ORIGINAL ARTICLE

Association of immigration background with kidney graft function in a publicly funded health system: a nationwide retrospective cohort study in Italy

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SUMMARY

The impact of immigration background on kidney graft function (eGFR) is unknown. Italy has a publicly funded health system with universal coverage. Since immigration from non-European Union (EU) countries beyond Eastern Europe is a recent and extensive phenomenon, Italy is a rather unique setting for studying the effect of immigration status as a socioeconomic and cultural condition. We retrospectively identified all adult deceased donor kidney transplant recipients (KTRs) in Italy (2010–2015) and followed them until death, dialysis or 5-years post-transplantation; 6346 were EU-born, 161 Eastern European-born, and 490 non-European-born. We examined changes in eGFR after 1-year post-transplant using multivariable-adjusted joint longitudinal survival random-intercept Cox regression. Compared to EU-born KTRs, in non-European-born KTRs the adjusted average yearly eGFR decline was −0.96 ml/min/year (95% confidence interval: −1.48 to −0.45; $P < 0.001$), whereas it was similar in Eastern European-born KTRs [+0.02 ml/min/year (−0.77 to +0.81; $P = 0.96$)]. Adjusted 5-year transplant survival did not statistically differ between non-European-born, Eastern European-born, and EU-born. In those surviving beyond 1-year, it was 91.8% in EU-born (87.1–96.8), 92.5% in Eastern European-born (86.1–99.4), and 89.3% in non-European-born KTRs (83.0–96.0). This study provides evidence that among EU KTRs, non-European immigration background is associated with eGFR decline.

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Introduction

In Italy, many adult patients with end-stage kidney disease (ESKD) are of non-European origin [1–3]. These patients account for 35% of the prevalent population on chronic dialysis treatment in some centers in Northern areas [1]. Immigration from non-European Union (EU) countries beyond Eastern Europe is a recent phenomenon in Italy when compared to other Central and Northern European countries [4]. The number of foreign-born individuals (i.e., first-generation immigrants) has grown from 1.9 to over 5 million between 2004 and 2017, the majority of whom were born outside the EU (3.5 million) [5]. Immigration is an important social determinant of health, carrying the potential for disparities in accessibility, quality, and outcomes of

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care [6,7]. The health of migrants and prevention of inequities for these populations are a priority of the World Health Organization [8]. Italy guarantees universal access to primary, secondary, and emergency care to regular and undocumented immigrants registered within the Italian National Health System. Kidney transplantation (KT) is the gold standard for treatment of ESKD; KT, post-transplant immunosuppressive medication and medical regimens are available for clinically eligible migrants with regular immigration status, regardless of ability to pay [9].

The immigrant patient population presents a variety of relational, cultural, social, economic, and biological factors that may be relevant to treatment outcomes [3,10–12]. In Italy, non-European-born individuals are more likely to be socioeconomically disadvantaged, with lower levels of education when compared to other EU countries, and with difficulties in oral and written communication [3,13–15]. Immigrants in Italy receive lower quality management of chronic conditions such as diabetes and are less likely to adhere to prescribed medical regimens, resulting in a higher risk of diminished treatment outcomes [16,17]. Also, limitations in integration policies may challenge overall health status over time after migration [18]. It is possible that the multiple aspects of vulnerability associated with immigrant status may affect long-term care and the clinical course of KT when comparing EU and non-European-born kidney transplant recipients (KTRs) [7].

European data suggest that immigration may be associated with inferior KT outcomes in some [19,20] but not all situations [21–25]. Studies on the association between immigration background and KT outcomes remain limited in Europe, and only few if any have assessed long-term kidney graft function decline rate (i.e., change over time in estimated Glomerular Filtration Rate, eGFR) beyond 1-year post-transplant. Previous studies have shown that eGFR decline at 1-year post-transplant does not differ significantly between KTRs with a non-European immigration background and natives [20,21,25]. Most registries lack long-term longitudinal data on eGFR. To fill this gap, we carried out a retrospective cohort study of adult KTRs in Italy, comparing long-term eGFR and transplant survival between Eastern European-born, non-European-born, and EU-born recipients. To our knowledge, this is the first Italian study examining whether non-EU-born individuals experience altered KT clinical outcomes compared to EU-born patients, and the first registry study that examines the relationship between immigration background and long-term kidney graft function.

