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HEMODYNAMIC PARAMETER ASSESSMENT AND MORTALITY RISK FACTOR IDENTIFICATION IN PATIENTS WITH PULMONARY ARTERIAL AND CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Summary of the Doctoral Thesis
for obtaining the degree of a Doctor of Medicine
Speciality – Internal Medicine

Riga, 2018

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The Doctoral Thesis is available in the RSU library and at RSU webpage: www.rsu.lv.

Secretary of the Doctoral Council:

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CONTENTS

LIST OF ABBREVIATIONS

ALT	alanine aminotransferase
ANA	antinuclear antibodies
AST	aspartate aminotransferase
ASD	atrial septal defect
USA	United States of America
AVSD	atrioventricular septal defect
BNP	B–Type natriuretic peptide
BMI	body mass index
CI	cardiac index
CO	cardiac output
CTD	connective tissue diseases
CTEPH	chronic thromboembolic pulmonary hypertension
DNA	deoxyribonucleic acid
ENA	extractable nuclear antigen
ES	Eisenmenger syndrome
FEV	forced expiratory volume
HIV	human immunodeficiency virus
HR	hazard ratio
HTEPH	chronic thromboembolic pulmonary hypertension
IPAH	idiopathic pulmonary arterial hypertension
IQR	interquartile range
RVSP	right ventricule systolic pressure
MI	million inhabitants
mPAP	mean pulmonary arterial pressure
NYHA	New York Heart association
NYHA FK	New York Heart Association functional class
PAH	pulmonary arterial hypertension
PAH–CHD	pulmonary arterial hypertension associated with congenital heart disease
PAH–CTD	pulmonary arterial hypertension associated with connective tissue disease
PCWP	pulmonary capillary wedge pressure

PDA	patent ductus arteriosus
PEA	pulmonary endarterectomy
PH	pulmonary hypertension
PoPH	pulmonary arterial hypertension associated with portal hypertension
PSCUH	Pauls Stradins Clinical university hospital
PVR	pulmonary vascular resistance
RAP	right atrial pressure
RHC	right heart catheterisation
RVSP	right ventricular systolic pressure
SD	standard deviation
TSH	thyroid – stimulating hormone
VSD	ventricular septal defect
WHO	World Health Organisation
WHO FC	WHO Functional classes of pulmonary hypertension
WHO PH group	Pulmonary Hypertension WHO classification group
WU	Wood units
6MWT	six minute walk test

INTRODUCTION

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary artery pressure ≥ 25 mmHg at rest. (Galiè et al., 2016). PH can be caused by either primary increase of pressure in pulmonary arteries, which is called precapillary PH, or it can occur secondary to increase of pressure in venous pulmonary system or pulmonary capillaries – described as pulmonary venous hypertension or postcapillary PH.

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are etiological groups of PH, which are characterized by increased pulmonary vascular resistence and increasing blood pressure in pulmonary arteries, that ultimately results in overload and failure of the right ventricle.

Both of these etiological groups have marked early mortality. Mortality of patients with PAH can be higher than mortality from different types of cancer, including breast and colorectal cancer. Mean survival for these patients without pathogenetic therapy is 2.8 years (Yang et al., 2013; D'Alonzo et al., 1991; Montani et al., 2013).

PAH and CTEPH belong to rare diseases. Prevalence of PAH is approximately 50 cases per 1 000 000 inhabitants. (Peacock et al., 2007). Separate cohorts have reported significantly higher prevalence: 0.5% in patients with HIV infection (Sitbon et al., 2008), up to 12% in patients with systemic scleroderma or other systemic diseases (Hachulla et al., 2005; Mukerjee et al., 2003). Prevalence of CTEPH is 38.4 cases per 1 000 000 inhabitants (Delcroix et al., 2016).

PAH mostly affects patients of working age (mean age on Czech registry is 51.9 years; Jansa et al., 2014).

Since epoprostenol, the first drug approved for treatment of pulmonary hypertension on 1996, PAH–targeted options of treatment have notably increased. Now there are 14 different drugs available for pathogenetic therapy of PAH.

However, there are still a lot of unsolved issues. As this is a rare disease, time until correct diagnosis is usually prolonged. Patients are frequently misdiagnosed or diagnosed in late stages of the disease.

To improve comprehension of possible pathogenetic causes of disease, to monitor the course of disease, to improve timely and precise diagnostic methods and to create more effective treatment strategies, a short–term and long–term PAH treatment evaluation REVEAL registry was created in USA, which is still active (McGoon et al., 2012). Thanks to data from REVEAL registry, the main factors that positively impact survival and quality of life for patients with PAH have been established. (Farber et al., 2015). Similarly, to REVEAL, other countries started creating their own national PAH patient registries. In result there were more patients for whom the progression of disease was slowed, the quality of life increased and mortality decreased. (Farber et al., 2015; Barst et al., 2013).

Evaluating the current situation in Latvia, there haven't been systematic patient follow–up done until 2007. This thesis reveals the first pulmonary hypertension patient study in Latvia, and from 2007 to 2016 patients with pulmonary hypertension were monitored and groups of disease were diagnosed. Epidemiological, hemodynamic and survival data was collected and identification of risk of mortality factors was done for patients with PAH and CTEPH.

When treating patients with pulmonary hypertension, it is important to use risk of mortality calculators that are created based on scientifically proven risk of mortality factors. The main aim of the study was to identify the increased risk of mortality factors. There are multiple ongoing studies in the world based

on PH registries, where by patient follow–up new risk of mortality factors are sought and identified.

Since the gold standard method in diagnosis of pulmonary hypertension is right heart catheterisation, the obtained results were used as the main factor used to calculate the risk of mortality.

When the patients who are in risk of greater mortality are identified, careful monitoring and combined therapy should be used, in cases of IPAH and CTEPH lung transplantation, and pulmonary endarterectomy must be provided respectively.

1. AIM, OBJECTIVES AND HYPOTHESES

1.1. Aim of the thesis

To identify mortality risk factors for patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

1.2. Objectives of the thesis

1. To identify patients from two of PH groups – PAH and CTEPH and collect data on prevalence and incidence of PAH and CTEPH in Latvia.
2. To estimate hemodynamic parameters of patients and calculate one, three and five–year survival of patients.
3. To estimate the impact of initial hemodynamic, functional un demographic parameters on mortality of PAH and CTEPH patients.
4. To establish Latvian PH registry and compare the results to data from other registries.

1.3. Hypotheses of thesis

1. The survival of patients is impacted by the hemodynamic parameters assessed during right heart catheterisation: right atrial pressure, pulmonary vascular resistence, cardiac index, as well as gender, age and functional capacity on time of diagnosis.
2. Mortality is variable for different subtypes of PAH, and it is the highest for patients with idiopathic PAH and PAH associated with connective tissue disease.

2. STUDY MATERIAL AND METHODS

2.1. Study design

Prospective, single–centre observational study on clinical manifestations, hemodynamic parameter values and survival of patients with pulmonary arterial hypertension (WHO PH group 1.) and chronic thromboembolic pulmonary hypertension (WHO PH group 4.).

As for adult patients in Latvia right heart catheterisation and confirmation of PH diagnosis is done only on PSCUH, this can be considered as a national level study.

The study design intends prolonged and regular monitoring of patients, collection of data, data analysis and further use to estimate risk of mortality factors in PAH and CTEPH.

2.2. Patients

Between September 1, 2007 and December 31, 2016, a total of 1239 patients were consulted in PSCUH with suspected pulmonary hypertension, referred after the results of echocardiography to pulmonary hypertension centre by general practicioners, pulmonologists, cardiologists, rheumatologists, internists and specialists of echocardiography.

