Pulmonary Hypertension Subtypes and Mortality in CKD

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Rationale & Objective: Pulmonary hypertension (PH) contributes to cardiovascular disease and mortality in patients with chronic kidney disease (CKD), but the pathophysiology is mostly unknown. This study sought to estimate the prevalence and consequences of PH subtypes in the setting of CKD.

Study Design: Observational retrospective cohort study.

Setting & Participants: We examined 12,618 patients with a right heart catheterization in the Duke Databank for Cardiovascular Disease from January 1, 2000, to December 31, 2014.

Exposures: Baseline kidney function stratified by CKD glomerular filtration rate category and PH subtype.

Outcomes: All-cause mortality.

Analytical Approach: Multivariable Cox proportional hazards analysis.

Results: In this cohort, 73.4% of patients with CKD had PH, compared with 56.9% of patients without CKD. Isolated postcapillary PH (39.0%) and combined pre- and postcapillary PH (38.3%) were the most common PH subtypes in CKD. Conversely, precapillary PH was the most common subtype in the non-CKD cohort (35.9%). The relationships between mean pulmonary artery pressure, pulmonary capillary wedge pressure, and right atrial pressure with mortality were similar in both the CKD and non-CKD cohorts. Compared with those without PH, precapillary PH conferred the highest mortality risk among patients without CKD (HR, 2.27; 95% CI, 2.00-2.57). By contrast, in those with CKD, combined pre- and postcapillary PH was associated with the highest risk for mortality in CKD in adjusted analyses (compared with no PH, HRs of 1.89 [95% CI, 1.57-2.28], 1.87 [95% CI, 1.52-2.31], 2.13 [95% CI, 1.52-2.97], and 1.63 [95% CI, 1.12-2.36] for glomerular filtration rate categories G3a, G3b, G4, and G5/G5D).

Limitations: The cohort referred for right heart catheterization may not be generalizable to the general population. Serum creatinine data in the 6 months preceding catheterization may not reflect true baseline CKD. Observational design precludes assumptions of causality.

Conclusions: In patients with CKD referred for right heart catheterization, PH is common and associated with poor survival. Combined pre- and postcapillary PH was common and portended the worst survival for patients with CKD

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Pulmonary hypertension (PH) affects 21% to 41% of patients with chronic kidney disease (CKD) and up to 60% of patients with kidney failure receiving hemodialysis.[1-6] Despite the high prevalence and increased mortality conferred by PH,[7] no targeted treatments exist for PH in patients with CKD. While most studies of PH in this population rely on transthoracic echocardiography to diagnose and quantify the severity of PH, invasive characterization of PH subtypes using the gold standard, right heart catheterization, can provide more detailed insight into potential underlying mechanisms of PH.

PH is defined as mean pulmonary artery pressure ≥ 25 mm Hg on right heart catheterization at rest.[8] PH is hemodynamically characterized by estimates of left ventricular filling pressures, using pulmonary capillary wedge pressure, and pulmonary arterial pressures, using pulmonary diastolic pressure gradient or pulmonary vascular resistance. Using these measures, PH can be further stratified into the following subtypes: precapillary PH, isolated postcapillary PH, and combined pre- and postcapillary PH (Fig 1). Precapillary PH or pulmonary arterial hypertension, which can be idiopathic or secondary to collagen vascular disease, infection (eg, human immunodeficiency virus), or portal hypertension, is characterized by normal pulmonary capillary wedge pressure (≤15 mm Hg).[8,9] Isolated postcapillary PH, typically caused by heart failure and valvular disease,[10] is defined as elevated pulmonary capillary wedge pressure (>15 mm Hg) with normal pulmonary vascular resistance (diastolic pressure gradient <7 mm Hg and pulmonary vascular resistance ≤3 Wood units).[8] Combined pre- and postcapillary PH occurs when pulmonary capillary wedge pressure and pulmonary vascular resistance (diastolic pressure gradient ≥ 7 mm Hg or pulmonary vascular resistance > 3 Wood units) are elevated.[8]

Our understanding of how CKD affects PH subtypes is limited due to the methods by which PH was characterized in prior studies, which either did not report PH subtypes or relied on only pulmonary capillary wedge pressure without incorporating estimates of pulmonary vascular resistance.[2,11,12] Among patients with CKD with PH, the combined pre- and postcapillary PH subtype (elevated pulmonary capillary wedge pressure with increased pulmonary vascular resistance) may be a substantial contributor to the overall PH burden in CKD due to a combination of: (1) chronic volume overload, (2) pulmonary vascular

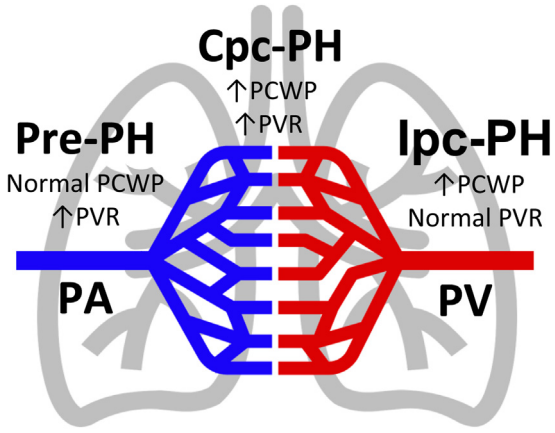


Figure 1. Schematic of pulmonary hypertension (PH) subtypes. Abbreviations: Cpc-PH, combined pre- and postcapillary pulmonary hypertension; Ipc-PH, isolated postcapillary pulmonary hypertension; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; pre-PH, precapillary pulmonary hypertension; PV, pulmonary vein; PVR, pulmonary vascular resistance.

