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ORIGINAL ARTICLE

Assessment of human leukocyte antigen matching algorithm PIRCHE-II on liver transplantation outcomes

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Abstract

For liver transplantations, human leukocyte antigen (HLA) matching is not routinely performed because observed effects have been inconsistent. Nevertheless, long-term liver transplantation outcomes remain suboptimal. The availability of a more precise HLA-matching algorithm, Predicted Indirectly Recognizable HLA Epitopes II (PIRCHE-II), now enables robust assessment of the association between HLA matching and liver transplantation outcomes. We performed a single-center retrospective cohort study of 736 liver transplantation patients. Associations between PIRCHE-II and HLAMatchmaker scores and mortality, graft loss, acute and chronic rejection, ischemic cholangiopathy, and disease recurrence were evaluated with Cox proportional hazards models. Associations between PIRCHE-II with 1-year, 2-year, and 5-year outcomes and severity of acute rejection were assessed with logistic and linear regression analyses, respectively. Subgroup analyses were performed for autoimmune and nonautoimmune indications, and patients aged 30 years and younger, and older than 30 years. PIRCHE-II and HLAMatchmaker scores were not associated with any of the outcomes. However, patients who received transplants for autoimmune disease showed more acute rejection and graft loss, and these risks negatively associated with age. Rhesus mismatch more than doubled the risk of disease recurrence. Moreover, PIRCHE-II was inversely associated with graft loss in the subgroup of patients aged 30 years and younger with autoimmune indications. The absence of associations between PIRCHE-II and HLAMatchmaker scores and the studied outcomes refutes the need for HLA matching for liver (stem cell) transplantations for nonautoimmune disease. For

Abbreviations: ABO, blood type; aHR, adjusted hazard ratio; CI, confidence interval; dnDSA, de novo donor-specific antibody; DSA, donor-specific antibody; HLA, human leukocyte antigen; HR, hazard ratio; MMF, mycophenolate mofetil; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes; RAI, rejection activity index.

Eric Spierings and Caroline M. den Hoed contributed equally to this work.

autoimmune disease, the activated immune system seems to increase risks of acute rejection and graft loss. Our results may suggest the benefits of transplantations with rhesus matched but PIRCHE-II mismatched donor livers.

INTRODUCTION

Human leukocyte antigen (HLA) matching has reduced incidences of acute and chronic rejection and improved allograft survival for various types of organ transplantations, including kidney,[1–4] heart,[5] and bone marrow transplantation.[6] In contrast, studies on liver transplantation repeatedly demonstrated conflicting results,[7–12] which has resulted in the current clinical practice of matching liver donor and recipients only by blood group and not HLA compatibility. Short-term outcomes of liver transplantation are currently very good, but long-term outcomes remain suboptimal, partially because of the long-term use of immunosuppressants.[13] Better donor–recipient matching holds the potential to improve transplantation outcomes but is hampered by the shortage of donor grafts. With the prospect of biobankable liver cell sources, including human liver organoids and stem cells, the question of whether HLA matching could improve the survival of allogenic cells or tissue constructs is becoming increasingly relevant.[14]

In recent years, more precise methods for HLA matching have been developed. Multiple studies suggest that epitope-based matching algorithms such as HLAMatchmaker[15–17] may predict graft outcome in kidney,[18] lung,[19] cornea,[20] pediatric heart,[21] and pediatric liver transplantation.[22] Epitopes are parts of HLA molecules that may be present on different HLA antigens. Eplets, small polymorphisms on the outer domains of HLA molecules that differ between donor and recipient, are identified by HLAMatchmaker and presented in a continuous score.[15–17] In addition to the B cell–mediated immune response, T cell–mediated alloreactivity plays a role after solid organ transplantation. The direct pathway comprises T cell recognition of allogeneic HLA molecules on the surface of allogeneic cells. In the indirect pathway, T cells recognize mismatched HLA-derived epitopes processed and presented by nonallogeneic cells. Indirect T cell alloreactivity plays an important role in the humoral response toward HLA. Identification of these indirectly recognizable epitopes provides an alternative to epitope-based matching, which is what the Predicted Indirectly Recognizable HLA Epitopes (PIRCHE-II) algorithm does.[23] This algorithm can estimate the likelihood of HLA-derived peptides to bind HLA class II molecules (HLA-DR, HLA-DQ, and HLA-DP).[24] PIRCHE-II was found to correlate with kidney graft loss[25] and provides a risk classification for the anti-HLA de novo donor-specific antibody (dnDSA) formation after kidney,[26–28] pancreas,[28,29] and liver transplantations.[30,31]

Unfortunately, the results from the aforementioned studies investigating these algorithms for liver transplantation have limited use for clinical practice because they were limited in size and inclusion criteria[22] or only investigated anti-HLA donor-specific antibody (DSA) formation, but no clinical outcomes.[30,31] Also, previous studies generally grouped recipients with immunological (autoimmune) and other transplantation indications. Yet, mismatching may theoretically decrease disease recurrence and improve allograft survival in patients with autoimmune liver disease.[32] In general, the activity of the immune system may play a role in rejection reactions. The interplay between a more active immune system in younger patients and the use of immunosuppressants may influence and/or mask the effects of matching.[33] Therefore, we performed a single-center retrospective cohort study that included 736 patients who underwent primary liver transplantation to evaluate the predictive value of PIRCHE-II scores on liver transplantation outcomes in recipients of varying ages with autoimmune and other liver diseases.