The main criteria of send the patient to PH specialist were matching clinical presentation and at least one of four PH echocardiography criteria, which are defined in European Society of Cardiologists pulmonary hypertension treatment guidelines of 2004 (Galie et al., 2004):

1) right ventricular systolic pressure (RVSP) of more than 45 mmHg

2) tricuspid regurgitation velocity higher than 3.4 m/s
3) dilation of right ventricle, right atrium
4) paradoxical movement of ventricular septum due to right ventricle overload.

Patients had preserved left ventricular ejection fraction (>50%) and there were no signs of significant aortic or mitral insufficiency or stenosis, FEV1>70% on pulmonary function tests like spirometry and/or bronchodilation test.

After examination and consultation of 1239 patients, 683 of patients matched the aforementioned criteria, and right heart catheterisation was done to confirm the diagnosis.

Pulmonary hypertension was confirmed for 503 patients. These patients were further examined according to diagnostical algorithm provided in pulmonary hypertension guidelines of European Society of Cardiologists on 2004, to determine the WHO pulmonary hypertension clinical group (WHO PH group 1.–5.). All 503 of patients were included in PH registry by their respective clinical group.

Patient inclusion criteria:

Only the patients from WHO PH group 1. and 4., matching the eligibility criteria were included in this study. Patient inclusion criteria (patient should match all the following criteria):

- patient age ≥ 18 years;
- patients who have signed written consent form;
- patients with confirmed pulmonary arterial hypertension (WHO PH group 1.) or patients with chronic thromboembolic pulmonary hypertension (WHO PH group 4.);
- patients with following hemodynamic parameters after right heart catheterisation:
    - mean pulmonary artery pressure ≥ 25 mmHg at rest;
    - pulmonary capillary wedge pressure ≤ 15 mmHg;

- pulmonary vascular resistence ≥ 3 Wood units;
- PAH or CTEPH functional class WHO FC II to WHO FC IV;
- patients with FEV_1 > 70 %.

Patient exclusion criteria:

- patients verified in second, third or fifth group of pulmonary hypertension (WHO PH group 2, 3 or 5);
- hemodynamical parameters acquired during right heart catheterization do not match inclusion criteria;
- significant valvular pathology of the left side (≥ grade 2 mitral or aortic insufficiency, moderate or severe aortic or mitral stenosis).

There were 174 patients overall matching the inclusion criteria of the study: diagnosis of pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension was confirmed and they were included in the study.

Physical examination, further diagnostic, if the necessary data had not been collected before, were done for the 174 patients included in study:

- full blood count (erythrocytes, haemoglobin, thrombocytes, leukocytes);
- biochemistry of blood (ALT, AST, creatinine, TSH, bilirubin);
- immunochemistry analysis (ANA, ENA, double stranded DNA);
- natriuretic peptide;
- pulmonary functional tests (spirography and (or) bronchodilation test);
- electrocardiogram;
- abdominal ultrasonography;
- computer tomography pulmonary angiogram (it was done in PSCUH for all the patients to ensure standardized results);
- 6–minute walk test (done in PSCUH for all patients);
- right heart catheterisation (done in PSCUH for all patients).

2.3. Diagnostic studies

Diagnosis of pulmonary hypertension is made according to the diagnostic algorithm published by European Society of Cardiologists in 2004.

Gold standard for confirmation of PH diagnosis is right heart catheterisation, which is described in the respective subchapter. In addition to right heart catheterisation, 6–minute walk test and other studies are done, to determine the clinical group of pulmonary hypertension (WHO group 1–5) and functional class (NYHA FC).

2.3.1. Right heart catheterisation

Right heart catheterisation (RHC) is done to confirm the diagnosis of PH, to analyse hemodynamic parameter values, assess severity of disease and to check vasoreactivity in pulmonary arteries.

The patient signs informed consent before the procedure. Procedure is relatively safe: mortality is 0.05% and risk of complications – 1.1%.

There are two methods available for RHC, and the choice depends on the presence of cardiac shunt:

1) thermodilution method with Swan–Ganz catheter for patients without a cardiac shunt;
2) Fick's method – for patients with a cardiac shunt (atrial septal defect, ventricular septal defect, abnormal drainage of pulmonary veins etc.).

2.3.2. Six–minute walk test

To evaluate functional status, 6–minute walk test (6MWT) was done for all of the patients according to American Thoracic Society commitee guidelines. (ATS *Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories*, 2002).

Test is done on distance of 30 metres. After the test, the distance covered is calculated and functional class is determined. Before and after the test, oximetry is done with peripheral oximeter, arterial blood pressure and heart rate is measured.

Test is done for newly diagnosed patients with confirmed PAH or CTEPH, and to control the effectiveness of treatment and changes in functional status.

2.4. Identification of analogical studies

To analyse the data obtained in this study in scope of Europe and to evaluate potential opportunities of collaboration between PH centres and registries in future, and to gain knowledge on current state of registries in this region, systematic review of published literature was done, with the aim to identify prospective studies based on data from European adult PH registries, which included patients with PH, PAH or CTEPH, reported registry design, patient hemodynamical parameters and survival.

Systematic literature search was performed to identify studies of registries that included adult patients with PH, PAH and/or CTEPH and reported registry design, patient hemodynamic characteristics and survival. This was done on 9 July 2017 in PubMed database using the following search string: (“pulmonary

hypertension" OR "pulmonary arterial hypertension" OR "chronic thromboembolic pulmonary hypertension") AND ("registry" OR "cohort") NOT (paediatric) [All Fields]. Time was restricted to studies published between January 2000 and October 2017. This search strategy identified 1615 publications. Studies were considered for inclusion by manual screening of article titles (and subsequently, of full articles) to identify prospective registry studies in relevant populations, published in English, which also included survival data. Very small studies (i.e., less than 100 patients with PH) were not included in analysis. In case of multiple similar (i.e., describing the same PH group) studies based on the same registry, the one with larger cohort was selected.

In addition to the three PH registries mentioned in Orphanet report (Humbert et al., 2006; Escribano–Subías et al., 2016; Escribano–Subías et al., 2012; Radegran et al., 2016), ten prospective studies of registries satisfied inclusion criteria (Olsson et al., 2013; Hoeper et al., 2013; Delcroix et al., 2016; Baptista et al., 2013; Korsholm et al., 2015; Mueller–Mottet et al., 2015; Gall et al., 2017; Hurdman et al., 2012; Ling et al., 2012; Cannon et al., 2016). One single–centre study (157 patients with PAH and 82 inoperable CTEPH patients) was excluded from analysis as it mainly focused on the presence of atrial flutter and fibrillation and its effect on patients' survival (Olsson et al., 2013).

Data obtained during the study for this thesis was also used, and it can be viewed in the results section. The results have also been partially published (Skride 2016a; Skride et al., 2016b; Skride et al., 2017).

2.5. Statistical procession of data

Data from this study was processed using *IBM SPSS Statistics 23.0* (*IBM Corp*., *Armonk*, NY, USA), *MedCalc 14.8* (*MedCalc Software bvba*, Belgium) and *Microsoft Excel 2016* (*Microsoft*, *Redmond*, WA, USA).

