Ukrainian Journal of Nephrology and Dialysis
Scientific and Practical, Medical Journal

Founder:
- National Kidney Foundation of Ukraine

ISSN 2304-0238;
eISSN 2616-7352

Journal homepage: https://ukrjnd.com.ua

Research article

Elmukhtar Habas[1], Amnna Rayani[2], Aml Habas[3], Gamal Alfitori[4], Ala Habas[5], Kalifa Farfar[6], Eshrak Habas[5], Khaled Alarbi[4], Mohamed Baghi[4], Almehdi Errayes[4], Abdelrahman Hamad[4], Abdel-Naser Elzouki[4]

doi: 10.31450/ukrjnd.2(86).2025.08

Burden of anemia in kidney transplant patients: Epidemiology, pathophysiology, and management

[1]Hamad General Hospital, Open Libyan University, Doha, Qatar
[2]Tripoli Children Hospital, Tripoli University, Tripoli, Libya
[3]Tripoli Pediatric Hospital, Open Libyan University, Tripoli, Libya
[4]Hamad General Hospital, Qatar University, Doha, Qatar
[5]Tripoli Central Hospital, Tripoli University, Tripoli, Libya
[6]Al Wakra General Hospital, Qatar University, Al Wakra, Qatar

Citation: Habas E, Rayani A, Habas A, Alfitori G, Habas A, Farfar K, et al. Burden of anemia in kidney transplant patients: Epidemiology, pathophysiology, and management. Ukr J Nephrol Dialys. 2025;2(86):71-89. doi: 10.31450/ukrjnd.2(86).2025.08.

Abstract. *Anemia following kidney transplantation (KTx) is a prevalent complication that adversely affects allograft function, graft survival, and patient survival. Its etiology is multifactorial, encompassing general causes of anemia and KTx-specific factors, such as immunosuppression and reduced erythropoietin production. Management primarily involves iron supplementation and erythropoiesis-stimulating agents (ESAs); however, specific guidelines for post-KTx anemia are lacking, and the optimal methods for treating iron deficiency in KTx recipients remain undefined. Emerging evidence suggests that sodium-glucose cotransporter-2 inhibitors may improve hemoglobin and hematocrit levels in patients with chronic kidney disease and KTx recipients.*

To review recent advances in the pathogenesis, epidemiology, treatment, and outcomes of post-KTx anemia, we conducted a literature search using PubMed, Google Scholar, and Google, with keywords including "anemia in kidney transplantation," "anemia etiology in KTx recipients," "iron deficiency in renal transplantation," and "short- and long-term effects of anemia in KTx recipients."

This review synthesizes evidence indicating that effective management of post-KTx anemia, through ESAs and supplementation of erythropoiesis essentials (iron, folate, vitamin B12), is safe and may confer renoprotective benefits. Targeted anemia correction enhances quality of life, reduces mortality, improves transplanted kidney function, and lowers the risk of graft rejection, underscoring the need for standardized treatment protocols.

Keyword: *anemia, kidney transplantation, erythropoietin, iron deficiencies, sodium-glucose transporter 2 inhibitors, graft rejection, graft survival, quality of life.*

Article history:
Received April 10, 2025
Received in revised form May 04, 2025
Accepted May 05, 2025

Conflict of interest. The authors declare no conflict of interest.

Correspondence should be addressed to Elmukhtar Habas: habas1962@gmail.com

УДК: 616.155.194:616.61-089.843

Ельмухтар Хабас[1], Амнна Раяні[2], Амль Хабас[3], Гамаль Альфіторі[4], Ала Хабас[5], Халіфа Фарфар[6], Ешрак Хабас[5], Халед Аларбі[4], Мохамед Багхі[4], Альмехді Еррає[4], Абдельрахман Хамад[4], Абдель-Насер Ельзоук[4]

Анемія у реципієнтів ниркового трансплантату: епідеміологія, патофізіологія та підходи до лікування

[1]Загальна лікарня Хамад, Відкритий Лівійський університет, Доха, Катар
[2]Дитяча лікарня Триполі, Університет Триполі, Триполі, Лівія
[3]Педіатрична лікарня Триполі, Відкритий Лівійський університет, Триполі, Лівія
[4]Загальна лікарня Хамад, Університет Катару, Доха, Катар
[5]Центральна лікарня Триполі, Університет Триполі, Триполі, Лівія
[6]Загальна лікарня Аль-Вакра, Університет Катару, Аль-Вакра, Катар

Резюме. *Анемія у реципієнтів ниркового тнсплантата (НТ) негативно впливає на функцію алотрансплантата, виживаність трансплантата та пацієнтів. Її етіологія є мультифакторною, охоплюючи загальні причини анемії і специфічні для НТ фактори, такі як імуносупресія та зниження продукування еритропоетину. Лікування переважно включає застосування засобів заліза та еритропоез-стимулюючі агенти (ЕСА); однак специфічні рекомендації щодо менеджменту пост-трансплантаційної анемії відсутні, а оптимальні методи лікування дефіциту заліза у реципієнтів НТ залишаються невизначеними. Нові дані свідчать, що інгібітори котранспортера натрію-глюкози 2 можуть покращувати рівні гемоглобіну та гематокриту у реципієнтів НТ з хронічною хворобою нирок.*

Для огляду останніх досягнень у вивченні патогенезу, епідеміології, лікування та наслідків пост-трансплантаційної анемії ми провели пошук літератури за допомогою PubMed, Google Scholar і Google, використовуючи ключові слова, зокрема «анемія за трансплантації нирки», «етіологія анемії у реципієнтів НТ», «дефіцит заліза у реципієнтів НТ» та «коротко- і довгострокові ефекти анемії у реципієнтів НТ».

Цей огляд узагальнює докази, які вказують на те, що ефективний менеджмент пост-трансплантаційної анемії за допомогою ЕСА та необхідних для еритропоезу компонентів (залізо, фолати, вітамін В12) є безпечним і може забезпечувати нефропротекторні переваги. Цілеспрямована корекція анемії покращує якість життя, знижує смертність, сприяє кращій функції трансплантованої нирки та зменшує ризик відторгнення трансплантата, підкреслюючи необхідність розробки стандартизованих протоколів лікування.

Ключові слова: *анемія, трансплантація нирки, еритропоетин, дефіцит заліза, інгібітори котранспортера натрію-глюкози 2, відторгнення трансплантата, виживаність трансплантата, якість життя.*

Introduction. Kidney failure is a major public health problem, and its impact is expected to escalate significantly because of the aging population and the increasing rates of diabetes (DM) and hypertension (HTN) [1]. The commonest cause of renal failure that requires regular dialysis and kidney transplantation (KTx) is chronic kidney disease (CKD). CKD's overall prevalence is almost 14% [2]. Globally, DM and HTN are the prevalent etiologies of CKD [3, 4]. Although dialysis is widely used globally for kidney failure, research has shown that KTx is more cost-effective.

KTx is linked with improved quality of life, greater survival rates, and higher economic productivity [5]. The framework established by the International Society of Nephrology (ISN) prioritizes KTx as the preferred method of kidney replacement treatment (RRT) [6]. However, the use of KTx is limited by many reasons, such as patient eligibility, the availability of donors, cultural prejudice against organs from dead donors, local or regional proficiency, and the expenses associated with KTx surgery and immunosuppressive drugs [7]. While it is probable that low-income nations have more challenges in accessing KTx, there is a lack of recorded data on the availability, accessibility, and quality of KTx care compared to countries with good economic levels.

A survey was conducted in 182 nations, with 155 responding to inquiries related to KTx. Approximately 74% reported the availability of KTx, with a median occurrence rate of 14/million and a median prevalence rate of 255/million. The accessibility of knowledge about KTx has shown significant disparities, with even high-income nations demonstrating significantly worse accessibility for ethnic minorities. Around 31% of individuals had access to universal health coverage for all KTx treatment expenses, whereas 57% maintained kidney transplant registries [8], affecting the rate of KTx.

Elmukhtar Habas
habas1962@gmail.com

The American Society of Transplantation and the World Health Organization (WHO) define anemia as Hb levels < 12 g/dL for females and < 13 g/dL for males [9, 10]. Normocytic normochromic anemia is a common CKD anemia linked to many negative clinical consequences [11]. A successful KTx can rectify anemia. Nevertheless, a significant proportion of KTx individuals, ranging between 20% and 51%, have anemia at different stages after KTx [12, 13]. Post-KTx (PKTx) anemia is often subdivided into early and late. Early anemia usually develops within 6 months of PKTx, affecting around 50% of patients, while Late anemia occurs in 23%-35% of KTx individuals after 6 months [13, 14].

PKTx anemia is connected with decreased physical ability, persistent tiredness, cognitive deterioration, and worsening life quality [15]. Furthermore, increasing evidence suggests that anemia might have an adverse correlation with long-term clinical results after KTX, including graft failure, death, and progression of kidney dysfunction. Therefore, addressing anemia in KTx recipients (KTRs) is justifiable, preferably initiating treatment promptly after transplantation. However, the guidelines need more appropriate or precise recommendations for managing anemia in KTxRs [16]. The KDIGO recommendations for KTRs and the position statement from the European Renal Best Practice Group both recommend managing anemia in KTxRs by adhering to the treatment guidelines for anemia in CKD. However, these recommendations have some drawbacks, as will be discussed later.

Epidemiology of post-kidney transplantation anemia. PKTx anemia prevalence was reported as 20–51% at different points in time after transplantation [12, 13]. The prevalence of early anemia in PKTxRs was about 50% in various studies [17, 18], and the prevalence decreased to approximately 23–35% during the eight-year follow-up [17, 18]. The prevalence rates of PKTx anemia at 1, 3, 6 months, and 1 year were 84.3%, 39.5%, 26.2%, and 21.6%, respectively [19]. Subsequent research indicates that the prevalence of PKTx anemia varies between 25% and 41.4% [20, 21], with a 2-year prevalence of 36.6%. The anemia incidence at 3, 5, and 10 years PKTx has been reported as 41.5%, 35.3%, and 93.2%, respectively [22]. Another study reported that anemia rates vary by definition and transplantation time. Research indicates that 50% of KTxRs are anemic at 6 months, 40% at 1 year, and 30% at 5 years of PKTx, with 12%-15% experiencing severe PKTx anemia (Hb <11 g/dL) [23]. PKTx anemia has a high prevalence, and its severity increases the risk of graft failure [24], mortality rate [12, 13], left ventricular hypertrophy [25], congestive heart failure [26], and the estimated glomerular filtration rate (eGFR) reduction [17]. The variation in PKTx anemia prevalence and anemia-related death rate may be due to heterogeneity in anemia definitions, patient characteristics, graft function, immunosuppression, inclusion criteria, and study methodologies. Standardized reporting and longer follow-ups could improve comparability.

Post-kidney transplantation anemia etiology and pathophysiology. Anemia incidence and severity are linked to kidney transplant graft dysfunction [27]. KTx causes folate, iron, and vitamin B12 deficits, causing anemia [28]. The graft secretes erythropoietin (EPO), which rises to 100% by 16 weeks PKTx, improving erythropoiesis and anemia. Second plasma EPO peaks depend on renal function recovery [29]. Serum EPO levels may vary with renal function in KTxRs [30]. As the transplanted kidney's glomerular filtration rate (GFR) drops, EPO production diminishes [30]. Acute rejection can rapidly lower serum EPO [31]. PKTx anemia patients may have high serum EPO or insufficiency and may develop intolerance to high EPO levels. Chronic allograft rejection, inflammation, iron insufficiency, hyperparathyroidism, infections, and immunosuppressive medication misuse increase resistance to the EPO effect [30].

Iron deficiency PKTx can cause early or late-stage anemia. Increased iron consumption due to allograft-induced serum EPO generation, hemorrhage during or after surgery, frequent sampling, anticoagulant usage, commencement of heavy menstrual cycles, and malignancies can cause an absolute iron deficiency [32]. Inflammation and mTOR inhibitors raise hepcidin levels, lowering blood iron and affecting erythropoiesis [32].