Materials and methods

We performed a retrospective cohort study of adult patients (≥18 years of age) who received KT from deceased donor (DD) from January 1, 2010, through December 31, 2015 in Italy. Non-EU-born KTRs were first-generation immigrants with migration experience [26,27] and with a regular immigration status. We distinguished individuals born outside the EU between Eastern European-born and non-European-born. Non-European-born KTRs included patients from four geographic areas: Asia, Latin America, North Africa and Middle-East, and Sub-Saharan Africa. Because they may not be regarded as exposed to social disadvantage and we should have analyzed them as a separate group, KTRs born in North America or Oceania were excluded ($n = 10$). Eastern European-born patients included individuals from Albania, Moldavia, Former Yugoslavia, Ukraine and other countries of the Eastern European and Balkans area. EU-born KTRs included all patients from the EU-28 member states including Switzerland. We did not further subdivide the Eastern European-born, non-European-born, and EU-born area-of-birth categories given limitations in the numbers in each category for statistical analyses. However, in order to verify whether specific ethnic subgroups might explain any relationship between immigration status and eGFR decline, we additionally classified non-European-born KTRs according to the four ethnic subgroups, namely Asian (South-East and North-East Asia), Hispanic (Latin America), African (Sub-Saharan Africa), and other (North-African and Middle-East) [28].

Data were collected from the Italian National Transplant Center's (CNT) Transplant Information System (SIT), a national-level mandatory registry (established by Law: 1 April 1999, no 91) collecting data relative to the entire transplant process (donation–procurement–transplant) drawn from the whole Italian National Transplantation Network. Data were available concerning recipients' demographics, primary kidney disease, dialysis vintage, time to wait-listing (WL), dialysis modality, donors' age, ethnic origin, HLA A/B/DR mismatches, re-transplantation, maximum Panel Reactive Antibody (PRA) value, transplant center, date of censoring, death, or dialysis. Data were also available on yearly post-transplant eGFR, according to the CKD-EPI equation, starting from the first post-transplant year.

This retrospective study was approved by the Italian CNT and included patients' data that were anonymized and de-identified directly in the Italian SIT database

Transplant International 2020; 33: 1405–1416

before extraction for the analysis. The study was carried out in accordance with the ethical principles of the Declaration of Helsinki (with amendments).

Statistical analyses

All analyses were performed using the Stata Statistical Software package, Release 16.0. (Statacorp. 2019, College Station, TX, USA). A two-tailed *P* value less than 0.05 was regarded as statistically significant, unless otherwise stated. Differences between groups in continuous variables were examined by Kruskal–Wallis and by Mann–Whitney two-sample test, in categorical variables by Fisher's exact test. The primary exposure was recipients' country of birth compared to EU-born patients. In all the analyses, we included only patients who had available data on HLA mismatch, dialysis vintage, and follow-up. Follow-up was continued until death or dialysis, whichever came first, otherwise it was censored 5-year post-transplantation. Because we believed that systematic differences between the observed and missing data could not be explained by associations with the observed data (i.e., we believed that the covariate patterns and outcomes were not Missing at Random), we did not make any attempt to perform multiple imputation as it would have caused biased estimates compared to complete case analysis [29]. We reported Kaplan–Meier plots as summary statistics of the survival of the study population and of the number of patients at risk at each time point in the period from year 1 to year 5. We fitted a joint longitudinal survival model [30,31], in which yearly eGFR and transplant survival time were analyzed jointly under the assumption that the longitudinal and survival processes are underpinned by shared latent patient random effects. The joint longitudinal survival model consists of two sub-models: a longitudinal sub-model (i.e., a linear mixed effects model for eGFR) and a time-to-event sub-model (i.e., a Cox proportional hazards model for transplant failure) which are linked using an association structure. Because the two outcomes of transplant survival time and graft function might be highly correlated, joint analysis can reduce bias and improve precision of estimated parameters from both survival and longitudinal models over simpler approaches. Additionally, major results available from joint analyses, as opposed to time-dependent Cox regression analysis, are that they naturally deal with eGFR measurement error, interval missing data, and whenever it happens, lack of consistency among subjects in timing of the eGFR assessment; they provide an optimal 'adjustment' for the pre-transplant failure longitudinal eGFR and provide a precise estimate of the impact of the eGFR on the hazard of graft failure (reported as the 'association parameter.') [31–33]. We fitted a joint longitudinal survival random-intercept model using the Stata user-written command *jmxtstcox* (StataCorp LLC) which allows to model the survival outcome semi-parametrically using Cox proportional hazard regression.