PATIENTS AND METHODS

Study design and patients

We retrospectively included all consecutive adult patients who received a primary liver transplantation in the Erasmus Medical Center, Rotterdam, The Netherlands, between January 1, 2000, and June 30, 2019. Patients for whom HLA typing of donor and recipient were unavailable and patients who received combined liver and kidney transplantation were excluded. We used electronic patient records to collect patient and donor characteristics, including transplantation indication, immune serology, blood group and HLA typing, surgery details, immunosuppressant use, and follow-up markers. The selected timeframe allowed for a minimum follow-up of 1 year. As part of the standard care, all patients were seen at least once a year. The date of the last visit was considered the latest follow-up.

PIRCHE-II and HLAMatchmaker scores

Patients and donors were typed for their HLA by molecular typing methods as per transplant protocol. Typings

were reported at the serological split level for all loci following the EuroTransplant guidelines. If HLA-C and/or HLA-DQ were missing (see Table S1), typings for these loci were imputed for epitope calculations as previously reported.[34] PIRCHE-II scores for donor–recipient matches were calculated using the PIRCHE-II Matching Service (Pirche AG) in February 2021 as described previously.[25] Because PIRCHE-II and antibody formation are logarithmically correlated,[26] PIRCHE-II scores were transformed by natural logarithm (ln(PIRCHE-II +1)) for further analyses. For comparison, HLAMatchmaker scores were calculated using HLAMatchmaker (Version 2.0).

Outcome measures

Primary outcomes included histology-confirmed acute rejection (defined as rejection activity index [RAI] >2), histology-confirmed chronic rejection, radiology-confirmed ischemic cholangiopathy, graft loss (defined as retransplantation or graft-related death), and mortality (all cause except procedure related). Disease recurrence (except malignancies) was a secondary outcome. Follow-up ended if the patient received another transplantation (e.g., kidney) or a retransplantation, if the patient died or was lost to follow-up, or at the last check of the electronic patient records.

Statistical analyses

All statistical analyses were performed with R (Version 4.0.5; R Foundation for Statistical Computing) packages tableone (0.12.0), survival (3.2–11), survminer (0.4.9), and lmtest (0.9–38). All continuous variables were checked for normal distribution. Kaplan–Meier curves were used to visualize the effect of ln(PIRCHE-II), divided into quartiles, on patient survival and graft survival, and log-rank was used to test for significant differences.

For each of the primary outcomes, univariate Cox proportional hazards models with recipient and donor age and sex, ischemia times, ABO and rhesus mismatches, and ln(PIRCHE-II) as covariates to determine independent risk factors were used. In addition, multivariable Cox proportional hazards models were used, correcting for recipient and donor age and sex, ABO and rhesus mismatches, and autoimmune indication (primary sclerosing cholangitis, primary biliary cirrhosis, acute/chronic autoimmune hepatitis). In these multivariable models, interactions between ln(PIRCHE-II) and the most common individual induction therapies (steroids, mycophenolate mofetil [MMF], tacrolimus, cyclosporin, and basiliximab) were tested. Subgroup analyses were performed for patients with autoimmune indications and nonautoimmune indications and for autoimmune indications in combination with age 30 years and younger.

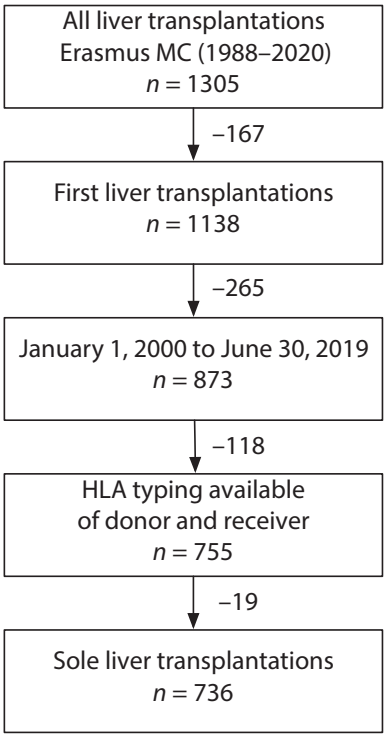

FIGURE 1 Flowchart of inclusion strategy

For both univariate and multivariable analyses, adjusted hazard ratios (aHRs) or hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated. The likelihood ratio test was used to determine the significance of interactions. Logistic regression analyses were performed to test the associations between ln(PIRCHE-II) and the primary outcomes after 1 year, 2 years, and 5 years of follow-up. Linear regression analysis was used to determine if there was an effect of ln(PIRCHE-II) on the severity of acute rejection (RAI score).

RESULTS

Study population

In the selected timeframe, a total of 873 primary liver transplantations were performed. Of these, 118 patients were excluded because of missing donor or recipient HLA typing, and a further 19 patients were excluded because they received combined liver and kidney transplantations. As a result, a total of 736 patients were included in this study (Figure 1).

The mean age of the recipients was 50.94 ± 12.26 years, and 479 (65.1%) were men. The untransformed PIRCHE-II and HLAMatchmaker scores had means of 85.88 ± 42.97 and 39.48 ± 12.45, respectively, and were significantly correlated (coefficient = 0.27, $p < 0.001$; Figure S1). Among the most common indications for transplantation were autoimmune diseases (229, 31.1%) followed by viral chronic active hepatitis (156, 21.2%)

and alcohol-induced cirrhosis (115, 15.6%). In addition to the primary disease, 215 patients (29.2%) were diagnosed with hepatocellular carcinoma, and 10 (1.4%) with cholangiocarcinoma (of which 8 had primary sclerosing cholangitis). Mean follow-up was 5.98 ± 5.47 years. Most patients retained their donor liver and were alive at the end of follow-up (438, 59.5%). The rest had died (181, 24.6%), received retransplants (86, 11.7%), or received another solid organ transplantation (9, 1.2%). A total of 22 patients (3.0%) were lost to follow-up, with a mean time to loss of follow-up of 6.82 ± 5.27 years. Except ischemia times and perioperative blood loss, all continuous variables were normally distributed. All baseline characteristics are summarized in Tables 1–4. The number of patients analysed (slashed) for each variable may differ from the total number of patients per (sub)group due to missing data or loss to follow-up.