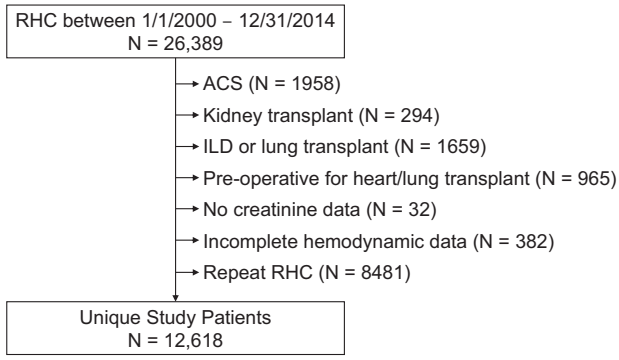


Figure 2. Flow diagram of exclusions and study participants. Abbreviations: ACS, acute coronary syndrome; ILD, interstitial lung disease; RHC, right heart catheterization.

remodeling due to increases in vasoactive factors (ie, nitric oxide, prostacyclin, and endothelin, among others), (3) inflammation, and (4) comorbid lung disease (eg, obstructive sleep apnea and chronic obstructive pulmonary disease) that are commonly associated with CKD.[13] Understanding the prevalence and pathophysiology of combined pre- and postcapillary PH in CKD may illuminate a subpopulation at significant risk for mortality, similar to patients with heart failure with combined pre- and postcapillary PH,[14,15] and identify novel therapies.[16]

We investigated the prevalence of different PH subtypes and their association with all-cause mortality stratified by CKD severity using 15 years of right heart catheterization data from the Duke Databank for Cardiovascular Disease (DDCD). We hypothesized that combined pre- and postcapillary PH would be the most common PH subtype and portend the highest risk for mortality in patients with CKD.

Methods

Study Population

The DDCD, which includes diagnostic catheterizations for more than 100,000 patients, has been described in detail previously.[17] Briefly, baseline demographic information, medical history, active medications, and laboratory data are obtained at the time of the diagnostic catheterization. Patients with a left heart catheterization are followed up longitudinally with questionnaires dispensed at 6 months, 12 months, and then annually. Telephone interviews are attempted for those failing to respond to surveys.

We examined the DDCD for all right heart catheterizations performed at Duke University Hospital from January 1, 2000, to December 31, 2014 (Fig 2). We excluded patients younger than 18 years at the time of catheterization. Because the DDCD data were collected within the context of clinical care, patients may have been referred for left heart catheterization or other procedures at the time of right heart catheterization. We excluded patients with a diagnosis of acute coronary syndrome within 7 days of the right heart catheterization per *International Classification of Diseases, Ninth Revision* codes. We excluded kidney transplant recipients from this analysis because we could not account for their differential accumulation of cardiovascular risk due to variable durations of kidney failure before transplantation, which we could not ascertain. Interstitial lung disease has a stronger association with PH than CKD. Thus, we specifically excluded patients with this diagnosis. We also excluded patients with a lung or heart transplant to similarly avoid catheterizations performed at the extremes of cardiopulmonary pathophysiology. Patients without a serum creatinine (Scr) measurement in the 6 months before right heart catheterization or with insufficient hemodynamic data to define PH subtype were also excluded. To limit the influence of right heart catheterizations obtained to monitor responses to PH treatment (eg, vasodilator therapy), we included only the first right heart catheterization for each patient after application of other exclusion criteria.

The Duke Institutional Review Board approved this study. Due to the retrospective nature of this study, individual-level informed consent was waived.

CKD Definition

We used the median of Scr data in the 6 months preceding the right heart catheterization to calculate estimated glomerular filtration rate (eGFR) using the CKD Epidemiology Collaboration (CKD-EPI) equation. We did not have sufficient proteinuria data to include it as a metric for CKD classification. Using the KDIGO GFR (G) categories, we separated patients into baseline categories: CKD G3a (eGFR, 45-49 mL/min/1.73 m^2), G3b (30-44 mL/min/1.73 m^2), G4 (15-29 mL/min/1.73 m^2), and G5/G5D (<15 mL/min/1.73 m^2 or on hemodialysis).[18] Due to

small sample sizes relative to other CKD GFR categories and their similar prevalences of PH and similar rates of specific PH subtypes, we combined patients with CKD G5 with patients receiving dialysis (CKD G5D) for the purposes of this analysis. We classified patients with eGFRs ≥ 60 mL/min/1.73 m^2 as not having CKD for the purposes of this study.

PH Subtypes

Consistent with the European Society of Cardiology/European Respiratory Society 2015 guidelines, we defined PH as mean pulmonary artery pressure ≥ 25 mm Hg at rest.[19] We then separated PH into subtypes based on pulmonary capillary wedge pressure, diastolic pulmonary gradient, and pulmonary vascular resistance. Precapillary PH was defined as PH with normal pulmonary capillary wedge pressure (≤15 mm Hg). Isolated postcapillary PH was defined as PH with elevated pulmonary capillary wedge pressure (>15 mm Hg) and normal pulmonary vascular resistance (≤3 Wood units and diastolic pressure gradient < 7 mm Hg). Combined pre- and postcapillary PH was defined as PH with elevated pulmonary capillary wedge pressure (>15 mm Hg) and abnormal pulmonary vascular resistance (>3 Wood units or diastolic pressure gradient ≥ 7 mm Hg).

Covariates

We obtained covariates from the standard data that are entered in the DDCD at the time of right heart catheterization and supplemented it with additional data from querying Duke's electronic health record using Duke Enterprise Data Unified Content Explorer (DEDUCE).[20] Covariates include age, sex, race, body mass index, medical history (diabetes mellitus, heart failure, hypertension, cirrhosis, systemic lupus erythematosus, scleroderma, obstructive sleep apnea, chronic obstructive pulmonary disease, moderate/severe aortic valve disease, moderate/severe mitral value disease, human immunodeficiency virus infection, and smoking), left ventricular ejection fraction, and hemoglobin level. If left ventricular ejection fraction, valvular data, or hemoglobin level was not present at the time of the catheterization, these data were obtained from a transthoracic echocardiogram that was closest to the time of the right heart catheterization within 6 months.

Outcome

The primary outcome of this analysis was all-cause mortality. We ascertained death events using the DDCD longitudinal follow-up protocol and supplemented these data with a query of the National Death Index.

Statistical Analysis

We used descriptive statistics to report baseline demographic and clinical characteristics of the study population according to the presence or absence of CKD and stratified by PH subtype. We report count with percentage for categorical covariates and median with interquartile range for continuous covariates. We generated Kaplan-Meier survival curves for each of the 4 PH subtype strata (no PH, precapillary PH, isolated postcapillary PH, and combined pre- and postcapillary PH) separately for patients with and without CKD. We tested for statistical differences between survival curves of the different PH subtypes using log-rank test.

