



# Kidney transplantation and withdrawal rates among wait-listed first-generation immigrants in Italy

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**Background:** Multiple barriers diminish access to kidney transplantation (KT) in immigrant compared to non-immigrant populations. It is unknown whether immigration status reduces the likelihood of KT after wait-listing despite universal healthcare coverage with uniform access to transplantation. **Methods:** We retrospectively collected data of all adult waiting list (WL) registrants in Italy (2010–20) followed for 5 years until death, KT in a foreign center, deceased-donor kidney transplant (DDKT), living-donor kidney transplant (LDKT) or permanent withdrawal from the WL. We calculated adjusted relative probability of DDKT, LDKT and permanent WL withdrawal in different immigrant categories using competing-risks multiple regression models. **Results:** Patients were European Union (EU)-born ( $n = 21\,624$ ), Eastern European-born ( $n = 606$ ) and non-European-born ( $n = 1944$ ). After controlling for age, sex, blood type, dialysis vintage, case-mix and sensitization status, non-European-born patients had lower LDKT rates compared to other immigrant categories: LDKT adjusted relative probability of non-European-born vs. Eastern European-born 0.51 (95% CI: 0.33–0.79;  $P = 0.002$ ); of non-European-born vs. EU-Born: 0.65 (95% CI: 0.47–0.82;  $P = 0.001$ ). Immigration status did not affect the rate of DDKT or permanent WL withdrawal. **Conclusions:** Among EU WL registrants, non-European immigration background is associated with reduced likelihood of LDKT but similar likelihood of DDKT and permanent WL withdrawal. Wherever not available, new national policies should enable coverage of travel and medical fees for living-donor surgery and follow-up for non-resident donors to improve uptake of LDKT in immigrant patients, and provide KT education that is culturally competent, individually tailored and easily understandable for patients and their potential living donors.

## Introduction

Migrants comprise a growing minority population in the European Union (EU). In January 2020, there were 23 million subjects from outside the EU living in EU countries.<sup>1</sup> This has resulted in an increase of non-European migrants with end-stage kidney disease (ESKD), accounting for more than 20% of patients on dialysis or enrolled in kidney transplant programs.<sup>2</sup> Kidney transplantation (KT) is the gold standard renal replacement therapy (RRT) for eligible patients with ESKD providing improved length and quality of life relative to dialysis.<sup>3</sup> Because equity is a major principle in organ transplantation, recommendations to address potential biological, socioeconomic, cultural, relational and administrative barriers to KT among immigrant populations in Europe have been proposed by EU scholars, transplant organizations and institutional administrators.<sup>4–7</sup> In the USA, disparities in deceased-donor kidney transplantation (DDKT) and living-donor kidney transplantation (LDKT) for individuals who are from ethnic minorities are well described.<sup>8</sup> Outside the USA and other Northern European countries, immigration from non-EU countries beyond Eastern Europe is relatively recent and extensive in Southern Europe, where adult ethnic minorities are largely first-generation (i.e. foreign-born) migrants of non-European origin.<sup>9</sup> However, although most health systems in the EU guarantee equal access to KT, most<sup>2,10–13</sup> but not all<sup>14,15</sup> EU studies demonstrate disparities similar to those in the USA, especially regarding LDKT. Research on the

association between immigration background and likelihood of KT remains limited in Europe and none has assessed KT likelihood after wait-listing. We performed a retrospective cohort study of adult waiting list (WL) registrants in Italy to assess the probability of WL outcomes (death; KT in a foreign country) including DDKT, LDKT and permanent withdrawal from the WL based on immigration background. To our knowledge, this is the first European study examining whether non-EU-born adult WL registrants experience inferior likelihood of KT compared to EU-born referents.

