Impact of sensitization on waiting time prior to kidney transplantation in Germany

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Impact of Sensitization on Waiting Time Prior to Kidney Transplantation in Germany

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Background. Assignment of unacceptable HLA mismatches (UAMs) prevents transplantation of incompatible grafts but potentially prolongs waiting time. Whether this is true in the Eurotransplant Kidney Allocation System (ETKAS) and the Eurotransplant Senior Program in Germany is highly debated and relevant for UAM policies. **Methods.** Donor pool restriction due to UAM was expressed as percent virtual panel-reactive antibodies (vPRAs). Kaplan-Meier estimates and multivariable Cox regression models were used to analyze the impact of vPRA levels on waiting time and transplant probability during a period of 2 y in all patients eligible for a kidney graft unter standard circumstances in Germany on February 1, 2019 (n = 6533). Utility of the mismatch probability score to compensate for sensitization in ETKAS was also investigated. **Results.** In ETKAS, donor pool restriction resulted in significant prolongation of waiting time and reduction in transplant probability only in patients with vPRA levels above 85%. This was most evident in patients with vPRA levels above 95%, whereas patients in the acceptable mismatch program had significantly shorter waiting times and higher chances for transplantation than nonsensitized patients. In the Eurotransplant Senior Program, vPRA levels above 50% resulted in significantly longer waiting times and markedly reduced the chance for transplantation. Compensation for sensitization by the mismatch probability score was insufficient. **Conclusions.** Donor pool restriction had no significant impact on waiting time in most sensitized patients. However, despite the existence of the acceptable mismatch program, the majority of highly sensitized patients is currently disadvantaged and would benefit from better compensation mechanisms.
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INTRODUCTION

In patients on the waiting list for a solid organ transplant, sensitization against nonself-HLA, resulting from prior transplantation, transfusion, or pregnancy, is a major risk factor for early graft failure due to antibody-mediated rejection (AMR). Sensitization has traditionally been determined using complement-dependent cytotoxicity (CDC) assays. In CDC, cell panels carry different HLA to reflect the HLA diversity of the donor population and bind antibodies against specific HLA found in the serum of sensitized patients. The results are reported as percent panel-reactive antibodies (PRAs) to reflect the proportion of the donor population against which a patient is sensitized. In the last decade, more sensitive test systems, most notably the Luminex single-antigen bead (SAB) test, have been used in addition to the CDC assay. If in any of these tests, antibodies are found, which are thought to carry a high risk of early graft loss for a patient, the corresponding HLA are reported as unacceptable HLA mismatches (UAMs) to the allocation authorities such as Eurotransplant (ET). Consequently, organs carrying these HLA will not be offered to this patient. ET converts these UAMs into percent virtual PRA (vPRA) to reflect the proportion of the donor pool excluded for this particular patient. A patient with a 50% vPRA, for example, has only access to 50% of the donor pool. It is commonly accepted that the smaller the donor pool, the longer the patients have to wait until transplantation.

HLAs are always defined as unacceptable against which patients have anti-HLA antibodies in CDC assays, as transplantation of incompatible organs based on CDC is associated with a high risk of AMR and early graft loss.[1] Whether and how results from the SAB assays should be incorporated into UAM algorithms is a matter of much debate. Despite a recent consensus on UAM assignment in Germany,[2] most transplant centers have developed and kept their own center-specific policies.[3,4] It is well established that patients with preformed donor-specific anti-HLA antibodies (DSAs) detected by the more sensitive SAB assays, but not by CDC testing, carry an increased risk of early AMR and graft loss.[5-8] However, the predictive value of these DSAs for the individual patient is low, and many patients with DSAs have favorable long-term outcomes.[9] Integrating SAB test results in UAM algorithms is, therefore, challenging, as the disadvantages of prolonged waiting times might outweigh the benefits of better HLA compatibility.[3,10]

There are 3 fundamentally different approaches to sensitization within the ET allocation schemes. Allocation within the acceptable mismatch (AM) program is based on acceptable rather than unacceptable HLA and has proved great success in transplanting highly sensitized patients.[11,12] In the main ET kidney allocation system (ETKAS), a patient's sensitization is taken into account by integrating the PRA into mismatch probability (MMP), the latter being one of several criteria that ultimately sum up to a point-based match score.[13] In the past, the definition of the PRA for imputation into the MMP was not unequivocally defined, but mostly, the CDC-PRA was used. To better reflect the true donor pool restriction in the MMP, ET replaced the PRA with the vPRA by February 1, 2020, and implemented the latter to be exclusively based on UAM as defined by a patient's transplant center. With a maximum of 100 points, the contribution of the MMP to the final match score is limited. It has, therefore, been questioned whether the MMP score is sufficient to compensate for higher degrees of sensitization.[10,14] In the ET Senior Program (ESP), allocation is primarily based on ABO blood group, waiting time, and short ischemia times (ie, regional allocation). UAMs are only considered during matching in case donor HLA typing is already available. In all other cases, transplant centers have to perform HLA matching themselves. In the ESP, donor HLA diversity is limited due to a restricted regional donor pool.[10] Therefore, in the ESP, sensitization might even have a more pronounced effect on waiting time compared with the ETKAS.[14]

