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Review article

Kidney transplantation in the presence of pulmonary hypertension: A clinical dilemma

Melina Farshbafnadi [a,1], Rad Ghannadzadeh Kermani Pour [a,1], Roya Sattarzadeh Badkoubeh [b], Babak Geraiely [b], Maryam Mehrpooya [b], Farnoosh Larti [b,*]

[a] School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Cardiology, Imam Khomeini Hospital Complex, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

End-stage renal disease (ESRD) is a progressive chronic condition that is strongly associated with cardiovascular mortality. ESRD patients usually benefit significantly from kidney transplantation. Pulmonary hypertension (PH) is a common finding in ESRD patients that adversely affects their survival. It has also been associated with adverse increased mortality and morbidity following kidney transplantation. However, PH has also been thought to improve following kidney transplantation. The exact underlying pathophysiology of PH in ESRD patients is unknown. However, it has been believed to be multifactorial, involving endothelial dysfunction, volume overload, and arteriovenous fistula. Management of PH in kidney transplant candidates and ESRD patients is remarkably understudied. Several treatment options are available for the treatment of PH. However, studies conducted on treating PH in ESRD patients are scarce. There is an increased need for studies on ESRD patients with PH.

1. Introduction

Chronic kidney disease (CKD) is a considerable global health concern. It is estimated that about 700 million people suffer from CKD worldwide. In 2017 alone, 1.2 million individuals with CKD died due to complications of the disease [1]. As the global population ages, the burden of CKD rises [2]. The interplay of the kidney and other organs can lead to multiple organ dysfunctions in kidney disease. CKD has been long associated with cardiovascular diseases such as coronary artery disease, heart failure, arrhythmias, and sudden cardiac death [3].

In comparison to the general population, patients with early stages of CKD (CKD stages 1–3) experience significantly higher rates of cardiovascular incidents. Predictably, the rates of cardiovascular events are even higher in patients with advanced stages of CKD (CKD stages 4–5). The most common reasons for mortality in patients with renal failure (CKD stage 5) who require regular dialysis are cardiovascular complications. However, most patients with progressive CKD don't reach renal failure as they perish due to high rates of cardiovascular mortality [3].

* Corresponding author. Department of Cardiology, Imam Khomeini Hospital Complex, School of Medicine, Tehran University of Medical Sciences, Keshavarz Boulevard, Tehran, Iran.
E-mail address: farnooshlarti@gmail.com (F. Larti).
[1] Both authors had the same contribution to the study process.

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Pulmonary hypertension (PH) is a disease of high blood pressure in the pulmonary artery and, generally, the pulmonary circulation. It presents with progressive difficulties in breathing and exercising, which is potentially able to establish right heart failure and death [4]. Several studies have estimated PH prevalence in CKD patients from 13 % to 50 % [5–12]. It is presumed that PH pathogenesis is multifactorial in CKD. Factors such as hypoxic status, left heart failure, metabolic dysfunction, and elevated cardiac output are implicated in PH pathogenesis. Besides, it is assumed that endothelial damage, arterial stricture due to calcium deposition, and arteriovenous (A-V) fistula used for hemodialysis are responsible [13–15]. The severity and intensity of PH are directly related to the extent of volume overload, stage of CKD, and dialysis duration [16,17]. CKD Patients suffering from PH confront higher mortality rates. The presence of underlying PH causes an immense drop in patients' 5-year survival from 89.6 % to 78.3 % [18].

Treatment for CKD combines one or more of the following: lifestyle changes, medications, dialysis (hemodialysis and peritoneal dialysis), and kidney transplantation [19]. Kidney transplantation is the suggested modality in individuals with highly advanced kidney disease [20,21]. Compared to maintenance dialysis, kidney transplantation promisingly enhances CKD patients' quality of life and long-term survival and can increase average survival for five years [21]. Kidney transplantation is recommended for all patients with CKD stages 4 and 5 (GFR <30 ml/min/1.73 m^2) [20]. Currently, some CKD patients are not considered suitable candidates for transplantation due to multiple medical issues. Although there is no definite contraindication for kidney transplantation, old age, underlying diabetes, and cardiovascular disease are related to higher 1-year mortality after kidney transplantation [22]. Since numerous transplantation candidates have underlying PH, the probable influence of elevated pulmonary arterial pressure on the transplantation outcome is crucial. There is an available risk score for kidney transplantation candidates applied for anticipating post-transplant survival, including age, presence of diabetes, prior transplant status, and duration of dialysis. Interestingly, this score doesn't incorporate cardiovascular risk or pulmonary hypertension [18]. Several studies have explored the underlying effects of PH on kidney transplantation outcomes. According to these investigations, the presence of pre-existing PH before kidney transplantation might lead to an unpleasant outcome, irrespective of kidney failure [5,6,23]. This may raise concern that individuals with elevated systolic pulmonary arterial pressure (sPAP) are not suitable candidates for kidney transplantation. On the other hand, some studies showed that PH and symptoms caused by chronic volume overload improve via kidney transplantation [8,24].

CKD and PH have an interwoven relationship. This review will discuss the pathophysiology of PH in CKD and ESRD patients and the risk factors associated with developing PH. This study will focus on the possible role of PH in predicting kidney transplant outcomes and how it may or should impact transplant candidacy. Furthermore, the clinical course of PH following kidney transplantation will be addressed. Management of PH in ESRD patients and before kidney transplantation is an essential yet understudied concept that will be discussed in detail.

