Systematic Reviews

RESEARCH

Open Access

A systematic review and meta-analysis of factors contributing to post-kidney transplant anemia and the effect of erythropoietin-stimulating agents

Kittiphan Chienwichai[1], Supitchaya Phirom[2], Thunyatorn Wuttiputhanun[2,3], Asada Leelahavanichkul[4,5], Natavudh Townamchai[2,3,6], Yingyos Avihingsanon[2,3,6] and Suwasin Udomkarnjananun[2,3,4,5,6*]

Abstract

Background The effects of various risk and associated factors on post-kidney transplant anemia (PTA) have not been fully compared and estimated. This meta-analysis aims to elucidate factors contributing to PTA and determine the influence of erythropoietin-stimulating agents (ESAs) on renal outcomes, thus offering potential pathways for enhanced management strategies post-transplant.

Methods A systematic review was conducted in electronical database. Studies reporting on risk factors (with cause-effect relationships) and associated factors (without definite cause-effect relationships) of PTA, and the effects of ESAs on post-kidney transplant outcomes, were included. Pooled odds ratios (ORs) and weighted mean differences (WMDs) were analyzed using random-effects models.

Results This systematic review encompassed 38,233 patients from 85 studies. Factors increased PTA risk included African American, older donor age, human antigen leukocyte mismatches, and low pre-transplant hemoglobin levels. Poor allograft function, high interleukine-6, *Cytomegalovirus*, delayed graft function, allograft rejections, immunosuppressive medications, and renin-angiotensin system blockades were associated with PTA. Native autosomal dominant polycystic kidney disease was a protective factor against PTA. Administration of ESAs with the aim of normalizing hemoglobin levels in patients with chronic allograft dysfunction slowed the decline in eGFR and reduce the risk of death, with a pooled OR of 0.36 (95% *CI*: 0.14 to 0.89; $p = 0.040$).

Conclusions The risks and associated factors for PTA have been elucidated, underscoring the need for individualized treatment approaches. Late ESA therapy, aimed at hemoglobin normalization, suggests a renal-protective effect and reduced mortality, which should be considered in the management of PTA.

Systematic review registration PROSPERO CRD42024545330.

Highlights

What was known

*Correspondence:
Suwasin Udomkarnjananun
suwasin.u@gmail.com
Full list of author information is available at the end of the article

• Post-kidney transplant anemia (PTA) leads to poor transplant outcomes, including graft loss and death, though the precise impact of each contributing factor remains unclear.

This study adds

• This meta-analysis identified several risk and associated pre- and posttransplant factors, such as donor age, cause of kidney disease, immunosuppressive medications, human leukocyte antigen mismatch, and allograft function, which contribute to PTA.

• The use of erythropoietin-stimulating agents (ESA) in recipients with chronic allograft dysfunction improved allograft function and reduced mortality.

Potential impact

• Factors contributing to PTA were identified and should be used to identify patients at risk.

• ESA therapy in patients with chronic allograft dysfunction is beneficial and should therefore be integrated in the recommendations for late posttransplantation care.

Keywords Anemia, Erythropoietin-stimulating agents, Kidney transplantation, Meta-analysis, Systematic review

Introduction

Posttransplant anemia (PTA) remains a significant complication following kidney transplantation. Studies have reported that PTA affects approximately 20–51% of kidney transplant recipients (KTR) [1–4], leading to adverse outcomes such as a 1.72-fold increase in mortality risk, a 2.28-fold higher risk of graft loss, and a 2.06-fold increase in cardiovascular death, according to a recent meta-analysis [5]. Cohort studies identify various risk factors associated with PTA in KTR. These include recipient age, delayed graft function, use of mammalian target of rapamycin (mTOR) inhibitor and antithymocyte globulin, renin-angiotensin system inhibitor (RASi), poor kidney allograft function, and viral infections [6–9]. However, estimating the exact impact of each risk factor on kidney transplant outcomes remains challenging. This is due to variations in cohorts, PTA definitions, transplant eras, clinical practices, and the limited sample size in each study. Importantly, there has been no study that systematically reviewed factors contributing to PTA.

While experimental studies in animals and cells have illustrated potential advantages of erythropoietin-stimulating agent (ESA), including immune regulatory effects [10–14], antiapoptotic properties [15], protection against ischemic injury [16, 17], and potential preservation of kidney function [18], clinical evidence supporting the benefit of ESA administration in the perioperative kidney transplant setting for preventing delayed graft function and reducing rejection rates is limited. Furthermore, the optimal timing for initiating ESA in anemic KTR and the target hemoglobin levels in the posttransplantation period remains to be established [19–24].

Given the numerous debatable factors regarding their status as true causal risks or merely associated factors for PTA, this systematic review and meta-analysis aimed to explore both types. The goal was to facilitate early detection and prevention strategies. The effects of ESAs in the post-kidney transplant period on transplant outcomes were investigated, including delayed graft function, rejection rates, and long-term kidney allograft function. The objective was to identify patients who may benefit from this therapeutic approach.

Methods

Data sources and searches

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline [25]. The search for eligible studies was conducted in MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials databases on June 1, 2024. In MEDLINE, the search strategy used was ("Kidney Transplantation"[Mesh]) AND ("Anemia"[Mesh] OR "Erythropoietin"[Mesh]). For Scopus, the search terms were (TITLE-ABS-KEY (kidney AND transplantation) AND TITLE-ABS-KEY (anemia) AND TITLE-ABS-KEY (erythropoietin)). In the Cochrane Central Register of Controlled Trials, MeSH descriptors that exploded all trees of [Kidney Transplantation] and ([Anemia] or [Erythropoietin]) were applied. Additionally, the reference lists of qualified articles were reviewed, and relevant studies were manually included if appropriate. The search protocol was registered in PROSPERO CRD42024545330.

Study selection

For inclusion in this systematic review and meta-analysis, cohorts or controlled trials were considered suitable if they provided data on both anemic and non-anemic patients, including demographic and clinical characteristics categorized by anemia status or odds ratios with confidence intervals for risk factors associated with PTA in KTR. Baseline demographic information, laboratory

results, and treatment details relevant to transplantation were extracted separately for anemic and non-anemic groups. The definitions of anemia used in the original articles were retained, recognizing variations across studies.

Additionally, studies were included if they reported on the use of ESA in KTR. This encompassed KTR who received ESA peri-operatively or post-transplant, with or without specific dosage or hemoglobin level targets, and documented kidney function post-treatment. In this review, early ESA therapy was defined as administration within the first week post-transplant, while late ESA therapy was administration after the first week. All outcomes following ESA treatment were considered.

Non-English articles were excluded due to limited access to non-English databases. Furthermore, previous studies have shown that language restrictions do not introduce significant bias in conventional medicine research [26, 27]. Only original articles with reported outcomes were included, and other study types such as editorials, opinions, and reviews were excluded. Case reports and case series were excluded from the meta-analysis to minimize the risk of selection and reporting bias. Studies involving pediatric populations (under 18 years old) were also excluded, as this study focuses on adult KTR, and the clinical practices for pediatric KTR differ from those for adults. In cases of potential duplication of study populations across multiple articles, preference was given to the study providing more comprehensive information on anemic and non-anemic patients. Screening of citations, abstracts, and full-text articles was performed independently by two authors (K. C. and S. P.), with any disagreements resolved through consensus or by a third author (S. U.).

Data extraction and quality assessment

A structured data collection form was utilized to gather essential information from selected studies. This form included various aspects including author names, publication date, journal title, country of origin, collaboration setting, study design (cross-sectional, cohort, or randomized controlled trial), posttransplant duration, follow-up period, recruitment timeframe, timing of PTA diagnosis and first ESA dose, ESA dosages, total number of KTR, anemia definition, and the count of anemic and non-anemic patients. For potential predictive factors, detailed patient characteristics, laboratory findings, and treatment specifics were recorded separately for each study and categorized based on anemia status.

The quality assessment process employed established tools: the Newcastle–Ottawa scale (NOS) for cohort studies [28, 29], the adapted NOS for cross-sectional studies [30], and the revised Cochrane risk-of-bias tool (RoB2) for randomized controlled trials [31]. The NOS and the adapted NOS assess three domains: selection, comparability, and outcome. The RoB2 includes the following domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Two researchers (K. C. and S. P.) independently conducted the quality assessment, resolving any disagreements through discussion and consensus before proceeding. Any unresolved discrepancies were addressed with a third reviewer (S. U.) to ensure accuracy and reliability in the assessment process.

The quality assessment tool's scaling involved converting results NOS into standards defined by the Agency for Healthcare Research and Quality (AHRQ) as "good," "fair," and "poor" quality. For studies assessed using NOS criteria, those receiving a rating of 3 or 4 stars in the selection domain (representativeness, selection of non-exposed cohort, ascertainment of exposure, and outcome not present at start), 1 or 2 stars in comparability (study controls and additional factors), and 2 or 3 stars in outcome/exposure (outcome assessment, follow-up time, and adequacy of follow-up) were deemed of good quality. Studies with a rating of 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcome/exposure were considered fair quality. Poor-quality studies were those with a rating of 0 or 1 star in selection, 0 star in comparability, or 0 or 1 star in outcome/exposure. The adapted NOS includes three domains: the selection (representativeness, sample size, non-response rate, and ascertainment of screening tool), comparability (potential confounders investigation), and outcome (assessment of outcome and statistical test). For studies evaluated using an adapted version of the NOS, those scoring 7–8 points were classified as good, 5–6 points as fair, and 0–4 points as poor. Regarding the RoB2, studies were categorized as having low risk of bias if they exhibited low risk across all domains for the given result. Studies raising concerns in at least one domain without being deemed high risk were classified as having some concerns. Those with high risk of bias were either determined to have high risk in at least one domain or raised concerns across multiple domains.

Data synthesis and analysis

We utilized random-effects models to calculate pooled weighted mean differences (WMD) for continuous variables, along with pooled odds ratios (OR) for binary variables. Our meta-analysis aimed to analyze the risk factors of PTA based on pretransplant variables to identify cause-effect relationships. Additionally, we examined associated factors between anemic and non-anemic patients in the posttransplant period, where cause-effect relationships cannot be clearly

confirmed. The study also compared kidney transplant outcomes between early ESA therapy versus no treatment, late ESA therapy versus no treatment, and late ESA therapy with high versus low hemoglobin target. An analysis of anemia outcomes for graft and patient survival was excluded in this study, as it had recently been reported in another notable meta-analysis [5].

The heterogeneity variance (τ^2) was estimated using restricted maximum likelihood procedures for continuous outcome data [32] and the Paule-Mandel estimator for binary effect size data [33]. Knapp-Hartung adjustments were used to calculate the confidence interval around the pooled effect [34]. In cases where studies provided only the median and range or interquartile range, the mean and standard deviations (SD) were estimated using the method described by Wan et al. [35] If the studies included in our analysis did not provide odds ratios (OR), the ORs were computed using the available raw data. Pooled ORs were calculated using the logarithm of effect size and standard error from each study. When studies encompassed multiple follow-up time periods, data from the longest follow-up duration available were used. Studies included in the meta-analysis had to be at least three to allow for pooling and analysis. Heterogeneity among the pooled effect sizes was assessed using the I^2 index and the Cochran's Q test. An I^2 index exceeding 75% indicates medium to high heterogeneity. Even in instances of low or absent heterogeneity, random-effects models were prioritized over fixed-effects models due to potential differences in clinical care among KTRs. A regression-based Egger's test and visual inspection of funnel plots were used to test for small-study effects. Finally, trends in anemia prevalence over time were analyzed by plotting time of analysis versus prevalence rates from multiple cohort studies reporting anemia assessment timing. Each data point represents a different study, with size and color indicating total population size. Author labels and a spline line were added for clarity. All analyses were performed using R Core Team (R version 4.3.1, 2023).

Ethical considerations

This meta-analysis and systematic review did not directly obtain data from human or animal subjects. All information from the included studies was sourced from published scientific journals without the ability to identify individual patients. The clinical and research activities reported adhere to the principles of the Declaration of Istanbul, as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism."

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Characteristics of the included studies

The flow diagram in Fig. 1 illustrates the study selection process. Initially, 3366 studies were identified based on the search criteria. After removing duplicate citations and irrelevant studies, 445 articles underwent full-text review. This process led to the inclusion of 85 articles in the final meta-analysis, aggregating data from 38,233 patients. Among these, 66 studies provided data on patients with and without anemia, along with their demographic and clinical characteristics categorized by anemia status [1–4, 7, 8, 36–95]. Additionally, 19 studies investigated the impact of ESA on kidney function and transplant outcomes in KTR [19–23, 96–109]. Among the final 85 studies included, no other potential duplicated datasets were identified.