Following descriptive and analytical statistical methods were used for data analysis:

- The normality of data distribution was assessed by Kolgomorov–Smirnov test. If the data were normally distributed, they were presented as mean value and standard deviation (SD). Otherwise – as median and interquartile range (IQR);
- Differences between two groups were assessed by independent sample t test or nonparametric test (Mann–Whitney test).
- When comparing differences in distribution of categorical parameters (gender) between two separate patient groups chi–squared test or Fishers test was used, if the number of patients in any group was smaller than 5;
- For parameters corresponding to normal distribution, mean values between 3 and more separate patient groups were compared using univariate ANOVA test and Bonferroni *post hoc* analysis;
- For parameters not corresponding to normal distribution, differences between 3 and more separate patient groups were compared using Kruskal–Wallis H test;
- Survival analysis was performed using the Kaplan–Meier method with log–rank test to determine statistically significant differences in survival between two or more separate patient groups;
- Univariate Cox proportional hazards analysis was used to examine the relationships between survival and several parameters measured at the

time of diagnosis. All variables with a $p < 0.2$ were included in multivariate Cox proportional hazards analysis to identify independent risk factors.

- Forest plots of log hazard ratios were constructed for hazard ratio data visualization.
- Probabity was considered statistically significant if value $p < 0.05$.

3. RESULTS

During the research from 2007 to 2016, 1239 patients with suspected pulmonary hypertension were consulted and examined in PSCUH pulmonary hypertension centre. Right heart catheterisation was done for 683 of patients. Pulmonary hypertension was confirmed for 503 of the patients and 174 of the patients matched the study inclusion criteria.

For patients with PAH, respective subgroup was determined according to WHO PH group classification.

By using the total number of patients included in study, prevalence and incidence of PAH and CTEPH was calculated. Lowest estimated incidence of PAH in Latvia in 2016 was 13.7 cases per million inhabitants (MI); prevalence in 2016 – 45.7 cases/MI. For calculations, data on population at the end of 2016 (1.97 million citizens) from Central Statistical Bureau of Latvia was used. Lowest estimated CTEPH incidence on December 2016 was 5.1 cases/MI, prevalence – 15.7 cases/MI.

3.1. Patient distribution by PAH subgroup

From 174 patients included in study, 75% were diagnosed with PAH (n = 130) and 25% with CTEPH (n = 44).

Most common subtypes in patients with PAH:

1) IPAH, n = 53;
2) PAH–CHD, n = 23;
3) PAH–CTD, n = 49;
4) PoPH, n = 4;
5) Drug induced PAH, n = 1.

3.2. Baseline characteristics of PAH un HTEPH patients on the time of diagnosis

Patient's gender, age, body mass index, BNP, functional capacity determined by 6–minute walk test and NYHA functional class, as well as the hemodynamical parameters were the most important parameters used in data analysis.

Patient baseline characteristics – age, gender, hemodynamic parameters, functional class on time of diagnosis in PAH and CTEPH groups are shown in table 3.1.

Table 3.1

Baseline characteristics of PAH and CTEPH patients on the time of diagnosis

Parameter	PAH	CTEPH	p value
Patients, n (%)	130 (75)	44 (25)	—
Females, n (%)	95 (73)	27 (61)	0.142
Age (median), years (IQR)	65 (47–71)	67 (47–73)	0.715
BMI, kg/m^2	28.1 ± 7.5	28.5 ± 7.3	0.736
BNP, pg/ml (IQR)	204 (98–413)	340 (181–756)	**0.044**
6MWT, m	322 ± 122	274 ± 111	0.106
NYHA FC, n (%)			
I	2 (2)	0 (0)	0.123
II	34 (26)	7 (16)	
III	85 (65)	33 (75)	
IV	7 (7)	4 (9)	

Table 3.1 (continued)

Parameter	PAH	CTEPH	p value
NYHA FC, n (%)			
I	2 (2)	0 (0)	0.123
II	34 (26)	7 (16)	
III	85 (65)	33 (75)	
IV	7 (7)	4 (9)	
Hemodynamic			
RVSP, mmHg	71 ± 23	79 ± 19	0.051
RAP, mmHg	11 ± 7	13 ± 8	0.104
mPAP, mmHg	49 ± 18	51 ± 15	0.482
PCWP, mmHg (IQR)	14 (9–15)	12 (8–15)	0.449
PVR, WU (IQR)	6.6 (4.4–10.9)	10.3 (6.9–13.8)	**0.003**
CO, l/min	4.6 ± 1.4	4.0 ± 1.1	**0.023**
CI, l/min/m^2	2.47 ± 0.73	1.93 ± 0.74	**< 0.001**

Values are expressed as mean ± SD or as median with interquartile range (IQR), where appropriate. BMI indicates body mass index; BNP, B–Type Natriuretic Peptide; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; NYHA FC, New York Heart Association functional classification; 6MWD, 6– minute walking test RVSP, right ventricular systolic pressure; PAH, pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WU, Wood units

3.2.1. Patient age

Most often the diagnosis of PAH was made for patients aged 60 to 79 (49% of all PAH patients were in this range); diagnosis of CTEPH was made for patients aged 70 to 79 (46% of all CTEPH patients).

In result median age in PAH and CTEPH groups was similar: in PAH group it was 65 years, interquartile range (IQR): 47–71 years, CTEPH group – 67 years, IQR: 47–73 years, p=0.715.

3.2.2. Patient body mass index

65% of PAH patients and 61% of CTEPH patients were overweight (BMI $\geq$ 25.0 kg/m^2) on the time of diagnosis, which altered the mean BMI in respective groups above normal values (18.5–24.9 kg/m^2): mean BMI in PAH group was 28.1 ± 7.5 kg/m^2, CTEPH group – 28.5 ± 7.3 kg/m^2 p = 0.736. Only 7% of PAH patients were underweight (BMI < 18.5 kg/m^2) on the time of diagnosis.

3.2.3. Patient gender

There were more females both in PAH and CTEPH groups, accounting to 73% and 61% of all patients in these groups respectively, but there was no statistically significant difference found in distribution of gender between these groups (p = 0.142).

Table 3.2

Male and female distribution between the patients included

Subgroup	Total number of patients, n	Number of females, n (%)	Female to male ratio
PAH	130	95 (73)	2.7 : 1
CTEPH	44	27 (61)	1.6 : 1

CTEPH – chronic thromboembolic pulmonary hypertension, PAH – pulmonary arterial hypertension

3.2.4. Patient functional class

On the time of diagnosis, patients of both groups had visible signs of heart failure, as only the smallest share of patients of both groups were in NYHA functional class I or II. In PAH group – 28% of patients, CTEPH – 16%. Comparing patient distribution by NYHA FC, majority of patients in CTEPH group (84%) were in NYHA FC III or IV, but in PAH group the share was slightly smaller (72%). There was not a statistically significant difference in distribution by NYHA FC between the two patient groups $p = 0.123$.

The situation was similar in six–minute walk test results, where CTEPH patients walked shorter distance (mean 322 ± 122 m) compared to PAH group (274 ± 111 m), but statistical significance was not found ($p = 0.106$).

Patients in CTEPH group had noticeably higher values of heart failure marker –BNP– the mean was 340 pg/ml compared to 204 pg/ml in PAH group, $p = 0.044$.

3.2.5. Patient distribution by PH group and NYHA class

To asess whether there were significant differences in 6MWT results and hemodynamic parameters depending on NYHA functional class at the time of diagnosis, PAH and CTEPH patients were divided in three subgroups depending on their NYHA FC. Since the number of patients in NYHA FC I was relatively small, for the purposes of this analysis they were added to NYHA FC II. Patients in NYHA FC III and IV were distinguished separately.

Statistically significant difference in PAH patient group with varying NYHA FC's was observed in mean 6MWT results, CO and CI mean values (p values – < 0.001, 0.043 un 0.012 respectively). After *post hoc* analysis of these

parameters using Bonferroni method, it was discovered that results of 6MWT statistically differed in all three subgroups ($p < 0.001$), but CO and CI values differed only between FC I–II and FC IV, as well as FC III and FC IV (p values for CO – 0.046 and 0.048 respectively; p values for CI – 0.009 and 0.021 respectively). There were no other statistically significant differences found for other parameters between the three NYHA FC subgroups.