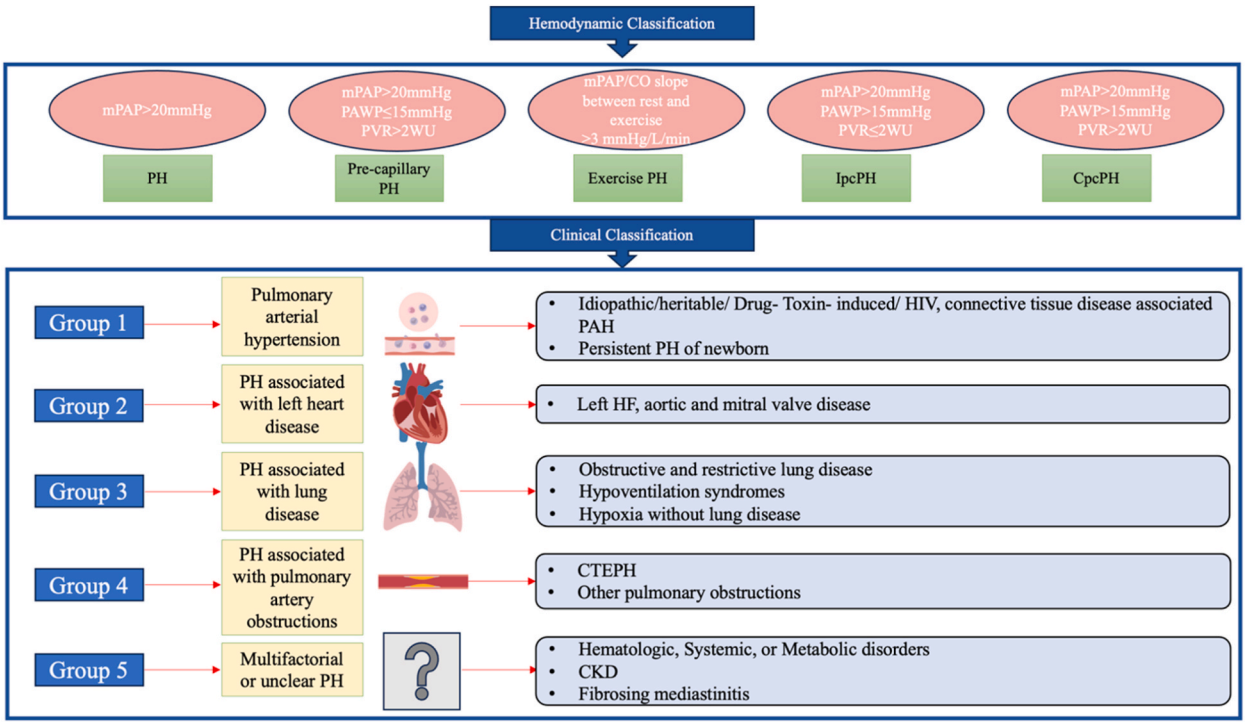

Fig. 1. The Hemodynamic classification of pulmonary hypertension (up proposed by the American College of Cardiology Foundation, and the clinical classification of pulmonary hypertension (down).
Pulmonary Hypertension (PH); IpcPH (Isolated Post-Capillary Pulmonary Hypertension); CpcPH (Combined Postcapillary and Precapillary Pulmonary Hypertension); HIV (Human Immunodeficiency Virus); Heart Failure (HF); Chronic Thromboembolic Pulmonary Hypertension (CTEPH); chronic kidney disease (CKD);.

2. Pulmonary hypertension

2.1. PH diagnosis and classification

PH presents with various non-specific cardiopulmonary manifestations, such as difficulties in breathing, tiredness, dizziness, and chest pain [25,26]. Initially, symptoms are provoked by exercising and physical activity, whereas in advanced cases, symptoms may be present while resting [25]. Right ventricular failure can gradually lead to systemic edema and ascites. These presentations can have an unpleasant impact on the patient physically, psychologically, and socially [27].

Right heart catheterization is an invasive diagnostic tool for measuring pulmonary arterial pressure directly. The parameters achieved from right heart catheterization are used to classify patients [4]. After approving the presence of PH, other variables like mean, pulmonary arterial wedge pressure (PAWP), and PVR, obtained from right heart catheterization, are used to interpret hemodynamic patterns. The definition of PH was changed first in the 1973 World Health Organization (WHO) symposium. It is defined by a mean pulmonary arterial pressure (mPAP) above 25 mmHg, which can be directly measured using the right heart catheterization. However, the threshold has recently been changed to 20 mmHg in the 2022 ESC guideline [4,25,27–29]. PH has been classified hemodynamically and clinically according to the latest guidelines published by the European Society of Cardiology, as summarized in Fig. 1 [29]. These classifications aid in differentiating different causes of PH, such as pulmonary vascular diseases, left heart dysfunction, increased pulmonary blood flow, or elevated intrathoracic pressure [29]. However, as most studies on CKD patients don't have the required confirmation by right heart catheterization, the true prevalence of hemodynamic subgroups of PH isn't known in this patient population [30].

Although right heart catheterization is the gold-standard diagnostic technique for pulmonary hypertension, it is invasive and expensive; therefore, echocardiography is the most commonly used technique [31]. In echocardiography, sPAP is estimated based on measured peak tricuspid regurgitation velocity (TRV), calculating tricuspid regurgitation pressure gradient (TRG), and adding RA pressure to the TRG. RA pressure is estimated considering the IVC size and collapse. Inaccurate determination of RA pressure, severe TR, high RA pressure, and technical errors in measuring TRV are among the factors that lead to inaccurate echocardiographic measurement of the sPAP [32].

Laboratory tests, including complete blood count, liver enzymes, kidney profile, thyroid hormones, and N-terminal pro-brain natriuretic peptide (NT-proBNP), should be performed in every patient. In addition, pulmonary function tests might provide beneficial and advantageous information for PH [32].