## Methods

We examined a retrospective cohort of adult patients ( $\geq 18$  years of age) wait-listed for KT from 1 January 2010, through 31 December 2020 in Italy. Among EU member states, Italy is third in non-national residents (5.1 million), most of whom were born outside the EU (3.5 million).<sup>16</sup> The increasing number of non-EU-born migrants in Italy has led to an increase of the prevalent adult migrant population on RRT, representing up to 35% in some centers in Northern areas.<sup>17</sup> The Italian National Health System (NHS) is a regionally based system providing free healthcare to all individuals. Regular migrants must register within the NHS to enjoy medical rights under the same conditions as nationals. Migrants who do not hold a valid residency permit, whose permit has expired for more than 60 days, or are pending regularization are required to be assigned a special code (the so-called ‘STP, Temporarily Present

Foreigner') to access essential and emergency care, including KT and post-transplant regimens. Most non-European-born subjects in Italy are socioeconomically disadvantaged, with lower levels of education, and with difficulties in oral and written communication. In fact, although Italy has a publicly funded health system with universal coverage, prior research has shown that non-European immigration background is associated with reduced kidney graft function following KT.<sup>18</sup>

Non-EU-born individuals were categorized as Eastern European-born and non-European-born as distinguished from EU-born. Geographical distribution of patients is shown in detail in [Supplementary figure S1](#) and [Supplementary table S1](#). Eastern European-born patients included subjects from Albania, Moldavia, former Yugoslavian countries, Ukraine and other countries of the Eastern European and Balkans area. Non-European-born patients included individuals from Asian, Latin American, Northern African and Middle Eastern and Sub-Saharan African countries. Because they are less likely socially disadvantaged, KT registrants born in North America or Oceania were excluded. The EU-born category included all patients from EU member states, including the UK and Switzerland. Further, to determine whether ethnic minority subgroups might elucidate any relationship between immigration status and likelihood of KT, we classified non-European-born registrants according to the four ethnic subgroups, namely Asian (South-East and North-East Asia), Hispanic (Latin America), African (Sub-Saharan Africa) and Other (Northern-Africa and Middle-East).<sup>19</sup>

Data were collected from the Transplant Information System (SIT) regarding patients' demographics, ethnic origin, dialysis modality, ABO blood type, maximum panel reactive antibody (PRA) value, patient case-mix score (the case-mix calculator is reported in the [Supplementary box S1](#)), re-transplantation, transplant center, dialysis vintage, date of censoring, death on the WL, permanent WL withdrawal, DDKT or LDKT. To avoid potential confounding, we limited our analyses to first-time WL registrants and considered primary center listing for patients with multiple registrations. Patients listed for re-transplantation were excluded.

### Statistical analyses

All analyses were performed using the Stata Statistical Software package, Release 17.0. (StataCorp. 2021, College Station, TX, USA). The follow-up time was calculated from time of first wait-listing date to DDKT, LDKT, permanent withdrawal from the WL, death on the WL, KT in a foreign country or 5 years of follow-up, whichever came first. Competing risk analyses were carried out in order to calculate the following estimates: (i) non-parametric crude cumulative probability and 95% confidence interval (95% CI) of DDKT, LDKT and permanent withdrawal from the WL in different immigrant categories.<sup>20,21</sup> (ii) Adjusted subhazard ratios of DDKT, LDKT and of permanent withdrawal from the WL, which we calculated based on competing-risks multiple regression models according to the method of Fine and Gray.<sup>22</sup> The subhazard ratio estimates can be interpreted as relative increase (decrease) of the rate of a given WL outcome. For example, a subhazard ratio for LDKT of non-European-born vs. EU-born of 0.65, means that the rate of LDKT was 35% lower in non-European-born compared to EU-born; accordingly, by reversing the index to the reference category, a subhazard ratio of EU-born vs. non-European-born of 1.54 ( $1/0.65 = 1.54$ ) means that the rate of LDKT was 54% higher in EU-born compared to non-European-born. To facilitate the interpretability of subhazard ratio estimates of each wait-listing outcome, we referred to them as 'relative probability' throughout the text.

