Research Article

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Analysis of pulmonary hypertension patient survival after treatment in referral center (data of first Ukrainian register)

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Abstract

The aims of the study were: (1) to evaluate the Ukrainian reality of survival in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH); and (2) to determine predictors of death. A total of 281 patients were enrolled (52 [18.5%] with CTEPH, 229 [81.5%] with PAH). Long-term survival (Kaplan–Meier) and its predictors (Stepwise binary logistic regression and Cox's proportional hazards analyses) were evaluated in adult patients with PH (diagnosed by right heart catheterization [RHC]) within a prospective registry at a single referral center in Kyiv, Ukraine. Follow-up period was up to 51 months. The Kaplan–Meier survival rate for the total cohort was 93.3%, 86.8%, and 81.5% at one, two, and three years, respectively. Survival was better in patients with congenital heart diseases (CHD) in comparison with idiopathic PAH (long rank $P = 0.002$), connective tissue diseases (CTD; long rank $P = 0.001$) and CTEPH (long rank $P = 0.04$). Univariate Cox's predictors of death were: functional class IV (odds ratio [OR] = 4.94; 95% confidence interval [CI] = 2.12–11.48), presence of ascites (OR = 4.52; 95% CI = 2.21–9.24), PAH-CTD (OR = 3.07; 95% CI = 1.07–8.87), PAH-CHD (OR = 0.28; 95% CI = 0.11–0.68), HR on treatment > 105 beats per min (OR = 7.85; 95% CI = 1.83–33.69), office systolic BP < 100 mmHg (OR = 2.78; 95% CI = 1.26–6.1), 6MWT on treatment < 340 m (OR = 3.47; 95% CI = 1.01–12.35), NT-proBNP > 300 pg/mL (OR = 4.98; 95% CI = 1.49–16.6), right atrium square > 22 cm^2 (OR = 14.2; 95% CI = 1.92–104.89), right ventricular square in diastole (OR = 1.08; 95% CI = 1.03–1.14), right ventricular square in systole (OR = 1.08; 95% CI = 1.02–1.11), mean pressure in right atrium per each 1-mmHg increase (OR = 1.02; 95% CI = 1.02–1.19). In multivariate Cox regression analyses only presence of ascites, office systolic BP < 100 mmHg, CHD etiology of PH, and NT-proBNP > 300 pg/mL were associated with survival.

Keywords

pulmonary hypertension, one referral center cohort study, survival, predictors

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Introduction

Pulmonary hypertension (PH) is severe progressive disease that without specific treatment could lead to death in a few years. In the first early registry trials, the survival of patients with idiopathic pulmonary arterial hypertension (IPAH) was 68%, 48%, and 34% at one, three, and five years, respectively.[1,2] Some further studies demonstrated improvement in survival on specific therapy: one-year survival was 83–91%.[3,4] Predictors of poor prognosis in PH patients were age, etiology, functional state (exercise tolerance, functional class, syncope), biomarkers, hemodynamic parameters evaluated by echocardiography (systolic function of right ventricle, eccentricity index, size of right atrium), and right heart catheterization (RHC; mean right atrial pressure [mRAP] and cardiac index).[5–9]

The first Ukrainian specialized center for PH patients was organized only in 2014 and mainly focused on pulmonary

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arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH). In 2016, a government drug-supporting program for patients with PAH and CTEPH was started. This study is the first analysis of patients' survival after treatment in the referral center. The aims of the study were: (1) to evaluate the Ukrainian reality of survival in patients with PAH and CTEPH who were treated in the referral center (there were no Ukrainian data before); and (2) to determine predictors of death.