Several novel biomarkers have been proposed for diagnosing PH, as timely diagnosis of PH is essential. Soluble suppression of tumorigenicity 2 is a novel marker associated with PH regardless of subtype [33]. It has been observed that elderly patients undergoing maintenance dialysis who develop PH tend to have higher serum soluble FAS, soluble FAS ligand, and post-dialysis potassium concentrations [34]. Indicators of volume status, such as extracellular water/total body water ratio and inferior vena cava expiratory diameter, predict sPAP in continuous ambulatory peritoneal dialysis patients [35]. Another indicator of fluid overload, the overhydration/extracellular water ratio $\geq$7 %, was significantly correlated to pulmonary arterial hypertension in hemodialysis patients [36]. This index is obtained from multifrequency bioelectrical impedance analysis. Serum sclerostin level is considered a potential biomarker associated with pulmonary hypertension. Pre-dialysis ESRD patients with more than 218.19 pmol/L serum sclerostin levels are significantly more likely to have PH [37]. Plasma levels of hepatocyte growth factor tend to be higher in patients with mild pulmonary arterial hypertension compared to healthy controls [38]. Although these biomarkers have been proposed, more studies should be conducted to assess their utilization in the CKD population.

2.2. Risk factors and pathophysiology for PH in ESRD

ESRD patients with pulmonary hypertension may have isolated post-capillary pulmonary hypertension (IpcPH), pre-capillary PH, combined postcapillary and precapillary pulmonary hypertension (CpcPH), and unexplained PH that is classified under clinical group 5 in the latest guideline. However, post-capillary PH appears more common in such patients [16]. In CKD patients, the pathophysiology of PH does not differ much from that of non-CKD patients in the same PH category. Therefore, pulmonary arterial pressure is expected to increase due to known factors contributing to cardiovascular diseases in CKD [30]. Patients with end-stage renal disease are said to have coronary plaques with different properties from those of non-uremic patients, with increased thickness of the tunica media of the arterial wall and pronounced calcification. This may translate into a higher risk of cardiovascular complications in ESRD patients [39,40]. The pattern of calcification of the vasculature in ESRD is distinguished by mineral accumulation in the tunica media as opposed to calcification of the atheromatous plaques in non-ESRD patients [41]. Mineral disturbances such as hyperphosphatemia and hypercalcemia have been suggested to be involved in vascular calcification in ESRD patients. Secondary hyperparathyroidism and increased serum calcium levels are linked to PH in patients with CKD. In diabetic patients, hyperglycemia tends to aid in the progression of the disease [42,43]. Animal models have shown metabolic acidosis prevalent in ESRD patients to be involved in the progression of vascular calcification [44]. Vascular calcification increases arterial stiffness, increasing afterload and left ventricular hypertrophy [45]. Furthermore, pulmonary hypertension is significantly linked to arterial stiffness in kidney transplant recipients [46].

A key factor not often mentioned in the pathogenesis of PH in CKD/ESRD patients is fibroblast growth factor 23 (FGF23). FGF23 is significantly elevated in CKD and ESRD patients and promotes left ventricular hypertrophy [47]. FGF23 levels positively correlate with pulmonary arterial pressure in hemodialysis patients [48]. Furthermore, FGF23 is closely linked to mineral disturbances, including elevated phosphate levels and vitamin D deficiency, which are common findings in CKD patients. FGF23, produced by osteocytes,

modulates phosphate and vitamin D metabolism and prompts phosphaturia. Urinary phosphate decreases in CKD patients.

Furthermore, higher FGF23 levels in kidney transplant candidates are linked to persistent vitamin D deficiency and worse graft outcomes. Vitamin D activity is crucial to FGF23 production. These findings suggest that therapies aimed at controlling phosphorus levels and augmenting vitamin D might modify the course of PH in CKD/ESRD patients. Future studies targeting FGF23 modulation, phosphate control, and vitamin D supplementation could be pivotal in understanding and managing PH in this population [49].

Numerous systemic diseases can affect both kidney and blood vessels and cause kidney failure and PH simultaneously. These conditions comprise autoimmune diseases like systemic lupus erythematosus and systemic sclerosis and diseases that influence the microvascular system of both kidney and pulmonary vessels, including thrombotic microangiopathies and sickle cell anemia. Pulmonary hypertension in systemic sclerosis is a consequence of vascular remodeling, possibly due to endothelial inflammation and injury, which results in the disruption of vasodilation-vasoconstriction equilibrium. SLE has a similar pathophysiology wherein antibodies and accumulation of immune-mediated constituents disturb the endothelium of the vasculature within the pulmonary circulation. Macrophages and lymphocytes have also been seen infiltrating the plexiform lesions of the pulmonary vasculature [50–53].

CKD can also independently alter and remodel pulmonary circulation through endothelial damage, elevated levels of toxic substances like urea, vessel dysregulation, and inflammatory processes [54]. CKD is a pro-inflammatory condition with raised inflammatory biomarkers and oxidative derivatives [55]. Systemic arteries across the body are involved in an inflammatory process due to the chemotaxis of circulating macrophages to the endothelial layer, and the pulmonary artery is not excluded [56]. Vascular endothelial dysfunction has also been observed in chronic kidney disease as a result of marked blood pressure, inflammation, factors related to diabetes, and uremic toxins [57]. Patients with even mild kidney insufficiency are at a higher risk for atherosclerosis. They tend to have a significantly higher plasma von Willebrand factor concentration and endothelial dysfunction even without clinically apparent atherosclerotic vascular disease, thus showing that endothelial dysfunction happens before atherosclerosis in patients with kidney insufficiency [58]. Endothelial dysfunction leads to decreased nitric oxide (NO) and increased production of endothelin-1 by endothelial cells [59]. Patients with pulmonary hypertension tend to have increased expression of endothelin-1 and reduced expression of NO in the vascular bed of the lungs [60–62].