Because of very stringent entry criteria, the AM program is only accessible to around 2% of all patients listed for a kidney transplant within the ET area.[12] As sensitization is increasingly recognized as a modifiable risk factor in kidney transplantation (KTX) and SAB test results are increasingly integrated into UAM algorithms, there is a growing population of patients considered highly sensitized by the local transplant centers and HLA laboratories. As many of them do not qualify for the AM program, these patients potentially accumulate on the waiting lists. The AM program has no counterpart in any other allocation system worldwide. Moreover, due to the low number of organ donors in Germany, average waiting times are longer than in many other kidney allocation systems and longer than in any other ET member state.[15] ETKAS in its current form was introduced in 1996 and the ESP in 1999. Ever since, there has not been a thorough analysis on the impact of sensitization on waiting time under the special allocation circumstances of Germany.

We, therefore, selected all patients eligible for a kidney-only transplant in ETKAS and the ESP on February 1, 2019, in Germany and analyzed the impact of donor pool restriction (expressed as percent vPRA) on waiting time until transplantation within 24 mo of follow-up. We then compared waiting times and transplant probability between highly sensitized patients in ETKAS and the ESP and patients listed in the AM program. Moreover, we analyzed the value of the MMP as a compensatory mechanism for sensitization in ETKAS.

MATERIALS AND METHODS

Patients

All adult (>18 y) patients listed for a deceased-donor kidney-only graft in Germany on February 1, 2019, were evaluated for study inclusion (n = 8037). To avoid confounding due to prioritized allocation, the following patients were excluded: patients with pediatric bonus or a high-urgency status at any time during the observation period, patients listed for a kidney-after-other-organ transplantation, and patients relisted after early graft failure and granting of return of waiting time. All patients that remained in status nontransplantable throughout the period of observation, patients without a date of first dialysis in the ET database, and all patients who started dialysis after February 1, 2019 were also excluded (**Figure S1, SDC**, http://links.lww.com/TP/C475). Finally, all patients that received a kidney transplant via recipient-oriented allocation or a competitive center offer during the period of observation were excluded as well. Follow-up was until January 31, 2021. The reported clinical and research activities are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism." The study was approved by the ethics committee of Regensburg University (21-2212-104).

Data Collection

All data were provided by ET. The proportion of the donor pool excluded due to UAMs was expressed as vPRA. UAMs were defined by each transplant center's individual UAM policy for HLA A, B, C, DR, and DQ and reported to ET at the time of listing and updated when new UAM were identified. Calculation of vPRA was based on the ETRL reference database 3.0, which contains HLA data of 10 000 deceased donors used for KTX between 2012 and 2018 within the ET area.[16] For calculation of MMP, PRA was used as reported to ET with no strict definition before February 1, 2020, and vPRA based on UAM thereafter. The date of first dialysis was reported to ET by the transplant center at the time of listing.

Statistical Analyses

Continuous data are presented as median (interquartile range), and categorical data as absolute and relative

frequencies. Patients were grouped according to their vPRA recorded at the beginning of the observation period (February 1, 2019): 0%, >0%–50%, >50%–85%, >85%–95%, and >95%. Given the prioritized allocation based on acceptable rather than unacceptable HLA in the AM program, these patients were grouped separately for comparison irrespective of their documented vPRA. Based on data type, comparisons between groups were performed using the Kruskal-Wallis test, Mann-Whitney-U test, or Pearson's χ^2 test of independence. Association of vPRA categories and waiting time (time between the date of first dialysis and transplantation) was visualized by Kaplan-Meier curves and analyzed using univariate log-rank tests as well as multivariable Cox regression models. Patients were censored when they were permanently removed from the waiting list for reasons other than transplantation or at the end of the observation period. If a patient was listed in ETKAS on February 1, 2019, but changed to the ESP during the observation period, he was censored either on the day of transplantation in the ESP or on the day he left ETKAS (in case he was not transplanted). Patients who did not receive a transplant but changed to the ESP during the observation period were included for both ETKAS and ESP analyses. The multivariable Cox regression models were calculated by adding the known confounders age, gender, and ABO blood group as well as the 7 organ procurement regions (established by Deutsche Stiftung Organtransplantation [DSO]) and the ratio of active to total days on the waiting list (ratio A/T WT) as covariates. Hazard ratios and corresponding 95% confidence intervals (CIs) are reported as effect estimates. *P* values are 2-tailed, and $P < 0.05$ was considered significant. Analyses were performed using IBM SPSS version 26 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of Waiting List Patients