Chronic bacterial or viral infections impair erythropoiesis by directly impacting the bone marrow, increasing the risk of PKTx anemia [33]. In the early months after transplantation, immunosuppressive medication increases the risk of infectious diseases [34]. Due to bone marrow suppression by parvovirus B19, reticulocyte counts might drop below 1% within 2 weeks of kidney transplantation, causing anemia [37].

Anemia caused by medication may be investigated when no other causes are found [20]. Calcineurin inhibitors, anti-thymocyte globulin, mTOR inhibitors, and antimetabolites can cause anemia. Anemia can be caused by toxic antivirals such as ganciclovir and valganciclovir. Antibacterials such as trimethoprim-sulfamethoxazole can impact bone marrow, and immune-mediated hemolysis can cause anemia [14, 35]. Azathioprine and mycophenolate mofetil can cause hemolytic or megaloblastic anemia in kidney transplant recipients [36, 37]. Long-term proton pump inhibitor use may impede intestinal iron absorption, causing iron-deficiency anemia [38]. PKTx anemia is linked to RAAS inhibitors [27]. The RAAS increases serum angiotensin II, which boosts erythropoiesis by increasing EPO synthesis in response to hypoxia and decreasing renal blood flow [16]. It also decreases hepcidin and stimulates red blood cell precursor production. The effect of RAAS on erythropoiesis may be minor in the general population, but blocking RAAS receptors decreases hematocrit in immunosuppressed individuals. RAAS inhibitors in PKTx may affect erythropoiesis, causing anemia [20, 39]. Delayed graft function delays EPO synthesis by

the transplanted kidney, causing PKTx anemia. Interstitial fibrosis and tubular atrophy are independently related to 12-month post-PKTx anemia [40].

Pathophysiologically, PKTx anemia has many causes. Iron deficiency, sometimes caused by preexisting deficits, causes anemia in PKTxRs. Vitamin B12 and folate deficits, albeit less common than iron deficiency, can cause anemia and impair erythropoiesis since they are essential for erythropoiesis. Rejection of transplanted kidneys, especially in situations of chronic injury, can cause interstitial fibrosis and tubular atrophy, limiting kidney function and erythropoietin synthesis.

Early kidney impairment often coincides with donor kidney health. Late dysfunction can arise from cumulative damage or rejection, affecting EPO production over time. Hepcidin, ferritin, and HIF dysregulation affect iron availability and EPO response. Hepcidin, an iron-regulatory hormone, is raised during inflammation, especially in transplant recipients, limiting iron availability. Erythropoietin synthesis and iron metabolism depend on hypoxia-inducible factors [41]. The primary causes and pathogenesis of PKTx anemia are shown in Table 1 and Fig. 1.

Table 1

Etiologies of post-kidney transplant early and late anemia

Early Anemia Etiology	Late Anemia Etiology
Iron deficiency	Allograft Dysfunction
Infections – Viruses causing aplastic anemia (parvovirus B19, Epstein-Barr virus, cytomegalovirus, adenovirus, BK virus, herpesviruses, and varicella-zoster virus) – Indolent infections (bacterial, fungal, viral, and parasitic)	Infections: Late-viral (cytomegalovirus, hepatitis B virus, and hepatitis C virus) Community-acquired pathogens
Allograft Quality	Immunosuppressive Treatment
Immunosuppression induction	Iron Deficiency
Extended donor criteria	Vitamin B12 and Folic acid deficiency
Acute Rejection	Acute rejection
Delayed graft function	Antimicrobials
Ischemia time	Drugs Renin-angiotensin system inhibitors Proton-pump inhibitors
Aggressive Hydration (dilutionary effect)	
Transplanted kidney	Transplanted kidney

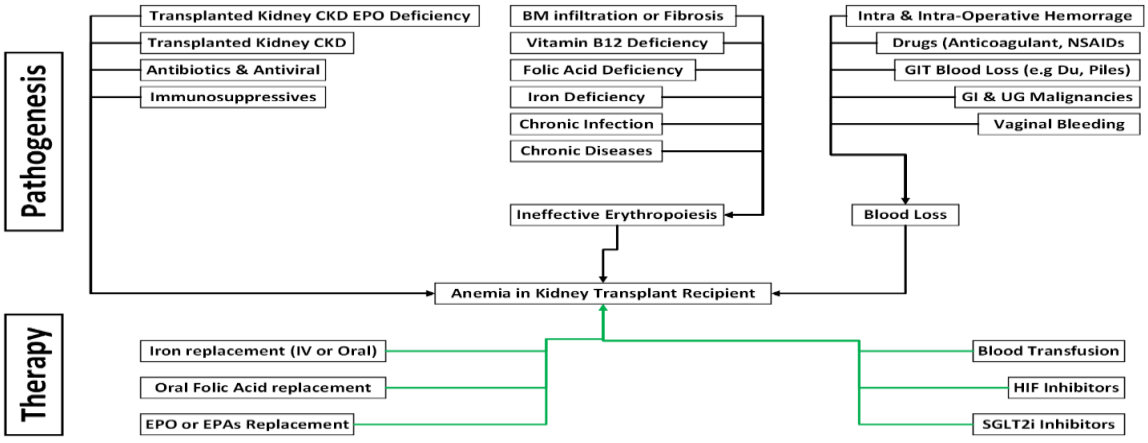

Fig. 1. Pathogenesis, etiology, and treatment of Post-kidney Transplantation Anemia.

Predictors of post-kidney transplant anemia. Multiple studies have sought to identify factors that might predict the occurrence of PKTx anemia. In retrospective research, 266 KTxRs between 2008 and 2011 were included [17]. Female sex, lower eGFR, and presence of hypochromic red blood cells were identified as variables linked with early PKTx anemia in a multivariate analysis. Early PKTx anemia and receiv-

ing a live donor kidney were identified as important factors related to late PKTx anemia occurring 2 years after transplantation. The latter factor, having a living donor as the source of transplantation, was shown to have a protective effect for late PKTx anemia [17]. The Transplant European Survey on Anemia Management (TRESAM) gathered figures from 72 transplant facilities in 16 countries, which included 4,263 KTxRs [20]. An evident correlation was seen between graft performance and Hb levels. In 904 KTx individuals with serum creatinine > 176.8 mmol/dL, 60.1% were anemic, compared to 29.0% of serum creatinine < 176.8 mmol/dL individuals, with a significant difference, $P < 0.01$. High serum creatinine levels (over 176.8 mmol/dL) were related to anemia occurrence in PKTx. Additional variables linked to PKTx anemia included donor age (especially over 60 years), the administration of ACE inhibitors, immunosuppressives such as mycophenolate mofetil and azathioprine, angiotensin receptor blockers, and infections.

In a study involving 626 patients who received transplantation at a single center in Pennsylvania, several factors were significantly linked to anemia 12 months after PKTx. These factors include anemia occurring 3 months after PKTx, the donor's age, creatinine levels at 3 months, and being female [42]. It has been concluded that after 12 months of PKTx, the occurrence of PKTx anemia has led to a higher risk of patient mortality. The presence of anemia 3 months after the transplantation is a significant factor in determining the occurrence of 12-month PKTx anemia [42]. Furthermore, a separate study conducted in Michigan, which included 192 kidney transplant patients, found that being female and having higher creatinine levels at the 3-month mark are indicators of late post-transplant allograft dysfunction [43]. The finding that anemia shortly after PKTx indicates that anemia will occur later [17] implies that improved measures to avoid and manage anemia in the early stages of PKTx might avert late PKTx anemia and graft failure, especially in severe and moderate anemia [12].

Approach to post-kidney transplant anemia. The diagnosis and the investigatory scheme of PKTx anemia include a good history and a physical examination. The important parts of the history are the history of bleeding, stool color, urine color, drug history, gastrointestinal chronic diseases, and previous surgical history. A history of anticoagulation and the type of immunosuppressive medication used are essential. Moreover, the history of when the anemia started after KTx is important to recognize the type of PKTx anemia and the history of anemia pre-KTx. Furthermore, careful, thorough clinical examination for signs of bleeding, anemia, and chronic kidney, liver, and cardiac diseases. A thorough general and systematic clinical examination is necessary to look for any causes of anemia. Complete laboratory workup, including complete blood count, differential count, urine examination, serum vitamin B12, folate, iron status (serum iron, ferritin, total iron binding capacity), serum thyroid, and parathyroid hormone levels, is all needed. In some instances, invasive investigations, such as endoscopies, bone marrow aspiration, and biopsy, might be required.

Post-kidney transplantation anemia and graft failure. Previous studies reported that KTx is linked to the combined occurrence of death from any cause and loss of the transplanted organ. Nevertheless, whereas most research has shown a noteworthy link with graft failure, findings addressing the connection between anemia and death are inconclusive. An investigation of 4,217 French PKTx individuals revealed that both death and graft failure were linked to PKTx anemia at 12 months [21]. Research conducted in Hungary followed 938 KTx patients and found that anemia was linked to increased death and graft failure after 4 years [44] and 8 years of follow-up [45]. An Austrian study on 2,031 KTx individuals revealed a substantial correlation between anemia and graft failure and mortality over a median period of 6 years [46]. A study conducted in Pennsylvania, including 626 KTx recipients, found that anemia at the 12-month mark had a higher mortality risk [42]. A study of 1,023 KTx recipients found that anemia after 3 months of PKTx was linked to increased graft failure and mortality [47]. A study of 170 KTxRs concluded that PKTx anemia during the first 30 days indicates poor graft outcome [48]. Another research, including 266 transplant patients, found that anemia occurring after PKTx at 2 years was also linked to higher death rates [44] and even during 8 years of follow-up [45]. An Austrian study of 2,031 KTx individuals revealed a substantial correlation between anemia and graft failure and mortality over a median period of 6 years [46]. A study of 1,023 KTx recipients found that anemia after 3 months of PKTx was linked to increased graft failure and mortality [47]. A study of 170 KTxRs concluded that PKTx anemia during the first 30 days indicates poor graft outcome [48]. Another research, including 266 transplant patients, found that PKTx anemia is significantly related to late mortality, graft dysfunction, and a rise in graft failure rate [12]. Another trial, including 1,139 patients, showed that anemia occurring between 6 and 18 months after PKTx is common and linked to graft failure and mortality [13]. A Japanese [51] and a Slovakian [52] study had comparable findings. A recent systematic review concluded that therapy with RAAS inhibitors can decrease death and graft loss in PKTx [53], although they may precipitate PKTx anemia [16]. However, further well-designed prospective trials are mandatory to validate these conclusions. A retrospective study that included 145 KTx recipients recently concluded that PKTx anemia significantly enhances graft failure, loss, and mortality [45].

On the contrary, subsequent research has shown contradictory findings concerning long-term fatality. In a retrospective analysis of 825 KTxRs in Europe during a follow-up period of 8 years, anemia was not shown to be correlated with all-cause mortality [49]. According to a study conducted on 2,102 Danish KTxRs, there

was no observed correlation between Hb levels and CV morbidity or death over 5 to 6 years [50]. China's retrospective research, examining 887 PKTx individuals, concluded that 12 months of PKTx anemia was not significantly linked to death [19]. On the contrary, subsequent research has shown contradictory findings concerning long-term fatality. Anemia was not shown to be correlated with all-cause mortality in a retrospective analysis of 825 KTxRs in Europe during a follow-up period of 8 years [49]. According to a study conducted on 2,102 Danish KTxRs, there was no observed correlation between Hb levels and CV morbidity or death over 5 to 6 years [50]. China's retrospective research examining 887 PKTx individuals concluded that 12 months of PKTx anemia was not linked significantly to death [19].

Regarding graft survival, anemia was consistently shown to be substantially correlated with graft loss in different studies. However, other studies did not find a connection with overall mortality, but a substantial link was noted between anemia and graft loss [13, 51]. However, other studies did not find a connection with overall mortality, but a substantial link was noted between anemia and graft loss [13, 51, 52]. Regarding graft survival, anemia was consistently shown to be substantially correlated with graft loss in different studies. However, other studies did not find a connection with overall mortality, but a substantial link was noted between anemia and graft loss [13, 51].