Multiple regression models were adjusted for age (included as polynomial variate), gender, blood type, dialysis vintage (log-transformed), sensitization status (indicator variate for CDC-PRA > 10%) and the case-mix classification status (see [Supplementary box S1](#)). We performed [supplementary analyses](#) to

verify whether there were differences between ethnicities within the non-European-born group. Because results did not develop any statistically significant differences these results are reported in the [Supplementary appendix](#) ([Supplementary figure S2](#) and [Supplementary table S2 and S3](#)). The Stata code for all of the analyses is freely available at <https://github.com/UMaggiore/Transplantation-Probability-in-Wait-Listed-Immigrants>.

This retrospective study was approved by the Italian National Transplantation Center and included patients' data that were already anonymized and de-identified in the Italian SIT database before extraction for the analysis. Therefore, the subjects may not be identified and, according to Italian legal regulations (D.L. 196/2003, art. 110-24 July 2008, art. 13), the study did not require Ethics Committee approval. The study was carried out in accordance with the ethical principles of the Declaration of Helsinki (with amendments).

## Results

### Baseline characteristics

Between 1 January 2010 and 31 December 2020, 24 174 WL registrants were eligible for this study. We excluded 764 patients who were <18 years old at time of wait-listing, 32 patients who had North-American or Oceanian origins and 209 patients with identification codes that could not be merged between databases and/or that were listed for re-transplantation. Baseline patient characteristics and risk factors are summarized in [table 1](#) (patient representation and characteristics according to ethnicity are reported in [Supplementary figure S1](#) and [Supplementary table S1](#)). Patients were EU-born ( $n = 21\ 624$ ), Eastern European-born ( $n = 606$ ) and non-European-born ( $n = 1944$ ). Eastern European-born and non-European-born KT registrants were younger at time of wait-listing relative to their EU-born referents. Eastern European-born and non-European-born patients were less likely to receive preemptive KT when compared to EU-born patients. Sensitization status (CDC-PRA > 10%) was comparable between groups. Patients with blood type O were more likely to be EU-born and non-European-born compared to Eastern European-born. Eastern European-born and non-European-born patients were less likely to be high-risk candidates relative to their EU-born counterparts.

