

Review Article

End-stage renal disease and pulmonary hypertension: epidemiologic, pathophysiologic, and hemodynamic characteristics and related risk factors

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Abstract: Pulmonary hypertension (PH) in end-stage renal disease (ESRD) is classified as Group 5 PH, a category defined by unclear or multifactorial mechanisms. The condition affects a substantial proportion of ESRD patients and contributes significantly to cardiovascular mortality; moreover, PH may persist or even progress despite renal replacement therapy. Right heart catheterization (RHC) and transthoracic echocardiography (TTE) have characterized the hemodynamic profiles and cardiac structural changes in these patients, implicating anemia, volume overload, uremic toxins, hypoxia, left heart disease, and pulmonary vascular dysfunction as major drivers, with arteriovenous fistula (AVF) as a possible disease modifier in susceptible subpopulations. This review synthesizes findings from invasive hemodynamic studies to delineate the principal mechanisms underlying PH in ESRD. Particular emphasis is placed on the potential roles of AVF flow and dialysis-related factors - including membrane biocompatibility, microbubble embolization, and shear stress-induced microhemolysis - in driving disease progression, an area that remains inadequately understood.

Keywords: End-stage renal disease (ESRD), pulmonary hypertension (PH), right heart catheterization (RHC), hemodialysis (HD), arteriovenous fistula (AVF)

Overview of chronic kidney disease and end-stage renal disease

Chronic kidney disease (CKD) encompasses structural and functional kidney impairments of various etiologies (duration ≥ 3 months) or an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² [1]. A further decline in eGFR to below 15 mL/min/1.73 m² defines End-Stage Renal Disease (ESRD) [2]. Globally, CKD is highly prevalent, with incidence rates among adults in North America, Europe, Australia, and China ranging from 10% to 15%, and is an independent risk factor for cardiovascular disease (CVD). Globally, the number of CKD patients reached 697.5 million in 2017, with nearly one-third residing in China and India [3]. CKD ranked as the 12th leading cause of death globally. The primary cause of death in CKD patients is CVD, accounting for 34% of mortality. Additionally, the creation of an arteriovenous fistula (AVF) for hemodialysis (HD)

significantly increases mortality in this population [4]. Epidemiologic surveys indicate that in China, the total number of ESRD patients was 2.16 million in 2014, rose to 2.57 million in 2016, and reached 2.9 million by 2017. It is projected that by 2030, the number of ESRD patients in China will surpass 4 million. HD treatment has become a substantial economic burden for CKD patients in China.

Hemodynamic characteristics and classification of PH

Update on hemodynamic definition of PH

In August 2022, the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) jointly published the “2022 Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension”, updating the hemodynamic diagnostic criteria for PH to a mean pulmonary artery pressure (mPAP) > 20 mmHg

at rest [5]. Right heart catheterization (RHC) remains the gold standard for PH diagnosis. However, due to its invasive nature, transthoracic echocardiography (TTE) is commonly used in clinical practice. Although the diagnostic standards and methods differ between these two approaches, their results show high consistency.

Updates on PH classification

The 2022 ESC/ERS guidelines continue to classify PH into five groups based on similar pathophysiologic mechanisms, clinical presentations, hemodynamics, and management strategies. The terms “due to” in the names of groups 2, 3, and 4 have been replaced with “associated with”, reflecting the multifactorial nature of the underlying conditions rather than a single causative factor. This terminology better captures the coexistence of multiple pathological states in PH patients, aligning with clinical observations. PH related to ESRD still falls under Group 5.

Basic pathophysiology of pulmonary arterial hypertension (PAH)

Pulmonary arterial hypertension (PAH), classified as Group 1 PH, is a severe and progressive condition characterized by pathogenic remodeling of the distal pulmonary small arteries [6]. This process leads to a progressive increase in pulmonary vascular resistance (PVR) and ultimately causes right ventricular hypertrophy, failure, and death. In developed countries, the incidence and prevalence of PAH are approximately 6.0 and 48.0-55.0 cases per million adults, respectively. Despite advances in diagnosis and treatment, PAH remains incurable and has a high mortality, with idiopathic PAH (IPAH) accounting for about half of the cases. The clinical presentation is heterogeneous, and patient prognosis is largely determined by the adaptive capacity and function of the right ventricle.

The pathogenesis of PAH is multifactorial, encompassing vasoconstriction, vascular remodeling, and in situ thrombosis [7]. At the cellular level, PAH is characterized by excessive proliferation of pulmonary artery endothelial and smooth muscle cells, resistance to apoptosis, and inflammatory infiltration, all of which thick-

en small pulmonary vessels and raise PVR. The relative contributions of these pathways differ by etiology. In ESRD, uremic toxins, volume overload, and dialysis-related factors introduce distinct pathogenic drivers not fully captured by the classical PAH paradigm; these ESRD-specific mechanisms are discussed in Section 7.4.

Epidemiology of PH associated with ESRD

Yigla et al. first identified PH by ultrasound in HD patients with AVF and no cardiopulmonary disease, describing it as PH of an unknown mechanism [8]. Existing observational studies report a high prevalence of PH in ESRD, particularly in HD patients, and it is associated with poor outcomes. In a cross-sectional study of maintenance HD patients, TTE performed within one hour after dialysis showed that 38% had PH. Similarly, a meta-analysis revealed that PH occurred in 40% of HD patients and 19% of peritoneal dialysis patients. Pabst and colleagues reported that 71% of ESRD patients not yet on renal replacement therapy and 81% of those undergoing HD had RHC-confirmed PH [9]. Longer dialysis duration was associated with higher prevalence of PH: among patients with dialysis duration less than 1 year, 25% had PH; in those with 1-2 years, 38%; and in those with more than 2 years, 58%. A retrospective epidemiological study in China showed that the prevalence of PH in maintenance hemodialysis (MHD) patients was 37.5%. A recent systematic review and meta-analysis incorporating 50 observational studies and 17,558 CKD patients reported a pooled PH prevalence of 38% (95% CI: 33%-43%), with subtype-specific estimates of 39% (95% CI: 25%-54%) for predialysis ESKD, 42% (95% CI: 35%-50%) for ESKD on hemodialysis, and 26% (95% CI: 19%-34%) for renal transplant recipients [10]. Longer dialysis duration (RR: 1.70; 95% CI: 1.18-2.46; $P = 0.005$) and diastolic dysfunction (RR: 1.88; 95% CI: 1.38-2.55; $P < 0.001$) were significant risk factors for PH in this population. Collectively, these findings demonstrate that MHD patients have a consistently elevated PH prevalence across studies and diagnostic methods, supporting systematic screening in this population. Additionally, some studies suggest that the incidence of PH may vary depending on the modality of renal replacement therapy.

Symptoms and signs of PH related to ESRD

The signs and symptoms of PH in CKD patients are nonspecific and similar to those in PH patients without CKD [6]. As PH progresses, patients typically present with exertional dyspnea, exercise intolerance, and signs of volume overload, leading to right ventricular dysfunction and failure. In CKD patients, dyspnea and exercise intolerance often stem from ischemic heart disease (IHD), left ventricular (LV) dysfunction, or volume overload rather than PH itself. PH should be suspected if symptoms persist despite optimal management of IHD and volume overload, or if they are out of proportion to the severity of kidney disease and LV dysfunction. In dialysis patients, worsening dyspnea following AVF creation or intolerance to ultrafiltration should also raise suspicion for PH. As PH progresses to right ventricular failure, patients may develop signs of systemic venous congestion, including jugular venous distension, hepatomegaly, ascites, and peripheral edema. However, these manifestations overlap with uremia-related complications such as pericardial effusion and pleural effusion, necessitating careful differential diagnosis. TTE is essential for distinguishing PH from isolated fluid overload or uremic cardiomyopathy by assessing pulmonary artery pressures, right ventricular function, and pericardial status [11].