A study reported an established correlation between anemia and mortality, which was detected to depend on the degree of severity [13]. The presence of severe anemia (Hb < 11 g/dL) was continuously linked to a higher death risk. However, moderate anemia has not been reported to correlate significantly with mortality. Moreover, iron deficiency triggers the activation and simultaneous splitting of fibroblast growth factor (FGF) 23 [53]. High levels of FGF23 have been observed as an independent predictor for graft loss, cardiovascular disease (CVD), and death in KTxRs. This is likely due to the unintended effects of FGF23 in non-target sites [32]. It is yet unknown if FGF23 might serve as a link between iron deficiency and negative consequences in KTx anemia cases, necessitating further research.

Research indicates that high serum ferritin in the absence of infection is linked to improved graft performance and survival [54]. In contrast, the study conducted on 438 KTx recipients did not find any connection between graft failure and the proportion of hypochromic anemia [49]. Nevertheless, one study found a significant correlation between the proportion of hypochromic anemia and overall mortality [49]. Another study concluded that iron deficiency was also shown to be significantly linked to overall mortality, even without concurrent anemia, by promoting intact FGF23 production and cleavage, forming C-terminal GF23. A high level of C-terminal GF23 is significantly prospectively related to patient survival [55]. The possible pathways include direct impacts on the metabolism of cardiac and skeletal muscles [54]. In contrast, the study conducted on 438 KTx recipients did not find any connection between graft failure and the proportion of hypochromic anemia [49].

Nevertheless, one study found a significant correlation between the proportion of hypochromic anemia and overall mortality [49]. The possible pathways include direct impacts on the metabolism of cardiac and skeletal muscles [55]. Iron deficiency may weaken the functioning of cardiac and skeletal muscle cells by reducing the amount of oxygen available inside the cells and hindering the Krebs cycle [32]. These findings may explain the inconsistency in research that demonstrated a correlation between death and anemia compared to those that did not report a relationship. Hence, further research is required to clarify this subject.

Post-kidney transplantation anemia effcts on the cardiovascular system. Canadian retrospective research of 473 KTxRs revealed that anemia is a recognized independent factor for LVH, which was detectable in electrocardiography for 1 to 5 years [56]. The presence of LVH and anemia was shown to be strongly correlated with a substantial risk of mortality. LVH before KTx is linked to a higher incidence of CVD among KTx patients [57]. A study involving 1063 individuals who underwent pretransplant echocardiography revealed a significant occurrence of LVH and increased wall thickness. In a multivariable survival regression analysis, these were statistically significant (P=0.02 and 0.04) and were independent factors associated with CVD events. This association remained significant even after accounting for common pretransplant CVD risk factors [58]. KTx results in regression of LVH, as shown by research that demonstrated a substantial reduction in LV mass index (P<0.001), together with a significant improvement in ejection fraction (P = 0.009) over a 24-month follow-up period [59]. Paoletti et al. demonstrated that enhancing LVH improved post-transplant outcomes [60]. A retrospective analysis was undertaken at two Canadian institutions, including 638 consecutive KTx recipients who were clear of cardiac illness one year after the transplantation. Moreover, they reported that anemia was an independent risk factor for congestive heart failure (CHF) in anemic KTxRs. The presence of LVH and anemia was shown to be strongly correlated with a substantial risk of mortality. LVH before KTx is linked to a higher incidence of CVD among KTx patients [57].

KTx generally leads to an increase in ejection fraction over time for most recipients. Following KTx, there is a significant occurrence of new-onset CHF, ranging from 10% to 18% at 12 and 36 months, which is linked to more graft function loss and death rates [61,62]. While KTx leads to improvements in LV volumes during systole and diastole, as well as a reduction in LV muscular masses, it is important to note that the dysfunction of the cardiorenal axis before and after the KTx can still contribute to ongoing LV dilation, myocardial infarction, CHF, and arrhythmia in recipients [62]. The exact prevalence of CHF with preserved ejec-

tion fraction (HFpEF) in KTxRs has yet to be fully understood [61, 62]. However, data obtained from echocardiographic strain measurements indicate that even individuals with normal LVEF may exhibit subtle abnormalities in global longitudinal strain, a highly sensitive measure of LV function. These abnormalities were observed in KTx recipients during a mean follow-up period of 11 months. A decrease in global longitudinal strain during the peri-transplant period may also be linked to an increased likelihood of CV disease events or mortality after kidney transplant [63]. Although it appears that KTx improves most, if not all, CKD CVS complications after KTx, there are some controversies regarding the reported evidence. Hence, further larger studies are required to clarify these controversies.

Post-kidney transplantation anemia effect on glomerular filtration rate. A study reported a decline of eGFR with time in patients with anemia and vice versa. There was more reduction of the eGFR at 2 years compared to 6 months in anemic recipients, while the eGFR improved in nonanemic recipients [17]. In the Correction of Anemia and Progression of Renal Insufficiency in Transplant Patients (CAPRIT) trial, normalization of Hb (13–15 g/dL), PKTx reduced the eGFR, progression to ESRD, improved creatinine clearance, and death-censored graft survival rates [64]. Another prospective study suggested that anemia correction (12.5-13.5 g/dL) delayed dysfunction of the transplanted kidney by >3 years in chronic allograft nephropathy [65]. This suggests that severe PKTx anemia significantly causes an eGFR decline, and anemia correction can reduce the eGFR decline rate, improving allograft survival, function, and KTxRs' life quality [64]. Another prospective study suggested that full anemia correction (12.5-13.5 g/dL) delayed Tx kidney dysfunction by >3 years in chronic allograft nephropathy [65]. This suggests that severe PKTx anemia significantly causes an eGFR decline, and anemia correction can minimize the eGFR decline rate, improving allograft survival, function, and KTxRs' life quality. Despite these reported negative effects of PKTx anemia, further longer follow-up studies are required.

Post-kidney transplant anemia and mortality. Despite the advancement in PKTx anemia therapy, there are conflicting reported data about the effect of anemia on mortality in KTxRs [16]. Studies on PKTx anemia and death showed inconsistent findings. A prospective cohort study found that anemia increased the risk of mortality after 4 years [66]. A Retrospective investigation indicated that every 1 g/dL rise in Hb reduced mortality by 18% [46]. Another retrospective study linked 12-month posttransplant anemia to death [42]. Anemia PKTx (3-12 months) was related to a higher risk of death up to 10 years, regardless of kidney function [67]. Early and late PKTx increased 4-year mortality [12]. However, other research has found no link between PKTx and death. These include two retrospective investigations, one with an 8-year follow-up [49]. Another study for 887 KTRs examined at 12 months [19], and a 5-6-year prospective cohort study [50].

In studies indicating no link between PKTx anemia and death rate, most patients had moderate anemia (mean Hb concentration >11 g/dL) with different Hb values in different studies, which may explain the inconsistencies. Severity of anemia correlated with death in a cohort analysis of 1,139 KTRs. Anemia (Hb concentration <11 g/dL) was closely linked to death [13]. In summary, most studies associate PKTx anemia with mortality; the relationship appears to be dose-dependent (stronger with severe anemia), time-sensitive (strongest early post-transplant), and potentially mediated through cardiovascular effects. Table 2 summarizes the effects of PKTx anemia on mortality.

Table 2

Summary of the effects of post-kidney transplant anemia on mortality

Study Population	Study Design	Follow-up	Key Findings	Reference
4,217 PKTxRs	Retrospective	12 months	Anemia associated with mortality & graft failure	[21]
938 PKTxRs	Retrospective	4-8 years	Anemia linked to mortality & graft failure	[45, 46]
2,031 PKTxRs	Retrospective	6 years (median)	Significant mortality/graft failure correlation	[46]
626 PKTxRs	Retrospective	12 months	12-month anemia mortality risk	[42]
1,023 PKTxRs	Retrospective	3 months	Anemia linked to graft failure & mortality	[47]
170 PKTxRs	Retrospective	30 days	Early anemia predicted poor outcomes	[49, 48]
266 PKTxRs	Retrospective	2-8 years	Late mortality association	[12, 44, 45]

Continuation of Table 2

Study Population	Study Design	Follow-up	Key Findings	Reference
1,139 PKTxRs	Retrospective	6-18 months	Graft failure & mortality link	[13]
145 PKTxRs	Retrospective	-	Graft failure & mortality	[45]
825 PKTxRs	Retrospective	8 years	No mortality association	[49]
2,102 PKTxRs	Retrospective	5-6 years	No Hb-CV mortality correlation	[50]
887 PKTxRs	Retrospective	12 months	No mortality link	[19]

Legend: PKTxRs (post-kidney transplant recipients).

The summary of the table and the texts above are: 1. Mortality: 8/12 studies (67%) reported a significant association, strongest for severe anemia (Hb <11 g/dL) [13], most consistent in the first 3 years post-transplant. 2. Graft Failure: More consistently associated (10/12 studies), present even when mortality link absent [13, 51]. 3. Negative Findings: 3 large studies found no association [19, 49, 50], all examined moderate anemia (Hb >11 g/dL). 4. Cardiac Impact: Anemia+LVH ↑ mortality risk [56-58], may explain some mortality associations.

Although there is reasonable evidence about the negative effects of PKTx anemia and the beneficial effects of normalizing the Hb PKTx, the existing research data about PKTx anemia exhibit limitations. Comparing transplant recipients to individuals still on dialysis may present challenges, as the former generally exhibit better health status, causing bias in the results and comparisons between patients. The other limitation is heterogeneity. The outcomes of studies are significantly influenced by variability in research demographics, follow-up duration, immunosuppressive regimens, and healthcare systems. Access to care, socioeconomic status, and comorbidities remain inadequately addressed. Some authors consider the observational characteristics of the available studies to be a limitation. Due to the predominance of non-randomized research, establishing causality presents significant challenges. The available data insufficiently provide the follow-up necessary for assessing long-term mortality outcomes, which is another limitation. Restrictions on reporting and registration data may contain absent variables or inconsistencies. Finally, the different definitions of anemia employed can affect the results of studies and should be carefully considered, as they may be a limitation.

Post-kidney transplant anemia therapy. PKTx anemia is frequent in KTxRs. Anemia occurring up to 6 months after transplantation is called early PKTx anemia, whereas anemia occurring beyond 6 months is called late PKTx anemia. Early PKTx anemia predicts late PKTx anemia. PKTx anemia, especially late-onset anemia, lowers GFR and graft survival rates and increases death [68]. The severity and cause of anemia affect mortality significantly. Urgent PKTx anemia treatment following kidney transplantation is advisable. Renal transplant patients with anemia should aim for 12.5-13 g/dL, which is greater than the recommended value for CKD patients. ESA and iron therapies are needed to reach this goal

Iron therapy. A study noted that high serum ferritin is linked to improved graft performance and survival [54]. In contrast, other studies conducted for KTxRs found no connection between graft failure and the proportion of hypochromic anemia [16, 69]. Nevertheless, the latter study found a significant correlation between the proportion of hypochromic anemia and overall mortality [69]. Another study concluded that iron deficiency was also shown to be significantly linked to overall mortality, even without concurrent anemia, by promoting intact FGF23 production and cleavage, forming C-terminal GF23. A high level of C-terminal GF23 is significantly and prospectively related to mortality [55]. The possible pathways include direct impacts on the metabolism of cardiac and skeletal muscles [54]. Iron deficiency may weaken the functioning of cardiac and skeletal muscle cells by reducing the amount of oxygen available inside the cells and hindering the Krebs cycle's normal progress [32].