The meta-analysis encompassed 48 cohort studies [1–3, 7, 36–39, 41, 43, 44, 46, 49, 52–54, 56–60, 62, 63, 65, 66, 72, 75–81, 84–86, 88–92, 94–96, 98, 99, 105, 107], 23 cross-sectional studies [4, 8, 40, 42, 45, 47, 48, 50, 51, 55, 61, 64, 67–71, 73, 74, 82, 83, 87, 93], and 14 randomized controlled studies [19–23, 97, 100–104, 106, 108, 109]. Detailed information for each study can be found in Supplementary Table S1. Most publications were from the years 2008 to 2015, with a median publication year of 2011. The USA had the highest number of publications (10 publications), followed by Spain (8 publications) and France (6 publications). Anemia definitions varied across studies. The World Health Organization's criteria, defining anemia as Hb < 12 g/dL for females and < 13 g/dL for males, were the most used. The duration of follow-up varied among the included studies, with a median of 24 months and a range from 12 to 60 months. The median prevalence of anemia among KTR in these studies was 36%, with a range from 26 to 46%. The overall risk of bias for the included trials and studies was considered moderate. The quality assessments based on the NOS, the adapted NOS, and RoB2 assessments for the included studies can be found in Supplementary Table S2 and Supplementary Table S3.

Given the extensive information analyzed in this meta-analysis, the risks and associated factors of PTA are summarized in Fig. 2 for clarity. Risk factors were identified when a clear temporal cause-and-effect relationship could be established based on the results of each study. Associated factors were reported when causality could

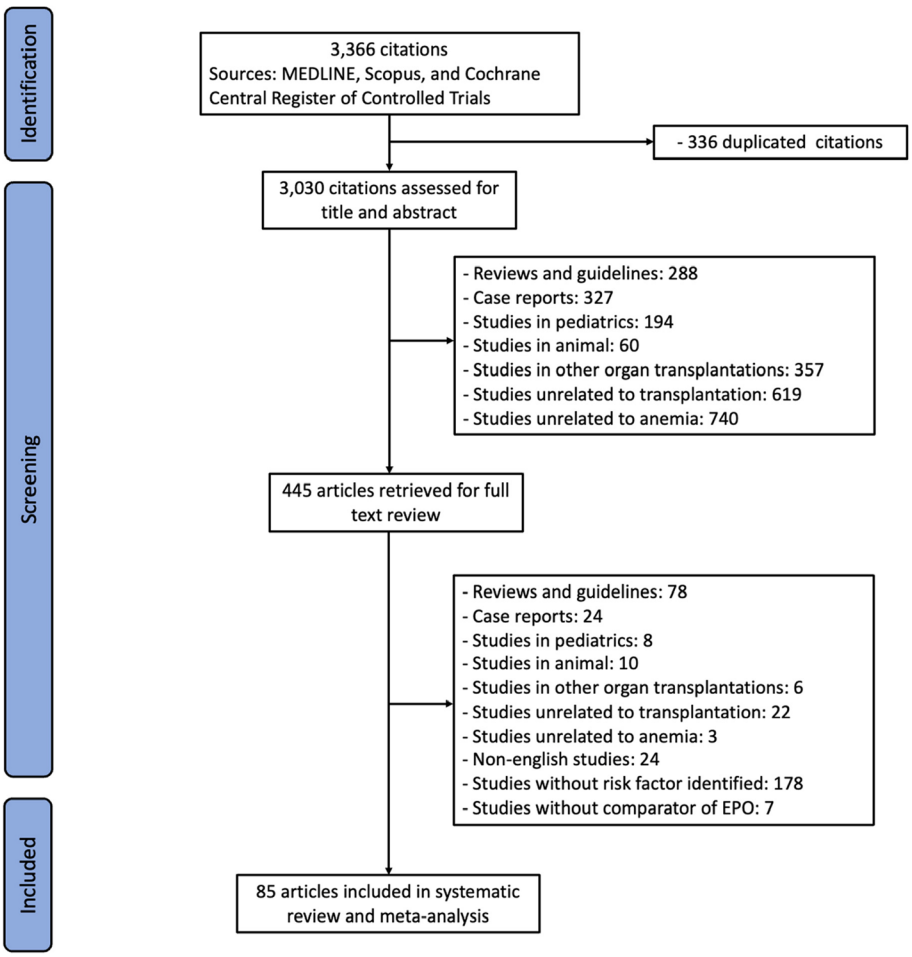


Fig. 1 Study selection flow diagram

not be definitively confirmed. Detailed results are provided in the subsequent section.

Meta-analysis of risk factors predicting PTA

The pooled estimates of risk factors of PTA can be found in Supplementary Table S4. The median number of studies reporting these clinical characteristics was 8, with a range of 5 to 10. The median number of patients across these studies was 6460, ranging from 3984 to 10,466.

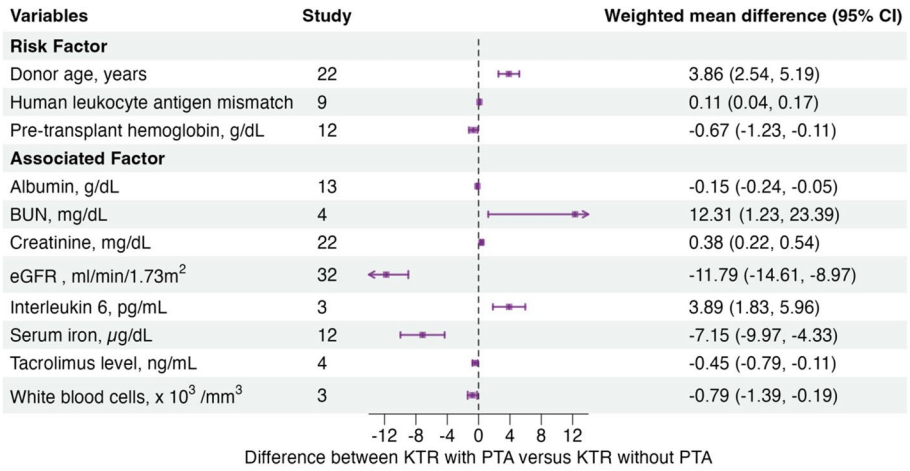
African American ethnicity was identified as a risk factor for a higher incidence of PTA (pooled *OR* 1.64, 95% *CI* 1.14 to 2.35, $p=0.007$). Interestingly, patients with end-stage kidney disease (ESKD) from autosomal polycystic kidney disease (ADPKD) showed a lower incidence of PTA (pooled *OR* 0.59, 95% *CI* 0.51 to 0.68, $p<0.0001$). Additionally, lower pretransplant hemoglobin levels were a predictor of anemia post-transplant (*WMD* −0.67 g/dL, 95% *CI* −1.23 to −0.11, $p=0.023$).

For transplant-related variables, an older kidney donor and an elevated number of human leukocyte antigen (HLA) mismatches were identified as risk factors for PTA (*WMD* 3.86 years, 95% *CI* 2.54 to 5.19, $p<0.0001$, and *WMD* 0.11, 95% *CI* 0.04 to 0.17, $p=0.006$, respectively).

Meta-analysis of factors associated with posttransplant anemia

Supplementary Table S4 details the pooled estimates of patient characteristics associated with PTA. The median number of studies reporting these clinical characteristics was 10, ranging from 5 to 13. The median number of patients included across these studies was 5345, ranging from 1898 to 9142.

Decreased kidney allograft function was significantly associated with PTA. This included higher blood urea nitrogen (BUN) levels (*WMD* 12.31 mg/dL, 95% *CI* 1.23 to 23.39, $p=0.039$) (Fig. 3A), elevated creatinine levels (*WMD* 0.38 mg/dL, 95% *CI* 0.22 to 0.54, $p<0.0001$) (Fig. 3B), and decreased estimated glomerular filtration rate (eGFR) (*WMD* −11.79 mL/min/1.73 m^2, 95% *CI* −14.61 to −8.97, $p<0.0001$) (Fig. 3C), all of which



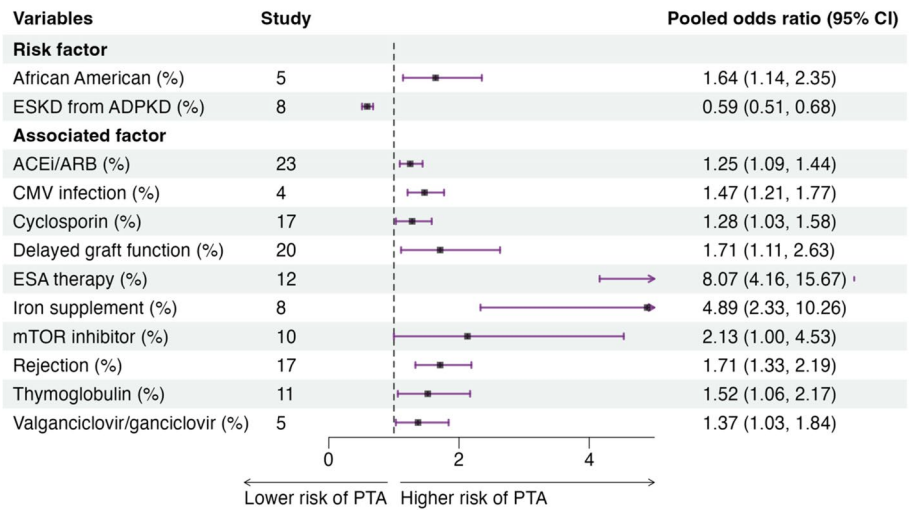


Fig. 2 Forest plots of the pooled effect sizes of risk and associated factors for PTA. ACEi, angiotensin-converting enzyme inhibitors; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin II receptor blockers; BUN, blood urea nitrogen; CI, confidence interval; CMV, *Cytomegalovirus*; ESA, erythropoietin-stimulating enzyme; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; mTOR, mammalian target of rapamycin; PTA, posttransplant anemia

were associated with PTA. Supplementary Figure S2 shows funnel plots for the association of renal function with PTA.

Lower serum albumin levels were observed in the anemic group (*WMD* − 0.15 g/dL, 95% *CI* − 0.24 to − 0.05, $p = 0.005$), and a reduction in serum iron was associated with anemia (*WMD* − 7.15 µg/dL, 95% *CI* − 9.97 to − 4.33, $p = 0.0002$). The pooled data did not show a statistically significant association between ferritin levels and anemia (*WMD* 33.64 ng/mL, 95% *CI* − 1.01 to 68.29, $p = 0.056$). Interleukin-6 (IL-6) (*WMD* 3.89 pg/mL, 95% *CI* 1.83 to 5.96, $p = 0.015$) were associated with anemia. Additionally, white blood cell count was found to be lower in anemic patients (*WMD* $-0.79 \times 10^3/\text{mm}^3$, 95% *CI* − 1.39 to − 0.19, $p = 0.03$).

There was an observed association between the development of anemia and the medication used during transplantation. An association was found with thymoglobulin therapy (pooled *OR* 1.52, 95% *CI* 1.06 to 2.17, $p = 0.020$) (Fig. 4A), mTOR inhibitor (pooled *OR* 2.13, 95% *CI* 1.00 to 4.53, $p = 0.05$) (Fig. 4B), and cyclosporin (pooled *OR* 1.28, 95% *CI* 1.03 to 1.58, $p = 0.024$) (Fig. 4C). The use of tacrolimus, mycophenolic acid, azathioprine, or prednisolone per se did not demonstrate a significant association with anemia. However, a lower tacrolimus pre-dose concentration showed significant association with PTA (*WMD* − 0.45 ng/mL, 95% *CI* − 0.79 to − 0.11, $p = 0.025$).