In CTEPH group, statistically significant difference between varying NYHA FC's was observed in 6MWT results, mean pulmonary artery pressure (mPAP) and PVR values (p values – 0.008, 0.011 and 0.033 respectively). *Post hoc* analysis using Bonferroni method revealed, that the difference in 6MWT results was statistically significant only between FC I–II an FC IV, $p= 0.006$, but for mPAP statistically significant difference was found between FC I–II and FC III, and FC I–II and FC IV (p values – 0.035 and 0.018 respectively). After analysing RVSP, RAP, PCWP, CO and CI values, there were no statistically significant differences among the FC subgroups.

3.3. Baseline characteristics of PAH subgroups

The baseline characteristics of disease for PAH subgroup patients on the time of diagnosis are shown in table 3.3.

Table 3.3

Baseline characteristics of PAH subgroup patients on the time of diagnosis

Parameter	PAH			
	IPAH	**PAH–CTD**	**PAH–CHD**	**PoPH**
Patients, n	53	23	49	4
Females, n (%)	34 (64)	21 (91)*	36 (73)	3 (75)
Age, years(IQR)	68 (55–74)	65 (42–68)	55 (38–72)*	44 (39–47)*
BMI, kg/m^2	30.7 ± 8.2	27.9 ± 6.3	24.8 ± 5.9*	31.2 ± 5.3
BNP, pg/ml (IQR)	217 (141–408)	253 (77–520)	177 (71–235)	174 (103–817)
6MWT, m	352 ± 122	239 ± 89*	358 ± 107	298 ± 211
NYHA FC, n (%)				
I	0 (0)	0 (0)	2 (4)	0 (0)
II	15 (28)	3 (13)	14 (29)	2 (50)
III	36 (68)	18 (78)	29 (59)	1 (25)
IV	2 (4)	2 (9)	4 (8)	1 (25)
Hemodynamic				
RVSP, mmHg	75 ± 18	63 ± 18*	70 ± 29	73 ± 9
RAP, mmHg	11 ± 6	11 ± 6	11 ± 7	20 ± 9*
mPAP, mmHg	48 ± 14	39 ± 11*	54 ± 22	60 ± 7
PCWP, mmHg (IQR)	14 (9–15)	13 (8–14)	–	15 (14–15)

Table 3.3 (continued)

Parameter	PAH			
	IPAH	PAH–CTD	PAH–CHD	PoPH
PVR, WU (IQR)	7.9 (4.9–12.6)	5.1 (3.6–8.4)*	5.4 (3.3–17.1)	7.7 (5.2–15.9)
CO, l/min	4.3 ± 1.4	4.8 ± 1.2	4.7 ± 1.6	5.8 ± 2.5*
CI, l/min/m^2	2.31 ± 0.74	1.57 ± 0.55	2.63 ± 0.79	2.88 ± 1.02

Values are expressed as mean ± SD or as median with interquartile range (IQR), where appropriate. BMI indicates body mass index; BNP, B–Type Natriuretic Peptide; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; NYHA FC, New York Heart Association Functinal classification; 6MWD, 6 minutes walking test RVSP, right ventricular systolic pressure; PAH, pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WU, Wood units. * $p < 0.05$, compared to IPAH

3.3.1. Patient age

The age structure of patients on time of diagnosis in different PAH subgroups was similar for PAH group in general, the patients were mostly diagnosed on age of 60 to 79, except for small group of patients in PoPH subgroup (n = 4), where all the patients were aged 38 to 47.

The calculated median age was 68 years (IQR: 55–74) in IPAH group, 65 years (IQR: 42–68) in PAH–CTD group, 55 years (IQR: 38–72) in PAH–CHD group and 44 years (IQR: 39–47) in PoPH group. The differences detected in PAH–CHD and PoPH groups were statistically significant comparing to IPAH group.

3.3.2. Gender

Analysing the distribution of patients between different PAH subgroups the lowest proportion of females was observed in idiopathic PAH subgroup, where females amounted for 64% of all IPAH patients, female to male ratio being 1.8:1. The highest proportion of females was observed in PAH–CTD subgroup, where females amounted to 91% of all patients of subgroup, resulting in female to male ratio of 10.5:1, and the difference was statistically significant compared to ratio seen in IPAH subgroup. ($p = 0.024$).

Female proportion in PAH–CHD subgroup was 73% of all patients of the subgroup, resulting in female to male ratio of 2.8 : 1, which is higher than the gender ratio of IPAH group, but the difference was not statistically significant ($p = 0.311$). In PoPH subgroup three out of four patients were female (75%), female to male ratio being 3 : 1, but due to small number of patients the ratio was not compared to IPAH subgroup.

3.3.3. Baseline characteristics of PAH associated with congenital heart disease subgroup

The type of congenital defect and baseline characteristics of disease for PAH–CHD patients is shown in table 3.4.

Table 3.4

Baseline characteristics of patients with PAH associated with congenital heart disease

Characteristic	Eisenmenger syndrome (n = 11)	Non–Eisenmenger syndrome		Total (n = 49)
		Closed defect (n = 10)	Defect not closed (n = 28)	
Females	64 %	40 %	89 %	73 %
Age, years(IQR)	29 (26–49)*	58 (47–71)	67 (54–74)	55 (38–72)
BMI, kg/m^2	20.9 ± 5.0*	27.1 ± 6.1	25.4 ± 5.7	24.8 ± 5.9
Type of defect, n (%)				
ASD	1 (9)	5 (50)	24 (86)	30 (61)
VSD	8 (73)	4 (40)	4 (14)	16 (33)
AVSD	1 (9)	0 (0)	0 (0)	1 (2)
PDA	0 (0)	1 (10)	0 (0)	1 (2)
Single ventricle	1 (9)	0 (0)	0 (0)	1 (2)
NYHA FC, n (%)				
I	0 (0)	1 (10)	1 (3,5)	2 (4)
II	1 (9)	3 (30)	10 (36)	14 (29)
III	9 (82)	5 (50)	15 (53,5)	29 (59)
IV	1 (9)	1 (10)	2 (7)	4 (8)
6MWT, m	341 ± 106	409 ± 112	344 ± 104	358 ± 107

Table 3.4 (continued)

Characteristic	Eisenmenger syndrome (n = 11)	Non–Eisenmenger syndrome		Total (n = 49)
		Closed defect (n = 10)	Defect not closed (n = 28)	
Hemodynamic parameters:				
RVSP, mmHg	82 ± 38	51 ± 16	73 ± 27	70 ± 29
RAP, mmHg	7 ± 4	14 ± 7	11 ± 8	11 ± 7
mPAP, mmHg	80 ± 9*	46 ± 12	47 ± 21	54 ± 22
PVR, WU (IQR)	17.9 ± 4.1*	5.7 ± 2.9	5.7 ± 5.5	8.9 ± 7.0
CO, l/min	4.7 ± 0.7	5.1 ± 2.4	4.5 ± 1.2	4.7 ± 1.6
CI, l/min/m^2	2.93 ± 0.55	2.65 ± 1.17	2.49 ± 0.56	2.63 ± 0.79

6MWT – 6–minute walk test, ASD – atrial septal defect, AVSD – atrioventricular septal defect, CO – cardiac output, CI cardiac index, IQR – interquartile range, BMI – body mass index, RVSP– right ventricular systolic pressure, mPAP – mean pulmonary artery pressure, NYHA FC – New York Heart Association functional classification, PDA – patent ductus arteriosus, PVR – pulmonary vascular resistence, RAP – right atrial pressure, VSD – ventricular septal defect.
* $p < 0.05$, comparing to patients with non–Eisenmenger syndrome

The median of age on the time of diagnosis was 55 years (range: 23–82 years). 11 patients (23%) had Eisenmenger syndrome (ES). Patients with ES were significantly younger than non–ES patients: median of age 29 (23–55) and 62 (23–82) years respectively, $p < 0.001$.

