

**RISK OF END STAGE KIDNEY DISEASE IN KIDNEY TRANSPLANT RECIPIENTS
VERSUS PATIENTS WITH NATIVE CHRONIC KIDNEY DISEASE:
MULTICENTER UNMATCHED AND PROPENSITY-SCORE MATCHED ANALYSES**

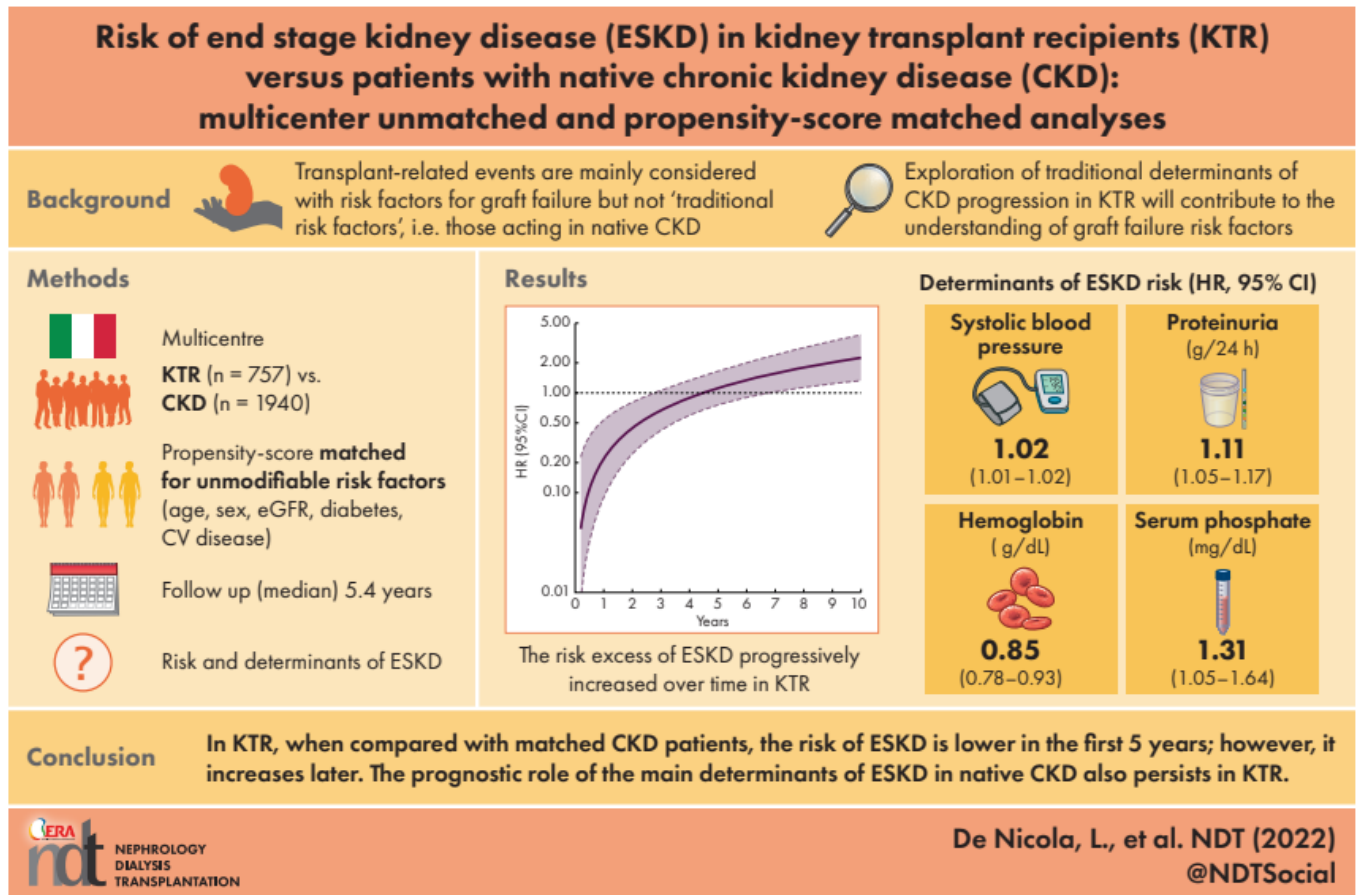
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GRAPHICAL ABSTRACT



ABSTRACT

Background. In kidney transplant recipients (KTRs), the ESKD risk dependent on the risk factors acting in native CKD remains undefined.

Methods. We compared risk and determinants of ESKD between 757 adult KTRs and 1940 patients with native CKD before and after propensity-score (PS) analysis matched for unmodifiable risk factors (age, sex, diabetes, cardiovascular disease and eGFR).

Results. In unmatched cohorts, eGFR was lower in CKD vs KTRs (45.9 ± 11.3 vs 59.2 ± 13.4 mL/min/1.73m², $P < 0.001$). During a median follow-up of 5.4 years, the unadjusted cumulative incidence of ESKD was consistently lower in unmatched KTR vs CKD. Conversely, in PS-matched analysis, the risk of ESKD in KTR was 78% lower vs CKD at one year of follow-up while progressively increased over time resulting similar to that of native CKD patients after 5 years, and 2.3-fold higher than that observed in CKD at 10 years. R² analysis in unmatched patients showed that the proportion of the outcome variance explained by traditional ESKD determinants was smaller in KTRs vs native CKD (31% vs 70%). After PS matching, the

risk of ESKD (HR, 95% CI) was significantly associated with systolic blood pressure (1.02, 1.01-1.02), phosphorus (1.31, 1.05-1.64), 24h proteinuria (1.11, 1.05-1.17) and hemoglobin (0.85, 0.78-0.93) irrespective of KTR status. Similar data were obtained after matching also for modifiable risk factors.

Conclusions. In KTRs, when compared with matched native CKD patients, the risk of ESKD is lower in the first 5 years and higher later on. Traditional determinants of ESKD account for one-third of variability of time-to-graft failure.

