Immunized Patients Face Reduced Access to Transplantation in the Eurotransplant Kidney Allocation System

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Background. The presence of donor-specific HLA antibodies before transplantation is associated with poor transplantation outcomes. Unacceptable antigens can be assigned for Eurotransplant kidney transplant candidates to prevent kidney offers against which the candidate has developed clinically relevant HLA antibodies. This retrospective cohort study aimed to assess to what degree unacceptable antigens affect access to transplantation in the Eurotransplant Kidney Allocation System (ETKAS). **Methods.** Candidates who underwent kidney-only transplantation between 2016 and 2020 were included (n = 19 240). Cox regression was used to quantify the relationship between the relative transplantation rate and virtual panel-reactive antibodies (vPRAs), which is the percentage of the donor pool with unacceptable antigens. Models used accrued dialysis time as the timescale; were stratified by country and blood group of patient and were adjusted for non-transplantable status, patient age, sex, history of kidney transplantations, and prevalence of 0 HLA-DR–mismatched donors. **Results.** Transplantation rates were 23% lower for vPRA 0.1% to 50%, 51% lower for vPRA 75% to 85%, and decreased rapidly for vPRA of >85%. Prior studies showed significantly lower ETKAS transplantation rates only for highly sensitized patients (vPRA of >85%). The inverse relationship between transplantation rate and vPRA is independent of Eurotransplant country, listing time, and 0 HLA-DR–mismatched donor availability. Results were similar when quantifying the relationship between vPRA and attainment of a sufficiently high rank for an ETKAS offer, suggesting lower transplantation rates for immunized patients are due to current ETKAS allocation. **Conclusions.** Immunized patients face lower transplantation rates across Eurotransplant. The current ETKAS allocation mechanism inadequately compensates immunized patients for reduced access to transplantation.

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INTRODUCTION

Eurotransplant (ET) allocates deceased-donor kidneys across 8 European countries, predominantly through the point-based ET Kidney Allocation System (ETKAS).[1] ETKAS awards geographical points to prevent extended cold ischemia times and country balance points to balance the international exchange of kidneys. Within these constraints, ETKAS awards priority points for accrued dialysis time to restrict maximum waiting times while emphasizing recipient–donor match quality by awarding points for matching HLAs between donor and recipient.

The presence of preformed HLA antibodies restricts a candidate's potential donor pool, and immunized patients could therefore face prolonged waiting times. This concern motivated ET to establish the Acceptable Mismatch (AM) program, which gives absolute priority to highly sensitized

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The study was conceptualized in joint discussions between all authors. H.d.F. acquired the data from the Eurotransplant database, designed initial statistical analyses of the data, and drafted the article. All authors critically revised the article, assisted in refining the analyses, and contributed to interpretation of the data. All authors approved the final version of the article. S.V. and F.S. arranged funding for the study.

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The data underlying this article are personal health information, which can be used by Eurotransplant for allocation development. Eurotransplant is not allowed to publicly release these data. For anonymous/de-anonymized versions of this data set, interested parties may send a data request to the Eurotransplant Kidney Advisory Committee.

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patients if a donor kidney with prespecified acceptable HLA mismatches becomes available. Over half of AM patients are transplanted within a year of AM entry,[2] but <10% of immunized patients meet AM entry criteria. The other 90% of immunized patients rely on ETKAS for access to transplantation.

ETKAS prioritizes immunized patients only indirectly through the mismatch probability (MMP), which is the probability that the next 1000 reported donors do not include a blood-type identical, HLA-acceptable kidney with at most 1 HLA mismatch. Criticisms of the MMP are that it is "underscored" in current ETKAS allocation[3] and that immunization increases the MMP only marginally for hard-to-match patients such as those with blood group AB.[4] Such criticisms suggest that the priority awarded to immunized patients in ETKAS is insufficient.

This motivated 2 prior studies toward the relationship between the relative transplantation rate and immunization with German cohorts. Both studies used virtual panel-reactive antibodies (vPRAs) to quantify immunization status, which is the percentage of historically reported donors against which the patient is immunized. Firstly, a 6-center study by Ziemann et al studied the impact of vPRA on time to transplantation with a 2012 cohort, using Cox proportional hazard (PH) models with time elapsed since 2012 as the timescale.[4] Adjusting for blood group, accrued dialysis time, and the vPRA, Ziemann et al reported that a 1% increase in vPRAs was associated with an approximate 1% decrease in transplantation rate. A limitation of the study by Ziemann et al is that the 2012 cohort precedes the actual implementation of vPRA for determining immunization status, such that those vPRA values may not reliably proxy the degree of immunization.

Zecher et al[5] studied the relationship between vPRA and transplantation rate with a 2019 German population–wide cohort, using time-on-dialysis as the timescale. Adjusting for recipient age, sex, blood group, percentage time being transplantable, allocation region, and enrollment in the AM program, Zecher et al found that only highly immunized patients (vPRA of >85%) had significantly lower transplantation rates (42% lower). These findings may not be generalizable to other ET countries because German transplant candidates require more than double the accrued dialysis time for transplantation through ETKAS than non-German candidates.

