Recombinant Human Erythropoietin for Kidney Transplantation: A Systematic Review and Meta-Analysis

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Purpose: The protective effect of recombinant human erythropoietin (rHuEPO) on kidney transplantation has not been established. Therefore, we conducted a systematic review and meta-analysis to evaluate the potential influence of rHuEPO on transplanted kidneys.

Materials and methods: To identify relevant studies, we searched electronic databases (PubMed, Medline, EMBASE, Ovid, the Cochrane Library, and major nephrology journals) from inception until June 15, 2018. Two independent reviewers assessed study quality. The systematic review and meta-analysis were performed with fixed- or random-effects models according to heterogeneity, and results are expressed as risk ratios (RR) or weighted mean differences.

Results: Six randomized controlled trials with a total of 435 patients met the inclusion criteria. rHuEPO, compared with placebo, had no statistically significant effect on delayed graft function (RR = 0.89, 95% confidence interval [CI] , 0.73 to 1.07; *P* = 0.22) and slow graft function (RR = 0.93, 95% CI, 0.60 to 1.43; *P* = 0.73). The rHuEPO and control groups did not differ in thromboembolic events, mortality, acute rejection, and blood transfusion. A significant difference was found in long-term estimated glomerular filtration rate (RR = 3.65, 95% CI, -4.45 to 11.75; *P* = 0.003).

Conclusion: Our findings suggests that rHuEPO has a limited nephroprotective effect in patients undergoing kidney transplantation and does not increase the susceptibility to adverse events.

Keywords: recombinant human erythropoietin; kidney transplantation; allograft function; delayed graft function; systematic review and meta-analysis

INTRODUCTION

Erythropoietin (EPO) is a hematopoietic growth factor synthesized in response to hypoxemia by fibroblast-like cells in the kidney cortex. It is widely used to treat renal and non-renal anemia, especially in chronic kidney disease and hematopoietic diseases.[1] However, it has pleiotropic effects beyond the maintenance of red blood cell mass,[2,3] playing a role in the protection from inflammation and apoptosis due to of hypoxia, toxicity, or injury.[4] Previous studies suggested recombinant human EPO (rHuEPO) has important cytoprotective effects on various cells and organs, as well as providing protection from ischemia-reperfusion injury (IRI).[5-7]
Kidney transplantation is the treatment of choice for patients with end-stage renal disease to optimize survival, with more favorable lifestyle results and a reduction in mortality rate.[8,9] Delayed graft function (DGF), leading to major comorbidities including IRI, plays a crucial role in long-term graft function after transplantation.[10,11] A previous report estimated an average annual DGF rate of 21.9% for deceased-donor kidney transplants and 3.5% for living-donor kidney transplants in the United States.[12] Improving renal allograft function and survival is a significant challenge in kidney transplantation.
Therefore, rHuEPO is also included in the post-kidney transplantation management, which is a classical model of acute kidney injury (AKI) due to IRI. To verify this finding, several randomized controlled trials (RCTs) have been performed in adult patients undergoing kidney transplantation; nevertheless, the results have been controversial.
In this study, we performed a comprehensive systematic review and meta-analysis of RCTs to examine the efficacy and safety of rHuEPO on allograft function in patients receiving kidney transplantation.

MATERIALS AND METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[13]

Literature search and selection criteria

Two reviewers (Jiaojiao Zhou and Jing Lu) independently searched PubMed, Medline, EMBASE, Ovid, the Cochrane Library, and major nephrology journals from inception to January 28, 2015 without any limitation. To identify eligible RCTs comparing the effect of rHuEPO versus placebo on the prevention of DGF and

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Table 1. The basic characteristics of studies included in the meta-analysis.

Author and year	Country	Study design	rHuEPO group	Control group	Patients (EPO/CON)	Follow-up time
Martine,2010	France	Open-label RCT	EPO-β	NA	51/53	3 months
Aydin, 2012	Netherlands	Double-blind RCT	EPO-β	Saline	45/47	12 months
Hafer, 2012	Germany	Double-blind RCT	EPO-α	Saline	44/44	12 months
Sureshkumar, 2012	USA	Double-blind RCT	EPO-α	Saline	36/36	1 month
Nafar, 2012	Iran	Double-blind RCT	EPO-α	NA	17/23	6 months
Coupes, 2015	UK	Double-blind RCT	EPO-β	Saline	19/20	3 months

rHuEPO: recombinant human erythropoietin; EPO: erythropoietin; NA: not available; RCT: randomized controlled trial; CON:control.

slow graft function (SGF) after transplantation, we used the search terms "EPO" OR "epoetin" OR "erythropoietin" OR "rHuEPO" AND "renal transplantation" OR "kidney transplantation." Reference lists of identified articles were searched for relevant studies and manually scanned to include additional eligible studies.