Keywords: chronic renal failure, epidemiology, ESRD, kidney transplantation, prognosis

ORIGINAL UNEDITED MANUSCRIPT

KEY LEARNING POINTS

What is already known about this subject?

- Several well-assessed (traditional) risk factors act as predictors for onset of End-Stage-Kidney-Disease (ESKD) in patients with native Chronic Kidney Disease (CKD).
- Risk prediction in Kidney Transplant Recipients (KTR) is based not only on specific immunologic factors but also on these traditional factors.
- This study adds knowledge on the contribution of traditional risk factors of CKD progression in KTR by matching these patients with native CKD patients that allows attaining similar characteristics at baseline.

What this study adds?

- We demonstrated that ESKD risk in KTR, as compared to native CKD, is lower in the early post-transplant period and becomes worse later on.
- Traditional risk factors acting in native CKD did associate with ESKD also in KTR, though with lower contribution, 31% versus 70% of explained variation of model for renal survival.

What impact this may have on practice or policy?

- This study should increase awareness of nephrologists on the importance of traditional risk factors for CKD progression also in KTR.
- Future studies should test in KTR nephroprotective interventions of proven effectiveness in native CKD.

ORIGINAL UNEDITED MANUSCRIPT

INTRODUCTION

Analysis of renal risk in kidney transplant recipients (KTRs) is today primarily aimed at graft survival over the long term. In the last decades, in fact, important advancements have been made in knowledge of the immunobiology of acute rejection; this has allowed implementation of more effective immunosuppressive strategies leading to approximately 90% of patient and graft survival in the first year after transplant [1-4]. Conversely, the most feared complication in KTR remains chronic allograft injury, basically unchanged since the late 1980s, with graft failure occurring in about 20% of cases within 5 years and in more than 50% after ten years [1,5].

To date, transplant-related events have mainly been considered as risk factors for this long-term complication in KTRs [4-6]. However, it is conceivable that, besides chronic antibody-mediated injury, viral infections and iatrogenic nephropathy associated with immunosuppressive treatment, the factors typically acting in native chronic kidney disease (CKD), including low renal function, hypertension, diabetes, proteinuria, anemia and mineral metabolism abnormalities, may also play a role in KTR [6-10]. In this regard, it is noteworthy that while a low eGFR at one year is associated with a higher rate of graft loss, its ability to predict graft failure over the long term remains limited [11,12].

In all the previous studies, the role of traditional determinants of CKD progression in KTRs has not been properly assessed due to the absence of a control group of non-transplanted CKD patients. This control group is essential to dissect the burden of renal risk specifically related to transplantation, which is principally attributable to (often unmeasurable) immunological factors, from that dependent on the non-immunological chronic dysfunction of graft. Only a single study has so far compared progression to kidney failure in KTRs and native CKD patients [13]. Authors found that progressive loss of kidney function was faster in CKD patients than in KTR. However, patients were enrolled from 1985 and 2001, thus making this population poorly representative of the current patient population; furthermore, the two groups were stratified only for basal CKD stage, estimated by the obsolete Cockcroft-Gault formula, thus leaving unexplored the contributing role of other major risk factors, *in primis* proteinuria that is now considered mandatory in any prediction model on renal outcome [14-17].

To fill this critical gap in knowledge, we assessed the long-term allograft survival and the prognostic effect on End-Stage-Kidney-Disease (ESKD) of traditional determinants of risk of graft failure in a multicentric cohort of KTRs compared with a propensity-score matched cohort of non-transplanted patients with native CKD. Results will improve understanding the contribution to graft survival of risk factors typically acting in native CKD.

MATERIALS AND METHODS

This is a multicenter study based on a prospective data collection in consecutive adult KTRs, transplanted in the period 1999-2009 and followed in six Italian outpatient nephrology clinics (Naples “Luigi Vanvitelli”, Naples “Federico II”, Salerno, Bari, Foggia, Catanzaro). In order to make homogeneous the KTR group, we selected only patients receiving their first transplant and only from deceased donor. KTRs were compared in terms of renal risk and its determinants with a contemporaneous (basal visit in 1999-2010) cohort of non-transplanted CKD patients receiving stable nephrology care in the same outpatient clinics from at least six months. In accordance with the aim of the study, we excluded subjects outside the 18-75-year age range as well as those with CKD stage 5. Patients signed informed consent to use their clinical data and study was approved by Institutional Ethical Committees. The paper adheres to the Declaration of Istanbul.

In KTRs, baseline visit was the one performed at 12 ± 2 months after kidney transplantation; this interval was chosen to ensure assessment in the presence of stability of renal function and therapy. Similarly, baseline in the CKD cohort was the 12 ± 2 month visit after the first (referral) visit in the clinic to allow analysis of data in patients fully managed by nephrologists in terms of treatment of risk factors [18].

Cohorts

Cohorts were originally built to collect prospective information of KTRs and CKD patients. Centers shared the same procedures. Briefly, at baseline visit, nephrologists collected medical history including history of cardiovascular disease (stroke, coronary heart disease, heart failure, peripheral vascular disease), performed physical examination and registered laboratory results, therapy and events in anonymous electronic case reports. Laboratory protocols were standardized with in-house analyses. We quantified

proteinuria by 24-hour urine collections; collection was considered inaccurate, and repeated, if creatinine excretion was outside the expected range [14]. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation; since creatinine was not standardized to isotope-dilution mass spectrometry values, levels were reduced by 5% according to Skali et al. [19].

Basal collection included demographic variables, diagnosis of primary kidney disease, transplant and dialysis vintage, history of delayed graft function (DGF, acute kidney injury in the first week of kidney transplantation that needed dialysis treatment), acute rejection (occurring in the first 12 months after surgery).

Aims and endpoints of the study

The study aimed at comparing risk and determinants of ESKD, between KTRs and non-transplanted CKD patients unmatched and matched for unmodifiable risk factors. All demographic, clinical and laboratory variables have been collected at baseline visit. Thereafter, patients were followed for survival analysis until the study endpoint, that is, ESKD (defined as start of chronic dialysis treatment in KTR and dialysis start or kidney transplantation in native CKD group) or all-cause death, as derived from medical records, or until the last clinical visit performed before December 31st, 2018.