From the patients included in the study, most were females (73%). After analysis of gender distribution between ES and non–ES groups, there was no

statistically significant difference observed p = 0.45. Female proportion in these groups was 64% and 76 % respectively.

Atrial septal defect (ASD) was the most frequent underlying defect among all patients (61%). Most of the ASD's and ventricular septal defects (VSD) (83%; n = 25 and 75%; n = 12, respectively) had not been closed. Of all patients with VSD and PAH, 8 (50%) patients had ES. In comparison, only 1 patient with ASD had ES (4% of all ASD patients). There was one patient with atrioventricular septal defect and one with single ventricle, both of which had ES.

In all three of subgroups the majority of patients were in NYHA FK class III or IV (91 %; 60 % and 61 % respectively), and after comparing patients with ES with NYHA FC I and II subgroups, no statistically significant difference was found in distribution of NYHA FC's – p value 0.15 and 0.12 respectively.

Mean 6–minute walk test result in study was 341± 106 m and there were no significant differences in 6MWT result depending on gender or presence of ES (p = 0.36 and 0.69, respectively).

Mean mPAP and PVR were significantly higher in ES patients than in non–ES patients (80 ± 9 mm Hg and 17.9 ± 4.1 WU vs. 47 ± 29 mm Hg and 5.7 ± 4.5 WU, respectively; p < 0.001 in both cases).

3.4. Analysis of parameters obtained during right heart catheterisation

Hemodynamic parameters for patients from PAH and CTEPH groups, obtained during right heart catheterization and transthoracic echocardiography reveal that patients with PAH and CTEPH have markedly elevated pressure on the right side of heart and in pulmonary arteries.

3.4.1. Right atrial pressure

Right atrial pressure (RAP), measured during right heart catheterisation was elevated (RAP upper limit of normal– 8 mmHg) in majority of (RAP upper limit of normal– 8 mmHg) patients: 65 % or 85 patients with PAH and 68 % or 30 patients with CTEPH. RAP in CTEPH group was 13 ± 8 mmHg, PAH group– 11 ± 6 mmHg; median 11 mmHg (IQR: 8–16) and 10 mmHg (IQR: 6–15) respectively. The difference was not statistically significant ($p = 0.12$).

The situation was similar for patients in different PAH subgroups. Highest RAP – 20 ± 9 mmHg – was observed in patients with portopulmonary hypertension, compared to 11 ± 6 mmHg in IPAH group, 11 ± 7 mmHg in patients with PAH–CHD and 10 ± 6 mmHg in patients with PAH–CTD (the only difference that was statistically important compared to IPAH group was observed in patients with portopulmonary hypertension, $p = 0.01$).

Right atrial pressure in other PAH subgroups (patients with idiopathic PAH associated with connective tissue disease, PAH associated with congenital heart disease) was equal.

3.4.2. Mean pulmonary artery pressure

The mean pulmonary artery pressure for CTEPH and PAH patient groups (mPAP upper limit of normal 20 mmHg) (Nauser et al., 2001)) was equal: 49 ± 18 mmHg in PAH group and 51 ± 15 mmHg in CTEPH group ($p = 0.482$). Median – 46 mmHg (IQR: 35–58) and 51 mmHg (IQR: 41–61) respectively. The difference observed had no statistical significance ($p = 0.482$).

After analysis of mean pulmonary artery pressure data among various PAH subgroups, it was concluded that mPAP in patients with idiopathic PAH,

PAH–CHD and portopulmonary hypertension is equal: mean mPAP in each group was 48 ± 14 mmHg, 54 ± 22 mmHg and 60 ± 7 mmHg respectively (the difference observed between these groups was not statistically significant p>0.05). Statistically significant difference was observed only for PAH–CTD group (in comparison to IPAH group), where mean mPAP was 39 ± 11 mmHg (p = 0.011).

3.4.3. Pulmonary vascular resistence

Significantly elevated pressure in right side of heart and pulmonary arteries may be present due to increased resistence of pulmonary blood vessels or pulmonary vascular resistence (PVR, upper limit of normal – 2 WU) which is noticeably greater in CTEPH patients: median PVR – 10.3 Wood units (IQR: 6.9–13.8) compared to 6.6 Wood units (IQR: 4.4–10.9) in PAH group, p = 0.016.

PVR was analysed between the various PAH subgroups. Mean pulmonary vascular resistence in patients with idiopathic PAH was 9.2 ± 4.8 Wood units, patients with PAH–CHD: 8.9 ± 7.0 Wood units and patients with portopulmonary hypertension: 9.6 ± 5.9 Wood units. The differences observed in comparison to IPAH group were not statistically significant (p > 0.05). Statistically significant difference in comparison to IPAH group was seen only patients with PAH–CTD, where mean PVR was 6.6 ± 3.5 WU (p = 0.021)

3.4.4. Other hemodynamic parameters

Cardiac output (CO) and cardiac index (CI) values were lower than normal in PAH and CTEPH patient groups, and both parameters were lower with a statistical significance in CTEPH group: 4.0 ± 1.1 l/min and

1.93 ± 0.74 l/min/m^2 in comparison to 4.6 ± 1.4 l/min and 2.47 ± 0.73 l/min/m^2 in PAH group, p value 0.023 un < 0.001 respectively.

Right ventricular systolic pressure (RVSP) measured on echocardiogram was 71 ± 23 mmHg and 79 ± 19 mmHg ($p = 0.051$) in PAH and CTEPH groups respectively.

3.5. Patient survival

Average duration of monitoring for all patients (n = 174) included in study was 34 ± 28 months, median– 26 (IQR: 13–49) months.

Among the patients included in study one patient with IPAH received a lung transplant and six patients with CTEPH underwent pulmonary endarterectomy, these patients were censored.

Survival of patients included in the study are shown on table 3.5.

Table 3.5.

One, three and five–year survival of included patients

Diagnosis	Survival		
	1 year	3 years	5 years
PAH	88 %	73 %	58 %
IPAH	85.8 %	63.6 %	63.6 %
PAH–CTD	78.3 %	67.5 %	39.4 %
PAH–CHD	98 %	90.4 %	68.6 %
CTEPH	84 %	76 %	44 %
Average for all patients	86.9 %	70.6 %	55.6 %

CTEPH – chronic thromboembolic hypertension, IPAH – idiopathic pulmonary arterial hypertension, PAH – pulmonary arterial hypertension, PAH–CHD – pulmonary hypertension associate with congenital heart disease, PAH–CTD – pulmonary hypertension associated with connective tissue disease

In study p value for total survival was calculated in comparison to IPAH patient group, and it was: PAH–CTD against IPAH – p = 0,436, PAH–CHD against IPAH – p = 0,034, CTEPH against IPAH – p = 0,526. Total one–year survival in PAH group was 88 %, CTEPH – 84 %. Three and five–year survival in PAH group is 73 % and 58 %; CTEPH group– 76 % and 44 % (p = 0,192).

Cumulative survival for patients in PAH subgroups – IPAH, PAH–CTD, PAH–CHD and CTEPH group was calculated in timeframe up to 120 months and is shown in figure 3.1.