Hemodynamic characteristics and associated risks of PH in ESRD

Hemodynamic features of ESRD-related PH

In the Duke University RHC registry, the prevalence of PH was 73.4% among CKD patients versus 56.9% among non-CKD patients. Among CKD patients, isolated post-capillary pulmonary hypertension (Ipc-PH) and combined post- and pre-capillary pulmonary hypertension (Cpc-PH) were the most common subtypes; among non-CKD patients, Group 1 PAH predominated. A study of 1,873 CKD patients who underwent RHC reported a PH prevalence of 68%, predominantly Ipc-PH. Pabst et al. performed RHC in ESRD patients with unexplained dyspnea and found PH in 81% of HD patients before dialysis, all with Ipc-PH [9]. Thirteen percent were diagnosed with pre-capillary PH after HD, and 65% had Ipc-PH post- HD; PH resolved in one patient after HD. Among ESRD

patients not on HD, 71% had PH, indicating that HD treatment can improve factors contributing to Ipc-PH. In MHD patients, 13% had pre-capillary PH, which is not improved by HD and may even be promoted by the dialysis procedure itself.

In all CKD categories, patients with Cpc-PH have worse survival compared to other PH subtypes, likely due to higher mPAP and right atrial pressure, indicating more severe PH and right ventricular dysfunction. These findings highlight that some MHD patients have pre-capillary PH and more severe right ventricular impairment, warranting further attention.

All-cause mortality risk in ESRD-related PH

Recent retrospective studies report that the prevalence of PH in HD patients ranges from 20% to 41% [12]. PH is an independent predictor of all-cause and cardiovascular mortality in MHD patients. In a prospective analysis of 90 HD patients, those with PH had a 1-year mortality rate of 26%, compared to 6% in patients without PH. Similarly, another study by Agrawal found higher mortality in HD patients with PH compared to those without [13]. These findings demonstrate that the presence of PH in ESRD indicates a poor prognosis, similar to PH caused by other etiologies.

Mechanisms of ESRD-associated PH

Mechanism integration: from the systemic uremic milieu to pulmonary vascular disease

PH in ESRD is not simply the sum of isolated renal or cardiac abnormalities; rather, it reflects the convergence of systemic uremic derangements in the pulmonary vascular bed. Chronic kidney disease imposes a persistent pro-inflammatory and pro-oxidative environment, driven by the accumulation of uremic toxins and metabolic waste products [14]. This milieu induces endothelial dysfunction, common to various PH subtypes [6], and renders the pulmonary circulation susceptible to superimposed hemodynamic stressors. Among these, volume overload and left ventricular diastolic dysfunction, both highly prevalent in ESRD patients, elevate left atrial pressure and trigger post-capillary PH [9, 15]. In parallel, anemia and high-flow AVF augment cardiac output, imposing increased shear stress on pul-

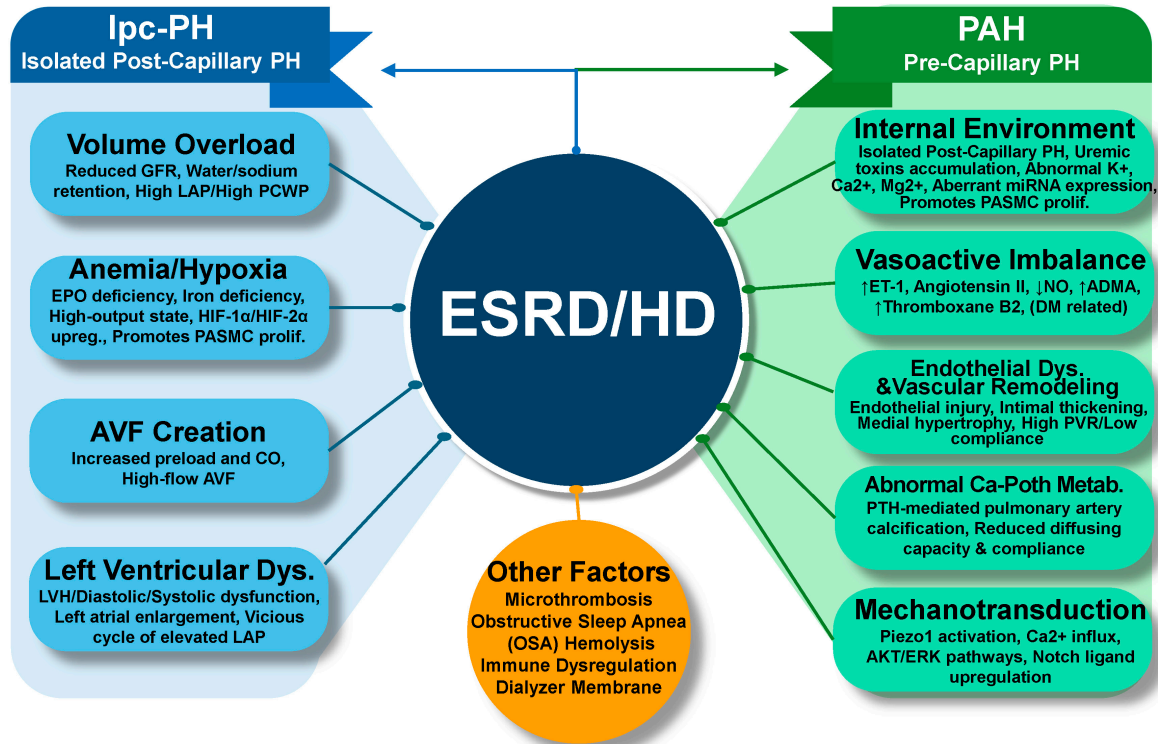


Figure 1. Pathophysiologic mechanisms of pulmonary hypertension in End-Stage Renal Disease (ESRD)/Pulmonary Hypertension (PH) patients. The schematic illustrates the multifactorial mechanisms underlying PH in ESRD/PH patients. Left (blue): Factors predominantly driving isolated post-capillary PH (lpc-PH), including volume overload, anemia/hypoxia, arteriovenous fistula (AVF) creation, and left ventricular dysfunction. Right (green): Factors predominantly driving pre-capillary PH, including internal environment disorders, vasoactive imbalance, endothelial dysfunction with vascular remodeling, abnormal calcium-phosphate metabolism, and Piezo1 activation. Bottom (amber): Additional contributing factors to pre-capillary PH, such as microthrombosis, obstructive sleep apnea (OSA), and hemolysis. The dashed arrow indicates the potential evolution from lpc-PH to pre-capillary PH. Abbreviations: ADMA, asymmetric dimethylarginine; AVF, Arteriovenous Fistula; DM, dialysis membrane; EPO, erythropoietin; ESRD, end-stage renal disease; ET-1, endothelin-1; GFR, glomerular filtration rate; HD, hemodialysis; lpc-PH, Isolated post-capillary PH; LAP, left atrial pressure; LVH, left ventricular hypertrophy; NO, nitric oxide; OSA, obstructive sleep apnea; PAH, pulmonary arterial hypertension; PASM C, pulmonary arterial smooth muscle cell; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PTH, parathyroid hormone; PVR, pulmonary vascular resistance.

monary arterioles [8, 16]. This mechanical load is transduced at the cellular level through mechanosensitive channels such as Piezo1, which, when activated, promotes PASM C proliferation and vascular remodeling [17, 18]. Over time, this combination drives the transition from predominantly passive, reversible lpc-PH to a phenotype with active pre-capillary remodeling. Thus, ESRD-associated PH is best understood as a systemic disease with pulmonary manifestations, a framework that informs both mechanistic understanding and therapeutic prioritization. The major pathophysiologic drivers of both post-capillary and pre-capillary phenotypes, as well as their interrelationship, are summarized schematically in **Figure 1**.