Of all patients listed in the ET database for a kidney-only graft on February 1, 2019 (n = 8037), n = 6533 were selected (**Figure S1, SDC**, http://links.lww.com/TP/C475). For 4806 (73.6%) patients, no UAMs were recorded (vPRA 0%) on February 1, 2019, whereas 744 (11.4%), 512 (7.8%), 167 (2.6%), and 154 (2.4%) patients had vPRA levels >0%–50%, >50%–85%, >85%–95%, and >95%, respectively. In addition, 150 patients (2.3%) were listed in the AM program (Table 1). There were significant differences in the proportion of patients in the different vPRA categories between the 7 German organ procurement regions ($P < 0.001$; **Figure S2, SDC**, http://links.lww.com/TP/C475). Patients with higher vPRA were more likely to be female. The majority of patients (n = 5824; 89.1%) were listed in ETKAS throughout the observation period. A total of 361 patients turned 65 between February 1, 2019, and January 31, 2021. Of these patients, n = 127 (35.2%) changed from ETKAS to the ESP. Waiting time (time since the first d of dialysis) on February 1, 2019, was significantly longer in patients with higher vPRA listed in both ETKAS and ESP (Table 1). Patients listed in the AM program had significantly shorter waiting times on February 1, 2019, compared with ETKAS patients with vPRA >85% (median 5.4 versus 6.6 y; $P = 0.009$).

During the observation period of 24 mo, 1453 patients (24.4% of all 5951 patients listed at any time in ETKAS) received a deceased-donor kidney transplant via ETKAS, including 121 patients transplanted in the AM program. In the ESP, 357 patients (50.4% of all 709 patients listed in the ESP at any time during the observational period) received a deceased-donor KTX (**Figure S1, SDC**, http://links.lww.com/TP/C475 and Table 1).

TABLE 1.

Characteristics of waiting list patients on 01.02.2019 according to vPRA category, n = 6533

vPRA	0%	>0%–50%	>50%–85%	>85%–95%	>95%	AM	*P*
n	4806	744	512	167	154	150	
Age, median (IQR) (y)	53 (44–60)	53 (44–60)	55(47–61)	54 (43–60)	55 (47–61)	51 (41–57)	<0.001[a]
Gender, n (%)							
Female	1429 (29.7)	353 (47.4)	310 (60.5)	114 (68.3)	103 (66.9)	83 (55.3)	<0.001[b]
ABO, n (%)							
A	1715 (35.7)	251 (33.7)	178 (34.8)	72 (43.1)	50 (32.5)	59 (39.3)	0.073[b]
AB	181 (3.8)	20 (2.7)	24 (4.7)	7 (4.2)	8 (5.2)	8 (5.3)	
B	724 (15.1)	93 (12.5)	69 (13.5)	24 (14.4)	24 (15.6)	27 (18.0)	
0	2186 (45.5)	380 (51.1)	241 (47.0)	64 (38.3)	72 (46.8)	56 (37.3)	
Always in ETKAS, n (%)	4258 (88.6)	671 (90.2)	453(88.5)	153 (91.6)	139 (90.3)	150 (100)	
Left ETKAS, n/n (%)[c]	99/269 (36.8)	9/30 (30.0)	15/36 (41.7)	3/10 (33.3)	1/9 (11.1)	0/7	
Always in ESP, n (%)	449 (9.3)	64 (8.6)	44 (8.6)	11 (6.6)	14 (9.1)		
WT ETKAS[d], median (IQR) (y)	4.6 (2.8–7.0)	5.6 (3.5–7.4)	5.6 (3.5–7.9)	6.6 (4.0–9.0)	6.7 (4.3–9.3)	5.4 (3.3–8.3)	<0.001[a]
WT ESP[e], median (IQR) (y)	3.1 (2.0–4.5)	3.8 (2.4–5.3)	4.0 (3.3–5.4)	4.8 (3.0–6.0)	7.7 (5.1–11.7)		<0.001[a]
TX ETKAS, n	929	166	142	59	36	121	
TX ESP, n	288	43	23	2	1		

[a]*P* values were calculated with Kruskal-Wallis.
[b]*P* values were calculated with Pearson's χ^2 test.
[c]Number of patients that left ETKAS for ESP/all patients that turned 65 between February 1, 2019, and January 31, 2021.
[d]Waiting time of all patients < 65 on February 1, 2019, or ≥65 but listed in ETKAS, n = 5951.
[e]Waiting time of all patients transplanted via ESP or listed in the ESP at the end of the observational period, n = 709.
AM, acceptable mismatch; ESP, Eurotransplant Senior Program; ETKAS, Eurotransplant Kidney Allocation System; IQR, interquartile range; TX, transplantation; vPRA, virtual panel-reactive antibody; WT, waiting time: time between the first d of dialysis and February 1, 2019.