Statistical analysis

Continuous variables were expressed as either mean \pm SD or median and interquartile range [IQR] according to their distribution, and categorical variables reported as percentages. Differences in basal characteristics between groups were tested by unpaired Student t-test, Wilcoxon test and Pearson chi-squared test, as appropriate. In the original database, after excluding the 28 patients with essential parameters unavailable, we registered the following missing data: active smoking (n=6), serum phosphorus (n=3), calcium (n=3), cholesterol (n=39), serum albumin (n=31). We tested the difference between patients with one or more missing values and those without missing values in terms of demographics, clinical features, laboratory parameters and outcomes. Next, as we did not find differences, we imputed missing data by implementing multiple imputation [20]. This strategy allowed to include all patients in the study analyses.

Median follow up was estimated by the inverse Kaplan-Meier approach. Cumulative incidence of ESKD, were built using the Aalen-Johansen method and compared with the Gray test [21]. Because ESKD and death before ESKD are competing events - that is, occurrence of death prevents ESKD - we calculated the cumulative incidence of ESKD by using the competing risk approach. This allows to assess the true probability of developing ESKD in CKD [14].

In the survival analysis, we used the Cox's proportional-hazard model to estimate the cause specific hazard ratio (HR) for ESKD and the corresponding 95% confidence intervals (CI). Proportional hazards assumptions were evaluated using Schoenfeld's residuals tests.

In unmatched cohorts, the contribution of each covariate to the model fit was estimated as percentage reduction of R^2 value of the model resulting from omitting each variable in turn from the full model [22]. Explained variation (R^2) of the whole models was estimated by means of Royston's modification of Nagelkerke's R^2 [22]. To evaluate the prognostic effect of risk factors for ESKD, two separate Cox models were fitted by including *a priori* traditional risk factors for ESKD that have been measured in either cohort. A further model was built in KTR patients by adding to traditional risk factors, those risk factors specific to KTRs.

The propensity score method (PS) was used to match KTRs and native CKD patients [23]. This method allows balancing of the characteristics of two groups, especially in the presence of a larger number of subjects in the control group (native CKD) compared with the group of interest (KTR). The propensity score was calculated using the logistic regression method including unmodifiable risk factors measured at baseline: age, sex, diabetes, eGFR, and cardiovascular disease and considering transplant status as outcome variable. A 1:1 match without replacement was used to pair each patient in the KTR group with one patient in the CKD group within the designated caliper size of 0.2 [24]. The method of standardized differences was used to assess the balance of covariates before and after matching [25]. The differences between matched groups were tested by means of a paired test.

A Cox model was therefore fitted to assess the role of kidney transplant on ESKD risk on the matched pairs with a robust sandwich estimate of the variance of the regression coefficient that accounted for the clustering within matched sets [26]. The model was fitted in the matched selection for unmodifiable risk

factors and included as covariates transplantation and the modifiable risk factors not included in the PS. Due to a violation of proportionally assumption of transplantation, an interaction between log(time) and transplantation was added and HR was estimated according to time. In the Cox model, the adjustment for transplantation allowed to estimate the effect of baseline determinants of ESKD risk regardless of the transplant status.

We performed a supplementary PS analysis by matching native CKD and KTR patients not only for unmodifiable but also for modifiable determinants of ESKD (smoking, systolic blood pressure -BP, phosphorus, hemoglobin, 24h proteinuria, body mass index (BMI) and use of Renin-Angiotensin-Aldosterone System inhibitors - RAASi). All variables included in the propensity score matching were collected at baseline study visit.

We repeated analyses after excluding the patients with autosomal dominant polycystic kidney disease (ADPKD) as primary renal disease. Rationale of this sensitivity analysis was that these patients can be characterized by a different risk of CKD progression as compared to other renal diseases. A second sensitivity analysis was performed using a caliper of 0.1 in the main PS matching (for unmodifiable risk factors).

A two-tailed P-value of <0.05 was considered significant. Statistical analyses were performed using software R version 3.6 (R Foundation for Statistical Computing, Vienna, Austria) and STATA version 11.0 (College Station, TX-US).

RESULTS

Patient flow is depicted in Figure 1. We studied 757 KTRs and 1940 patients with native CKD followed in the same nephrology clinic. The KTR group had been dialyzed for 3.98 [2.52-6.50] years on median before transplant. After surgery, a delayed graft function was reported in 26.2% of cases, while acute rejection in the first-year post-transplantation was reported in 14.1% of cases.

Baseline features

Table 1 reports the main features of the two cohorts at baseline. Patients were all Caucasian. The two study populations were remarkably different, with unmatched CKD patients being characterized by a greater burden of cardiorenal risk factors. Controls were in fact older, had higher BMI and BP, and had more frequently smoking habit, diabetes and cardiovascular disease. Diabetic and hypertensive nephropathies were the most frequent cause of renal disease among native CKD patients while in KTRs, glomerulonephritis was the leading cause of CKD. Native CKD patients had more severe kidney disease, as testified by lower eGFR and higher proteinuria. Consequently, the therapy also differed, with higher use of RAASi in native CKD (Table S1).

After matching for unmodifiable risk factors, the number of patients included in each group was 458 (Figure 1). The full logistic regression model used to build the PS-matching is shown in Table S2. As expected, standardized differences between covariates decreased after PS-matching for unmodifiable risk factors (Figure S1), but the native-CKD cohort still differed from KTRs in terms of modifiable risk factors: BMI, smoking, hemoglobin, serum albumin and phosphorus, 24h proteinuria and use of RAASi (Table 1).

Optimal balance of baseline characteristics was obtained by matching patients for both unmodifiable and modifiable risk factors; patients included in this analysis were 340 in each group (Table S3, Table S4, Figure 1 and Figure S2).