Mechanisms of lpc-PH

Volume overload

Patients with CKD are prone to volume overload, primarily due to reduced glomerular filtration rate (GFR) and a high prevalence of cardiomyopathy and ischemic heart disease (IHD) [15]. Approximately 75% of CKD patients exhibit left ventricular hypertrophy (LVH) when requiring renal replacement therapy. In addition to LVH and IHD, declining GFR can lead to diastolic dysfunction, increased left atrial volume (LAV), and a predisposition to volume overload. Pabst et al. found that mPAP decreased significantly after dialysis on both RHC and TTE, suggesting that acute pressure reductions reflect

fluid removal and volume optimization [9]. Yilmaz's bioelectrical impedance analysis of HD patients indicated that those with volume overload had significantly higher relative water load (OH/ECW), pre-dialysis blood pressure, and NT-BNP levels [19]. Han's study found that fluid balance parameters such as OH/ECW were markedly higher in CKD patients with PH compared to those without, and these parameters were positively correlated with tricuspid regurgitant maximum velocity [20]. Chronic volume overload is a cornerstone of lpc-PH pathogenesis: in the Duke registry, over 77% of CKD patients with PH had elevated pulmonary capillary wedge pressure (PCWP), and rigorous volume management forms the therapeutic foundation for this phenotype.

Anemia

Due to insufficient erythropoietin (EPO) production, anemia is very common in CKD and is recognized as a risk factor for high-output heart failure [21]. In a cross-sectional analysis of the NHANES dataset, Kovesdy et al. found that approximately 25% of patients with stage 3-5 CKD had anemia [22]. Increased cardiac output (CO) may also contribute to PH in CKD, primarily driven by anemia and AVF creation. Early studies confirmed that ESRD-related PH patients have lower iron and hemoglobin levels compared to those without PH. In HD patients, anemia is a major complication that may cause local and systemic hypoxia due to inadequate oxygen delivery. Lower hemoglobin levels can induce hypoxia, promoting proliferation of pulmonary arterial smooth muscle cells (PASMCs) [23]. Findings on erythropoietin-stimulating agents (ESAs) are conflicting [24]: some animal models suggest a protective effect against PH, while others report a positive correlation with PH. Chronic anemia causes hypoxia, which drives lpc-PH and also contributes to PAH pathogenesis via hypoxia-inducible factors (HIF)-mediated signaling. Hypoxia upregulates HIF-1 α and HIF-2 α , leading to increased expression of endothelin-1 (ET-1), VEGF, and FGF, which promote pulmonary artery endothelial cells (PAEC) and PASMC proliferation and pulmonary vascular wall thickening. Studies have shown that HIF-1 α and HIF-2 α are significantly upregulated in PAH patients, and selective HIF-2 α inhibitors can inhibit vascular remodeling and reverse PAH in various animal models [25].

Recent research indicates that under hypoxic conditions, HIF-1 α induces CD146 expression in pulmonary vascular smooth muscle cells, and CD146 promotes HIF-1 α transcription via the NF- κ B pathway [26]. In animal models, anti-CD146 antibodies alleviate hypoxia-induced pulmonary vascular remodeling in animal models. Anemia caused by decreased renal EPO production, combined with the iron deficiency seen in PAH and CKD, appears to be mainly regulated by elevated hepcidin levels, which inhibit intestinal iron transport and absorption. Therefore, iron deficiency may influence pulmonary vascular regulation downstream of HIF. Current KDIGO guidelines recommend maintaining hemoglobin levels between 10 and 11.5 g/dL in CKD patients [27]; however, the optimal target range specifically for PH risk mitigation remains undefined. Transfusion-dependent anemia, frequently observed in ESRD, may further exacerbate pulmonary vascular dysfunction through iron overload and alloimmunization-related inflammatory responses, though direct evidence linking transfusion burden to PH incidence is limited. The risk of PH appears greatest when hemoglobin falls below 10 g/dL, although dedicated prospective studies are lacking.

Effect of AVF creation: from primary determinant to disease modifier

The role of AVF creation in ESRD-related PH has been debated. Current evidence indicates that AVF is not an independent primary determinant of PH in the general ESRD population, but may act as a disease modifier that exacerbates pre-existing pulmonary vascular disease in susceptible subpopulations, particularly those with high-flow AVF or impaired cardiopulmonary reserve.

General evidence against AVF as a primary determinant of PH: AVF creation increases venous return and cardiac output through shunting of high-pressure arterial blood into the venous system [28]. Acute hemodynamic monitoring during AVF occlusion has shown that pressures in the pulmonary circulation and both ventricles, as well as cardiac output, all decline after AVF closure [29]. Although these observations suggest a direct contribution of AVF to PH, prospective studies have not consistently demonstrated an independent asso-

ciation between AVF flow and PH in the general HD population. Dagli et al. [30] and Unal et al. [31] reported no correlation between AVF blood flow and mPAP, and Unal et al. further found that the incidence of PH did not significantly increase after AVF formation. Similarly, Manzur-Pineda et al. observed that right ventricular systolic pressure decreased or stabilized after AVF creation, likely reflecting improved volume status [32]. Collectively, current evidence indicates that AVF creation *per se* is not an independent primary determinant of PH in unselected ESRD patients.

High-flow AVF as a “second hit” in susceptible subpopulations: High-flow AVF (conventionally defined as flow > 1,500-2,000 mL/min) located in the upper limbs can precipitate high-output heart failure and may be associated with an increased incidence of PH or right ventricular dysfunction in susceptible individuals. Sustained high flow imposes increased shear stress on the pulmonary endothelium, promoting vascular remodeling, while chronic volume overload from high-output states elevates left atrial pressure. In patients with critically compromised cardiopulmonary reserve, these changes can act as a “second hit” that unmasks or worsens pre-existing pulmonary vascular disease. Yigla et al. reported that increased blood flow after AVF formation was associated with elevated mPAP [8], and transplantation cohorts have shown that PH often regresses after AVF ligation or flow reduction [33, 34], supporting a causal contribution of high-flow AVF to PH in selected individuals.

Clinical implications: Individualized assessment of AVF flow and right ventricular function is therefore crucial, particularly in symptomatic patients or those with high-flow AVF. In patients with RHC-confirmed high-output states or progressive PH attributable to AVF, flow-reduction procedures (e.g., MILLER banding) or ligation should be considered. Ligation is most strongly supported in kidney transplant recipients, in whom the AVF no longer serves a functional role and ligation has been shown to produce sustained regression of left ventricular hypertrophy and reduction in cardiac output and atrial volumes [33, 34].

Left ventricular dysfunction

Normal pulmonary circulation is a high-volume, low-resistance system. LV dysfunction can ele-

vate LV pressure, impede pulmonary venous return, increase pulmonary venous pressure, and ultimately raise pulmonary arterial pressure. Therefore, left ventricular dysfunction is an early and important cause of PH [35]. Left ventricular systolic and diastolic dysfunction are very common in CKD patients. Primary diseases, anemia, and uremic toxin accumulation collectively alter cardiac structure and function in CKD, with an increasing burden of cardiovascular disease as CKD progresses. These changes manifest as left atrial enlargement, LVH, and impaired systolic and diastolic function.