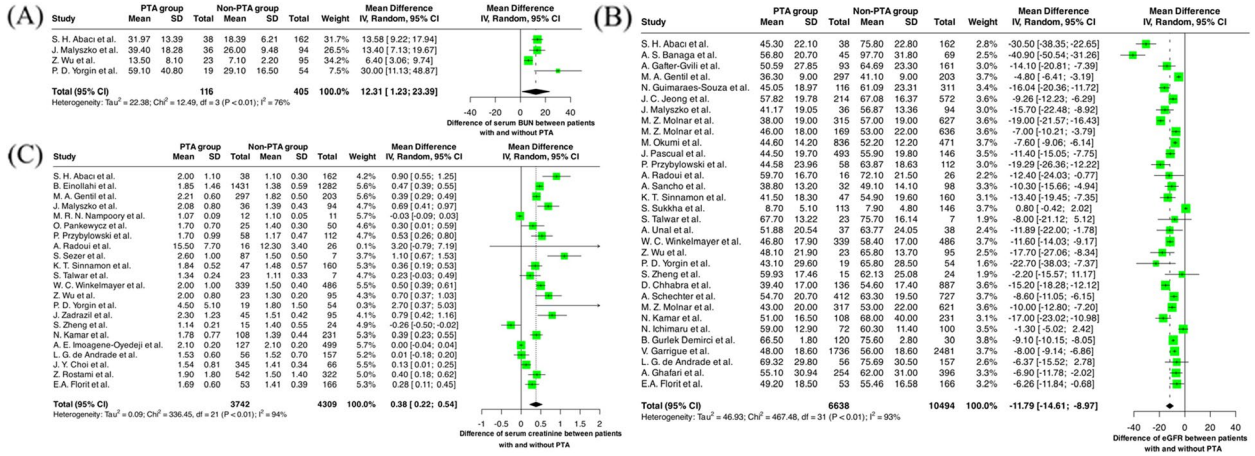


Fig. 3 Forest plots of the association between kidney functions and PTA. **A** BUN (mg/dL). **B** eGFR (ml/min/1.73 m^2). **C** Creatinine (mg/dL). BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; IV, inverse variance method; PTA, posttransplant anemia; SD, standard deviation

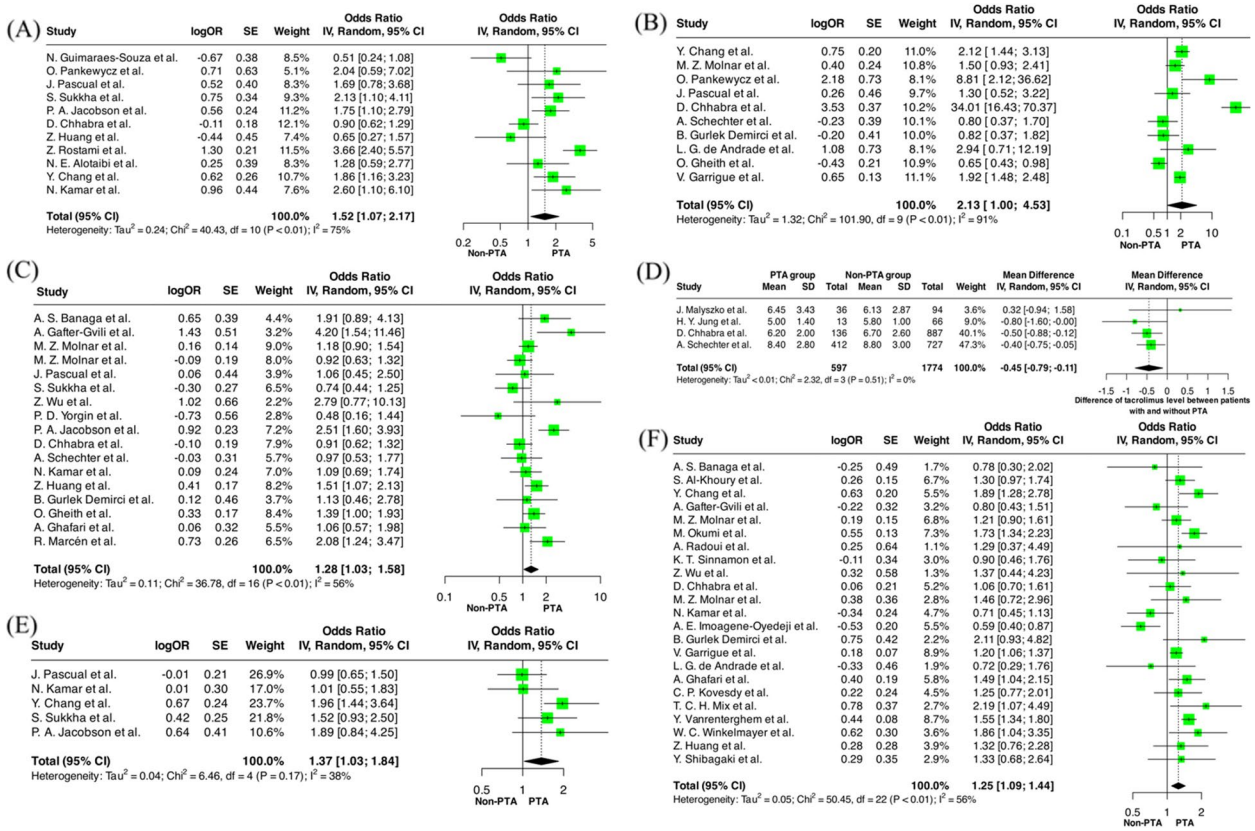


Fig. 4 Forest plots of the association between medications and PTA. **A** Thymoglobulin. **B** mTOR inhibitor. **C** Cyclosporin. **D** Tacrolimus level (ng/mL). **E** Valganciclovir/ganciclovir. **F** ACEi/ARB. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CI, confidence interval; IV, inverse variance method; mTOR, mammalian target of rapamycin; OR, odds ratio; PTA, posttransplant anemia; SD, standard deviation; SE, standard error

Angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blocker (ARBs) was associated with PTA (pooled *OR* 1.25, 95% *CI* 1.09 to 1.44, $p=0.001$).

Iron supplementation (pooled *OR* 4.89, 95% *CI* 2.33 to 10.26, $p<0.0001$) and the use of erythropoietin (pooled *OR* 8.07, 95% *CI* 4.16 to 15.67, $p<0.0001$) were found more frequently in KTR with PTA. Treatment with valganciclovir/ganciclovir was also associated with a higher occurrence of PTA (pooled *OR* 1.37, 95% *CI* 1.03 to 1.84, $p=0.033$). Supplementary Figure S3 shows a funnel plot for the significant association between medication and PTA.

Transplant-related factors were also significantly associated with PTA. PTA was associated with delayed graft function (pooled *OR* 1.71, 95% *CI* 1.11 to 2.63, $p=0.015$) (Fig. 5A), *Cytomegalovirus* (CMV) infection (pooled *OR* 1.47, 95% *CI* 1.21 to 1.77, $p<0.0001$) (Fig. 5B), and rejection episodes (pooled *OR* 1.71, 95% *CI* 1.33 to 2.19, $p<0.0001$) (Fig. 5C). Supplementary Figure S4 shows a funnel plot for the significant association between transplant-related factors and PTA.

Meta-analysis of early (before or within the first transplant week) ESA therapy vs. no therapy in anemic KTR

The pooled estimates detailing the effect of early ESA are presented in Supplementary Table S5, along with the respective study and patient counts. Among these clinical characteristics, a median of 4 studies (range 3–4) was reported, involving a median of 349 patients (range 215–364). Notably, ESA was administered intraoperatively in four studies [19, 103, 104, 106], within 1-week post-kidney transplantation in five studies [20, 59, 96, 97, 105] and before kidney transplantation in two studies [100, 101]. The median follow-up period was 6 months (range 3–12 months).

Early ESA administration did not show an association with improved kidney function, as evidenced by the lack of change in serum creatinine at 1 month (*WMD* −0.04 mg/dL, 95% *CI* −0.52 to 0.44, $p=0.821$), at 3 months (*WMD* −0.01 mg/dL, 95% *CI* of −0.35 to 0.33, $p=0.937$), and at 6 months (*WMD* −0.11 mg/dL, 95% *CI* −0.50 to 0.28, $p=0.350$). Similarly, the eGFR at 1 month, at 3 months, and at 6 months did not exhibit notable improvements. Regarding hemoglobin changes, there was no improvement in hemoglobin levels at 2 weeks (*WMD* 0.17 g/dL, 95% *CI* −0.54 to 0.88, $p=0.414$) and 3-month post-kidney transplant (*WMD* −0.26 g/dL, 95% *CI* of −0.07 to 0.60, $p=0.085$) between KTR who received and did not receive early ESA.

Early ESA administration was not associated with a reduction in delayed graft function (pooled *OR* 1.18, 95% *CI* 0.80 to 1.75, $p=0.336$) (Fig. 6A). Similarly, there was no notable impact on rejection rates, graft loss, and death (Figs. 6B, C, D). Supplementary Figure S5 shows funnel plots for the impact of early ESA therapy vs. no therapy in KTR.

Meta-analysis of late (beyond the first transplant week) ESA therapy vs no therapy in anemic KTR

The pooled estimates detailing the effect of late ESA therapy compared with no treatment are presented in Supplementary Table S6. Among these outcomes, a median of 3 studies (range 3–3) were reported, involving a median of 652 patients (range 405–660). The analysis included two randomized studies [21, 102] and two retrospective

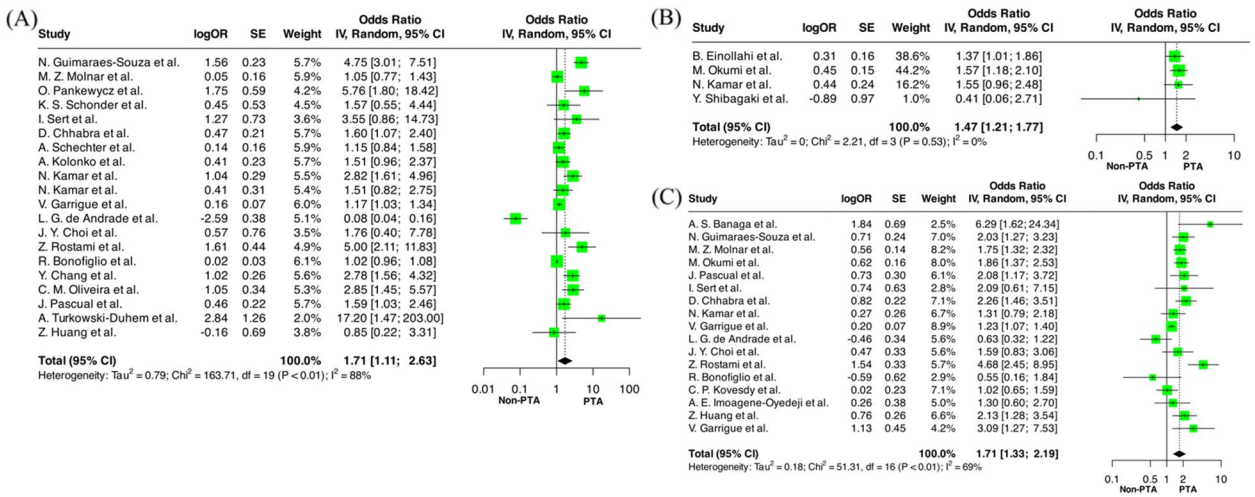


Fig. 5 Forest plots of the association between transplant-related factors and PTA. **A** Delayed graft function. **B** *Cytomegalovirus* infection. **C** Rejection. CI, confidence interval; IV, inverse variance method; OR, odds ratio; PTA, *posttransplant* anemia; SE, standard error

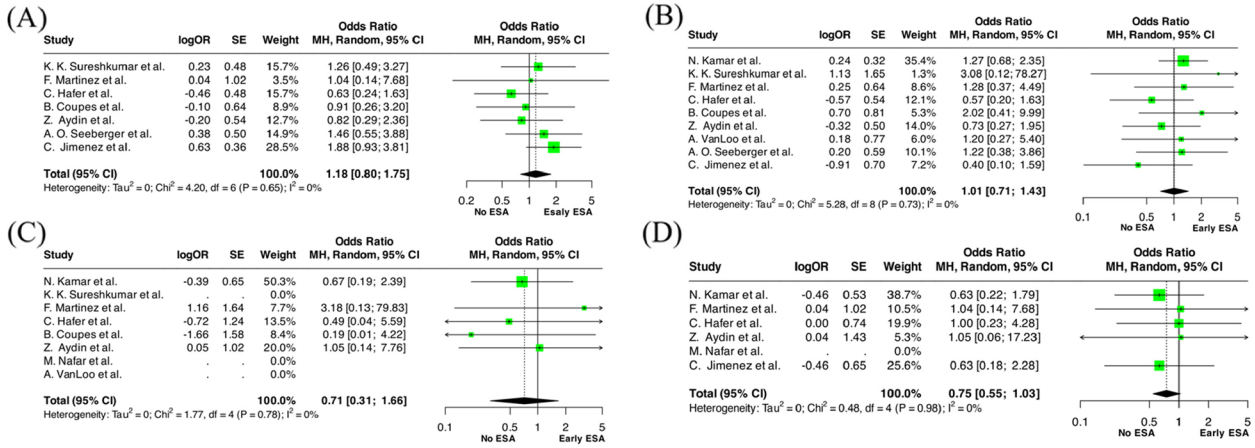


Fig. 6 Forest plots of the effect of early vs. no ESA therapy in KTR. **A** Delayed graft function. **B** Rejection. **C** Death. **D** Graft loss. CI, confidence interval; ESA, erythropoietin-stimulating agent; KTR, kidney transplant; MH, Mantel–Haenszel method; OR, odds ratio; SE, standard error

cohort studies [98, 107]. The follow-up period was 16 months (range 7.5–27.5 months).

