SUPPLEMENTAL MATERIALS

Supplemental Tables.....2

Supplemental table 1.....2

Supplemental table 2.....3

Supplemental table 3.....4

Supplemental table 4.....5

Supplemental table 5.....6

Supplemental table 6.....7

Supplemental table 7.....8

Supplemental Figures and Figure Legends.....9

Supplemental figure 1.....9

Supplemental figure 2.....10

Supplemental figure 3.....11

Supplemental References.....13

Supplemental Tables

Supplemental table 1. Diuretics and PAH prescribed treatment at first visit's discharge

	Number of patients (%) n=179
Specific PAH treatments	
Cumulative number of PAH treatment categories	
• 1	142 (79.3%)
• 2	7 (3.9%)
• 3	2 (1.1%)
Endothelin receptor antagonists	115 (64.2%)
• Bosentan	109 (60.9%)
• Ambrisentan	6 (3.4%)
Phosphodiesterase type 5 inhibitors	86 (48.0%)
• Sildenafil	82 (45.8%)
• Tadalafil	4 (2.2%)
Prostacyclin agonists	54 (30.2%)
• Epoprostenol (IV)	52 (29.1%)
• Iloprost (IV)	2 (1.1%)
Diuretics	
Cumulative number of prescribed diuretics:	
• 1	56 (31%)
• 2	76 (42%)
• 3	1 (<1%)
Loop diuretics	122 (68%)
Spironolactone	83 (46%)
Thiazides	3 (2%)

PAH: pulmonary arterial hypertension; IV: intravenous.

Supplemental table 2. Main variables at diagnosis reported by PAH etiological categories.

	Idio	**CHD**	**CTD**	**Tox**	**PPH**	**HIV**	**Hered**	***p***
eGFR MDRD (mL/min/1.73m^2)	71.1 ± 25.9	84.8 ± 20.4	73.0 ± 24.7	54.1 ± 21.7*†	89.7 ± 30.1*‡	82.1 ± 18.2	77.5 ± 15.5	<0.01
mPAP (mmHg)	42 ± 13	53 ± 14*	40 ± 12	40 ± 11	46 ± 11	42 ± 9	49 ± 10	0.01
Cardiac index (L/min/m2)	2.4 ± 0.7	3.2 ± 1.7*	2.6 ± 0.6	2.7 ± 0.5	2.9 ± 0.9*	2.7 ± 0.8	2.0 ± 0.8	<0.01
Right atrial pressure (mmHg)	7 ± 5	7 ± 3	7 ± 5	9 ± 6	9 ± 7	5 ± 5	9 ± 7	0.65

Data shown are mean ± SD.

*: $p<0.05$, compared to reference factor (idiopathic PAH).

†: eGFR in toxic and drug-induced PAH patients was significantly lower, compared to idiopathic PAH. Anorectic drugs were the main toxic trigger for this etiological PAH category. As a consequence, toxic and drug induced PAH patients were significantly older, presented more frequently diabetes, and systemic hypertension, as well as a significantly higher body mass index (Table 5). This PAH category shows a high prevalence of identified metabolic, cardio-vascular and renal risk-factors, which may explain the observed lower eGFR [1].

‡: eGFR in porto-pulmonary hypertension was significantly higher, compared to idiopathic PAH. GFR estimation in cirrhotic patients is frequently overestimated due to low body mass index, low muscle mass, and haemodilution, resulting in low plasmatic creatinine levels [2].

CHD: congenital heart diseases; CTD: connective tissue diseases; eGFR: estimated glomerular filtration rate; Hered: hereditary PAH; HIV: human immunodeficiency virus related PAH; Idio: idiopathic PAH; MDRD: Modification of Diet in Renal Disease; mPAP: mean pulmonary arterial pressure; PAH: pulmonary hypertension; PPH: porto-pulmonary hypertension; Tox: toxic and drug induced PAH.

Supplemental table 3. Comparison of baseline characteristics of patients with toxic and drug-induced PAH and other PAH etiologies.

