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***Pulmonary hypertension and chronic renal
pathology***

DOCTORAL THESIS SUMMARY

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The Fundamental Research Problem

This doctoral thesis focused on the association between pulmonary hypertension (PH) and chronic renal pathology. The topic is relevant in the current context of scientific research from two different perspectives: the cardio-pulmonary perspective (of PH expert clinicians) and the nephrological perspective.

From the point of view of pulmonary vascular pathology, the trend of recent years is toward a paradigm of PH—and particularly pulmonary arterial hypertension (PAH)—as a disease with multisystemic resonance. The involvement of other organ systems in PAH is relevant for understanding the pathophysiological interactions between the pulmonary and systemic circulation, but especially for evaluating the severity and prognosis of patients. PAH is a severe and progressive disease [1–3], with a vast therapeutic arsenal [4].

The choice of therapeutic strategy depends inextricably on risk stratification: a strategy by which a series of parameters are used to predict the patients' risk of death. Although current strategies for risk stratification have good predictive power, validated on large cohorts of patients, there are patients who do not fit satisfactorily into these scores. For them, new prognostic parameters are needed, and functional changes in other organs represent a potential source for such new parameters. Renal function, in particular, has repeatedly proven to be associated with survival in PAH and in PH of other etiologies [5–10].

From the nephrological perspective, PH has long been described as one of the most important cardiovascular complications of chronic kidney disease (CKD) [5, 11, 12]. The prevalence of PH is much higher in patients with CKD than in the general population, and all the higher as the CKD is more advanced [13]. The maximum prevalence is recorded in hemodialysis patients, suggesting a possible role of hemodialysis in increasing pulmonary arterial pressure [5]. PH is associated with a negative prognosis in CKD, with a higher risk of death from any cause, cardiovascular death, and acute cardiovascular events [14]. In a world where primary pulmonary vascular pathology (PAH) is increasingly well-known and treatments are widely available, understanding the mechanisms of PH in patients with CKD is essential to ensure the correct approach to this large group, which tends to increase due to the rising prevalence of CKD in the general population.

This thesis addressed the topic from both perspectives, with the aim of clarifying certain epidemiological and pathophysiological aspects of the interaction between PH and

CKD. The results presented provide information on how renal dysfunction should be understood and addressed in PH and PAH, as well as on the main mechanisms of increased pulmonary arterial pressure in CKD and the correct prevention and treatment strategies.

Hypotheses and objectives

This work had two central hypotheses, corresponding to the two perspectives of the association between PH and renal pathology:

1. In CKD requiring dialysis, PH correlates with the duration of dialysis and the type of vascular access.
2. In PAH, renal dysfunction improves the prognostic discrimination power of the main scores recommended for risk stratification.

To analyze the first hypothesis, we established a series of objectives:

- establishing the prevalence of PH in a cohort of patients undergoing dialysis in a tertiary nephrology center in Romania;
- exploring the associations of PH in dialysis patients with relevant clinical and biological parameters in CKD;
- exploring the associations of PH in dialysis patients with echocardiographic parameters of volume overload;
- exploring the associations of PH in dialysis patients with parameters related to the dialysis process: hemodialysis vs. peritoneal dialysis, vintage of dialysis, type of vascular access, and location of vascular access.

For the second hypothesis, the objectives were as follows:

- evaluating the prevalence of renal dysfunction in patients with PH of any cause in the French Pulmonary Hypertension Registry (FPHR);
- exploring the associations between renal dysfunction and lung transplant-free survival in patients with PH from the FPHR;
- analyzing the interactions between renal function and other variables with prognostic value in PAH;
- evaluating the independent prognostic power of renal function in patients with PAH after adjusting for the main risk scores recommended by the current guidelines;

- analyzing the dynamics of renal function in patients with PAH between the time of diagnosis and the first re-evaluation;
- evaluating the prognostic value of renal function at re-evaluation and the changes in renal function.

Methodology

The first stage of this research was to establish the current level of knowledge. To this end, I conducted a systematic synthesis of the literature at the intersection of the fields of pulmonary hypertension and renal dysfunction / CKD. I searched for relevant publications in the Pubmed and MEDLINE databases using "pulmonary hypertension" and "chronic renal failure" as search terms, as well as terms derived from these. I also included in the analysis publications mentioned in the references of those identified through the search strategy. Given the heterogeneity of the information and methodologies identified, I organized the results in the form of a narrative literature synthesis [15].