All multivariable-adjusted regression models included the following characteristics: year of transplantation (continuous variate), donor and recipient age, recipient gender, dialysis vintage (log-transformed), number of HLA A/B/DR mismatch (continuous variate), sensitization status (maximum CDC-PRA >10%), and re-transplantation. There were 33 patients with missing CDC-PRA values, which were evenly distributed between immigrant groups. In fact, the multiple regression models that included CDC-PRA yielded virtually identical results. Anyhow, we reported the results of regression models including CDC-PRA throughout.

For the longitudinal component of the model (eGFR), time was modeled both as a categorical variate (yearly change in eGFR from the baseline value 1-year post-transplantation) and as a continuous variate (average linear decline of eGFR from year 1 to year 5). The main analyses consisted in the comparison between eGFR changes in the two immigrant groups, namely Eastern European- and non-European-born, with eGFR change in EU-born KTRs. However, in additional models, we split the non-European-born KTRs into four ethnic groups and compared each of them with EU-born KTRs. We also performed statistical tests of every pairwise comparison between ethnic groups, for which a two-tailed *P* value of less than 0.01 was regarded as statistically significant to allow for multiple testing.

Results

Baseline characteristics

Between January 1, 2010, through December 31, 2015, 6997 DD KTRs were eligible for the present study: 163 patients with missing follow-up and 1480 patients with missing covariate status were excluded. The summary of baseline patient demographics and risk factors is reported in Table 1, and crude transplant survival since time of transplantation is reported in Fig. 1. EU-born (6346), Eastern European-born (161), and non-European-born (490) KTRs were identified. Eastern

Table 1. Baseline characteristics of adult patients who received deceased donor kidney transplant.

	Total	EU-born	Eastern European-born	Non-European-born	*P* value
Origin		Italy: 6202 Germany: 20 Romania: 67 Switzerland: 21 Other: 36	Albania: 76 Moldavia: 17 Rep. of Yugoslavia: 18 Ukraine: 23 Other: 27	Argentina: 8 Bangladesh: 9 Burkina Faso: 7 Brazil: 7 China: 34 Colombia: 6 Dominican Republic: 6 Ecuador: 7 Egypt: 22 Ghana: 27 India: 17 Ivory Coast: 12 Lybia: 6 Morocco: 85 Nigeria: 30 Pakistan: 19 Peru: 9 Philippines: 51 Other Latin American: 19 Other North-African and Middle-Eastern: 15 Other North-East and South-East Asian: 12 Other Sub-Saharan African: 32 Senegal: 28 Tunisia: 16 Venezuela: 6	
N	6997	6346	161	490	–
Recipient's age, years	52.4 (12.2)	53.2 (11.9)	44.4 (12.5)	44.9 (11.4)	<0.001*,†
Recipient's ethnic origin					
European	6457 (93.0)	6297 (100)	160 (100)		<0.001*,†
Asian	142 (2.0)	23 (0.4)		142 (29.0)	
Hispanic	68 (1.0)			68 (13.9)	
African	135 (1.9)			135 (27.6)	
Other	144 (2.1)			144 (29.4)	
Donor's age, years	54.6 (16.3)	55.3 (16.2)	47.9 (16.1)	48.8 (16.1)	<0.001*,†
Donor's ethnic origin					
European	6796 (97.8)	6173 (98.1)	151 (94.4)	472 (96.5)	<0.001*,†
Asian	30 (0.4)	23 (0.4)	3 (1.9)	4 (0.8)	
Hispanic	77 (1.1)	66 (1.0)	6 (3.7)	5 (1.0)	
African	19 (0.3)	15 (0.2)	0 (0.0)	4 (0.8)	
Other	24 (0.3)	20 (0.3)	0 (0.0)	4 (0.8)	
Male gender, %	5535 (65%)	5067 (65%)	108 (57%)	360 (65%)	0.076
Primary kidney disease					
Glomerulonephritis	2700 (38.9)	2400 (38.1)	74 (46.5)	226 (46.2)	<0.001*,†,‡
ADKPD	1265 (18.2)	1222 (19.4)	17 (10.6)	26 (5.3)	
Hypertension/Vascular	748 (10.8)	657 (10.4)	12 (7.5)	79 (16.2)	
Diabetes	271 (3.9)	246 (3.9)	3 (1.9)	22 (4.5)	
Pyelonephritis/tubule-interstitial disease	469 (6.7)	426 (6.8)	19 (11.9)	24 (4.9)	
Congenital	150 (2.2)	140 (2.2)	6 (3.7)	4 (0.8)	
Other or unknown	1343 (19.3)	1206 (19.1)	29 (18.1)	108 (22.1)	
Dialysis vintage, years	3.6 (2.1–5.8)	3.5 (2.1–5.8)	4.0 (2.3–5.9)	4.3 (2.6–6.4)	<0.001†

Transplant International 2020; 33: 1405–1416

Table 1. Continued.