Comparison of ESKD risk

No difference between the two cohorts was observed in the median follow-up (native-CKD: 5.3 years [IQR 3.9-8.4]; KTR 5.6 years [IQR 3.6-10.8]). We registered 428 ESKD events in native CKD patients and 125 ESKD events in KTRs. No pre-emptive transplant was registered in the CKD cohort. All-cause death was registered in 279 and 70 native CKD patients and KTRs, respectively. In the whole population, the

analysis of cumulative incidence of ESKD showed higher incidence of renal events in native CKD versus KTR (Figure 2A). This finding was expected due to the higher eGFR level at baseline in KTR vs CKD patients. This difference, however, disappeared following PS matching ($p=0.995$, Figure 2B). Figure 2 is presented for visualization purposes only since it provides a univariate estimation of the event probability.

In PS-matched patients, multivariable analysis disclosed a renal risk in KTRs coherent with the faster increase of the unadjusted incidence of ESKD vs native CKD depicted in Figure 2. Indeed, adjusted time-dependent Hazard Ratio (HR) showed better kidney survival in KTRs than in native CKD in the early follow up while survival worsened in the late period (Figure 3). Specifically, as depicted in Table 2, KTR status conferred a 78% lower risk for ESKD versus native CKD at one year (HR 0.22; 95% CI 0.09-0.54, $p<0.001$) whereas it was associated with a two-fold higher risk at ten years (HR 2.25; 95% CI 1.33-3.81, $p=0.003$).

These results persisted in the full-matched analysis, which encompasses patients balanced for both unmodifiable and modifiable risk factors (Figure S3, Figure S4 and Table S5). KTR status conferred protection against ESKD event at one year follow-up (HR 0.31; 95% CI 0.11-0.92, $p=0.035$) whereas it was associated with a higher risk (HR 2.40; 95% CI 1.31-4.41, $p=0.005$) after ten years.

We also ran two sensitivity analyses. After exclusion of ADPKD patients (first sensitivity analysis), the ESKD risk related to KTR did not change as compared to the main analysis reported in Table 2 (KTR vs native CKD at 1 year HR 0.18; 95% CI 0.07-0.47; at 5 year HR 1.34; 95% CI 0.88-2.05; at 10 year HR 3.17; 95% CI 1.72-5.83). The PS matching with caliper 0.1 (second sensitivity analysis), showed similar results of the original analysis with 0.2 caliper (KTR vs native CKD at 1 year HR 0.22; 95% CI 0.09-0.52; at 5 year HR 1.07; 95% CI 0.73-1.56; at 10 year HR 2.12; 95% CI 1.25-3.59).

Determinants of ESKD risk

At multivariable-adjusted Cox analysis in unmatched patients (Table 3), the two groups shared a significant role of the two major risk factors for ESKD, namely low eGFR and higher proteinuria. Additional determinants, statistically significant only in KTRs, were history of cardiovascular disease and smoking, while younger age, male sex, lower hemoglobin, higher serum phosphate, and higher blood pressure were associated with worse renal outcome only in native CKD. This discrepancy may be dependent on the advanced kidney damage in native CKD which associated with higher prevalence of uncontrolled risk factors acting on renal risk. However, when the two groups were matched (Table 2), and therefore started survival analysis with similar basal conditions, higher systolic BP (HR 1.02; 95% CI 1.01-1.02, $p < 0.001$), proteinuria (HR 1.11; 95% CI 1.05-1.17, $p < 0.001$), serum phosphorus (HR 1.31; 95% CI 1.05-1.64, $p = 0.018$) and lower hemoglobin (HR 0.85; 95% CI 0.78-0.93, $p < 0.001$), significantly heralded higher renal risk independently from the KTR status (Table 2).

When estimating the hierarchy of prognostic factors by R^2 reduction analysis (Table 3), eGFR accounted for the greatest contribution to the model fit in each group (19.1 % in KTR and 48.9% in native CKD) and the same held true for proteinuria (15.3% in KTR and 6.2% in native CKD) among the modifiable risk factors. The proportion of the outcome variance explained by the whole survival models was tested by computing the R^2 value; this analysis showed that traditional ESKD determinants accounted for 31% of the variation in KTRs and 70% in native CKD patients.

We also retested the KTR model by adding four main risk factors of ESKD specific to kidney transplantation, that is, dialysis vintage, delayed graft function, history of acute rejection and use of calcineurin inhibitors. All these factors, with the exception of calcineurin inhibitors, did associate with ESKD (Table 3). By adding these KTR-specific covariates, model prediction increased from 31 to 47%, with dialysis vintage and delayed graft function accounting for the greatest contribution to model fit (Table 3).

DISCUSSION

This is the first study that evaluates long-term renal prognosis and its determinants in KTRs as compared with propensity-score matched patients with native CKD.

We found that balancing the two study groups for the determinants of renal survival acting in native CKD allows disclosing a different pattern of ESKD incidence over time versus unmatched analysis (Figure 2). Indeed, while standard survival analysis showed a cumulative incidence of ESKD that increased linearly over time in native CKD patients, and remained steadily higher vs KTRs, the pattern changed after PS matching, with the increment of ESKD risk in KTRs progressively overcoming that observed in native CKD patients. This finding was unrelated to differences in mortality rates because it was obtained by competing risk analysis that considers death and the ESKD event as competitive events -that is, death prevents onset of ESKD- and corrects for this effect.

The results obtained in unadjusted analysis -cumulative incidence- were confirmed, and quantified, by the multivariable Cox analyses (Table 2 and Figure 3). Specifically, in PS-matched patients, we estimated a 78% lower ESKD risk in KTRs at one year of follow up; thereafter, renal risk progressively increased to become more than two-fold higher vs native CKD patients by the end of observation. It is noteworthy that the biphasic shape of ESKD risk in KTRs vs matched controls became apparent after the main PS analysis, which only included unmodifiable risk factors, and persisted in a similar manner after adding modifiable factors to the main PS analysis (Table S5 and Figure S4).

Among the unmodifiable determinants, the role of basal eGFR was possibly predominant because it showed the largest difference between unmatched patients, with the most remarkable change after matching (Table 1 and Figure S1), and accounted for the greatest contribution to the model fit in unmatched KTRs and native CKD patients as well (Table 3).