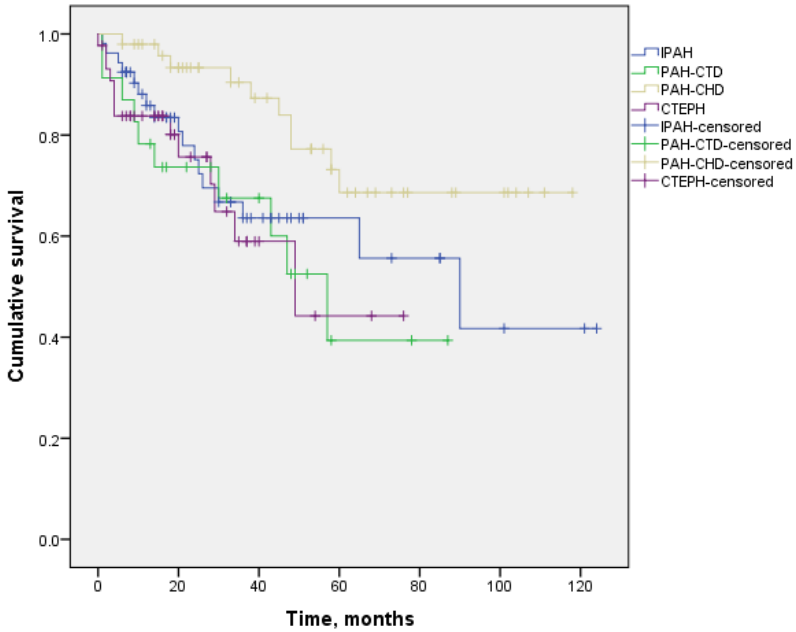

Figure 3.1. ***Kaplan–Meier*** **estimates of cumulative survival for patients with various groups of PAH and CTEPH**

IPAH – idiopathic pulmonary arterial hypertension, PAH–CHD – pulmonary arterial hypertension in association with congenital heart disease, PAH–CTD – pulmonary arterial hypertension in association with connective tissue disease, CTEPH – chronic thromboembolic pulmonary hypertension

Based on data from this study, patients with PAH–CHD had the highest cumulative survival after 120 months, compared to the other two PAH subgroup patient groups. For patients with PAH–CTD and CTEPH the curve of cumulative survival does not reach 120 months, in CTEPH patient group it is 76 months, but in PAH–CTD – 87 months. For patients with CTEPH this relatively short time of follow up can be explained with late diagnosis of the disease which decreases survival. Calculating, whether the cumulative survival varies with statistical significance for patients with IPAH, PAH–CTD, PAH–CHD and CTEPH p value was – 0.032.

3.6. Identification of mortality risk factors

To identify the mortality risk factors for PAH and CTEPH patients included in this study, Cox's regression analysis was used to determine hazard ratio for several of the characteristic parameters: age, gender, 6MWT, right atrial pressure, mean pulmonary artery pressure, pulmonary vascular resistence and cardiac index values. In addition, to analyse mortality of risk factors –age and 6MWT – each group of patients was divided in two fractions, considering age of total PH population and mean 6MWT result, which were 65 years and 300 m (table 3.6).

Table 3.6

Risk of mortality factors for patients with PAH and CTEPH

Risk factor	PAH [HR (95 % CI)]	p value	CTEPH [HR (95 % CI)]	p value
Age, years	1.01 (0.99–1.03)	0.254	0.97 (0.94–1.00)	**0.025**
≤ 65	Reference		Reference	
> 65	1.53 (0.81–2.89)	0.188	0.29 (0.09–0.95)	**0.041**
Gender				
Females	Reference		Reference	
Males	1.13 (0.57–2.21)	0.733	0.72 (0.22–2.36)	0.590
6MWT, m	0.99 (0.99–1.00)	**0.004**	1.00 (0.99–1.01)	0.906
> 300	Reference		Reference	
≤ 300	3.36 (1.27–8.89)	**0.015**	1.91 (0.73–4.64)	0.329
RAP, mmHg	1.10 (1.05–1.16)	< **0.001**	1.07 (0.99–1.14)	0.077
mPAP, mmHg	1.00 (0.99–1.02)	0.857	1.05 (1.01–1.10)	**0.024**
PVR, WU	1.02 (0.96–1.08)	0.552	1.13 (1.00–1.27)	**0.045**
CI, l/min/m^2	1.02 (0.64–1.61)	0.935	0.90 (0.31–2.61)	0.853

6MWT – 6–minute walk test, CI – cardiac index, mPAP – mean pulmonary artery pressure, PVR – pulmonary vascular resistence, RAP – right atrial pressure

3.6.1. Identification of independent mortality risk factors in both patient groups

To discover independent mortality risk factors in both patient groups, parameters that had p value <0.2 by Cox's regression method, were included in multivariate analysis.

In PAH patient group four parameters corresponded this criteria: age – > 65 years, 6MWT result – ≤ 300 m and right atrial pressure; in CTEPH group –

five parameters: age, age – > 65 years, right atrial pressure, mean pulmonary artery pressure and pulmonary vascular resistence.

After analysis of multivariate regression, in PAH patient group higher 6MWT result and higher pressure reached statistical significance as independent mortality risk factors – their hazard ratio (95% CI) was 0.99 (0.98–1.00), p = 0.016, and 1.09 (1.01–1.18), p = 0.027 respectively. None of the analysed parameters were identified as independent risk of mortality factor in CTEPH group (table 3.7).

Thereby, the independent mortality risk factors in PAH patient group can be considered as sufficiently credible, however the data obtained from CTEPH groups is not representable due to small number of patients (and cases of death).

Table 3.7

Results from analysis of mortality risk factors multivariate regression

Parameter	HR (95 % TI)	p value
PAH: Age >65 years	0.63 (0.20–2.03)	0.442
PAH: 6MWT, m	0.99 (0.98–1.00)	**0.016**
PAH: 6MWT ≤ 300 m	0.76 (0.14–4.12)	0.746
PAH: RAP, mmHg	1.09 (1.01–1.18)	**0.027**
CTEPH: Age, years	0.95 (0.90–1.01)	0.094
CTEPH: Age > 65 years	0.81 (0.06–10.36)	0.868
CTEPH: RAP, mmHg	1.05 (0.97–1.15)	0.250
CTEPH: mPAP, mmHg	1.00 (0.93–1.07)	0.927
CTEPH: PVR, WU	1.06 (0.89–1.25)	0.514

6MWT – 6–minute walk test, CTEPH – chronic thromboembolic pulmonary hypertension, mPAP – mean pulmonary artery pressure, PAH – pulmonary arterial hypertension, RAP – right atrial pressure, PVR – pulmonary vascular resistence, WU – Wood unit

4. DISCUSSION

The data obtained during the study shows that from 2006 the number of patients has increased, with the fastest increase occurring over the last few years. This tendency can be explained with improvements in diagnostics and knowledge about this disease among specialists.

In this study patients with pulmonary hypertension were divided in groups based on multiple criteria: by diagnosis – CTEPH and PAH patient groups, by subgroup of PAH, by functional class, age, gender and hemodynamical parameters. The groups and subgroups were analysed and compared.

Researching the patient distribution by PH group, there were four times more patients' in PAH group than in CTEPH. In CTEPH group there were proportionally more males, patients were slightly older and in worse functional class – higher proportion of patients in NYHA FC III and IV, lower six–minute walk test results; as well as higher right ventricular systolic pressure, right atrial pressure and mean pulmonary artery pressure. In addition, CTEPH patients had statistically significant higher natriuretic peptide level, higher pulmonary vascular resistence and lower cardiac output and cardiac index values, confirming that in general patients with CTEPH are diagnosed in hemodynamically worse state than PAH patients.