The study of renal dysfunction in patients with PH

The study on patients with PH was an observational, retrospective cohort study. The study population included adult patients with PH of any cause, with a subsequent focus on those with PAH. The data source was the French Pulmonary Hypertension Network (FPHR) registry, a national database that has prospectively recorded all incident patients with PH of any cause throughout France since 2006. All patients with a mean pulmonary arterial pressure (mPAP) value above 20 mmHg were included. Patients < 18 years old, those on dialysis, and those with incomplete data at the time of PH diagnosis for New York Heart Association (NYHA) / World Health Organization (WHO) functional class, 6-minute walk distance (6MWD), serum levels of brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP), right atrial pressure (RAP), pulmonary artery wedge pressure (PAWP), cardiac output (CO), cardiac index (CI), pulmonary vascular resistance (PVR), and serum creatinine were excluded.

For all patients, I calculated the estimated glomerular filtration rate (eGFR) at the initial assessment based on age, sex, and serum creatinine using the CKD-EPI 2021 equation [16]. I divided patients according to eGFR into four categories overlapping the CKD stages

from the KDIGO guideline [17]: ≥ 60 mL/min/1,73 m², 45-59 mL/min/1,73 m², 30-44 mL/min/1,73 m² and < 30 mL/min/1,73 m².

I calculated the prevalence of each eGFR category in the total cohort and in each PH group. I performed a survival analysis using death or lung transplantation as the event of interest. I used the Kaplan-Meier method to analyze survival according to the eGFR category in the total cohort and in each PH group.

Subsequently, a more in-depth analysis focused on Group 1 (PAH). For these patients, I performed comparisons between eGFR categories regarding demographic parameters, comorbidities, and clinical, biological, and hemodynamic parameters relevant to PAH. Subsequently, I searched for predictors of eGFR using univariable linear regression models. I introduced significant variables from the univariable regression into a multivariable regression model to identify independent predictors.

I further deepened the survival analysis in patients with PAH by creating Kaplan-Meier curves and univariable Cox proportional hazards models adjusted for the 3-strata European Society of Cardiology (ESC) / European Respiratory Society (ERS) risk score. The 3-strata ESC/ERS risk score was calculated at the initial assessment for all patients based on WHO functional class, 6MWD, BNP or NT-proBNP, and hemodynamic variables according to recommendations [18]. The same analysis was also performed using the French risk score (FPHR), calculated according to international recommendations [18]. Additional Cox models were performed that included other variables such as age, sex, and comorbidities to isolate the association of eGFR with survival.

Among the patients with PAH, I selected those who had a re-evaluation visit with a complete set of data for the same variables from the initial assessment, at an interval of 3-12 months after diagnosis. In this subgroup of patients, I analyzed the dynamics of eGFR and the association of eGFR and its dynamics with survival using the Kaplan-Meier and Cox methods. For the re-evaluation, I used the 4-strata ESC/ERS score.

For Cox models that included risk scores, I calculated concordance indices (C-index) to analyze the influence of adding eGFR on the prognostic power of the statistical model.

The study of pulmonary hypertension in dialysis patients

For the analysis of PH in CKD, I conducted a cross-sectional, retrospective observational study. The study population was a cohort of patients with end-stage CKD undergoing hemodialysis or peritoneal dialysis under the follow-up of a tertiary public

nephrology center. The inclusion criterion was an age over 18 years. The exclusion criteria were a dialysis duration of less than 90 days and the lack of an echocardiography after starting dialysis.

The primary measurements were echocardiographic. I used an estimated systolic pulmonary arterial pressure (sPAP) value >35 mmHg to define PH. I performed comparisons between peritoneal dialysis and hemodialysis patients and between patients with and without PH. I analyzed the predictor variables of sPAP using the linear regression method, with univariable and multivariable models.

Chapter 1. Pulmonary hypertension

Chapter 1 represents a review of the main relevant information in the field of PH to highlight the importance of the research topic. I focused on the main historical milestones in the evolution of the PH field, centered around the world symposia. Reviewing the publications from the world symposia allows for a better appreciation of the spectacular development of this field.

Pulmonary hypertension, and PAH in particular, has been the subject of sustained and impressive research efforts over the last 50 years. These efforts have allowed not only a nuanced understanding of pathophysiological mechanisms and diagnostic methods but have also led to the development of an impressive therapeutic arsenal with multiple molecules and interventional methods. These have allowed a significant improvement in life expectancy for these patients, but PAH remains a severe and progressive disease with lethal potential. The current treatment paradigm is based on drug combinations and rigorous staging using death prediction scores.