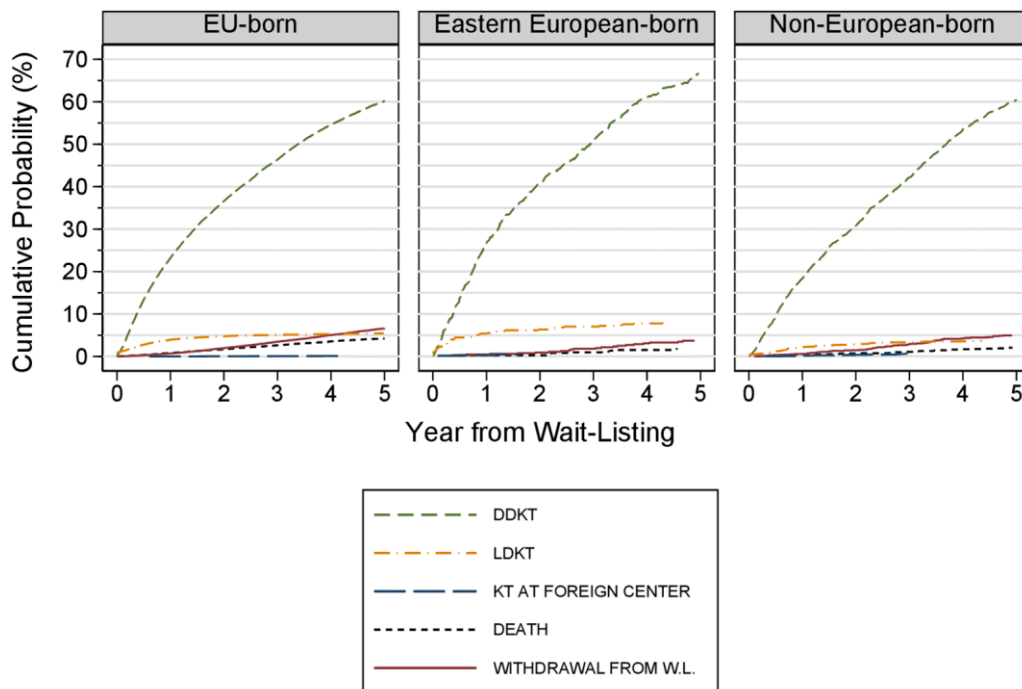
### Wait-list outcomes

After a follow-up of 56 640 person-years (median 2.0 years, maximum 5.0 years), 14 801 patients underwent DDKT, 1272 underwent LDKT, 2346 were withdrawn from the WL, 1292 patients died on the WL, 43 received KT at a foreign center and 4420 were still active on the WL. Crude cumulative probability of each outcome in different immigrant categories since initial wait-listing are reported in [figure 1](#) (crude cumulative probability of each outcome in different ethnicity categories is indicated in [Supplementary figure S2](#)); the corresponding numerical values of 5-year probability are reported in [table 2](#). There was a numerical trend of Eastern European-born patients of having the highest 5-year probability of LDKT [7.9% (95% CI: 5.9–10.3)], and of DDKT [65.7% (61.4–69.0)], and also the lowest rate of withdrawal from the WL [4.4% (2.8–6.5)]; of EU-born of having the highest rate of withdrawal from the WL [6.7% (6.3–7.0)]; and of non-European-born of having the lowest rates of LDKT [4.0% (3.2–5.0)] ([figure 1](#) and [table 2](#)). Because the comparison between these cumulative probability estimates could be confounded by uneven distribution of determinants of transplantation rate between immigrant categories, we performed adjusted analyses. The results of the adjusted analyses are reported in [table 3](#) in the form of adjusted ratio of transplantation rate in the index relative to the reference category (named as 'adjusted relative probability'). After controlling for age, sex, blood type, dialysis vintage, case-mix and sensitization status, the only statistically significant

**Table 1** Baseline characteristics of adult patients wait-listed for KT in Italy (2010–20)

	Total	EU-born	Eastern European-born	Non-European-born	P-value
N	24 174	21 624	606	1944	–
Pt age at wait-listing—years	51.0 (12.4)	51.9 (12.2)	42.9 (12.1)	43.6 (11.4)	<0.001
Recipient's ethnic origin	<0.001				
European	22 230 (92.0)	21 624 (100)	606 (100)		
Asian	614 (2.5)	–	–	614 (31.6)	
Hispanic	297 (1.2)	–	–	297 (15.3)	
African	525 (2.2)	–	–	525 (27)	
Other	508 (2.1)	–	–	508 (26.1)	
Male gender—%	15 513 (64.2%)	13 975 (64.6%)	334 (55.2%)	1204 (61.9%)	<0.001
Dialysis vintage—years	2.0 (3.1)	2.0 (3.2)	2.2 (2.9)	2.2 (2.5)	0.000
Dialysis modality					<0.001
Preemptive	1505 (13.9)	1432 (14.8)	26 (9.2)	47 (5.4)	
HD	7408 (68.2)	6474 (66.7)	220 (77.5)	714 (82.0)	
PD	1947 (17.9)	1799 (18.5)	38 (13.4)	110 (12.6)	
CDC-PRA>0%	5785 (23.9)	5127 (23.7)	146 (24.1)	512 (26.3)	0.034
Blood type					<0.001
O	11 340 (46.9)	10 174 (47.0)	240 (39.6)	926 (47.6)	
A	8764 (36.3)	8002 (37.0)	224 (37.0)	538 (27.7)	
B	3089 (12.8)	2598 (12.0)	98 (16.2)	393 (20.2)	
AB	937 (3.9)	808 (3.7)	43 (7.1)	86 (4.4)	
NA	44 (0.2)	42 (0.2)	1 (0.2)	1 (0.1)	
Case-mix					<0.001
Standard risk	5602 (27.4)	4860 (26.7)	192 (36.2)	550 (33.0)	
Low risk	3938 (19.3)	3390 (18.6)	125 (23.5)	423 (25.4)	
Intermediate risk	4248 (20.8)	3854 (21.1)	102 (19.2)	292 (17.5)	
High risk	6641 (32.5)	6128 (33.6)	112 (21.1)	401 (24.1)	

Notes: EU, European Union; Eastern European-born, born in Eastern Europe or Balkans; HD, hemodialysis; PD, peritoneal dialysis; PRA, panel reactive antibody; CDC-PRA, complement-dependent cytotoxicity panel reactive antibody.