Patients undergoing hemodialysis who developed PH may have increased cardiac output and higher fistula flow rates. A 1-min arterial (A-V) fistula compression in hemodialysis patients could meaningfully decrease cardiac output and PAP [63,64]. One study has investigated the effect of this maneuver on systemic and pulmonary circulation. Following digital compression in eight patients, PAP and cardiac output dropped from 47.2 ± 3.8 to 34.6 ± 2.8 mmHg and from 6.4 ± 0.6 to 5.3 ± 0.5 l/min, respectively [65].

Anemia is another factor related to the increased cardiac output in the ESRD [66,67]. Under normal conditions, increased cardiac output may not result in PH, as small vessels have vast capacities. However, the decreased capacities of small vessels due to

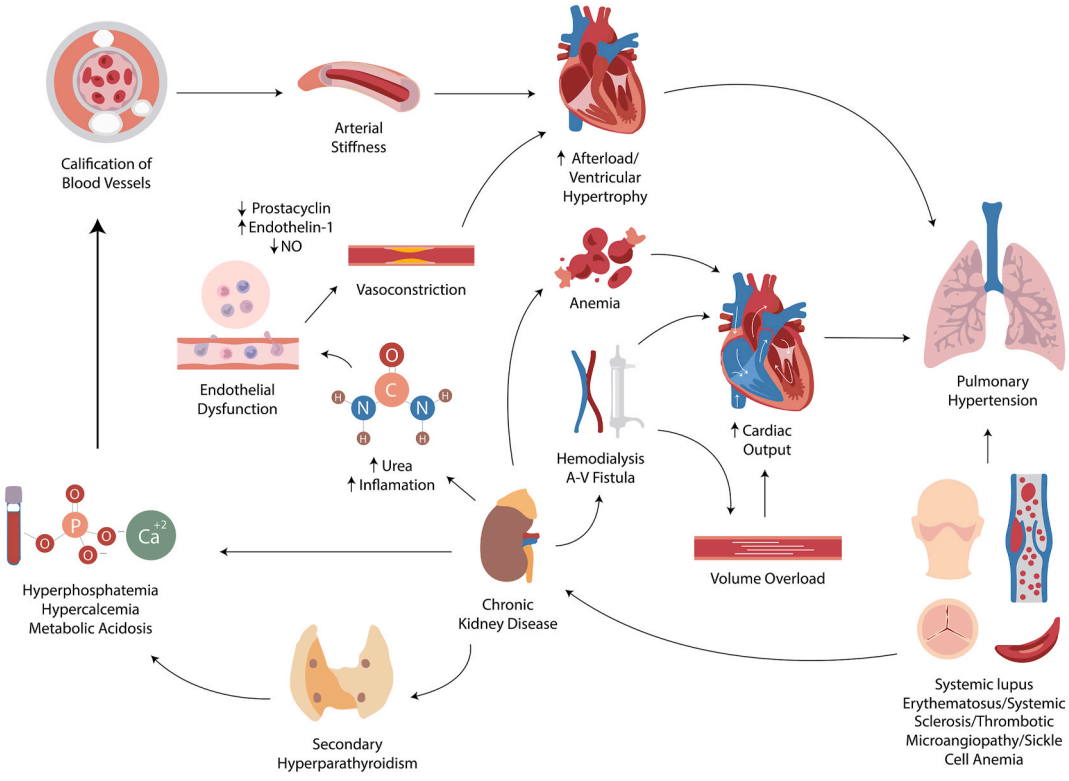

Fig. 2. Mechanisms involved in the pathogenesis of pulmonary hypertension.
Nitric Oxide (NO); A-V fistula (Arterio-Venous Fistula);.

vasoconstriction and calcification in CKD can be another contributor to this equation. It is widely acknowledged that prostacyclin, nitric oxide, thromboxane A2, and endothelin-1 balance the balance between vasodilation and vasoconstriction to maintain the proper vascular tone. As previously mentioned, these factors are influenced by CKD [68].

Furthermore, PAP and cardiac output decrease following kidney transplantation. This reduction is not significant in patients with an open fistula. These findings demonstrate the importance of A-V fistula in the pathophysiology of PH in ESRD patients, which shows the inability of the pulmonary circulation to adapt to the newly increased cardiac output resulting from the creation of the A-V fistula [69–71].

PH seems more prevalent in hemodialysis patients than in the peritoneal dialysis [72]. Although it has been debated, peritoneal dialysis is also associated with PH. Peritoneal dialysis may reduce pulmonary arterial and right atrial pressure and ameliorate LVEF [67]. In contrast, another study showed an insignificant difference between pulmonary hypertension in patients undergoing peritoneal dialysis and hemodialysis [73]. One of the most prominent triggers of PH in CKD patients is volume overload. That is why dialysis patients experience a noticeable drop in pulmonary arterial pressure after a dialysis session.

Furthermore, during the interval between dialysis sessions, progressive left atrial expansion and dysfunction are observed, which leads to decreased LV filling capacity and LV compliance, which results in volume overload within the pulmonary circulation. This concurs with the increased occurrence of pulmonary edema towards the end of the dialysis interval. A combination of volume overload and LV impairment increases pulmonary capillary wedge pressure in hemodialysis patients [74]. Fig. 2 summarizes the mechanisms involved in PH in CKD patients.