Compared with no therapy, late ESA therapy did not slow eGFR decline, as evidenced by no difference in eGFR at 6 months (*WMD* − 13.03 ml/min/1.73 m^2, 95% *CI* − 32.98 to 6.91, $p = 0.107$) after treatment. Furthermore, no improvement in hemoglobin levels was observed after the treatment at 1, 6, and 12 months.

Only one study reported the number of patient deaths [21], and no studies reported the number of patients with graft failure. Therefore, we could not pool the estimates for death and graft failure.

Meta-analysis of late ESA therapy to target high vs. low hemoglobin level in anemic KTR with chronic allograft dysfunction

The pooled estimates detailing the effect of late ESA are presented in Supplementary Table S7. The analysis included four randomized studies that involved patients with functioning grafts for more than 1 year with chronic allograft dysfunction [22–24, 109]. All patients received ESA therapy either to achieve higher hemoglobin levels (mean ± SD 12.47 ± 2.53 g/dL) or to maintain a low target of hemoglobin level (mean ± SD 11.37 ± 1.45). The follow-up period was 24 months (range 21–27 months).

ESA therapy aimed at high hemoglobin levels, compared to a low hemoglobin group, preserved kidney allograft function as evidenced by a higher eGFR at the end of the study (*WMD* 3.65 ml/min/1.73 m^2, 95% *CI* 1.48 to 5.83, $p = 0.013$) (Fig. 7A) and a smaller decline in eGFR from baseline to the end of the study (*WMD* 3.07 ml/min/1.73 m^2, 95% *CI* 0.91 to 5.24, $p = 0.026$) (Fig. 7B). Additionally, ESA therapy to normalize hemoglobin levels reduced the risk of death (pooled *OR* 0.36, 95% *CI* 0.14 to 0.89, $p = 0.040$) (Fig. 7C). However, ESA therapy aimed at normalizing hemoglobin levels did not significantly reduce the rates of graft loss or acute rejection. Supplementary Figure S6 shows funnel plots of the effect

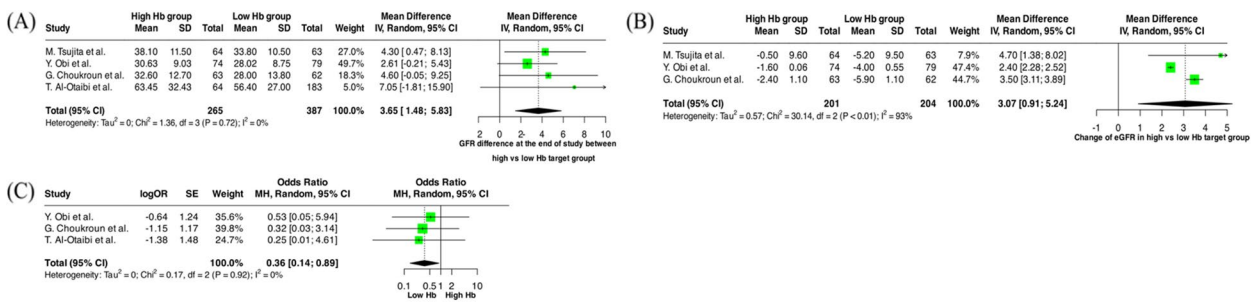


Fig. 7 Forest plots of the outcomes between maintaining high vs. low Hb target levels in KTRs undergoing ESA therapy. **A** eGFR difference at the end of study between high vs low Hb target group. **B** Change of eGFR in high vs low Hb target group. **C** Death. CI, confidence interval; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; IV, inverse variance method; KTR, kidney transplant; MH, Mantel–Haenszel method; OR, odds ratio; SD, standard deviation; SE, standard error

of maintaining high Hb vs. low Hb target levels on eGFR and death in KTRs undergoing ESA therapy.

Prevalence trend of anemia after kidney transplantation

Figure 8 displays the prevalences of anemia across all 41 studies included in this meta-analysis, plotted against the respective dates of anemia assessment. The analysis reveals a high prevalence of anemia during the initial 3-month post-kidney transplantation, with a median prevalence of 59.8% (range 37.7–77.2% in 13 studies). Following this period, there is a marked decline in anemia prevalence, reaching its lowest point between 24 to 36 months post-transplantation, with a median of 27.2% (range 20.5–39.1% in 7 studies). The trend demonstrates a gradual increase in anemia prevalence over time, starting 36 months after kidney transplantation.

Discussion

This systematic review and meta-analysis highlights a wide range of factors linked to PTA, including both risk factors and associated elements. Key risk factors identified include donor age, HLA mismatch, African American ethnicity, and low pretransplant hemoglobin levels. Additionally, poor kidney function, elevated IL-6 levels, reduced white blood cell count, and low albumin and serum iron levels were notable associated factors. The development of PTA was also linked to CMV infection, delayed graft function, rejection episodes, and the use of various medications including ACE inhibitors, ARBs, cyclosporine, mTOR inhibitors, thymoglobulin, ESA therapy, iron supplements, valganciclovir/ganciclovir, and decreased tacrolimus levels. Interestingly, a history of ADPKD was associated with a lower risk of developing PTA. Regarding ESA therapy, early administration did not improve kidney function, reduce delayed graft function, or affect rejection rates. Similarly, late ESA therapy did not show any association with a slower decline in eGFR when compared to no ESA therapy. Additionally, there was no improvement in hemoglobin levels observed after treatment at 1, 6, and 12 months. However, ESA therapy aimed at achieving higher hemoglobin levels compared to lower targets was associated with a slower progression of eGFR decline and reduced mortality. Nonetheless, this therapy did not reduce the incidence of graft loss or acute rejection.

PTA is a common complication following kidney transplant. PTA has been associated with several adverse outcomes including a decline in eGFR [3, 54], reduced graft survival [3, 46, 49, 54, 72, 84, 95], increased motality [3, 46, 95], diminished quality of life [82, 110], and cardiovascular complication such as heart failure [111, 112], left ventricular hypertrophy [83, 113], and cardiovascular mortality [43, 81]. These consequences are well-documented in the literatures and widely recognized among clinicians. Therefore, identifying the risks and associated factors of PTA is imperative to formulate preventive

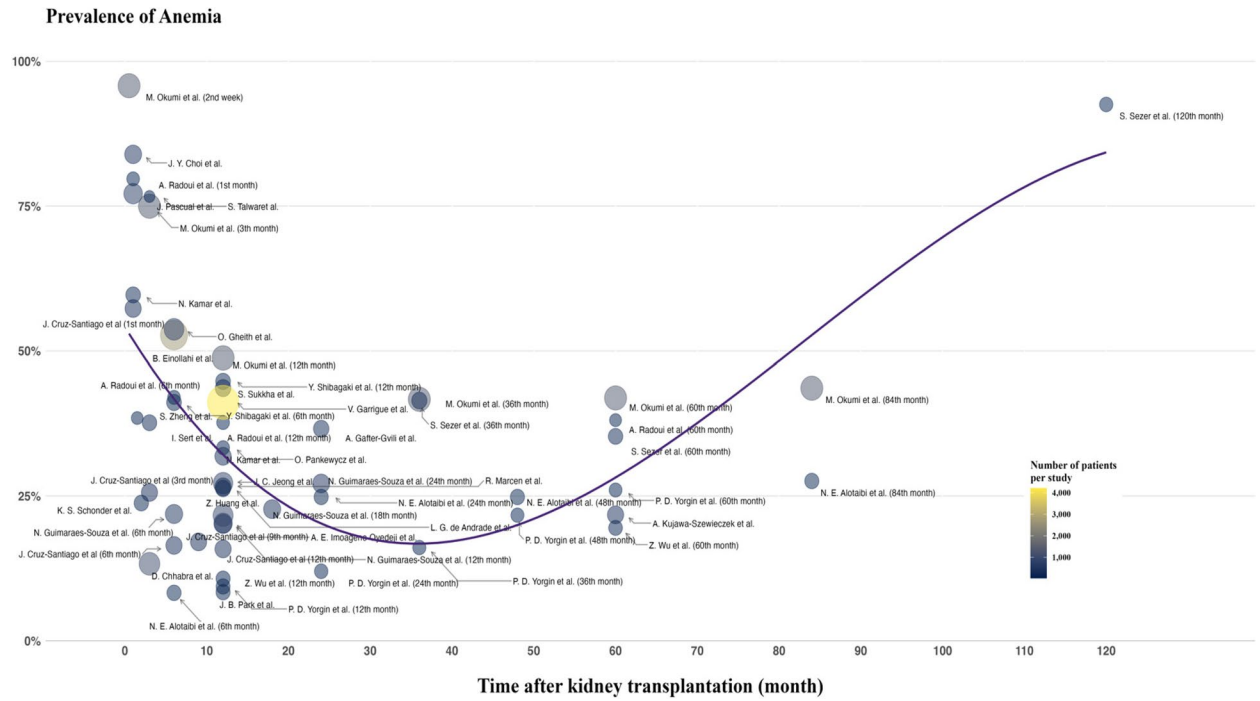


Fig. 8 Prevalence of anemia plotted against time after kidney transplantation in each included study

measures and treatments aimed at mitigating these adverse consequences.

African American recipients of kidney transplants are more prone to experience reduced graft function and higher rejection rates compared to other ethnic groups [114–116]. These factors may contribute to the development of PTA. Additionally, genetic variations in ABCB1 (MDR1) and cytochrome P450 3A5 (CYP3A5) among individuals of African ancestry can affect the metabolism of immunosuppressive medications [117]. For example, African-ancestry KTR have a low frequency of the *C3435T MDR1* polymorphism and a low frequency of *CYP3A5*3* [118–120]. This genetic profile often necessitates higher doses of tacrolimus to achieve the therapeutic targets. This can lead to high peak concentrations and toxicity, potentially resulting in nephrotoxicity in the kidney allograft and PTA [118, 121].

Increased donor age is also a risk factor for PTA. Aging kidneys are associated with interstitial fibrosis and tubular atrophy [122], which independently correlate with PTA at 12 months post-transplantation [123]. Higher HLA mismatch is linked to poor graft survival [124, 125] and increased rejection episodes [126, 127]. Both factors can contribute to PTA by decreasing erythropoietin production and causing erythropoietin resistance through inflammation. Lower pretransplant hemoglobin levels may indicate underlying systemic medical conditions that can lead to PTA. These conditions include nutritional deficiencies, undetected cancer, chronic infections before transplantation, and hemoglobinopathy.

Remarkably, ADPKD serves as a protective factor against PTA. KTR with ADPKD typically present with higher hemoglobin levels compared to those suffering ESKD from other causes [128]. Additionally, ADPKD is often associated with erythrocytosis [129, 130]. It is hypothesized that individuals with ADPKD may have the native kidneys that are still capable of producing erythropoietin [128]. This hypothesis is supported by observations in hemodialysis patients, where those with ADPKD-related ESKD exhibit higher serum erythropoietin levels than those with ESKD from other etiologies [131]. The increased erythropoietin levels in ADPKD can be attributed to pericystic cells hypoxia. This hypoxia results from the compression of adjacent microvasculature due to the expansion of cysts. The low oxygen levels induce the stabilization of hypoxia-inducible factor-2α within erythropoietin-producing stromal cells, leading to elevated erythropoietin levels characteristic of ADPKD [132]. Furthermore, existing evidence has demonstrated that native kidney nephrectomy in ADPKD KTR results in a significant drop in hemoglobin levels [128, 133].