These results, while on one side support the findings of previous studies identifying low eGFR as the major determinant of graft failure [11,12,27,28], on the other side raise the question on the potential causes of the reversed risk over time. The current analysis does not allow conclusive interpretation because it only incorporates parameters available in daily nephrology practice. However, we can hypothesize that the

transplanted kidney may be characterized in the early post-transplant period by a greater renal functional reserve (RFR) vs native CKD in the presence of similar eGFR, therefore making the allograft less vulnerable to kidney injuries. As support for this hypothesis, there is the pivotal observation of Ader et al. that tested RFR in KTRs about 7-8 months after transplantation [29]. Authors reported that in their KTR group, with a mean basal GFR (54 ± 4 mL/min) similar to that of our PS-matched transplanted patients (54.1 mL/min/ 1.73m^2), amino-acid infusion elicited a normal response. Conversely, patients with native CKD are characterized by reduced or any RFR [30]. On the other hand, in the late post-transplant period, factors typically associated with graft loss, namely chronic rejection, recurring or de novo glomerulonephritis, calcineurin inhibitor toxicity as well as a reduced adherence to immunosuppression, may all contribute to reverse the direction of ESKD risk, from lower to higher in KTRs vs CKD patients [5,31,32].

Similar to renal survival, also the prognostic role of risk factors differed in the two groups (Table 3). We found that in KTRs the renal survival model globally explained 31% of the variance of outcome. This percentage is expectedly lower as compared with the 70% estimated in native CKD because of the multifactorial nature of graft failure including mechanisms specific to transplant status that are hardly identifiable, and often unpredictable [32]. The contribution to prognosis of unmeasured risk factors widely persisted even after inclusion of the main ESKD determinants specific to KTR (dialysis vintage, history of acute rejection, delayed graft function and use of calcineurin inhibitors); in the latter model, R^2 increased to 47%, therefore suggesting that more than half of the survival model variance in KTRs is still related to additional unmeasured transplant-specific factors (donor characteristics, infections, HLA mismatch, Donor-Specific Antibodies). Nevertheless, we cannot exclude a contribution to the prognosis of other unmeasured factors because in the native CKD cohort there is still 30% of variance in ESKD unexplained by the model.

These results reinforce the need of ameliorating knowledge on the causes of allograft failure in the long term. More important, according to the original objective of this study, we can reasonably argue that treatable risk factors typical of native CKD also act in KTR though to a lower extent. Specifically, we observed that the two groups, while sharing the universal role of eGFR and proteinuria in heralding ESKD, differed for the additional determinants in terms of HR and R^2 reduction (Table 3). Again, the substantially (23 mL/min) lower eGFR in native CKD patients vs unmatched KTRs likely acted as the main driver of this

difference because risk factors strictly correlated with renal function, such as hemoglobin, BP and phosphorus, had a greater prognostic effect in CKD patients compared with KTRs. Similarly, it is possible that the prognostic role of cardiovascular disease and smoking disclosed in KTRs may not become apparent in native CKD patients, because in these patients the entity of risk associated with these factors is mitigated by the major prognostic effect of low eGFR.

The heterogeneous risk profile emerging from the Cox analyses in the two distinct groups does support the PS matched analyses in order to gain insights into the effects on graft survival of the modifiable determinants of ESKD typical of native CKD (Table 2). This analysis, multi-adjusted and balanced for unmodifiable determinants, showed a significantly higher renal risk in the presence of higher BP levels, serum phosphorus, 24h proteinuria and lower hemoglobin, with the effects being independent from KTR status.

It is well known that hypertension in KTRs is result and cause of allograft dysfunction. More important, a pivotal analysis of 1666 KTRs disclosed a 5% increased risk of ESKD and death for each 10 mmHg of systolic BP increase [33]. Albuminuria forecasts renal events in KTRs as it reflects renal microvascular damage besides being a feature of chronic rejection and recurrent or de novo glomerulonephritis [34-36]. Anemia occurring more than 6 months after transplantation is a common chronic complication mainly caused by the reduction of graft function though other causes have been identified including inflammation, viral infections and antiviral agents, as well as immunosuppressive drugs [7,9]. As regards serum phosphorus, an ancillary study in 3,138 participants in the FAVORIT (Folic Acid for Vascular Outcome Reduction in Transplantation) trial has demonstrated that each 1-mg/dL higher serum phosphorus level associates with a 36% higher risk of kidney transplant failure [37]. Interestingly, in non-transplanted CKD patients, hyperphosphatemia may accelerate progression of kidney damage at an early stage of the disease and even in the presence of low proteinuria, as observed in our KTR patients [38]. These findings overall highlight the need of improving awareness of the multiple non-immune mediated mechanisms of graft dysfunction.

Our study has limitations, the main being the observational design that precludes interpretation of results regarding causality. Furthermore, we included only white patients receiving a first transplant from cadaveric

donors, and the PS analysis selected KTR with moderate kidney dysfunction at one year after surgery (eGFR around 50 mL/min/1.73 m²). The study design therefore prevents generalizability of results to all transplanted patients; however, selection criteria still allow to encompass a large subgroup of KTR, and PS is considered an optimal tool to balance measurable confounders (baseline characteristics in our case) in cohort studies. Furthermore, we underestimated the residual risk in KTRs linked to all immunological determinants of graft failure; however, this was not the objective of this study. Indeed, the (original) aim was to gain insights into the renal prognosis of KTR in comparison with native CKD and, more importantly, into the comparison of “traditional” ESKD determinants between KTR and native CKD patients. On the other hand, strengths of the study are the control CKD group matched for several risk factors, the long follow up, and the ESKD risk estimated by accounting for the competing risk of death.