	Total	EU-born	Eastern European-born	Non-European-born	*P* value
Time to wait-listing, years	1.3 (0.7–2.4)	1.3 (0.7–2.3)	1.6 (0.8–2.8)	1.6 (0.8–2.9)	<0.001*,†
Dialysis modality					
Preemptive	85 (1.2)	83 (1.3)	1 (0.7)	1 (0.2)	<0.001†
HD	5583 (78.6)	5069 (77.9)	120 (81.8)	394 (88.5)	
PD	1431 (20.2)	1354 (20.8)	27 (18.2)	50 (11.2)	
CDC-PRA >10%	1316 (19.0)	1187 (18.8)	32 (20.0)	97 (19.8)	0.78
CDC-PRA, %	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–4)	0.96
HLA A/B/DR mm, *n*	3.2 (1.2)	3.2 (1.2)	3.3 (1.2)	3.6 (1.1)	<0.001†,‡
HLA DR, mm					
0 mm	2334 (31)	2177 (32)	46 (27)	111 (22)	<0.001†
1 mm	5163 (69)	4654 (68)	123 (73)	386 (78)	

Continuous variates are reported as mean (standard deviation) or median (interquartile range). Categorical variates as number (percentage).

EU, European Union; Eastern European-born, born in Eastern Europe or Balkans; HD, hemodialysis; PD, peritoneal dialysis; mm, mismatch; PRA, Panel reactive antibody; CDC-PRA, Complement-dependent cytotoxicity Panel Reactive Antibody; ADPKD, Autosomal Dominant Polycystic Kidney Disease.

Superscripts indicate statistical significance ($P < 0.05$), as follows:

*EU-born vs. Eastern European-born.

†EU-born vs. non-European-born.

‡Eastern European-born vs. non-European-born.

European-born and non-European-born KTRs were younger compared with EU-born KTRs. Because of the donor-recipient age-matching algorithm, Eastern European-born and non-European-born KTRs had also younger donor ages. However, dialysis vintage, time to WL, and number of HLA mismatches tended to be slightly higher in Eastern European-born and non-European-born compared to EU-born KTRs .

Joint analysis of transplant survival and graft function (eGFR)

Among the 6281 DD KTRs who were followed beyond 1-year post-transplantation, 594 had transplant failure (301 of them because of death with a functioning graft) after a mean follow-up of 3.4 years since transplantation. Overall, in the period from year 1 to year 5, DD

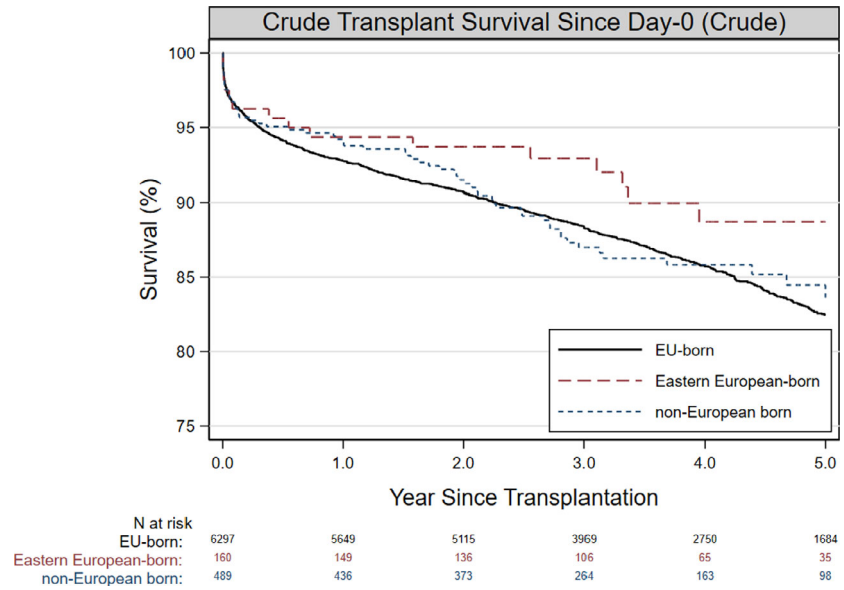

Figure 1 Crude survival probability and number at risk of EU-born, Eastern European-born, and non-European-born kidney transplant recipients. Joint longitudinal survival analyses include patients surviving beyond 1-year post-transplantation, the time of the first eGFR measurement.