	Toxic PAH	**Other PAH etiologies**	***p***
	n = 14	**n = 165**	
Age (years)	68.9 ± 10.0	59.6 ± 16.7	<0.01
Gender (female)	11 (78.6%)	98 (59.4%)	0.25
Body mass index (kg/m^2)	31.9 ± 5.9	26.0 ± 5.2	<0.01
Diabetes	7 (50.0%)	17 (10.3%)	<0.01
Systemic hypertension	12 (85.7%)	64 (38.8%)	<0.01
Six-Minute Walking distance (m)	306 ± 150	331 ± 136	0.56
NYHA functional class			0.70
• *I*	0 (0%)	8 (4.8%)	
• *II*	8 (57.1%)	71 (43.0%)	
• *III*	5 (35.7%)	75 (45.5%)	
• *IV*	0 (0%)	11 (6.7%)	
Systolic pulmonary arterial pressure (mmHg)	64 ± 22	71 ± 20	0.27
Diastolic pulmonary arterial pressure (mmHg)	23 ± 8	27 ± 10	0.07
Mean pulmonary arterial pressure (mmHg)	40 ± 11	43 ± 13	0.30
Pulmonary arterial pulse pressure (mmHg)	41 ± 17	44 ± 14	0.59
Pulmonary artery wedge pressure (mmHg)	11 ± 3	9 ± 4	0.04
Pulmonary vascular resistances (dyn.s.cm^{-5})	674 ± 263	859 ± 444	0.03
Mean arterial pressure (mmHg)	87 ± 22	87 ± 13	0.99
Systemic arterial pulse pressure (mmHg)	61 ± 21	55 ± 19	0.29
Right atrial pressure (mmHg)	9 ± 6	7 ± 5	0.44
Cardiac index (L/min/m^2)	2.7 ± 0.5	2.6 ± 0.8	0.61
Systemic pressure gradient (mmHg)	78 ± 24	81 ± 14	0.75
Systemic vascular resistances (dyn.s.cm^{-5})	1225 ± 435	1537 ± 485	0.15
Plasmatic creatinine (µmol/L)	109.9 ± 36.8	90.2 ± 44.0	0.08
eGFR MDRD (mL/min/1.73m^2)	54.1 ± 21.7	76.0 ± 26.0	<0.01
Renal dysfunction at diagnosis	7 (50.0%)	45 (27.3%)	0.12

Data are mean ± SD or count (percentage).

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease equation; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; SD: standard deviation.

Supplemental table 4. Multivariate analysis of variables associated with initial eGFR in the diagnosis cohort (n=179)

	eGFR at diagnosis (mL/min/1.73m^2)	
	Estimate ± SE	***p***
Age (per 5-year increase)	-3.2±0.7	<0.01
Gender (woman)	-1.8±4.0	0.65
PAH etiological categories (compared to idiopathic PAH):		
• *Congenital heart diseases*	-8.0±7.5	0.29
• *Connective tissue diseases*	0.01±4.5	0.99
• *Porto-pulmonary hypertension*	6.7±6.1	0.27
• *Drug and toxic induced PAH*	-10.5±7.1	0.14
• *HIV-related PAH*	-6.3±9.0	0.49
• *Hereditary PAH*	-8.0±13.4	0.55
Diabetes	0.3±5.5	0.95
Systemic hypertension	-8.0±4.0	0.048
Mean pulmonary arterial pressure (per 10 mmHg increase)	1.3±1.7	0.45
Right atrial pressure (per 1 mmHg increase)	-0.2±0.4	0.63
Cardiac index (per 1 L/min/m^2 increase)	8.4±2.3	<0.01

eGFR: estimated glomerular filtration rate; HIV: human immunodeficiency virus; PAH: pulmonary arterial hypertension; SE: standard error.