Adequate research is needed on the use of iron supplements in KTx recipients, and it is still being determined whether intravenous (IV) iron is more effective than oral iron [16]. Furthermore, more study needs to investigate the best preparation of iron that is more beneficial in reducing FGF23 levels and correcting anemia. Oral iron treatments are often favored because of their affordable price and convenient administration. Nevertheless, the gastrointestinal adverse effects of oral iron preparations hamper iron absorption in the small intestines, and low patient compliance limits the efficacy of oral iron. The efficacy and tolerability of newer oral iron treatments such as ferric maltol, ferric citrate, and Sucrosomial® Iron, which are superior to conventional iron salts, have yet to be assessed in KTxRs. Nevertheless, oral iron has detrimental effects on the gut microbiota [70], which has a significant role in determining the success of the allograft [71].

Comparing oral preparations to IV iron, it is found that IV iron is more effective in correcting iron deficiency and increasing Hb levels in CKD undergoing dialysis or with non-dialysis-dependent CKD. Additionally, IV iron's safety profile is comparable to oral preparations in CKDs [72]. Administration of IV iron sucrose for KTx recipients resulted in a notable rise in

Hb levels and a decrease in the rate of decline in the eGFR in 48 recipients [73]. There was no elevated risk of infection seen with intravenous iron (polymaltose) compared to oral therapy (ferrous sulfate) [74]. Intravenous iron treatments, such as ferric carboxymaltose and ferric derisomaltose, must be infused at slower rates to reduce the likelihood of severe hypersensitivity events [75]. IV ferric carboxymaltose has excellent tolerability and safety [76].

An important clinical issue to consider while administering IV iron polymaltose and ferric carboxymaltose is worsening preexisting hypophosphatemia due to a sudden increase in FGF23 metabolism [77]. The resulting hypophosphatemia is most prevalent in KTxRs, who usually have high FGF23 levels. However, out of the 23 KTx recipients given a maximum dose of ferric carboxymaltose, only 1 patient needed temporary phosphate supplementation [78]. Further inquiries are needed to comprehend the clinical impact on KTxRs caused by hypophosphatemia generated by IV iron [79]. Individualized Hb level goals were advisable in PKTx anemia. In this scenario, IV iron treatment is underutilized, and iron deficiency and antecedent events (blood transfusion or hospital stay) explain most ESA hypo-responsiveness. This suggests that post-transplant anemia patients require better treatment techniques due to missed prescriptions, targeting, and guideline adherence [80].

Iron supplementation might be advantageous in KTx, and intravenous delivery may be a sensible option [12]. Nevertheless, several matters remain unsettled. The extent to which iron depletion or administration impacts long-term clinically important consequences has yet to be firmly determined in KTxRs [81]. Further elucidation is required about IV iron in combination with ESA delivery [81]. Furthermore, no successful treatment plan is available to address disruptions in iron metabolism in KTxRs. Recent research showed that a proactive high-dose intravenous iron treatment was safe and more effective than a low-dose IV iron treatment in hemodialysis-dependent ESRD patients. However, such therapeutic approaches have yet to be studied in large studies on KTxRs. Therefore, it is necessary to conduct prospective studies to assess the most effective therapeutic method for iron deficiency in KTxRs.

Erythropoietin or erythropoietin-stimulating agents therapy. ESA treatment stimulates the production of erythrocytes. It has significantly transformed the treatment of anemia in CKD [11]. However, it is presently considered that ESA therapy needs to be used to its full potential in KTxRs with certain cautions [81].

The earliest randomized control trial (RCT) for KTx recipients with an Hb of < 12 g/dL was randomly distributed to receive subcutaneous beta-epoetin thrice/week to achieve an Hb > 12.5 g/dL, and a control group received a placebo. The groups had no observable differences regarding Hb levels or allograft function during the first 3 months. However, the group receiving ESAs achieved the goal of Hb level more quickly and needed fewer blood transfusions [82]. An RCT involved patients with Hb levels ranging from 8 to 10 g/dL during the first week of PKTx. The patients were randomly injected with EPO biosimilar three times weekly subcutaneously or placebo. The results of this trial revealed that after six months, while the Hb levels were similar in both groups, the intervention group exhibited lower serum creatinine levels and higher creatinine clearance [83]. In contrast, in another study, KTx recipients who had anemia within 3 months after KTx were divided into two groups; one group received beta-epoetin to maintain Hb levels between 11.5 and 13.5 g/dL, while the placebo group received no medication [84]. After 2 years, the group that received ESA had a notably elevated Hb level [83]. However, no discernible differences between the groups regarding eGFR receiving ESA had enhanced quality of life [84].

The CAPRIT study investigated the impact of normalizing Hb (13-15 g/dL) versus partially corrected Hb (10.5-11.5 g/dL) using subcutaneous beta-epoetin on graft survival and life quality in KTx recipients who had late PKTx anemia for over 2 years [64]. The Hb normalized group had a decline in estimated creatinine clearance, a lower risk of progression to renal failure, superior graft survival without death-related causes, and substantially improved life quality [64]. Tsujita et al. conducted a 3-year study on KTx recipients treated with either darbepoetin alpha or beta-epoetin, administered subcutaneously or intravenously. Hb correction (12.5-13.5 g/dL) versus low Hb levels (10.5-11.5 g/dL) effect on the graft function decline rate was studied as a primary measure of effectiveness [65]. The decrease in the eGFR was substantially more pronounced in the group with low Hb levels compared to the group with higher Hb [65]. The decrease in the eGFR was substantially more pronounced in the group with low Hb levels compared to the group with higher Hb [65].

Another study investigated a total of 153 KTx recipients who were randomly allocated to two groups: one with a high goal level of Hb (≥12.5 g/dL) and the other with a low target level (<10.5 g/dL). Additionally, the participants were divided into two subgroups: one receiving cholecalciferol and the other serving as a control group. All participants received subcutaneous beta-epoetin [85]. The main endpoint of the research was the alterations in the eGFR based on creatinine levels during two years [85]. Patients with high Hb had a lesser decrease in kidney function than those with low Hb ($P < 0.05$), and there was no significant change in the drop in kidney function between the cholecalciferol and control groups [85].

The findings of these cited studies indicate that in KTx, anemia is linked to the eGFR decline, and addressing anemia correction may effectively slow down the graft function decline rate and time. This contradicts a recent meta-analysis that found no evidence of the renoprotective benefits of ESA in PKTx recipients [86]. Nevertheless, heterogeneity and disparate main outcomes were noted as limitations of this study [81].

In KTx animal models, the administration of EPO effectively reduced the development of chronic allograft nephropathy by regulating antioxidant expression and antiapoptotic and angiogenic characteristics inside the transplanted kidney tissue [87]. Nevertheless, studies noted that blood transfusions, which restore normal HB values after a transplant, do not have any impact on the damage to the transplanted kidney. This suggests that the protective effect of EPO on the kidney outweighs the benefits of correcting anemia alone [87]. It was reported that EPO demonstrated the immunomodulatory effects required for the natural acceptance of foreign kidneys in both laboratory models using mouse cells and clinical research involving patients with stage 4 CKD who were treated with ESAs [88]. Nevertheless, the first clinical trials failed to reveal any tissue-preserving advantage of using ESA in the post-transplant period.[86] Nonetheless, more studies are needed to accurately determine the potential of ESA in protecting the kidneys after KTx [86]. However, more studies are needed to accurately determine the potential of ESA in protecting the transplanted kidney.

ESA early administration for treating PKTx anemia should be considered on a case-by-case basis. However, ESA must be cast in late PKTx anemia to improve graft survival and normalize the Hb (12.5-13.5 g/dL), though caution is needed in high malignancy-risk KTx recipients [81]. EPO is prescribed for cancer- and chemotherapy-associated anemia. Paradoxically, EPO might promote tumor growth and jeopardize patient survival in cancer [89]. The current Hb goal level is comparable to the previously proposed Hb target level of 12-13 g/dL [14]. The recommended goal level for Hb in KTx recipients is higher than the recommended levels advised for the CKD population by the KDIGO (Hb 11.5 g/dL) and KDOQI (Hb 11 g/dL) recommendations [90]. ESA medication for hemoglobin normalization may protect the kidneys and minimize mortality, according to a systematic review of 38,233 participants from 85 studies [91].

The decision to focus on lower Hb in CKD was based on the unfavorable outcomes seen in extensive trials that evaluated the safety and success of ESA treatment aiming at higher Hb levels in CKD patients [92]. Current research indicates that using ESA in anemic KTxRs is secure and linked to a potentially positive result. However, high Hb levels can lead to hemoconcentration, which can cause thrombosis [93]. Various forms of ESAs have shown similar effectiveness in managing PKTx anemia. Long-acting ESAs are more convenient for controlling PKTx anemia; however, there is no preferred method (subcutaneous or intravenous) for administering ESAs. Further clarity about the best use of ESA regarding dose and goal level of Hb in KTxRs is required.

Blood transfusion. KTxRs often receive packed red blood cell transfusions (PRBCT), especially during the first month after the transplant [94]. A study that included 12,000 KTxRs found a link between early transfusion and transplant failure (defined as graft loss or death with a functioning graft) [94]. Transfusion within 1 month after KT decreased graft survival and increased antibody-mediated rejection and infections at 1 year [95]. Transfusion may also cause venous thromboembolism [96]. A new retrospective cohort study found that venous thromboembolism increased with transfusions following transplantation [97]. In KTxR, venous thromboembolic events increase graft loss and mortality risks [25, 98]. Considering the mentioned complications, volatility in Hb levels, and limited availability, PRBCT cannot be seen as a viable alternative for controlling PKTx anemia [11]. Transfusions are risky, expose patients to substantial Hb-level variations, and are limited in availability. Thus, they cannot be used to treat posttransplant anemia [11]. The existing data underscores the necessity of cautiously using PRBCT in KTx, considering the balance between risks and benefits, and exploring other approaches to correcting anemia, such as managing iron levels or using ESAs [97]. New research emphasizes the necessity for careful transfusion usage for KTxR, balancing the risk-benefit ratio, and investigating alternate anemia correction techniques, including optimizing iron reserves or ESA use [97].

Hypoxia-inducible factor-prolyl hydroxylase inhibitors. Recently, there have been oral medications called hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitors that may be used to treat CKD-induced anemia. This new category of medications raises the natural levels of EPO in the blood, activates the process of copying the EPO gene in the kidneys and liver, and seems to decrease hepcidin levels and enhance iron balance in the body [99]. Therefore, suppressing HIF-PH may effectively and via different mechanisms control the pathogenic variables linked to CKD-related anemia. Roxadustat, a HIF-PH inhibitor, received authorization from the European Medicines Agency in 2021 to treat CKD-induced anemia, regardless of whether they are dialysis-related or not. On the other hand, daprodustat was recently licensed by the USA Food and Drug Administration specifically for patients on dialysis for a minimum of 4 months [16].

Data on the use of HIF-PH inhibitors in KTx recipients is scarce. The primary reason for this is likely due to a theoretically heightened susceptibility to cancer (such as the elevation of vascular endothelial growth factor and angiogenesis) in an immunocompromised population that is already predisposed to acquiring malignancies [81]. An observational study was conducted on KTx recipients with Hb values < 11 g/dL to assess the impact of administering roxadustat (20-100 mg) thrice a week [100]. The goal level for Hb was set at 11-13 g/dL, and ESAs were administered if Hb levels diminished below 10 g/dL. Out of the 31 patients that were registered, 25 individuals successfully finished the 20-week study, whereas 6 patients had early postoperative transient atrial fibrillation. The average Hb levels gradually rose from 9.8 g/dL at the beginning, reaching a stable value of 12.4

g/dL after 20 weeks. Iron insufficiency necessitating iron supplementation was noted at 8 weeks in 12 patients receiving ESAs. The study was terminated because three patients had a severe drop in Hb levels, two patients had gastrointestinal complications, and one patient suffered from a myocardial infarction [100]. Li et al. conducted a study on 21 KTx recipients, 6 of whom were treated with ESA. These patients were hospitalized due to difficulties following the kidney transplantation, and their Hb was below 10 g/dL. The researchers closely observed the impact of Roxadustat, administered thrice a week, depending on the patient's weight [101]. Eleven patients were excluded from the trial with roxadustat before its completion (after 10 weeks) due to either an initial or subsequent lack of response or upon attaining the desired Hb level. Among the participants who finished the trial, there was a notable rise in Hb concentration from 6.9 to 10.4 g/dL.

