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INVITED COMMENTARY

Renal allograft performance in immigrant transplant recipients

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The growing immigration in EU countries has resulted in gradual increments of immigrant patients with end-stage renal disease (ESRD) which may account for more than 20% in dialysis units or in kidney transplant programmes [1]. The common unfavourable socio-economic situation of these immigrant populations has been considered potentially detrimental for transplant outcomes which led to analyse transplant results mainly evaluating graft and patient survival.

In the current issue of *Transplant International*, Grossi *et al.* [2] report an interesting Italian study analysing deceased donor kidney transplant performance according to estimated-GFR (eGFR) evolution in EU-born patients, Eastern EU-born immigrants and non-EU-born immigrants by using a multivariable-adjusted joint longitudinal survival model. The change in renal function was evaluated from baseline eGFR at 1-year after transplantation up to 5 years. The evolution in eGFR was similar in EU-born kidney transplant recipients (KTRs) and in EU Eastern-born KTRs, but there was a significant decline in eGFR in non-EU-born KTRs (−5 ml/min/1.73 m^2) at 5 years, despite that the mean baseline 1-year eGFR values were similar in the three groups. Importantly, even though that poor renal function may be considered as a surrogate marker for late graft loss, at 5 years these differences in eGFR did not result in inferior transplant survivals, although there was a trend for worse outcomes in non-EU-born KTRs with a hazard ratio of 1.36 for transplant failure vs. EU-born KTR ($P = 0.09$). Interestingly, EU-born KTRs and EU Eastern-born KTRs, with a vast majority of Caucasians, had similar changes in eGFR and transplant survival rates despite the immigrant background of the second group of recipients. After stratifying non-European-born patients according to the ethnic groups, eGFR decline did not present statistically significant differences between groups, and African ethnicity was associated with increased hazard of transplant failure within 5 years, despite similar decline in eGFR.

The relevance of Grossi's study derives from the identification of poorer functional kidney allograft performance after transplantation among non-EU born, without an apparent negative impact on transplant survivals in the mid-term, but which might herald reduced survivals in the long-term. On the other hand, the lack of significant differences between EU-born KTR and Eastern EU-born KTR may indicate that the immigration background *per se* may not fully account for the differences observed on transplant performance. The worse outcomes in African ethnicity as compared with other non-EU ethnicities may also suggest that biological factors may impact on transplant outcomes beyond the immigrant background.

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First-generation immigrants usually suffer from socio-economic disadvantages with cultural and linguistic barriers which may make more difficult the access to health care. In the case of Italy with a public health care system with universal coverage such impediments may have been attenuated. Another concern on the management of non-EU-born KTR has been the adherence to therapy and overall clinical care compliance. The guaranteed supply of immunosuppressive medications by the public health care system may have facilitated treatment adherence. In this regard, taking into account the poorer transplant performance among non-EU-born KTR, it seems advisable to implement especial programmes to evaluate treatment adherence in these transplant populations [3], and a strict pharmacokinetic monitoring quantifying tacrolimus intra-patient variability [4] in selected subset of patients, among which Africans may deserve an especial attention considering their poorer transplant outcomes.

On top of the adverse socio-economic situation that immigration entails, distinct biological factors in ethnicities different from Caucasians may contribute to the poorer outcomes in kidney transplantation in non-EU-born immigrants observed in the current study.

The main described differences among ethnicities are related to alloreactivity and pharmacogenomics. It is well known that African American transplant recipients usually develop more frequent and severe rejection episodes, require higher doses of immunosuppressants, have higher tacrolimus levels variability, and are high-risk patients for steroid withdrawal strategies [5–7]. Racial differences of polymorphisms in genes encoding tacrolimus-metabolizing enzymes and transporters influence drug exposure and the risk of rejection. Patients of African descent are more frequently expressers of CYP3A5, which is associated to low tacrolimus exposure and may be responsible for the higher acute rejection risk after kidney transplantation in recipients of this ethnicity. Asian populations also show genotype differences with Africans and Caucasians that might affect the tacrolimus-metabolizing phenotype [8]. Pharmacogenomic studies in distinct ethnicities may help to refine tacrolimus dosage and exposure to improve patients' management.

Other factors mainly related to the cardiovascular risk profile, such as hypertension and diabetes mellitus, which may also influence transplant outcomes, vary among ethnic groups [7]. In African descent population $APOL_1$ gene has been associated to an increased risk of end-stage renal disease and might be a high-risk genotype for reduced graft survival, which emphasizes the potential relevance of assessing this genotype in kidney donors and recipients [9].

The assessment of eGFR change in the Grossi's study only includes patients with functioning allografts at 1 year after transplantation, which obviated those recipients with failing grafts in the most critical period after surgery when important clinical events, such as acute rejection and delayed graft function, take place and may influence the fate of transplantation [10].

A more holistic approach since the day of transplantation would allow to elicit the detrimental factors that may negatively impact on renal function throughout the entire evolution of renal transplantation in the different ethnic groups. Obviously, such approach would require overcoming the limitations of registry data with prospective designs for immigrant KTRs. These prospective studies may help to identify the risk factors that may account for graft damage and validate potential interventions to preserve renal function in these vulnerable KTR populations.

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