Supplemental table 5. Comparisons of baseline characteristics of patients with and without rapid eGFR decline during follow-up (n=159)

	Non-rapid decliners	**Rapid decliners**	***p***
	n = 121	**n = 38**	
Age (years)	56.1 ± 16.8	68.2 ± 11.4	<0.01
Gender (female)	80 (66.1%)	19 (50.0%)	0.09
Body mass index (kg/m^2)	26.3 ± 5.3	27.3 ± 5.8	0.34
PAH etiological categories:			0.56
• *Idiopathic PAH*	49 (40.5%)	16 (42.1%)	
• *Congenital heart diseases*	12 (9.9%)	1 (2.6%)	
• *Connective tissue diseases*	28 (23.1%)	10 (26.3%)	
• *Porto-pulmonary hypertension*	16 (13.2%)	5 (13.2%)	
• *Toxic and drug induced PAH*	7 (5.8%)	5 (13.2%)	
• *HIV-related PAH*	5 (4.1%)	1 (2.6%)	
• *Hereditary PAH*	4 (3.3%)	0 (0%)	
Diabetes	11 (9.1%)	9 (23.7%)	0.03
Systemic hypertension	46 (38%)	18 (47.4%)	0.35
Six-Minute Walking distance (m)	356 ± 141	267 ± 112	<0.01
NYHA functional class			0.60
• *I*	4 (3.3%)	3 (7.9%)	
• *II*	55 (45.5%)	15 (39.5%)	
• *III*	55 (45.5%)	18 (47.4%)	
• *IV*	5 (4.1%)	2 (5.3%)	
Systolic pulmonary arterial pressure (mmHg)	72 ± 22	71 ± 17	0.75
Diastolic pulmonary arterial pressure (mmHg)	28 ± 11	27 ± 9	0.41
Mean pulmonary arterial pressure (mmHg)	44 ± 13	42 ± 11	0.49
Pulmonary arterial pulse pressure (mmHg)	44 ± 15	44 ± 13	0.88
Pulmonary artery wedge pressure (mmHg)	9 ± 4	10 ± 3	0.04
Pulmonary vascular resistances (dyn.s.cm^{-5})	876 ± 479	824 ± 344	0.47
Mean arterial pressure (mmHg)	86 ± 15	92 ± 11	0.09
Systemic arterial pulse pressure (mmHg)	55 ± 19	56 ± 19	0.81
Right atrial pressure (mmHg)	7 ± 5	8 ± 5	0.34
Cardiac index (L/min/m^2)	2.6 ± 0.7	2.5 ± 0.5	0.12
Systemic pressure gradient (mmHg)	79 ± 16	84 ± 10	0.23
Systemic vascular resistances (dyn.s.cm^{-5})	1491 ± 523	1502 ± 370	0.93
Plasmatic creatinine (µmol/L)	92.0 ± 45.1	86.5 ± 29.8	0.39
eGFR MDRD (mL/min/1.73m^2)	74.9 ± 27.2	75.2 ± 24.3	0.94
Renal dysfunction at diagnosis	37 (30.6%)	8 (21.1%)	0.31

Data are mean ± SD or count (percentage). Rapid decline is defined as an annual eGFR decrease of 5 mL/min/1.73m^2/year or more [1]. Renal dysfunction is defined as an eGFR <60 mL/min/1.73m^2.
eGFR: estimate glomerular filtration rate; HIV: human immunodeficiency virus; MDRD: Modification of Diet in Renal Disease equation; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension.

Supplemental table 6. Comparison of multivariate models of eGFR with one hemodynamic input variable (longitudinal dataset)

	Models statistics					ANOVA	
	AIC	**BIC**	**Log-likelihood**	**Deviance**	**Residuals**	**Models**	***p***
CI model	4268	4347	-2115	4230	-0.03 [-0.5; 0.6]	*RAP vs. CI*	<0.01
mPAP model	4279	4358	-2121	4241	-0.01 [-0.5; 0.6]	*RAP vs. mPAP*	0.9
RAP model	4271	4351	-2117	4233	0.01 [-0.6; 0.6]	*CI vs. mPAP*	<0.01

Multivariate linear mixed-effect models were built using this structure:

eGFR ~ one hemodynamic variable + all covariates + (random effect)

Covariates: age, gender, PAH etiological category, diabetes, systemic hypertension, prescribed treatments, elapsed time since diagnosis.

Statistical difference between models was tested with ANOVA.