Additionally, the treatment response rate was observed in 71.4% of participants, without discernible adverse responses observed [101]. Among 5 KTx recipients with late PKTx anemia who transitioned from using epoetin beta l to roxadustat thrice a week for 9 months, all patients had a rise in their Hb after just 1 month. Furthermore, a good improvement in anemia was consistently maintained throughout the period. Nevertheless, excessive improvement in Hb levels occurred, leading to one patient discontinuing roxadustat after one month and three patients requiring a reduction in medication dose; however, none noted significant adverse effects [102]. Roxadustat is a safe medication in KTxRs, and possible side effects of roxadustat include an increased risk of thromboembolism and hypertension. There are no reported data about the increased risk of malignancy in KTXR [103].

Post-organ transplantation, cancer risk increases due to various reasons, such as immunosuppression, viral infections, and prior cancer, which are major risk drivers. The common post-transplant malignancies are non-melanoma skin cancer (~50% of cases), post-transplant lymphoproliferative disorder (PTLD) due to EBV-driven B-cell proliferation, Kaposi sarcoma, liver cancer, and native renal cell carcinoma [104].

HIF-PH inhibitors' role as a cause of malignancy remains investigational. In KTxRs, the use of HIF-PH inhibitors data is limited [16]. In immunocompromised people already prone to cancer, elevation of vascular endothelial growth factor and angiogenesis may enhance cancer risk [81]. It is documented that Hypoxia-Inducible Factor 1-Alpha has pro-tumorigenic effects, increasing angiogenesis and driving immune evasion [105]. Preclinical evidence links HIF-1-alpha to clear cell renal carcinoma [106]. However, limited safety data in KTxRs. KDIGO 2023 Guideline avoids recommendations due to a lack of transplant data [107]. Until confirmed data is available, practical approaches include avoiding high-risk KTxRs (prior malignancy, EBV+), monitoring aggressively for skin cancer, PTLD, and BK virus, and preferentially using ESAs. More observational research projects are required to elucidate the long-term malignant side effects of these medications and other immunosuppressive agents used to prevent allograft dysfunction and rejection.

Based on the existing information regarding using HIF-PH inhibitors for PKTx anemia therapy, it is recommended to begin treatment with a small dosage and gradually increase the titration while providing more iron due to the increased iron utilization [33]. Further RCTs are necessary to elucidate the extended effectiveness and safety of HIF-PH inhibitors for treating PKTx anemia.

Sodium-glucose co-transporter 2 inhibitors use for post-kidney transplantation anemia therapy. Diabetes prevalence is predicted to rise to 10.2%, reaching 578 million by 2030, and by 2045, it is predicted to increase by 10.9%, reaching 700 million people [108]. Glucose reabsorption by the nephrons ends at the end of the proximal convoluted tubule (PCT). PCT is divided into three segments. Both segments one and two reabsorb almost 90% of the filtered glucose mediated by SGLT2 receptors. In contrast, SGLT1, located in the straight segment of the proximal tubule (segment 3), accounts for roughly a tenth of total glucose reabsorption [109]. Blockage of glucose receptors in these sites will decrease glucose reabsorption by the brush border cells of the PCT, increasing the osmotic diuresis and urine excretion.

Seven SGLT2 inhibitors are currently in clinical use: empagliflozin, dapagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, and canagliflozin. In addition to cardio- and renoprotection, SGLT2 inhibitors exhibit hematopoietic effects [110, 111]. Although SGLT2i shows unforeseen renal-protective properties in diabetes mellitus type 2 (DM2) and those without DM2 with and without CKD, doubts about their usage in KTx remain owing to worries about an elevated risk of genital mycotic and urinary tract infections. There is substantial evidence of Fournier gangrene and vaginal mycotic, and other chronic infections in SLGT2 inhibitors treated individuals [112], potentially elevating the incidence of anemia, which might appear more in KTx recipients with impaired immune systems. However, a review article concluded that SGLT2i can be practiced in diabetic KTx recipients safely and effectively in selected recipients [113]. A 2022 study of 323 PKTx recipients reported that empagliflozin, dapagliflozin, and canagliflozin are safe [114]. Research conducted for 24 weeks examined the empagliflozin effect in diabetic KTxRs. The study found a substantial decrease in HbA1C levels and body weight among recipients treated with empagliflozin. However, no significant change was seen in the eGFR [115]. Another study noted no change in the eGFR in diabetic KTxRs on SGLT2 inhibitors [113]. The lack of considerable improvement in the eGFR was attributed to the vasoconstriction of the afferent arterioles caused by SGLT2 inhibitors. The natriuretic impact of SGLT2 inhibitors is believed to cause an increase in tubule-glomerular feedback and

constriction of the afferent arteriole, even in a KTx that has lost its nerve supply.

SGLT2i, such as empagliflozin, increased Hb and hematocrit in 3726 heart-disease patients [116]. Improving Hb and hematocrit levels in PKTx recipients could also be due to the diuretic effect of SLGT2i that masks anemia [117] or the eGFR improvement [118]. Although SLGT2 inhibitor usage appears promising, further larger studies in diabetic and non-diabetic KTxRs are required to assess this thought further. It was reported that SGLT2 inhibitors improve PKTx anemia, possibly by improving the effectiveness of EPAs [119]. Improving Hb and hematocrit levels in PKTx recipients could also be due to the diuretic effect of SLGT2i that masks anemia [117] or the eGFR improvement [118]. Although SLGT2 inhibitor usage appears promising, larger studies in diabetics and diabetic KTxRs are required to assess this hypothesis further.

SGLT2i boosts EPO synthesis, decreasing kidney hypoxia. However, the precise process is unknown [120,121]. SGLT2 inhibitors improved Hb and increased hematocrit in T2D and CKD patients [122]. However, it was unclear whether the increase in hematocrit was because of fluid volume reduction or an improved primary erythropoietic response [123]. Recent human investigations have further shown the stimulatory impact of empagliflozin and dapagliflozin on erythropoietin synthesis in individuals with native kidneys [124]. Anemia is estimated to affect 30-40% of kidney transplant recipients and is recognized as a prevalent risk factor for graft failure and death during the first three years post-transplantation [13, 125]. The etiology of anemia in kidney transplant recipients is often complicated, potentially including iron deficiency, compromised renal function, bone marrow suppression due to immunosuppression, antiviral prophylaxis, or infection [125]. SGLT2 inhibitors may mitigate anemia in kidney transplant recipients and enhance allograft outcomes [123].

Two post hoc analyses of the CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation) and DAPA-CKD trials suggest additional anemia-related benefits from canagliflozin and dapagliflozin treatment [126]. Despite these encouraging post hoc analysis results, CREDENCE and DAPA-CKD trial design may have limited their therapeutic significance. A cohort study comparing SGLT2i and SGLP receptor antagonists concluded that SGLT2i could be deemed an adjunct treatment to diminish the anemia rate by 19% in 13,799 CKD-DM2 patients [121]. A study showed a significant difference in Hb concentrations between DM2 patients with coronary artery disease treated with 10 mg empagliflozin and placebo at six months: 13.9 (g/dl) in the placebo group and 14.6 in the empagliflozin group [124]. Empagliflozin increased Hb and hematocrit in 3726 heart failure patients [116]. The mechanism by which SGLT2 inhibitors decrease anemia is unknown, although increasing EPO synthesis could be a mechanism.

Post-kidney transplantation anemia correction effects on the cardiovascular system. The data from KTx recipients managed with ESA agents do not indicate an elevated risk of cardiovascular (CV) complications reported [16]. The CAPRIT research found that there were no instances of cardiac diseases, stroke, HF, arrhythmia, or myocardial infarction in the full correction Hb levels group. However, certain CV events occurred in a lower Hb level group [64]. No CV events were noted in the trial conducted by Tsujita et al. [65], and research conducted by Obi et al. [64] did not prove a higher occurrence of stroke among KTx recipients who were assigned to the arm with a higher goal level of Hb [85]. Additionally, a 2-year trial on KTx recipients who were administered epoetin beta with a target Hb concentration of 11.5-13.5 g/dL showed no negative effects on the CV system or blood clotting events [84]. The observed disparities in population sizes between individuals with non-transplant CKD and KTx recipients may be credited to variations in the environments or circumstances in which these populations were studied. Chronic allograft nephropathy and CKD vary significantly regarding their underlying mechanisms and eventual results [64]. Furthermore, a long-term KTx effectiveness may demonstrate greater effectiveness than a kidney from a patient with CKD who does not need dialysis regarding histology, hemodynamics, and immune biology [65]. However, further studies are required to explore these issues in KTxRs.

Guidelines: Challenges in post-kidney transplant anemia. Various pathophysiological mechanisms, iron metabolism dynamics, immunosuppressive effects, and the lack of convincing evidence in transplant-specific cohorts limit the applicability of the KDIGO and other CKD-induced anemia guidelines to managing PKTx anemia. KDIGO (2012, with updates in 2023) and other guidelines, including the ERA and the NKF-KDOQI, provide recommendations for anemia management in CKD. The application of these recommendations to the treatment of anemia in KTxRs is a subject of controversy. Transplant-specific factors, such as immunosuppression-induced bone marrow suppression, altered iron metabolism post-kidney transplantation, varying responsiveness to ESA, and the absence of large RCTs in KTxRs, restrict their applicability to managing anemia in PKTx. Given these limitations, the existing anemia guidelines may not be ideal for treating anemia post-kidney transplantation. Although immunosuppressant agents have been shown to suppress bone marrow function, some studies have suggested no correlation between immunosuppression and post-transplant anemia.

Chronic inflammation and viral-induced hemolysis (BK virus nephropathy and parvovirus B19 infection) reduce EPO sensitivity. Furthermore, KTRs exhibit distinct iron metabolism and hepcidin dynamics. ESO agents' hyporesponsiveness has also been documented in KTRs [127]. KDIGO recommends ESA therapy for hemoglobin levels below 10 g/dL in CKD

patients; however, KTRs may exhibit resistance to this treatment due to factors such as chronic inflammation, the use of ACE inhibitors or ARBs, suppressed endogenous EPO synthesis, and iron-restricted erythropoiesis despite normal ferritin levels. The absence of available RCTs demonstrating the efficacy and safety of ESA in KTRs leads guidelines to extrapolate from CKD data.

Managing PKTx anemia as CKD-induced anemia may result in an overcorrection of Hb levels exceeding 11 g/dL, thereby increasing the risk of thrombosis. The KDIGO guideline advises against allowing Hb levels to exceed 11.5 g/dL in CKD patients due to the heightened risk of stroke and thrombosis. Elevated Hb levels may be tolerated in KTxRs; however, the current guidelines do not specify Hb targets for these recipients.

The existing KDIGO, ERA, and KDOQI anemia guidelines are not transplant-specific. This may lead to abuse of ESAs without demonstrated benefit, improper iron supplementation levels, and missing secondary causes of PKTx anemia. Using transplant RCT data, new guidelines address Hb targets, and immunosuppressant-ESA interactions are needed.

Conclusions and prospects for further research. PKTx anemia is a multifaceted condition that significantly impacts patient outcomes and quality of life. PKTx anemia is mainly caused by iron deficiency. Decreased graft function has been linked to an increased incidence of late PKTx, and early PKTx anemia is a good predictor of late PKTx anemia. Decreased graft survival, increased mortality, and a drop in GFR are linked to PKTx anemia. The anemia's underlying cause and severity have a strong correlation with death.

Kidney transplantation should generally start as soon as feasible. The ideal goal Hb level for KTX patients with anemia is likely closer to 12.5–13 g/dL. A suitable course of therapy with iron and erythropoiesis-stimulating drugs is recommended to reach this goal, manifesting in better life quality, graft survival, and reduced mortality rates. Therapy with SGLT2I for anemic KTxRs showed promising potential. However, further research in different aspects of PKTx anemia effects and treatment, and setting a target Hb level for PKTx is required. Large-scale controlled RCTs for SGLT2i and standardized protocols for iron therapy are needed. Finally, there are no guidelines for anemia definition and targeted hemoglobin levels for KTxRs in CKD. Therefore, guidelines are urgently required based on large-scale studies for kidney transplanted patients.