By dividing patients from each group – PAH and CTEPH– in three subgroups depending on NYHA FC, confirmed that six–minute walk test result had statistically significant difference in patients in different NYHA FC's both in PAH and CTEPH groups. In PAH group differences were observed for CO and CI values, but in CTEPH group – mPAP and PVR values. Althought the results did not reach statistical significance, in NYHA FC IV patients compared to NYHA FC I–II subgroups, had higher RAP, PCWP and PVR, indicating on

higher pressure and resistence in pulmonary circulation if the functional class is worse.

After dividing PAH patients in subgroups, the most patients were in IPAH subgroup. Overall the parameters of PAH subgroup patients were relatively homogenic, with few exceptions.

Analysing patients with PAH–CHD, it was observed that patients with Eisenmenger syndrome are younger and are being diagnosed in worse functional state (higher NYHA FC), higher mPAP and PVR than non–Eisenmenger syndrome patients. The limitation of functional capacity for patients with Eisenmenger syndrome can be explained with high PVR values, which results in right ventricular overload and leads to reversion of shunt from right to left side of heart, significantly decreasing oxygen concentration in arterial blood.

Since right heart catheterisation is considered gold standard in diagnosis of PH, for identification of factors impacting patient survival, hemodynamic parameters measured during this procedure were analysed primarily. As the total amount of PAH and CTEPH patients is relatively small, when analysing significance of mortality risk factors criteria in addition to p value of the specific parameter the mean hazard ratio and 95% confidence interval was calculated.

Results of this study show that for PAH patients the most important mortality risk factors are: greater age on the time of diagnosis (specifically >65 years), male gender, lower 6MWT result (specifically ≤ 300 m) and higher PVR value. From these risk factors only 6MWT result and right atrial pressure were statistically significant.

In CTEPH group the most important mortality risk factors were: younger age on the time of diagnosis (≤ 65 years), female gender, 6MWT result ≤ 300 m, higher right atrial pressure, higher mPAP, and higher PVR value. Statistically significant were: age, mPAP and PVR.

The data obtained in this study was compared to 13 prospective studies, based on data from 11 national and multinational PH registries from 17 European

countries (16 of them from European Union) and Canada (single PH centre in Toronto as a part of international CTEPH registry). Four of the studies were based on single–centre registry, all the other studies encompassed from 5 (Portuguese registry) to 31 (Spanish REHAP registry) centres per study.

The combined PH patient study population was 10 109 (5 164 PAH and 3 326 CTEPH patients). Three largest studies represented 44% of combined study population.

All registries had prospective design with inclusion criteria mainly based on international guidelines requiring confirmation of PH by RHC– mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest, and (for PAH and CTEPH) pulmonary capillary wedge pressure (PCWP) ≤15 mmHg. Only international CTEPH registry permitted inclusion of patients with mPAP ≥30 mmHg during exercise, a diagnostic criterion, which due to the lack of reliable data was abandoned by expert consensus in 2009 and not reintroduced in the recent PH guidelines (Simonneau et al., 2013; Badesch et al., 2009).

When analysing studies by the study cohort, 4 studies described only PAH (or its subgroup) cohort, 3 studies– CTEPH only, 4 studies described both PAH and CTEPH patients and 3 studies included all 5 PH groups. Majority of studies included only adult patients (≥18 years old), however Portuguese and REHAP registries included patients >14 years old, and both Denmark and Giessen (Gi–PH–Reg) registries did not specify patient age in their inclusion criteria. Data from eleven PAH registries is shown in table 4.1.

Table 4.1

Demographic, clinical, and hemodynamic characteristics of PAH patients in national and multinational registries from different countries in Europe

Registry	Age, years	NYHA II/III/IV, %	6MWT, m	RAP, mm Hg	mPAP, mmHg	PVR, VU	PCWP, mmHg	CI, $L \cdot min^{-1} \cdot m^{-2}$
Latvian	59 ± 16	26/65/7	322 ± 122	11 ± 7	49 ± 18	8 ± 5	12 ± 4	2.4 ± 0.7
Portugese (Baptista et al., 2013)	43 ± 16	27/51/20	–	8 ± 6	51 ± 18	11 ± 7	10 ± 4	2.7 ± 1.1
REHAP (Escribano–Subías et al., 2012)	45 ± 17	31[a]/58/11	363 ± 120	9 ± 5	54 ± 16	12 ± 6	–	2.6 ± 0.9
Swedish (Radegran et al., 2016)	67 ± 22	21/68/9	280 (224)[b]	7 (6)[b]	45 (16)[b]	9 (6)[b]	8 (5)[b]	2.4 (1.0)[b]
Danish (Korsholm et al., 2015)	50 ± 21	30[a]/62/8	328 ± 131	10 ± 6	49 ± 15	10 ± 7	11 ± 5	2.4 ± 0.9
Swiss (Mueller–Mottet et al., 2015)	57 ± 16	24/57/17	362 ± 137	9 ± 4	48 ± 15	9 ± 6	12 ± 7	2.5 ± 0.8
Gi–PH–Reg (Gall et al., 2017)	51 ± 16	19/59/22	325 ± 126	8 ± 6	51 ± 16	11 (9)[b]	8 ± 4	2.3 ± 0.8
ASPIRE[c] (Hurdman et al., 2012)	54 ± 18	–/64/14	–	10 ± 6	48 ± 13	10 ± 6	9 ± 3	2.7 ± 0.9

Table 4.1 (continued)

Registry	Age, years	NYHA II/III/IV, %	6MWT, m	RAP, mm Hg	mPAP, mmHg	PVR, VU	PCWP, mmHg	CI, $L \cdot min^{-1} \cdot m^{-2}$
UK and Irish (Ling et al., 2012)	50 ± 17	16[a]/67/17	292 ± 123	10 ± 6	54 ± 14	13 ± 6	9 ± 4	2.1 ± 0.7
French (Humbert et al., 2006)	50 ± 15	–/75 (III–IV)	329 ± 109	8 ± 5	55 ± 15	–	8 ± 3	2.5 ± 0.8
COMPERA[e] (Hoeper et al., 2013)	65 ± 15	9/75/16	293 ± 126	8 ± 5	44 ± 12	10 ± 6	10 ± 3	2.2 ± 0.7

[a] – NYHA class I–II [b] – Data presented as median (interquartile range), where available. [c] – patients with pulmonary veno occlusive disease (n = 2) not included in analysis, [d] – IPAH, HPAH and anorexigenic induced PAH, [e] – only IPAH patients
CI – cardiac index, CTEPH – chronic thromboembolic pulmonary hypertension, mPAP – mean pulmonary artery pressure, NYHA FC– NYHA functional classification, PCWP – pulmonary capillary wedge pressure, PAH – pulmonary arterial hypertension, PVR – pulmonary vascular resistence, RAP – right atrial pressure, WU – Wood units, 6MWD – six–minute walk test

Most studies, being prospective, included only incident patients, however, REHAP, French, Swiss and Gi–PH–Reg registries had a proportion (ranging 3–84%) of prevalent patients for whom diagnosis had been established before enrolment in the registry. Data collection in several registries (e.g., Gi–PH–Reg, UK and Ireland registry) had started in 1990s, however, most registries were established in 2000s. Study duration ranged from 1 to 18.6 years.