Chapter 2. Pulmonary hypertension and chronic kidney disease

This chapter provides a synthesis of the main concepts related to the association between PH and renal pathology, analyzing, on the one hand, the literature on renal dysfunction in PH and, on the other hand, the literature on PH in chronic kidney disease.

In PH, renal dysfunction has raised interest as a potential predictor of survival. In a progressive disease where medications must be individualized according to the risk of early mortality, any parameter with predictive value deserves study. Efforts to predict the survival duration of patients with PAH date back to the 1990s [19]. Subsequently, studies on cohorts

of patients with PAH and PH of other etiologies have demonstrated one by one the predictive power of key parameters. Among the parameters with prognostic value is renal function, and the first associations date back to 2007 [6]. Currently, there are multiple large-scale cohort studies demonstrating the prognostic value of eGFR in PH and PAH [5]. However, it is not clear whether eGFR provides additional prognostic information compared to the risk scores recommended by the guidelines [1, 2].

In patients with CKD, the notion of PH as a frequent and severe complication dates back to 2003, when a high prevalence of PH in dialysis patients was described for the first time [11]. Based on these observations, CKD-associated PH was included in the clinical classification of PH [3]. Subsequent studies were based on cohorts of patients with CKD in whom PH was defined echocardiographically. Several hypotheses have been proposed regarding the pathophysiological mechanisms of this interaction, from endothelial dysfunction to circulating uremic compounds, to right-sided cardio-renal syndrome, based on decreased cardiac output and renal venous congestion [5]. Hemodialysis also seems to contribute to the occurrence of PH, particularly through arteriovenous fistulas.

Chapter 3. Renal function in patients with pulmonary hypertension: prevalence and prognostic relevance

The methodology used for this study was described above. 7701 patients with PH of any etiology were included, of whom 3383 had PAH. Among the patients with PAH, 1667 also had re-evaluation data.

The main results showed that, in patients with PAH, renal function defined by eGFR has independent prognostic value compared to the 3- and 4-strata ESC/ERS risk scores, both at the initial assessment and at re-evaluation. In addition, in patients with normal initial renal function, a decrease of $\geq 10\%$ in eGFR is independently associated with reduced survival. In this cohort of patients with PAH, renal function seems to be associated more with age and associated pathologies than with hemodynamic impairment. It is true that patients who improved their eGFR had the most severe hemodynamic profile and, under aggressive medication, had the most extensive improvement in pressures and flows. This fact highlights the cardio-renal interaction in PAH. However, at the level of the entire cohort, eGFR had a non-linear association with survival, which lost statistical significance after adjusting for age, sex, and comorbidities.

Nevertheless, the results are valuable because they demonstrate that adding eGFR can improve the predictive power of the main risk scores in PAH.

Chapter 4. Pulmonary hypertension in dialysis patients: prevalence and predictors

The methodology of this study was presented above. 51 patients were included, 44 with hemodialysis and 7 with peritoneal dialysis.

The main results show that the prevalence of PH in dialysis patients is approximately 30%, higher in hemodialysis than in peritoneal dialysis.

The predictors of PH were mainly volume overload (represented by left atrial volume), left ventricular diastolic dysfunction (represented by the E/e' ratio), and left ventricular systolic dysfunction (represented by the left ventricular ejection fraction). The hypothesis that the duration of dialysis and the type of vascular access for hemodialysis are associated with PH was invalidated by the study results. However, the low statistical power makes it possible that a weaker association might have been missed.

The results are valuable because they highlight the essential value of volume control for the prevention and treatment of PH in dialysis patients.

Conclusions and Personal Contributions

The work explores the bidirectional link between pulmonary hypertension (PH) and chronic kidney disease (CKD), highlighting the increasing importance of the interaction between pulmonary circulation and renal function in current medicine. The research shows that PH is a frequent complication of CKD, with maximum prevalence among dialysis patients, where mechanisms such as endothelial dysfunction, venous congestion, and the impact of arteriovenous fistulas play a determining role. Conversely, renal dysfunction is present in approximately one-quarter of patients with PH, being an indicator of severe prognosis: a low glomerular filtration rate or its degradation in the first year of monitoring is associated with shorter survival, independent of validated risk scores.