We included studies that met the following criteria: (1) study population composed of adult patients (≥18 years of age) undergoing kidney transplantation; (2) rHuEPO was compared with placebo; (3) the primary outcomes were the incidence of DGF and SGF; (4) RCT study design. Only articles that met all inclusion criteria were included in this study.

Definitions

The classical definition of DGF as the need for dialysis within the first week after kidney transplantation was generally used, either totally unaltered or with minor additions. SGF was defined as a ≤40% decrease in serum creatinine at postoperative day 3. Short- and long-term estimated glomerular filtration rates (eGFRs) were considered as the values obtained 4 to 6 weeks and 6 months postoperatively, respectively. Short-term blood pressure was defined as the value obtained 4 to 6 weeks postoperatively.

Data extraction and outcomes

Data extraction was performed by two reviewers (Jiaojiao Zhou and Jing Lu); the following items of were extracted: first author, publication year, baseline characteristics of patients, sample size, study design, intervention in the rHuEPO group, intervention in the control group, the incidence of DGF and SGF, and adverse events related to rHuEPO. Additionally, extracted data were reexamined by a third reviewer (Diming Cai), and any disagreements were resolved by discussion. The primary outcomes were the incidence of DGF and SGF. Secondary outcomes were allograft function, adverse events related to rHuEPO, and mortality.

Statistical Analysis

Outcome data were analyzed quantitatively using RevMan software version 5.3 (Cochrane Collaboration, 2014, London, UK). Study quality was independently evaluated by two reviewers (Jiaojiao Zhou and Jing Lu) using a risk of bias summary graph. For categorical outcomes, risk ratios (RR) with 95% confidence intervals (CI) were estimated. For continuous outcomes, weighted mean differences (WMD) with 95% CI were calculated. Cochran's Q-test and □2 index were used to assess statistical heterogeneity. Fixed-effects analysis (I2 < 50%) and random-effects analysis (I2 > 50%) were used in the systematic review and meta-analysis according to standard protocol. For sensitivity analyses, we removed each study separately, calculating RR or WMD after each removal for related outcomes and examined whether any significant changes occurred.

RESULTS

Study Characteristics

Of the 427 records identified, 404 were excluded after initial screening: 43 were duplicate records and 361 studies were rejected based on the title and abstract. Of the remaining 23 full texts, 15 were excluded and 8 studies were retrieved for detailed evaluation. Finally, six RCTs fulfilled the inclusion criteria and were included in our study.[14-19] A flow diagram of the systematic literature search is presented in **Figure 1**, and the basic characteristics of the included RCTs are summarized in **Table 1**. In total, 435 patients were included; of these, 212 patients (48.7%) were treated with rHuEPO and 223 (51.3%) served as controls. Most included studies showed a low to moderate risk of bias; detailed findings are displayed in **Table 2**. Remarkably, the RCT of Martinez et al.[17] had a high risk of bias because it was an open-label study in which the control group did not receive EPO. Moreover, the method of allocation

Table 2. The risk of bias summary graph.

References	Random sequence generation	Allocation Concealment	Blinding of participans and personnel	Blinding of outcome assessment	Selective reporting	Incomplete Outcome data	Other
Martine, 2010	?	?	_	+	+	?	+
Aydin, 2012	+	**?**	+	+	+	+	**?**
Hafer, 2012	**?**	?	+	?	+	+	+
Sureshkumar□ 2012	+	**?**	+	**?**	+	**?**	**?**
Nafar, 2012	+	**?**	+	**?**	+	+	?
Coupes, 2015	+	**?**	+	**?**	+	+	+

Symbol explanation: (+): low risk of bias, (?): unclear risk of bias, (_): high risk of bias.

Table 3. The detail and method of rHuEPO.