In conclusion, this study adds original knowledge on the long-term renal outcome in KTR. The study provides evidence that in KTRs the traditional determinants of renal risk (i.e., those acting in native CKD) overall account for about one-third of variability of time to graft failure. The propensity-score analyses disclose that (I) in KTRs, as compared with native CKD, graft survival is characterized by biphasic trajectory, better in the first 5 years of follow up and worse in the subsequent period, and (II) the prognostic role of the main determinants of ESKD in native CKD also persist significant in KTRs. Of note, these results can only be hypothesis-generating (not hypothesis-testing) because of the observational design and should be independently validated in other cohorts. Nevertheless, our data call for additional studies in the KTR population aimed at optimizing risk stratification and verifying the effects of nephroprotective interventions of proven efficacy in native CKD.

ACKNOWLEDGEMENTS

We thank all the Investigators who participated to data collection and manuscript elaboration.

FUNDING

This project was not funded.

CONFLICT OF INTEREST STATEMENT

LDN received fees for lectures and scientific consultations from Astellas, AstraZeneca, MundiPharma, NovoNordisk. GG declared participation on a Data Safety Board/Advisor Board for AstraZeneca, GSK and Astellas. VB declared consulting fees from Dr Shaer and honoraria for lectures/manuscript from Fresenius Kabi. RM received payment or honoraria from Amgen, Astellas and Bayer and declared participation on a Data Safety Monitoring Board or Advisory Board for Amgen, Astellas and Bayer.

MP, SB, GS, RS, NI, CG, AM, MA, PC, CI, SF, RC and LG report no conflicts of interest.

AUTHORS' CONTRIBUTIONS

Conception or design, or analysis and interpretation of data, or both: LDN, RS, PC and MA. Drafting the article or revising it, LDN, RS, PC, MA & MP. Providing intellectual content of critical importance to the work described: LDN, RS, PC, MA, MP, RM, AM, NI, SF, RC, VB, CG, CI, SB, GG, GS, LG Final approval of the version to be published: LDN, RS, PC, MA, MP, RM, AM, NI, SF, RC, VB, CG, CI, SB, GG, GS, LG. The results presented in this paper have not been published previously in whole or part, except in abstract form.

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Table 1. Demographic and clinical characteristics of kidney transplant recipients (KTR) and native CKD patients before and after propensity-score (PS) match for unmodifiable determinants of ESKD

| | Unmatched patients | | | PS-matched patients | | |
|---|--------------------|-------------------------|----------|---------------------|-----------------------|----------|
| | KTR (N=757) | Native CKD (N=1,940) | <i>p</i> | KTR (N=458) | Native CKD (N=458) | <i>p</i> |
| Age (years) | 45.9±11.3 | 59.2±13.4 | <0.001 | 49.9±10.0 | 49.0±15.7 | 0.283 |
| Men (%) | 66.5 | 59.5 | 0.001 | 63.5 | 61.1 | 0.454 |
| Body Mass Index (kg/m ²) | 25.4±3.9 | 27.8±5.2 | <0.001 | 25.6±3.9 | 27.1±4.7 | <0.001 |
| Active smokers (%) | 4.7 | 15.2 | <0.001 | 5.7 | 22.3 | <0.001 |
| Diabetes (%) | 12.4 | 28.7 | <0.001 | 17.6 | 14.6 | 0.209 |
| History of CVD (%) | 20.9 | 32.7 | <0.001 | 34.9 | 35.1 | 0.146 |
| Cause of CKD | | | <0.001 | | | <0.001 |
| HTN | 10.3 | 18.9 | | 11.6 | 18.8 | |
| DKD | 1.7 | 28.8 | | 2.6 | 14.6 | |
| GN | 30.5 | 17.6 | | 31.2 | 30.8 | |
| TIN | 6.1 | 9.6 | | 6.8 | 12.6 | |
| ADPKD | 11.9 | 5.3 | | 13.8 | 6.8 | |
| Other/unknown | 39.5 | 19.9 | | 34.0 | 16.4 | |
| CKD stages (%) | | | <0.001 | | | 0.043 |
| Stage 1-2 | 54.5 | 12.2 | | 35.5 | 30.6 | |
| Stage 3A | 21.0 | 20.8 | | 27.3 | 28.2 | |
| Stage 3B | 18.6 | 33.6 | | 28.2 | 27.9 | |
| Stage 4 | 5.8 | 33.5 | | 9.0 | 13.3 | |
| eGFR (mL/min/1.73m ²) | 63.4±22.7 | 40.3±19.2 | <0.001 | 53.4±18.4 | 54.1±25.1 | 0.620 |
| Hemoglobin (g/dL) | 13.3±1.7 | 12.9±1.9 | 0.119 | 13.1±1.8 | 13.5±1.8 | <0.001 |
| Albumin (g/dL) | 4.29±0.41 | 4.03±0.52 | <0.001 | 4.20±0.41 | 4.03±0.57 | <0.001 |
| Calcium (mg/dL) | 9.96±0.82 | 9.41±0.62 | <0.001 | 9.87±0.83 | 9.46±0.63 | <0.001 |
| Phosphorus (mg/dL) | 3.22±0.68 | 3.74±0.77 | <0.001 | 3.22±0.72 | 3.68±0.72 | <0.001 |
| Cholesterol (mg/dL) | 193±41 | 198±45 | 0.007 | 196±43 | 202±51 | 0.050 |
| Proteinuria (g/24h) | 0.15 [0-0.29] | 0.44 [0.13-1.30] | <0.001 | 0.20 [0.08-0.38] | 0.45 [0.13-1.40] | <0.001 |
| SBP (mmHg) | 129±15 | 138±20 | <0.001 | 132±15 | 132±21 | 0.811 |
| RAASi use (%) | 48.2 | 72.0 | <0.001 | 48.7 | 66.6 | <0.001 |

CVD, Cardiovascular Disease; CKD, Chronic Kidney Disease; eGFR, estimated Glomerular Filtration Rate; HTN, Hypertensive nephropathy; DKD, Diabetic Kidney Disease; GN, Glomerulonephritis; TIN, Tubulo-interstitial nephritis; ADPKD, Autosomal Dominant Polycystic Kidney Disease; SBP, Systolic Blood Pressure, RAASi, Renin-Angiotensin-Aldosterone System inhibitors.

