Association of pre-transplant erythropoiesis-stimulating agent responsiveness with post-transplant outcomes

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Abstract

Background. The role of pre-transplant erythropoiesis-stimulating agent (ESA) responsiveness in affecting post-transplant outcomes is not clear.

Methods. Linking the 5-year patient data of a large dialysis organization to the 'Scientific Registry of Transplant Recipients', we identified 8795 hemodialyzed patients who underwent first kidney transplantation. Mortality or graft failure, delayed graft function (DGF) and acute rejection risks were estimated by Cox regression [hazard ratio (HR)] and logistic regression, respectively.

Results. Patients were 48 ± 14 years old and included 38% women and 36% diabetics. Compared to renal allograft recipients who were in the first quartile of pre-transplant ESA responsiveness index (ERI), i.e. ESA dose divided by hemoglobin and weight, recipients in second, third and fourth quartiles had higher adjusted graft-censored death HR (and 95% confidence intervals) of 1.7 (1.0–2.7), 1.8 (1.1–2.9) and 2.3 (1.4–3.9) and higher death-censored graft failure HR of 1.6 (1.0–2.5), 2.0 (1.2–3.1) and 1.6 (0.9–2.6), respectively. No significant association between pre-transplant ERI and post-transplant DGF or acute rejection was detected.

Conclusions. Higher pre-transplant ERI during the hemodialysis treatment period was associated with worse post-transplant long-term outcomes including increased all-cause death and higher risk of graft failure.

Keywords: anemia; erythropoietin-stimulating agent therapy; graft failure; kidney transplantation; mortality

Introduction

Anemia is present in most patients with chronic kidney disease (CKD) treated with renal replacement therapy [1, 2]. Observational studies have repeatedly found anemia to be associated with adverse clinical outcomes in patients with various degrees of CKD [3, 4]. Several studies have shown an association between erythropoiesis-stimulating agent (ESA) responsiveness and mortality in CKD patients [5, 6]. A recent secondary analysis of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) showed that a poor initial response to ESA therapy was associated with increased cardiovascular and all-cause mortality [7]. It has been suggested that the required dose of ESA to achieve a certain hemoglobin level, also known as ESA hyporesponsiveness index, has a bearing on ESA survival associations [8]. In addition to the CKD population not yet on dialysis, poor response to ESA therapy is associated with increased mortality in hemodialyzed patients as well [9, 10]. It is possible, although never tested in randomized trials, that ESA itself, rather than targeted hemoglobin concentration, mediates the increased risk of adverse vascular outcomes due to platelet increase and activation followed by thromboembolic events [11].

However, some data suggested not just ESA itself, but some patient-related factors (such as chronic inflammation, iron deficiency and hyperparathyroidism, among other conditions) [12, 13] also contribute to the increased risk in these patients. Supporting this hypothesis, in CKD patients and kidney-transplant patients, higher endogenous serum erythropoietin levels and resistance to endogenous erythropoietin were associated with increased mortality [14]. This endogenous risk may carry over in a kidney transplant recipient after kidney transplantation.

To the best of our knowledge, only two previous studies have examined the association between pre-transplant ESA responsiveness index (ERI) and post-transplant outcomes [15, 16]. A study of >15 000 kidney transplant recipients described higher mortality and higher incidence of graft failure at 5 years in ESA-hyporesponsive patients [15]. In our study, we assess the association between ERI before transplantation and short-term outcomes such as delayed graft function (DGF) and acute rejection and long-term outcomes such as mortality and graft failure after kidney transplantation. We hypothesized that higher pre-transplant ERI during the dialysis period prior to
kidney transplantation is associated with worse post-transplant patient and graft survival, acute rejection and DGF in a large prospective cohort of incident kidney transplant recipients across the USA.

Materials and methods

Patients

We linked data on all kidney transplant recipients listed in the ‘Scientific Registry of Transplant Recipients’ (SRTR) up to June 2007 to a list of individuals with CKD who underwent maintenance hemodialysis (MHD) or peritoneal dialysis treatment from July 2001 to June 2006 in one of the outpatient dialysis facilities of a US-based large dialysis organization (DaVita Inc., prior to its acquisition of former Gambro dialysis facilities) using the patients’ social security numbers. The study was approved by the Institutional Review Boards of both Los Angeles Biomedical Research Institute at Harbor-UCLA and DaVita Clinical Research.