KTRs provided 17 047 eGFR data and 23 294 person-years of time at risk to the joint longitudinal survival analysis. After adjusting for confounders, mean 1-year (baseline) eGFR was similar between groups [52.4 ml/min/1.73 m^2 in the EU-born KTRs, 54.4 ml/min/1.73 m^2 in Eastern European-born ($P = 0.24$ vs. EU-born), and 53.7 ml/min/1.73 m^2 in non-European-born KTRs ($P = 0.20$ vs. EU-born)]. In EU-born KTRs, the average yearly change in eGFR was +0.19 ml/min/1.73 m^2/year (95% CI +0.06 to +0.31). It was similar in Eastern European-born KTRs [difference with EU-born: +0.02 ml/min/1.73 m^2/year (−0.77 to +0.81; $P = 0.96$)]. In contrast, compared to EU-born KTRs, non-European-born KTRs had a significant decline in eGFR [difference with EU-born: −0.96 ml/min/1.73 m^2/year (−1.48 to −0.45; $P < 0.001$)]. Compared to EU-born KTRs, in non-European-born KTRs the adjusted difference at 4 years in the change from 1-year eGFR was −3.1 ml/min/1.73 m^2 (95% CI: −5.2 to −1.1; $P = 0.003$); at 5 years, it was −4.7 ml/min/1.73 m^2 (−7.3 to −2.2; $P < 0.001$), whereas EU and Eastern European-born KTRs had similar eGFR decline throughout (Table 2). After stratifying non-European-born KTRs according to ethnicity, each ethnic group had similar eGFR decline at 5 years (P value >0.01 for every multiple pairwise comparison between ethnic

Table 2. Adjusted difference in change from 1-year eGFR and adjusted hazard ratio from joint longitudinal survival analysis based on Cox regression for the analysis of survival time.

	Eastern European-born vs. EU-born ΔeGFR, ml/min/1.73 m^2 Difference between groups (95% CI) *P* value	Non-European-born vs. EU-born ΔeGFR, ml/min/1.73 m^2 Difference between groups (95% CI) *P* value
Year since transplantation		
2-year	+1.1 (−1.3 to +3.6) $P = 0.36$	−2.6 (−4.2 to −1.1) $P = 0.001$
3-year	−0.5 (−3.0 to +2.1) $P = 0.73$	−1.9 (−3.6 to −0.2) $P = 0.029$
4-year	+0.8 (−2.3 to +4.0) $P = 0.60$	−3.1 (−5.2 to −1.1) $P = 0.003$
5-year	−0.4 (−4.4 to +3.6) $P = 0.84$	−4.7 (−7.3 to −2.2) $P < 0.001$

	Eastern European-born vs. EU-born HR (95% CI) *P* value	Non-European-born vs. EU-born HR (95% CI) *P* value
	0.91 (0.44–1.88) $P = 0.79$	1.36 (0.95–1.95) $P = 0.090$
Association parameter γ (logarithm of HR of graft failure per 1 ml/min/1.73 m^2 *increase* in eGFR)	−0.31 (95% CI: −0.28 to −0.35)	
Association parameter γ expressed as HR of graft failure per 1 ml/min/1.73 m^2 *decrease* in eGFR	1.37 (95% CI: 1.33–1.41)	

Results from joint longitudinal survival analysis (fitted via Cox regression). eGFR differences represent adjusted differences between groups in the change from baseline eGFR (1-year post-transplantation) estimated by linear mixed models with time modeled as categorical variate (differences in eGFR by year are estimated from the interaction term between group and categorical time, and may be affected by random differences in baseline 1-year eGFR). Adjusted 1-year eGFR did not differ between groups (see text). The analysis was performed in transplant recipients survived beyond 1-year post-transplantation. The joint longitudinal survival analysis was adjusted for donor and recipient age, recipient gender, dialysis vintage, number of HLA mismatches, and re-transplantation. The association parameter γ between longitudinal and survival patient latent random effects had a negative estimate, which implies a negative association between eGFR and transplant survival: the higher the eGFR, the lower the chance of transplant failure. The association parameter is reported as log (hazard ratio) of graft failure per 5 ml/min/1.73 m^2 *increase* in eGFR, and as hazard ratio per 5 ml/min/1.73 m^2 *decrease* in eGFR. The likelihood ratio test of no latent association between longitudinal and survival random effect (H0: $\gamma = 0$) yielded $\chi^2(1) = 362$ ($P < 0.001$).