Non-parametric competitive crude cumulative incidence

**Figure 1** Non-parametric crude cumulative probability of wait-list outcomes in different immigrant categories since wait-listing. Cumulative probability was estimated using non-parametric competing risk estimation. DDKT, deceased-donor kidney transplant; EU, European Union; KT, kidney transplant; LDKT, living-donor kidney transplant; WL, waiting list

difference was that the non-European-born had lower LDKT rates compared to the other two immigrant categories: LDKT adjusted relative probability of non-European-born vs. Eastern European-born 0.51 (0.33–0.79;  $P=0.002$ ); of non-European-born vs. EU-born: 0.65 (0.47–0.82;  $P=0.001$ ).

## Discussion

To the best of our knowledge, this is the first study assessing the association of immigration background with likelihood of KT among adult WL registrants in Europe. Our study provides the first

**Table 2** Five-year crude cumulative probability (%) of LDKT, DDKT and permanent withdrawal from the WL in different immigrant categories

	EU-born	Eastern European-born	Non-European-born
LDKT	5.4 (5.1–5.7)	7.9 (5.9–10.3)	4.0 (3.2–5.0)
DDKT	59.4 (58.7–60.1)	65.7 (61.4–69)	59.6 (57.1–62.0)
Permanent withdrawal from the WL	6.7 (6.3–7.0)	4.4 (2.8–6.5)	4.9 (3.9–6.1)

Notes: The 5-year crude cumulative probability of each outcome was estimated by non-parametric competing risk analysis. Number in parentheses represents 95% confidence intervals. LDKT, living-donor kidney transplantation; DDKT, deceased-donor kidney transplantation; WL, waiting list; EU, European Union.

**Table 3** Adjusted relative probability of LDKT, DDKT and permanent withdrawal from the WL in different immigrant categories

	Eastern European-born vs. EU-born	Non-European-born vs. Eastern European-born	Non-European-born vs. EU-born
<b>Adjusted probability (95% CI)P-value</b>			
LDKT	1.21 (0.86–1.71) P = 0.267	0.51 (0.33–0.79) P = 0.002	0.62 (0.47–0.82) P = 0.001
DDKT	1.09 (0.97–1.21) P = 0.136	0.92 (0.81–1.03) P = 0.156	1.00 (0.94–1.06) P = 0.878
Permanent withdrawal from the WL	0.79 (0.47–1.34) P = 0.389	1.33 (0.76–2.38) P = 0.310	1.07 (0.83–1.38) P = 0.627

Notes: Adjusted relative probability refers to the ratio of the rate of the outcome in the index category to the reference category, as estimated by the competing risk multiple regression analysis. Estimates were adjusted for age, sex, blood type, sensitization status, dialysis vintage and case-mix. DDKT, deceased-donor kidney transplant; EU, European Union; LDKT, living-donor kidney transplant; WL, waiting list.

evidence that non-European immigration background is associated with a slight but significantly decreased likelihood of receiving LDKT, but not with a diminished probability of DDKT or higher likelihood of permanent WL withdrawal. We performed this study in Italy, where, in the Italian context, immigration is a proxy for disadvantaged socioeconomic condition and cultural diversity. In fact, as in other Southern European countries, immigration is a fairly recent and emergent phenomenon in Italy and adult ethnic minority individuals generally overlap with first-generation migrants.<sup>9</sup> Our findings show that, relative to EU-born and Eastern European-born patients, non-European-born registrants reported a lower likelihood of LDKT. While similar studies have been performed previously, most focus on ethnic or racial background or pediatric patient populations, and do not assess immigration background or examine the likelihood of KT after wait-listing.<sup>2,10–14</sup> Similar to prior reports, it is likely that, because Italy guarantees universal healthcare coverage including access to KT and post-transplant regimens regardless of immigrant and socioeconomic status, this may mitigate the adverse effect of socioeconomic disadvantage on likelihood of DDKT or permanent WL withdrawal.<sup>8,12</sup>