In the pathogenesis of MHD-related PH, cardiac structural alterations may be a key pathological basis [36]. Cardiac abnormalities are common in MHD patients, with some patients exhibiting structural and functional changes even before reaching ESRD. An epidemiological study in Shanghai showed that 89.1% of MHD patients had cardiac structural abnormalities. Kim proposed that left atrial enlargement might be an early structural change in dialysis patients [37]. Agarwal's study found that, when grouped by presence or absence of PH, the PH group had significantly larger left atrial diameters; left atrial enlargement is a risk factor for PH in MHD patients [13]. Wan's analysis of 90 MHD patients showed that increased left atrial diameter was significantly associated with PH. Franczyk et al. indicated that increased LAV and early left ventricular filling velocity are independent predictors of PH in CKD patients [38]. These findings suggest that elevated left atrial pressure (LAP) is an important condition for increased pulmonary circulation pressure. When MHD patients experience decreased left ventricular diastolic function, increased preload, and reduced compliance, LAP remains elevated, leading to left atrial enlargement. The contractile and compliance functions of the left atrium also decline, creating a vicious cycle that results in persistent elevation of pulmonary pressures. Naveethan's research indicated that increased left ventricular filling pressures caused by LVH and reduced LVEF are key mechanisms in PH, but LVEF decline is not directly related to PH, possibly due to patients' previous medical history [39]. Some MHD patients already have left heart failure before dialysis. Diastolic dysfunction mainly relates to hypertension and isch-

emic heart disease, and with age, diastolic function continues to decline. These common comorbidities may underpin PH development.

In summary, early changes in the left atrium serve as early markers or contributors to PH development in MHD patients; timely management of factors elevating LAP can help control PH development. Changes in ventricular size and acute reductions in pulmonary load during HD may be caused by myocardial shock and non-myocardial mechanisms, while LV systolic function remains relatively stable.

From lpc-PH to pre-capillary PH: mechanisms, susceptibility, and reversibility

The mechanisms detailed in Section 7.2 predominantly explain the development of isolated post-capillary PH (lpc-PH) driven by elevated left atrial pressure. However, in a substantial subset of ESRD patients, the disease does not remain confined to the post-capillary compartment; the following section addresses the critical transition from a purely passive, volume-dependent state of lpc-PH to one with an active pre-capillary component, exploring its pathobiology, identifying susceptible individuals, and assessing the reversibility window.

Pathobiological sequence: Persistent LAP elevation induces alveolar-capillary stress failure, activates endothelial cells and alveolar macrophages, and promotes the release of endothelin-1, transforming growth factor- β , platelet-derived growth factor, and pro-inflammatory cytokines [40]. The downstream effect is intimal fibrosis, medial hypertrophy, and luminal narrowing of the normally non-muscularized distal pulmonary arterioles, which raise PVR independent of the post-capillary component and define the Cpc-PH phenotype [5].

Susceptible subpopulations: The transition is most frequently reported in patients with long dialysis vintage (> 2-5 years), recurrent volume overload, coexisting left ventricular diastolic dysfunction, high-flow AVF (> 1,500-2,000 mL/min), obstructive sleep apnea, or secondary hyperparathyroidism. These conditions superimpose a pre-capillary component on chronic post-capillary congestion.

Reversibility and therapeutic window: Early lpc-PH is volume-dependent and largely reversible:

a single HD session lowers mPAP by 5-15 mmHg in fluid-overloaded patients [9], and AVF ligation in high-flow states reduces pulmonary pressures in transplant recipients [33, 34]. Established structural remodeling, however, is only partially reversible. Pulmonary vascular calcification regresses after parathyroidectomy in uremic animals [41], and mPAP often decreases after successful kidney transplantation, although Cpc-PH persists in patients with prolonged pre-transplant PH. These data define a clinical window in which upstream intervention may still alter disease trajectory.

Strategies to interrupt progression: Bioimpedance spectroscopy (BIS)- or lung-ultrasound-guided volume control, individualized AVF flow assessment with ligation or flow reduction, optimization of dialysis modality, and treatment of left heart disease are the principal strategies to interrupt the transition. PAH-targeted pharmacotherapy is reserved for RHC-confirmed pre-capillary-dominant disease.

Mechanisms of pre-capillary PH in ESRD

While Section 7.2 detailed the mechanistic insight into lpc-PH, the majority of ESRDs develop a pre-capillary or combined phenotype. Here, we sought to address the distinct mechanisms directly affecting the pulmonary arterioles, which is largely independent of left heart filling pressures. Once the transition to a pre-capillary or combined phenotype has occurred, the disease is sustained and propagated by a distinct set of molecular and structural mechanisms that directly affect the pulmonary arterioles. These pre-capillary drivers, which are largely independent of left heart filling pressures, are discussed below. The prevalence of pre-capillary PH in ESRD is significantly higher than in the general population. RHC confirms that up to 10% of ESRD patients have a pre-capillary PH pattern. Current research suggests the following factors may contribute to pre-capillary PH in ESRD patients.

Internal environment disorders

In ESRD patients, PH may result from imbalances in blood urea nitrogen (BUN), creatinine (Cr), and other toxins (including large-molecule toxins) caused by renal failure [14]. Abnormal serum ion concentrations may also contribute to PH, as ions play various biological roles in

cell proliferation, migration, and differentiation. Potassium (K^+) and calcium (Ca^{2+}) ions are implicated in pulmonary vascular remodeling. Under hypoxic conditions, extracellular calcium influx into PASMCs directly affects their contractility, inducing pulmonary artery constriction. This process is related to abnormal miRNA expression under hypoxia, with 78 differentially expressed miRNAs identified in plasma from PAH patients [42]. Animal studies have shown that in PAH rats, miR-21 levels are down-regulated and miR-146a levels are upregulated. Under hypoxia, these miRNAs promote extracellular Ca^{2+} influx into PASMCs, regulate vasoconstrictor factors, and enhance PASMCM migration and proliferation, leading to pulmonary artery constriction. Additionally, miRNAs participate in regulating fibroblast proliferation, migration, and inflammatory cytokine secretion. Activation of DNA damage pathways causes persistent accumulation of repair defects, stimulating PASMCM proliferation and inhibiting apoptosis, ultimately resulting in pulmonary arterial adventitial remodeling and PH. Research on magnesium (Mg^{2+}) mainly focuses on its effects on cAMP response element-binding protein (CREB) in neurons. Mg^{2+} also influences cell proliferation and protein synthesis, but its role in cardiovascular disease remains unclear. Accumulation of uremic toxins such as indoxyl sulfate, homocysteine, and advanced oxidation protein products in CKD increases oxidative stress, promotes inflammatory mediator release, enhances monocyte chemotaxis, and damages endothelial cells. The HEMO study found no survival benefit with higher dialysis doses, suggesting that the contribution of uremic toxin clearance to PH outcomes remains difficult to quantify.

Vasoactive substance imbalance and pulmonary vascular endothelial dysfunction

Beyond cardiac and volume-related mechanisms, the pulmonary vasculature directly participates in the pathogenesis of pre-capillary PH in ESRD patients. Uremic physiology disrupts normal pulmonary vascular tone and structure primarily by altering the balance between vasodilators and vasoconstrictors, which sequentially leads to endothelial dysfunction and vascular remodeling.

Vasoactive substance imbalance: CKD and ESRD patients exhibit a profound imbalance in

vasoactive peptides [43]. Research indicates that these patients have increased levels of vasoconstrictors, such as endothelin-1 (ET-1) and angiotensin II, and decreased levels of endogenous vasodilators, notably nitric oxide (NO). HD patients tend to have lower vasodilator levels and higher concentrations of vasoconstrictors, including ET-1, thromboxane B2, and asymmetric dimethylarginine (ADMA).

ET-1 is a potent vasoconstrictor produced within the vascular bed, and its elevation is linked to CKD progression. Conversely, the NO pathway is severely impaired; ADMA, an endogenous inhibitor of NO synthesis, accumulates in CKD and is directly associated with impaired endothelial-dependent vasodilation and increased arterial stiffness [44]. However, the role of ADMA in ESRD-PH remains controversial, as some studies involving peritoneal dialysis (PD) patients found no independent correlation between ADMA levels and PH. Compared to pre-dialysis ESRD patients, HD patients have increased thromboxane levels, possibly due to neutrophil degranulation caused by the interaction of blood with dialysis membranes. Nakhoul et al. confirmed that impaired NO production is a hallmark in MHD patients, and the vascular system in ESRD patients also appears less sensitive to NO [45]. This persistent imbalance directly induces pulmonary artery vasoconstriction and elevates pulmonary vascular resistance (PVR).