Impact of vPRA on Waiting Time in ETKAS

In ETKAS, unadjusted Kaplan-Meier analyses revealed that waiting time (time from first dialysis until transplantation) was significantly longer in patients with vPRA >95% (median 13.2 y; 95% CI, 12.2-14.3) compared with patients in the lower vPRA categories: 0%: 10.7 y (95% CI, 10.5-10.9), $P < 0.001$; >0%–50%: 10.8 y (95% CI, 10.4-11.1), $P < 0.001$; >50%–85%: 11.0 y (95% CI, 10.5-11.5), $P < 0.001$; and >85%–95%: 11.8 y (95% CI, 10.8-12.8), $P = 0.018$. Waiting time in patients with vPRA >85%–95% was significantly longer only in comparison with patients without documented UAM (vPRA 0%; $P = 0.037$). Patients transplanted via the AM program had significantly shorter waiting times (7.1 y, 95% CI, 6.0-8.2 y) compared with patients in all other vPRA categories ($P < 0.001$; Figure 1).

The Cox multivariable regression model revealed that a vPRA between 85% and 95% reduced the chance for transplantation by 42% (hazard ratio [HR], 0.58; 95% CI, 0.44-0.76; $P < 0.001$) and a vPRA above 95% by 65% (HR, 0.35; 95% CI, 0.25-0.49; $P < 0.001$) compared with nonsensitized patients. Participation in the AM program, on the other hand, increased transplant probability by 34% (HR, 1.34; 95% CI, 1.09-1.65; $P = 0.006$). As expected, a higher proportion of active days on the waiting list and ABO blood group also had a strong influence on the transplant probability. Finally, the DSO regions had a significant impact on the chance for transplantation (Table 2).

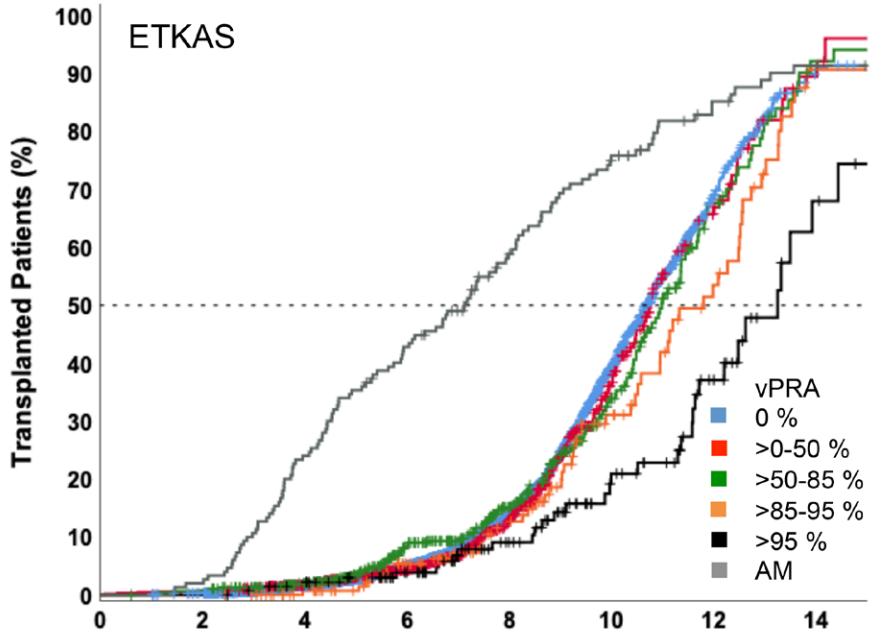
Impact of vPRA on Waiting Time in the ESP

In the ESP, unadjusted Kaplan-Meier analysis revealed a significant prolongation of waiting time in all patients with a vPRA above 50% compared with patients without documented UAM (vPRA 0%): 0% vPRA median 6.1 y (95% CI, 5.5-6.6); >0%–50%: 6.0 y (95% CI, 4.9-7.1), $P = 0.49$; and >50%–85%: 10.7 y (95% CI, 5.1-16.3), $P < 0.001$. Of the 29 patients with a vPRA >85%, only 3 patients were transplanted during the period of observation (vPRA >85%–95% $P = 0.004$, >95% $P < 0.001$ versus 0% vPRA) (Figure 2).