Impaired kidney function is a recognized risk factor for anemia in chronic kidney disease (CKD) patients. Our findings suggest that it also poses a risk for PTA, likely due to a decline in erythropoietin production [134]. Elevated IL-6 may contribute to both T-cell-mediated rejection (TCMR) and antibody-mediated rejection (ABMR) through several mechanisms, including promoting Th17 cells and germinal center formation [135–138]. Persistent inflammation associated with allograft rejection may induce resistance to erythropoietin, exacerbating anemia [139–141]. Patients with anemia had lower white blood cell counts compared to those without anemia. This suggests that the underlying cause of anemia might be affecting the bone marrow response. Examples of such causes include drug-induced bone marrow suppression, systemic infection, or bone marrow disease, which can lead to both anemia and leukopenia.

Compared to treatment with mycophenolate mofetil, mTOR inhibitor has been associated with higher prevalence of PTA [142]. Various mechanisms underlying this association have been explored, including direct effects on iron homeostasis [143], chronic inflammation [144, 145], and erythropoietin resistance [146, 147]. Long-term use of cyclosporine A carries a higher risk of calcineurin inhibitor (CNI) nephrotoxicity compared to tacrolimus. This can result in arteriolopathy, nephron ischemia, and tubular atrophy/interstitial fibrosis [148]. Consequently, these effects lead to decreased erythropoietin production and PTA. Additionally, decreased tacrolimus levels were associated with PTA, likely due to the cellular pharmacokinetics that lower erythrocyte-binding capacity of tacrolimus in anemic KTR [149].

Renin-angiotensin system (RAS) inhibitors can cause anemia through several mechanisms. First, angiotensin II stimulates the proliferation of early erythroid progenitors [150, 151]. Thus, inhibition of RAS by ACEi or ARB can induce anemia, as demonstrated in setting such as CKD, congestive heart failure, and kidney transplantation [152]. Second, the N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), an inhibitor of hematopoietic stem cell proliferation, is hydrolyzed in vitro by ACE, and ACEi can increase Ac-SDKP by 5.5-fold [153]. Lastly, insulin-like growth factor 1 (IGF-1), which promotes erythropoiesis in vitro [154], is reduced by ACEi therapy [155].

Despite promising results from animal models suggesting that ESAs can prevent ischemic reperfusion injury (IRI) [156–161], our meta-analysis found no significant impact of early ESA administration on critical outcomes like prevention of delayed graft function, eGFR improvement, or reduction in rejection rates. This may be because of the low expression and function of erythropoietin receptors (EPOR) in the renal tissue [162, 163]. In addition, in animal model, there is only pure IRI without other pathology. However, in human, there may be the effects of heterogeneous processes such as rejection,

calcineurin inhibitor toxicities, and preexisting atherosclerosis which might render ESA therapy ineffective [164].

From our meta-analysis, ESA therapy can slow the decline of eGFR by targeting higher hemoglobin concentrations. The notable difference from non-transplant CKD may arise from the distinct histopathologic etiologies of eGFR decline in kidney transplants, most commonly due to alloimmune process [165, 166]. The mechanism by which erythropoietin slows eGFR progression could be attributed to its erythropoiesis-independent immunosuppressive properties. EPOR is expressed in CD4+and CD8+T cells [11]. ESA can inhibit the proliferation of conventional T cells by dephosphorylating signals downstream of the IL-2Rβ chain [10, 167] and promote regulatory T cell by stimulating local TGFβ production [10]. In vitro and in vivo studies have shown that EPO binding to its receptor on CD4+T cells directly inhibits Th17 cell. This inhibition occurs through the SGK1-dependent pathway [12]. Furthermore, in vitro data suggest that ESA therapy may reduce the production of murine macrophage-derived interleukin-6 [168, 169], which promotes both acute and chronic rejection [170–172]. Animal studies have demonstrated that chronic ESA treatment can mitigate tubulointerstitial and glomerular injury in a fully mismatched rat model of chronic allograft injury [18]. This protective effect is linked to the preservation of peritubular capillaries and an increase in phosphorylated AKT within the tubular cells [18]. However, correcting anemia alone did not protect against chronic graft injury and dysfunction [18]. Based on the pooled data, we recommend the use of ESA to normalize hemoglobin levels in anemic patients with late allograft nephropathy as a strategy to slow the decline in eGFR. While the optimal target hemoglobin range requires further investigation, a target hemoglobin level of ≥ 12.5 g/dL is proposed based on the findings from the included studies [22–24, 109].

This meta-analysis has several strengths. First, it includes a comprehensive literature search, predefined protocol, and analytical plan. Second, it provides a detailed summary of the risk and associated factors for PTA, along with the pooled magnitude of effect for each factor. Third, it confirms the benefits of ESA therapy in normalizing hemoglobin levels in KTR. The study also included a large sample size, consisting of 38,233 patients from 85 studies. This is the first systematic review and meta-analysis to examine the factors contributing to PTA and the effects of ESA use after kidney transplantation. The results from this study can be used to classify the risk of PTA and enable more personalized surveillance for each patient. Furthermore, these factors can be utilized to prevent and treat PTA. The summarized information regarding the risk and associated factors for PTA is shown in Fig. 2.

This systematic review and meta-analysis has limitations. First, for some variables, the included studies did not consistently provide the timeframe between the exposure to potential risk factors and the development of PTA. This requires cautious interpretation of any causal relationships, as much of the data is cross-sectional. Second, the variability in the timing of anemia diagnosis across studies could influence how different risk factors impact early versus late PTA. Third, there is significant heterogeneity among the included factors. Variations in the definition of anemia, the eGFR equation used, the immunosuppressive protocols of different centers, the variability in infectious prophylaxis protocols, and the methods of confounder adjustment all contribute to this variability. To address these limitations, the I^2 index, Egger's test, and funnel plots are provided and should be considered alongside the effect sizes of the meta-analysis.

In conclusion, PTA arises from an intricate set of patient-related and donor-related factors, impaired kidney function, states of inflammation, and various therapeutic approaches employed. Early administration of ESAs has not demonstrated definitive benefits for kidney outcomes such as delayed graft function. However, later administration of ESA may be more effective. In KTR with chronic allograft dysfunction after the first transplant year, targeting hemoglobin levels between 12.5 and 13.5 g/dL appears to be beneficial. This approach can offer renal protection and reduce mortality compared to maintaining a lower hemoglobin target. Future studies should aim to solidify the benefits of ESA therapy, particularly for patients with chronic allograft dysfunction. These studies should endeavor to compare ESA therapy for different hemoglobin targets or utilize other modalities to maintain hemoglobin levels in a larger patient cohort over a long follow-up period.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02709-8.

Supplementary Material 1: Supplementary figures: Supplementary Figure S1: Funnel plots of pre-transplant risk factors of PTA: (A) Donor age, (B) Human leukocyte antigen mismatch, (C) Pre-transplant hemoglobin, (D) African American, (E) ESKD from ADPKD. ADPKD, autosomal dominant polycystic kidney disease; ESKD, end stage kidney disease; PTA, post-transplant anemia. Supplementary Figure S2: Funnel plots of the association between kidney function and PTA: (A) BUN, (B) Creatinine, and (C) eGFR. PTA, post-transplant anemia; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate. Supplementary Figure S3: Funnel plots of the significant association between medications and PTA. (A) Thymoglobulin, (B) mTOR inhibitor, (C) Cyclosporin, (D) Tacrolimus level, (E) Valganciclovir/ganciclovir, (F) ACEi/ARB. PTA, post-transplant anemia; mTOR, mammalian target of rapamycin; ACEi, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II receptor blockers. Supplementary Figure S4: Funnel plots of the association between transplant-related factors and PTA. (A)

Delayed graft function, (B) Cytomegalovirus infection, (C) Rejection. PTA, post-transplant anemia. Supplementary Figure S5: Funnel plots of the effect of early vs. no ESA therapy in KTR. (A) Delayed graft function, (B) Rejection, (C) Graft loss, (D) Death. Supplementary Figure S6: Funnel plots of the effect of maintaining high vs. low Hb target levels in KTRs undergoing ESA therapy. (A) eGFR difference at the end of study between high vs low Hb target group, (B) Death, (C) Change of eGFR in high vs low Hb target group. Hb, hemoglobin; KTR, kidney transplant; ESA: erythropoietin stimulating agent. Supplementary tables: Supplementary Table S1: Characteristics and information of the included studies. Supplementary Table S2: Risk of bias assessment of the included studies (The modified Newcastle-Ottawa Scale for cross-sectional studies and Newcastle-Ottawa Scale for cohort and case control studies). Supplementary Table S3: Risk of bias assessment of the included studies (Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)). Supplementary Table S4: Meta-analysis of the risk and associated factors of PTA. Supplementary Table S5: Meta-analysis of early ESA vs. no therapy in KTRs. Supplementary Table S6: Meta-analysis of late ESA therapy vs. no therapy in KTRs. Supplementary Table S7: Meta-analysis of maintaining high vs. low Hb target levels in KTRs undergoing ESA therapy.

Acknowledgements
The authors thank Stephen J. Kerr for his assistance in manuscript preparation and language editing.

Authors' contributions
KC designed the study, collected data, planned and executed analysis, and wrote the manuscript. SP collected data. TW, AL, NT, and YA reviewed and edited the manuscript. SU designed the study, planned and executed the analysis, wrote the first draft of the manuscript, and reviewed and edited the manuscript. Kittiphan Chienwichai, ble_sama@hotmail.com; Supitchaya Phirom, pongphirom@gmail.com; Thunyatorn Wuttiputhanun, ja_wutti@yahoo.com; Asada Leelahavanichkul, a_leelahavanit@yahoo.com; Natavudh Townamchai, ntownamchai@gmail.com; Yingyos Avihingsanon, yingyos.a@gmail.com; Suwasin Udomkarnjananun, suwasin.u@gmail.com.

Funding
This study was supported by the National Research Council of Thailand: N42A661041.

Data availability
All data relevant to this study has been included in the manuscript. The data code supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The data in this systematic review and meta-analysis were derived from published literature, making it impossible to identify individual subjects. No data were directly obtained from human or animal subjects.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Division of Nephrology, Department of Medicine, Hatyai Hospital, Songkhla, Thailand. [2]Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok, Thailand. [3]Excellence Center for Organ Transplantation (ECOT), King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok, Thailand. [4]Department of Microbiology, Immunology Unit, Chulalongkorn University, Bangkok, Thailand. [5]Department of Microbiology, Center of Excellence On Translational Research in Inflammation and Immunology (CETRII), Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. [6]Center of Excellence in Renal Immunology and Renal Transplantation, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Received: 21 August 2024 Accepted: 30 October 2024
Published online: 12 November 2024