To investigate multivariable-adjusted associations of each PH subtype with all-cause mortality, we first evaluated the interaction term between PH subtype and CKD GFR category. Using the non-PH group as the referent, we used Cox proportional hazards modeling to generate hazard ratios (HRs) with 95% confidence intervals (95% CIs) for all-cause mortality for the different PH subtypes stratified by CKD GFR category. We then performed analyses adjusted for the listed covariates.

Using Cox proportional hazards regression, we also evaluated the association of right heart catheterization parameters (mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, and mean right atrial pressure) with mortality stratified by the presence or absence of CKD. Based on the nonlinear relationship between these hemodynamic parameters with mortality, we evaluated associations with mean pulmonary artery pressure and right atrial pressure using 2 linear splines with a single knot at mean pulmonary artery pressure of 55 mm Hg and right atrial pressure of 5 mm Hg. To address the violation of the linearity assumption for the mean pulmonary capillary wedge pressure, we analyzed the relationship between pulmonary capillary wedge pressure and mortality using categories (10-30 and >30 vs <10 mm Hg). We present multivariable-adjusted associations between hemodynamic parameters and risk for mortality graphically.

Results

Study Population

We evaluated 12,618 patients with a qualifying right heart catheterization. Baseline characteristics for patients with and without CKD stratified by PH subtype are listed in Tables 1 and 2. The average age for patients with CKD was 69 years compared to 57 years in patients without CKD. Although patients without PH tended to be older in the CKD cohort, age did not differ among PH subtypes. Within the CKD G5/G5D group, 70.5% were receiving dialysis. Regardless of CKD status, PH disproportionately affected African American patients, and African Americans represented the highest proportion of patients with the combined pre- and postcapillary PH subtype (31.7% of patients with combined pre- and postcapillary PH and CKD, 33.9% of patients with combined pre- and postcapillary PH but no CKD). Compared with other PH subtypes, precapillary PH predominantly affected women in both the CKD and non-CKD cohorts (59.7% of

Table 1. Baseline Patient Characteristics Stratified by PH Subtype for Patients With Chronic Kidney Disease

Variable	No PH (n = 1,268)	PH			Total (N = 4,772)
		Precapillary (n = 794)	Isolated postcapillary (n = 1,367)	Combined[a] (n = 1,343)	
Demographics					
Age, y	71.0 [62.0-78.0]	68.0 [60.0-76.0]	68.0 [59.0-75.0]	68.0 [59.0-76.0]	69.0 [60.0-76.0]
Race					
White	983 (79.1%)	528 (68.0%)	1,000 (74.3%)	869 (65.6%)	3,380 (72.1%)
African American	220 (17.7%)	217 (27.9%)	319 (23.7%)	420 (31.7%)	1,176 (25.1%)
Native American	19 (1.5%)	8 (1.0%)	11 (0.8%)	11 (0.8%)	49 (1.0%)
Other	20 (1.6%)	24 (3.1%)	15 (1.1%)	24 (1.8%)	83 (1.8%)
Male sex	705 (55.6%)	320 (40.3%)	813 (59.5%)	630 (46.9%)	2,468 (51.7%)
Vitals and Medical History					
BMI, kg/m^2	27.0 [23.8-31.4]	27.9 [24.1-33.1]	29.5 [25.3-35.3]	28.2 [24.3-33.7]	28.1 [24.4-33.2]
Smoking	436 (34.4%)	259 (32.6%)	451 (33.0%)	418 (31.1%)	1,564 (32.8%)
COPD	60 (4.7%)	64 (8.1%)	87 (6.4%)	72 (5.4%)	283 (5.9%)
PVD	97 (7.6%)	55 (6.9%)	114 (8.3%)	119 (8.9%)	385 (8.1%)
CVD	154 (12.1%)	72 (9.1%)	162 (11.9%)	191 (14.2%)	579 (12.1%)
Cirrhosis	26 (2.1%)	17 (2.1%)	35 (2.6%)	18 (1.3%)	96 (2.0%)
HF	824 (65.0%)	529 (66.6%)	1,173 (85.8%)	1,167 (86.9%)	3,693 (77.4%)
DM	328 (25.9%)	222 (28.0%)	537 (39.3%)	555 (41.3%)	1,642 (34.4%)
HIV infection	7 (0.6%)	4 (0.5%)	10 (0.7%)	10 (0.7%)	31 (0.6%)
HTN	871 (68.7%)	493 (62.1%)	948 (69.3%)	943 (70.2%)	3,255 (68.2%)
HLD	645 (50.9%)	320 (40.3%)	677 (49.5%)	636 (47.4%)	2,278 (47.7%)
SLE	16 (1.3%)	20 (2.5%)	12 (0.9%)	11 (0.8%)	59 (1.2%)
Scleroderma	13 (1.0%)	30 (3.8%)	3 (0.2%)	5 (0.4%)	51 (1.1%)
Laboratory Data					
Scr, mg/dL	1.4 [1.2-1.7]	1.4 [1.2-1.8]	1.6 [1.3-2.2]	1.6 [1.3-2.0]	1.5 [1.3-1.9]
eGFR, mL/min/1.73 m^2	46.9 [36.2-54.0]	45.8 [34.2-53.8]	41.8 [29.1-51.7]	41.7 [30.1-50.8]	43.6 [32.1-52.6]
Hemoglobin, g/dL	12.2 [10.9-13.7]	12.1 [10.8-13.7]	11.2 [9.7-12.8]	11.5 [10.1-13.1]	11.7 [10.3-13.3]
CAD	482 (38.0%)	189 (23.8%)	420 (30.7%)	371 (27.6%)	1,462 (30.6%)
Imaging and Hemodynamic Data					
Valvular heart disease	191 (15.1%)	91 (11.5%)	228 (16.7%)	237 (17.6%)	747 (15.7%)
AV disease[b]	113 (8.9%)	46 (5.8%)	113 (8.3%)	112 (8.3%)	384 (8.0%)
MV disease[b]	5 (0.4%)	6 (0.8%)	58 (4.2%)	72 (5.4%)	141 (3.0%)
LVEF, %	58.8 [42.0-66.4]	58.9 [43.1-67.2]	53.4 [36.2-63.0]	53.3 [35.0-64.6]	55.5 [38.5-65.2]
mPAP, mm Hg	20.0 [17.0-22.0]	32.0 [27.0-43.0]	33.0 [29.0-38.0]	42.0 [37.0-48.0]	32.0 [24.0-41.0]
PCWP, mm Hg	10.0 [8.0-13.0]	12.0 [10.0-14.0]	23.0 [20.0-27.0]	23.0 [20.0-27.0]	18.0 [12.0-24.0]
RA pressure, mm Hg	5.0 [3.0-7.0]	8.0 [6.0-12.0]	12.0 [9.0-17.0]	14.0 [10.0-19.0]	10.0 [6.0-15.0]

Note: Covariates presented as count (percentage) or median [interquartile range].