AIC: Akaike information criteria; BIC: Bayesian information criteria; CI: cardiac index; eGFR: estimated glomerular filtration rate; mPAP: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension; RAP: right atrial pressure.

Supplemental table 7. Cox proportional hazard ratios of death in the diagnosis cohort (n=179)

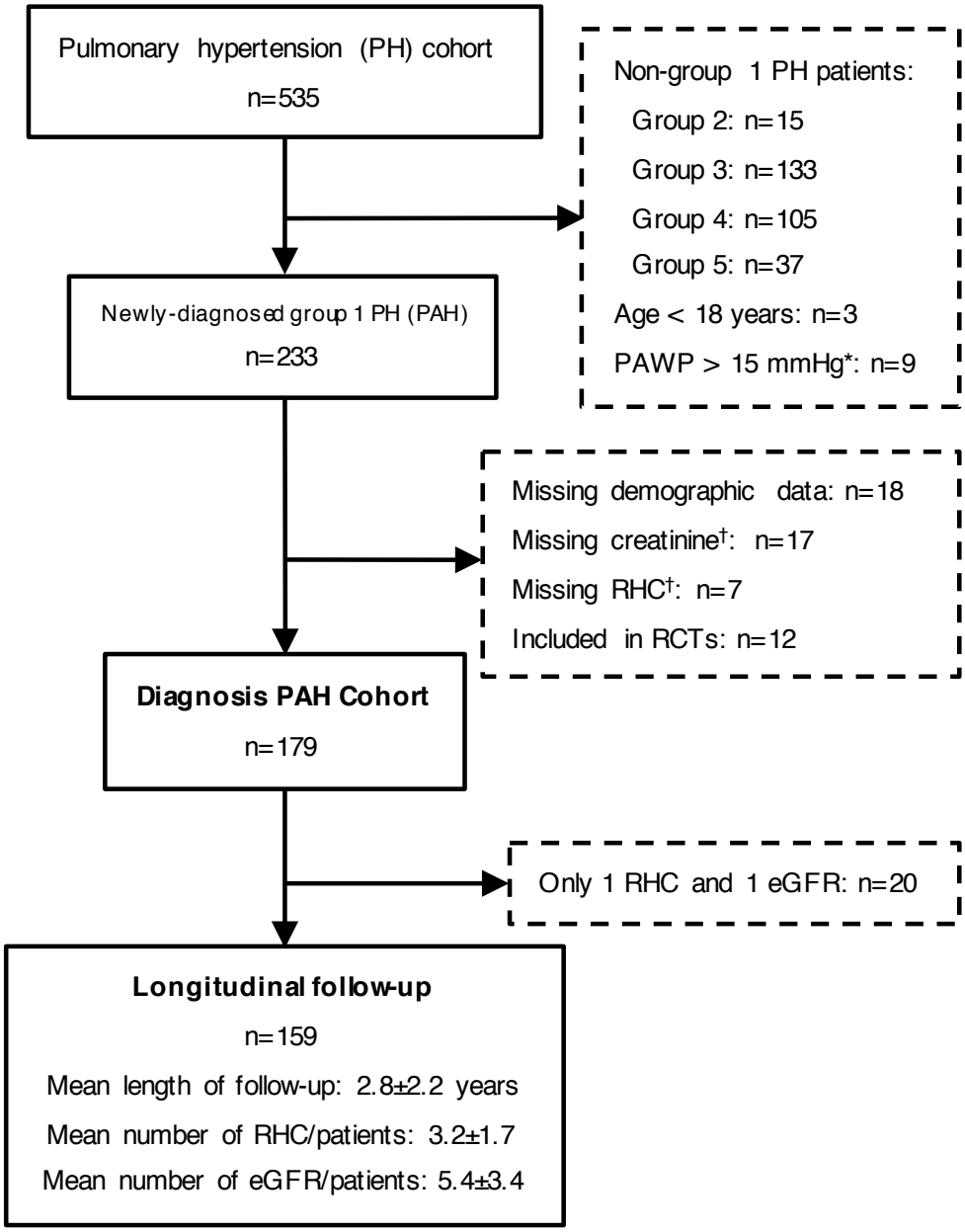
	Univariate analysis		**Multivariate analysis**	
	HR [95% CI]	***p***	**HR [95% CI]**	***p***
Age at diagnosis <60 years	0.32 [0.17; 0.58]	<0.01	0.38 [0.20; 0.75]	<0.01
Gender (woman)	0.41 [0.24; 0.71]	<0.01	0.32 [0.18; 0.58]	<0.01
NYHA functional class (compared to NYHA I and II)				
• *III*	1.32 [0.74; 2.33]	0.34	1.63 [0.89; 2.97]	0.11
• *IV*	3.39 [1.28; 8.99]	0.02	6.63 [2.33; 18.85]	<0.01
Mean pulmonary arterial pressure at diagnosis (per 10 mmHg increase)	0.73 [0.57; 0.92]	0.01	0.84 [0.65; 1.09]	0.20
Right atrial pressure at diagnosis (per 1 mmHg increase)	1.00 [0.95; 1.05]	0.92	-	-
Cardiac index at diagnosis (per 1 L/min/m^2 increase)	0.79 [0.52; 1.19]	0.26	-	-
eGFR MDRD at diagnosis (per 10 mL/min/1.73m^2 increase)	0.82 [0.74; 0.92]	<0.01	-	-
• *eGFR MDRD <60 mL/min/1.73m^2 at diagnosis (RD)*	2.27 [1.32; 3.92]	<0.01	1.81 [1.01; 3.25]	0.049