Analyses

Patient survival and graft survival did not differ between quartiles of ln(PIRCHE-II) scores (Figure 2A,B) nor did acute and chronic rejection (Figure 2C,D).

In univariable analyses, the continuous ln(PIRCHE-II) and HLAMatchmaker scores were not associated with the primary outcomes mortality, graft loss, acute rejection, chronic rejection, and ischemic cholangiopathy (Tables 5 and 6). Recipient age was independently associated with mortality (HR = 1.03, 95% CI = 1.02–1.05, $p < 0.001$; see Figure S2 for causes of death), graft loss (HR = 0.98, 95% CI = 0.96–0.99, $p = 0.002$), and acute rejection (HR = 0.98, 95% CI = 0.97–0.99, $p = 0.001$). Likewise, an autoimmune transplantation indication was independently associated with mortality (HR = 0.65, 95% CI = 0.48–0.89, $p = 0.008$; see Figure S3 for causes of death), graft loss (HR = 1.47, 95% CI = 1.01–2.14, $p = 0.04$; see Table S2 for causes of graft loss), and acute rejection (HR = 1.74, 95% CI = 1.32–2.30, $p < 0.001$). Both were not independently associated with chronic rejection, ischemic cholangiopathy, or disease recurrence.

Logistic regression analyses revealed no associations between ln(PIRCHE-II) and any of the primary outcomes after 1 year, 2 years, and 5 years of follow-up (Table 7). Furthermore, ln(PIRCHE-II) was not correlated with severity of acute rejection, classified as RAI score, as determined by linear regression (coefficient = 0.22, $p = 0.23$).

Similarly, ln(PIRCHE-II) and HLAMatchmaker scores were not associated with any of the primary outcomes in multivariable analyses. However, in the ln(PIRCHE-II) models, recipient age was correlated with an increased risk of mortality (aHR = 1.03, 95% CI = 1.02–1.05, $p < 0.001$), yet decreased risks of graft loss (aHR = 0.98, 95% CI = 0.97–1.00, $p = 0.01$) and acute rejection (aHR = 0.99, 95% CI = 0.98–1.00, $p = 0.02$). Rhesus mismatch led to an increased risk of ischemic cholangiopathy (aHR = 2.19, 95% CI = 1.11–4.34, $p = 0.03$). Those who received transplants for autoimmune indications were at an increased risk of acute rejection (aHR = 1.63, 95% CI = 1.22–2.19, $p = 0.001$).

Subgroup analyses: Autoimmune and nonautoimmune indications

Multivariable subgroup analyses revealed no statistically significant associations between ln(PIRCHE-II) and any of the primary outcomes both for transplantations for autoimmune indications ($n = 229$) and transplantations for nonautoimmune indications ($n = 507$). Likewise, no associations between HLAMatchmaker

TABLE 1 General baseline characteristics divided by PIRCHE-II quartiles

	PIRCHE-II and ln(PIRCHE-II) quartiles				
	[0, 55.5]	(55.5, 78.2]	(78.2, 108]	(108, 273]	
	[0, 4.03]	(4.03, 4.37]	(4.37, 4.69]	(4.69, 5.61]	
Baseline characteristics, general	***n* = 184**	***n* = 185**	***n* = 183**	***n* = 184**	***p***
Follow-up, years, median [range]	4.01 [0.00, 20.06]	4.85 [0.00, 20.54]	4.32 [0.00, 20.57]	4.24 [0.00, 20.53]	0.52
Reason for end of follow-up, *n* (%)					0.83
Alive	111 (60.3)	111 (60.0)	99 (54.1)	117 (63.6)	
Deceased	44 (23.9)	44 (23.8)	50 (27.3)	43 (23.4)	
Loss to follow-up	7 (3.8)	6 (3.2)	5 (2.7)	4 (2.2)	
Other Tx	1 (0.5)	4 (2.2)	2 (1.1)	2 (1.1)	
Re-Tx	21 (11.4)	20 (10.8)	27 (14.8)	18 (9.8)	
PIRCHE-II score, mean (SD)	38.98 (11.87)	66.85 (6.67)	92.40 (8.20)	145.44 (31.25)	<0.001
HLAMatchmaker score, mean (SD)	36.34 (18.00)	38.52 (10.64)	39.22 (9.36)	43.84 (8.21)	<0.001

Abbreviations: ln(PIRCHE-II), natural logarithm of PIRCHE-II+1; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes II; SD, standard deviation; Tx, transplantation.