Abbreviations: AV, aortic valve; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HIV, human immunodeficiency virus; HLD, hyperlipidemia; HTN, hypertension; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; MV, mitral valve; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVD, peripheral vascular disease; RA, right atrium; Scr, serum creatinine; SLE, systemic lupus erythematosus.

[a]Combined pre- and postcapillary.

[b]Moderate or severe valvular disease.

precapillary PH in CKD, 60.7% of precapillary PH in patients without CKD). Chronic obstructive pulmonary disease and scleroderma were overrepresented in the precapillary PH subtype, whereas heart failure and diabetes mellitus dominated the PH subtypes with elevated pulmonary capillary wedge pressure (isolated postcapillary PH and combined pre- and postcapillary PH). Within the CKD cohort, GFR tended to be worse in the isolated postcapillary PH and combined pre- and postcapillary PH subtypes. Valvular heart disease tended to be more prevalent and left ventricular ejection fraction lower in the isolated postcapillary PH and combined pre- and postcapillary PH subtypes. Mean pulmonary artery pressure and mean right atrial pressures were also higher for the isolated postcapillary PH and combined pre- and postcapillary PH subtypes.

Table 2. Baseline Patient Characteristics Stratified by PH Subtype for Patients Without Chronic Kidney Disease

Variable	No PH (n = 3,381)	PH			Total (N = 7,846)
		Precapillary (n = 1,604)	Isolated postcapillary (n = 1,516)	Combined[a] (n = 1,345)	
Demographics					
Age, y	56.0 [45.0-66.0]	56.0 [46.0-66.0]	58.0 [47.0-67.0]	57.0 [48.0-67.0]	57.0 [46.0-67.0]
Race					
White	2,588 (78.8%)	966 (62.4%)	1,028 (69.4%)	815 (61.9%)	5,397 (70.7%)
African American	543 (16.5%)	490 (31.7%)	393 (26.5%)	447 (33.9%)	1,873 (24.5%)
Native American	34 (1.0%)	15 (1.0%)	19 (1.3%)	14 (1.1%)	82 (1.1%)
Other	121 (3.7%)	76 (4.9%)	41 (2.8%)	41 (3.1%)	279 (3.7%)
Male sex	1,842 (54.5%)	631 (39.3%)	900 (59.4%)	625 (46.5%)	3,998 (51.0%)
Vitals and Medical History					
BMI, kg/m^2	26.8 [23.5-31.1]	27.7 [23.4-32.9]	29.8 [25.3-35.5]	28.7 [24.5-34.5]	27.8 [23.9-32.8]
Smoking	1,037 (30.7%)	536 (33.4%)	527 (34.8%)	435 (32.3%)	2,535 (32.3%)
COPD	207 (6.1%)	209 (13.0%)	94 (6.2%)	94 (7.0%)	604 (7.7%)
PVD	79 (2.3%)	40 (2.5%)	41 (2.7%)	55 (4.1%)	215 (2.7%)
CVD	236 (7.0%)	76 (4.7%)	119 (7.8%)	97 (7.2%)	528 (6.7%)
Cirrhosis	49 (1.4%)	19 (1.2%)	31 (2.0%)	12 (0.9%)	111 (1.4%)
HF	1,526 (45.1%)	791 (49.3%)	1,124 (74.1%)	1,082 (80.4%)	4,523 (57.6%)
DM	455 (13.5%)	284 (17.7%)	360 (23.7%)	323 (24.0%)	1,422 (18.1%)
HIV infection	10 (0.3%)	7 (0.4%)	8 (0.5%)	5 (0.4%)	30 (0.4%)
HTN	1,522 (45.0%)	694 (43.3%)	845 (55.7%)	733 (54.5%)	3,794 (48.4%)
HLD	1,122 (33.2%)	395 (24.6%)	555 (36.6%)	459 (34.1%)	2,531 (32.3%)
SLE	36 (1.1%)	34 (2.1%)	12 (0.8%)	13 (1.0%)	95 (1.2%)
Scleroderma	44 (1.3%)	60 (3.7%)	2 (0.1%)	8 (0.6%)	114 (1.5%)
Laboratory Data					
Scr	0.9 [0.8-1.0]	0.9 [0.8-1.0]	1.0 [0.8-1.1]	0.9 [0.8-1.1]	0.9 [0.8-1.1]
eGFR, mL/min/ 1.73 m^2	84.1 [72.7-97.4]	86.3 [71.9-100.1]	80.8 [70.0-93.8]	78.7 [68.6-92.5]	82.9 [71.1-96.6]
Hemoglobin	13.5 [12.3-14.6]	13.2 [11.9-14.5]	12.9 [11.5-14.1]	12.8 [11.3-14.0]	13.2 [11.9-14.4]
CAD	702 (20.8%)	241 (15.0%)	418 (27.6%)	301 (22.4%)	1,662 (21.2%)
Imaging and Hemodynamic Data					
Valvular heart disease	615 (18.2%)	126 (7.9%)	341 (22.5%)	289 (21.5%)	1,371 (17.5%)
AV disease[b]	332 (9.8%)	48 (3.0%)	152 (10.0%)	99 (7.4%)	631 (8.0%)
MV disease[b]	37 (1.1%)	13 (0.8%)	117 (7.7%)	145 (10.8%)	312 (4.0%)
LVEF	59.4 [48.5-66.4]	60.3 [48.6-67.7]	55.6 [34.4-65.4]	54.4 [32.5-63.8]	58.1 [43.4-66.1]
mPAP	19.0 [16.0-22.0]	32.0 [27.0-45.0]	32.0 [28.0-36.0]	42.0 [36.0-50.0]	26.0 [20.0-37.0]
PCWP	10.0 [7.0-12.0]	11.0 [8.0-13.0]	22.0 [18.0-26.0]	23.0 [19.0-28.0]	13.0 [9.0-20.0]
RA mean	5.0 [3.0-7.0]	8.0 [5.0-10.0]	11.0 [8.0-15.0]	13.0 [9.0-17.0]	8.0 [5.0-12.0]