2.3. Pulmonary hypertension and mortality in ESRD

It has been estimated that the presence of PH increases the probability of mortality and cardiovascular complications by 38 % and 23 %, respectively [75]. Pulmonary hypertension also increases mortality in ESRD patients undergoing hemodialysis [76]. Table 1

Table 1
Outcomes of ESRD patients with pulmonary hypertension.

Study	Population	PH prevalence	Inclusion criteria/PH definition/	Results
Yigla, 2009 [77]	127 hemodialysis patients	**PH:** 29.1 % **Severe PH:** not mentioned	**PH:** sPAP>45 mmHg in echocardiography **Severe PH:** not mentioned	Increased mortality in hemodialysis patients with PH
Ramasubbu, 2010 [79]	90 hemodialysis patients	**PH:** 47 % **More Severe PH:** 20 %	**PH:** TRV≥2.5 m/s ~ sPAP≥35 mmHg in echocardiography **More Severe PH:** TRV≥3 m/s	Increased mortality in hemodialysis patients with PH
Agarwal, 2012 [78]	288 hemodialysis patients	**PH:** 38 % **More Severe PH:** 16 %	**PH:** sPAP>35 mmHg in echocardiography **More Severe PH:** sPAP≥45 mmHg	PH was an independent risk factor for death in ESRD patients
Xu, 2014 [82]	618 peritoneal dialysis patients	**PH:** 16 % **Severe PH:** not mentioned	**PH:** sPAP>35 mmHg in echocardiography **Severe PH:** not mentioned	PH increased risk of both all-cause and cardiovascular mortality in peritoneal dialysis patients
Wolfe, 2018 [83]	150 ESRD patients	**PH:** 66 % (echocardiography) 59 % (right heart catheterization) **Severe PH:** not mentioned	**PH:** sPAP>36 mmHg in echocardiography/mPAP≥25 in right heart catheterization	In patients with mPAP≥25, PVR>3 is a significant prognostic factor
Song, 2021 [80]	578 hemodialysis patients	**PH:** 26.1 % **More Severe PH:** 15 %	**PH:** sPAP≥35 mmHg in echocardiography **More Severe PH:** sPAP≥45 mmHg in echocardiography	Increased mortality in hemodialysis patients with PH
Rroji, 2021 [73]	125 stable hemodialysis and peritoneal patients	**PH:** 28 % **Severe PH:** not mentioned	**PH:** sPAP≥35 mmHg in echocardiography **Severe PH:** not mentioned	Patients with PH have significantly lower survival rates
Liu, 2023 [81]	192 hemodialysis patients	**PH:** 30.9 % **Severe PH:** not mentioned	**PH:** Resting sPAP>35 mmHg in echocardiography **Severe PH:** not mentioned	Higher all-cause mortality in hemodialysis patients with PH

Pulmonary Hypertension (PH); TRV (Tricuspid Regurgitation Velocity); systolic Pulmonary Arterial Pressure (sPAP); mean Pulmonary Arterial Pressure (mPAP).

describes the results of studies investigating the role of PH in the mortality of CKD and ESRD patients [73,77–83]. PH tends to increase the mortality of hemodialysis patients regardless of the existence of PH before the hemodialysis [77–81]. Pulmonary hypertension doesn't correlate with A-V fistula failure, and one study didn't find A-V fistula to be a risk factor for PH in dialysis patients. Studies demonstrating lower PH prevalence in peritoneal dialysis patients compared to hemodialysis patients are relatively small. They may be affected by the fact that patients on peritoneal dialysis are generally younger. Furthermore, PH is also a risk factor for cardiovascular and all-cause mortality in peritoneal dialysis patients [73,80,82]. A recent study conducted on CKD patients' stage 3b–5 showed that the mildly elevated PVR (>2 to ≤ 3 WU) was independently linked to major adverse cardiovascular outcomes in CKD patients, and early diagnosis of PH in CKD patients may improve prognosis [84].

3. Pulmonary hypertension and kidney transplant

3.1. Kidney transplantation candidates and recommendations

Kidney transplantation is recommended for patients with CKD grades 4 or 5 (with a GFR less than 30 ml/min/1.73 m2) who are anticipated to progress into ESRD. 2020 Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines recommend essential steps before kidney transplantation in patients with pulmonary hypertension. All patients undergoing kidney transplantation should be evaluated for the presence and severity of cardiac diseases. Patients with active cardiac diseases such as angina, arrhythmias, heart failure, or symptomatic valvular heart disease should be assessed and treated before further consideration for renal transplantation. Patients with asymptomatic coronary artery disease (CAD) with progressive triple vessel coronary artery disease should be excluded from renal transplantation unless they have an acceptable survival. Although revascularization does not lower the risk of mortality either in diabetic asymptomatic CAD patients or in major vascular surgery candidates, no valid investigation has been performed on asymptomatic CAD patients with underlying CKD to determine whether revascularization is warranted or not. Patients with untreatable, symptomatic heart disease with a New York Heart Association (NYHA) Functional Class III/IV (severe CAD, left ventricular dysfunction with ejection fraction below 30 %, or severe valvular disease) should be excluded from kidney transplantation unless they have factors that make their post-transplant survival acceptable [20].

Echocardiography is recommended for those with at least a two-year history of dialysis or the presence of risk factors for pulmonary hypertension, including portal hypertension, connective tissue disease, congenital heart disease, and chronic obstructive pulmonary disease. A cardiologist must assess the patient if echocardiographic findings suggest sPAP of more than 45 mmHg. It is not recommended to exclude patients from renal transplantation if right heart catheterization reveals an sPAP of more than 60 mmHg [20].

3.2. Pretransplant pulmonary hypertension and kidney transplant outcomes

PH is linked to increased mortality and morbidity in patients going through noncardiac surgeries. They are at a higher risk of cardiac failure, arrhythmias, hemodynamic instability, respiratory failure, extended respiratory support, and intensive care [28].