Clinical and demographic measures

The creation of the national DaVita dialysis patient cohort has been described previously [17, 18]. To minimize measurement variability, all repeated measures for each patient during any given calendar quarter, i.e. over a 13-week interval, were averaged and the summary estimate was used in all models. Average values were obtained from up to 20 calendar quarters (q1 through q20) for each laboratory and clinical measure for each patient for up to 6 years of follow-up. The first (baseline) studied quarter for each patient was the calendar quarter in which the patient’s dialysis vintage was >90 days. Demographic data and details of medical history were collected, with information on age, gender, race, type of insurance, marital status, presence of diabetes, height, post-hemodialysis dry weight [to calculate averaged body mass index (BMI)] and dialysis vintage. Dialysis vintage was defined as the duration of time between the first day of dialysis treatment and the day of kidney transplantation. Histories of tobacco smoking and preexisting comorbid conditions were obtained by linking the DaVita database to the Medical Evidence Form 2728 of the United States Renal Data System, and the latter was categorized into seven comorbid conditions: ischemic heart disease, congestive heart failure, history of hypertension, cerebrovascular events, peripheral vascular disease, chronic obstructive pulmonary disease and cancer.

Laboratory measures

Blood samples were drawn using uniform techniques in all the DaVita dialysis clinics and were transported to the DaVita Laboratory in Deland, Florida, typically within 24 h. All laboratory values were measured by automated and standardized methods in the DaVita Laboratory. Most laboratory values were measured monthly, including serum urea, creatinine, albumin, calcium, phosphorus, bicarbonate and total iron-binding capacity (TIBC). Serum ferritin and intact parathyroid hormone were measured at least quarterly. Hemoglobin was measured at least monthly in essentially all patients and weekly to biweekly in most patients. Most blood samples were collected pre-dialysis with the exception of post-dialysis serum urea nitrogen to calculate urea kinetics. KeFV (single pool) was calculated using urea kinetic modeling equations as described elsewhere [19]. The 3-month-averaged weekly ESA dose was used in our analyses. ERI was calculated by the following rule: time-averaged weekly pre-transplant ESA dose/time-averaged hemoglobin × time-averaged weight) in each quarter before transplantation. To examine the relationship of pre-transplant ESA dose increments/ERI to mortality after kidney transplantation, we divided our patients into quartiles.

Statistical methods

Data were summarized using proportions and means (±SD). We examined P-values for trends across quartiles of pre-transplant ERI. For all-cause and cardiovascular mortality and graft failure, defined as re-initiation of dialysis treatment or re-transplantation, time-to-event was used in all survival analyses. For DGF, defined as the need for any dialysis therapy in the first week after transplantation [20], time-to-event was not accounted for. Acute rejection data were captured from SRTR. Survival analyses to calculate hazard ratios (HRs) and 95% confidence interval (95% CI) of death or graft failure employed Cox proportional hazards regression. In the mortality analyses, the patients were followed until event (death) or censoring (graft failure or end of follow-up period) whichever happened first. In the graft failure analyses, the patients were followed until event (graft failure) or censoring (death or end of follow-up period) whichever happened first. In the combined outcome analyses, patients were followed until event (death or graft failure) or censoring (end of follow-up period) whichever happened first. Logistic regression models were employed to estimate the odds ratio (OR) and 95% CI of post-transplant DGF and acute rejection.

For each regression analysis, four levels of multivariate adjustment were examined: (i) an unadjusted model that included pre-transplant ESA dose/ERI as the predictor, (ii) case-mix-adjusted models that included the above plus age, gender, recipient race-ethnicity (African-Americans and other self-categorized blacks, non-Hispanic whites, Asians, Hispanics and others), diabetes mellitus, dialysis vintage (<6 months, 6 months to 2 years, 2 to <5 years and ≥5 years), primary insurance (Medicare, Medicaid, private and others), marital status (married, single, divorced, widowed and other or unknown), standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by KeFV (single pool), presence or absence of a hemodialysis catheter and residual renal function during the entry quarter and eight comorbidities (atherosclerotic heart disease, congestive heart failure, cancer, chronic obstructive pulmonary disease, cerebrovascular disease, hypertension, peripheral vascular disease, tobacco use), (iii) malnutrition–inflammation complex syndrome (MICS)-adjusted models which included all the above covariates plus 10 surrogates of nutritional status and inflammation measured during the last calendar quarter before transplantation including BMI and nine laboratory variables, i.e. normalized protein catabolic rate as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance [21], and serum or blood concentrations of TIBC, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count, lymphocyte percentage and albumin (and hemoglobin in ESA dose models) and (iv) case-mix-, MICS- and transplant data-adjusted models included all the above plus nine transplant-related variables: (i) donor type (deceased or living), (ii) donor age, (iii) donor gender, (iv) panel reactive antibody (PRA) titer (last value prior to transplant), (V) number of HLA mismatches, (vi) cold ischemia time, (vii) DGF (except when DGF was a dependent variable in our logistic regression models), (viii) history of acute rejection (except when acute rejection was a dependent variable in logistic regression models) and (ix) extended donor criteria using standard definition (donor history of hypertension and/or serum creatinine of donor >1.5 mg/dL and/or cause of death in donor is cerebrovascular event). All analyses were carried out with SAS version 9.1, SAS Institute Inc., Cary, NC, and STATA version 11.1 (STATA Corporation, College Station, TX).