This study aims to quantify the relationship between vPRA and relative transplantation rate in the ET-wide cohort, using a 2016–2020 cohort of all kidney-only transplant candidates on the ETKAS waiting list. Unlike the previously mentioned studies, we were able to adjust for time-varying vPRA and nontransplantable status, allow for delayed entry of patients, and stratify models by blood group and recipient country. With adjustment for patient's age, sex, history of kidney transplantation, number of 0 HLA-DR–mismatched donors, and nontransplantable status, we found that all immunized patients have significantly lower transplantation rates across the ET region. Using time until a patient attains a rank high enough on a kidney match list to receive an offer as a secondary outcome, we found that immunized patients also face reduced organ offer rates. A policy implication of these findings is that MMP points inadequately compensate immunized patients for the reduction in their potential donor pool.

MATERIALS AND METHODS

The Ethical Review Board of the Eindhoven University of Technology approved this study (reference: ERB2023MCS1) and waived the need for informed consent. Strengthening the Reporting of Observational Studies in Epidemiology guidelines[6] were used to report this study.

Study Population and Data Set

Kidney-only transplant candidates on the ETKAS waiting list between January 1, 2016, and January 1, 2020, were included. This period was chosen as the median vPRA reported for immunized patients stabilized in 2016 (**Table S1, SDC**, http://links.lww.com/TP/C791), and coronavirus disease 2019 substantially reduced transplant activity in 2020.[7] Candidates waiting for a living transplantation and transplant candidates with additional priority in allocation (patients requiring combined transplantations, pediatric patients, and patients with high urgency bonus points) were not included. Our analyses use accrued dialysis time as the timescale, implying that the relative transplantation rate cannot be modeled when a patient is not on dialysis yet. Patients listed preemptively entered our analysis only on the date they started dialysis, and patients transplanted preemptively were excluded. Transplant candidates were censored when they turned 65 and became eligible for allocation through the ET Senior Program (ESP) or on entry of the AM program. Time-varying information (nontransplantable status and the vPRA) could be retrieved from monthly snapshots of the ET waiting list.

Outcome Variables

Time to transplantation was used as the primary outcome. Patients waiting for a transplant on January 1, 2020, were censored, as were patients delisted for reasons other than transplantation (waitlist death or removal).

An unmeasured confounder of the relationship between vPRA and the transplantation rate may be local (center) policies with respect to acceptance of kidney offers. For example, risk-averse centers/doctors may use a liberal definition of unacceptability (increasing the vPRA) and have strict requirements for donor–recipient match quality (turning down more kidney offers, thereby prolonging waiting time). A higher vPRA could then be associated with a decreased transplantation rate even if immunized patients are not disadvantaged in ETKAS allocation.

This motivated us to also assess the relationship between vPRA and kidney offer rate. Pivotal for this is careful definition of what constitutes an offer. The relationship between vPRA and time to actual offer can also be confounded by kidney offer acceptance policies because ETKAS candidate donor profiles can be used to specify that a candidate wishes to be excluded from potential kidney offers (eg, based on donor age, extended criteria donors, and HLA match quality). To avoid confounding bias in a time-to-offer analysis, we define time to offer as the first time a patient was ranked high enough on a kidney match list to have received an offer (ignoring offer turndowns because of donor profiles). This information is retrievable

from unfiltered match lists from the ET database. We refer to this outcome as "time to any offer." Time to any offer may be clinically less relevant because such offers include poor-quality kidneys turned down by many higher-ranked patients. Therefore, we also assess the relationship between vPRA and a "high-quality" offer. This "high-quality" offer is defined as a 0 HLA-DR–mismatched offer not rejected for quality reasons by ≥5 higher-ranked patients.

Adjustment Variables, Transformations, and Stratification

Multivariable Cox PH models were used to study the relationship between time to transplant and the vPRA. Used vPRAs were calculated against ETRL database, version 3.0, which includes HLA data on the serological split level for HLA-A, -B, -C, -DR, and -DQ. Antigens are defined as unacceptable by centers and local HLA laboratories, which can work with different definitions of unacceptability.[4] For over half of immunized patients, the set of unacceptable antigens changed while on the ETKAS waiting list. This motivated adjustment for vPRA as a time-varying covariate.

Cox models used time-on-dialysis as the timescale because ETKAS allocation is driven by accrued dialysis time and not accrued ETKAS waiting time. A potential issue with using time-on-dialysis as the timescale is that patients may have accrued dialysis time before the ETKAS listing. Such previously accrued dialysis time could bias the analysis because a standard Cox model would consider patients with previously accrued dialysis time to have been at risk of transplantation before they were actually listed with ET. We circumvent this source of bias with a Cox model that allows for delayed entry.

