# University of Medicine and Pharmacy Tîrgu Mureş

# Doctoral School

## PhD Thesis Summary

## ASSESSMENT OF PROGNOSIS IN PEDIATRIC PULMONARY ARTERIAL HYPERTENSION

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### Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease diagnosed at any age. Despite the recent therapeutic advances and the important benefits of applying clinical trial results to the adult population, pediatric PAH remains a devastating disease. The evaluation of PAH in children is complex because of the multifactorial etiology, the complexity of the diagnosis, and the poor understanding of the natural history of this pathology.

### 1st Study: Epidemiological Profile of Pediatric Pulmonary Arterial Hypertension

The first study of the PhD thesis is a prospective and observational study that evaluated the epidemiological characteristics of pediatric PAH patients diagnosed and longitudinally evaluated at Pediatric Cardiology Department from Emergency Institute for Cardiovascular and Transplant Diseases, Tîrgu Mureş. The study demonstrated that pediatric PAH is characterized by age-specific diagnosis, the most frequent forms of PAH being associated with congenital heart disease. Pediatric patients diagnosed with congenital heart disease associate a wide range of cardiac lesions with specific haemodynamic profile and clinical outcomes, which determine the heterogeneity of this group of patients. The study was conducted in the only national center specialized in the diagnosis and treatment of congenital and acquired cardiopathy with addressability from all the regions of our country; from this point of view, the study is valuable because we consider it to reflect the national epidemiological profile of pediatric PAH, currently in our country there are no published data on PAH in the pediatric age group.

### 2nd Study: Markers as predictors of clinical worsening at 24 months in pediatric pulmonary arterial hypertension

Prognostic assessment is a crucial element in PAH management, despite recent advances pediatric PAH remains a devastating disease. The correlation between clinical worsening and biomarkers, functional, ECG and echocardiographic parameters in children with PAH has not been assessed so far. The second study of the PhD thesis is a prospective, longitudinal, non-interventional study that has proposed to assess the role of several functional, serum and imaging markers, such as biomarkers, ECG and echocardiography-derived parameters characterizing right ventricular (RV) function and RV hemodynamic status in predicting clinical worsening at 24 months in pediatric patients with PAH. At the same time, we aimed to identify the optimum cut-off values for assessed markers for defining the group of pediatric patients at risk of clinical worsening from the patients who may have a stable clinical evolution. Dynamic changes in the distance walked in 6 minute (6MWT) demonstrated the prognostic value of the 6MWT in follow-up (cut-off 333 m). The prognostic value of 6MWT is augmented by measuring oxygen saturation (SO2), a cut-off value for SO2 determined post6MWT at baseline < 77 mmHg is associated with clinical worsening in children with PAH. The current study has shown that b-type natriuretic peptide (BNP), biomarker of RV dysfunction, correlates significantly with clinical evolution at time of clinical worsening, a BNP cut-off value > 70 pg/mL in follow-up allows the identification of pediatric PAH patients at risk of clinical worsening. The prognostic

value in follow-up of biomarkers of end-organ failure is supported by the results of the current study, a cut-off value for uric acid > 4.82 mg/dL and a cut-off value for bilirubin > 1.020 mg/dL were associated with clinical worsening. The QTc has been shown to be a prognostic marker in the follow-up (cut-off 400 ms), while a PR over 160 ms at baseline is associated with adverse clinical outcome. The results of the study indicated the prognostic value at baseline of some echocardiographic parameters characterizing RV overload and dysfunction, such as: tricuspid annular plane systolic excursion (TAPSE) (cut-off 17.7 mm), RV fractional area change (FAC) (cut-off 42%), isovolumic contraction time (100 ms), systolic pulmonary arterial pressure (sPAP) (cut-off 102 mmHg), pulmonary artery diameter (cut-off 23.6 mm), tricuspid annulus diameter (cut-off 28 mm). Other echocardiographic parameters have proven their prognostic value in follow: RV myocardial performance index (Tei) (cut- off 0.6), mean pulmonary artery pressure (mPAP) (cut-off 44 mmHg), pulmonary acceleration time (cut-off 80 ms), pulmonary vascular resistance estimated by echocardiography (cut-off 8.5 uW), right atrial area (cut-off 16.2 $cm^2$), left ventricular end-systolic eccentricity index (cut-off 1.63), left ventricular end-diastolic eccentricity index (cut-off 1.42) and isovolumic relaxation time (cut-off 92 ms). Our data indicate the power of non-invasive markers in assessing the risk of clinical worsening and monitoring the effect of treatment in children with PAH. This is particularly important in the youngest patients in whom other clinical endpoints usually used for PAH are difficult to obtain.

## 3rd Study: A correlative study of spirometric parameters and markers of right ventricular dysfunction in pediatric patients with pulmonary arterial hypertension

The third study of the PhD thesis is a prospective, noninterventional study assessing the correlation of spirometric variables with functional and echocardiographic parameters, markers of RV dysfunction in pediatric patients with PAH. The study has a considerable value, representing the first study that evaluated the correlation of pulmonary function indices with echocardiographic parameters that reflect the RV function. The results of the study demonstrated the positive correlations of pulmonary function indices with BNP and with echocardiographic parameters that reflect RV function supporting the idea that resting lung function measurements can be introduced among the follow-up tools in children with PAH. The restrictive pattern was associated with most of the patients of the study, proving that lung compliance is affected in pediatric patients with PAH.

## 4th Study: Effects of MDR1 gene polymorphism on the evolutive course of pediatric pulmonary arterial hypertension

The role of genetics in PAH, both in the risk of developing the disease and in the progression of pulmonary vascular lesions, has been proven. MDR1 gene polymorphism, by modulating P-glycoprotein activity, with role in the inflammatory process and in the protection against oxidative stress, could have important consequences in the development and progression of PAH. The fourth study of the PhD thesis is a prospective, case-control study that evaluated three MDR1 gene polymorphisms: MDR C1236T, MDR G2677T, and MDR C3435T in pediatric patients with PAH. This is the first study to evaluate the role of MDR1 polymorphism in the clinical course of pediatric PAH patients. The results of the study have not demonstrated the role of MDR C1236T, MDR G2677T and MDR C3435T polymorphisms in the evolution of pediatric PAH, however, the present study has opened a new perspective on the genetic and molecular mechanisms involved in PAH progression, including the role of MDR1 polymorphism.

The PhD thesis contribute to the progress of pediatric PAH research by studying the epidemiological profile of pediatric PAH, by evaluating the non-invasive markers as predictors of clinical worsening, by evaluating the pulmonary function at rest, and by evaluating the role of MDR1 gene polymorphisms on the evolutive course of pediatric patients with PAH. A better understanding of the genetic and molecular mechanisms involved in the development and progression of PAH, a better understanding of the natural history and epidemiology of PAH, as well as a multiparametric risk stratification would lead to optimizing the management of pediatric PAH patients.

**Keywords:** pulmonary arterial hypertension, children