Author	Type	Single rHuEPO dose	Total rHuEPO dose	No. of doses	Method of rHuEPO
Martine, 2010	EPO-β	30 000 IU	120 000 IU	4	0.5–3 h before KT 12–24 h after KT 7 days after KT 14 days after KT
Aydin, 2012	EPO-β	33 000 IU	99 000 IU	3	3 h before KT 24 h after KT 48 h after KT
Hafer, 2012	EPO-α	40 000 IU	120 000 IU	3	At intraoperation 3 days after KT 7 days after KT
Sureshkumar,2012	EPO-α	40 000 IU	40 000 IU	1	At intraoperation
Nafar, 2012	EPO-α	2000 U	6000 U	3	Thrice per week, 1 day after KT for one week
Coupes, 2015	EPO-β	33 000 IU	99 000 IU	3	At intraoperation 24 h after KT 48 h after KT

rHuEPO: recombinant human erythropoietin; EPO: erythropoietin; KT: kidney transplantation

concealment was unclear in all studies.[14-19] Details of rHuEPO treatment, as well as demographic and clinical characteristics of recipients and donors, are shown in **Tables 3 and 4**, respectively.

Allograft function

The incidence of DGF and SGF, primary non-function (PNF), and eGFR values were recorded as the common parameters of allograft function endpoints. As described in **Figure 2A**, a trend of reduced incidence of DGF was found in the rHuEPO group (rHuEPO vs. control groups: RR=0.89). However, this decrease did not reach statistical significance (five RCTs, 95% CI, 0.73 to 1.07; $P = 0.22$). There was also no statistically significant difference in the occurrence of SGF between the two groups (three RCTs, RR = 0.93, 95% CI, 0.60 to 1.43; $P = 0.73$). Statistical heterogeneity across studies was not significant ($P = 0.57$, I2 = 0%, **Figure 2B**). PNF rates were documented in three studies, and no significant difference was detected between patients treated with rHuEPO and the control groups (**Figure 2C**). No significant difference was detected in the occurrence of graft loss between the two groups (**Figure 2D**). Short-term eGFR data are shown in **Figure 3A**; no significant difference was found between groups. On the contrary, a significant difference was seen in long-term eGFR between the rHuEPO and control groups (**Figure 3B**).

Adverse events

Based on 435 patients in 6 trials, thromboembolic events were observed in 21 (10%) of 212 patients in the rHuEPO groups and in 13 (5.8%) of 223 patients in the control groups. An efficacy meta-analysis indicated that, compared with control groups, rHuEPO groups did not show a significant increase in the risk of thromboembolic events (five RCTs, RR =1.64, 95% CI, 0.86 to

Table 4. The demographic and clinical characteristics of recipients and donors.

Study	Martine EPO/CON	Aydin EPO/CON	Hafer EPO/CON	Sureshkumar EPO/CON	Nafar EPO/CON	Coupes EPO/CON
Age(years)	60.0 ± 7.7/58.9±9.5	51.0 ± 14.0	53.6 ± 1.8/49.8±1.6	58.0 ± 11.0/56.0 ± 13.0	45.4 ± 12.2/48.3 ± 15.5	51(43-63)/53(46-66)
Gender(males %)	66.7%/56.6%	71.0%/70.0%	56.8%/59.1%	56.0%/53.0%	59.0%/52.0%	53.0%/65.0%
BMI(Kg/m^2)	25.1 ± 4.6/23.8 ± 4.1	NA	25.3 ± 0.6/25.9 ± 0.6	27.8 ± 5.4/28.3 ± 6.4	NA	25(23-27)/ 25(23-29)
Cold ischemia time (hours)	18.8 ± 4.9/19.9 ± 6.9	17.0 ± 4.0/17.0 ± 4.0	12.5 ± 0.6/13.4 ± 0.8	24.1 ± 6.1/26.3 ± 8.0	NA	16.9/16.8
Donor age (years)	65.3 ± 9.4/65.1 ± 8.4	45.0 ± 13.0/49.0±17.0	NA	39.0 ± 17.0/41.0 ± 17.0	NA	52(45-58)/ 53(46-66)
Donor death from CVA(%)	64.7%/73.6%	44%/40%	NA	19%/39%	NA	74%/70%
Donor renal function	91.6 ± 39.5/92.3 ± 36.0 (eGFR,ml/min)	0.86 ± 0.58/0.93 ± 0.57 (sCr, mg/dl)	NA	1.14 ± 0.85/1.18 ± 0.90 (sCr, mg/dl)	NA	61(51-87)/ 77(66-96) (μmol/L)
Induction Immunosuppr-ession Maintenance	Basiliximab	Daclizumab	Basiliximab	Basiliximab or alemtuzumab or ATG	NA	Basiliximab
Immunosuppr-ession	Tacrolimus, MMF, prednisone	Cyclosporine, MMF, steroids	Tacrolimus or cyclosporine, MMF, prednisone	Tacrolimus or cyclosporine, MMF, steroids	Cyclosporine MMF, prednisone	Tacrolimus, MMF, prednisolone
Recipient Previous dialysis	48%/50% (%)	4.3 ± 1.7 /4.0 ± 1.9 (years)	88.4 ± 5.1/67.6 ± 4.9 (month)	NA	NA	30(6-51)/42(22-52) (month)