One prior study of the relationship between vPRA and the relative transplantation rate adjusted for continuous vPRA,[4] implicitly making the (unrealistic) assumption that a 1% increase in vPRA of 0% has the same effect as a 1% increase in vPRA of 99%. Another study allowed for a nonlinear effect of vPRA by discretizing vPRA (0%, 0.1%–50%, 50.1%–85%, 85.1%–95%, and >95%). Disadvantages to discretization are that patients in the same group (eg, 0.1%, 50%) are assumed to have the same reduction in relative transplant rate and that discretization of continuous variables wastes statistical information.[8] We therefore adjusted in our preferred specification for vPRA with spline terms, which models a continuous nonlinear effect for the vPRA (penalized spline terms with 8 degrees of freedom were used). We compare this strategy to adjustment for a fine-grained discretization of the vPRA (0%, >0%–25%, 25%–50%, 50%–75%, 75%–85%, 85%–95%, 95%–99%, 99%–100%) with which a clinical audience may be more familiar.

Confounders adjusted for include the patient age at listing, patient sex, and the number of previous kidney transplants (none, 1, or 2+). We also adjusted for the number of 0 HLA-DR–mismatched kidneys among the last 10 000 donors reported to ET (ignoring blood group identity). Patients with few such matches may be disadvantaged in ETKAS allocation because ETKAS allocation prioritizes the number of HLA-A, HLA-B, and HLA-DR mismatches. We chose to adjust for number of 0 HLA-DR–mismatched kidneys over adjustment for the MMP because the MMP is indirectly based on the vPRA, leading to multicollinearity issues. Finally, we adjusted for whether the patient was nontransplantable. Reporting of all adjusted for confounders is mandatory for entry into ETKAS, such that there were no missing data. We adjusted for penalized spline terms of continuous confounders with 4 degrees of freedom (age, number of 0 HLA-DR–mismatched kidneys).

Accrued dialysis time required to be ranked high enough in ETKAS for kidney offers depends strongly on the recipient country and blood group (because of a historical disadvantage for patients with blood group O and B in ETKAS[9]). For instance, the median time-on-dialysis until transplantation through ETKAS is 8.8 y in Germany, compared with only 2.3 y in Croatia. Within Germany, the median time is 10.4 y for blood group O compared with 7.8 y for blood group A. Such heterogeneity makes a PH assumption for blood group and recipient country implausible and motivated us to stratify Cox PH models by recipient country and blood group. Within Germany, we stratified on the basis of organ procurement region (7 in total) as ETKAS allocation prioritizes regional allocation and donor rates differ by region.

RESULTS

This study included 19 420 patients on the ETKAS waiting list between January 1, 2016, and January 1, 2020 (Table 1). In total, 1316 patients were excluded for preemptive transplantation (ie, transplantation without dialysis time). Unacceptable antigens were reported for approximately 21% of patients at patient registration or before the study started. For almost 21% of patients, the set of unacceptable antigens reported changed after their registration/January 1, 2016. In total, unacceptable antigens were reported for almost 30% of patients during the study period. Compared with nonimmunized patients, a higher vPRA was associated with female sex, being a retransplant candidate, more accrued dialysis time, and having spent more time on the waiting list than nonimmunized patients (p <0.001; see Table 1). **Figure S1** (**SDC**, http://links.lww.com/TP/C791) shows the distribution in vPRA for immunized patients per ET center. Although there is slight center-to-center variation in reported vPRAs, most variation in vPRA is at the patient level (and not explained by center-based policies in assigning antigens as unacceptable).

Reduced Transplantation Chances for Patients With High vPRA

The gray curve in Figure 1 shows the relationship between the relative transplantation rate and the vPRA. The relative transplantation rate decreases with higher vPRA. Adjusting for vPRA categories rather than with a vPRA spline term yields similar results (horizontal dotted lines, Figure 1). The relative transplantation rate for patients with vPRA 0.1% to 50% is estimated to be 23% lower than nonimmunized patients, and 51% lower for patients with vPRA 75% to 85%. For vPRAs exceeding 85%, the relative transplantation rate decreases rapidly, at 35% for patients with vPRA from 85% to 95% to only 6% for patients with vPRA 99% to 100%.

TABLE 1.