ΔeGFR, difference in eGFR change from baseline eGFR (1-year post-transplantation); HR, hazard ratio; 95% CI, 95 percent confidence interval.

Transplant International 2020; 33: 1405–1416

groups). In fact, compared to non-European-born KTRs, the average yearly change in eGFR was −0.58 ml/min/1.73 m^2/year (95% CI: −1.52 to +0.35; $P = 0.22$) in Asians, −2.24 ml/min/1.73 m^2/year (−3.50 to −0.98; $P < 0.001$) in Hispanics, −0.59 ml/min/1.73 m^2/year (−1.64 to +0.47; $P = 0.28$) in Africans, and −1.00 ml/min/1.73 m^2/year (−1.90 to −0.11; $P = 0.028$) in others; GFR decline at 5 years was −3.3 ml/min/1.73 m^2 (−8.0 to +1.3; $P = 0.16$) in Asians, −7.0 ml/min/1.73 m^2 (−13.4 to −0.7; $P = 0.030$) in Hispanics, −4.2 ml/min/1.73 m^2 (−9.6 to +1.1; $P = 0.12$) in Africans, and −5.5 ml/min/1.73 m^2 (−9.9 to −1.0; $P = 0.016$) in 'Other' ethnic groups.

Compared to EU-born KTRs, non-European-born KTRs had a hazard ratio of transplant failure of 1.36 (95% CI: 0.95–1.95; $P = 0.090$), and Eastern European-born KTRs of 0.91 (0.44–1.88; $P = 0.79$) (Table 2). In those surviving 1-year post-transplantation, adjusted 5-year transplant survival was 91.8% in EU-born (95% CI: 87.1–96.8), 92.5% in Eastern European-born (86.1–99.4), and 89.3% in non-European-born KTRs (83.0–96.0). After stratifying non-European-born patients according to ethnicity, African was the only group showing significantly increased mortality compared to EU-born KTRs [hazard ratio of transplant failure being 0.84 (95% CI: 0.38–1.80) for Asians, 1.14 (0.41–0.38) for Hispanics, 3.84 (2.28–6.45) for Africans, 0.69 (0.32–1.50) for other].

Discussion

To the best of our knowledge, this is the first study examining the relationship between long-term eGFR decline and immigration status in adult KTRs in Europe (Table 3). This study provides the first evidence that non-European immigration background is associated with long-term eGFR decline. This study was performed in Italy which is a rather unique setting for studying the effect of immigration status as a socioeconomic and cultural condition. Since immigration from non-EU countries beyond Eastern Europe is a relatively recent and extensive phenomenon, ethnic minorities among adult subjects are largely composed by first-generation immigrants as opposed to native-Italians and natives of the other EU-28 member States. Moreover, Italy has a publicly funded health system with universal coverage, which may dampen the adverse effect of economic status on health outcomes. Our findings show that compared to EU-born KTRs and unlike Eastern European-born KTRs, non-European-born KTRs had an eGFR decline of almost −5 ml/min/1.73 m^2 at 5-years post-transplantation.

It is likely that the observed 5-year differences in eGFR longitudinal changes would have been even sharper had we extended our longitudinal follow-up for ten or more years. The eGFR slope after KT has been put forward as a surrogate for long-term death and death-censored graft failure [34,35] and as a reliable surrogate endpoint of long-term death and ESKD in chronic kidney disease trials [36,37]. Moreover, eGFR is one of the main mediators of the relation between immigration background and long-term clinical outcomes in KTRs, since immigration background may adversely affect kidney graft function (see below) and graft dysfunction is a cause of ESKD and death. Our analysis started 1-year post-transplantation, at the time when the first eGFR measurement was available. In fact, in agreement with previous studies [20,21,25], we did not find significant differences in adjusted 1-year post-transplant eGFR in KTRs with non-European immigration background compared to their native referents. We contend that while immigration background may only minimally affect early transplant outcomes given intensive early management, factors such as adherence to medication regimens or clinic visits may have a greater impact over time after the first year post-transplant. Immunological factors appear to be less often the cause of graft loss beyond 1 year after KT [38]. In our study, baseline immunological (i.e., HLA, sensitization status) and non-immunological risk variables (i.e., recipient and donor age, dialysis vintage, time to WL) were comparable between Eastern European-born and non-European-born KTRs.