The Cox multivariable regression model revealed that the chance to receive an organ was dramatically reduced in ESP patients with a vPRA above 50%. Moreover, patient age had a small but significant impact with older age increasing transplant probability. Contrary to ETKAS, patients in the ESP with blood group AB had a significantly reduced chance for transplantation compared with patients with blood group A. The impact of the active time on the waiting list (ratio A/T WT) and the DSO regions on transplant probability were comparable with the analyses in ETKAS (Table 3).

Consideration of UAM During Allocation Is Incomplete

In ETKAS, the proportion of patients with at least 1 positive CDC-crossmatch (CM) during allocation



# at risk								
vPRA category								
0	4357	4334	3687	2462	1379	557	135	19
>0-50	680	675	610	457	281	101	28	4
>50-85	468	464	416	297	192	94	29	4
>85-95	156	156	144	111	79	43	23	3
>95	140	140	131	107	74	45	22	6
AM	150	147	114	84	52	29	13	7

FIGURE 1. Waiting time (time between first dialysis and transplantation) and vPRA in ETKAS. Patients listed in ETKAS on February 1, 2019 (n = 5951) were censored at the time of removal from the waiting list for reasons other than transplantation, at the time they left ETKAS for ESP or at the end of follow-up. AM, acceptable mismatch program; ESP, Eurotransplant Senior Program; ETKAS, Eurotransplant Kidney Allocation System; vPRA, virtual panel-reactive antibody.

TABLE 2.

Multivariable Cox regression model on transplant probability in ETKAS

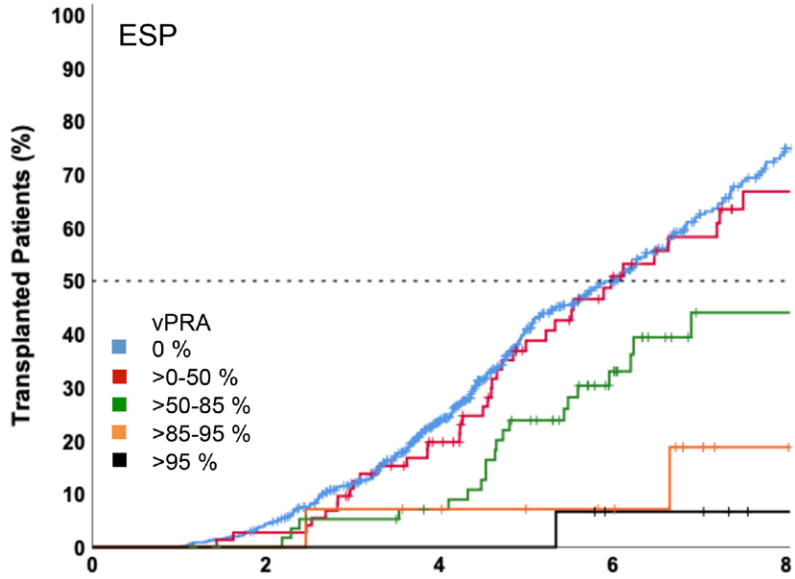
	HR (95% CI)	*P*
Age	1.00 (1.00-1.00)	0.934
Gender[a]	1.05 (0.94-1.17)	0.387
Blood group[b]		
AB	2.02 (1.60-2.54)	<0.001
B	0.53 (0.45-0.62)	<0.001
0	0.34 (0.3-0.39)	<0.001
Ratio A/T WT	3.94 (3.04-5.11)	<0.001
DSO region[c]		
2	1.19 (0.97-1.45)	0.096
3	2.19 (1.76-2.72)	<0.001
4	0.90 (0.75-1.08)	0.274
5	0.83 (0.67-1.04)	0.100
6	1.56 (1.31-1.87)	<0.001
7	1.37 (1.10-1.72)	0.006
vPRA category[d]		
>0%–50%	0.95 (0.8-1.12)	0.515
>50%–85%	0.91 (0.76-1.08)	0.283
>85%–95%	0.58 (0.44-0.76)	<0.001
>95%	0.35 (0.25-0.49)	<0.001
AM program	1.34 (1.09-1.65)	0.006

Reference categories
[a]Female,
[b]Blood group A,
[c]Region 1,
[d]0% vPRA.
AM, acceptable mismatch; CI, confidence interval; DSO region, organ procurement region defined by Deutsche Stiftung Organtransplantation; ETKAS, Eurotransplant Kidney Allocation System; HR, hazard ratio; Ratio A/T WT, ratio of active to total d on the waiting list; vPRA, virtual panel-reactive antibody.

increased significantly with increasing vPRA (Table 4 [A]). The number of positive CDC CMs per patient, however, was comparable across all vPRA categories (median 1). The proportion of patients for whom organ offers were declined at least once before transplantation was not different between patients with and those without UAM. However, the proportion of patients for whom at least 1 organ offer was declined for immunological reasons increased significantly with increasing vPRA (Table 4 [A]). The number of declined offers per patient was comparable between the groups (median 2). In the ESP, the proportion of patients for whom at least 1 organ was declined until transplantation was higher compared with ETKAS across all vPRA categories. Moreover, the proportion of patients for whom at least 1 organ had to be declined for immunological reasons increased considerably with increasing vPRA (Table 4 [B]).