By analysing patient distribution between PAH and CTEPH groups (not taking in account studies analysing these groups separately) it is seen, that in these mixed registry studies there are more patients with PAH than CTEPH: PAH patients contributed from 33% of total patients in publication of Gi–PH–Reg registry to 84% in publication of REHAP registry. After reviewing studies, which

included PAH patients, and patient distribution by PAH subgroups, it can be seen, that although the proportion changes, most patients have IPAH. Moreover, there are separate registries (like international COMPERA registry) where IPAH patients are studied exclusively. The second and third in terms of number of patients are PAH–CTD and PAH–CHD groups respectively: PAH–CTD is more common in data published using Portugese, Swedish (SPAHR), Gi–PH–Reg and French national registries (26%, 31 %, 21 % and 16 % of all patients with PAH respectively); PAH–CTD was more frequent in studies of Latvian, REHAP, Danish and ASPIRE registries (38 %, 36 % and 33 % of all patients with PAH respectively). It should be noted, that a fair share of PAH patients (> 20 % of PAH patients) from REHAP, Gi–PH–Reg and French registries did not belong to any of the before mentioned three PAH subgroups – IPAH, CTD–PAH, CHD–PAH, and most patients had PoPH (6 %, 7 % and 10 % of all patients with PAH respectively). For comparison: other PAH subgroups contributed merely to 4% of total number of PAH patients in this study (only 3% of PAH patients had PoPH).

Review of studies that included patients with CTEPH, reveals that proportion of CTEPH patients in context of all other patients is quite variable, except for international CTEPH registry and REHAP, United Kingdom and Irish registry studies, created solely for research of CTEPH patients and in which CTEPH patients amount to total of 100% of patient population. It is variable in other registries – from 16% in mixed REHAP registry study and 18% in ASPIRE registry, up to 42% in data published from Portugese registry.

Table 4.2

Demographic, clinical, and hemodynamic characteristics of CTEPH patients in national registries from different countries in Europe

Registry		Age, years	NYHA II/III/IV, %	6M WT, m	RAP, mm Hg	mPAP, mmHg	PVR, WU	PCWP, mmHg	CI, $L \cdot min^{-1} \cdot m^{-2}$
Latvian	All CTEPH patients.	59 ± 17	16/75/9	274 ± 111	13 ± 8	51 ± 15	10 ± 5	11 ± 4	2.0 ± 0.6
Portuguese (Baptista et al., 2013)	All CTEPH patients.	60 ± 13	21/46/32	–	11 ± 5	47 ± 10	11 ± 6	10 ± 3	2.5 ± 1.1
REHAP (Escribano–Subías et al., 2016)	PEA	50 (24) [a]	28[b]/68/4	400 (185) [a]	–	48 ± 13	9 (7)[a]	–	–
	No PEA	69 (20)[a]	30[b]/62/9	320 (197) [a]	–	45 ± 12	8 (7)[a]	–	–
Swedish (Radegran et al., 2016)	All CTEPH patients	70 ± 14	20/73/8	345 (198) [a]	7 (7)[a]	46 (17)[a]	9 (5)[a]	10 (6)[a]	2.2 (1,0)[a]
Swiss (Mueller–Mottet et al., 2015)	All CTEPH patients.	63 ± 14	–	365 ± 138	9 ± 6	45 ± 12	10 ± 6	12 ± 6	2.3 ± 0.6
Gi–PH–Reg (Gall et al., 2017)	All CTEPH patients	62 ± 13	15/60/25	308 ± 116	8 ± 5	44 ± 13	9 (7)[a]	9 ± 4	2.2 ± 0.6

Table 4.2 (continued)

Registry		Age, years	NYHA II/III/IV, %	6MWT, m	RAP, mmHg	mPAP, mmHg	PVR, WU	PCWP, mmHg	CI, L·min^{-1}·m^{-2}
ASPIRE (Hurdman et al., 2012)	All CTEPH patients	61 ± 15	—/70/17	—	11 ± 6	48 ± 11	9 ± 5	11 ± 5	2.5 ± 0.7
UK and Irish (Cannon et al., 2016)	PEA	57 ± 15	9/68/23	260 ± 126	—	47 ± 11	10 ± 5	—	—
International CTEPH (Delcroix et al., 2016)	PEA	60	19[b]/69/12	340[a]	9[a]	48[a]	9[a]	10[a]	2.2[a]

[a] – Data presented as median (interquartile range), where available. [b] – NYHA class I–II

PAH incidence ranged from 0.9 cases per million inhabitants (MI) in ASPIRE registry to 13.7 cases/MI in Latvia. Lowest PAH prevalence was reported in France– 15 cases per million adult inhabitants (MAI), however, French registry study reported data obtained over period of only one year, therefore considerably underestimating true PAH prevalence in France. Highest PAH prevalence was observed in Sweden– 49 cases/MI and Latvia– 45.7 cases/MI.

Only 4 registries reported incidence and/or prevalence of CTEPH. The incidence of CTEPH was approximately 3 times lower than that of PAH, ranging from 0.3–3.7 cases/MI in ASPIRE registry to 5.1 cases/MI in Latvia. Lowest

CTEPH prevalence was reported in Spain– 3.2 cases/MAI, highest– in Sweden– 19 cases/MI.

Comparing data from this study to the data collected during the systematic literature review of studies of European PH registries, diagnosis of PH or patient inclusion criteria in these studies have been united, because they had been based on internationally recognized guidelines made by PH expert commission, even though the guidelines have slightly changed in the extensive time range of these studies (Poscia, 2014).

Age, gender as well as distribution by PH diagnosis did not significantly differ between Latvian and European registries and similarly to Europe, PH patients in Latvia are diagnosed with progressed disease which is reflected in their worse functional status (high NYHA functional class, low 6MWT and hemodynamic parameters (high RAP, mPAP, PVR, low CI).

Pulmonary endarterectomy was performed in only 16% of Latvian CTEPH patients which is one of the lowest proportions in Europe and translates in mere 7 PEA procedures performed over period of 9 years. This could possibly be due to the high procedure costs (approximately 30 000 euros) and lack of financial support from government, despite the positive effect of PEA on patient quality of life and survival. Given the low CTEPH patient survival in Latvia, it is clear that Latvia must make a better effort to offer procedure for more CTEPH patients who could benefit from PEA. (Galie et al., 2016).

PAH and CTEPH are diseases with different underlying pathogenetic mechanisms and negative impact on survival of the patients. In the last 20 years, five new classes of drugs have become available, which have changed prognosis for these patients, but survival is still low.

Current models of PH patient survival prognosis are incomplete, and further research of prognostic factors that impact survival of patients with PH, to identify patients in need of closer monitoring and possibly intensification of therapy.

CONCLUSIONS

1. In 2016 lowest estimated incidence of PAH in Latvia was 13.7 cases per 1 million inhabitants; prevalence on December 2016 – 45.7 cases per million inhabitants. On December 2016 the lowest estimated incidence of CTEPH was 5.1 cases per million and prevalence of 15.7 cases per million inhabitants.
2. Overall one–year survival in PAH group was 88%, in CTEPH – 84%. Three and five–year survival was 73% and 58%; in CTEPH group – 76% and 44% respectively.
3. As the result of this study 2 statistically significant mortality risk factors were identified for patients with pulmonary arterial hypertension: 6–minute walk test result (specifically – <300m) and increased right atrial pressure, which partially confirms the hypothesis of the study. There were 3 statistically significant mortality risk factors found for patients with chronic thromboembolic pulmonary hypertension: young age (≤ 65 years), higher mean pulmonary artery pressure and higher pulmonary vascular resistence.
4. By analysing subtypes of PAH, it was concluded that patients with PAH associated with congenital heart disease were more than two times less mortality rate, compared to patients with idiopathic pulmonary hypertension. Patients with PAH associated with connective tissue disease had a trend for higher risk of mortality, compared to patients with iPAH; this data confirms the hypothesis of thesis.

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