Conflict of interest. The authors declare no conflict of interest in this review item.

Acknowledgment. The authors acknowledge the support from the Open Libyan University.

Authors contribution.

Elmukhtar Habas: Principal author, conceptualization, project manager, original draft preparation;

Amnna Rayani: Conceptualization, review, and editing;

Aml Habas, Kalifa Farfar, Khaled Alarbi, Mohamed Baghi: Literature analysis;

Gamal Alfitori, Almehdi Errayes, Abdelrahaman Hamad, Abdel-Naser Elzouki: Review and editing;

Ala Habas: Literature analysis, table preparation;

Eshrak Habas: Literature analysis, figure preparation.

References:

1. *Fraser SDS, Roderick PJ.* Kidney disease in the Global Burden of Disease Study 2017. Nat Rev Nephrol 2019;15:193–194. https://doi.org/10.1038/s41581-019-0120-0.
2. *Kovesdy CP.* Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022;12(1):7-11. doi: 10.1016/j.kisu.2021.11.003.
3. *Okoro RN, Farate VT.* The use of nephrotoxic drugs in patients with chronic kidney disease. Int J Clin Pharm. 2019;41(3):767-775. doi: 10.1007/s11096-019-00811-9.
4. *Nwose EU, Obianke J, Richards RS, Bwitit PT, Igumbor EO.* Prevalence and correlations of hepatorenal functions in diabetes and cardiovascular disease among stratified adults. Acta Biomed. 2019;90(1):97-103. doi: 10.23750/abm.v90i1.6576.
5. *Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, Zhao MH, et al.* Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet. 2015;385(9981):1975-82. doi: 10.1016/S0140-6736(14)61601-9.
6. *Tonelli M, Nkunu V, Varghese C, Abu-Alfa AK, Alrukhaimi MN, Fox L, et al.* Framework for establishing integrated kidney care programs in low- and middle-income countries. Kidney Int Suppl (2011).2020 ;10(1):e19-e23. doi: 10.1016/j.kisu.2019.11.002.
7. *Davidson B, Du Toit T, Jones ESW, Barday Z, Manning K, Mc Curdie F, et al.* Outcomes and challenges of a kidney transplant programme at Groote Schuur Hospital, Cape Town: A South African perspective. PLoS One. 2019;14(1):e0211189. doi: 10.1371/journal.pone.0211189.
8. *Mudiayi D, Shojai S, Okpechi I, Christie EA, Wen K, Kamaleldin M, et al.* Global Estimates of Capacity for Kidney Transplantation in World Countries and Regions. Transplantation. 2022;106(6):1113-1122. doi: 10.1097/TP.0000000000003943.
9. *Kasiske BL, Vazquez MA, Harmon WE, Brown RS, Danovitch GM, Gaston RS, et al.* Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. Recommendations for the outpatient surveillance of renal transplant recipients. J Am Soc Nephrol. 2000:11 Suppl 15:S1-86.

10. *Habas E Sr, Al Adab A, Arryes M, Alfitori G, Farfar K, Habas AM, et al.* Anemia and Hypoxia Impact on Chronic Kidney Disease Onset and Progression: Review and Updates. Cureus. 2023;15(10):e46737. doi: 10.7759/cureus.46737.
11. *Bonomini M, Del Vecchio L, Sirolli V, Locatelli F.* New treatment approaches for the anemia of CKD. Am J Kidney Dis. 2016;67(1):133–142. doi: 10.1053/j.ajkd.2015.06.030.
12. *Gafter-Gvili A, Ayalon-Dangur I, Cooper L, Shochat T, Rahamimov R, Gafter U, et al.* Post-transplantation anemia in kidney transplant recipients: a retrospective cohort study. Medicine. 2017;96(32):e7735. doi: 10.1097/MD.0000000000007735.
13. *Schechter A, Gafter-Gvili A, Shepshelovich D, Rahamimov R, Gafter U, Mor E, et al.* Post renal transplantation anemia: causes, severity and their association with graft and patient survival. BMC Nephrol. 2019;20(1):51. doi: 10.1186/s12882-019-1244-y.
14. *Malyszko J, Basak G, Batko K, Capasso G, Capasso A, Drozd-Sokolowska J, et al.* Haematological disorders following kidney transplantation. Nephrol Dial Transplant. 2022;37(3):409–20. doi: 10.1093/ndt/gfaa219.
15. *Molina M, Sorolla C, Samsó E, Carcaña M, Martín ML, Jatem E, et al.* Quality of life in long-term renal transplant patients: a controversial subject. Transplant Proc. 2022;54(1):91–93. doi: 10.1016/j.transproceed.2021.11.025.
16. *Bonomini M, Di Liberato L, Sirolli V.* Treatment Options for Anemia in Kidney Transplant Patients: A Review. Kidney Med. 2023;5(8):100681. doi: 10.1016/j.xkme.2023.100681.
17. *Gafter-Gvili A, Cohen E, Avni T, Grossman A, Vidal L, Garty M, et al.* Predicting the emergence of anemia—A large cohort study. Eur J Intern Med. 2015;26(5):338–43. doi: 10.1016/j.ejim.2015.04.010.
18. *Lorenz M, Kletzmayr J, Perschl A, Furrer A, Hörl WH, Sunder-Plassmann G.* Anemia and iron deficiencies among long-term renal transplant recipients. J Am Soc Nephrol. 2002;13(3):794-797. doi: 10.1681/ASN.V133794.
19. *Huang Z, Song T, Fu L, Rao Z, Zeng D, Qiu Y, Wang X, et al.* Post-renal transplantation anemia at 12 months: prevalence, risk factors, and impact on clinical outcomes. Int Urol Nephrol. 2015;47(9):1577-85. doi: 10.1007/s11255-015-1069-y.
20. *Vanrenterghem Y, Ponticelli C, Morales JM, Abramowicz D, Baboolal K, Eklund B, et al.* Prevalence and management of anemia in renal transplant recipients: a European survey. Am J Transplant. 2003;3(7):835–45. doi: 10.1034/j.1600-6143.2003.00133.x.
21. *Garrigue V, Szwarc I, Giral M, Soulillou JP, Legendre C, Kreis H, et al.* Influence of anemia on patient and graft survival after renal transplantation: results from the French DIVAT cohort. Transplantation. 2014;97(2):168–75. doi: 10.1097/TP.0b013e3182a94a4d.
22. *Tang Y, Guo J, Zhou J, Wan Z, Li J, Qiu T.* Risk factors and current state of therapy for anemia after kidney transplantation. Front Med (Lausanne). 2024;10:1170100. doi: 10.3389/fmed.2023.1170100.
23. *Goldsmith D, Al-Khoury S, Shah N, Covic A.* Anemia after renal transplantation—role of immunosuppressive drugs and a pathophysiological appraisal. Nephron Clin Pract. 2006;104:c69–74. doi: 10.1159/000093992.
24. *Huang G, Wu LW, Yang SC, Fei JG, Deng SX, Li J, Chen GD, et al.* Factors Influencing Graft Outcomes Following Diagnosis of Polyomavirus -Associated Nephropathy after Renal Transplantation. PLoS One. 2015;10(11):e0142460. doi: 10.1371/journal.pone.0142460.
25. *Mekraksakit P, Leelaviwat N, Benjanuwattra J, Duangkham S, Del Rio-Pertuz G, Thongprayoon C, et al.* A Systematic Review and Meta-Analysis of Posttransplant Anemia With Overall Mortality and Cardiovascular Outcomes Among Kidney Transplant Recipients. Prog Transplant. 2023;33(1):78-89. doi: 10.1177/15269248221145046.
26. *Lentine KL, Schnitzler MA, Abbott KC, Li L, Burroughs TE, Irish W, et al.* De novo congestive heart failure after kidney transplantation: a common condition with poor prognostic implications. Am J Kidney Dis. 2005;46(4):720-33. doi: 10.1053/j.ajkd.2005.06.019.
27. *Shah N, Al-Khoury S, Afzali B, Covic A, Roche A, Marsh J, et al.* Post-transplantation anemia in adult renal allograft recipients: prevalence and predictors. Transplantation. 2006;81(8):1112-8. doi: 10.1097/01.tp.0000205174.97275.b5.
28. *Górska M, Kurnatowska I.* Nutrition Disturbances and Metabolic Complications in Kidney Transplant Recipients: Etiology, Methods of Assessment and Prevention-A Review. Nutrients. 2022;14(23):4996. doi: 10.3390/nu14234996.
29. *Kalantzi M, Kalliakmani P, Papachristou E, Papasotiriou M, Savvidaki E, Zavvos V, et al.* Parameters influencing blood erythropoietin levels of renal transplant recipients during the early post-transplantation period. Transplant Proc. 2014;46(9):3179-82. doi: 10.1016/j.transproceed.2014.10.035.
30. *Afzali B, Al-Khoury S, Shah N, Mikhail A, Covic A, Goldsmith D.* Anemia after renal transplantation. Am J Kidney Dis. 2006;48(4):519-36. doi: 10.1053/j.ajkd.2006.07.006.
31. *Besarab A, Caro J, Jarrell BE, Francos G, Erslev AJ.* Dynamics of erythropoiesis following renal trans-

plantation. Kidney Int. 1987;32(4):526-36. doi: 10.1038/ki.1987.241.