EPO: erythropoietin; CON:control; BMI: body mass index; NA: not available; CVA: cerebral vascular accident; MMF: mycophenolate mofetil; eGFR: estimated glomerular filtration rate; sCr: serum creatinine ; ATG: antithymocyte globulin. Data are presented as percentages or mean±standard deviation or median (IQR).

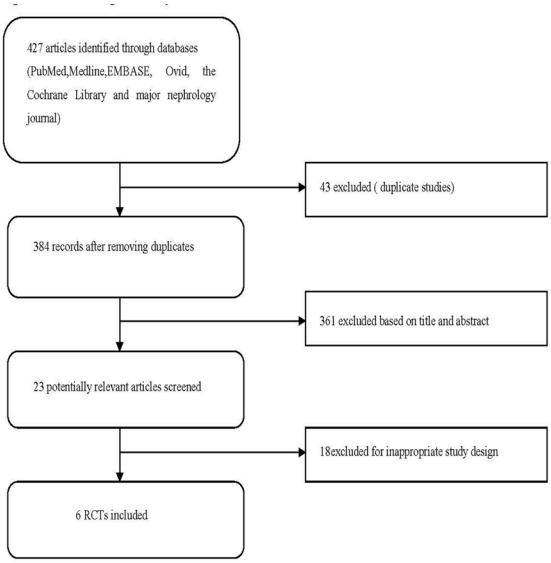

Figure 1. Flow diagram of systematic literature search

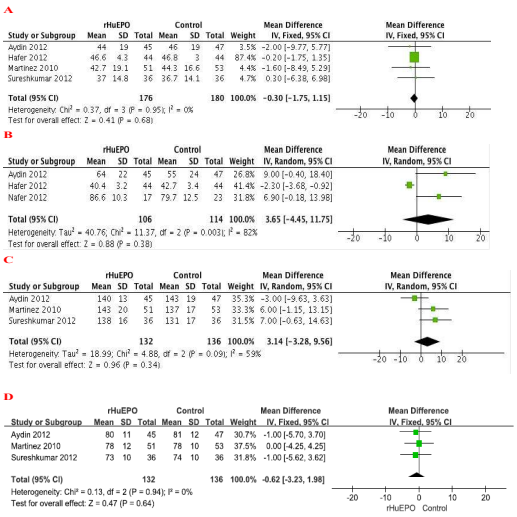

Figure 3. Forest plot of the effects of rHuEPO on short-time eGFR (A), long-time eGFR (B), short-time SBP (C), and short-time DBP (D) in patients treated with rHuEPO compared with controls.

3.13; $P = 0.13$) with negligible statistical heterogeneity (I2 = 41%, **Figure 4A**). Four studies showed no statistically significant difference in the occurrence of acute rejection between the two groups (**Figure 4B**). Furthermore, the incidence of blood transfusion was similar in the two groups (**Figure 4C**). Mortality was documented in all studies; Sureshkumar et al.[14] and Nafar et al.[18] reported no deaths in their studies (**Figure 4D**).