Endothelial dysfunction and vascular remodeling: The chronic imbalance of vasoactive substances, combined with metabolic and hormonal disturbances in uremic patients, causes severe pulmonary vascular endothelial dysfunction. Experimental studies show that elevated left atrial pressure (LAP) damages the alveolar-capillary membrane; ongoing injury leads to persistent pulmonary edema, which further triggers vascular remodeling characterized by increased intimal thickness and medial hypertrophy [40]. Hormonal and metabolic disturbances reduce pulmonary vascular compliance, fostering an environment where endothelial-dependent vasodilation abnormalities develop [46].

Abnormal calcium-phosphate metabolism and vascular calcification: Vascular calcification is a key structural consequence of endothelial dysfunction in CKD. Calcium deposition in pulmo-

nary vessels is considered a significant contributor to PH in CKD, increasing PVR and reducing vascular compliance. Early physiologic studies in animals exposed to high levels of parathyroid hormone (PTH) demonstrated pulmonary artery calcification, decreased diffusing capacity, and reduced pulmonary vascular compliance, with reversal after parathyroidectomy [41]. However, this seminal observation predates the era of modern CKD-MBD management and must be interpreted with caution. Human evidence remains conflicting and largely observational: while some studies report elevated PTH levels in CKD patients with PH, others find no significant association after adjustment for confounders such as phosphate load, calcium-phosphate product, and FGF23. Whether currently available MBD therapies, including calcimimetics, non-calcium-based phosphate binders, and active vitamin D analogs, can modify pulmonary vascular calcification or PH progression remains an open question requiring dedicated investigation.

Mechanotransduction and smooth muscle proliferation (Piezo1 Activation): As vascular remodeling progresses and vascular compliance decreases, the pulmonary vasculature experiences altered mechanical stress. The entire pulmonary artery wall can sense these mechanical stimuli: pulmonary artery endothelial cells (PAECs) respond to shear stress, and pulmonary arterial smooth muscle cells (PASMCs) respond to pressure changes. The mechanosensitive receptor Piezo1 plays a crucial role in this context. In patients with idiopathic PAH and experimental PAH models, Piezo1 expression is significantly upregulated. In PASMCs, Piezo1 induces contraction and proliferation through extracellular calcium influx and intracellular calcium release [17]. Further studies show that in PAECs, Piezo1 activates calcium-dependent AKT and ERK pathways, leading to the upregulation of Notch ligands (Jag-1/2 and DLL4) [18]. These ligands can activate receptors on PASMCs, causing pulmonary artery constriction, medial hypertrophy, and obliterative intimal lesions. This mechanotransduction pathway serves as a critical bridge linking the hemodynamic stress of ESRD to the structural progression of pre-capillary PH.

Microthrombosis

Microbubbles originating from hemodialysis circuits or dialyzers are considered another

potential mechanism for thromboembolism [47]. Although this has not been extensively studied, microbubbles can often occlude capillaries, leading to vascular inflammation and PH. Other theories explaining PH in ESRD patients include recurrent thromboembolic disease associated with vascular access thrombectomy, which may be related to subclinical pulmonary embolism and increased PVR. In a controlled study, patients who underwent AVF thrombectomy showed increased mPAP compared to ESRD controls without thrombectomy, although this difference was not statistically significant [48].

Obstructive sleep apnea (OSA)

Sleep-disordered breathing is highly prevalent in CKD patients, with a prevalence of up to 57% in ESRD patients, and the prevalence increases as glomerular filtration rate (GFR) declines [49]. There is a bidirectional relationship between CKD and OSA: OSA exacerbates fluid overload in ESRD, which in turn worsens OSA. During supine sleep, increased nocturnal venous volume in the neck may worsen OSA severity, especially in patients with volume-overloaded states such as chronic heart failure, ESRD, and resistant hypertension. In HD patients, changes in nocturnal rostral fluid shift are also associated with apnea-hypopnea index (AHI) and neck circumference. Fluid overload in ESRD patients establishes a vicious cycle between OSA and volume overload.

Research by Roumelioti et al. highlighted the importance of maintaining dry weight in managing OSA in ESRD. Ogna et al. monitored nocturnal fluid shifts before and after HD, finding that nocturnal fluid transfer to the neck correlated positively with volume overload, and HD significantly reduced the AHI. Other studies suggest that ultrafiltration can reduce the severity of AHI in HD patients. The impact of dialysis modality on volume status and OSA severity varies. Maintaining dry weight in MHD patients may be important for alleviating OSA. Although routine ultrafiltration during HD can reduce pulmonary congestion, it cannot eliminate it entirely, and thus OSA is not fully resolved with HD alone.

Compared to conventional thrice-weekly HD, nocturnal hemodialysis (NHD) appears more effective in alleviating OSA. The benefits of

NHD may stem from reversing pharyngeal narrowing and reducing chemoreflex sensitivity.

Factors independent of volume overload may also contribute to OSA in dialysis patients, as active fluid removal does not always correct OSA, especially in obese individuals. Carbon dioxide diffusion into the dialysate, coupled with hypoventilation and hypoxemia during HD, may also affect upper airway patency. Changes in chemical stimuli, such as hypoxia or hypercapnia, can alter vascular tone and adversely affect upper airway patency.

Dialysis-related factors

Beyond the systemic uremic milieu and hemodynamic perturbations, the dialysis procedure itself may contribute to PH pathogenesis through several mechanisms.

Biocompatibility of dialyzer membranes: The use of cellulose-based (bioincompatible) membranes has been associated with complement activation, neutrophil degranulation, and increased release of thromboxane B_2 , a pro-inflammatory and vasoconstrictive molecule that is also elevated in PAH patients; one study further compared changes in systolic pulmonary artery pressure (sPAP) before and after using cellulose-based versus biocompatible polysulfone high-flux dialyzers [50]. In some HD patients, elevated thromboxane B_2 appears to be related to increased monocyte release when cellulose-based membranes are used [50]. Whether this inflammatory cascade translates directly to pulmonary vascular injury remains to be established, but it represents a plausible pathway by which the dialysis procedure per se may contribute to endothelial dysfunction and PH.

Microbubble formation and microembolization: Microbubbles originating from the dialyzer or air traps in the extracorporeal circuit can occlude pulmonary capillaries, induce local inflammation and potentially contribute to PH [47]. Although systematic data in ESRD patients are lacking, microembolization from vascular access thrombectomy procedures has been associated with increased mPAP in some reports [48].

Extracorporeal shear stress and microhemolysis: The mechanical pumping of blood through

the dialysis circuit exposes erythrocytes to supraphysiological shear forces. In vitro studies have established that shear stress exceeding 560 Pa can induce hemolysis within a very short time [51]. Whether pump-induced microhemolysis during routine HD generates sufficient cell-free hemoglobin to scavenge nitric oxide and promote pulmonary vasoconstriction remains hypothesis-generating and awaits direct clinical confirmation. The downstream vascular consequences of such hemolysis are discussed in Section 7.4.6.

Intermittent volume and osmotic shifts: Conventional thrice-weekly HD imposes cyclical volume and osmotic fluctuations, with rapid ultrafiltration during sessions and progressive interdialytic fluid accumulation. This intermittent pattern may impose repeated episodes of myocardial stunning and transient elevation of pulmonary arterial pressure, although direct evidence linking these cyclical changes to persistent PH is limited.

Dialysate composition: The diffusion of CO_2 into the dialysate, coupled with hypoventilation during dialysis, may alter arterial blood gases and pulmonary vascular tone [49]. Acetate-containing dialysates have also been implicated in vasodilation and hypotension, though their specific effects on pulmonary circulation remain unclear.