Several researchers have studied the effects of pre-transplant pulmonary hypertension on renal transplantation outcomes. Based on these studies, pulmonary hypertension was assessed through various variables such as sPAP, right ventricular systolic pressure (RVSP), etc. These studies explored multiple unpleasant post-transplant outcomes. These unfavorable outcomes were delayed graft function, early graft dysfunction, kidney graft failure, all-cause mortality, and unfavorable graft or patient survival [7].

Early graft dysfunction is when hemodialysis is required within one week after kidney transplantation (delayed graft function) or patients not on dialysis with serum creatinine concentration above 3 mg/dl on day five after transplantation. It was explored in a study conducted by Zlotnick et al. The existence of PH before kidney transplantation puts the patient at a higher risk for early graft dysfunction, resulting in more extended hospital stays, irrespective of other factors. sPAP of more than 40 was found to predict early graft dysfunction with an 83 % sensitivity and 70 % specificity [7].

Another investigated outcome that was correlated with pulmonary hypertension before renal transplantation was delayed graft function. Many other studies investigated the delayed graft function, which defined the need to proceed with hemodialysis seven days after transplantation. These explorations revealed a substantial relationship between pulmonary hypertension and delayed graft function incidence. This discovery was obtained after adjustment of other variables [85–87]. The duration of CKD was not an independent predictor of delayed graft function [85].

Several studies focused on the association between pulmonary hypertension and graft failure or survival. Although multiple studies were performed, the results were conflicting. A survey conducted by Foderaro et al. [88] in 2017 on patients undergoing kidney transplantation showed that patients with PH before kidney transplantation had a 3-fold elevated risk of kidney graft failure. Nguyen et al. obtained similar results [86].

In contrast, such a relationship between sPAP value and graft failure was not observed in the Jarmi et al. investigation [89]. Several studies deduced that PH before transplantation did not correlate with graft failure incidence. In contrast, a significant correlation was found between all-cause mortality and patients' survival after kidney transplantation [5,18,89]. Based on these studies, pre-transplant PH highly affects mortality after transplantation and shortens a patient's survival compared to graft failure. Various studies improve the effect of PH on post-transplant mortality [86,90]. Although most studies exhibited a significant association between PH and poor transplantation outcomes, few did not demonstrate such a relationship. Rabih et al. did not observe an increased risk of short-term or 5-year mortality in patients with pulmonary hypertension [91]. Similarly, a study performed in 2021 noted that mild to moderate PH did not have unfavorable consequences on overall survival or post-transplant graft loss [92].

Table 1 summarizes the characteristics and results of these studies. Interestingly, these studies have different and more severe PH

cut-offs, none comparable to the recent guidelines [29]. The recent change of the cut-off point for PH makes further investigations mandatory.

3.3. Clinical course of pulmonary hypertension following kidney transplant

It is important to note that kidney transplantation can reverse pulmonary hypertension in ESRD patients. In a study by Casas-Aparicio et al., kidney transplantation improved left ventricular systolic and diastolic function. It also alleviated pulmonary hypertension in patients [93]. In a survey by Bozbas et al. mean sPAP levels after kidney transplantation improved from an average of 45.9 ± 8.8 mmHg to 41.8 ± 7.4 mm Hg in an average course of 53 months of follow-up [94]. In another study by Frost et al., 61 patients underwent post-transplant echocardiography. Of these patients, 25 (41 %) still suffered from pulmonary hypertension. In the other 36 patients, it took a median of 37.5 months for their pulmonary hypertension to resolve [95]. In a small study, four out of five patients with pulmonary hypertension who had undergone successful kidney transplantation had improved pulmonary hypertension [96]. In 124 patients studied by Reddy et al. sPAP was measured before transplantation. PH was defined as sPAP> 35 mmHg 1 h following dialysis, and 28.2 % of patients had PH before transplantation. Most patients with baseline PH had a reduced sPAP following kidney

Tables 2
Summary of therapeutic classes used in pulmonary hypertension and their possible considerations in patients with chronic kidney disease (CKD).

Therapeutic class	Mechanism of action	Medication(s)	Dose adjustment in CKD population	Additional consideration in the CKD population	Adverse effects
5-phosphodiesterase inhibitors	Vasodilation of the pulmonary arteries	**Sildenafil** **Tadalafil** **Vardenafil**	- CKD or dialysis patients require no dose adjustment - If creatinine clearance rate< 30 mL/min or on hemodialysis: dose ≤5 mg every 72 h - If creatinine clearance 30–50 mL/min: A starting dose of 5 mg not more than once per day is recommended- - CKD patients require no dose adjustment - It has not been evaluated in patients on dialysis-	- Initiated with lowest feasible dosage and gradually increased in severe renal disease	- Headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb
Endothelin receptor antagonists	Competitive inhibition of endothelin-1 receptors (strong vasoconstrictors)	**Bosentan** **Ambrisentan** **Macitentan**	- CKD or dialysis patients require no dose adjustment - CKD patients require no dose adjustment - Limited information in patients with severe renal impairment and on hemodialysis- - CKD patients require no dose adjustment - Limited information in patients on hemodialysis-	- Could worsen preexisting peripheral edema	Liver toxicity, peripheral edema, anemia
Prostacyclin analog	Relaxation of pulmonary artery through prostacyclin pathway	**Treprostinil** **Iloprost** **Epoprostenol** **Selexipeg**	- CKD or dialysis patients require no dose adjustment - CKD patients require no dose adjustment - Limited information in patients on hemodialysis- - Limited information in patients with renal impairment- - CKD or dialysis patients require no dose adjustment-	- Catheter-related issues with intravenous preparations may add risk in dialysis - Initiated with lowest feasible dosage and gradually increased to achieve clinical improvement	Flushing, tachycardia, diarrhea, nausea, headaches, pain; sepsis, hemorrhage, pulmonary embolism with intravenous infusions, hypotension
Soluble guanylyl cyclase inhibitor	Increases vascular cyclic guanosine monophosphate concentrations causing vasodilation of pulmonary artery	**Riociguat**	- Not recommended if creatinine clearance rate <15 ml/min	- Initiated with lowest feasible dosage and gradually increased to achieve clinical improvement	Hypotension if combined with nitrates