32. *Vinke JSJ, Francke MI, Eisenga MF, Hesselink DA, de Borst MH.* Iron deficiency after kidney transplantation. Nephrol Dial Transplant. 2021;36:1976–85. doi: 10.1093/ndt/gfaa123.
33. *Moore LW, Smith SO, Winsett RP, Acchiardo SR, Gaber AO.* Factors affecting erythropoietin production and correction of anemia in kidney transplant recipients. Clin Transplant. [Internet].1994;8(4):358–64. Available from: https://pubmed.ncbi.nlm.nih.gov/7949539/.
34. *Nissaisorakarn V, Nissaisorakarn P, Kantachuvesiri S.* The current therapeutic approach for anaemia after kidney transplant. Curr Opin Nephrol Hypertens. 2023;32(1):35–40. doi: 10.1097/MNH.0000000000000842.
35. *Saad EJ, Fern ndez P, Cardozo Azua AE, Ellena V, Diz C, Giordano G, Borgogno P, et al.* Infections in the first year after renal transplant. Medicina (B Aires). [Internet]. 2020;80(6):611-621. Available from: https://pubmed.ncbi.nlm.nih.gov/33254105/.
36. *Baradaran H, Hashem Zadeh A, Dashti-Khavidaki S, Laki B.* Management of drug-induced neutropenia, thrombocytopenia, and anaemia after solid organ transplantation: a comprehensive review. J Clin Pharm Ther. 2022;47(12):1895–1912. doi: 10.1111/jcpt.13775.
37. *Habas E, Khammaj A, Rayani A.* Hematologic side effects of azathioprine and mycophenolate in kidney transplantation. Transplant Proc. 2011;43(2):504-6. doi: 10.1016/j.transproceed.2011.01.077.
38. *Al Qahtani SA.* Drug-induced megaloblastic, aplastic, and hemolytic anemias: current concepts of pathophysiology and treatment. Int J Clin Exp Med. [Internet]. 2018;11(6):5501–12. Available from: https://e-century.us/files/ijcem/11/6/ijcem0068128.pdf.
39. *Boonpheng B, Thongprayoon C, Bathini T, Sharma K, Mao MA, Cheungpasitporn W.* Proton pump inhibitors and adverse effects in kidney transplant recipients: A meta-analysis. World J Transplant. 2019;9(2):35-47. doi: 10.5500/wjt.v9.i2.35.
40. *Tsuchimoto A, Masutani K, Haruyama N, Nagata M, Noguchi H, Okabe Y, et al.* Renal interstitial fibrosis in 0-hour biopsy as a predictor of post-transplant anemia. Am J Nephrol. 2013;38(4):267-74. doi: 10.1159/000354647.
41. *Moore LW, Smith SO, Winsett RP, Acchiardo SR, Gaber AO.* Factors affecting erythropoietin production and correction of anemia in kidney transplant recipients. Clin Transplant. [Internet]. 1994;8(4):358–64. Available from: https://pubmed.ncbi.nlm.nih.gov/7949539/.
42. *Watts D, Gaete D, Rodriguez D, Hoogewijs D, Rauner M, Sormendi S, et al.* Hypoxia Pathway Proteins are Master Regulators of Erythropoiesis. Int J Mol Sci. 2020;21(21):8131. doi: 10.3390/ijms21218131.
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(11):3240–7. doi: 10.1681/ASN.2006010027.
44. *Shibagaki Y, Shetty A.* Anaemia is common after kidney transplantation, especially among African Americans. Nephrol Dial Transplant. 2004;19(9):2368–73. doi 10.1093/ndt/gfh256.
45. *Molnar MZ, Czira M, Ambrus C, Szeifert L, Szentkiralyi A, Beko G, et al.* Anemia is associated with mortality in kidney-transplanted patients – a prospective cohort study. Am J Transplant. 2007;7(4):818-24. doi: 10.1111/j.1600-6143.2006.01727.x.
46. *Alotaibi NE, Mohsin B, Alharbi S, Odah NO, Sindi D, Bargawi S, Abid RB, et al.* Postrenal transplant anemia and its effects on patients and graft outcomes: Seven years follow-up. Saudi Pharm J. 2023;31(8):101696. doi: 10.1016/j.jsps.2023.101696.
47. *Heinze G, Mitterbauer C, Regele H, Kramar R, Winkelmayer WC, Curhan GC, et al.* Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. J Am Soc Nephrol. 2006;17(3):889-99. doi: 10.1681/ASN.2005090955.
48. *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(4):1168-74. doi: 10.2215/CJN.04641007.
49. *Sert I, Colak H, Tugmen C, Dogan SM, Karaca C.* Anemia in living donor kidney transplantation. Transplant Proc. 2013;45(6):2238-43. doi: 10.1016/j.transproceed.2012.12.008.
50. *Winkelmayer WC, Chandraker A, Alan Brookhart M, Kramar R, Sunder-Plassmann G.* A prospective study of anaemia and long-term outcomes in kidney transplant recipients. Nephrol Dial Transplant. 2006;21(12):3559-66. doi: 10.1093/ndt/gfl457.
51. *Schjelderup P, Dahle DO, Holdaas H, Mjøen G, Nordby G, Abedini S, et al.* Anemia is a predictor of graft loss but not cardiovascular events and all-cause mortality in renal transplant recipients: follow-up data from the ALERT study. Clin Transplant. 2013;27(6):636-43. doi: 10.1111/ctr.12220.
52. *Kamar N, Rostaing L, Ignace S, Villar E.* Impact of post-transplant anemia on patient and graft survival rates after kidney transplantation: a meta-analysis. Clin Transplant. 2012;26(3):461–9. doi: 10.1111/j.1399-0012.2011.01545.x.
53. *Freiberg M, Chiurchiu C, Capra R, Eckhardt A, De La Fuente J, Douthat W, et al.* [Associated factors and clinical implications of post transplant

renal anemia]. Medicina (B Aires). [Internet]. 2013;73(2):136–40. Available from: https://pubmed.ncbi.nlm.nih.gov/23570761/.

54. *Eisenga MF, De Jong MA, Van der Meer P, Leaf DE, Huls G, Nolte IM, et al.* Iron deficiency, elevated erythropoietin, fibroblast growth factor 23, and mortality in the general population of the Netherlands: A cohort study. PLoS Med. 2019;16(6):e1002818. doi: 10.1371/journal.pmed.1002818.
55. *Vaugier C, Amano MT, Chemouny JM, Dussiot M, Berrou C, Matignon M, et al.* Serum Iron Protects from Renal Postischemic Injury. J Am Soc Nephrol. 2017;28(12):3605-15. doi: 10.1681/ASN.2016080926.
56. *Eisenga MF, Minović I, Berger SP, Kootstra-Ros JE, van den Berg E, Riphagen IJ, et al.* Iron deficiency, anemia, and mortality in renal transplant recipients. Transpl Int. 2016;29(11):1176-83. doi: 10.1111/tri.12821.
57. *Rigatto C, Foley R, Jeffery J, Negrijn C, Tribula C, Parfrey P.* Electrocardiographic left ventricular hypertrophy in renal transplant recipients: prognostic value and impact of blood pressure and anemia. J Am Soc Nephrol. 2003;14(2):462-8. doi: 10.1097/01.asn.0000043141.67989.39.
58. *Birdwell KA, Park M.* Post-Transplant Cardiovascular Disease. Clin J Am Soc Nephrol. 2021;16(12):1878-89. doi: 10.2215/CJN.00520121.
59. *Malyala R, Rapi L, Nash MM, Prasad GVR.* Pre-Transplant Left Ventricular Geometry and Major Adverse Cardiovascular Events After Kidney Transplantation. Ann Transplant. 2019;24:100-7. doi: 10.12659/AOT.913649.
60. *Kensinger C, Hernandez A, Bian A, Fairchild M, Chen G, Lipworth L, et al.* Longitudinal assessment of cardiac morphology and function following kidney transplantation. Clin Transplant. 2017;31(1):e12864. doi: 10.1111/ctr.12864.
61. *Paoletti E, Bellino D, Signori A, Pieracci L, Marsano L, Russo R, et al.* Regression of asymptomatic cardiomyopathy and clinical outcome of renal transplant recipients: a long-term prospective cohort study. Nephrol Dial Transplant. 2016;31(7):1168-74. doi: 10.1093/ndt/gfv354.
62. *Laskar SR, Dries DL.* The prognostic significance of renal dysfunction in patients with chronic systolic heart failure. Curr Cardiol Rep. 2003;5(3):205-10. doi: 10.1007/s11886-003-0050-z.
63. *Fujikura K, Peltzer B, Tiwari N, Shim HG, Dinhofer AB, Shitole SG, et al.* Reduced global longitudinal strain is associated with increased risk of cardiovascular events or death after kidney transplant. Int J Cardiol. 2018;272:323-8. doi: 10.1016/j.ijcard.2018.07.088.
64. *Choukroun G, Kamar N, Dussol B, Etienne I, Cassuto-Viguier E, Toupance O, et al.* Correction of postkidney transplant anemia reduces progression of allograft nephropathy. J Am Soc Nephrol. 2012;23(2):360-8. doi: 10.1681/ASN.2011060546.
65. *Tsujita M, Kosugi T, Goto N, Futamura K, Nishihira M, Okada 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(8):1409-16. doi: 10.1093/ndt/gfy365.
66. *Molnar MZ, Czira M, Ambrus C, Szeifert L, Szentkiralyi A, Beko G, et al.* Anemia is associated with mortality in kidney-transplanted patients--a prospective cohort study. Am J Transplant. 2007;7(4):818-24. doi: 10.1111/j.1600-6143.2006.01727.x.
67. *Majernikova M, Rosenberger J, Prihodova L, Jarcuskova M, Roland R, Groothoff JW, et al.* Posttransplant Anemia as a Prognostic Factor of Mortality in Kidney-Transplant Recipients. Biomed Res Int. 2017;2017:6987240. doi: 10.1155/2017/6987240.
68. *Gafter-Gvili A, Gafter U.* Post-transplantation Anemia in Kidney Transplant Recipients. Acta Haematol. 2019;142(1):37-43. doi: 10.1159/000496140.
69. *Winkelmayer WC, Lorenz M, Kramar R, Hörl WH, Sunder-Plassmann G.* Percentage of hypochromic red blood cells is an independent risk factor for mortality in kidney transplant recipients. Am J Transplant. 2004;4(12):2075-81. doi: 10.1046/j.1600-6143.2004.00604.x.
70. *Ribeiro M, Fonseca L, Anjos JS, Capo-Chichi JCC, Borges NA, Burrowes J, et al.* Oral iron supplementation in patients with chronic kidney disease: can it be harmful to the gut microbiota? Nutr Clin Pract. 2021;37(1):81–93. doi: 10.1002/ncp.10662.
71. *Ardalan M, Vahed SZ.* Gut microbiota and renal transplant outcome. Biomed Pharmacother. 2017;90:229-236. doi: 10.1016/j.biopha.2017.02.114.
72. *Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A.* Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-analysis. Am J Kidney Dis. 2016;68(5):677-90. doi: 10.1053/j.ajkd.2016.04.018.
73. *Rozen-Zvi B, Gafter-Gvili A, Zingerman B, Levy-Drummer RS, Levy L, Mor E, et al.* Intravenous iron supplementation after kidney transplantation. Clin Transplant. 2012;26(4):608–14. doi: 10.1111/j.1399-0012.2012.01602.x.
74. *Mudge DW, Tan KS, Miles R, Johnson DW, Badve SV, Campbell SB, et al.* A randomized controlled trial of intravenous or oral iron for post-transplant anemia in kidney transplantation. Transplantation. 2012;93(8):822–6. doi: 10.1097/TP.0b013e318248375a.
75. *Bazeley J, Wish J.* Recent and emerging therapies for iron deficiency in anemia of CKD: a review. Am

J Kidney Dis. 2022;79(6):868–6. doi: 10.1053/j.ajkd.2021.09.017.

