PhD THESIS

ABSTRACT

Evaluation of Pulmonary Hypertension Management in Romania — The Romanian Pulmonary Hypertension Registry (PHYRE-RO)

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TÂRGU MUREȘ

2026

1. Introduction

Pulmonary hypertension (PH) represents a heterogeneous group of conditions characterised by increased pressure within the pulmonary circulation and a progressive course towards right heart failure and premature mortality in the absence of appropriate management. Although historically considered a rare disease, PH is currently recognised as a condition with significant clinical impact, contributing substantially to morbidity, mortality and impaired quality of life.

Over recent decades, major advances in the understanding of the underlying pathophysiological mechanisms have led to a transformation in the management of PH. In particular, insights into pulmonary vascular remodelling—driven by endothelial dysfunction and dysregulation of key vasoactive pathways—have enabled the development of targeted therapies, which have significantly improved clinical outcomes and patient prognosis.

In parallel, international guidelines developed by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) have established a structured framework for diagnosis, haemodynamic classification, risk stratification and therapeutic management. These guidelines emphasise early diagnosis, systematic risk assessment and timely initiation of appropriate treatment strategies.

Despite these advances, the implementation of guideline recommendations in real-world clinical practice remains heterogeneous. This variability is influenced by multiple factors, including delays in diagnosis, differences in access to specialised centres and advanced diagnostic investigations, and variability in the availability of specific therapies. As a result, a persistent gap exists between guideline recommendations and routine clinical practice.

In this context, pulmonary hypertension registries represent essential tools for capturing real-world data and for improving the understanding of disease characteristics, management strategies and clinical outcomes. By enabling the systematic collection of standardised data,

registries facilitate the evaluation of clinical practice and support the optimisation of patient care.

In Romania, epidemiological and clinical data on PH have been limited until recently, restricting comprehensive evaluation of disease management at a national level. The development of the Romanian National Pulmonary Hypertension Registry (PHYRE-RO) addresses this need by enabling the standardised collection of data from patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

Through its multicentric and structured design, PHYRE-RO provides an integrated perspective on patient characteristics, therapeutic strategies and clinical outcomes in real-world practice, representing a key step towards improving the management of pulmonary hypertension in Romania.

2. Aim and Objectives

The aim of this doctoral thesis was to develop and implement the Romanian National Pulmonary Hypertension Registry (PHYRE-RO) as a multicentre platform for the standardised collection of clinical data in real-world practice, and to utilise these data to evaluate the management of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), as well as to identify relevant prognostic factors.

The specific objectives included:

- the development and implementation of a national multicentre registry dedicated to patients with PAH and CTEPH;
- the characterisation of the demographic, clinical, biological and haemodynamic profile of the included patients;
- the evaluation of diagnostic and therapeutic strategies used in real-world clinical practice;

- the assessment of the degree of implementation of ESC/ERS guideline recommendations;
- the investigation of the prognostic role of traditional and emerging biomarkers (NT-proBNP/albumin ratio [NTAR] and RDW/eGFR ratio [RGR]) in risk stratification and outcome prediction;
- the evaluation of haematological inflammatory indices as prognostic markers;
- the analysis of factors associated with length of hospital stay and short- and mid-term mortality.

3. Materials and Methods

The study was designed as an observational analysis with both retrospective and prospective components, based on data collected within the Romanian National Pulmonary Hypertension Registry (PHYRE-RO), a multicentre registry dedicated to patients diagnosed with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).

The PHYRE-RO registry was developed as an integrated platform for the standardised collection of demographic, clinical, functional, imaging, haemodynamic and therapeutic data from centres involved in the diagnosis and management of pulmonary hypertension. Data collection complied with ethical standards and data protection regulations (GDPR) and was supported by established quality control procedures to ensure data accuracy and consistency.

The analysed cohort included adult patients with PAH and CTEPH, with haemodynamic confirmation established by right heart catheterisation. The evaluated variables comprised clinical parameters, including WHO functional class and comorbidities, functional capacity assessed by the 6-minute walk distance, serum biomarkers—particularly NT-proBNP—echocardiographic findings, haemodynamic measurements, and the therapeutic strategies applied.

In addition, the analysis incorporated the assessment of renal function, hepatic impairment and lipid metabolism. Composite biomarkers, including the NT-proBNP/albumin

ratio (NTAR) and the RDW/eGFR ratio (RGR), were evaluated alongside haematological inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and the systemic immune-inflammation index (SII).

The predefined endpoints included disease severity, length of hospital stay (LOS), prolonged hospitalisation (ELOS), in-hospital mortality and all-cause mortality during follow-up.

Statistical analysis included descriptive and inferential methods, regression models and survival analyses, aimed at identifying independent predictors of clinical outcomes and prognosis.

4. Results

The implementation of the PHYRE-RO registry enabled the development of a standardised national database, providing a comprehensive and realistic overview of the management of patients with PAH and CTEPH in Romania. Data analysis revealed significant heterogeneity in clinical presentation, as well as variability in the diagnostic and therapeutic strategies applied in routine clinical practice.

The results highlighted variability in the timing of diagnosis and a heterogeneous implementation of ESC/ERS-recommended risk stratification strategies. Furthermore, the use of monotherapy persists in certain clinical contexts, despite the current trend towards early initiation of combination therapy.

The analysed biomarkers demonstrated significant prognostic value. NT-proBNP, NTAR and RGR were independently associated with length of hospital stay and mortality, with higher values correlating with an increased risk of adverse clinical outcomes.

Haematological inflammatory indices also showed a significant association with patient prognosis, supporting the role of systemic inflammation in disease progression. Parameters such as the neutrophil-to-lymphocyte ratio and the systemic immune-inflammation index were identified as independent predictors of mortality.

Risk stratification using ESC/ERS models (3-strata and 4-strata) demonstrated a strong correlation between risk category and clinical outcomes, confirming the applicability and clinical utility of these tools in real-world settings.

5. Conclusions

The Romanian National Pulmonary Hypertension Registry (PHYRE-RO) represents a valuable and robust tool for evaluating the management of pulmonary hypertension in Romania under real-world conditions, as well as for assessing the implementation of international guideline recommendations.

The findings of this study highlight the existence of discrepancies between guideline-based recommendations and routine clinical practice, underscoring the need to optimise strategies for early diagnosis, risk stratification and therapeutic management.

Emerging biomarkers, such as NTAR and RGR, together with haematological inflammatory indices, demonstrate significant potential in prognostic assessment and risk stratification, supporting the development of more individualised management approaches in patients with PAH and CTEPH.

The integration of data derived from national registries into clinical practice and decision-making processes has the potential to improve the quality of care and to support the development of healthcare policies tailored to the real needs of patients with pulmonary hypertension.

Overall, this doctoral thesis contributes to advancing knowledge in the field of pulmonary hypertension and provides a foundation for the development of modern, patient-centred management strategies aimed at improving clinical outcomes.