Variables selected for multivariate analysis were: age at diagnosis <60 years, gender, NYHA functional class, mean pulmonary arterial pressure, and eGFR at diagnosis <60 mL/min/1.73m^2.

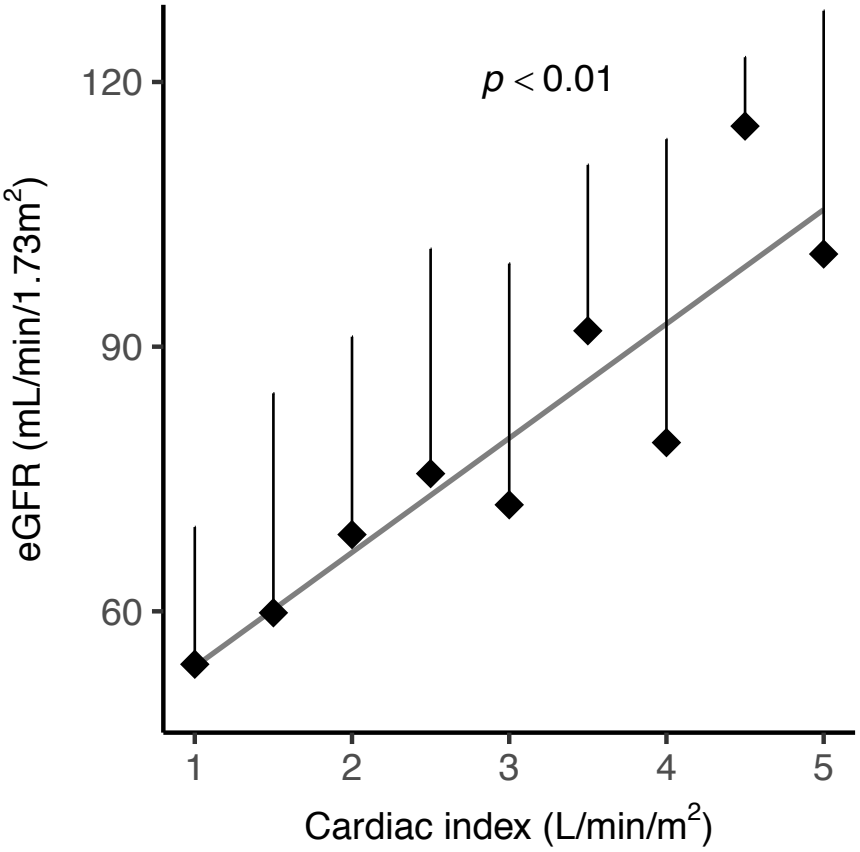
95% CI: 95% confidence interval; eGFR: estimated glomerular filtration rate; HR: hazards ratio; MDRD: Modified Diet in Renal Disease; NYHA: New York Heart Association.