Results

The original 5-year (July 2001 to July 2006) national database of all DaVita patients included 164 789 adult subjects. Of 65 386 DaVita patients who were identified in the SRTR database, 17 629 had undergone one or more kidney transplantation during their life time, but only 14 508 dialysis patients had undergone kidney transplantation for the first time. From these 14 508 dialyzed patients, we excluded patients on chronic peritoneal dialysis (n = 2092), patients who did not have ESA dose data (n = 1402), weight data (n = 486) and the ones without hemoglobin data (n = 1733). We examined the remaining 8795 patients who underwent first kidney transplantation during the observation period and who were followed until death, graft failure, loss of follow-up or survival until 30 June 2007 (Supplementary figure S1). There were 681 deaths (7.7%) and 777 graft failures (8.8%) irrespective of subsequent deaths. The median follow-up time was 724 days (interquartile range was: 357–1201 days). The basic characteristics of waitlisted, but non-transplanted patients, have been described elsewhere [22].
Supplementary table S1 shows the clinical, demographic and laboratory data of the 8795 included and 3621 excluded transplant patients. The graft loss rate was significantly higher in the excluded patients.

Table 1 shows the clinical, demographic and laboratory data of the 8795 transplant patients across four quartiles of pre-transplant ERI. Patients with higher pre-transplant ERI included more women and fewer African-Americans and had higher crude all-cause mortality rate, cardiovascular death rate, crude graft loss and DGF rate and higher PRA level. The rate of acute rejection was not different between groups.

The crude all-cause mortality rate was 33.4/1000 patient-years (95% CI: 31.2–35.8). The crude all-cause mortality rate was increasing across pre-transplant ERI quartiles; it was 25.5/1000 patient-years (95% CI: 21.7–30.0) in the first quartile and 31.2/1000 patient-years (95% CI: 26.7–36.5), 33.8/1000 patient-years (95% CI: 29.1–39.3) and 40.6/1000 patient-years (95% CI: 35.4–46.5) in the second, third and fourth quartiles, respectively. The associations of pre-transplant ERI with the post-transplant risk of death, cardiovascular death, graft failure or the composite of graft failure or death, DGF and acute rejection are shown in Table 2 and Supplementary table S1. Compared to patients in the first quartile of pre-transplant ERI, those in the third and fourth quartiles had 30% [HR: 1.30 (1.04–1.62)] and 57% [HR: 1.57 (1.27–1.94)] higher unadjusted death risk. After additional adjustment for case-mix, MICS and transplant-related variables patients in the second, third and fourth quartiles of the pre-transplant ERI had 68% [HR: 1.68 (1.04–2.72)], 76% [HR: 1.76 (1.09–2.86)] and 135% [HR: 2.35 (1.41–3.91)] higher death risk than recipients in the lowest quartile (Table 2A). Figure 1 and Supplementary figure S2 show the cubic spline models for the association of the entire range of pre-transplant ERI and ESA dose with post-transplant outcomes consistent with the findings in Table 2. The association of pre-transplant ERI (Figure 1A) and ESA dose (Supplementary figure S2A) with mortality was monotonously upgoing until extremely high values. Figure 2 shows fully adjusted HRs of all-cause mortality associated with the fourth quartile compared to the first quartile of pre-transplant ERI in selected patient subgroups. The death HRs were above unity in all examined subgroups, indicating a higher risk of poor outcomes associated with higher pre-transplant ERI. Similar associations were found for cardiovascular death. Compared to patients in the first quartile of pre-transplant ERI, those in the third [HR: 1.27 (0.47–3.42)] and fourth [HR: 2.01 (0.76–5.34)] quartiles had a trend toward higher cardiovascular death risk in our fully adjusted models (Table 2B). Moreover, the association of pre-transplant