MMP as Compensatory Mechanism for Sensitization in ETKAS

MMP takes into account the frequency of a patient's own HLA, ABO blood group, and sensitization determined by PRA levels with higher scores compensating for a lower chance to receive an organ with 0 or 1 HLA mismatches (**Figure S3, SDC**, http://links.lww.com/TP/C475). Simple linear regression revealed that before February 1, 2020, there was no correlation between percent vPRA and MMP, illustrating that the CDC-PRA does not at all reflect the true donor pool restriction determined by the vPRA (R^2 = 0.035; Figure 3A). After the uniform integration of the vPRA into the MMP on February 1, 2020, vPRA levels were able to explain 20% of the variance of the MMP



vPRA category	# at risk					
0	548	522	339	140	38	
>0-50	73	71	52	23	10	
>50-85	59	57	50	25	11	
>85-95	14	14	12	9	3	
>95	15	14	14	12	9	

FIGURE 2. Waiting time (time between first dialysis and transplantation) and vPRA in the ESP. Patients listed in the ESP at any time during follow-up (n = 709) were censored at the time of removal from the waiting list for reasons other than transplantation or at the end of follow-up. ESP, Eurotransplant Senior Program; vPRA, virtual panel-reactive antibody.

TABLE 3.

Multivariable Cox regression model on transplant probability in the ESP

	HR (95% CI)	*P*
Age	1.08 (1.05-1.10)	<0.001
Gender[a]	0.97 (0.76-1.22)	0.764
Blood group[b]		
AB	0.58 (0.34-0.99)	0.044
B	0.24 (0.17-0.36)	<0.001
0	0.39 (0.31-0.50)	<0.001
Ratio A/T ET	2.80 (1.89-4.16)	<0.001
DSO region[c]		
2	0.78 (0.52-1.15)	0.207
3	2.34 (1.43-3.83)	0.001
4	0.85 (0.57-1.26)	0.417
5	0.74 (0.50-1.11)	0.141
6	1.75 (1.2-2.54)	0.004
7	1.61 (1.03-2.51)	0.037
vPRA category[d]		
>0%–50%	0.79 (0.56-1.10)	0.157
>50%–85%	0.36 (0.29-0.56)	<0.001
>85%–95%	0.14 (0.03-0.56)	<0.001
>95%	0.03 (0.04-0.19)	0.006

Reference categories
[a]Female,
[b]Blood group A,
[c]Region 1,
[d]0% vPRA.
CI, confidence interval; DSO region, organ procurement region defined by Deutsche Stiftung Organtransplantation; ESP, Eurotransplant Senior Program; HR, hazard ratio; Ratio A/T WT, ratio of active to total d on the waiting list; vPRA, virtual panel-reactive antibody.

(R^2 = 0.201; Figure 3B). Given the design of the MMP equation, each of the 3 variables ABO blood group, HLA, and PRA can independently result in high MMP scores (**Figure S3, SDC**, http://links.lww.com/TP/C475). Blood group AB, for example, resulted in high MMP scores independent of vPRA levels (red dots in Figure 3B). This illustrates that compensation for sensitization via MMP is incomplete and occurs only in patients who do not already have high MMP scores due to a less common blood group or a rare HLA.

DISCUSSION

In our study, an increasing donor pool restriction due to UAM significantly prolonged waiting time and reduced the chance to receive a transplant in both ETKAS and the ESP. However, in ETKAS, this was only true for patients with a vPRA above 85%, whereas in the ESP, vPRA levels above 50% resulted in a significant reduction of the transplant probability. Highly sensitized patients listed in the AM program, on the contrary, had reduced waiting times compared with patients in ETKAS with an increased chance for transplantation.

These findings have several implications. As sensitization levels below a vPRA of 85% did not significantly prolong waiting times in ETKAS, a liberal UAM strategy up to a vPRA of 85% seems justified to enable optimal HLA compatibility and longevity of transplanted organs. In the ESP, however, donor pool restriction had a much stronger impact on transplant probability. As waiting times are shorter in the ESP than ETKAS, it is currently unclear whether sensitized patients above the age of 65 should remain in ETKAS.