Collectively, these dialysis-related factors suggest that the HD procedure is not a passive bystander but may actively contribute to pulmonary vascular pathology, particularly in patients with long dialysis vintage. Further research is needed to delineate the relative contribution of each mechanism.

Hemolysis and cell-free hemoglobin-mediated vascular injury

While Section 7.4.5 identified pump-induced microhemolysis during dialysis as a potential mechanical trigger, this section focuses on the established molecular mechanisms through which cell-free hemoglobin (CFH) drives pulmonary vascular pathology, irrespective of the source of hemolysis.

Hemolysis refers to the rupture of red blood cells and the release of hemoglobin [51]. While cell-free hemoglobin has been implicated in

endothelial dysfunction and vasoconstriction in conditions such as PAH and sickle cell disease [52, 53], its role in ESRD-associated PH remains speculative. Pump-induced microhemolysis during routine hemodialysis is currently a hypothesis-generating mechanism, with no direct clinical evidence linking it to incident or worsening PH in ESRD patients. Hemolysis in mechanical circulatory support devices (such as extracorporeal membrane oxygenation, ECMO) is also a concern. When shear stress in the blood flow is extremely high, hemolysis can occur instantaneously. Shear stress thresholds in circulatory support devices must be limited to prevent hemolysis. Under low-shear, high-frequency conditions, red blood cells undergo a fatigue process involving echinocyte-to-spherocyte transformation, suggesting a combined mechanical-biochemical mechanism of hemolysis. The cyclic mechanical forces influence the rate of ATP release and generation, leading to deformation and damage of the cell membrane and cytoskeleton connections. Brittain et al. found the presence of circulatory free hemoglobin (CFH) in the blood of PAH patients. When hemoglobin is released from red blood cells, it acts as a potent oxidant and vasoconstrictor, and is associated with poor clinical outcomes. Elevated CFH levels are observed in patients with sickle cell anemia, sepsis, and patients after transfusion. In all these patient groups, CFH is linked to adverse prognosis, including acute kidney injury, myocardial infarction, and death. The mechanisms underlying this association include CFH's damaging effects on vascular endothelium, as well as inducing oxidative injury and increased NO clearance, both of which can lead to vasoconstriction. Conger and colleagues discovered that hemoglobin can increase leukocyte adhesion and activate pulmonary microvascular endothelium via Toll-like receptor 4 [52]. Meegan et al. found that in PAH patients, the clearance mechanism for CFH is impaired, leading to vascular dysfunction characteristic of PAH [53]. During HD, mechanical pump squeezing of blood may also cause microhemolysis; for example, stresses exceeding 560 Pa can induce hemolysis in a very short time. Whether dialysis pump-induced microhemolysis contributes to PH development in ESRD patients requires direct measurement studies of plasma free hemoglobin and pulmonary hemodynamics.

Immune dysregulation

A substantial body of evidence suggests that uremia is associated with chronic inflammation [54]. Studies have shown that increased pro-inflammatory monocytes, proliferation of mast cells, abnormal T lymphocyte function, and reduced T regulatory cells lead to immune dysfunction [55]. The elevation of circulating inflammatory mediators also contributes to oxidative stress, which in turn causes endothelial dysfunction.

Other factors

Some studies suggest that fibroblast growth factor 23 (FGF23), which reflects the severity of renal dysfunction, may directly influence pulmonary vascular remodeling [56, 57]. However, direct mechanistic evidence linking FGF23 to pulmonary vascular remodeling in ESRD is currently limited.

Clinical management and therapeutic strategies

Currently, there are no randomized controlled trials or specific guidelines tailored to the management of PH in ESRD patients. The therapeutic approach remains largely empirical and requires a stepwise, phenotype-directed strategy (**Figure 3**), focusing on identifying hemodynamic phenotypes, correcting reversible risk factors, and cautious consideration of PAH-targeted therapies.

Screening and diagnostic confirmation

Given the high prevalence and insidious onset of PH in ESRD, early detection is essential. Transthoracic echocardiography (TTE) is the recommended first-line screening tool. However, to minimize false positives caused by volume overload, TTE should ideally be performed when the patient is close to his or her estimated dry weight, typically within 1-2 hours post-dialysis [58]. Right heart catheterization (RHC) remains the gold standard for confirming the diagnosis and is strongly recommended in the following scenarios: (1) to differentiate lpc-PH from Cpc-PH, pre-capillary PH, or non-specific PH, as this distinction fundamentally alters the therapeutic approach; (2) when planning for kidney transplantation, as severe uncorrected PH is associated with high perioperative mor-

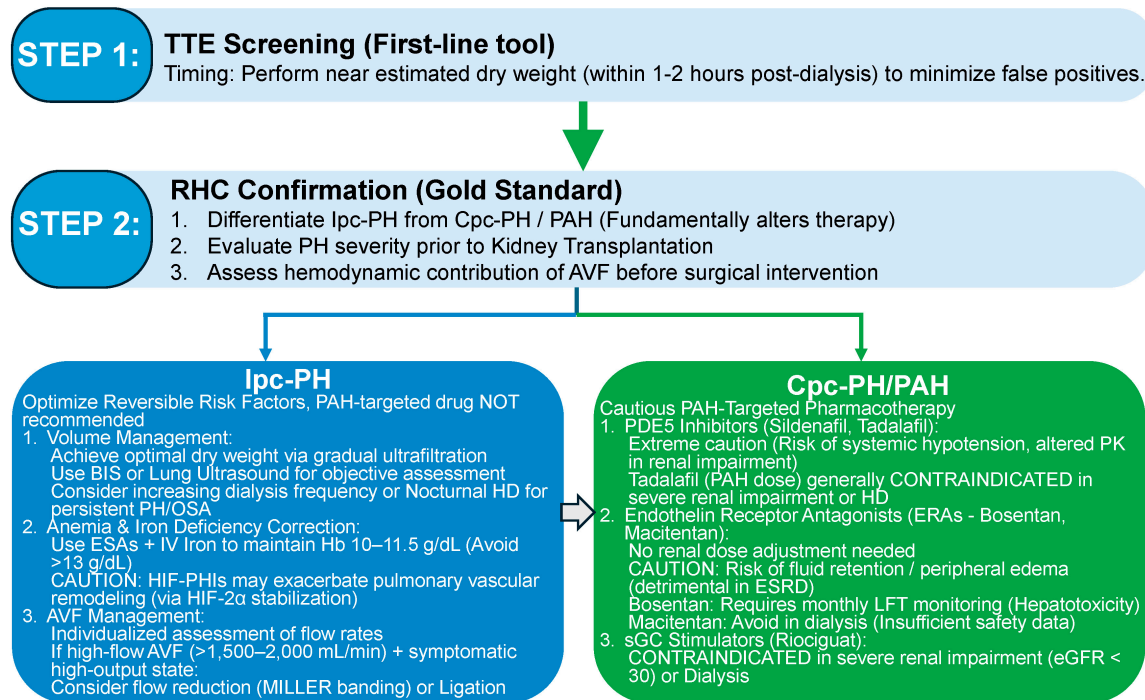


Figure 2. Clinical screening and diagnostic workflow for pulmonary hypertension in patients with ESRD. This algorithm outlines the initial screening pathway using transthoracic echocardiography (TTE) performed near dry weight (1-2 hours post-dialysis) to minimize false positives, defines the indications for confirmatory right heart catheterization (RHC), and provides the primary therapeutic branches (optimization of reversible risk factors versus cautious consideration of PAH-targeted therapy). This workflow serves as a practical roadmap for clinicians at the point of care. Abbreviations: AVF, arteriovenous fistula; BIS, bioimpedance spectroscopy; Cpc-PH, combined post- and pre-capillary pulmonary hypertension; eGFR, estimated glomerular filtration rate; ERAs, endothelin receptor antagonists; ESAs, erythropoietin-stimulating agents; ESRD, end-stage renal disease; Hb, hemoglobin; HD, hemodialysis; HIF-PHIs, HIF-prolyl hydroxylase inhibitors; lpc-PH, isolated post-capillary PH; IV, intravenous; LFT, liver function test; OSA, obstructive sleep apnea; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; PH, pulmonary hypertension; PK, pharmacokinetics; RHC, right heart catheterization; sGC, soluble guanylate cyclase; TTE, transthoracic echocardiography.

tality; and (3) when evaluating the hemodynamic contribution of an AVF prior to potential surgical intervention. A structured clinical screening workflow incorporating TTE indications, optimal timing, and RHC referral criteria is presented in **Figure 2**.

