not be generalized to a population of different ethnicity and without access to continued immunosuppression, at higher immunological risk. Also, the HLA-A, B, and DRB1 antigen matching used in the allocation scheme for this population through the Eurotransplant allocation system may have led to some bias that cannot be corrected for.

Moreover, an important limitation is that treating only the borderline changes in the setting of graft dysfunction and not having more information on histological findings other than acute TCMR, borderline TCMR (eg, BK nephropathy, recurrent disease), or the type of treatment used to treat TCMR could have impacted the graft outcome in our cohort. Further studies need to validate our findings in larger populations with different ethnicities and clinical settings and by use of in vitro assays.

Finally, the stringency used in the PIRCHE-II score is possibly too low, and future refinement of the stringency for prediction of the T-cell epitope targets and assessing the actual immunogenicity of the different peptide targets is warranted. This low stringency could also explain the small hazard ratios observed in our study.

In conclusion, this study suggests that PIRCHE-II scores for HLA-DRB1 and DQB1 molecules are consistently independent predictors for the development of acute TCMR and kidney graft failure. This study provides clinical evidence of the importance of the HLA class II molecular mismatches on the development of cellular alloimmunity in the absence of overt humoral alloreactivity. Our clinical findings suggest that in the presence of standard immunosuppression, donor HLA class II–directed immune responses play a crucial role in T-cell alloimmune activation from very early after kidney transplantation. Further validation of these findings and refinement of the exact allorecognition in early rejection episodes is warranted, taking into consideration the different immunogenicity of DRB1 and DQB1 molecular mismatches. These insights will help in better predicting the occurrence of the TCMR after kidney transplantation and could be used for improved risk stratification.

Supplementary Material

Supplementary File (PDF)

Figure S1: Violin plots of total PIRCHE-II score per number of HLA antigen and allele mismatches.

Table S1: Main demographic and clinical characteristics of the study population.

Table S2: Adjusted HRs for the occurrence of acute TCMR or acute/borderline TCMR in absence of concomitant C4d-positive ABMR according to the different PIRCHE-II scores in the cohort without pre-existing HLA-DSA, censored at the time of de novo HLA-DSA detection.

Table S3: Median PIRCHE-II scores in patients who developed TCMR and those without TCMR within the first 3 months after transplantation in the absence of HLA-DSA.

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Table S4: Adjusted HRs for the occurrence of early acute TCMR or acute/borderline TCMR within the first 3 months after transplantation according to the different HLA eplet mismatches in the HLA-DSA negative cohort censored at the time of de novo HLA-DSA occurrence.

Table S5: Adjusted HRs for graft failure by different PIRCHE-II scores in the cohort without pre-existing HLA-DSA censored at the time of de novo HLA-DSA occurrence.

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Support: This project is funded by the Research Foundation–Flanders (FWO) and the Flanders Innovation & Entrepreneurship agency (VLAIO), with a TBM (Toegepast Biomedisch onderzoek met een primair Maatschappelijke finaliteit) project (grant no. IWT.150199; "TEMPLATE"). Dr Naesens is senior clinical investigator of FWO (1844019N) and is also funded by a C3 internal grant from the KU Leuven University (grant no. C32/17/049). Dr Sprangers is a senior clinical investigator of FWO (1842919N). Dr Callemeyn is supported by a PhD fellowship grant from the FWO (1196119N). Dr van Loon is supported by a PhD fellowship grant from the FWO (1143919N). None of the funders had any role in study design, data collection, analysis, reporting, or the decision to submit for publication.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Acknowledgements: The authors thank the clinicians, surgeons, nursing staff, and the patients of University Hospitals Leuven and the biostatistician Jan van den Brand.

Prior Presentation: Portions of this work were presented at the American Society for Histocompatibility and Immunogenetics 47th Annual Meeting on September 28, 2021.

Peer Review: Received July 16, 2021. Evaluated by 3 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form April 9, 2022.

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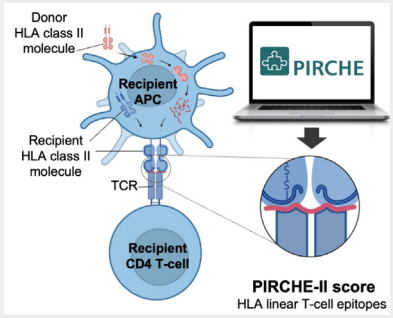
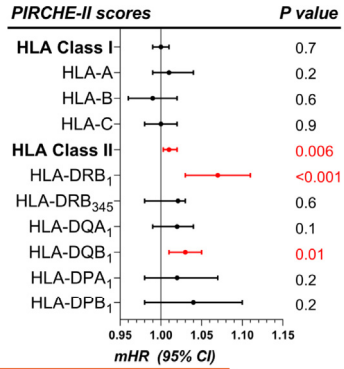
Predicted HLA T-Cell Epitope Targets and TCMR Posttransplantation

Setting & Participants	Exposures	Findings
University Hospitals Leuven, Belgium Kidney transplantations N = 893 NGS HLA genotyping	Predicted HLA T-Cell Epitope Targets	Associations With Acute TCMR/Borderline TCMR





CONCLUSION: This study illustrates the importance of HLA-DRB1 and DQB1 molecular mismatches on the development of TCMR even in the absence of HLA donor-specific antibodies.

TCMR: T Cell–Mediated Rejection

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@AJKDonline | DOI: 10.1053/j.ajkd.2022.04.009

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