Ethnicity per se did not seem to account for the relation between immigration background and decline in eGFR. In fact, after stratifying non-European-born patients according to the four ethnic groups (i.e., Asian, Hispanic, African, Other), eGFR decline did not present statistically significant differences between groups, apart from numerical differences likely related to the sparse number of subjects within each stratum. African ethnicity was associated with increased hazard of transplant failure within 5 years, despite similar decline in eGFR. Our findings are similar to those of a previous study from the United Kingdom (UK) [39] that found comparable 1- and 5-year median eGFR in Black and South Asian KTRs, despite increased hazard of graft failure in Blacks. However, in that study, the analysis on eGFR was based on unadjusted two-sample test between groups and the immigration background of the patients was not assessed [39]. Yet, given the longer-standing

Table 3. Studies of kidney transplant outcomes in non-European-born recipients with an immigration background.

Study ID	Study location	Study type	Study period	Number of patients	Patient population	Length of follow-up	Assessment of immigration background	Access to post-Tx care	Non-EU-born KTRs' origin	Assessment of Post-Tx eGFR	Timing of eGFR measurement post-Tx	Effect of eGFR decline
1) Roodnat *et al.* [19]	Netherlands	SC	1983–1997	509	Adult	54 months (mean, Europeans) 44 months (mean, non-Europeans)	Yes	Yes	AF (*n* = 37), AS (*n* = 44), AR (*n* = 13), TR (*n* = 16)	No	–	–
2) Pallet *et al.* [21]	France	SC	1987–2003	1092	Adult	NS	Yes	Yes	SSA (*n* = 39), CARIB (*n* = 101)	Yes (ClCr CG)	6, 12 months, 5 years	NA
3) Oztek *et al.* [24]	Austria	SC	1997–2005	59	Pediatric	3 years (mean)	Yes	Yes	YU (*n* = 10), TR (*n* = 3), PL, NG, BG, TH (*n* = 1 each)	Yes (Schwartz formula)	NS	NA
4) Mérida *et al.* [22]	Spain	SC	1996–2006	76	Adult	76 months (mean, AF) 68 months (mean, *N*)	Yes	Yes	MA, GN, NG (*n* = 27)	Yes (MDRD)	1 month, end of follow-up (NS)	NA
5) Oztek *et al.* [25]	Austria	SC	1978–2007	197	Pediatric	6.4 years (mean)	Yes	Yes	YU (*n* = 22), TR (*n* = 9), LY (*n* = 9), Other (*n* = 8)	Yes (Schwartz formula)	First outpatient visit (NS), 1 year	NA
6) Tromp *et al.* [20]	Netherlands/ Belgium	MC	2007–2011	119	Pediatric	18 months (median)	Yes	Yes	MA (*n* = 8), TR (*n* = 9) SR (*n* = 7), AS (*n* = 4), CARIB (*n* = 2) Other AF (*n* = 7) Other ME (*n* = 4)	Yes (Schwartz formula)	3, 12 months	NA
7) Laging *et al.* [23]	Netherlands	SC	2000–2010	1338	Adult	4.5 years (median)	Yes	Yes	AF (*n* = 112), AR (*n* = 48), AS (*n* = 132), TR (*n* = 69)	No	–	–

AF, African; AR, Arab; AS, Asian; BG, Bulgaria; CARIB, Caribbean; ClCr CG, Cockcroft–Gault equation for Creatinine Clearance; EU, European; eGFR, Estimated Glomerular Filtration Rate; GN, Guinea; KTR, Kidney Transplant Recipient; LY, Lybia; MA, Morocco; MC, Multicenter; MDRD, Modification of Diet in Renal Disease equation; ME, Middle-East; N, Natives; NG, Nigeria; NA, Not Assessed; NS, Not Specified; PL, Poland; SC, Single Center; SSA, Sub-Saharan Africa; SR, Suriname; TH, Thailand; TR, Turkey; Tx, Transplant; YU, Former Yugoslavia.