Optimization of reversible risk factors

The cornerstone of managing ESRD-associated PH is the optimization of modifiable risk factors, particularly those driving lpc-PH.

Volume management and dialysis prescription

Chronic volume overload is the primary driver of elevated left atrial pressure and lpc-PH. Achieving and maintaining optimal dry weight through gradual ultrafiltration is critical. Using BIS or lung ultrasound to objectively assess

volume status has been shown significantly associated with elevated pulmonary artery pressure [19, 36]. A 2023 study employing bioimpedance spectroscopy in 198 hemodialysis patients demonstrated that overhydration (OH/ECW $\geq 7\%$) was significantly associated with PH (OR: 2.89; 95% CI: 1.53-5.46; $P = 0.001$), and fluid overload was an independent risk factor for elevated pulmonary artery pressure [36]. For patients with persistent PH despite conventional dialysis, increasing dialysis frequency or nocturnal hemodialysis (NHD) should be considered. NHD provides more sustained fluid removal and can alleviate PH-associated complications, such as obstructive sleep apnea, and reduce pulmonary artery pressure more effectively than conventional thrice-weekly HD. Emerging data suggest that intensive ultrafiltration can reverse echocar-

End-stage renal disease and pulmonary HTN

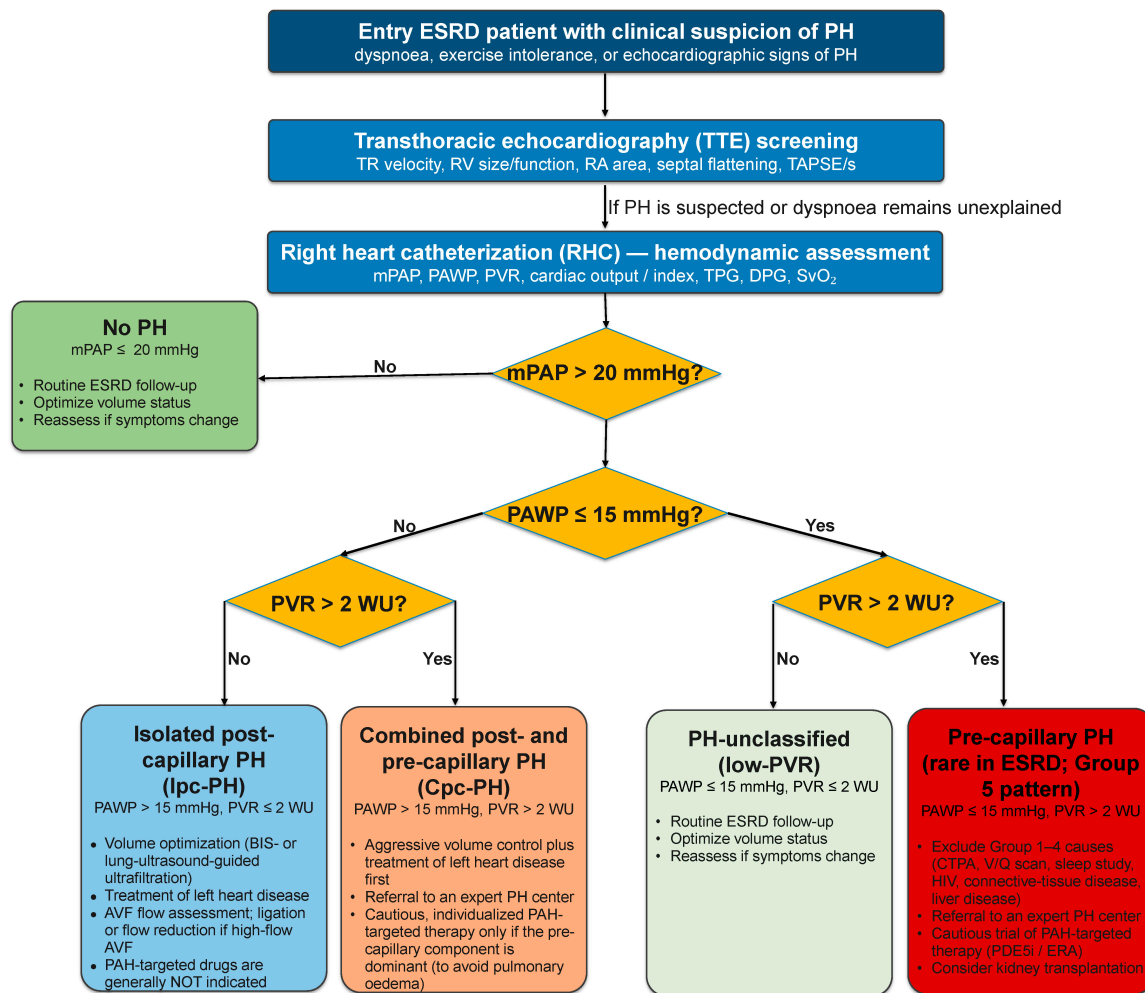


Figure 3. Hemodynamic phenotyping and phenotype-directed management algorithm based on right heart catheterization. This detailed decision flowchart stratifies patients into specific hemodynamic subtypes (no PH, isolated post-capillary PH [lpc-PH], combined post- and pre-capillary PH [Cpc-PH], pre-capillary PH, and non-specific PH) using the 2022 ESC/ERS hemodynamic thresholds (mPAP > 20 mmHg, PAWP > 15 mmHg, PVR > 2 WU). For each phenotype, it provides precise, guideline-adherent therapeutic recommendations, with PAH-targeted drugs strictly reserved for pre-capillary-dominant disease. This algorithm is intended for use after diagnostic confirmation by RHC. Abbreviations: AVF, arteriovenous fistula; BIS, bioimpedance spectroscopy; Cpc-PH, combined post- and pre-capillary PH; CTPA, computed tomography pulmonary angiography; DPG, diastolic pulmonary gradient; ERA, endothelin receptor antagonist; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; lpc-PH, isolated post-capillary PH; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PDE5i, phosphodiesterase type 5 inhibitor; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrium; RHC, right heart catheterization; RV, right ventricle; SvO₂, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; TR, tricuspid regurgitation; TTE, transthoracic echocardiography; V/Q scan, ventilation/perfusion scan.

diography-diagnosed PH and restore kidney transplant candidacy in patients previously deemed ineligible due to elevated pulmonary pressures [59].

Anemia and iron deficiency correction

Anemia induces a high-output state and tissue hypoxia, both of which contribute to PH [22]. Management should adhere to current KDIGO

guidelines, utilizing erythropoiesis-stimulating agents (ESAs) and intravenous iron to maintain hemoglobin levels between 10 and 11.5 g/dL [27]. Overcorrection (Hb > 13 g/dL) should be avoided due to increased blood viscosity and thrombotic risk.

Iron deficiency is prevalent in both CKD and PAH and may influence pulmonary vascular regulation independent of erythropoiesis. In-

travenous iron supplementation may attenuate hypoxia-inducible factor (HIF) signaling in pulmonary vascular smooth muscle cells.