In the analysis of dialysis patients, it was observed that the determining factors for increased pulmonary arterial pressure are, primarily, volume overload and left ventricular dysfunction. Although the literature suggests links with the type of vascular access or the duration of dialysis, the present research emphasizes that fluid volume control and

optimizing cardiac health remain the essential pillars in the prevention of PH in these patients. Although the studies have limitations related to their retrospective nature, they provide a scientific basis for a multidisciplinary approach to patients. Future research directions include conducting prospective studies using rigorous diagnostic methods to elucidate complex pathophysiological mechanisms and advance toward personalized medicine.

Selective Bibliography

- 1 Humbert M, Kovacs G, Hoeper MM, *et al.* 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal* 2022; 43: 3618–3731.
- 2 Humbert M, Kovacs G, Hoeper MM, *et al.* 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2023; 61: 2200879.
- 3 Kovacs G, Bartolome S, Denton CP, *et al.* Definition, classification and diagnosis of pulmonary hypertension. *Eur Respir J* 2024; 64: 2401324.
- 4 Chin KM, Gaine SP, Gerges C, *et al.* Treatment algorithm for pulmonary arterial hypertension. *Eur Respir J* 2024; 64: 2401325.
- 5 Zeder K, Siew ED, Kovacs G, *et al.* Pulmonary hypertension and chronic kidney disease: prevalence, pathophysiology and outcomes. *Nat Rev Nephrol* 2024; 20: 742–754.
- 6 Leuchte HH, El Nounou M, Tuerpe JC, *et al.* N-terminal Pro-Brain Natriuretic Peptide and Renal Insufficiency as Predictors of Mortality in Pulmonary Hypertension. *Chest* 2007; 131: 402–409.
- 7 Shah SJ, Thenappan T, Rich S, *et al.* Association of Serum Creatinine With Abnormal Hemodynamics and Mortality in Pulmonary Arterial Hypertension. *Circulation* 2008; 117: 2475–2483.
- 8 O’Leary JM, Assad TR, Xu M, *et al.* Pulmonary hypertension in patients with chronic kidney disease: invasive hemodynamic etiology and outcomes. *Pulm circ* 2017; 7: 674–683.
- 9 Chakinala MM, Coyne DW, Benza RL, *et al.* Impact of declining renal function on outcomes in pulmonary arterial hypertension: A REVEAL registry analysis. *The Journal of Heart and Lung Transplantation* 2018; 37: 696–705.
- 10 Meservey A, Al-Naamani N, Minhas J, *et al.* Renal dysfunction and outcomes in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: an individual participant data meta-analysis. *Eur Respir J* 2025; 66: 2402400.
- 11 Yigla M, Nakhoul F, Sabag A, *et al.* Pulmonary Hypertension in Patients With End-Stage Renal Disease. *Chest* 2003; 123: 1577–1582.
- 12 Yigla M, Fruchter O, Aharonson D, *et al.* Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients. *Kidney International* 2009; 75: 969–975.
- 13 Li Z, Liang X, Liu S, *et al.* Pulmonary Hypertension: Epidemiology in Different CKD Stages and Its Association with Cardiovascular Morbidity. Lahm T, ed. *PLoS ONE* 2014; 9: e114392.
- 14 Tang M, Batty JA, Lin C, *et al.* Pulmonary Hypertension, Mortality, and Cardiovascular Disease in CKD and ESRD Patients: A Systematic Review and Meta-analysis. *American Journal of Kidney Diseases* 2018; 72: 75–83.

- 15 Neagu A, Bogdan MA. Pulmonary hypertension and renal dysfunction: a narrative review. *Pneumologia* in press; .
- 16 Inker LA, Eneanya ND, Coresh J, *et al.* New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. *N Engl J Med* 2021; 385: 1737–1749.
- 17 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International* 2024; 105: S117–S314.
- 18 Dardi F, Boucly A, Benza R, *et al.* Risk stratification and treatment goals in pulmonary arterial hypertension. *Eur Respir J* 2024; 64: 2401323.
- 19 D’Alonzo GE, Barst RJ, Ayres SM, *et al.* Survival in Patients with Primary Pulmonary Hypertension: Results from a National Prospective Registry. *Ann Intern Med* American College of Physicians; 1991; 115: 343–349.

List of Publications

Neagu A, Bogdan MA. Pulmonary hypertension and renal dysfunction: a narrative review. *Pneumologia* 2026; in press. Based on chapter 2, pages 34-40.

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Neagu A, Căpușă C, Zugravu A, *et al.* Prevalence and Predictors of Pulmonary Hypertension in End-Stage Renal Disease: a Single-Center Cross-Sectional Study. *Maedica* 2026; 21: 1. DOI: 10.26574/maedica.2026.21.1.35. Based on chapter 4, pages 84-94.