Supplemental Figures and Figure Legends

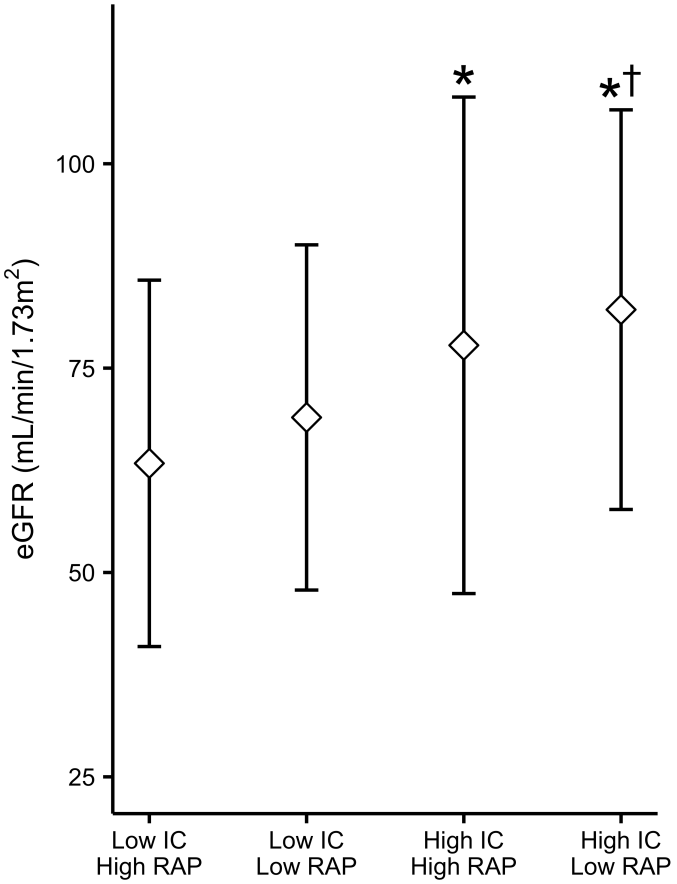
Supplemental figure 1.



Supplemental figure 2.



Supplemental figure 3.



Supplemental figure 1. Study flowchart.

Group 2 pulmonary hypertension: pulmonary hypertension due to left heart disease; group 3 pulmonary hypertension: pulmonary hypertension due to lung disease and/or hypoxia; group 4 pulmonary hypertension: chronic thromboembolic pulmonary hypertension; group 5 pulmonary hypertension: pulmonary hypertension with unclear multifactorial mechanisms [3].

*: PAWP was > 15 mmHg at PAH diagnosis in 9 patients classified as having group 1 PAH.

†: at diagnosis. eGFR: estimated glomerular filtration rate; PAH: pulmonary arterial hypertension; PAWP: pulmonary artery wedge pressure; RCTs: randomized clinical trials; RHC: right heart catheterization.

Supplemental figure 2. Graphical representation of the relationship between eGFR and cardiac index at baseline.

eGFR and cardiac index values originate from the cross-sectional dataset at baseline. Black squares are means and vertical lines represent one-sided standard deviation (for graphical-reading simplification). The grey line represents a linear function fit for CI ($y \sim \alpha . x + \beta$). p values is the result of univariate non-mixed-effects regressions.

eGFR: estimated glomerular filtration rate.

Supplemental figure 3. Relative effect of cardiac index and right atrial pressure on eGFR level.

Data is from the longitudinal dataset. IC is low if < 2.5 L/min/1.73m^2, RAP is low if < 7 mmHg. Error bars are standard deviations. *: p<0.01 when compared to "low IC, high RAP" level. †: p<0.01 when compared to "low IC, low RAP" level. CI: cardiac index; eGFR: estimated glomerular filtration rate; RAP: right atrial pressure.

Supplemental References

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3 Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R: Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:D34-41.