### Table 1. Baseline characteristics of 8795 dialysis patients who underwent renal transplantation between July 2001 and June 2006a

<table>
<thead>
<tr>
<th></th>
<th>1 quartile of ERI</th>
<th>2 quartile of ERI</th>
<th>3 quartile of ERI</th>
<th>4 quartile of ERI</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (%)</strong></td>
<td>2199</td>
<td>2199</td>
<td>2199</td>
<td>2198</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>50 ± 13</td>
<td>49 ± 14</td>
<td>48 ± 14</td>
<td>45 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deaths (n) (crude death rate %)</td>
<td>146 (6.6)</td>
<td>159 (7.2)</td>
<td>170 (7.7)</td>
<td>206 (9.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiovascular deaths (n) (crude CV death rate %)</td>
<td>41 (1.9)</td>
<td>32 (1.5)</td>
<td>40 (1.8)</td>
<td>62 (2.8)</td>
<td>0.015</td>
</tr>
<tr>
<td>Graft failure (n) (crude death rate %)</td>
<td>116 (5.3)</td>
<td>194 (8.8)</td>
<td>201 (9.1)</td>
<td>266 (12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DGF (n) (crude DGF %)</td>
<td>470 (22.0)</td>
<td>476 (22.5)</td>
<td>443 (21.2)</td>
<td>407 (20.1)</td>
<td>0.084</td>
</tr>
<tr>
<td>Acute rejection episode (n) (crude rejection %) b</td>
<td>51 (4.4)</td>
<td>40 (3.1)</td>
<td>52 (4.1)</td>
<td>53 (4.5)</td>
<td>0.57</td>
</tr>
<tr>
<td>Gender (% women)</td>
<td>28</td>
<td>35</td>
<td>39</td>
<td>49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race (% African-American)</td>
<td>29</td>
<td>28</td>
<td>27</td>
<td>26</td>
<td>0.016</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>35</td>
<td>39</td>
<td>38</td>
<td>32</td>
<td>0.009</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.0 ± 6.1</td>
<td>27.1 ± 5.3</td>
<td>26.4 ± 5.5</td>
<td>24.7 ± 5.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83 ± 19</td>
<td>79 ± 18</td>
<td>76 ± 18</td>
<td>70 ± 18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 ± 12</td>
<td>170 ± 13</td>
<td>169 ± 15</td>
<td>167 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dialysis vintage (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6 Months</td>
<td>5</td>
<td>7</td>
<td>13</td>
<td>20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6–24 Months</td>
<td>24</td>
<td>28</td>
<td>31</td>
<td>25</td>
<td>0.13</td>
</tr>
<tr>
<td>2–5 Years</td>
<td>45</td>
<td>41</td>
<td>34</td>
<td>29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;5 Years</td>
<td>26</td>
<td>24</td>
<td>22</td>
<td>26</td>
<td>0.82</td>
</tr>
<tr>
<td>nPCR (g/kg/day)</td>
<td>1.05 ± 0.24</td>
<td>1.06 ± 0.25</td>
<td>1.06 ± 0.26</td>
<td>1.04 ± 0.28</td>
<td>0.064</td>
</tr>
<tr>
<td>KRU (mL/min)</td>
<td>0.5 ± 1.7</td>
<td>0.5 ± 1.3</td>
<td>0.4 ± 1.3</td>
<td>0.3 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>10.9 ± 3.2</td>
<td>10.8 ± 3.1</td>
<td>10.6 ± 3.2</td>
<td>10.2 ± 3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood hemoglobin (g/dL)</td>
<td>12.4 ± 1.0</td>
<td>12.3 ± 1.1</td>
<td>12.3 ± 1.2</td>
<td>12.0 ± 1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC (&gt;10³/L)</td>
<td>6.9 ± 1.9</td>
<td>6.8 ± 1.9</td>
<td>6.7 ± 1.9</td>
<td>6.8 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESARi/weight (U/kg/g/dL/week)</td>
<td>7.8 ± 2.8</td>
<td>15.4 ± 2.0</td>
<td>23.7 ± 3.1</td>
<td>49.5 ± 25.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of KGA mismatch</td>
<td>3.7 ± 1.8</td>
<td>3.6 ± 1.8</td>
<td>3.5 ± 1.9</td>
<td>3.7 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRA (%)</td>
<td>7.2 ± 20.2</td>
<td>9.3 ± 23.1</td>
<td>11.2 ± 24.9</td>
<td>13.7 ± 27.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>39 ± 15</td>
<td>39 ± 15</td>
<td>39 ± 15</td>
<td>39 ± 15</td>
<td>0.38</td>
</tr>
<tr>
<td>Donor gender (% women)</td>
<td>45</td>
<td>46</td>
<td>48</td>
<td>49</td>
<td>0.012</td>
</tr>
<tr>
<td>Donor type (% living)</td>
<td>24</td>
<td>30</td>
<td>35</td>
<td>38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDC kidney (%)</td>
<td>18</td>
<td>18</td>
<td>21</td>
<td>17</td>
<td>0.94</td>
</tr>
<tr>
<td>Cold ischemia time (hours)</td>
<td>15.2 ± 9.5</td>
<td>14.4 ± 9.7</td>
<td>14.1 ± 9.4</td>
<td>13.5 ± 9.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