Characteristics for ETKAS patients, stratified by level of the vPRA

	First vPRA (registration or January 1, 2016)				Total
	0% (N = 15 319)	0.1%–49.9% (N = 1442)	50%–84.9% (N = 1534)	85%–100% (N = 1110)	Total (N = 19 405)
Patient sex					
Female	5097 (33.3%)	741 (51.5%)	828 (53.9%)	600 (53.1%)	7266 (37.4%)
Male	10 219 (66.7%)	699 (48.5%)	707 (46.1%)	529 (46.9%)	12 154 (62.6%)
Age at registration					
Median (Q1–Q3)	50 (41–57)	49 (40–56)	48 (40–55)	47 (39–54)	50 (41–56)
Recipient blood group					
A	5856 (38.2%)	528 (36.6%)	602 (39.2%)	445 (40.1%)	7431 (38.3%)
AB	690 (4.5%)	55 (3.8%)	80 (5.2%)	67 (6.0%)	892 (4.6%)
B	2215 (14.5%)	208 (14.4%)	228 (14.9%)	160 (14.4%)	2811 (14.5%)
0	6558 (42.8%)	651 (45.1%)	624 (40.7%)	438 (39.5%)	8271 (42.6%)
Accrued dialysis time at registration/ January 1, 2016 (y)					
Median (Q1–Q3)	2.0 (0.82–4.5)	3.0 (1.2–5.6)	3.1 (1.3–5.8)	3.7 (1.8–6.6)	2.2 (0.91–4.8)
0	14 366 (93.8%)	925 (64.1%)	658 (42.9%)	361 (32.5%)	16 310 (84.1%)
1	895 (5.8%)	462 (32.0%)	714 (46.5%)	567 (51.1%)	2638 (13.6%)
2+	58 (0.4%)	55 (3.8%)	162 (10.6%)	182 (16.4%)	457 (2.4%)
Final vPRA (before waitlist exit, or AM/ESP entry)					
0%	13 522 (88.3%)	68 (4.7%)	26 (1.7%)	5 (0.5%)	13 621 (70.2%)
0.1%–49.9%	868 (5.7%)	1049 (72.7%)	40 (2.6%)	2 (0.2%)	1959 (10.1%)
50%–84.9%	565 (3.7%)	199 (13.8%)	1068 (69.6%)	63 (5.7%)	1895 (9.8%)
85%–100%	364 (2.4%)	126 (8.7%)	400 (26.1%)	1040 (93.7%)	1930 (9.9%)
Changed vPRA during the study period (between January 1, 2016, and December 31, 2019)					
Yes	1797 (11.7%)	611 (42.4%)	841 (54.8%)	775 (69.8%)	4024 (20.7%)
No	13 522 (88.3%)	831 (57.6%)	693 (45.2%)	335 (30.2%)	15 381 (79.3%)
Status on January 1, 2020					
Transplanted (ETKAS)	5982 (39.1%)	535 (37.2%)	547 (35.6%)	242 (21.4%)	7306 (37.6%)
Death/delisted unfit	719 (4.7%)	79 (5.5%)	97 (6.3%)	68 (6.0%)	963 (5.0%)
Delisted	155 (1.0%)	12 (0.8%)	16 (1.0%)	11 (1.0%)	194 (1.0%)
Censored (AM entry)	89 (0.6%)	39 (2.7%)	118 (7.7%)	265 (23.5%)	511 (2.6%)
Censored (ESP)	1009 (6.6%)	108 (7.5%)	102 (6.6%)	63 (5.6%)	1282 (6.6%)
Censored (waiting)	7362 (48.1%)	667 (46.3%)	655 (42.7%)	480 (42.5%)	9164 (47.2%)
Time transplantable (y, between January 1, 2016, and December 31, 2019)					
Median (Q1–Q3)	1.1 (0.42–2.2)	1.4 (0.51–2.7)	1.3 (0.51–2.6)	1.3 (0.47–2.6)	1.1 (0.42–2.3)
Proportion time transplantable (between January 1, 2016, and December 31, 2019)					
Median (Q1–Q3)	0.91 (0.59–1.0)	0.95 (0.65–1.0)	0.95 (0.67–1.0)	0.96 (0.66–1.0)	0.92 (0.60–1.0)

The Kruskal-Wallis test was used for group comparisons of continuous variables and the Fisher exact test for group comparisons of categorical variables.
AM, Acceptable Mismatch; ESP, Eurotransplant Senior Program; ETKAS, Eurotransplant Kidney Allocation System; vPRA, virtual panel-reactive antibody.

Predicted Transplant Probabilities for a Synthetic Patient Across ET Regions and Blood Groups

To illustrate that the transplantation rates depends strongly on ET country and blood group of recipients, Figure 2 shows predicted transplant probabilities for a patient based on the Cox PH model fitted with delayed entry. We assumed that this synthetic patient was a 49-y-old male primary transplant candidate, had accrued 2 y of dialysis time at listing, and remained transplantable and nonimmunized (vPRA of 0%) during waitlist registration.

The predicted survival probability is almost 100% within the first 4 y of registration in all ET countries, except for Germany, where the predicted transplant probability is just over 25% (except for blood group AB). A similar plot showing predicted survival probabilities per German allocation region is shown in **Figure S2** (SDC, http://links.lww.com/TP/C791). Comparing survival probabilities across blood groups shows that patients with blood group AB have the highest transplantation rates in Austria, Hungary, and Germany, but not in The Netherlands and Belgium. This suggests that a PH assumption is implausible for blood group and highlights the need for stratifying Cox models by both blood group and location of recipients.