Patients and methods

Patients

In the study, we recruited 281 eligible patients of aged ≥ 18 years who were treated in the referral center between June 2014 and July 2018. PH was confirmed by right heart catheterization (RHC): mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg; pulmonary vascular resistance (PVR) > 300 dynes*s/cm^5; and pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg at rest.[10] Patients with PAWP > 15 mmHg and/or PVR < 300 dynes*s/cm^5 (if not on specific treatment) were excluded from analysis. RHC was provided in our center or in some surgical centers for patients with congenital heart diseases (CHD). All patients were included in the register after a signed informed consent form was received for personal data process. Patients were assigned to a PH etiology subgroup based on the results of the examination according to local protocol (based on ESC-2015 guidelines) and the main cause of PH was stated: IPAH (n = 68); PAH associated with CHD (n = 136); PAH associated with connective tissue diseases (CTD) (n = 15); PAH associated with portal hypertension or HIV infection (n = 10); and CTEPH (n = 52). Some patients started PH-specific therapy before the first visit to our center; for others, PH was diagnosed in our center and targeted therapy was started. All patients were hospitalized in our center for examination, mostly because of social reasons (citizens of other regions of Ukraine). The signs of ascites were evaluated during physical examination and abdominal ultrasound investigation. The 6-min walk test (6MWT) was provided twice at admittance and twice at discharge (on treatment) and the best result was entered in database. Echocardiography (EchoCG) evaluations were done by the same specialists using standard measurements (Artida, Toshiba, Japan).

Survival status was determined by contacting the patient or her/his relatives. Dates and causes of death were obtained from death certificates. If no information was available, the patient was classified as lost to follow-up. The date of last visit was the date of censoring. In this study, we evaluated only all-cause mortality. Baseline demographics, PH etiology, medication use, biochemical patterns, biomarkers (N-terminal pro-B-type natriuretic peptide (NT-proBNP), iron status (ferritin), EchoCG parameters, data from exercise testing, and RHC were entered into an electronic database. Date of first visit to our center was taken as the start date. The study was approved by local committee of State Institute National Scientific Center "MD Starzhesko Institute of Cardiology" of the Ukrainian National Academy of Medical Science.

Treatment

Only two drugs for target treatment of PAH and CTEPH were available at time of study: sildenafil and inhalation iloprost. Possibilities in change of therapy were limited by a combination of these drugs or, in case of intolerance, by switching from one to another. Mostly monotherapy was used. Ten patients did not take any therapy because of personal reasons or intolerance to the available drugs. CTEPH patients were referred to a surgical center. Six patients underwent pulmonary thromboendarterectomy (one died, two had residual PH). Others were assessed as inoperable or at high risk or refused to provide the surgery due to personal reasons, including financial reasons (in Ukraine, patients self-pay for surgery). Balloon pulmonary angioplasty is not currently available in Ukraine.

Statistical analysis

Continuous variables were reported as means $\pm$ SD. Categorical variables were reported as absolute frequencies and percentages. All patients were divided into groups as survivors or non-survivors; significant differences between groups were evaluated. The statistical significance of the differences between groups was estimated using the independent t-test of mean values for continuous variables and chi-square analysis for categorical variables. Detected significant different parameters were included in stepwise binary logistic regression analysis for assessing relationships between variables and outcome. Survival analysis was performed using Kaplan–Meier curves, with the date of entry into the study defined as the date of the first visit to center. The log-rank test was used for comparison between etiology groups. Statistically significant variables found during binary logistic regression analysis were included in univariate Cox's proportional hazard analysis. Significant variables on the univariate analysis were used in multivariate Cox's proportional hazard models in order to identify independent predictors of death in the overall PH population.

Results

Group comparisons

Over a median follow-up period of 51 months (mean $= 23.6 \pm 14.1$), 31 patients died. All patients were divided into two groups: survivors (n = 250) or non-survivors (n = 31). Baseline characteristics of the groups are shown in Table 1. Groups were not significantly differed by age,

Table 1. Clinical and demographic characteristics of patients in groups (mean ± SD or n (%)).