References

1. Winkelmayer WC, Chandraker A, Alan Brookhart M, Kramar R, Sunder-Plassmann GA. prospective study of anaemia and long-term outcomes in kidney transplant recipients. Nephrol Dialysis Transplant. 2006;21:3559–66. https://doi.org/10.1093/ndt/gfl457.
2. Schechter A, et al. Post renal transplant anemia: severity, causes and their association with graft and patient survival. BMC Nephrology. 2019;20:51. https://doi.org/10.1186/s12882-019-1244-y.
3. Gafter-Gvili A, et al. Posttransplantation anemia in kidney transplant recipients: a retrospective cohort study. Medicine (Baltimore). 2017;96:e7735. https://doi.org/10.1097/md.0000000000007735.
4. Vanrenterghem Y, et al. Prevalence and management of anemia in renal transplant recipients: a European survey. Am J Transplant. 2003;3:835–45. https://doi.org/10.1034/j.1600-6143.2003.00133.x.
5. Mekraksakit P, et al. A systematic review and meta-analysis of post-transplant anemia with overall mortality and cardiovascular outcomes among kidney transplant recipients. Progress Transplant. 2023;33:78–89. https://doi.org/10.1177/15269248221145046.
6. Kim HC, Park SB, Han SY, Whang EA. Anemia following renal transplantation. Transplant Proc. 2003;35:302–3. https://doi.org/10.1016/s0041-1345(02)03958-1.
7. Chang Y, Shah T, Min DI, Yang JW. Clinical risk factors associated with the post-transplant anemia in kidney transplant patients. Transpl Immunol. 2016;38:50–3. https://doi.org/10.1016/j.trim.2016.07.006.
8. Unal A, et al. An underappreciated problem in renal transplant recipients: anemia. Transplant Proc. 2008;40:1399–403. https://doi.org/10.1016/j.transproceed.2008.03.080.
9. Turkowski-Duhem A, et al. Predictive factors of anemia within the first year post renal transplant. Transplantation. 2005;80:903–9. https://doi.org/10.1097/01.tp.0000173791.42893.08.
10. Purroy C, et al. Erythropoietin receptor-mediated molecular crosstalk promotes T cell immunoregulation and transplant survival. J Am Soc Nephrol. 2017;28:2377–92. https://doi.org/10.1681/asn.2016101100.
11. Cravedi P, et al. Immunosuppressive effects of erythropoietin on human alloreactive T cells. J Am Soc Nephrol. 2014;25:2003–15. https://doi.org/10.1681/asn.2013090945.
12. Donadei C, et al. Erythropoietin inhibits SGK1-dependent TH17 induction and TH17-dependent kidney disease. JCI Insight 2019;5. https://doi.org/10.1172/jci.insight.127428.
13. Guglielmo C, et al. Erythropoietin reduces auto- and alloantibodies by inhibiting T follicular helper cell differentiation. J Am Soc Nephrol. 2021;32:2542–60. https://doi.org/10.1681/asn.2021010098.
14. Horwitz, J. K. et al. Linking erythropoietin to Treg-dependent allograft survival through myeloid cells. JCI Insight 2022;7. https://doi.org/10.1172/jci.insight.158856.
15. Pallet N, et al. Antiapoptotic properties of recombinant human erythropoietin protects against tubular cyclosporine toxicity. Pharmacol Res. 2010;61:71–5. https://doi.org/10.1016/j.phrs.2009.08.010.
16. Ishii Y, et al. Renoprotective effect of erythropoietin against ischaemia–reperfusion injury in a non-human primate model. Nephrol Dialysis Transplant. 2010;26:1157–62. https://doi.org/10.1093/ndt/gfq601.
17. Okada T, Sawada T, Kubota K. Asialoerythropoietin has strong renoprotective effects against ischemia-reperfusion injury in a murine model. Transplantation. 2007;84:504–10. https://doi.org/10.1097/01.tp.0000277672.02783.33.
18. Cassis P, et al. Erythropoietin, but not the correction of anemia alone, protects from chronic kidney allograft injury. Kidney Int. 2012;81:903–18. https://doi.org/10.1038/ki.2011.473.
19. Van Biesen W, Vanholder R, Veys N, Verbeke F, Lameire N. Efficacy of erythropoietin administration in the treatment of anemia immediately after renal transplantation. Transplantation. 2005;79:367–8. https://doi.org/10.1097/01.Tp.0000150370.51700.99.
20. Yasari F, et al. Effect of erythropoietin on kidney allograft survival: early use after transplantation. Iran J Kidney Dis. 2012;6:44–8.
21. Pile T, et al. Treating posttransplant anemia with erythropoietin improves quality of life but does not affect progression of chronic

kidney disease. Exp Clin Transplant. 2020;18:27–33. https://doi.org/10.6002/ect.2018.0283.
22. Choukroun G, et al. Correction of postkidney transplant anemia reduces progression of allograft nephropathy. J Am Soc Nephrol. 2012;23:360–8. https://doi.org/10.1681/asn.2011060546.
23. Tsujita M, et al. The effect of maintaining high hemoglobin levels on long-term kidney function in kidney transplant recipients: a randomized controlled trial. Nephrol Dial Transplant. 2019;34:1409–141. https://doi.org/10.1093/ndt/gfy365.
24. Obi Y, et al. Correcting anemia and native vitamin D supplementation in kidney transplant recipients: a multicenter, 2 × 2 factorial, open-label, randomized clinical trial. Transpl Int. 2021;34:1212–25. https://doi.org/10.1111/tri.13885.
25. Liberati A, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6:e1000100. https://doi.org/10.1371/journal.pmed.1000100.
26. Jüni P, Holenstein F, Sterne J, Bartlett C, Egger M. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol. 2002;31:115–23. https://doi.org/10.1093/ije/31.1.115.
27. Morrison A, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28:138–44. https://doi.org/10.1017/s0266462312000086.
28. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603–5. https://doi.org/10.1007/s10654-010-9491-z.
29. Zeng X, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015;8:2–10. https://doi.org/10.1111/jebm.12141.
30. Herzog R, et al. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? a systematic review. BMC Public Health. 2013;13:154. https://doi.org/10.1186/1471-2458-13-154.
31. Sterne JAC. et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.
32. Viechtbauer W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. J Educ Behav Stat. 2005;30:261–93. https://doi.org/10.3102/10769986030003261.
33. Paule RC, Mandel J. Consensus values and weighting factors. J Res Natl Bur Stand. 1977;1982(87):377–85. https://doi.org/10.6028/jres.087.022.
34. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Stat Med. 2003;22:2693–710. https://doi.org/10.1002/sim.1482.
35. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135. https://doi.org/10.1186/1471-2288-14-135.
36. Nampoory MR, Johny KV, al-Hilali N, Seshadri MS, Kanagasabhapathy AS. Erythropoietin deficiency and relative resistance cause anaemia in post-renal transplant recipients with normal renal function. Nephrol Dial Transplant. 1996;11:177–81.
37. Yorgin PD, et al. Late post-transplant anemia in adult renal transplant recipients. An under-recognized problem? Am J Transplant. 2002;2:429–435. https://doi.org/10.1034/j.1600-6143.2002.20506.x.
38. Mix TCH, et al. Anemia: a continuing problem following kidney transplantation. Am J Transplant. 2003;3:1426–33. https://doi.org/10.1046/j.1600-6135.2003.00224.x.
39. Shibagaki Y, Shetty A. Anaemia is common after kidney transplantation, especially among African Americans. Nephrol Dial Transplant. 2004;19:2368–73. https://doi.org/10.1093/ndt/gfh256.
40. Molnar MZ, et al. Anemia in kidney transplanted patients. Clin Transplant. 2005;19:825–33. https://doi.org/10.1111/j.1399-0012.2005.00428.x.
41. Turkowski-Duhem A, et al. Predictive factors of postrenal transplant anemia. Transplant Proc. 2005;37:1009–11. https://doi.org/10.1016/j.transproceed.2004.12.199.
42. Al-Khoury S, et al. Post-transplantation anaemia in adult and paediatric renal allograft recipients-Guy's Hospital experience. Nephrol Dial Transplant. 2006;21:1974–80. https://doi.org/10.1093/ndt/gfl121.
43. Imoagene-Oyedeji AE, Rosas SE, Doyle AM, Goral S, Bloom RD. Post-transplantation anemia at 12 months in kidney recipients treated with mycophenolate mofetil: risk factors and implications for mortality. J Am Soc Nephrol. 2006;17:3240–7. https://doi.org/10.1681/asn.2006010027.
44. Sezer S, Ozdemir FN, Tutal E, Bilgic A, Haberal M. Prevalence and etiology of anemia in renal transplant recipients. Transplant Proc. 2006;38:537–40. https://doi.org/10.1016/j.transproceed.2005.12.067.
45. Chadban, S. J. et al. Anemia after kidney transplantation is not completely explained by reduced kidney function. Am J Kidney Dis. 2007;49:301–309. https://doi.org/10.1053/j.ajkd.2006.11.034.
46. Molnar MZ, et al. Anemia is associated with mortality in kidney-transplanted patients–a prospective cohort study. Am J Transplant. 2007;7:818–24. https://doi.org/10.1111/j.1600-6143.2006.01727.x.
47. Sinnamon KT, et al. Level of renal function and serum erythropoietin levels independently predict anaemia post-renal transplantation. Nephrol Dial Transplant. 2007;22:1969–73. https://doi.org/10.1093/ndt/gfm100.
48. Zadrazil J, et al. Endogenous erythropoietin levels and anemia in long-term renal transplant recipients. Kidney Blood Press Res. 2007;30:108–16. https://doi.org/10.1159/000100906.
49. Chhabra D, Grafals M, Skaro AI, Parker M, Gallon L. Impact of anemia after renal transplantation on patient and graft survival and on rate of acute rejection. Clin J Am Soc Nephrol. 2008;3:1168–74. https://doi.org/10.2215/cjn.04641007.
50. Gentil MA, et al. Factor deficiency in the anemia of renal transplant patients with grade III-IV chronic kidney disease: baseline results of the ARES study. Transplant Proc. 2008;40:2922–4. https://doi.org/10.1016/j.transproceed.2008.08.083.
51. Ghafari A, Noori-Majelan N. Anemia among long-term renal transplant recipients. Transplant Proc. 2008;40:186–8. https://doi.org/10.1016/j.transproceed.2007.12.004.
52. Gheith O, et al. Does posttransplant anemia at 6 months affect long-term outcome of live-donor kidney transplantation? A single-center experience Clin Exp Nephrol. 2009;13:361–6. https://doi.org/10.1007/s10157-009-0171-9.
53. Imamović G, Zerem E, Omerović S, Osmanović E, Hodzić E. The possible role of early post-transplant inflammation in later anemia in kidney transplant recipients. Bosn J Basic Med Sci. 2009;9:307–12. https://doi.org/10.17305/bjbms.2009.2786.
54. Kolonko A, et al. Anemia and erythrocytosis after kidney transplantation: a 5-year graft function and survival analysis. Transplant Proc. 2009;41:3046–51. https://doi.org/10.1016/j.transproceed.2009.07.090.
55. Malyszko J, Malyszko JS, Mysliwiec M. A possible role of hepcidin in the pathogenesis of anemia among kidney allograft recipients. Transplant Proc. 2009;41:3056–9. https://doi.org/10.1016/j.transproceed.2009.08.003.
56. Park JB, et al. Clinical implications of quantitative real time-polymerase chain reaction of parvovirus B19 in kidney transplant recipients - a prospective study. Transpl Int. 2009;22:455–62.
57. Zheng S, et al. Iron deficiency anemia and iron losses after renal transplantation. Transpl Int. 2009;22:434–40. https://doi.org/10.1111/j.1432-2277.2008.00814.x.
58. Guimarães-Souza N, et al. Clinical implications of initial renal function after deceased donor transplant. Transplant Proc. 2010;42:1084–9. https://doi.org/10.1016/j.transproceed.2010.03.067.
59. Kamar N, et al. Impact of very early high doses of recombinant erythropoietin on anemia and allograft function in de novo kidney-transplant patients. Transpl Int. 2010;23:277–84. https://doi.org/10.1111/j.1432-2277.2009.00982.x.
60. Pankewycz O, et al. A prospective protocol-based trial of darbepoetin alfa therapy to correct the early anemia following renal transplantation. Transplant Proc. 2010;42:3537–41. https://doi.org/10.1016/j.transproceed.2010.06.035.
61. Przybylowski P, et al. Anemia in heart and kidney allograft recipients: is there a role for hepcidin? Transplant Proc. 2010;42:4255–8. https://doi.org/10.1016/j.transproceed.2010.09.034.
62. Radoui A, et al. Prevalence and predictive factors of anemia after renal transplantation: a Moroccan report. Transplant Proc. 2010;42:3542–9. https://doi.org/10.1016/j.transproceed.2010.07.092.