Sensitivity Checks

The relative transplantation rate was found to significantly decrease with increasing vPRA, and this decrease accelerates for vPRA values of >85%. Figure 3 shows sensitivity checks for this result. For panel A, models were reestimated separately for German and non-German patients. The inverse relationship between the vPRA and relative transplantation rate is reproducible in both regions. Discrepancies are that for German patients, the relative transplantation rate only appears to decrease for

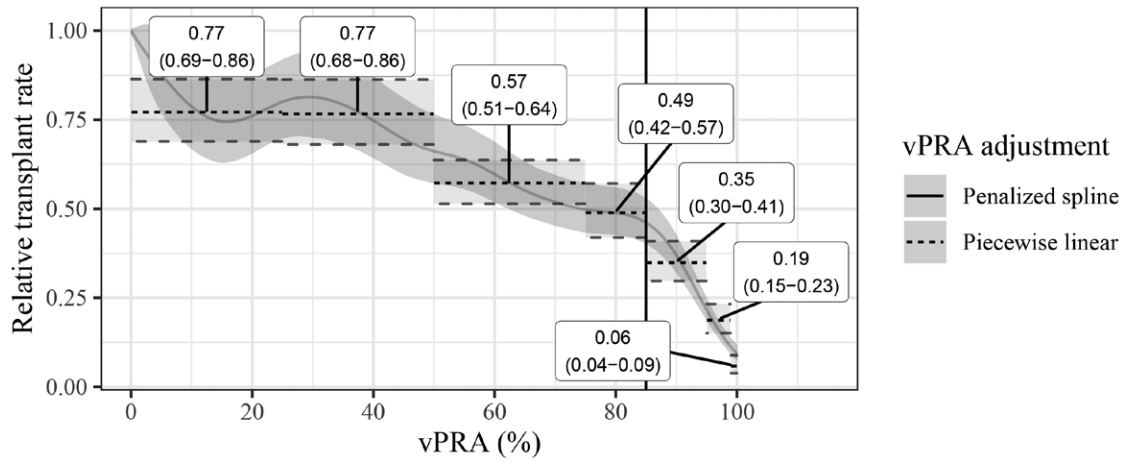

FIGURE 1. Relationship between the relative ETKAS transplantation rate and vPRA, estimated with a Cox PHs model with adjustment for time-varying vPRA. The solid gray line was estimated with penalized spline terms with 8 degrees of freedom, and the dotted lines were obtained by adjusting for discretized vPRA. Labels show point estimates for hazard ratios of vPRA categories, with 95% confidence intervals. ETKAS, Eurotransplant Kidney Allocation System; PH, proportional hazard; vPRA, virtual panel-reactive antibody.

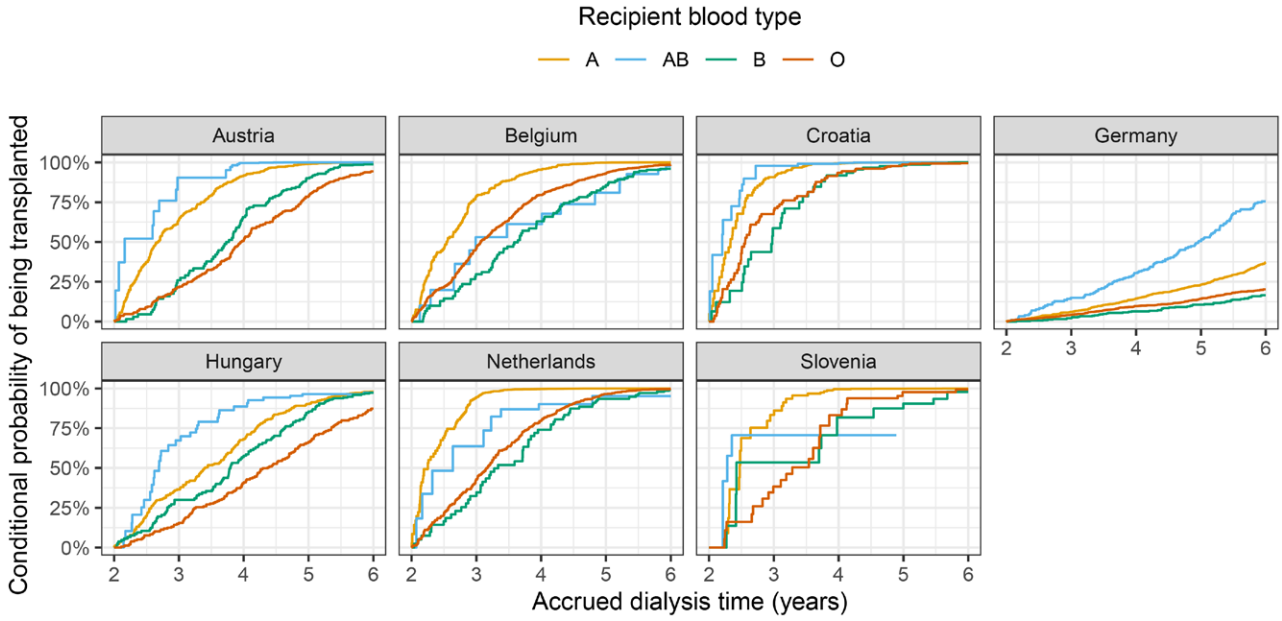

FIGURE 2. Predicted conditional probabilities of being transplanted within the next 4 y on entering the waitlist with 2 y of dialysis time, for combinations of blood group and listing country. Predictions were made for a 49-y-old male primary transplant candidate.

vPRAs >50%, whereas a decrease is visible over the whole domain for non-German patients. In panel B, we reestimated models separately in patients registered before and after the study starte (January 1, 2016). We assessed sensitivity to moment of listing because patients listed before January 1, 2016, are only included in our analysis if they are still waiting on January 1, 2016, thereby may poorly represent the kidney transplant candidate population. Estimated splines are again very similar. In panel C, we compared adjustment for vPRA as time-varying covariate compared with adjustment for the first or last reported vPRA per patient. Obtained curves differ minimally, although it appears that adjustment for time-fixed versions of the vPRA modestly increases effect sizes. Finally, in panel D, we assessed the heterogeneity of the relation with quantiles of the number of 0 HLA-DR–mismatched donors historically reported to ET. There appears to be little such heterogeneity.