TABLE 2 Donor and recipient baseline characteristics divided by PIRCHE-II quartiles

Baseline characteristics, donor and recipient	PIRCHE-II and ln(PIRCHE-II) quartiles [0, 55.5] [0, 4.03] *n* = 184	 (55.5, 78.2] (4.03, 4.37] *n* = 185	 (78.2, 108] (4.37, 4.69] *n* = 183	 (108, 273] (4.69, 5.61] *n* = 184	*p*
Donor					
Age, years, mean (SD)	51.29 (15.65)	46.89 (15.52)	49.53 (15.69)	48.76 (14.82)	0.05
Sex, male, *n* (%)	101/184 (54.9)	88/185 (47.6)	88/183 (48.1)	99/184 (53.8)	0.36
Recipient					
Age, years, mean (SD)	50.03 (13.20)	51.29 (11.67)	51.43 (12.35)	51.01 (11.81)	0.70
Sex, male, *n* (%)	116/184 (63.0)	115/185 (62.2)	124/183 (67.8)	124/184 (67.4)	0.56
BMI, mean (SD)	26.18 (4.65)	25.62 (4.34)	25.76 (4.25)	26.00 (4.46)	0.62
MELD score at Tx, mean (SD)	22.87 (7.23)	23.19 (7.30)	22.25 (6.84)	23.38 (7.28)	0.59
Primary Tx indication, *n(%)*					0.02
Acute liver failure: autoimmune	2 (1.1)	7 (3.8)	0 (0.0)	0 (0.0)	
Acute liver failure: e.c.i.	6 (3.3)	2 (1.1)	4 (2.2)	2 (1.1)	
Acute liver failure: other	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	
Acute liver failure: viral	3 (1.6)	2 (1.1)	3 (1.6)	5 (2.7)	
Biliary atresia	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	
Budd–Chiari syndrome	0 (0.0)	1 (0.5)	2 (1.1)	1 (0.5)	
Chronic-active hepatitis: autoimmune	10 (5.4)	7 (3.8)	6 (3.3)	6 (3.3)	
Chronic-active hepatitis: viral	33 (17.9)	36 (19.5)	35 (19.1)	52 (28.3)	
Cryptogenic cirrhosis	11 (6.0)	13 (7.0)	14 (7.7)	16 (8.7)	
Genetic/metabolic disease	12 (6.5)	13 (7.0)	15 (8.2)	14 (7.6)	
Nonalcoholic steatohepatitis	14 (7.6)	9 (4.9)	4 (2.2)	12 (6.5)	
Polycystic liver disease	2 (1.1)	10 (5.4)	5 (2.7)	6 (3.3)	
Primary biliary cirrhosis	3 (1.6)	10 (5.4)	4 (2.2)	10 (5.4)	
Primary liver tumor, *n* (%)	0 (0.0)	5 (2.7)	1 (0.5)	1 (0.5)	
Primary sclerosing cholangitis, *n* (%)	49 (26.6)	43 (23.2)	43 (23.5)	29 (15.8)	
Secondary biliary cirrhosis, *n* (%)	3 (1.6)	1 (0.5)	2 (1.1)	3 (1.6)	
Toxic: alcohol induced, *n* (%)	29 (15.8)	24 (13.0)	40 (21.9)	22 (12.0)	
Toxic: drug induced, *n* (%)	3 (1.6)	2 (1.1)	3 (1.6)	2 (1.1)	
Other, *n* (%)	3 (1.6)	0 (0.0)	1 (0.5)	1 (0.5)	

Abbreviations: BMI, body mass index; e.c.i., et cause ignora; ln(PIRCHE-II), natural logarithm of PIRCHE-II+1; MELD, Model for End-Stage Liver Disease; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes II; SD, standard deviation; Tx, transplantation.

score and any of the primary outcomes were found in these subgroups. Furthermore, ln(PIRCHE-II) and HLAMatchmaker scores were not associated with disease recurrence in either subgroup.

As in the full cohort, the association between age and mortality remained intact in both subgroups (autoimmune: aHR = 1.04, 95% CI = 1.01–1.07, $p = 0.003$; nonautoimmune: aHR = 1.03, 95% CI = 1.01–1.05, $p < 0.001$). However, the association with graft loss remained only in the autoimmune group (aHR = 0.98, 95% CI = 0.95–1.00, $p = 0.04$), and the association with acute rejection was not significant in both subgroups. In addition, a male donor increased the risk of acute rejection in the nonautoimmune subgroup (aHR = 1.66, 95% CI = 1.13–2.44, $p = 0.01$), and an association between rhesus mismatch and disease recurrence was found in the autoimmune subgroup (aHR = 2.43, 95% CI = 1.05–5.62, $p = 0.04$).

Subgroup analyses: Young patients with autoimmune indications

There were no formal interactions between PIRCHE-II and age or age 30 years or younger. However, the

TABLE 3 Procedure and matching baseline characteristics divided by PIRCHE-II quartiles