63. Schonder KS, Corman SL, Hung WY. Early risk factors for persistent anemia after kidney transplantation. Pharmacotherapy. 2010;30:1214–20. https://doi.org/10.1592/phco.30.12.1214.
64. Banaga AS, Yousif ME, Elmusharaf K. Risk factors of post renal transplant anaemia among Sudanese patients, a study in three renal transplant centres. BMC Nephrol. 2011;12:37. https://doi.org/10.1186/1471-2369-12-37.
65. Bonofiglio R, Lofaro D, Greco R, Senatore M, Papalia T. Proteinuria is a predictor of posttransplant anemia. Transplant Proc. 2011;43:1063–6. https://doi.org/10.1016/j.transproceed.2011.01.125.
66. Einollahi B, et al. Anemia after kidney transplantation in adult recipients: prevalence and risk factors. Transplant Proc. 2011;43:578–80. https://doi.org/10.1016/j.transproceed.2011.01.065.
67. Jacobson PA, et al. Genetic determinants of mycophenolate-related anemia and leukopenia after transplantation. Transplantation. 2011;91:309–16. https://doi.org/10.1097/TP.0b013e318200e971.
68. Kovesdy CP, et al. Association of serum phosphorus level with anemia in kidney transplant recipients. Transplantation. 2011;91:875–82. https://doi.org/10.1097/TP.0b013e3182111edf.
69. Molnar MZ, et al. Association between the malnutrition-inflammation score and post-transplant anaemia. Nephrol Dial Transplant. 2011;26:2000–6. https://doi.org/10.1093/ndt/gfq690.
70. Rostami Z, Shafighi N, Baghersad MM, Einollahi B. Risk factors for immediate anemia in renal transplant recipients: a single-center experience. Transplant Proc. 2011;43:581–3. https://doi.org/10.1016/j.transproceed.2011.01.072.
71. Sancho A, et al. Posttransplantation anemia: relationship with inflammatory markers, oxidation, and prohepcidin levels. Transplant Proc. 2011;43:2196–8. https://doi.org/10.1016/j.transproceed.2011.05.019.
72. de Andrade LG, Abrão JM, Carvalho MF. Anemia at one year is an independent risk factor of graft survival. Int Urol Nephrol. 2012;44:263–8. https://doi.org/10.1007/s11255-010-9854-0.
73. Elsayed H, et al. Prevalence and association of post-renal transplant anemia. Saudi J Kidney Dis Transpl. 2012;23:461–6.
74. Florit EA, et al. Anemia in kidney transplants without erythropoietic agents: levels of erythropoietin and iron parameters. Transplant Proc. 2012;44:2590–2. https://doi.org/10.1016/j.transproceed.2012.09.044.
75. Marcén R, et al. Anemia at 1 year after kidney transplantation has a negative long-term impact on graft and patient outcomes. Transplant Proc. 2012;44:2593–5. https://doi.org/10.1016/j.transproceed.2012.09.033.
76. Choi JY, Kwon OJ. The impact of post-transplant hemoglobin level on renal allograft outcome. Transplant Proc. 2013;45:1553–7. https://doi.org/10.1016/j.transproceed.2012.11.030.
77. Oliveira CM, et al. Post-transplant anemia and associated risk factors: the impact of steroid-free therapy. Sao Paulo Med J. 2013;131:369–76. https://doi.org/10.1590/1516-3180.2013.1316523.
78. Pascual J, et al. Early-onset anemia after kidney transplantation is an independent factor for graft loss: a multicenter, observational cohort study. Transplantation. 2013;96:717–25. https://doi.org/10.1097/TP.0b013e31829f162e.
79. Sert I, Colak H, Tugmen C, Dogan SM, Karaca C. Anemia in living donor kidney transplantation. Transplant Proc. 2013;45:2238–43. https://doi.org/10.1016/j.transproceed.2012.12.008.
80. Wu Z, et al. Prevalence and management of post-transplant anemia in long-term follow-up of Chinese kidney transplant recipients: a single-center report. Eur J Med Res. 2013;18:45. https://doi.org/10.1186/2047-783x-18-45.
81. Garrigue V, et al. Influence of anemia on patient and graft survival after renal transplantation: results from the French DIVAT cohort. Transplantation. 2014;97:168–75. https://doi.org/10.1097/TP.0b013e3182a94a4d.
82. Abacı SH, et al. Assessment of anemia and quality of life in patients with renal transplantation. Transplant Proc. 2015;47:2875–80. https://doi.org/10.1016/j.transproceed.2015.10.043.
83. Gurlek Demirci B, et al. Post-transplantation anemia predicts cardiovascular morbidity and poor graft function in kidney transplant recipients. Transplant Proc. 2015;47:1178–81. https://doi.org/10.1016/j.transproceed.2015.01.025.
84. Huang Z, et al. Post-renal transplantation anemia at 12 months: prevalence, risk factors, and impact on clinical outcomes. Int Urol Nephrol. 2015;47:1577–85. https://doi.org/10.1007/s11255-015-1069-y.
85. Kitamura K, et al. Pre-transplant erythropoiesis-stimulating agent hypo-responsiveness and post-transplant anemia. Transplant Proc. 2015;47:1820–4. https://doi.org/10.1016/j.transproceed.2015.06.012.
86. Ichimaru N, et al. Post-transplant anemia has strong influences on renal and patient outcomes in living kidney transplant patients. Transplant Proc. 2016;48:878–83. https://doi.org/10.1016/j.transproceed.2016.01.033.
87. Lim AKH, Kansal A, Kanellis J. Factors associated with anaemia in kidney transplant recipients in the first year after transplantation: a cross-sectional study. BMC Nephrol. 2018;19:252. https://doi.org/10.1186/s12882-018-1054-7.
88. Jeong JC, et al. Characteristics of anemia and iron deficiency after kidney transplant. Transplant Proc. 2019;51:1406–9. https://doi.org/10.1016/j.transproceed.2019.01.140.
89. Okumi M, et al. The interaction between post-transplant anemia and allograft function in kidney transplantation: the Japan Academic Consortium of Kidney Transplantation-II study. Clin Exp Nephrol. 2019;23:1066–75. https://doi.org/10.1007/s10157-019-01737-2.
90. Cruz-Santiago J, et al. Change in the pattern of posttransplantation anemia in kidney receptors: sex role in recipients and type of donor. Transplant Proc. 2020;52:1163–8. https://doi.org/10.1016/j.transproceed.2019.12.050.
91. Jung HY, et al. Mycophenolic acid trough concentration and dose are associated with hematologic abnormalities but not rejection in kidney transplant recipients. J Korean Med Sci. 2020;35:e185. https://doi.org/10.3346/jkms.2020.35.e185.
92. Sukkha S, et al. Incidence and factors associated post-transplantation anemia in kidney transplant patients at a tertiary-care hospital in Thailand. Pharmaceutical Sci Asia. 2020;47:294–300. https://doi.org/10.29090/psa.2020.03.019.0029.
93. Ayerdem G, et al. Iron deficiency, with and without anaemia, across strata of kidney function in kidney transplant recipients. Nephrol Dial Transplant. 2021;36:2342–4. https://doi.org/10.1093/ndt/gfab173.
94. Talwar S, et al. Prevalence of posttransplant anemia in patients undergoing renal transplantation at a tertiary care center in Kerala - a prospective observational study. Indian J Transplant 2021;15:93–8. https://doi.org/10.4103/ijot.ijot_41_20.
95. Alotaibi NE, et al. Postrenal transplant anemia and its effects on patients and graft outcomes: seven years follow-up. Saudi Pharm J. 2023;31:101696. https://doi.org/10.1016/j.jsps.2023.101696.
96. Seeberger AO, Tibell A, Tydén G. Renal transplantation in r-HuEPO-treated patients. Transpl Int. 1992;5(Suppl 1):S104–106. https://doi.org/10.1007/978-3-642-77423-2_33.
97. Van Loo A, Vanholder R, Bernaert P, De Roose J, Lameire N. Recombinant human erythropoietin corrects anaemia during the first weeks after renal transplantation: a randomized prospective study. NephrolDialysis Transplant. 1996;11:1815–21. https://doi.org/10.1093/oxfordjournals.ndt.a027674.
98. Molina P, et al. Erythropoietin treatment in the sixth posttransplant month as a prognostic factor for renal allograft survival. Transplant Proc. 2006;38:2441–4. https://doi.org/10.1016/j.transproceed.2006.08.086.
99. Kamar N, Rostaing L. Negative impact of one-year anemia on long-term patient and graft survival in kidney transplant patients receiving calcineurin inhibitors and mycophenolate mofetil. Transplantation. 2008;85:1120–4. https://doi.org/10.1097/TP.0b013e31816a8a1f.
100. Martinez F, et al. High dose epoetin beta in the first weeks following renal transplantation and delayed graft function: results of the Neo-PDGF study. Am J Transplant. 2010;10:1695–700. https://doi.org/10.1111/j.1600-6143.2010.03142.x.
101. Aydin, Z. et al. Randomized trial of short-course high-dose erythropoietin in donation after cardiac death kidney transplant recipients. Am J Transplant 2012;12, 1793-1800. https://doi.org/10.1111/j.1600-6143.2012.04019.x.
102. Bartels, V. et al. Influence of erythropoietin on arterial stiffness and endothelial function in renal transplant recipients. Am J Nephrol 2012;36:355-361. https://doi.org/10.1159/000343140.
103. Hafer, C. et al. High-dose erythropoietin has no effect on short- or long-term graft function following deceased donor kidney transplantation. Kidney international 2012;81:314-320.https://doi.org/10.1038/ki.2011.349.