Lower Chances for Time to Offer and Time to Transplant

Hazard ratios for time to any offer and time to high-quality offer are shown in Table 2. Obtained hazard ratios for time to any offer (first row, Table 2) differed minimally from hazard ratios obtained for the relative transplantation rate, at 28% lower for vPRAs 50% to 75%, 61% lower for vPRA 75% to 85%, and a strong decrease for vPRA of >85%. When using a high-quality offer as an outcome, the inverse relation also reproduces (second row), although estimated hazard ratios show some attenuation. For example, patients with vPRA 75%

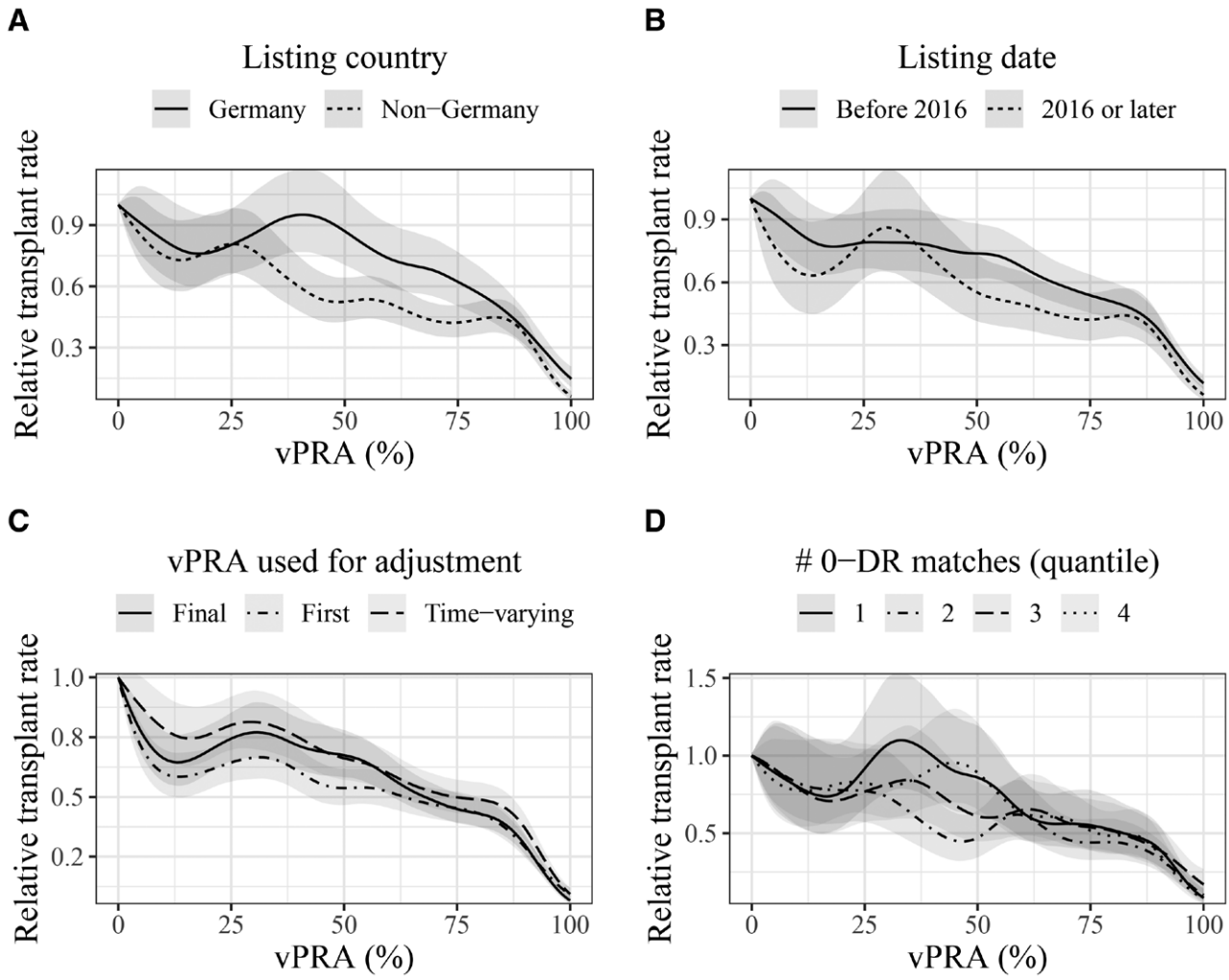

FIGURE 3. Robustness checks of the relationship between the vPRA and relative transplantation rate. A shows penalized spline terms estimated separately for German allocation regions and ET countries. B shows penalized spline terms estimated separately for patients already on the waiting list on January 1, 2016, vs those registered afterward. C shows how estimated spline terms depend on the definition of the vPRA. D shows how the relationship between the relative transplantation rate and vPRA varies by quantiles of the number of 0 HLA-DR–matchable donors. A, B, and D adjust for time-varying vPRA. ET, Eurotransplant; vPRA, virtual panel-reactive antibody.