Baseline characteristics, procedure and matching	PIRCHE-II and ln(PIRCHE-II) quartiles [0, 55.5] [0, 4.03] *n* = 184	 (55.5, 78.2] (4.03, 4.37] *n* = 185	 (78.2, 108] (4.37, 4.69] *n* = 183	 (108, 273] (4.69, 5.61] *n* = 184	*p*
Procedure					
Graft type n/total	n/179	n/181	n/175	n/178	0.003
Full, *n* (%)	179 (100.0)	172 (95.0)	171 (97.7)	177 (99.4)	
Split, *n* (%)	0 (0.0)	9 (5.0)	4 (2.3)	1 (0.6)	
Donor type *n*/total	*n*/184	*n*/184	*n*/183	*n*/184	0.55
Deceased, *n* (%)	41 (22.3)	51 (27.7)	48 (26.2)	52 (28.3)	
Living, *n* (%)	142 (77.2)	133 (72.3)	135 (73.8)	132 (71.7)	
Living related, *n* (%)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Cold ischemia time, h, median [range]	6.56 [3.27, 16.47]	6.20 [2.32, 13.92]	6.48 [2.90, 14.90]	6.57 [2.75, 14.80]	0.35
Warm ischemia time, h, median [range]	0.47 [0.25, 1.17]	0.47 [0.18, 1.17]	0.47 [0.23, 1.50]	0.48 [0.27, 1.42]	0.52
Total ischemia time, h, median [range]	6.98 [3.63, 17.63]	6.72 [2.67, 14.68]	7.07 [3.53, 15.38]	7.07 [3.22, 15.60]	0.39
Blood loss, L, median [range]	4.12 [0.00, 62.00]	3.50 [0.00, 39.00]	3.85 [0.50, 34.00]	3.50 [0.00, 58.00]	0.17
Donor–recipient matching, *n/total (%)*					
ABO mismatch	4/184 (2.2)	1/185 (0.5)	1/182 (0.5)	2/184 (1.1)	0.39
Rhesus mismatch	34/184 (18.5)	21/185 (11.4)	11/183 (6.0)	22/184 (12.0)	0.003
HBsAg mismatch	0/182 (0.0)	1/182 (0.5)	0/181 (0.0)	0/183 (0.0)	0.39
HCVAb mismatch	0/182 (0.0)	0/183 (0.0)	0/181 (0.0)	0/183 (0.0)	NA
CMVIgG mismatch	36/182 (19.8)	34/183 (18.6)	33/181 (18.2)	27/184 (14.7)	0.61
EBVIgG mismatch	8/163 (4.9)	3/163 (1.8)	6/156 (3.8)	5/165 (3.0)	0.48
HIVAb mismatch	0/182 (0.0)	0/182 (0.0)	0/180 (0.0)	0/176 (0.0)	NA

Abbreviations: ABO, blood group; CMVIgG, cytomegalovirus IgG; EBVIgG, Epstein-Barr virus IgG; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; HIVAb, human immunodeficiency virus antibody; ln(PIRCHE-II), natural logarithm of PIRCHE-II+1; NA; not available; PIRCHE-II Predicted Indirectly Recognizable HLA Epitopes II

multivariable subgroup analyses of patients with autoimmune indications and age 30 years or younger (n = 31) revealed an inverse association between ln(PIRCHE-II) with graft loss (12 events: aHR = 0.14, 95% CI = 0.03–0.63, p = 0.01). No such association was observed for the HLAMatchmaker score. The ln(PIRCHE-II) score was not associated with acute rejection (14 events). Donor age was associated with decreased graft loss (aHR = 0.95, 95% CI = 0.90–1.00, p = 0.049). Insufficient events occurred to reliably determine associations with mortality (5 events), chronic rejection (3 events), ischemic cholangiopathy (2 events), and disease recurrence (6 events).

Immunosuppressants

Finally, in the full cohort, no statistically significant interactions were found between ln(PIRCHE-II) and the most common individual induction therapy drugs (steroids, basiliximab, MMF, tacrolimus, and cyclosporin) for any of the primary outcomes in the multivariable analyses. Similarly, these interactions were not present for the HLAMatchmaker score.

DISCUSSION

In this single-center retrospective cohort study of 736 first liver transplantations, we investigated whether the PIRCHE-II score is a predictor of liver transplantation outcomes. For comparison, we also performed all analyses using the HLAMatchmaker score.

We found no associations between PIRCHE-II scores and mortality, graft loss, acute rejection, chronic rejection, ischemic cholangiopathy, or disease recurrence. Furthermore, we found no associations in the subgroups of patients with and without autoimmune indications. Similarly, there were no associations of HLAMatchmaker score with any of the outcomes in the full cohort and subgroups. The finding that both scores overall did not predict transplantation outcomes confirms previous