AM patients had significantly shorter waiting times compared with all other patients awaiting transplantation in ETKAS. Allocation in the AM program occurs for all ET member states simultaneously and primarily does not take waiting times into account.[17] Therefore, this observation merely reflects the relatively short waiting times in non-German ET countries compared with the very long waiting times in ETKAS in Germany. Plans to adjust waiting times in the AM program to average national waiting times—as planned by ET—seem, therefore, justified. Most importantly, however, these findings highlight the clinical conundrum that the entry criteria for participation in the AM program are highly selective and disadvantage a patient population considered to be highly sensitized (vPRA > 85%) by the local HLA laboratories and transplant centers that is twice as large as the AM population (5% versus 2.3% in our cohort). The AM program currently requires at least 1 CDC-reactive anti-HLA antibody as an entry criterion and only accepts additional Luminex-based UAM if the respective anti-HLA antibodies can be explained by a documented sensitizing event such as a previous transplantation.[17] Even if this strategy is compelling, several aspects are problematic. First, reactivity in CDC testing is variable and can vanish over time in case a sensitizing event lies far back. Second, peak sera are often not available for determination of maximal CDC reactivity in the past. Third, information on sensitizing events is often not available due to incomplete donor HLA typing in the past or unavailable child fathers' HLA in case of women with previous pregnancies. Fourth, there is no evidence so far that anti-HLA antibodies without a documented sensitizing event are not clinically relevant. Given these challenges, the ET reference laboratory is planning to accept additional antigens for AM eligibility if they belong to a clear epitope reactivity pattern based on indisputably antibody-verified epitopes.[18] Additional Luminex reactivity that cannot be explained by an immunizing event will also be considered if mean fluorescence intensity values are ≥3000, and all unacceptable antigens sum up to a chance below 2% to receive an offer within ETKAS.

It has recently been shown that patients transplanted via the AM program have excellent long-term outcomes comparable with nonsensitized patients.[11] In contrast, highly sensitized patients listed in the AM program but transplanted in ETKAS based on UAM have significantly reduced long-term graft survival compared with patients transplanted via the AM program.[11,12] Therefore, the available evidence strongly supports the extension of a kidney allocation strategy based on acceptable rather than unacceptable HLA to all waiting list patients considered (highly) sensitized.

Although statistically significant, prolongation of waiting time in highly sensitized patients (vPRA > 85%) not listed in the AM program was moderate compared with less sensitized patients (median 12.5 versus 10.8 y; P < 0.001 log-rank test). The question of whether there is an upper limit for waiting time on dialysis can only be answered on an individual patient basis. The same is true for the risk of early AMR following a less stringent UAM assignment strategy. Data from other allocation systems, however, indicate that there is a subset of ultrasensitized

TABLE 4.

Consideration of UAM during allocation in ETKAS (A) and ESP (B) is incomplete

(A) vPRA	0%	>0%–50%	>50%–85%	>85%–95%	>95%	AM	*P*
n	929	165	142	58	35	124	
Pos. CDC-CM in donor center ≥1	18 (1.9)	3 (1.8)	5 (3.5)	5 (8.6)	4 (11.4)	5 (4.0)	0.001
Offered, not accepted ≥1: all reasons	531 (57.2)	87 (52.7)	80 (56.3)	39 (67.2)	19 (54.3)	72 (58.1)	0.526
Offered, not accepted ≥1: immunological reasons	20 (2.2)	13 (7.9)	7 (4.9)	4 (6.9)	9 (25.7)	22 (17.7)	<0.001
(B) vPRA	**0%**	**>0%–50%**	**>50%–85%**	**>85%–95%**	**>95%**	***P***	
n	288	43	23	2	1		
Pos. CDC-CM in donor center ≥1	7 (2.4)	2 (4.7)	1 (4.3)	0	0	0.914	
Offered, not accepted ≥1: all reasons	223 (77.4)	39 (90.7)	19 (82.6)	2 (100.0)	0	0.074	
Offered, not accepted ≥1: immunological reasons	14 (4.9)	9 (20.9)	7 (30.4)	0	0	<0.001	

Data are shown as n (%). All *P* values were obtained by Pearson's χ^2 test.
AM, acceptable mismatch; CDC-CM, complement-dependent cytotoxicity crossmatch; ESP, Eurotransplant Senior Program; ETKAS, Eurotransplant Kidney Allocation System; UAM, unacceptable HLA mismatches; vPRA, virtual panel-reactive antibody.