Characteristics	Survivors (n = 250)	Non-survivors (n = 31)	*P* value
Age (years)	45.93 ± 13.9	41.7 ± 14.6	NS
Duration from first diagnosis (months)	112.6 ± 142.2	33.3 ± 53.0	0.003
Body mass index (kg/m^2)	25.5 ± 4.7	24.6 ± 5.7	NS
Systolic BP at admittance (mmHg)	116.5 ± 15.5	114.4 ± 13.2	NS
Diastolic BP at admittance (mmHg)	75.7 ± 10.9	77.0 ± 8.8	NS
Heart rate at admittance (bpm)	80.9 ± 13.6	89.1 ± 16.5	0.002
Systolic BP on treatment (mmHg)	110.9 ± 15.2	104.5 ± 20.7	0.042
Diastolic BP on treatment (mmHg)	72.2 ± 5.3	72.2 ± 7.8	NS
Heart rate on treatment (bpm)	77.2 ± 9.6	83.5 ± 12.3	0.002
Arterial saturation (%)	92.6 ± 6.1	87.5 ± 12.0	0.032
6MWT baseline (m)	344.9 ± 107.1	292.7 ± 115.1	0.016
Borg score baseline (points)	4.3 ± 1.9	4.6 ± 2.1	NS
6MWT on treatment (m)	373.1 ± 89.3	314.23 ± 63.29	0.026
Borg score on treatment (m)	3.4 ± 1.6	4.2 ± 1.3	NS
Male	61 (24.4)	12 (38.7)	NS
Female	189 (75.6)	19 (61.3)	NS
Idiopathic PAH	54 (21.6)	14 (45.2)	< 0.05
PAH, associated with congenital heart diseases	130 (52.0)	6 (19.4)	< 0.05
PAH, associated with connective tissue disease	11 (4.4)	4 (12.9)	NS
Chronic thromboembolic PH	45 (18.0)	7 (22.6)	NS
PAH, associated with other cause	10 (4.0)	0	< 0.05
WHO functional class			
I	4 (1.6)	0	NS
II	64 (25.6)	3 (9.7)	< 0.05
III	171 (68.4)	21 (67.7)	NS
IV	11 (4.4)	7 (22.6)	< 0.05
Atrial fibrillation history	22 (8.8)	2 (6.5)	NS
Ascites	31 (12.4)	13 (41.9)	< 0.05
Syncope history	40 (16)	5 (16.1)	NS
Iron deficit\anemia	70 (28)	12 (38.7)	NS
Treatment			
Sildenafil	113 (45.2)	30 (96.8)	< 0.05
Mean daily dose of sildenafil (mg)	71.5 ± 22.0	92.9 ± 33.6	0.001
Iloprost	64 (25.6)	6 (19.4)	NS
Mean daily dose of iloprost (μg)	30.4 ± 5.8	26.7 ± 5.2	NS
Combination therapy	60 (24.0)	6 (19.4)	NS
Calcium channel blockers	34 (13.6)	0 (0)	< 0.05
No specific therapy	9 (3.6)	1 (3.2)	NS
Diuretics	131 (52.4)	28 (90.3)	< 0.05
Mean daily dose of furosemide (mg)	55.7 ± 39.4	82.0 ± 46.6	NS
Mean daily dose of torasemide (mg)	5.7 ± 3.4	8.0 ± 4.9	0.013
Oral anticoagulants	126 (50.4)	25 (80.6)	< 0.05

*Associated with HIV or portal hypertension.

gender, body mass index, history of atrial fibrillation, syncope, or iron/anemia status. However, survivors had significantly lower heart rate and higher office blood pressure at time of discharge from the center than non-survivors. Baseline mean arterial saturation was lower in non-survivors. Among survivors were more patients with CHD and other causes of PAH (associated with HIV or portal hypertension) and fewer patients with IPAH. Functional status

Table 2. Blood analysis and biochemical markers in patient groups (mean ± SD).

Characteristics	Survivors (n = 250)	Non-survivors (n = 31)	*P* value
NT-proBNP (pg/mL)	1179.6 ± 248.6	2817.52 ± 232.4	0.001
Ferritin (ng/mL)	87.33 ± 129.2	61.6 ± 89.4	NS
TSH (μUnits/mL)	2.3 ± 1.5	5.34 ± 10.4	0.001
Hemoglobin (g/L)	146.8 ± 27.6	137.3 ± 29.7	NS
Thrombocytes ($*10^9$)	238.4 ± 84.9	254.9 ± 97.6	NS
White blood cells ($*10^9$)	7.2 ± 2.3	8.7 ± 3.3	0.02
International normalization ratio	1.65 ± 0.62	2.02 ± 0.72	0.003
Potassium (mmol/L)	4.6 ± 0.48	4.5 ± 0.53	NS
Sodium (mmol/L)	141.5 ± 37.9	142.1 ± 76.5	NS
Creatinine (μmol/L)	85.2 ± 24.9	89.2 ± 32.6	NS
ALT (U)	32.2 ± 21.8	28.6 ± 10.9	NS
AST (U)	28.9 ± 13.5	25.1 ± 10.2	NS
Bilirubin (μmol/L)	25.1 ± 25.2	30.5 ± 32.2	NS
Glucose (mmol/L)	4.9 ± 1.1	4.7 ± 0.7	NS

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TSH, thyroid-stimulating hormone.

determined by 6MWT and functional class WHO was worse in non-survivors. In addition, non-survivors more frequently had signs of ascites. Sildenafil, diuretics, and oral anticoagulants were more frequently used in non-survivors. The mean dose of sildenafil was also higher in this group.