TABLE 4 Details of follow-up divided by PIRCHE-II quartiles

	PIRCHE-II and ln(PIRCHE-II) quartiles				
	[0, 55.5]	(55.5, 78.2]	(78.2, 108]	(108, 273]	
	[0, 4.03]	(4.03, 4.37]	(4.37, 4.69]	(4.69, 5.61]	
Follow-up	***n* = 184**	***n* = 185**	***n* = 183**	***n* = 184**	***p***
Deceased, *n*/total (%)	52/180 (28.9)	57/182 (31.3)	65/179 (36.3)	49/180 (27.2)	0.27
Age of death, years, mean (SD)	55.87 (12.26)	59.26 (10.43)	57.95 (9.29)	57.61 (12.17)	0.45
Cause of death *n*/total	*n*/52	*n*/57	*n*/65	*n*/49	0.64
Postoperative complications, *n* (%)	8 (15.4)	11 (19.3)	14 (21.5)	7 (14.3)	
Graft related, *n* (%)	11 (21.2)	10 (17.5)	11 (16.9)	4 (8.2)	
Medical comorbidity, *n* (%)	18 (34.6)	22 (38.6)	22 (33.8)	24 (49.0)	
Malignancy, de novo, *n* (%)	7 (38.9)	13 (59.1)	9 (40.9)	9 (37.5)	
Infection/sepsis, *n* (%)	5 (27.8)	4 (18.2)	7 (31.8)	7 (29.2)	
Organ failure, excluding liver, *n* (%)	2 (11.1)	0 (0.0)	2 (9.1)	2 (8.3)	
Hemorrhage, excluding cerebral, *n* (%)	3 (16.7)	1 (4.5)	0 (0.0)	1 (4.2)	
Cardiac event, *n* (%)	0 (0.0)	2 (9.1)	1 (4.5)	2 (8.3)	
Stroke, *n* (%)	1 (5.6)	1 (4.5)	2 (9.1)	1 (4.2)	
Other comorbidity, *n* (%)	0 (0.0)	1 (4.5)	1 (4.5)	2 (8.3)	
Procedure related, *n* (%)	5 (9.6)	2 (3.5)	2 (3.1)	2 (4.1)	
Recurrence: malignancy, *n* (%)	7 (13.5)	6 (10.5)	6 (9.2)	7 (14.3)	
Recurrence: primary disease, *n* (%)	0 (0.0)	4 (7.0)	5 (7.7)	2 (4.1)	
Other, *n* (%)	2 (3.8)	1 (1.8)	2 (3.1)	3 (6.1)	
Unknown, *n* (%)	1 (1.9)	1 (1.8)	3 (4.6)	0 (0.0)	
Re-Tx, *n* (%)	21 (11.4)	22 (11.9)	28 (15.3)	20 (10.9)	0.57
Loss to follow-up, *n* (%)	7 (3.8)	6 (3.2)	5 (2.7)	4 (2.2)	0.82
Ischemic cholangiopathy, *n* (%)	11 (6.0)	13 (7.0)	10 (5.5)	13 (7.1)	0.90
Acute rejection, *n* (%)	51 (27.7)	48 (25.9)	53 (29.0)	51 (27.7)	0.94
RAI, mean (SD)	5.00 (1.29)	4.82 (1.21)	4.92 (1.51)	5.25 (1.20)	0.40
Chronic rejection, *n* (%)	6 (3.3)	6 (3.2)	12 (6.6)	5 (2.7)	0.21
Disease recurrence, *n* (%)	18 (9.8)	26 (14.1)	22 (12.0)	24 (13.0)	0.63
Induction therapy regimen, *n* (%)					0.39
Steroids + calcineurin inhibitor	3 (1.6)	4 (2.2)	11 (6.0)	5 (2.7)	
Steroids + calcineurin inhibitor + IL2 inhibitor	49 (26.6)	61 (33.0)	62 (33.9)	63 (34.2)	
Steroids + calcineurin inhibitor + IL2 inhibitor + MMF	5 (2.7)	5 (2.7)	5 (2.7)	8 (4.3)	
Steroids + calcineurin inhibitor + MMF	11 (6.0)	9 (4.9)	14 (7.7)	11 (6.0)	
Steroids + IL2 inhibitor + MMF	99 (53.8)	97 (52.4)	83 (45.4)	89 (48.4)	
None	4 (2.2)	1 (0.5)	2 (1.1)	2 (1.1)	
Other ($n < 10$)	13 (7.1)	8 (4.3)	6 (3.3)	6 (3.3)	

Abbreviations: IL2, interleukin 2; ln(PIRCHE-II), natural logarithm of PIRCHE-II+1; MMF, mycophenolate mofetil; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes II; RAI, rejection activity index; SD, standard deviation; Tx, transplantation.

failures to show consistent advantages of HLA matching and is in line with results from a review of different studies on HLA matching and liver transplantation.[35] It also aligns with the current recommendation to not routinely use HLA matching for liver transplantation.

We found an important role for the activated immune system in patients who received transplants for autoimmune indications. These patients had a 74% (univariate) or 63% (multivariable) increase in risk of acute rejection and a 47% (univariate) increase in risk of graft loss, independent of PIRCHE-II or HLAMatchmaker scores. We further found a negative association between age and graft loss, which was most pronounced in the autoimmune group and may