aValues in brackets indicate the crude death and cardiovascular death rate, crude graft failure rate and crude DGF rate in the indicated group during the 6 years of observation. Data are presented as mean ±SD. DGF, delayed graft function; PRA (last value prior to transplant); WBC, white blood cell count; EDC, extended donor criteria; CRU, residual renal function; nPCR, normalized protein catabolic rate.

bAcute rejection data available from 4883 patients.
ERI (Figure 1B) and ESA dose (Supplementary figure S2B) with mortality was monotonously upgoing until extremely high values.

The crude graft failure rate was 52.2/1000 patient-years (95% CI: 49.4–55.1). The crude graft failure rate was increasing across pre-transplant ERI quartiles; it was 20.3/1000 patient-years (95% CI: 16.9–24.3) in the first quartile and 38.1/1000 patient-years (95% CI: 33.1–43.9), 40.0/1000 patient-years (95% CI: 34.8–45.9) and 52.4/1000 patient-years (95% CI: 46.4–59.1) in the second, third and fourth quartiles, respectively. Compared to recipients who were in first quartile of the pre-transplant ERI, recipients in the second, third and fourth quartiles had 57% [HR: 1.57 (1.00–2.49)], 97% [HR: 1.97 (1.24–3.14)] and 58% [HR: 1.58 (0.95–2.64)] higher graft failure risk in our fully adjusted model (Table 2C). Interestingly, the association of pre-transplant ERI (Figure 1C) and ESA dose (Supplementary figure S2C) with graft failure had an inverted U-shape when modeled as a continuous variable and using fractional polynomials and cubic splines. Figure 3 shows fully adjusted HRs of graft failure associated with the fourth quartile compared to the first quartile of pre-transplant ERI in selected patient subgroups. The graft failure HRs were above unity in all examined subgroups, indicating a trend toward higher risk of poor outcomes with higher pre-transplant ERI. Similar associations were found for the combined outcome (Table 2D).

We did not find significant associations between pre-transplant ERI and DGF. Compared to recipients in the first quartile of pre-transplant ERI, recipients in the second [OR: 1.15 (0.91–1.45)], third [OR: 1.07 (0.83–1.37)] and fourth [OR: 1.16 (0.88–1.52)] quartiles had only slightly higher DGF risk in our fully adjusted models (Supplementary table S2A). This observation was confirmed in our cubic spline analyses of the association of pre-transplant ERI (Figure 1D) and ESA dose (Supplementary figure S2D). Supplementary figure S3 shows fully adjusted ORs of DGF associated with the fourth quartile compared to the first quartile of the pre-transplant ERI in selected patient subgroups. The DGF ORs were above unity in almost all examined subgroups, indicating a trend toward a higher risk of DGF, but none of these was significant.

We did not find significant associations between pre-transplant ERI and acute rejection. Compared to recipients in the first quartile of pre-transplant ERI, recipients in the second [OR: 0.91 (0.52–1.59)], third [OR: 0.80 (0.44–1.45)] and fourth [OR: 1.30 (0.72–2.34)] quartiles had similar risks in our fully adjusted models (Supplementary table S2B). This observation was confirmed in our subgroup analyses (Supplementary figure S4).
Discussion

In 8795 kidney transplant recipients with comprehensive pre-transplant data during hemodialysis treatment who were followed for up to 6 years post-transplantation, higher pre-transplant ERI and ESA dose was associated with increased all-cause mortality and graft loss. The association between higher pre-transplant ERI and higher mortality was strong and incremental. Our findings may have major clinical and public health implications in providing care to transplant-waitlisted hemodialysis patients. If our findings are verified in additional studies, assessment of potential causes of high ERI in waitlisted dialysis patients may become an important task in the care of transplant-waitlisted patients.