transplantation. 65 % of patients with mild PH (sPAP >35 and ≤ 45 mmHg) before kidney transplantation reached the normal state following transplantation. Most patients with moderate PH (sPAP >45 and ≤ 55 mmHg) had lower PH severity following kidney transplantation. 25 % of patients with severe PH (sPAP >60 mmHg) had normal PAP following transplantation [97].

3.4. Management of pulmonary hypertension in CKD and ESRD patients

PH treatment combines specific therapy with treatment of the underlying disease leading to PH. In CKD patients, PH treatment targets three significant pathways in PH pathogenesis. The clinical classifications mentioned above are important in proper management. Table 2 summarizes the drugs used to manage PH and their considerations in CKD patients [98–108].

3.4.1. Management of PH associated with left heart disease

PH associated with left heart disease (clinical class 2) is generally regarded as the most common cause of PH, which also applies to CKD [109]. Management of this group of patients usually involves treating the underlying heart disease [30], including optimized hypertension management and achieving euvolemic status with satisfactory dialysis sessions and management of valvular heart diseases based on the latest guidelines.

3.4.2. Management of pulmonary arterial hypertension (PAH)

Routinely, pulmonary arterial hypertension (clinical class 1) can be managed by targeting pathways containing nitric oxide, endothelin, and prostacyclin. Therefore, IV prostacyclin (epoprostenol), prostacyclin analogs (iloprost, treprostinil), prostacyclin receptor agonists (selexipag), phosphodiesterase type 5 inhibitors (Sildenafil, Tadalafil, and Vardenafil), guanylate cyclase inhibitors (riociguat), and endothelin receptor antagonist (Bosentan, Ambrisentan, and Macitentan) can be helpful [30,110,111]. Theoretically, these drugs should also be beneficial in the CKD population. Still, several measures have to be taken under consideration. Some drugs may not be effective in hemodialysis patients because they are removed during dialysis. Endothelin receptor antagonists that majorly bond to plasma proteins are immune from removal. They also have hepatic excretion; thus, they do not require dose adjustment in ESRD individuals. However, they may worsen pre-existing peripheral edema [30,105].

Drugs directing the prostacyclin pathway may also be beneficial in the CKD population and don't usually require dose adjustment.

Table 3
Summary of Studies Conducted on treating pulmonary hypertension in end-stage renal disease patients.

Study	Study type	Number of patients	Patient population	Treatment	Outcome
Liefeldt, 2004 [113]	Case report	1	ESRD patient with PH	Bosentan	After 12 months of treatment the patient had normal PAP.
Yamanaka, 2007 [114]	Case report	1	ESRD patient with PH, mild aortic stenosis, and syncope	Bosentan	After treatment with Bosentan, syncope discontinued.
Watanabe, 2017 [115]	Case report	1	Patient with severe PH and CKD on hemodialysis	Subcutaneous Treprostinil	Normalized pulmonary hemodynamics after 9 months of treatment.
Santos, 2020 [105]	Case report	1	HIV-1 positive patient with ESRD and PH	Ambrisentan	Minimal removal of Ambrisentan by hemodialysis in patients with ESRD.
Nishimura, 2016 [116]	Retrospective observational study	15	ESRD patients with idiopathic precapillary PH	Bosentan, Ambrisentan, Macitentan	Administration of ETAs can potentially improve the survival by reducing heart failure death.
Arevalo, 2021 [117]	Retrospective case-series	18	ESRD patients with PH	Tadalafil monotherapy, Tadalafil + Ambrisentan	Significant improvement in hemodynamics during repeat right heart catheterization which allowed some patients to be eligible for renal transplantation.
Kimuro, 2022 [118]	Retrospective observational study	7	Pre-Capillary PH in Patients with CKD on Hemodialysis	Bosentan, Macitentan, Ambrisentan, Sildenafil, Selexipag, Treprostinil	Pulmonary vasodilators improved the symptoms, exercise tolerance, and pulmonary vascular resistance. Improved 6MWT and WHO functional class.
del Valle, 2024 [119]	Retrospective cohort	37	PH patients with stage IV/V CKD or ESRD	Inhaled NO	Significant decreases in mPAP and PVR
Akiash, 2021 [120]	Prospective clinical trial	31	ESRD patients with PH	Intensive hemodialysis and hemoglobin concentration correction (SQ erythropoietin)	Significant decrease in PAP and improved LV systolic function
Cangialosi, 2023 [111]	Retrospective analysis	8	ESRD patients with PH	Riociguat (soluble guanylate cyclase stimulators)	This study shows improvement in both functional and objective measures of pulmonary hypertension disease severity following treatment with Riociguat

End-Stage Renal Disease (ESRD); Pulmonary Hypertension (PH); Pulmonary Arterial pressure (PAP); chronic kidney disease (CKD); Human Immunodeficiency Virus (HIV); Endothelin-A (ETA); 6-Minute Walk Test (6MWT); World Health Organization (WHO); Nitric Oxide (NO); Subcutaneous (SQ).