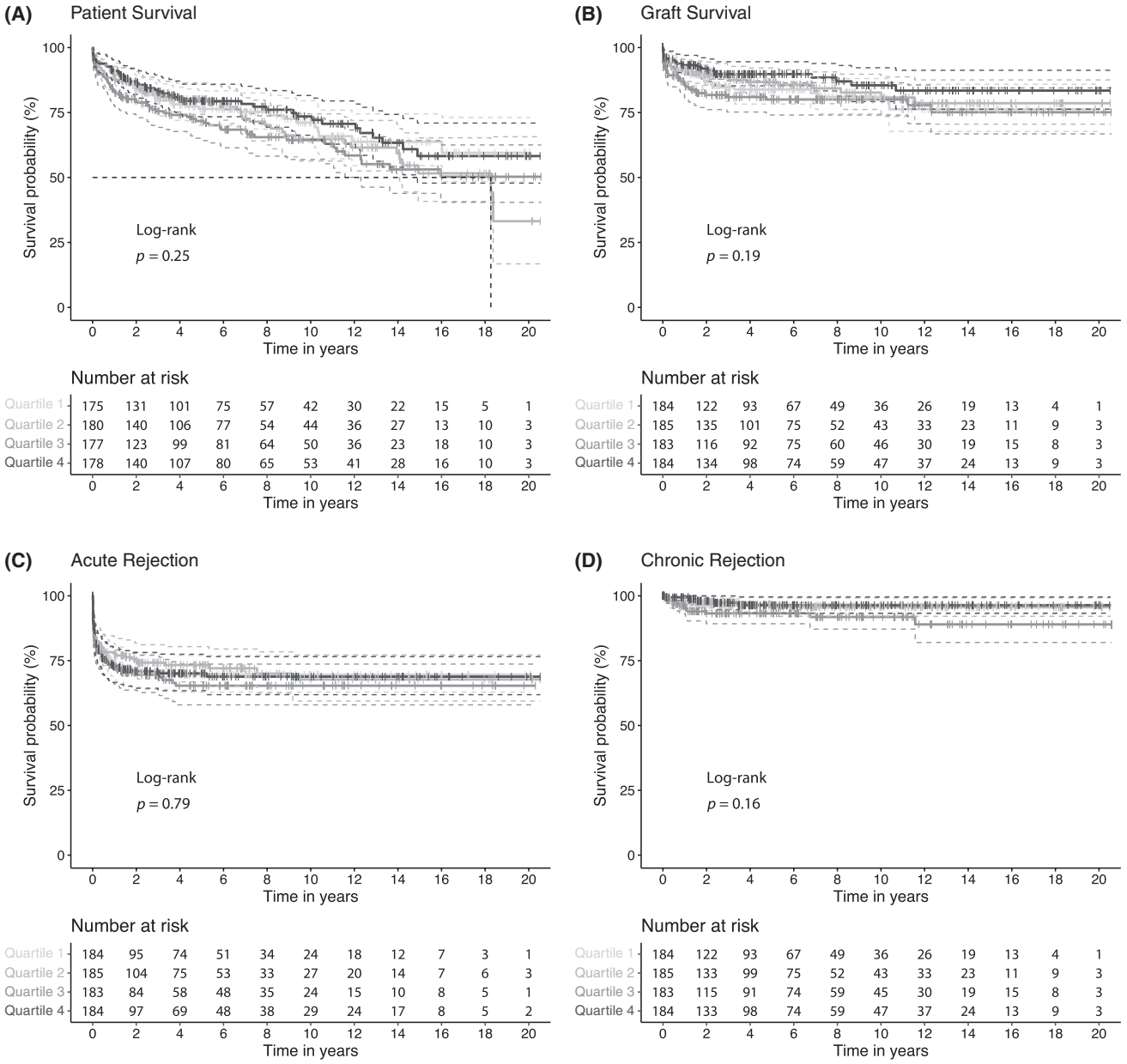

FIGURE 2 Kaplan–Meier curves for quartiles of the natural logarithm of PIRCHE-II+1 of (A) patient survival (excluding procedure-related death), (B) graft survival, (C) acute rejection, and (D) chronic rejection: quartile 1 = [0, 4.03], quartile 2 = (4.03, 4.37], quartile 3 = (4.37, 4.69], and quartile 4 = (4.69, 5.61]

TABLE 5 Univariable and multivariable Cox regression analyses for ln(PIRCHE-II) on the primary outcomes mortality (excluding procedure related), graft loss, acute rejection, chronic rejection, and ischemic cholangiopathy

Cox regression for ln(PIRCHE-II) versus outcome	Univariable		Multivariable		Events per total *n*
	HR (95% CI)	*p*	aHR (95% CI)	*p*	
Mortality	1.03 (0.81–1.31)	0.80	0.99 (0.78–1.26)	0.96	212/710
Graft loss	0.88 (0.65–1.19)	0.40	0.91 (0.67–1.24)	0.56	113/736
Acute rejection	1.10 (0.86–1.41)	0.46	1.17 (0.91–1.51)	0.21	203/726
Chronic rejection	1.11 (0.57–2.14)	0.76	1.11 (0.57–2.16)	0.75	29/736
Ischemic cholangiopathy	0.99 (0.60–1.63)	0.97	1.05 (0.63–1.76)	0.85	46/735

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; ln(PIRCHE-II), natural logarithm of PIRCHE-II+1; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes II

TABLE 6 Univariable and multivariable Cox regression analyses for HLAMatchmaker scores on the primary outcomes mortality (excluding procedure related), graft loss, acute rejection, chronic rejection, and ischemic cholangiopathy

Cox regression for HLAMatchmaker versus outcomes	Univariable		Multivariable		Events per total *n*
	HR (95% CI)	*p*	aHR (95% CI)	*p*	
Mortality	1.02 (0.92–1.13)	0.72	1.04 (0.93–1.17)	0.44	212/710
Graft loss	1.04 (0.90–1.21)	0.56	1.02 (0.88–1.19)	0.75	113/736
Acute rejection	1.11 (0.99–1.24)	0.07	1.09 (0.98–1.21)	0.13	203/726
Chronic rejection	1.03 (0.77–1.38)	0.83	1.03 (0.76–1.38)	0.86	29/736
Ischemic cholangiopathy	0.99 (0.79–1.26)	0.96	1.01 (0.80–1.27)	0.95	46/735

Note: aHR and HR given per 10-point increase of HLAMatchmaker score.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; ln(PIRCHE-II), natural logarithm of PIRCHE-II+1; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes II

TABLE 7 Logistic regression analyses for ln(PIRCHE-II) on the primary outcomes mortality (excluding procedure related), graft loss, acute rejection, chronic rejection, and ischemic cholangiopathy at the follow-up time points of 1 year, 2 years, and 5 years

Logistic regression for ln(PIRCHE-II) versus outcomes	OR (95% CI)	*p*	Events per total *n*
Mortality			
1 year	1.01 (0.65–1.55)	0.98	73/720
2 years	0.96 (0.65–1.40)	0.82	98/719
5 years	0.97 (0.70–1.34)	0.84	146/720
Graft loss			
1 year	0.93 (0.60–1.44)	0.75	70/720
2 years	0.88 (0.60–1.30)	0.54	88/719
5 years	0.87 (0.60–1.25)	0.44	101/719
Acute rejection			
1 year	1.11 (0.81–1.52)	0.50	174/732
2 years	1.05 (0.78–1.42)	0.73	189/731
5 years	1.06 (0.79–1.42)	0.68	199/730
Chronic rejection			
1 year	0.64 (0.31–1.33)	0.24	16/732
2 years	1.02 (0.47–2.19)	0.96	22/731
5 years	1.07 (0.52–2.19)	0.85	26/729
Ischemic cholangiopathy			
1 year	1.08 (0.57–2.08)	0.81	32/730
2 years	1.28 (0.67–2.45)	0.46	35/729
5 years	0.99 (0.56–1.73)	0.96	41/727