Blood pressure was assessed at different timepoints in each study. In the studies by Sureshkumar et al. 14) and Martinez et al.[17] blood pressure was reported at 4 weeks after transplantation, while Aydin et al. recorded blood pressure 6 weeks postoperatively.[15] We defined blood pressure recorded 4 to 6 weeks postoperatively as short-term blood pressure. No significant difference was found in short-term systolic blood pressure (SBP) and diastolic blood pressure (DBP, $P > 0.05$, **Figure 3C, 3D**).

DISCUSSION

Our findings of this individual patient data systematic review and meta-analysis show that rHuEPO has a certain nephroprotective effect in patients with kidney transplantation without increasing the susceptibility

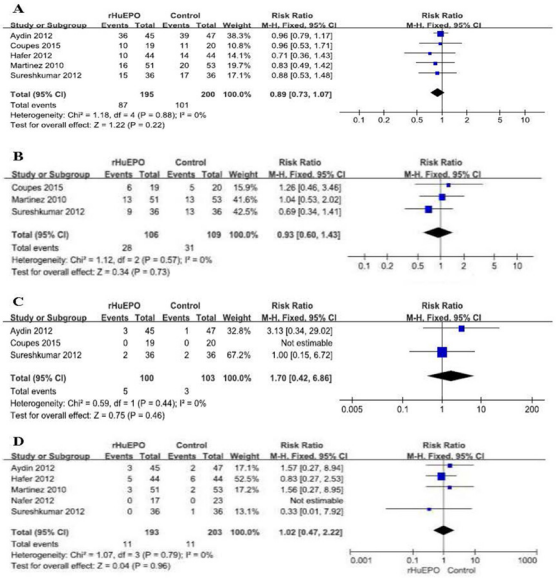

Figure 2. Forest plot with 95% confidence interval in DGF **(A)**, SGF **(B)**, PNF **(C)**, and graft loss **(D)** in patients treated with rHuEPO compared with controls.

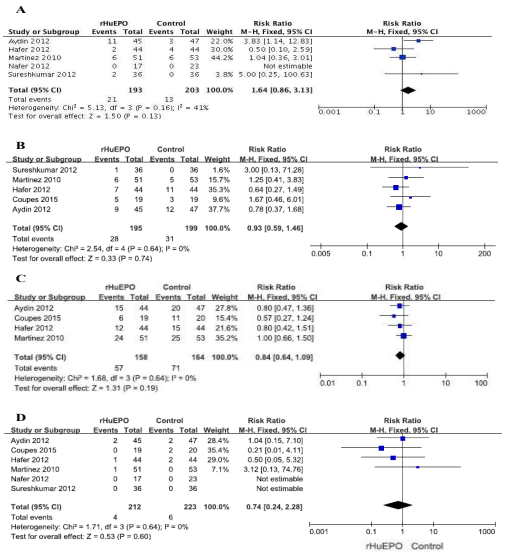

Figure 4. Forest plot with 95% confidence interval in thromboembolic events **(A)**, acute rejection **(B)**, blood transfusion **(C)**, and mortality **(D)** in patients treated with rHuEPO compared with controls.

to adverse events. A recent large clinical study with a total of 3716 kidney transplantations with a long-term follow-up of 25-30 years showed that the outcomes of living unrelated and related donors were comparable in terms of patient and graft survival.[20] Therefore, transplants from living unrelated donors might be an acceptable management alternative for patients with end-stage renal disease. Recent trials and meta-analyses have raised concerns about the safety of rHuEPO use in patients with renal failure, malignancies, chronic heart failure, and acute ST-segment elevation myocardial infarction, but also in kidney transplantation.[21-23] Although Vlachopanos et al.[24] and Xin et al.[25] have conducted meta-analyses examining the clinical efficacy and safety of high-dose rHuEPO in kidney transplant recipients including four RCTs, we included additional studies, one of which was recently published.[18,19] The six RCTs were of relatively high quality and included samples from Europe, America, Oceania, and Asia. Except for the study by Martinez et al., which was an open-label study, there was a low risk of bias since the other studies were double-blind RCTs.[17] Although Nafar et al.[18] used lower rHuEPO doses than other studies, the impact of rHuEPO administration on DGF was not examined. The use of low-dose rHuEPO was also evaluated as part of the endpoints. Since their results may be different or explained from a new perspective, their study was also included.