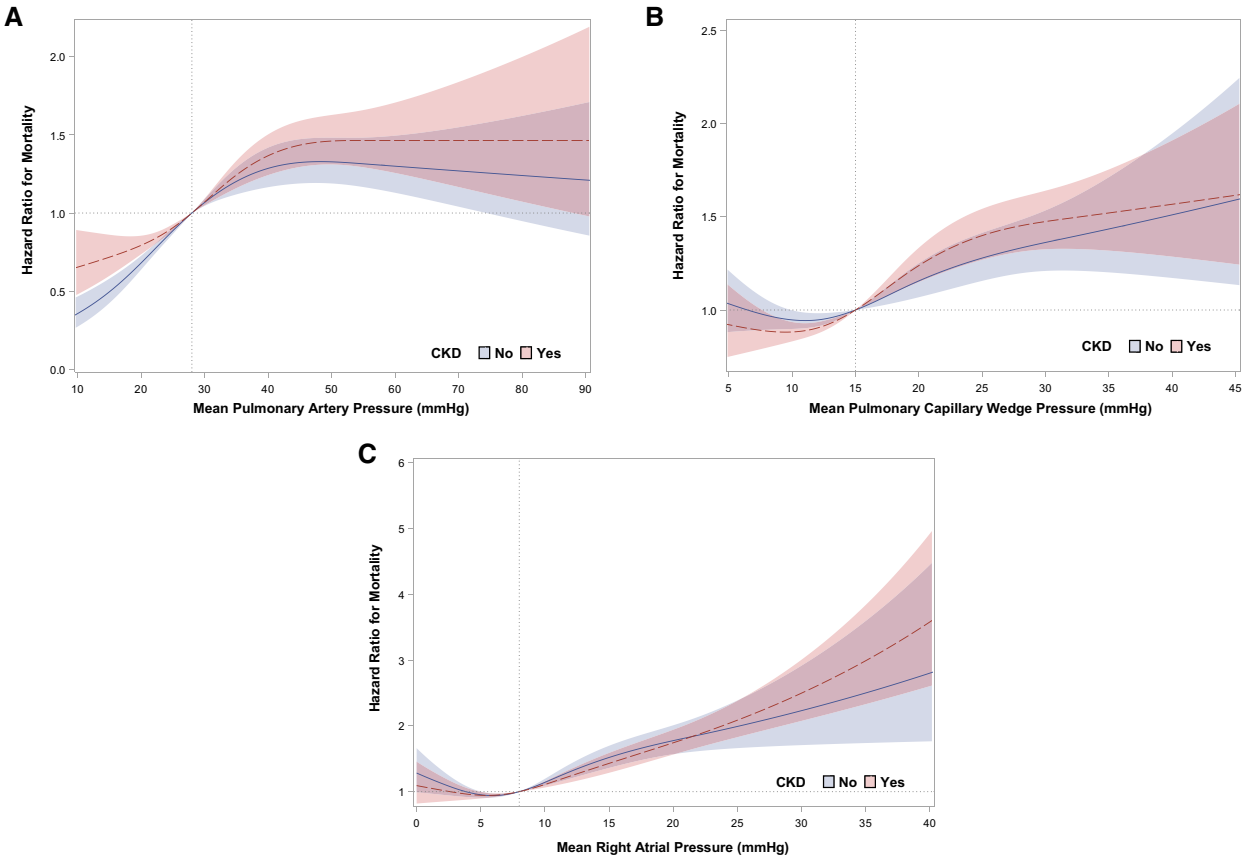
Note: Covariates presented as count (percentage) or median [interquartile range].
Abbreviations: AV, aortic valve; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HIV, human immunodeficiency virus; HLD, hyperlipidemia; HTN, hypertension; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; MV, mitral valve; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVD, peripheral vascular disease; RA, right atrium; Scr, serum creatinine; SLE, systemic lupus erythematosus.
[a]Combined pre- and postcapillary.
[b]Moderate or severe valvular disease.

Hemodynamic Data and Mortality

The association of right heart catheterization hemodynamic parameters with mortality is shown in Figure 3. Relative to the median value of each parameter, mortality increased above mean pulmonary artery pressure of 28 mm Hg (Fig 3A), mean pulmonary capillary wedge pressure of 15 mm Hg (Fig 3B), and mean atrial pressure of ~7 mm Hg (Fig 3C) in patients with and without CKD. In adjusted analyses, the presence versus absence of CKD did not modify any of the relationships between hemodynamic parameters and mortality.

PH Subtype Distribution

The prevalence of PH in patients with CKD was 73.4% compared with 56.9% in patients without CKD at the time of right heart catheterization. In all patients with CKD, isolated postcapillary PH (39.0%) and combined pre- and postcapillary PH (38.3%) were the most common PH



Figures 3. Association between mortality risk and mean (A) pulmonary artery pressure, (B) pulmonary capillary wedge pressure, and (C) right atrial pressure. Hazard ratio with 95% confidence interval is relative to the median value of the parameter. Abbreviation: CKD, chronic kidney disease.

subtypes. In patients without CKD, precapillary PH was the most prevalent PH subtype (35.9%). Figure 4 depicts PH subtype distribution stratified across all CKD GFR categories. Both PH subtypes with elevated pulmonary capillary wedge pressure (isolated postcapillary and combined pre- and postcapillary PH) were the most common subtypes of PH at every CKD GFR category examined. Right ventricular size and function derived from the echocardiogram are presented in Tables 3 and 4. For both the CKD and non-CKD cohorts, right ventricular enlargement was most common in the precapillary PH subgroup. Impaired right ventricular function was most common in the precapillary and combined pre- and postcapillary PH subtypes.

PH Subtypes and Mortality

Kaplan-Meier survival curves for each PH subtype for patients with and without CKD are depicted in Figure 5A and B, respectively. Among patients with CKD, the combined pre- and postcapillary PH subtype had the poorest survival, whereas in patients without CKD, precapillary PH had the worst survival. The association of PH subtype with mortality was modified by the presence or absence of CKD (P for interaction < 0.001), but CKD severity did not modify the association within those with CKD (P for interaction $= 0.3$).