76. *Grimmelt AC, Cohen CD, Fehr T, Serra AL, Wuethrich RP.* Safety and tolerability of ferric carboxymaltose (FCM) for treatment of iron deficiency in patients with chronic kidney disease and in kidney transplant recipients. Clin Nephrol. 2009;71(2):125–9. doi: 10.5414/cnp71125.
77. *Schaefer B, Tobiasch M, Viveiros A, Tilg H, Kennedy NA, Wolf M, et al.* Hypophosphataemia after treatment of iron deficiency with intravenous ferric carboxymaltose or iron isomaltoside—a systematic review and meta-analysis. Br J Clin Pharmacol. 2021;87(5):2256–73. doi: 10.1111/bcp.14643.
78. *Sari V, Atiqi R, Hoorn EJ, Heijboer AC, van Gelder T, Hesselink DA.* Ferric carboxymaltose-induced hypophosphataemia after kidney transplantation. Neth J Med. [Internet]. 2017;75(2):65-73. Available from: https://pubmed.ncbi.nlm.nih.gov/28276325/.
79. *Kassianides X, Bhandari S.* Hypophosphataemia, fibroblast growth factor 23 and third-generation intravenous iron compounds: a narrative review. Drugs Context. 2021;10:1-29. doi: 10.7573/dic.2020-11-3.
80. *Portoles J, Crespo M, Martínez Belotto M, Martínez Morales E, Calatayud Aristoy E, Mora Lopez P, et al.* Post-transplant renal anemia: a call to action from a national study in routine clinical practice. Clin Kidney J. 2024;17(10):sfae269. doi: 10.1093/ckj/sfae269.
81. *Alshamsi I.* Extended literature review of the role of erythropoietin stimulating agents (ESA) use in the management of post renal transplant anaemia. Transplant Rep. 2022;7(2): 100097. doi: 10.1016/j.tpr.2022.100097.
82. *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(3):367-8. doi: 10.1097/01.tp.0000150370.51700.99.
83. *Yasari F, Nafar M, Alipour Abdei B, Ahmadpoor P, Pour-Reza-Gholi F, Samadian F, et al.* Effect of erythropoietin on kidney allograft survival: early use after transplantation. Iran J Kidney Dis. [Internet]. 2012;6(1):44-8. Available from: https://pubmed.ncbi.nlm.nih.gov/22218119/.
84. *Pile T, Raftery M, Thuraisingham R, Kirwan CJ, Harwood S, Yaqoob MM.* Treating posttransplant anemia with erythropoietin improves quality of life but does not affect progression of chronic kidney disease. Exp Clin Transplant. 2020;18(1):27–33. doi: 10.6002/ect.2018.0283.
85. *Obi Y, Ichimaru N, Sakaguchi Y, Iwadoh K, Ishii D, Sakai K, et al.* ANDLE-KIT Trial Investigators. 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(7):1212-1225. doi: 10.1111/tri.13885.
86. *Elliott S, Tomita D, Endre Z.* Erythropoiesis stimulating agents and reno-protection: a meta-analysis. BMC Nephrol. 2017 ;18(1):14. doi: 10.1186/s12882-017-0438-4.
87. *Cassis P, Gallon L, Benigni A, Mister M, Pezzotta A, Solini S, et al.* Erythropoietin, but not the correction of anemia alone, protects from chronic kidney allograft injury. Kidney Int. 2012;81(9):903-18. doi: 10.1038/ki.2011.473.
88. *Purroy C, Fairchild RL, Tanaka T, Baldwin WM 3rd, Manrique J, Madsen JC, et al.* Erythropoietin Receptor-Mediated Molecular Crosstalk Promotes T Cell Immunoregulation and Transplant Survival. J Am Soc Nephrol. 2017;28(8):2377-92. doi: 10.1681/ASN.2016101100.
89. *Cao Y.* Erythropoietin in cancer: a dilemma in risk therapy. Trends Endocrinol Metab. 2013;24(4):190-9. doi: 10.1016/j.tem.2012.10.007.
90. *Kliger AS, Foley RN, Goldfarb DS, Goldstein SL, Johansen K, Singh A, et al.* KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. Am J Kidney Dis. 2013;62(5):849-59. doi: 10.1053/j.ajkd.2013.06.008.
91. *Chienwichai K, Phirom S, Wuttiputhanun T, Leelahavanichkul A, Townamchai N, Avihingsanon Y, et al.* A systematic review and meta-analysis of factors contributing to post-kidney transplant anemia and the effect of erythropoietin-stimulating agents. Syst Rev. 2024;13(1):278. doi: 10.1186/s13643-024-02709-8.
92. *Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D*; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355(20):2085-98. doi: 10.1056/NEJMoa065485.
93. *Olivas-Martinez A, Corona-Rodarte E, Nuñez-Zuno A, Barrales-Benítez O, Oca DM, Mora JD, et al.* Causes of erythrocytosis and its impact as a risk factor for thrombosis according to etiology: experience in a referral center in Mexico City. Blood Res. 2021; :56(3):166-174. doi: 10.5045/br.2021.2021111.
94. *Gaiffe E, Vernerey D, Bardiaux L, Leroux F, Meurisse A, Bamoulid J, et al.* Early Post-Transplant Red Blood Cell Transfusion Is Associated With an Increased Risk of Transplant Failure: A Nationwide French Study. Front Immunol. 2022;13:854850. doi: 10.3389/fimmu.2022.854850.
95. *Silva BDPC, Lasmar MF, Nascimento E, Fabreti-Oliveira RA.* Impact of early blood transfusion after kidney transplantation on the clinical outcomes and allograft survival. Transpl Immunol. 2023;77:101807. doi: 10.1016/j.trim.2023.101807.

96. *Goel R, Patel EU, Cushing MM, Frank SM, Ness PM, Takemoto CM, et al.* Association of perioperative red blood cell transfusions with venous thromboembolism in a north American registry. JAMA Surg. 2018;153(9):826–33. doi: 10.1001/jamasurg.2018.1565.

97. *Massicotte-Azarniouch D, Sood MM, Fergusson DA, Chassé M, Tinmouth A, et al.* The association of venous thromboembolism with blood transfusion in kidney transplant patients. Transfusion. 2022;62(12):2480–9. doi: 10.1111/trf.17154.

98. *Lam NN, Garg AX, Knoll GA, Kim SJ, Lentine KL, McArthur E, et al.* Venous thromboembolism and the risk of death and graft loss in kidney transplant recipients. Am J Nephrol. 2017;46(4):343–54. doi: 10.1159/000480304.

99. *Koury MJ, Haase VH.* Anaemia in kidney disease: harnessing hypoxia responses for therapy. Nat Rev Nephrol. 2015;11(7):394-410. doi: 10.1038/nrneph.2015.82.

100. *Miki K, Nakamura Y, Yokoyama T, Kamiyama M, Ishii Y.* Therapeutic effect of roxadustat on patients with posttransplant anemia. Transplant Proc. 2022;54(3):671–77. doi: 10.1016/j.transproceed.2022.02.004.

101. *Li J, Ma K, Wang L, Qi H, Lv J, Rao Y, Peng W.* Efficacy and safety of roxadustat in the treatment of renal allograft anemia patients: a case series. Ann Palliat Med. 2021;10(11):11859-67. doi: 10.21037/apm-21-2916.

102. *Naganuma T, Iwai T, Takemoto Y, Uchida J.* Experience with the use of a novel agent, hypoxia-inducible factor prolyl hydroxylase inhibitor, for posttransplant anemia in renal transplant recipients: a case report. Transplant Proc. 2022;54(2):544–48. doi: 10.1016/j.transproceed.2021.10.022.

103. *Abdelazeem B, Shehata J, Abbas KS, El-Shahat NA, Malik B, Savarapu P, et al.* The efficacy and safety of roxadustat for the treatment of anemia in non-dialysis dependent chronic kidney disease patients: An updated systematic review and meta-analysis of randomized clinical trials. PLoS One. 2022;17(4):e0266243. doi: 10.1371/journal.pone.0266243.

104. *Turshudzhyan A.* Post-renal transplant malignancies: Opportunities for prevention and early screening. Cancer Treat Res Commun. 2021;26:100283. doi: 10.1016/j.ctarc.2020.100283.

105. *Basheeruddin M, Qausain S.* Hypoxia-Inducible Factor 1-Alpha (HIF-1α) and Cancer: Mechanisms of Tumor Hypoxia and Therapeutic Targeting. Cureus. 2024;16(10):e70700. doi: 10.7759/cureus.70700.

106. *Shirole NH, Kaelin WG Jr.* von-Hippel Lindau and Hypoxia-Inducible Factor at the Center of Renal Cell Carcinoma Biology. Hematol Oncol Clin North Am. 2023;37(5):809-25. doi: 10.1016/j.hoc.2023.04.011.

107. KDIGO 2023 Clinical Practice Guideline for the Care of Kidney Transplant Recipients. Kidney Int Suppl. [Internet]. 2023;13(1):1–164. Available from: https://consultorsalud.com/wp-content/uploads/2023/09/KDIGO-2023-CKD-Guideline-Public-Review-Draft_5-July-2023.pdf.

108. *Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al.* Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843. doi: 10.1016/j.diabres.2019.107843.

109. *Wright EM, Hirayama BA, Loo DF.* Active sugar transport in health and disease. J Intern Med. 2007;261(1):32–43. doi: 10.1111/j.1365-2796.2006.01746.x.

110. *Vallon V, Verma S.* Effects of SGLT2 inhibitors on kidney and cardiovascular function. Annu Rev Physiol. 2021;83:503–28. doi: 10.1146/annurev-physiol-031620-095920.

111. *Yoshida Y, Takahashi K, Hashimoto R, Oya T, Sato J.* Relationship Between SGLT2 Inhibitors and Hemoglobin Levels: A Retrospective Observational Study. In Vivo. 2023;37(5):2327-33. doi: 10.21873/invivo.13336.

112. *Lemke A, Brokmeier HM, Leung SB, Mara KC, Mour GK, Wadei HM, et al.* Sodium-glucose cotransporter 2 inhibitors for treatment of diabetes mellitus after kidney transplantation. Clin Transplant. 2022;36(8):e14718. doi: 10.1111/ctr.14718.

113. *Chewcharat A, Prasitlumkum N, Thongprayoon C, Bathini T, Medaura J, Vallabhajosyula S, Cheungpasitporn W, et al.* Efficacy and safety of SGLT-2 inhibitors for treatment of diabetes mellitus among kidney transplant patients: A systematic review and meta-analysis. Med Sci (Basel). 2020;8(4):47. doi: 10.3390/medsci8040047.

114. *Carro C, Raba A, Deras E, Sánchez LA, Cecilio RV, López-Gómez JJ, et al.* FC 116: SGLT2 Inhibitors in Kidney Transplantation: A Multicenter Study, Nephrology Dialysis Transplantation. 2022;37(3):884–87. doi 10.1093/ndt/gfac124.001.

115. *Halden TAS, Kvitne KE, Midtvedt K, Rajakumar L, Robertsen I, Brox J, et al.* Efficacy and safety of empagliflozin in renal transplant recipients with posttransplant diabetes mellitus. Diabetes Care. 2019;42(6):1067–74. doi: 10.2337/dc19-0093.

116. *Ferreira JP, Anker SD, Butler J, Filippatos G, Iwata T, Salsali A, et al.* Impact of anaemia and the effect of empagliflozin in heart failure with reduced ejection fraction: findings from EMPEROR-Reduced. Eur J Heart Fail. 2022;24(4):708-15. doi: 10.1002/ejhf.2409.

117. *Schwarz Y, Klein P, Lev-Shalem L.* Masked anemia and hematocrit elevation under sodium glu-

cose transporter inhibitors: findings from a large real-world study. Acta Diabetol.2024;61(1):99-105. doi: 10.1007/s00592-023-02174-0.

118. *Pham PT, Pham PT.* Optimal use of SGLT2 inhibitors in diabetic kidney transplant recipients. Front Nephrol. 2022;2:1014241. doi: 10.3389/fneph.2022.1014241.

119. *Qu W, Yao L, Liu X, Xu T, Tian B.* Effects of Sodium-Glucose Co-transporter 2 Inhibitors on Hemoglobin Levels: A Meta-analysis of Randomized Controlled Trials. Front Pharmacol. 2021;12:630820. doi: 10.3389/fphar.2021.630820.

120. *Packer M.* Mechanisms of enhanced renal and hepatic erythropoietin synthesis by sodium-glucose co-transporter 2 inhibitors. Eur Heart J. 2023;44(48):5027-35. doi: 10.1093/eurheartj/ehad235.

121. *Hu JC, Shao SC, Tsai DH, Chuang AT, Liu KH, Lai EC.* Use of SGLT2 Inhibitors vs GLP-1 RAs and Anemia in Patients With Diabetes and CKD. JAMA Netw Open. 2024;7(3):e240946. doi: 10.1001/jamanetworkopen.2024.0946.

122. *Ku E, Del Vecchio L, Eckardt KU, Haase VH, Johansen KL, Nangaku M, et al.* Novel anemia therapies in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2023;104(4):655-80. doi: 10.1016/j.kint.2023.05.009.

123. *Ujjawal A, Schreiber B, Verma A.* Sodium-glucose cotransporter-2 inhibitors (SGLT2i) in kidney transplant recipients: what is the evidence? Ther Adv Endocrinol Metab. 2022;13:20420188221090001. doi: 10.1177/20420188221090001.

124. *Mazer CD, Hare GMT, Connelly PW, Gilbert RE, Shehata N, Quan A, et al.* Effect of empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. Circulation. 2020;141(8):704–7. doi: 10.1161/CIRCULATIONAHA.119.044235.

125. *Yabu JM, Winkelmayer WC.* Post-transplantation anemia: mechanisms and management. Clin J Am Soc Nephrol. 2011;6(7):1794-801. doi: 10.2215/CJN.01190211.

126. *Koshino A, Schechter M, Chertow GM, Vart P, Jongs N, Toto RD, et al.* Dapagliflozin and anemia in patients with chronic kidney disease. NEJM Evidence. 2023;2(6):EVIDoa2300049. doi: 10.1056/EVIDoa2300049.

127. *Hai An HP, Diem HT, Cuong NT.* Parvovirus B19-Associated Anemia in Kidney Transplant Recipients: A Single-Center Experience. Transplant Proc. 2019;51(8):2693-96. doi: 10.1016/j.transproceed.2019.03.076.