TABLE 2.

Hazard ratios for the time-to-offer analyses, estimated with a Cox PHs model adjusting for time-varying vPRA

	vPRA category						
	0.1%–24.9%	**25%–49.9%**	**50%–74.9%**	**75%–84.9%**	**85%–94.9%**	**95%–98.9%**	**99%–100%**
Any offer	0.93 (0.85–1.01)	0.72 (0.66–0.79)	0.56 (0.51–0.6)	0.39 (0.35–0.44)	0.27 (0.24–0.31)	0.16 (0.14–0.19)	0.06 (0.05–0.08)
High-quality offer	0.88 (0.77–1.02)	0.90 (0.78–1.03)	0.72 (0.63–0.81)	0.67 (0.56–0.8)	0.51 (0.43–0.62)	0.46 (0.37–0.57)	0.2 (0.15–0.29)

PH, proportional hazard; vPRA, virtual panel-reactive antibody.

to 85% showed an approximate 33% lower high-quality offer rate than nonimmunized peers (compared with a 51% lower transplantation rate and 61% lower any offer rate).

Priority Obtained Through MMP Points

Prioritization of immunized patients in ETKAS is indirect through the MMP, that is, the probability that there is no blood-type identical, HLA-acceptable kidney with at most 1 HLA mismatch at HLA-A, -B, or -DR among the next 1000 donors. Current ETKAS allocation awards MMP points equal to the MMP, at most 100. Concerns have been voiced which leaves the MMP underscored relative to waiting time (33 points/y), geographic points (up to 300), and HLA match quality (up to 400 points).[3] Immunization may also not result in extra priority when

patients are already hard-to-match. To highlight this, we calculated for all immunized patients the difference between MMP points calculated on the basis of their actual vPRA and MMP points based on a vPRA of 0%. Figure 4 shows distributions of extra MMP points obtained on the basis of the vPRA. Immunization indeed only marginally increases prioritization of patients with rare blood groups (the median immunized patient with blood group AB receives <20 points). Moreover, even for the highest vPRA groups (vPRA of >85%) >25% of patients receive <50 extra MMP points based on the vPRA. The number of extra points awarded on the basis of the vPRA thus appears meager compared with the median number of ETKAS points needed for transplantation through ETKAS, which exceeded 900 points between January 1, 2016, and January 1, 2020.

DISCUSSION

Over 90% of immunized ET kidney transplant candidates rely on ETKAS for access to transplantation. Concerns exist that compensation in ETKAS for immunization through the MMP is inadequate[3-5] and that immunized patients face extended waiting times. This motivated us to study the relationship between the vPRA and relative transplantation rate in ETKAS. Previously, this relationship was studied in German cohorts,[4,5] and our study is the first to quantify the relationship with a ET-wide cohort.

We studied the relationship with Cox regression stratified by blood group and country of recipients, using accrued dialysis time as the timescale, allowing for delayed entry with adjustment for vPRA as a time-varying variable. This study design avoids some methodological issues of the previous studies. Dialysis time is a more fitting timescale than the time-since-listing by Ziemann et al, because ETKAS allocation prioritizes on the basis of accrued dialysis time, not waiting time. Zecher et al used total accrued dialysis time as the outcome, with adjustment for vPRA at study start (on January 1, 2019). This appears problematic as over half of the immunized patients modify the set of unacceptable antigens during registration, making the vPRA not predetermined to total waiting time. Our analyses avoided this issue by allowing for a delayed entry of transplant candidates (not modeling transplantation rates before January 1, 2016) and adjustment for time-varying vPRA.

Results show that a higher vPRA is associated with significantly reduced relative transplantation rates. Unlike prior studies, reductions in transplantation rates are already highly significant for vPRAs <85%, with transplantation rates 23% lower for vPRAs from 0.1% to 50% (p <0.001) and 51% lower for vPRAs 75% to 85% (p <0.001). Patients with vPRA of >85% have even lower transplantation rates (up to 94% lower for vPRA >99%). Such patients may not be eligible for the AM program as AM entry criteria require a vPRA of >85% based solely on complement-dependent cytotoxicity (CDC) reactivity or detection by solid phase assays in combination with documentable evidence of a sensitization event.[2] Sensitivity checks showed that the inverse relationship between vPRA and the transplantation rate generalizes beyond Germany, is independent of whether the patient was listed before or after 2016, independent of the type of vPRA adjusted for (time-varying, first vPRA, or final vPRA), and independent of difficulty of finding a high-quality match (proxied by the number of 0 HLA-DR–mismatched donors). Immunized ETKAS kidney-only transplant candidates thus experience longer time to transplantation than their nonimmunized peers.