Iloprost is an outlier demonstrating decreased clearance in CKD and is suggested to be administered with a 50 % lower initial dosage. Phosphodiesterase type 5 inhibitors, with negligible side effects, are usually applied as a first line. Sildenafil doesn't require dose adjustment in CKD or dialysis patients. Tadalafil can be used with a 50 % reduced starting dose in patients with a creatinine clearance rate between 30 and 80 and should be avoided in patients with a creatinine clearance rate of 30 or less. Vardenafil should be avoided in dialysis patients [30].

3.4.3. Management of PH before kidney transplantation

Table 3 lists the studies focusing on treating the CKD population with PH. Patients with ESRD are usually hypervolemic and should be able to achieve and maintain euvolemia, which can be challenging. Intradialytic hypotension, systolic blood pressure reduction of more than 20 mmHg or mean arterial pressure of more than 10 mmHg, and low blood pressure clinical symptoms limit the volume reduction. Patients with PH undergoing surgery, including kidney transplantation, should be assessed and managed carefully as they are at a higher risk of cardiovascular complications.

Kidney transplantation is challenging in ESRD patients with PH, and perioperative management is essential. First, the risk factors in each patient should be assessed and evaluated for the type of PH, which leads to an efficient management of PH before surgery. 6-minute walking distance (6MWD), NYHA functional class, blood pressure, heart rate, BNP, NT-proBNP, echocardiography, and oxygen saturation are tools that aid in the preoperative assessment of patients.

Recent studies have proved that BNP can be used as a non-invasive marker representing PH, which is directly associated with the severity of high PAP. It has to be noted that the application of BNP is a disputed matter as its concentration is dependent on kidney clearance, which restricts its potential to be applicable as an indicator of volume status. As of today, multiple studies have addressed this controversy. A recent systematic review identified 61 studies and concluded that ESRD-specific threshold for NT-proBNP and BNP levels may still be necessary in predicting cardiovascular outcomes. Therefore, further investigations are required to determine the exact threshold for the ESRD population [112].

Unsatisfactory 6MWD and functional class are significantly correlated with perioperative complications in non-cardiac surgeries. Any sign of undesirable disease control should be managed with diuretics, targeted PH treatment, afterload reduction, and arrhythmia control. Targeted therapies for PH usually require 6–12 weeks for maximal impact. Intraoperative systemic hypotension should be avoided to prevent right ventricular ischemia. All patients should maintain a normal heart rate to preserve right ventricular contractility. Metabolic disturbances such as acidosis, hypercarbia, and hypoxia should be managed carefully [28]. Although these measures can be applied to ESRD patients, the perioperative management of PH patients who are candidates for kidney transplants has challenging issues. Limited studies are conducted on treating PH in ESRD and CKD patients. Available studies have a small number of subjects. More studies are needed to address the CKD and ESRD populations, which may improve their outcomes.

4. Conclusion

Pulmonary hypertension is a crucial matter in patients with ESRD that can increase their mortality rates. These patients are at a higher risk for PH, and PH adversely affects patients with CKD and kidney transplant outcomes. Due to poor prognosis, patients with moderate to severe pulmonary hypertension are usually not good candidates for kidney transplantation. Although there is evidence that suggests increased pulmonary hypertension is linked to increased mortality and morbidity following kidney transplantation, it is also suggested that pulmonary hypertension may regress following kidney transplantation.

Furthermore, the definition of PH has been changed recently and extended to mPAP of more than 20 mmHg rather than the previously stated mPAP of more than 25 mmHg. It is essential to conduct more studies to aid cardiologists and nephrologists in better determining ESRD patients with underlying PH who will benefit from kidney transplantation. Additionally, most studies don't address the exact mPAP significantly affecting kidney transplantation outcomes, and they have different definitions for severe PH.

Moreover, there is a need for more studies on the management of PH in patients with CKD, as most studies on the treatment of PH exclude such patients, and the studies conducted on such patients have a small patient population. Preoperative and postoperative management of PH can significantly improve the outcomes of kidney transplantation and alleviate the vicious cycle that patients with PH and CKD are currently trapped in. CKD patients are at a higher risk for PH, and PH adversely affects patients with CKD and kidney transplantation outcomes.

Due to poor prognosis, patients with moderate to severe pulmonary hypertension are usually not good candidates for kidney transplantation. Although there is evidence that suggests increased pulmonary hypertension is linked to increased mortality and morbidity following kidney transplantation, it is also suggested that pulmonary hypertension may regress following kidney transplantation [24].

In conclusion, patients with pulmonary hypertension comprise a significant group of patients with CKD who are understudied and need much further research in different aspects of their management to improve their prognosis.

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Declaration of competing interest

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Abbreviation

Abbreviation	Original phrase
ESRD	End-Stage Renal Disease
PH	Pulmonary Hypertension
CKD	Chronic Kidney Disease
NT-proBNP, BNP	N-Terminal Prohormone of Brain Natriuretic Peptide, Brain Natriuretic Peptide
PAP, sPAP, mPAP	Pulmonary Arterial Pressure, systolic Pulmonary Arterial Pressure, mean Pulmonary Arterial Pressure
PAWP	Pulmonary Arterial Wedge Pressure
A-V	Arterio-venous
IpcPH	Isolated Postcapillary Pulmonary Hypertension
CpcPH	Combined Postcapillary and Precapillary Pulmonary Hypertension
FGF23	Fibroblast Growth Factor 23.
KDIGO	Kidney Disease Improving Global Outcomes
CAD	Coronary Artery Disease
6MWD	6-min walking distance
COPD	Chronic Obstructive Lung Disease
NYHA	New York Heart Association

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