Previous research has shown a higher risk of ESKD among first-generation immigrant groups of Eastern European, African and Asian origin relative to their native referents, including second-generation immigrants (i.e. native-born with at least one foreign-born parent).<sup>23</sup> This may suggest that exposure to mechanisms related to the migration process and ethnicity may lead to an increased risk of ESKD<sup>23</sup> and may explain the younger age of Eastern European-born and non-European-born registrants when compared to their EU-born counterparts in our study.

Our analysis shows that ethnicity/race *per se* does not explain the relation between immigration background and likelihood of DDKT, LDKT or permanent WL withdrawal. In fact, stratification of non-European-born patients based on the four ethnic groups (Asian, Hispanic, African and Other) reveals no statistically significant differences between groups. Therefore, it seems plausible that other

latent factors related to non-European immigration background may explain the diminished probability of LDKT among these populations (see below). Although we could not retrieve any data on the patients' socioeconomic status, research suggests that ethnic disparities in LDKT persist even after adjustment for socioeconomic deprivation.<sup>11,12</sup> More favorable attitudes toward living donation may explain the highest 5-year probability of LDKT among Eastern European-born patients relative to their non-European-born referents.<sup>14,24</sup> Besides, the highest rate of withdrawal from the WL among EU-born subjects may be associated with their older age and higher presence of comorbidities relative to immigrant groups.<sup>25</sup>

Like our findings, prior studies of adult and pediatric RRT patients in the EU and Canada (which has a similar healthcare system to Italy) have shown that Black, Asian and other ethnic minority patients are all less likely than their White referents to receive LDKT. However, these studies did not assess immigration background and explored likelihood of KT since RRT start or referral for KT, but not since WL registration.<sup>2,11,13,26</sup> Further, because EU studies focus on racial or ethnic background, we were unable to distinguish between EU-born and non-EU-born White individuals.<sup>2,11,13</sup>

Interaction among multiple determinants at the level of patients, donors, providers and the healthcare system may play a role in the diminished likelihood of LDKT in non-European-born patients. Unique barriers to LDKT that these populations may experience include limited language proficiency; lack of knowledge of LDKT; inferior health literacy levels; lack of confidence to ask questions due to insufficiently tailored and/or understandable educational material; fears, anxieties and misunderstandings of the procedure; personal, religious, spiritual and cultural beliefs preventing discussions with potential living donors; negative influences of social networks when communicating about RRT; less favorable attitudes toward LDKT in some ethnic groups, and uncertainty about the attitude of their community toward organ transplantation and living donation.<sup>27–32</sup> As for donor-related factors, different religious interpretations, culture, beliefs, family influences and other socioeconomic factors including financial concerns, inability to take time off work,

absence of family members living sufficiently close to enable the identification of a potential living donor at the time of first KT assessment and ABO mismatch between potential living donors and KT registrants may all contribute to delay and/or hinder access to LDKT.<sup>28,33</sup> Further, at the provider-level physicians may present individual biases<sup>8</sup> and concerns about non-resident donors' medical follow-up, risk of donor coercion<sup>4</sup> and higher risk of developing long-term kidney-related conditions and risk factors for the progression toward ESKD (i.e. hypertension) in certain ethnic minority living-donor categories.<sup>34</sup> As for healthcare system-related factors, it is unlikely that transplant services in Italy are equipped with adequate resources to deliver KT education that is individually tailored, easily understandable, and culturally competent.<sup>28,35–37</sup> Although the NHS covers all expenses for KT, in some Italian Regions, non-resident donors must pay travel and medical fees for living-donor surgery and follow-up with the potential to diminish the likelihood to pursue LDKT among these socioeconomically disadvantaged populations. We could not determine the influence of these factors on the likelihood of LDKT, although it is likely that universal healthcare coverage *per se* is not an independent determinant of LDKT.