104. Sureshkumar KK, Hussain SM, Ko TY, Thai NL, Marcus RJ. Effect of high-dose erythropoietin on graft function after kidney transplantation: a randomized, double-blind clinical trial. Clin J Am Soc Nephrol. 2012;7:1498–506. https://doi.org/10.2215/CJN.01360212.
105. Jiménez, C. et al. The impact of darbepoietin alfa in early post-transplant anaemia management: retrospective exploratory study. Nefrologia 2013;33:107–115. https://doi.org/10.3265/Nefrologia.pre2012.Oct.11473.
106. Coupes, B. et al. rherythropoietin-b as a tissue protective agent in kidney transplantation: a pilot randomized controlled trial. BMC Res Notes 2015;8, 21. https://doi.org/10.1186/s13104-014-0964-0.
107. Ruiz-Fuentes, M. D., Pérez-Marfil, A., Ruiz-Fuentes, N., De Gracia-Guindo, C. & Osuna-Ortega, A. Treatment with darbepoetin during the first year after renal transplantation: the starting point. Transplant Proc 2015;47, 2622–2625. https://doi.org/10.1016/j.transproceed.2015.10.007.
108. Obi, Y. et al. Correcting anemia and native vitamin D supplementation in kidney transplant recipients: a multicenter, 2 × 2 factorial, open-label, randomized clinical trial. Transplant Int 2021;34, 1212-1225. https://doi.org/10.1111/tri.13885.
109. Al-Otaibi, T. et al. Full correction of posttransplant anemia is associated with stabilized cardiac dimensions among kidney transplant recipients: a prospective randomized controlled trial. Exp Clin Transplant 2024;22, 323–331. https://doi.org/10.6002/ect.MESOT2023.P112.
110. Kawada, N. et al. Negative effects of anemia on quality of life and its improvement by complete correction of anemia by administration of recombinant human erythropoietin in posttransplant patients. Clin Exp Nephrol 2009;13, 355–360. https://doi.org/10.1007/s10157-009-0170-x.
111. Rigatto C. et al. Congestive heart failure in renal transplant recipients: risk factors, outcomes, and relationship with ischemic heart disease. J Am Soc Nephrol 2002;13, 1084–1090. https://doi.org/10.1681/asn.V1341084.
112. Lentine KL et al. De novo congestive heart failure after kidney transplantation: a common condition with poor prognostic implications. Am J Kidney Dis 2005;46, 720–733. https://doi.org/10.1053/j.ajkd.2005.06.019.
113. Rigatto, C. et al. Electrocardiographic left ventricular hypertrophy in renal transplant recipients: prognostic value and impact of blood pressure and anemia. J Am Soc Nephrol. 2003;14:462–468. https://doi.org/10.1097/01.asn.0000043141.67989.39.
114. Katznelson S, Gjertson DW, Cecka JM. The effect of race and ethnicity on kidney allograft outcome. Clin Transpl. 1995:379–394.
115. Ilori TO. et al. Racial and ethnic disparities in graft and recipient survival in elderly kidney transplant recipients. J Am Geriatr Soc. 2015;63:2485–2493. https://doi.org/10.1111/jgs.13845.
116. Wilkins LJ, et al. A contemporary analysis of outcomes and modifiable risk factors of ethnic disparities in kidney transplantation. J Natl Med Assoc. 2019;111:202–9. https://doi.org/10.1016/j.jnma.2018.10.011.
117. Padiyar A, Hricik DE. Immune factors influencing ethnic disparities in kidney transplantation outcomes. Expert Rev Clin Immunol. 2011;7:769–78. https://doi.org/10.1586/eci.11.32.
118. Udomkarnjananun, S. et al. Therapeutic drug monitoring of immunosuppressive drugs in hepatology and gastroenterology. Best Pract Res Clin Gastroenterol 2021;54–55, 101756. https://doi.org/10.1016/j.bpg.2021.101756.
119. Schaeffeler E, et al. Frequency of C3435T polymorphism of MDR1 gene in African people. Lancet. 2001;358:383–4. https://doi.org/10.1016/s0140-6736(01)05579-9.
120. Leschziner GD, Andrew T, Pirmohamed M, Johnson MR. ABCB1 genotype and PGP expression, function and therapeutic drug response: a critical review and recommendations for future research. Pharmacogenomics J. 2007;7:154–79. https://doi.org/10.1038/sj.tpj.6500413.
121. Udomkarnjananun S, et al. P-glycoprotein, FK-binding protein-12, and the intracellular tacrolimus concentration in T-lymphocytes and monocytes of kidney transplant recipients. Transplantation. 2023;107:382–91. https://doi.org/10.1097/tp.0000000000004287.
122. Denic A, Rule AD, Glassock RJ. Healthy and unhealthy aging on kidney structure and function: human studies. Curr Opin Nephrol Hypertens. 2022;31:228–34. https://doi.org/10.1097/mnh.0000000000000780.
123. Tsuchimoto A, et al. Renal interstitial fibrosis in 0-hour biopsy as a predictor of post-transplant anemia. Am J Nephrol. 2013;38:267–74. https://doi.org/10.1159/000354647.
124. Opelz G, Döhler B. Effect of human leukocyte antigen compatibility on kidney graft survival: comparative analysis of two decades. Transplantation. 2007;84:137–43. https://doi.org/10.1097/01.tp.0000269725.74189.b9.
125. Takemoto SK, Terasaki PI, Gjertson DW, Cecka JM. Twelve years' experience with national sharing of HLA-matched cadaveric kidneys for transplantation. N Engl J Med. 2000;343:1078–84. https://doi.org/10.1056/nejm200010123431504.
126. Wissing KM, et al. HLA mismatches remain risk factors for acute kidney allograft rejection in patients receiving quadruple immunosuppression with anti-interleukin-2 receptor antibodies. Transplantation. 2008;85:411–6. https://doi.org/10.1097/TP.0b013e31816349b5.
127. Lim WH, et al. Human leukocyte antigen mismatches associated with increased risk of rejection, graft failure, and death independent of initial immunosuppression in renal transplant recipients. Clin Transplant. 2012;26:E428-437. https://doi.org/10.1111/j.1399-0012.2012.01654.x.
128. Rothem, Y. et al. Elevated hemoglobin levels in renal transplant recipients with polycystic kidney disease versus other etiologies: exploring mechanisms and implications for outcomes. J Nephrol 2024. https://doi.org/10.1007/s40620-023-01868-6.
129. Hofstetter L, et al. Post-transplantation erythrocytosis in kidney transplant recipients-a retrospective cohort study. Eur J Haematol. 2021;107:595–601. https://doi.org/10.1111/ejh.13696.
130. Mekraksakit P, et al. Risk factors and outcomes of post-transplant erythrocytosis among adult kidney transplant recipients: a systematic review and meta-analysis. Transpl Int. 2021;34:2071–86. https://doi.org/10.1111/tri.14016.
131. Chandra M, Miller ME, Garcia JF, Mossey RT, McVicar M. Serum immunoreactive erythropoietin levels in patients with polycystic kidney disease as compared with other hemodialysis patients. Nephron. 1985;39:26–9. https://doi.org/10.1159/000183332.
132. Buchholz B, Eckardt K-U. Role of oxygen and the HIF-pathway in polycystic kidney disease. Cell Signal. 2020;69:109524. https://doi.org/10.1016/j.cellsig.2020.109524.
133. Bellini MI, et al. Bilateral nephrectomy for adult polycystic kidney disease does not affect the graft function of transplant patients and does not result in sensitisation. Biomed Res Int. 2019;2019:7423158. https://doi.org/10.1155/2019/7423158.
134. Fehr T, et al. Interpretation of erythropoietin levels in patients with various degrees of renal insufficiency and anemia. Kidney Int. 2004;66:1206–11. https://doi.org/10.1111/j.1523-1755.2004.00880.x.
135. Jordan SC, et al. Interleukin-6: an important mediator of allograft injury. Transplantation. 2020;104:2497–506. https://doi.org/10.1097/tp.0000000000003249.
136. Chandran S, Tang Q. Impact of interleukin-6 on T cells in kidney transplant recipients. Am J Transplant. 2022;22:18–27. https://doi.org/10.1111/ajt.17209.
137. Chavele KM, Merry E, Ehrenstein MR. Cutting edge: circulating plasmablasts induce the differentiation of human T follicular helper cells via IL-6 production. J Immunol. 2015;194:2482–5. https://doi.org/10.4049/jimmunol.1401190.
138. Jordan SC, Ammerman N, Huang E, Vo A. Importance of IL-6 inhibition in prevention and treatment of antibody-mediated rejection in kidney allografts. Am J Transplant. 2022;22(Suppl 4):28–37. https://doi.org/10.1111/ajt.17207.
139. López-Gómez JM, et al. Presence of a failed kidney transplant in patients who are on hemodialysis is associated with chronic inflammatory state and erythropoietin resistance. J Am Soc Nephrol. 2004;15:2494–501. https://doi.org/10.1097/01.Asn.0000137879.97445.6e.
140. Borrelli, S. et al. Resistance to erythropoiesis stimulating agents in a dialysis patient after kidney graft failure. J Nephrol 2024. https://doi.org/10.1007/s40620-023-01836-0.
141. Almond MK, Tailor D, Marsh FP, Raftery MJ, Cunningham J. Increased erythropoietin requirements in patients with failed renal transplants returning to a dialysis programme. Nephrol Dial Transplant. 1994;9:270–3.
142. Augustine JJ, et al. Comparative effects of sirolimus and mycophenolate mofetil on erythropoiesis in kidney transplant patients. Am J Transplant. 2004;4:2001–6. https://doi.org/10.1111/j.1600-6143.2004.00612.x.

143. Maiorano A, et al. Sirolimus interferes with iron homeostasis in renal transplant recipients. Transplantation. 2006;82:908–12. https://doi.org/10.1097/01.tp.0000235545.49391.1b.
144. Thaunat O, et al. Anemia after late introduction of sirolimus may correlate with biochemical evidence of a chronic inflammatory state. Transplantation. 2005;80:1212–9. https://doi.org/10.1097/01.tp.0000179106.07382.6a.
145. Przybylowski P, Malyszko JS, Macdougall IC, Malyszko J. Iron metabolism, hepcidin, and anemia in orthotopic heart transplantation recipients treated with mammalian target of rapamycin. Transplant Proc. 2013;45:387–90. https://doi.org/10.1016/j.transproceed.2012.02.040.
146. Augustine JJ, et al. Reduction in erythropoietin resistance after conversion from sirolimus to enteric coated mycophenolate sodium. Transplantation. 2008;86:548–53. https://doi.org/10.1097/TP.0b013e3181814a96.
147. Jefferies R. et al. mTOR inhibitors induce erythropoietin resistance in renal transplant recipients. Front Med. 2022:9. https://doi.org/10.3389/fmed.2022.722058.
148. Labes R, et al. Daprodustat prevents cyclosporine-A-mediated anemia and peritubular capillary loss. Kidney Int. 2022;102:750–65. https://doi.org/10.1016/j.kint.2022.04.025.
149. Udomkarnjananun, S., Eiamsitrakoon, T., de Winter, B. C. M., van Gelder, T. & Hesselink, D. A. Should we abandon therapeutic drug monitoring of tacrolimus in whole blood and move to intracellular concentration measurements? Br J Clin Pharmacol 2023. https://doi.org/10.1111/bcp.15946.
150. Mrug M, Stopka T, Julian BA, Prchal JF, Prchal JT. Angiotensin II stimulates proliferation of normal early erythroid progenitors. J Clin Invest. 1997;100:2310–4. https://doi.org/10.1172/jci119769.
151. Vlahakos DV, et al. Association between activation of the renin-angiotensin system and secondary erythrocytosis in patients with chronic obstructive pulmonary disease. Am J Med. 1999;106:158–64. https://doi.org/10.1016/s0002-9343(98)00390-8.
152. Cheungpasitporn W, Thongprayoon C, Chiasakul T, Korpaisarn S, Erickson SB. Renin-angiotensin system inhibitors linked to anemia: a systematic review and meta-analysis. QJM Int J Med. 2015;108:879–84. https://doi.org/10.1093/qjmed/hcv049.
153. Azizi M, et al. Acute angiotensin-converting enzyme inhibition increases the plasma level of the natural stem cell regulator N-acetyl-seryl-aspartyl-lysyl-proline. J Clin Invest. 1996;97:839–44. https://doi.org/10.1172/jci118484.
154. Correa PN, Axelrad AA. Production of erythropoietic bursts by progenitor cells from adult human peripheral blood in an improved serum-free medium: role of insulinlike growth factor 1. Blood. 1991;78:2823–33.
155. Morrone LF, et al. Interference of angiotensin-converting enzyme inhibitors on erythropoiesis in kidney transplant recipients: role of growth factors and cytokines: 1. Transplantation. 1997;64:913–8.
156. Sharples, E. J. et al. Erythropoietin protects the kidney against the injury and dysfunction caused by ischemia-reperfusion. J Am Soc Nephrol 2004;15, 2115–2124. https://doi.org/10.1097/01.Asn.0000135059.67385.5d.
157. Vesey, D. A. et al. Erythropoietin protects against ischaemic acute renal injury. Nephrol Dial Transplant 2004;19, 348–355. https://doi.org/10.1093/ndt/gfg547.
158. Patel, N. S. et al. Pretreatment with EPO reduces the injury and dysfunction caused by ischemia/reperfusion in the mouse kidney in vivo. Kidney Int 2004;66, 983–989. https://doi.org/10.1111/j.1523-1755.2004.00847.x.
159. Spandou E. et al. Erythropoietin attenuates renal injury in experimental acute renal failure ischaemic/reperfusion model. Nephrol Dial Transplant. 2006;21:330–336. https://doi.org/10.1093/ndt/gfi177.
160. Hu L. et a. Erythropoietin ameliorates renal ischemia and reperfusion injury via inhibiting tubulointerstitial inflammation. J Surg Res. 2012;176:260–266. https://doi.org/10.1016/j.jss.2011.06.035.
161. Kwak J, et al. Erythropoietin ameliorates ischemia/reperfusion-induced acute kidney injury via inflammasome suppression in mice. Int J Mol Sci. 2020;21. https://doi.org/10.3390/ijms21103453.
162. Elliott S, et al. Lack of expression and function of erythropoietin receptors in the kidney. Nephrol Dialysis Transplant. 2011;27:2733–45. https://doi.org/10.1093/ndt/gfr698.
163. Sinclair AM, et al. Functional erythropoietin receptor is undetectable in endothelial, cardiac, neuronal, and renal cells. Blood. 2010;115:4264–72. https://doi.org/10.1182/blood-2009-10-248666.
164. Pallet N, Rabant M, Legendre C, Martinez F, Choukroun G. The nephroprotective properties of recombinant human erythropoietin in kidney transplantation: experimental facts and clinical proofs. Am J Transplant. 2012;12:3184–90. https://doi.org/10.1111/j.1600-6143.2012.04287.x.
165. El-Zoghby ZM, et al. Identifying specific causes of kidney allograft loss. Am J Transplant. 2009;9:527–35. https://doi.org/10.1111/j.1600-6143.2008.02519.x.
166. Sellarés J, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant. 2012;12:388–99. https://doi.org/10.1111/j.1600-6143.2011.03840.x.
167. Peng B, Kong G, Yang C, Ming Y. Erythropoietin and its derivatives: from tissue protection to immune regulation. Cell Death Dis. 2020;11:79. https://doi.org/10.1038/s41419-020-2276-8.
168. Wang S, et al. Erythropoietin protects against rhabdomyolysis-induced acute kidney injury by modulating macrophage polarization. Cell Death Dis. 2017;8:e2725–e2725. https://doi.org/10.1038/cddis.2017.104.
169. Nairz M, et al. Erythropoietin contrastingly affects bacterial infection and experimental colitis by inhibiting nuclear factor-κB-inducible immune pathways. Immunity. 2011;34:61–74. https://doi.org/10.1016/j.immuni.2011.01.002.
170. Van Oers MH, Van der Heyden AA, Aarden LA. Interleukin 6 (IL-6) in serum and urine of renal transplant recipients. Clin Exp Immunol. 1988;71:314–9.
171. Waiser J. et al. Interleukin-6 expression after renal transplantation. Nephrol Dial Transplant. 1997;12:753–759. https://doi.org/10.1093/ndt/12.4.753.
172. Vandenbroecke C, et al. Differential in situ expression of cytokines in renal allograft rejection. Transplantation. 1991;51:602–9.

Publisher's Note