Unadjusted and adjusted HRs for all-cause mortality for each PH subtype stratified by CKD stage are reported in Table 5. Among patients without CKD and compared with no PH as the reference group, precapillary PH had the highest HR for mortality in unadjusted and adjusted (HR, 2.27; 95% CI, 2.00-2.57) analyses. Both isolated postcapillary PH and combined pre- and postcapillary PH also had significantly greater mortality.

Within each CKD GFR category, combined pre- and postcapillary PH conferred the highest HR of mortality compared with no PH as the reference group. For the CKD G5/G5D cohort, only the combined pre- and postcapillary PH subtype had higher risk for mortality compared with the no PH group (HR, 1.63; 95% CI, 1.12-2.36).

Discussion

PH is a common but often underrecognized driver of morbidity and mortality in patients with CKD.[2,7] We demonstrate high rates of PH in a cohort of patients with

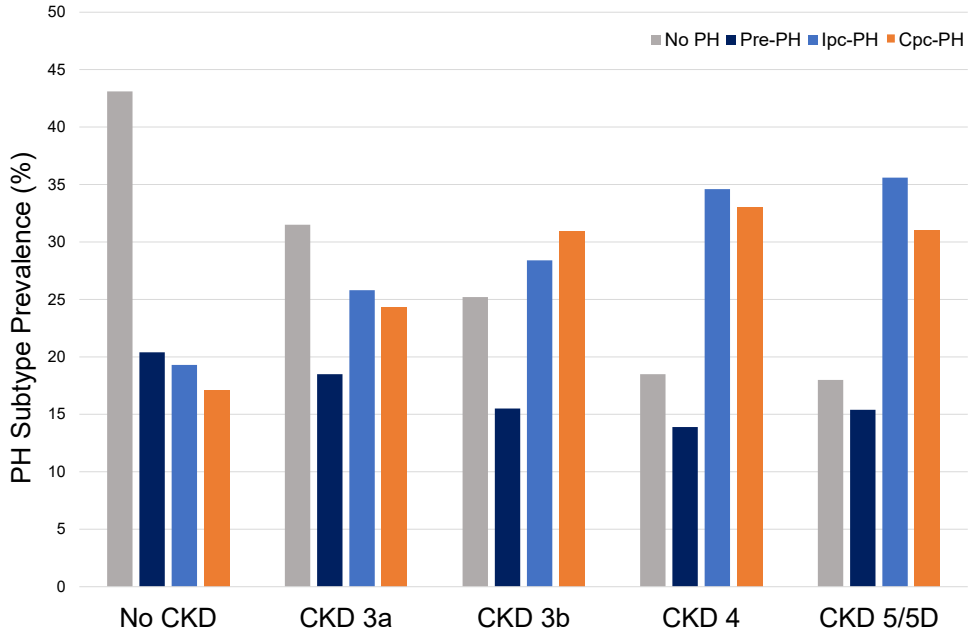


Figure 4. Pulmonary hypertension (PH) subtype prevalence stratified by chronic kidney disease (CKD) severity. Abbreviations: Cpc-PH, combined pre- and postcapillary pulmonary hypertension; Ipc-PH, isolated postcapillary pulmonary hypertension; pre-PH, precapillary pulmonary hypertension.

CKD referred for right heart catheterization. Both PH subtype and related mortality are strongly affected by the presence or absence of CKD. For patients without CKD, precapillary PH was the predominant subtype and was associated with the highest risk for mortality. In contrast, combined pre- and postcapillary PH and isolated postcapillary PH accounted for the majority of PH subtypes in CKD. However, patients with combined pre- and postcapillary PH consistently had the highest mortality risk across all CKD GFR categories.

The high rates of PH demonstrated in our study align with other CKD cohorts referred for right heart catheterization.[12] In addition, the prevalence of precapillary PH in our cohort is nearly identical to that seen in the only other large-scale analysis of right heart catheterization data in patients with CKD.[12] Unlike prior studies, separation of the postcapillary PH into isolated postcapillary PH and combined pre- and postcapillary PH allowed for demonstration of a survival difference between PH subtypes in patients with CKD. The poor survival of the combined pre- and postcapillary PH cohort aligns with studies of PH subtypes in patients with heart failure.[14,15]

The reduced survival of combined pre- and postcapillary PH compared with other PH subtypes across all CKD GFR categories is a major finding of our study. Multiple factors may contribute to this phenomenon. Patients with both combined pre- and postcapillary PH had higher mean pulmonary artery and right atrial pressures compared with most other groups, which suggests more severe PH and right ventricular dysfunction. These findings

Table 3. Indexes of Right Ventricular Function in Patients With CKD

Variable	No PH (n = 1,268)	PH			Total (N = 4,772)
		Precapillary (n = 794)	Isolated postcapillary (n = 1,367)	Combined[a] (n = 1,343)	
RV size					
Normal	83.0%	48.6%	66.1%	54.2%	63.8%
Small	0.8%	0%	0.2%	0.1%	0.3%
Enlarged	16.2%	51.4%	33.7%	45.7%	35.9%
RV function[b]					
Normal	85.2%	52.0%	65.5%	51.1%	63.8%
Hypercontractile	0%	0%	0%	0.1%	0%
Impaired	14.8%	48.0%	34.5%	48.8%	36.2%

Abbreviations: CKD, chronic kidney disease; PH, pulmonary hypertension; RV, right ventricle.
[a]Combined pre- and postcapillary.
[b]Right ventricular function assessed qualitatively.

Table 4. Indexes of Right Ventricular Function in Patients Without CKD

Variable	No PH (n = 3,381)	PH			Total (N = 7,846)
		Precapillary (n = 1,604)	Isolated postcapillary (n = 1,516)	Combined[a] (n = 1,345)	
RV size					
Normal	81.0%	45.1%	73.3%	57.3%	67.4%
Small	0.2%	0%	0.3%	0.1%	0.2%
Enlarged	18.8%	54.9%	26.4%	42.6%	32.4%
RV function[b]					
Normal	88.4%	55.1%	73.0%	56.1%	72.4%
Hypercontractile	0%	0.1%	0.1%	0%	0.1%
Impaired	11.6%	44.8%	26.9%	43.9%	27.5%

Abbreviations: CKD, chronic kidney disease; PH, pulmonary hypertension; RV, right ventricle.
[a]Combined pre- and postcapillary.
[b]Right ventricular function assessed qualitatively.