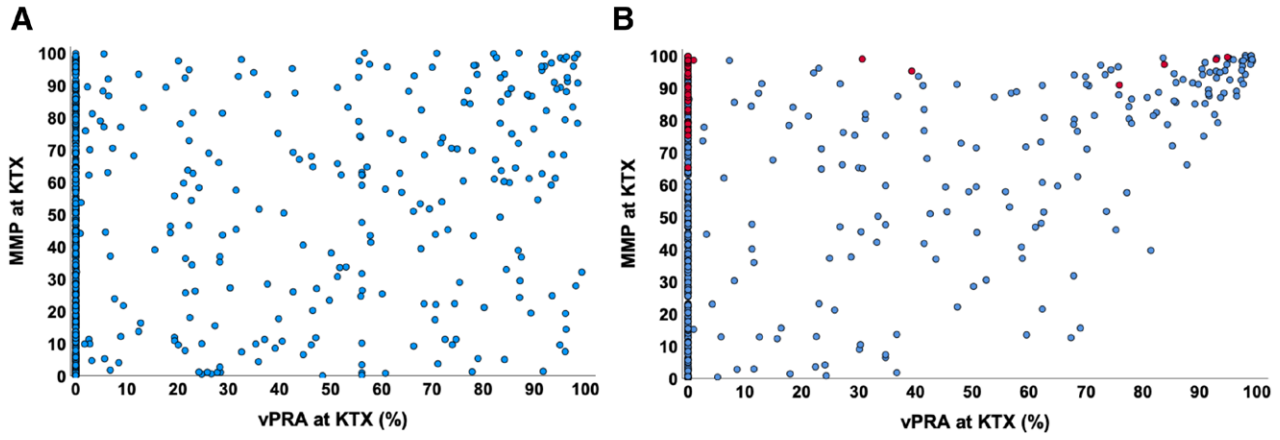


FIGURE 3. Association of % vPRA with the MMP score at transplantation the y before integration of vPRA into MMP calculation on February 1, 2020 (A) (n = 869) and the y after (B) (n = 584). In (B), patients with blood group AB are highlighted in red. KTX, kidney transplantation; MMP, mismatch probability; vPRA, virtual panel-reactive antibody.

patients that will hardly ever find a compatible donor due to additional barriers such as a rare own HLA.[12,19] This is very likely true for patients in both ETKAS and the AM program and can only be solved by a further extension of the donor pool, for example, via a pan-European collaboration[20,21] or, ultimately, by carefully designed desensitization programs. Moreover, all efforts should be undertaken to refine SAB test results and potentially reduce sensitization levels in these patients as was recently shown using various SAB kits in comparison or by integrating epitope analysis.[21,22]

Our study reveals important information on the prevalence of both positive crossmatches during allocation as well as organs rejected for immunological reasons by the transplant centers. Whereas the former was a relatively rare event, the high number of organs rejected for immunological reasons underscores the need for a full reporting of UAM to ET as well as consideration of all UAMs during organ allocation in both ETKAS and ESP. The upcoming introduction of the virtual crossmatch by ET will inevitably require a full UAM reporting, including HLA-DQA, -DPB, and -DPA.

Harmonization of the MMP by the uniform integration of the vPRA after February 1, 2020, moderately improved the correlation between vPRA and MMP. The observation time of 12 mo following adaptation of MMP in our study is not sufficient to gauge the impact of these changes on waiting time. However, due to the calculation algorithm, the MMP score adequately reflects sensitization only in some patients (Figure 3B). Moreover, the MMP is limited to a maximum of 100 points. As the median total match score at transplantation in Germany is above 800 (data not shown), it is unlikely that these changes will significantly improve compensation in sensitized patients in the long term.

In the ESP, no compensation mechanisms exist at all with a strong focus on short ischemia times during allocation. As HLA matching is equally important for long-term graft survival in older recipients[23] and lack of HLA incompatibility has a particularly detrimental impact in extended criteria donors,[24] these factors should be equally considered and compensated for in older recipients.

In both ETKAS and ESP, we observed significant differences in waiting time depending on the region in which the transplantation was performed. The 7 regions were established by the DSO for logistic purposes. As regional allocation is the main ESP priority to keep ischemia times short and there are 200 points for regional allocation in ETKAS, this finding did not come as a surprise and is hypothesized to be due to differences in regional organ procurement rates. Of note, differences in waiting times between regions were in the same magnitude than differences in waiting

time between nonsensitized and highly sensitized recipients (data not shown), illustrating that sensitization is only one of many variables that ultimately determine waiting time until KTX in Germany.

Our study has several limitations, most importantly, the relatively short observation time of 2 y, which limits generalizability of our findings. On the other hand, our study has important strengths. The careful selection of our patient population, the precise distinction between patients listed in ETKAS versus the ESP, and the comprehensive and up-to-date dataset allowed for a precise analysis of the impact of sensitization on waiting time in Germany.

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