In our study, compared to recipients in the first quartile of pre-transplant ERI, recipients in the second, third and fourth quartiles had 68, 76 and 135% higher death risk. Similar results were reported in two previous studies [15, 16]. Several potential mechanisms can explain the association between pre-transplant ERI and post-transplant outcomes. Some of these mechanisms are related to the patients themselves and are present after kidney transplantation. Patients on dialysis with higher ESA requirements may be at higher risk for adverse outcomes due to the underlying reasons for their ESA hyporesponsiveness such as protein-energy wasting, inflammation [13], comorbidities [23] and additional yet unmeasured factors due to potential ‘off-target’ non-erythropoietic effects of the higher administered ESA doses or conditions precipitated by the higher doses of ESA, such as iron depletion and platelet activation [11], or due to a combination of these. Protein-energy wasting and inflammation could still be present after kidney transplantation and could contribute to elevated mortality and graft loss risk [24, 25]. Indeed, a re-analysis of the ‘Correction of Hemoglobin and Outcomes in Renal Insufficiency’ (CHOIR) trial led to a similar conclusion that the severity of comorbidities may have confounded the associations between ESA use and outcomes [26].

A recent secondary analysis of the TREAT showed that the demographic, laboratory and clinical parameters of poor versus better ESA responders were not dissimilar except for gender, BMI and smoking status [7]. Hence, the determinants of ESA responsiveness among CKD patients are far from clear. ESA responsiveness may be a
surrogate marker of yet to be recognized pathophysiological conditions that continue to exist in these patients even after renal transplantation and that contribute to the elevated mortality risk and poor long-term graft survival. This notion is supported by another recent observation of ours, that higher levels of endogenous erythropoietin is associated with elevated mortality risk in kidney-transplant patients [14]. In contrast to mortality and long-term graft failure, we did not find any association between pre-transplant ERI and DGF or acute rejection, the two main short-term post-transplant outcomes. DGF and acute rejection are often attributed to immunological injuries to the graft [27], whereas the main contributor to mortality is cardiovascular disease. Hence, the factors related to ESA hyporesponsiveness are likely different from immunological risk factors, leading to higher mortality and long-term graft failure without affecting short-term outcomes.

Our study should be qualified for several potential limitations. Like all observational studies, ours too cannot prove causality. The time period used for this analysis is 2001–06, when the ESA doses were very different from those used nowadays. There is a possibility that the data in our paper may not represent current anemia management in MHD patients. Repeated post-transplant measures of ERI or other laboratory variables and immunosuppressive and other medical regimens were not available in the SRTR database, but in the full model, we did adjust for a number of transplant-related variables. Generalizability may be limited compared to the US CKD population, given the lower proportion of diabetics and the lack of peritoneal dialysis and re-transplanted patients in our cohort. Moreover, the doses of ESA used in Europe and Australia are significantly different from those used in the USA, which weakens the generalizability of our results. We did not have more detailed comorbidity data (only baseline comorbidity was recorded) nor did we analyze dialysis treatment time, which might have impacted the associations. We did not have access to data pertaining to death after graft loss, hospitalizations, surgeries and infections. It is important to note that the excluded patients had lower crude mortality rates and higher graft failure rates, which may bias our study. Erythropoiesis is a slow process, and the impact of any ESA dose level (or change in dose) may not be seen for 2–3 months. Thus, patients with frequent ESA dose changes or fluctuations in hemoglobin are notoriously difficult to assign an ERI to. While we averaged the measurements obtained in any 13-week time period in the study, this does not completely remove the reality that ERI is a ‘blunt tool’ to probe outcomes. Another limitation of our study is that we lacked detailed and updated data of comorbid states or explicit laboratory markers of inflammation, such as C-reactive protein.
To our knowledge, this is one of the first studies examining the association between pre-transplant ERI and post-transplant short-term and long-term outcomes. Strengths of this study include the high number of patients, the relatively long follow-up time and multilevel adjustment, which include several important pre-transplant measures.

Conclusions

In our large and contemporary national database of 8795 kidney transplant recipients, higher pre-transplant ERI and ESA dose during the hemodialysis treatment period was associated with worse post-transplant long-term outcomes including increased all-cause death and higher risk of graft failure. The association between pre-transplant ERI and post-transplant mortality was robust in almost all subgroups of patients.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org.

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References


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