Our study has several limitations. First, this is a retrospective study based on data derived from the Italian SIT registry which, while reliable, does not include all potential confounding variables. No data were available regarding patients' socioeconomic status, educational level, health literacy, language proficiency, time elapsed since immigration as a proxy for acculturation (i.e. the degree of adaptation to/acquisition of the host country's culture) and the presence of family members living sufficiently close to enable LDKT. No data of the ancestries of EU-born patients can be retrieved. Yet, since immigration from non-EU countries beyond Eastern Europe is rather recent in Italy, it seems plausible that only few adult EU-born KT registrants had non-European ancestries. Further, although we were unable to distinguish between different immigrant categories, KT in more vulnerable groups of patients (i.e. undocumented immigrants, asylum seekers and refugees) is infrequent in Europe.<sup>38</sup> Also, the analysis was performed on patients wait-listed for DDKT, representing a subgroup of patients with ESKD eligible for KT. Therefore, disparities in KT eligibility at the time of wait-listing could not be explored. Besides, while no data were available of patients' comorbidities, the patient case-mix score mitigates this deficiency. Finally, the findings of this study may not apply to other countries with different health care and/or social security systems.

Since immigration is likely to increase in Europe and elsewhere, future studies including socioeconomic, sociocultural, relational, psychosocial, transplant providers' and transplant system's (inter)cultural competence and KT education data are needed to better describe the causal mechanisms linking immigration and ethnicity with access to LDKT. These may enable the identification of potential areas for intervention on modifiable factors. At the level of patients and their potential living donors, linguistically and culturally competent KT care (i.e. home-based educational interventions, patient-decision aids and other culturally tailored educational sessions) may be an effective means to improve knowledge, communication, decision capacity, understanding of complex medical information and attitudes toward available treatment alternatives (including LDKT) among patients and their potential living donors.<sup>35,37,39,40</sup> Further, training in cultural competence for transplant professionals may enhance providers' intercultural communicative abilities, social history taking and enable the prevention of preconceived biases and concerns. Besides, at the healthcare system level, specific programs addressing priorities

for immigrant populations, adaptation of processes and services and improved care coordination among healthcare providers all have the potential to provide a more effective response to the diverse needs of patients with an immigration background.<sup>37</sup> In addition, wherever they are not already available, new national policies should enable coverage of travel and medical fees for living-donor surgery and follow-up for non-resident donors to improve uptake of LDKT in immigrant patients. Future studies will explore the effectiveness of targeted and/or tailored interventions on modifiable barriers to meet the needs of immigrant populations and guarantee provision of equitable transplant care in this vulnerable group of patients.

## Supplementary data

Supplementary data are available at *EURPUB* online.

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## Key points

- It is unknown whether among adult kidney transplant candidates, in countries with universal healthcare coverage and where immigration is a recent phenomenon, immigration background (as opposed to ethnic/racial background) affects the probability of kidney transplantation (KT).
- We retrospectively followed-up for 5 years since time from wait-listing (which allows a fair comparison between immigration categories) 24,174 transplant candidates from the Italian National Transplantation Network until they received deceased-donor kidney transplantation (DDKT), living-donor kidney transplantation (LDKT) and permanent wait-list (WL) withdrawal.
- This study newly shows that non-European-born patients have lower LDKT rates compared to other immigrant categories, and to EU-born patients, whereas immigration status does not affect the rate of DDKT or permanent WL withdrawal since WL registration.
- Wherever they are not already available, new national policies should enable coverage of travel and medical fees for living-donor surgery and follow-up for non-resident donors to improve uptake of LDKT in immigrant patients, and provide KT education that is culturally competent, individually tailored and easily understandable for patients and their potential living donors.

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