history of immigration in the UK, it is likely that only a minority of Black patients were first-generation immigrants [4]. Another Dutch study, which did assess immigration background but not eGFR, reported equal graft and patient survival in non-European as opposed to European KTRs over a mean follow-up of 54 months. However, after introducing ethnicity in their model, the authors found an increased risk of either death or graft failure in KTRs of Arab and African origin [19]. A monocentric study from France reported 5-year creatinine clearance in African immigrants and their native-born counterparts. However, 5-year creatinine clearance was available in only 37 subjects, and the results were simply based on a summary statistics report [21]. A Dutch study with subject ethnicities similar to ours (i.e., African, Arabian, Asian and Turkish) found no significant influence of non-European origin on either patient or graft survival over a median follow-up of 4.5 years. This study included, however, second and third generation immigrants with higher socioeconomic status and better integration compared to the previous Dutch study and did not examine long-term eGFR [23]. It is possible that the overall socioeconomic disadvantage and communicative difficulties specific to first-generation immigrants in Italy and other European countries may have impacted the post-transplant course in non-European-born KTRs [13–15,19,23]. Also, more vulnerable immigrant categories (i.e., refugees, protection status holders, immigrants for family reasons) are all less likely to be well-integrated [13].

Interplay among multiple determinants may have played a role in lower eGFR in non-European-born KTRs. Additional factors contributing to reduced kidney graft function among these patients may include reduced utilization of living donor transplantation, undetermined epidemiologic exposures and risk for opportunistic infections, and other immunological and biological factors such as increased alloreactive immune responses, and different pharmacokinetics of immunosuppressive drugs [20,22,23,38]. Lack of strategies to accommodate the needs of immigrant populations may have equally played a role [40]. Similarly, progressive worsening of kidney graft function over time can also be attributed to non-adherence in KTRs [41]. The effects of poorer levels of health literacy, lower educational levels, the complexity of immunosuppressive medications, inadequate patient-provider communication, and lack of understanding of patients' cultural influences (i.e., medication beliefs, misconceptions about the post-transplant course, language barriers) on self-management and behaviors cannot be excluded as potential determinants of non-adherence and of consequently reduced kidney graft function among non-European-born KTRs [12,42–45]. We were unable to assess the contribution of these factors to lower eGFR in this study, although it seems plausible that access to care alone is unlikely to be an independent determinant of successful KT outcomes.

Our study has several limitations. First, the retrospective nature of the research relies on data included within a national database which, while accurate, cannot identify all the potential confounding variables. No data relative to time elapsed since immigration, post-transplant migration routes, language proficiency, socioeconomic and educational status, rejection episodes, delayed graft function, chronic allograft nephropathy, type of immunosuppressive treatment, immunological and pharmacokinetic biomarkers, and other psychosocial variables including treatment adherence can be retrieved. No data regarding ancestries of EU-born KTRs can be obtained. However, because immigration from non-EU countries beyond Eastern Europe is a recent phenomenon in Italy, we basically did not have adult EU-born individuals with non-European ancestries receiving KT and this mitigates the deficiency. The heterogeneity of the non-European-born categories and the lack of data to further subcategorize these patients based on biomarkers of anti-rejection drug metabolism or increased alloreactivity and immigrant category may conceal disparities in more disadvantaged immigrant groups. Yet, although undocumented immigrants with kidney failure are granted a so-called Temporarily Present Foreigner permit and are entitled to receive DDKT, KT in this particularly vulnerable group of patients is rather infrequent (i.e., less than 10 cases) and there were none included in our study. Other psychosocial outcomes related to immigration status could not be explored. Finally, we focused on the immigrant patient population; other vulnerable groups might equally merit inclusion into future studies of disparities in KT outcomes. Prospective studies are needed to further elucidate the causal pathways linking immigration and ethnicity with KT outcomes. As immigration worldwide increases, future studies should include psychosocial, sociocultural, and socioeconomic data to generate a more accurate picture of KT patient populations. This will enable to determine the need for targeted strategies to accommodate these vulnerable patients and guarantee provision of high-quality care throughout the transplant process.

Authorship

AAG and UM: contributed equally. AAG: conceived the idea, developed the theoretical framework, interpreted the findings, and drafted the article. UM: designed the statistical framework, analyzed the data, interpreted the findings, and drafted the article. PF: extracted and provided the clinical data, critically revised, and approved the article. PAG: contributed to data collection, critically revised, and approved the article. MP: critically revised and approved the article. MC: provided the clinical data, critically revised, and approved the article.

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Conflicts of interest

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