The advent of HIF-prolyl hydroxylase inhibitors (HIF-PHIs) introduces a novel paradigm. While Phase 3 trials have demonstrated the efficacy of daprodustat and roxadustat in maintaining hemoglobin, theoretical concerns have been raised regarding their use in PH patients, given that HIF-2 α (but not HIF-1 α) activation plays a central role in pulmonary vascular remodeling and PAH pathogenesis [60]. HIF-PHIs stabilize both HIF- α isoforms; whether this translates to clinically relevant pulmonary vascular effects in ESRD patients remains unknown. To date, no clinical study has demonstrated that roxadustat, daprodustat, or other HIF-PHIs increase the incidence or worsen the severity of PH in patients with ESRD. This concern therefore remains hypothetical at present. Until dedicated safety studies with hemodynamic endpoints are available, individualized decision-making is advised, and where feasible, baseline and periodic echocardiographic assessment of pulmonary pressures may be considered in ESRD patients receiving HIF-PHIs, particularly in those with established pre-capillary PH.

Arteriovenous fistula management

In selected patients with RHC-confirmed high-flow AVF (> 1,500-2,000 mL/min) and hemodynamically significant PH, AVF flow reduction or ligation should be considered as a disease-modifying intervention [61]. This applies particularly to kidney transplant recipients, in whom the AVF is no longer required for vascular access and in whom ligation has been shown to prevent *de novo* high-output heart failure and to produce sustained regression of left ventricular hypertrophy [33, 34]. For maintenance HD patients who require AVF preservation for dialysis access, flow-reduction procedures (e.g., MILLER banding) represent intermediate options, although data on pulmonary hemodynamic outcomes remain sparse [62]. Ligation or flow reduction is not a routine measure in all AVF carriers and should be reserved for individuals with confirmed hemodynamic contribution of the AVF to PH.

PAH-targeted pharmacotherapy: indications and cautions

Once RHC has confirmed the diagnosis, the phenotype-directed algorithm in **Figure 3** strati-

fies patients by mPAP, PAWP, and PVR thresholds. This algorithm guides phenotype-specific management and strictly contraindicates PAH drugs in pure lpc-PH. The use of PAH-specific therapies in ESRD-related PH remains controversial and should be reserved for highly selected patients. Current guidelines do not endorse PAH-targeted drugs for Group 5 PH driven by left heart disease (lpc-PH), as vasodilation can precipitate pulmonary edema - an absolute red line in this setting [5]. For patients with lpc-PH, PAH-targeted therapy is generally not recommended. However, in patients with confirmed pre-capillary hemodynamics by RHC (elevated mPAP > 20 mmHg, normal PCWP $\leq$ 15 mmHg, and elevated PVR > 2 Wood units), indicative of Cpc-PH or pre-capillary PH, individualized use of PAH-targeted therapy may be considered [63].

The key pharmacokinetic properties, renal dose adjustments, dialyzability, and safety considerations for each PAH-targeted drug class in the ESRD population are summarized in **Table 1**.

PDE5 Inhibitors: Sildenafil and tadalafil should be used with extreme caution due to the risk of systemic hypotension and altered pharmacokinetics in renal impairment. Tadalafil (at PAH doses) is generally contraindicated in severe renal impairment or patients on hemodialysis due to limited safety data and increased drug exposure.

Endothelin Receptor Antagonists (ERAs): While ERAs do not require renal dose adjustment, they carry a risk of fluid retention and peripheral edema, which is particularly detrimental in ESRD patients prone to volume overload. Bosentan also carries hepatotoxicity risk requiring monthly monitoring. Macitentan is often avoided in dialysis patients due to insufficient safety data.

Soluble Guanylate Cyclase (sGC) Stimulators: The standard dose of 1 mg TID is recommended for patients with CrCl $\geq$ 30 mL/min, a starting dose of 0.5 mg TID for CrCl 15-29 mL/min. Riociguat is contraindicated in patients with CrCl < 15 mL/min or those on dialysis.

Future perspectives

Significant knowledge gaps persist in the management of ESRD-PH. The evolution from lpc-

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Table 1. PAH-targeted drugs in ESRD: renal considerations, dialyzability, and safety

Drug class	Agent	Standard PAH dose	Renal dose adjustment	Protein binding	Dialyzability/post-dialysis supplement	ESRD/HD considerations
PDE5 inhibitors	Sildenafil	20 mg TID	No dose adjustment required, including severe impairment (CrCl < 30 mL/min)	~96%	Not dialyzable; no post-dialysis supplement required	Use with caution for hypotension
	Tadalafil (PAH dose)	40 mg once daily	Mild-moderate: start 20 mg daily; severe (CrCl < 30 mL/min) and HD: avoid use	~94%	Not significantly dialyzable	Avoid in severe renal impairment and HD patients due to increased AUC and limited experience
Endothelin receptor antagonists sGC stimulator	Bosentan	62.5 mg BID → 125 mg BID	No dose adjustment required in renal impairment or dialysis	> 98%	Not dialyzable; no post-dialysis supplement required	Requires monthly liver function monitoring; fluid retention risk
	Macitentan	10 mg once daily	No dose adjustment required; severe renal impairment: use with caution	≥ 99%	Dialysis unlikely to be effective	Not recommended in dialysis patients; monitor for hypotension and anaemia
	Riociguat	1 mg TID, titrate to max 2.5 mg TID	CrCl ≥ 30 mL/min: 1 mg TID; CrCl 15-29 mL/min: 0.5 mg TID, titrate cautiously; CrCl < 15 mL/min or dialysis: not recommended	~95%	Not expected to be dialyzable	Contraindicated in severe renal impairment (CrCl < 15 mL/min) and dialysis; higher hypotension risk

Abbreviations: AUC, area under the curve; BID, twice daily; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ERAs, endothelin receptor antagonists; ESRD, end-stage renal disease; HD, hemodialysis; IV, intravenous; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; SC, subcutaneous; sGC, soluble guanylate cyclase; TID, three times daily.

PH to Cpc-PH or pre-capillary PH remains poorly characterized, and longitudinal RHC studies are needed to identify therapeutic windows. Randomized trials comparing AVF flow reduction strategies in maintenance HD patients are lacking. The safety and efficacy of HIF-PHs and combination PAH-targeted therapy in ESRD populations with confirmed pre-capillary disease require dedicated prospective evaluation with robust hemodynamic endpoints. While AVF ligation has been shown to improve cardiac structure and pulmonary pressures in kidney transplant recipients [33, 34], systematic RHC-based data on the trajectory of PH after transplantation remain limited. Contemporary studies comparing pulmonary artery pressure before and after kidney transplantation have reported improvements in mean pulmonary artery pressure and ejection fraction at one year post-transplant [34], yet the proportion of patients in whom PH completely resolves, persists, or progresses-particularly under the updated mPAP > 20 mmHg threshold-remains to be defined. Prospective RHC-based studies with longitudinal follow-up are needed to identify predictors of irreversible pulmonary vascular disease and to define the optimal timing of transplantation in patients with advanced PH.

Summary

The proportion of ESRD patients and HD patients with concomitant pre-capillary PH is higher than in other disease groups. PH often predates HD initiation, and prevalence increases as renal function declines. At the pre-dialysis stage, PH is closely associated with hypertension, diabetes, and other comorbidities, as well as with volume overload, uremic anemia, uremic hypertension, metabolic disturbances, and endocrine changes resulting from GFR decline. While HD can partially improve PH, it does not prevent progression in some patients, even after kidney transplantation. This suggests that HD or AVF creation may harbor inherent mechanisms that promote PH, warranting further investigation. Therefore, a stepwise management strategy is needed, focusing on optimizing volume status, correcting anemia, and carefully evaluating AVF hemodynamics, while PAH-targeted therapies should be reserved for highly selected patients with confirmed pre-capillary hemodynamics.

Disclosure of conflict of interest

None.

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