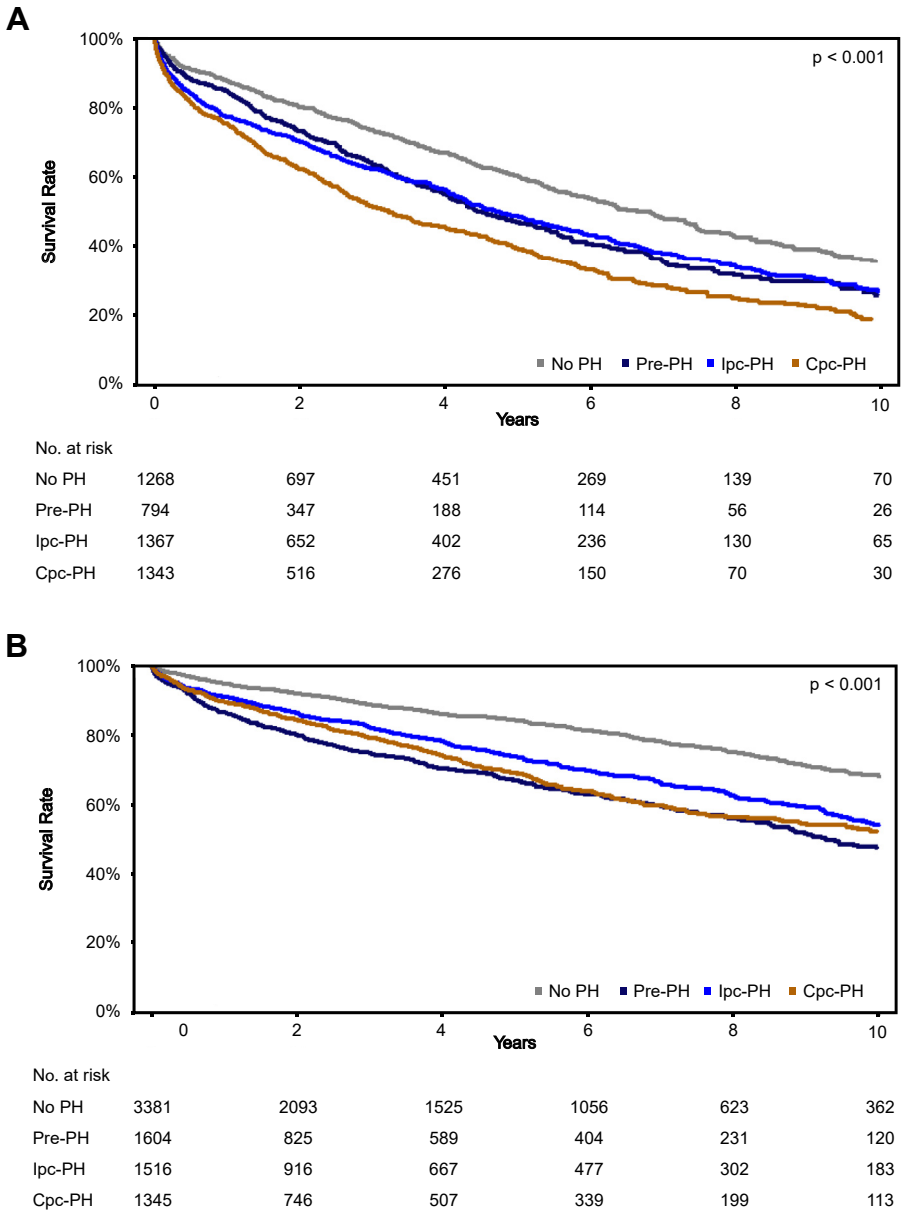
are further supported by high rates of right ventricular enlargement and impairment in the combined pre- and postcapillary PH group. These right ventricular changes may reflect severe or longstanding PH, chronic volume overload, maladaptive responses to volume overload, or elevated left-sided pressure, which would portend worse survival. The predominance of severe life-limiting pulmonary diseases may explain the poor survival of patients with precapillary PH in the non-CKD cohort. Additional studies targeted at providing further granularity to the differences among these PH subtypes in patients with CKD are needed to elucidate the mechanisms underlying this survival difference.

Although the exact mechanisms underlying the high prevalence of PH in CKD are mostly unknown, factors related to decreased GFR and the management of kidney failure have been implicated. Volume overload dominates the current paradigm of PH progression and remains the predominant modifiable factor.[11,21] Of the patients with CKD and PH, >77% had elevated pulmonary capillary wedge pressures, which further highlights the importance of volume management in these patients. However, the high prevalence of combined pre- and postcapillary PH in our CKD cohort suggests that volume overload often exists in concert with other factors that increase pulmonary vascular resistance. Chronic volume overload may accelerate pulmonary vascular remodeling and lead to combined pre- and postcapillary PH in certain susceptible subpopulations of patients with CKD.[22] Alternatively, non–volume-related factors may contribute pulmonary vascular remodeling in subgroups of patients with CKD. Longitudinal studies of PH subtypes in patients with CKD are needed to determine whether combined pre- and postcapillary PH develops predominantly as a transformation from isolated postcapillary PH, precapillary PH, or de novo.

Apart from volume overload, other potential factors that contribute to altered pulmonary vascular resistance or remodeling must be considered. Nitric oxide signaling regulates pulmonary vascular tone and is a common target for drug therapies for patients with pulmonary arteriolar hypertension.[23] Multiple mediators of nitric oxide metabolism are adversely affected by CKD, such as asymmetric dimethylarginine, L-arginine, and homocysteine.[24-34] Fibroblast growth factor 23 (FGF-23) levels also increase in CKD and are associated with various cardiovascular complications, including left ventricular hypertrophy and heart failure.[35] Although FGF-23 level correlates with pulmonary artery pressures in some populations,[36] this relationship remains unclear in patients with CKD.[37] CKD and hemodialysis also promote inflammation.[38,39] Various inflammatory markers are associated with PH, including transforming growth factor β, interleukin 6 (IL-6), IL-10, IL-1 receptor α, and IL-1β.[40-43]

Our study also reports similar relationships of pulmonary artery, pulmonary capillary wedge, and right atrial pressures with mortality in the CKD and non-CKD cohorts. The relationship was nonlinear for each parameter, with inflection points present near cutoffs known to portend worse outcomes in other populations: pulmonary artery pressures > 25 mm Hg and pulmonary capillary wedge pressures > 15 mm Hg. These findings suggest that survival at a given severity of these hemodynamic parameters is comparable in patients with and without CKD. However, as evidenced by the substantial proportion of combined pre- and postcapillary PH in CKD, more patients with CKD experience the extremes of these hemodynamic parameters and this likely contributes to the poor overall survival for patients with both CKD and PH.