Abbreviations: CI, confidence interval; OR, odds ratio; PIRCHE-II, Predicted Indirectly Recognizable HLA Epitopes II; ln(PIRCHE-II), natural logarithm of PIRCHE-II+1

well result from decreasing reactivity of the immune system with increasing age. It was previously proposed that HLA matching could have adverse effects for patients with autoimmune diseases.[32] Although we did not find this in the full subgroup of recipients with autoimmune diseases, we observed an inverse association between PIRCHE-II and graft loss, thus a decreased risk of graft loss upon higher mismatch in young patients (30 years and younger). This may be explained by the autoreactivity in this group of patients, where more mismatches lower the risk of a recurring autoimmune reaction. We would also expect an inverse association with disease recurrence, but there were insufficient events in this subgroup to reach statistical significance. We further found that rhesus mismatch more than doubled the risk of autoimmune disease recurrence, putatively through further activation of the immune system. Interestingly, this is not among the known risk factors for autoimmune disease recurrence. To improve transplantation outcomes for autoimmune disease, it may thus be advisable to transplant a donor liver that is PIRCHE-II mismatched but rhesus matched.

Donor preformed and anti-HLA dnDSA have been shown to correlate with rejection in kidney,[36] heart,[37] pancreas,[38] and lung[37] transplantations.[31] Concordantly, it was recently shown that patients with class II anti-HLA dnDSA following liver transplantation had higher PIRCHE-II scores[30] and that PIRCHE-II and HLAMatchmaker scores predict class II anti-HLA dnDSA formation after liver transplantation.[31] In our cohort, we found no association between PIRCHE-II and rejection. Unfortunately, we did not have anti-HLA DSA information for the patients in our study to confirm such an association between PIRCHE-II and anti-HLA dnDSA.

It remains possible that associations between ln(PIRCHE-II) and any of the primary outcomes were masked by drug-induced immune suppression. However, the absence of interactions between ln(PIRCHE-II) and the individual immunosuppressant drugs used suggests that any such influence would be evenly spread over the cohort because most patients received similar combinations of induction therapy. A previous study of 41 patients undergoing calcineurin inhibitor withdrawal found that those with PIRCHE-II scores <68 (or ln(PIRCHE-II) 4.23) had a significantly decreased risk of graft loss compared with those with

scores PIRCHE-II ≥68.[39] Because of the retrospective nature of our study, it was not possible to accurately detect changes in (dosage) of medication and therapy withdrawal.

Our study stands out in the inclusion and follow-up of a large number of patients, the length of follow-up, the variety of primary transplantation indications, robustness of outcome parameters, and completeness of the data. Limitations of our study include the single-center, retrospective design; the absence of anti-HLA DSA information; and limited patient numbers in some of the analyzed subgroups.

In conclusion, we found no associations between PIRCHE-II and HLAMatchmaker scores and mortality, graft loss, acute rejection, chronic rejection, ischemic cholangiopathy, or disease recurrence in our single-center cohort of primary liver transplantations. This implies that HLA matching is not needed for upcoming biobankable liver cell sources, which greatly facilitates the generation of a biobank. Our findings of inverse associations between liver transplantation outcomes and age, especially in patients who received transplants for autoimmune disease, suggest that the activity of the immune system plays an important role and that PIRCHE-II may be an inverse predictor of liver graft loss in younger patients (age 30 years and younger) with autoimmune diseases. Further studies are needed to evaluate whether PIRCHE-II mismatching and rhesus matching should be used to improve outcomes for (young) patients with autoimmune disease.

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CONFLICT OF INTEREST

The University Medical Center Utrecht has filed a patent application on the prediction of an alloimmune response against mismatched human leukocyte antigen. Dr. Spierings is listed as inventor on this patent. The other authors declare to have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Sabine A. Fuchs, Eric Spierings, and Luc J. W. van der Laan conceptualized the study. Gautam Kok designed the database, collected the data, performed the analyses, and wrote the manuscript. Monique M. A. Verstegen and Luc J. W. van der Laan provided access to patient records. Herold J. Metselaar, Caroline M. den Hoed, and Wojciech G. Polak were involved in the clinical care of the patients. Roderick H. J. Houwen, Caroline M. den Hoed, and Edward E. S. Nieuwenhuis provided further clinical insights. Eric Spierings provided access to the Predicted Indirectly Recognizable HLA Epitopes II (PIRCHE-II) platform and calculated PIRCHE-II and HLAMatchmaker scores. All authors checked and edited the final version of the manuscript.

ETHICAL APPROVAL

This study was performed with medical ethical approval granted by the Medical Ethics Committee of Erasmus University Medical Center (Erasmus MC), Rotterdam (MEC-2014-060). Written informed consent for use of anonymized patient records for scientific research purposes was obtained from all patients prior to transplantation.

DATA AVAILABILITY STATEMENT

Syntax and output from analyses can be shared upon reasonable request to the corresponding author. Access to individual patient data is restricted.

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SUPPORTING INFORMATION

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