There were various differences in dosage and timing administration between the studies, which warrant caution when interpreting the results. The doses of rHuEPO used in the included studies ranged from 2000 to 40,000 IU of singe doses and 6000 to 120,000 IU of total dosage. Single doses of 30,000 to 40,000 IU were used in most RCTs, which was considered enough to confer a routine nephroprotective effect and to increase hypertension and thromboembolic events. We considered that this rHuEPO dosage was the smallest dose administered in experimental studies for safety reasons.[18] The timing of rHuEPO dosing also varied considerably among the included studies. Some patients received the first dose of rHuEPO every 3 h or thrice per week, while others received the first dose during surgery. After successful transplantation, the timing of administration ranged from 12 h to 14 days. Previous data have suggested that nephroprotective drugs should be administered from at least 30 min before ischemia until 6 h after ischemia. However, the included RCTs continued rHuEPO administration until postoperative day 14.[17]

We conducted a systematic review and meta-analysis of RCTs evaluating early and rHuEPO administration for DGF as the primary endpoint. This review (Figure 2A) including data from five trials yielded an overall estimate of the RR for DGF of 0.89, a modest effect in favor of rHuEPO, but not demonstrating a significant difference between rHuEPO and control groups. The result was very close to previous studies including four RCTs.(24, 25) In the latest RCT by Coupes et al.[19] DGF was higher than that reported in three previous studies (10/19 = 52.6% and 11/20 = 55.0% in rHuEPO and control groups, respectively), but lower than that reported in the study by Aydin et al.[15] We also found that the occurrence of SGF was not significantly different between the two groups. Including two more RCTs and performing a meta-analysis did not did not lead to different results regarding DGF, PNF, and graft loss compared to previous reviews.[24,25] However, it was encouraging that long-term eGFR, which was not included in previous meta-analyses, was improved in the rHuEPO group compared with the control group.[24,25] This finding indicates that high-dose rHuEPO could improve eGFR 6 months after transplantation.

Sureshkumar et al.[14] and Coupes et al.[19] measured two novel biomarkers, neutrophil gelatinase-associated lipocalin and IL-6, which have been demonstrated to identify patients at risk of developing IRI-AKI earlier. However, they found similar levels between rHuEPO-treated patients and controls. Three of the studies[14,15,19] showed no significant differences between groups, while two[16,17] found higher hemoglobin levels in rHuEPO-treated patients.

As for adverse events, we mainly included thromboembolic events, which are common in patients receiving rHuEPO. After pooling data from six RCTs, we demonstrated that high-dose rHuEPO could increase the incidence of thromboembolic events. Seizures were only noted in one patient treated with rHuEPO in Coupes et al.[19] In the meta-analysis by Vlachopanos et al., SBP was significantly higher in rHuEPO-treated patients at 4 weeks after kidney transplantation.[24] Nevertheless, short-term SBP and DBP were significantly different in rHuEPO-treated patients in our analysis. On the contrary, rHuEPO did not affect mortality, acute rejection, and the incidence of blood transfusion.

Some potential limitations should be considered. First, only six RCTs with a total of 435 patients were included. An incorrect estimation of the effect of rHuEPO is more likely to occur in smaller trials. Second, the timing of administration and type of rHuEPO varied across the six RCTs. Based on the existing literature, selection models centered on heterogeneity testing have some limitations. However, the analysis of binary data using fixed-effect models uses large sample asymptotic variances, so it may perform poorly for studies with very low or very high event rates or small sample sizes. On the other hand, in random-effect models, the weight distribution mainly depends on its accuracy. The weight of each study is equal to the reciprocal of variance (W=1/V). Therefore, the contribution of studies with large samples to the total merged effect is larger than that of studies with small samples, which makes the findings from small sample studies easier to overlook, resulting in them having less weight allocated to them.

CONCLUSIONS

In summary, although there was a trend in favor of rHuEPO in all studies, it failed to reach statistical significance regarding allograft function; however, long-term eGFR was improved. The clinical safety of high-dose rHuEPO was explored in patients with kidney transplantation. Primary adverse events occurring during the transplantation procedure and follow-up period, including thromboembolic events, acute rejection, seizures, and mortality, were distributed equally between the rHuEPO and control groups. To verify the clinical relevance of rHuEPO administration, additional larger, prospective studies of patients undergoing kidney transplantation with uniform rHuEPO administration methods and long follow-up periods are needed.

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