Our study has several limitations. Despite the large number of patients in this study, these data reflect a single-center experience and thus limit the generalizability of the study findings. Most right heart catheterization referrals occurred at the discretion of the provider as part of routine clinical care. Variations in operator technique may affect the uniformity of certain catheterization parameters. We did not exclude patients receiving peritoneal dialysis; the PH subtype distribution and association with mortality may differ by dialysis modality. We also do not have data for vascular access for hemodialysis in this study. Arteriovenous fistulas can contribute to high-output heart failure and may influence the risk for PH in this population. We excluded patients with a heart or lung transplant



Figures 5. Kaplan-Meier survival curves for patients (A) with and (B) without chronic kidney disease (CKD). Abbreviations: Cpc-PH, combined pre- and postcapillary pulmonary hypertension; Ipc-PH, isolated postcapillary pulmonary hypertension; PH, pulmonary hypertension; pre-PH, precapillary pulmonary hypertension.

to limit the inclusion of protocol right heart catheterizations in this analysis. Because interstitial lung disease has a stronger association with PH than CKD, we specifically excluded patients with this diagnosis. Despite these exclusions, these limitations may limit the generalizability of our study findings. Future studies could address these limitations by obtaining right heart catheterizations in a random sample of individuals with CKD, including those treated by dialysis. Alternatively, because echocardiography is a more feasible method to study larger populations, future studies could investigate the ability of certain echocardiographic findings (eg, right heart changes) and biomarker data to distinguish among PH subtypes in individuals with CKD.

The assessment of baseline CKD status is also limited by the information available in the electronic health record. We chose to use the median of Scr data in the 6 months preceding the right heart catheterization to calculate baseline eGFR instead of mean Scr level or cutoffs closer to the time of the catheterization used in other studies.[2,12] We used this strategy to limit the influence of acute Scr level changes near the time of catheterization. However,

Table 5. Unadjusted and Adjusted HRs for All-Cause Mortality for Each CKD GFR Category, Stratified by PH Subtype

CKD Stage and PH Subtype	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
No CKD		
Precapillary PH	2.17 (1.92-2.45)	2.27 (2.00-2.57)
Isolated postcapillary PH	1.66 (1.47-1.89)	1.52 (1.34-1.74)
Combined pre-/postcapillary PH	1.89 (1.66-2.15)	1.76 (1.53-2.01)
No PH	1.00 (reference)	1.00 (reference)
CKD G3a		
Precapillary PH	1.35 (1.09-1.66)	1.52 (1.23-1.88)
Isolated postcapillary PH	1.14 (0.94-1.37)	1.19 (0.98-1.44)
Combined pre-/postcapillary PH	1.78 (1.48-2.14)	1.89 (1.57-2.28)
No PH	1.00 (reference)	1.00 (reference)
CKD G3b		
Precapillary PH	1.52 (1.18-1.96)	1.65 (1.28-2.14)
Isolated postcapillary PH	1.56 (1.27-1.93)	1.51 (1.22-1.88)
Combined pre-/postcapillary PH	1.83 (1.49-2.25)	1.87 (1.52-2.31)
No PH	1.00 (reference)	1.00 (reference)
CKD G4		
Precapillary PH	1.42 (0.94-2.13)	1.57 (1.04-2.36)
Isolated postcapillary PH	1.73 (1.25-2.39)	1.68 (1.21-2.34)
Combined pre-/postcapillary PH	1.97 (1.41-2.74)	2.13 (1.52-2.97)
No PH	1.00 (reference)	1.00 (reference)
CKD G5/G5D		
Precapillary PH	0.89 (0.56-1.43)	1.04 (0.65-1.68)
Isolated postcapillary PH	1.13 (0.79-1.61)	1.18 (0.82-1.70)
Combined pre-/postcapillary PH	1.46 (1.01-2.11)	1.63 (1.12-2.36)
No PH	1.00 (reference)	1.00 (reference)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; Gn, glomerular filtration rate category n; HR, hazard ratio; PH, pulmonary hypertension.

[a]Cox proportional hazards model adjusted for age, sex, race, body mass index, diabetes mellitus, heart failure, hypertension, cirrhosis, systemic lupus erythematosus, scleroderma, obstructive sleep apnea, chronic obstructive pulmonary disease, moderate/severe aortic valve disease, moderate/severe mitral valve disease, human immunodeficiency virus infection, smoking, left ventricular ejection fraction, and hemoglobin level.

the absence of standardized Scr collection or quantification of proteinuria limits the accuracy of CKD classification in our analysis. We also combined patients with eGFRs < 15 mL/min/1.73 m^2 with those receiving dialysis. This heterogeneous group may not reflect the risk profile of each group in isolation. Estimates of left-sided pressures may be influenced by the timing of the last dialysis treatment, which was not standardized in this retrospective study. Among other changes, the recent 6th World Symposium on PH proposed a lower cutoff for PH diagnosis.[44] How this increased sensitivity will affect PH diagnosis in CKD remains to be seen.

PH remains an underrecognized yet significant cardiovascular complication for patients with CKD. Unlike other cardiovascular diseases in patients with CKD, the exact mechanism of this association remains largely unknown and no targeted treatments exist. Our study suggests that processes that increase pulmonary vascular resistance and/or remodeling represent a prominent mechanism and potential therapeutic target for patients with CKD that is complicated by PH. In addition, patients with combined pre- and postcapillary PH are a particularly vulnerable subgroup with the highest risk for mortality. As demonstrated by trials of vasodilator therapy in patients with heart failure and combined pre- and postcapillary PH,[16] the recognition of this large combined pre- and postcapillary PH cohort in CKD may present new therapeutic options.

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