Table 2. Multivariable-adjusted Cox regression of determinants of ESKD risk in KTRs and patients with native CKD matched for unmodifiable risk factors by propensity-score analysis

| | HR | 95% CI | p |
|------------------------------------|------|-----------|--------|
| Transplantation (vs native CKD) * | | | |
| Year 1 | 0.22 | 0.09-0.54 | <0.001 |
| Year 5 | 1.12 | 0.76-1.65 | 0.574 |
| Year 10 | 2.25 | 1.33-3.81 | 0.003 |
| Smoking | 1.16 | 0.73-1.83 | 0.537 |
| Body mass index, kg/m ² | 0.97 | 0.93-1.00 | 0.079 |
| Hemoglobin, g/dL | 0.85 | 0.78-0.93 | <0.001 |
| Serum phosphate, mg/dL | 1.31 | 1.05-1.64 | 0.018 |
| Proteinuria, g/24h | 1.11 | 1.05-1.17 | <0.001 |
| Systolic blood pressure, mmHg | 1.02 | 1.01-1.02 | <0.001 |
| RAASi use | 0.96 | 0.70-1.31 | 0.792 |

HR, hazard ratio; CI, Confidence interval; RAASi, Renin-Angiotensin-Aldosterone System inhibitors. Estimates are adjusted for age, gender, diabetes, eGFR, and cardiovascular disease that have been included in the PS-matched analysis. *See Figure 3 for representation of HR throughout entire follow-up.

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Table 3. Multivariable-adjusted Cox analysis of risk factors for ESKD in unmatched KTR and CKD cohorts (Base Model) and KTR-full model (Base Model + variables specific to KTR)

| BASE MODEL | KTR | | | Native CKD | | |
|------------------------------------|------------------|--------|------------------------------|------------------|--------|------------------------------|
| | HR (95%CI) | p | R ² reduction (%) | HR (95%CI) | p | R ² reduction (%) |
| Age, 1 year | 0.99 (0.97-1.01) | 0.209 | 2.1 | 0.96 (0.96-0.97) | <0.001 | 7.7 |
| Male sex | 0.87 (0.58-1.31) | 0.499 | 0.6 | 1.65 (1.33-2.03) | <0.001 | 2.0 |
| Diabetes | 0.68 (0.37-1.25) | 0.220 | 2.2 | 1.14 (0.90-1.44) | 0.285 | 0.1 |
| History of CVD | 1.72 (1.14-2.61) | 0.010 | 9.0 | 1.07 (0.86-1.34) | 0.550 | 0.04 |
| Smoking | 2.51 (1.28-4.92) | 0.007 | 8.2 | 1.21 (0.94-1.57) | 0.146 | 0.2 |
| Body mass index, kg/m ² | 1.02 (0.98-1.06) | 0.288 | 1.5 | 0.98 (0.96-1.00) | 0.094 | 0.3 |
| Hemoglobin, g/dL | 0.92 (0.83-1.03) | 0.137 | 3.0 | 0.91 (0.86-0.97) | 0.003 | 0.8 |
| Serum phosphate, mg/dL | 0.92 (0.72-1.19) | 0.547 | 0.5 | 1.18 (1.06-1.31) | 0.003 | 0.7 |
| Proteinuria, g/24h | 1.60 (1.26-2.04) | <0.001 | 15.3 | 1.16 (1.13-1.19) | <0.001 | 6.2 |
| eGFR, ml/min/1.73m ² | 0.98 (0.97-0.99) | <0.001 | 19.1 | 0.92 (0.92-0.93) | <0.001 | 48.9 |
| SBP, mmHg | 1.01 (1.00-1.02) | 0.093 | 3.7 | 1.00 (1.00-1.01) | 0.047 | 0.4 |
| RAASi use | 0.68 (0.45-1.01) | 0.058 | 4.7 | 0.98 (0.79-1.22) | 0.861 | <0.01 |
| R² value | 31.2 (22.5-52.7) | | | 70.0 (65.4-75.9) | | |
| BASE MODEL plus | | | | | | |
| Dialysis vintage, 1 year | 1.01 (1.00-1.03) | 0.014 | 17.4 | | | |
| History of acute rejection | 1.71 (1.06-2.77) | 0.029 | 7.4 | | | |
| Delayed graft function | 2.70 (1.71-4.29) | <0.001 | 17.9 | | | |
| Use of calcineurin inhibitors | 0.89 (0.45-1.78) | 0.756 | 0.2 | | | |
| R² value | 47.1 (38.2-70.7) | | | | | |

HR, hazard ratio; CI, Confidence interval. CVD, cardiovascular disease; SBP, systolic blood pressure, RAASi, Renin-Angiotensin-Aldosterone System inhibitors.