A limitation to our study is that attention was restricted to patients eligible for ETKAS only, with patients excluded on AM enrollment or ESP eligibility. Zecher et al instead adjusted in their analyses for enrollment in the AM program. We instead censored patients on entry into the AM program because AM allocation ignores accrued dialysis

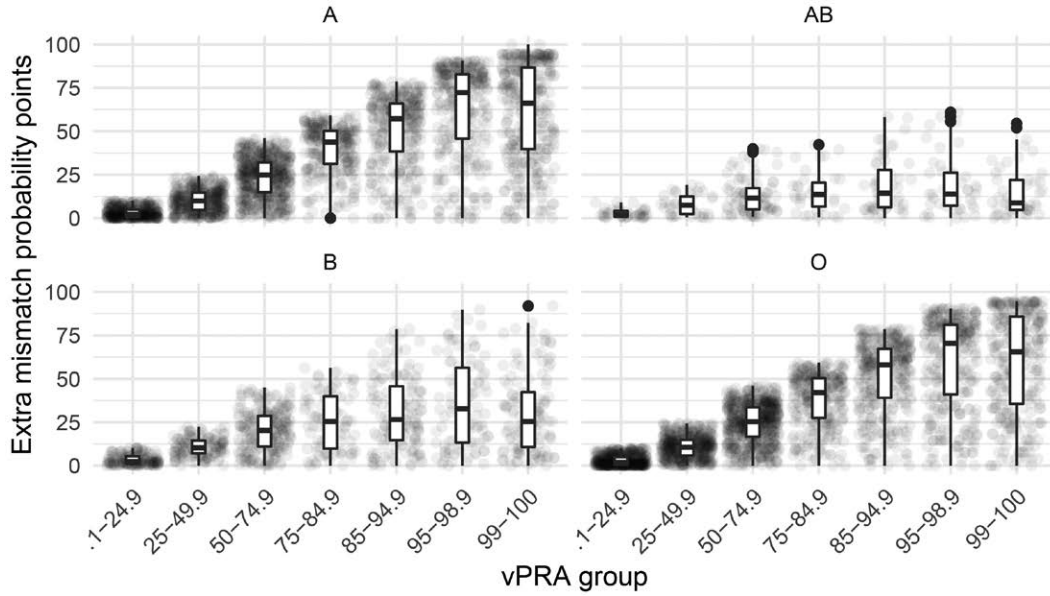

FIGURE 4. MMPs immunized patients obtained on the basis of the vPRA. Each dot represents a patient in the cohort. Statistics were obtained by calculating the difference in MMP calculated with the actual vPRA and with a vPRA of 0%. MMP, mismatch probability point; vPRA, virtual panel-reactive antibody.

time, making the PH assumption implausible. Time to transplant for ESP patients was studied by both Ziemann et al and Zecher et al. We did not pursue this because most immunized German patients opt-out of ESP, and it is unclear how to correct for such selection bias. Moreover, elderly patients outside Germany are not required to choose between ESP and ETKAS and can receive offers through both. Another limitation to our study is that sensitization against HLA-DQA, -DPB, and -DPB may further limit transplantation because of positive physical crossmatches, but these antibody specificities were not captured in the vPRA used.

Secondary analyses showed that the vPRA is also inversely related to ETKAS kidney offer rates, both when considering any offer as an outcome and when considering only high-quality offers as an outcome. This suggests that the reduced transplantation rate for immunized patients is also inherent to ETKAS allocation. We showed that the number of extra MMP points currently received on the basis of the vPRA is marginal for most immunized patients. A potential policy implication of our work is thus that it seems worthwhile to revise the number of points awarded based on the MMP. The maximum number of MMP points received has remained capped at 100 since 1996,[1] an era with a completely different kidney waitlist composition. One option could be to increase the maximum points awarded for the MMP >100, let the number of MMP points awarded depend nonlinearly on the MMP, and make the MMP blood group specific. With such amendments, the MMP comes closer to the concept of "matchability," which was introduced in the United Kingdom to prioritize hard-to-match kidney transplant candidates. An alternative option is to disentangle the MMP into separate prioritization mechanisms for genetically hard-to-match recipients and immunized patients. This brings allocation closer to kidney allocation in the United States, where prioritization for immunized patients is directly based on the vPRA with a sliding scale.[10]

Finally, our work can help inform decision-making on whether to assign non-CDC reactive antigens as unacceptable. For ETKAS, such decisions are made on the basis of personalized risk assessments by doctors and local HLA laboratories, not on criteria prescribed by ET. Our finding that increases in vPRA of >85% strongly decrease the relative transplantation rate may, for instance, motivate local transplant professionals to be cautious in assigning antigens without CDC reactivity as unacceptable for patients with already high vPRA (>85%). In this way, our work could help avoid situations in which caution of local transplant teams unintentionally leads to extreme waiting times.

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