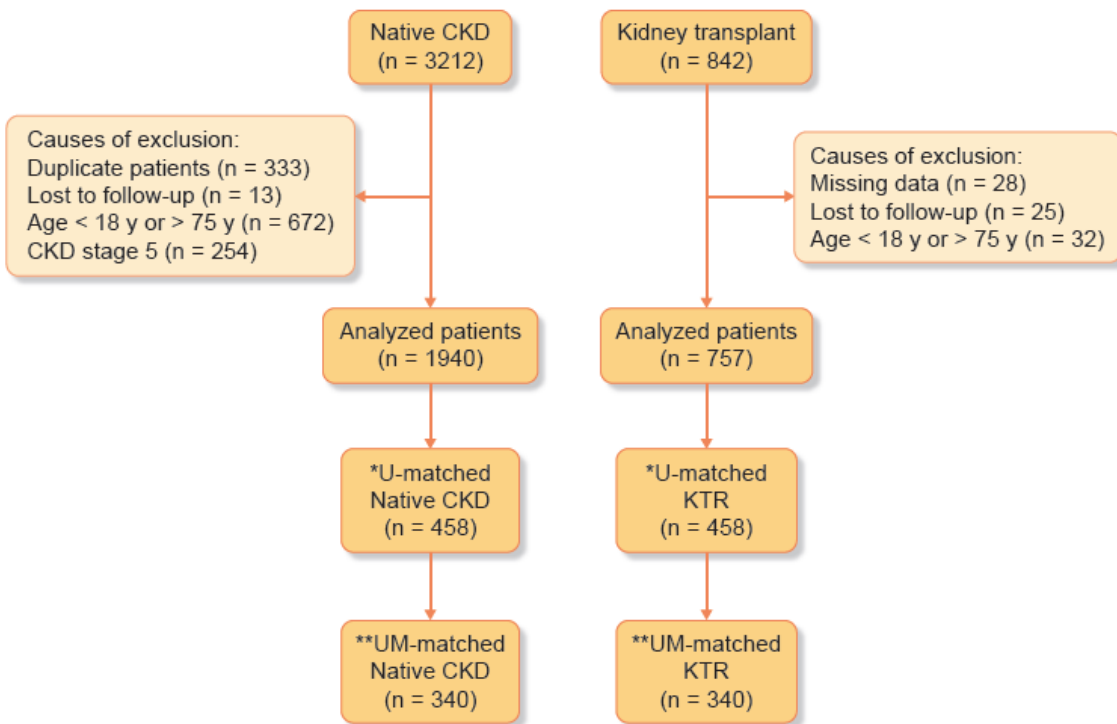


Figure 1. Study flow-chart. * Matched for unmodifiable (U: age, sex, diabetes, eGFR, and cardiovascular disease) risk factors; ** Matched for unmodifiable and modifiable (M: smoking, systolic blood pressure, phosphorus, hemoglobin, 24h proteinuria, body mass index and use of RAASi) risk factors. Patients excluded for missing data were those with no information on essential features (eGFR, proteinuria, blood pressure, RAASI use).

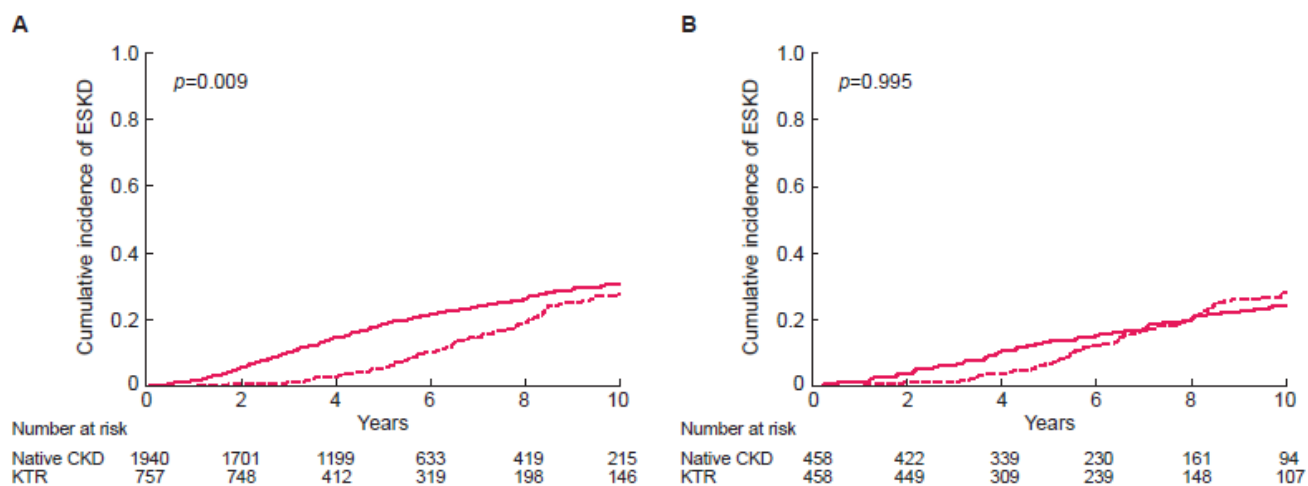


Figure 2. Cumulative incidence of ESKD in native CKD patients (Solid line) and kidney transplant recipients (dashed line) unmatched (panel A), and PS-matched (panel B). For visualization purposes only.

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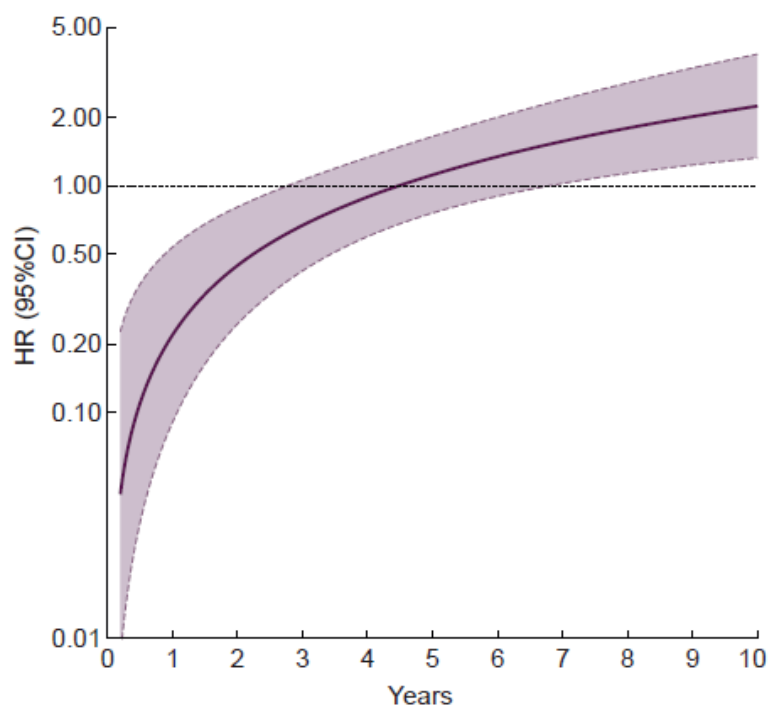


Figure 3. Time-dependent hazard ratio (HR) of KTR status (yes vs no) for ESKD risk in patients (n=458 in either group) matched for unmodifiable risk factors (age, gender, diabetes, eGFR, and cardiovascular disease). Hazards are also adjusted for the variables reported in Table 2.

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