Results of blood analysis, including biomarkers, are shown in Table 2. Non-survivors had more white blood cells and international normalization ratio (more were on anticoagulants) than survivors. NT-proBNP and thyroid-stimulating hormone levels were higher in non-survivors. No significant differences in ferritin levels and other characteristics were found between groups.

Hemodynamic patterns evaluated by EchoCG and RHC are shown in Table 3. Non-survivors had a significantly larger right atrium and right ventricle. We also found a tendency of worse systolic right ventricle function in this group evaluated by tricuspid annular plane systolic excursion (TAPSE). In survivors, the low mPAP estimated by EchoCG was not confirmed by RHC. Among RHC characteristics, only mRAP was higher in the group of non-survivors.

Survival analysis

The Kaplan–Meier survival curve for the total cohort is demonstrated in Fig. 1. Estimated survival rates were 93.3%, 86.8%, and 81.5% at one, two, and three years, respectively. Figure 2 illustrates the estimated cumulative proportion survival according to the different etiology. Survival was better in patients with CHD in comparison with IPAH (long rank $P = 0.002$), CTD (long rank $P = 0.001$), and CTEPH (long rank $P = 0.04$). Numerically, survival was worse in patients with CTD, but statistically significant differences were only in CHD (long rank $P = 0.001$) and other PAH (long rank $P = 0.05$) patients.

Predictors of survival

Stepwise binary logistic regression analysis results are shown in Table 4. Statistically significant clinical predictors of death were functional class WHO IV (odds ratio [OR] = 6.34; $P < 0.001$), presence of ascites (OR = 5.65; $P < 0.001$), HR at admittance ≥ 100 beats per min (OR = 3.07; $P = 0.021$) and on treatment ≥ 105 beats per min (OR = 12.9; $P = 0.039$), office systolic blood pressure on treatment ≤ 100 mmHg (OR = 3.34; $P = 0.009$). 6MWT at admittance ≤ 349 m (OR = 2.39; $P = 0.042$) and at discharge ≤ 340 m (OR = 5.45; $P = 0.01$) were also predictors of poor prognosis in our patients. Signs of right ventricular dysfunction as NT-proBNP > 300 pg/mL (OR = 5.26; $P = 0.009$), EchoCG enlargement of right atrium square ≥ 22 cm^2 (OR = 3.6; $P = 0.013$), right ventricular square (OR = 1.12; $P = 0.005$ for systolic square and 1.12; $P = 0.012$ for diastolic square), and RHC increased RAP ≥ 10 mmHg (OR = 3.44; $P = 0.023$) were statistically significant factors associated with survival in overall population. The blood pressure level in pulmonary artery did not correlate with death rate.

Some clinical characteristics at admittance lost their significance during univariate Cox's proportional hazards analysis – HR and 6MWT (Table 5). CHD etiology of PAH (OR = 0.28; $P = 0.005$) decreased and CTD etiology (OR = 3.07; $P = 0.037$) increased the probability of death

Table 3. Data of baseline echocardiography and right heart catheterization (mean ± SD).

Characteristics	Survivors (n = 250)	Non-survivors (n = 31)	*P* value
Echocardiography			
Left atrium square (cm^2)	19.3 ± 9.1	21.2 ± 11.8	NS
Right atrium square (cm^2)	24.5 ± 9.3	29.4 ± 8.7	0.009
Right atrium volume index (mL/m^2)	50.7 ± 31.3	64.3 ± 33.6	0.041
Ejection fraction of LV (%)	62.4 ± 7.2	62.8 ± 6.8	NS
Right ventricular square in diastole (cm^2)	28.3 ± 8.2	35.3 ± 8.1	0.003
Right ventricular square in systole (cm^2)	19.6 ± 6.7	24.8 ± 7.2	0.006
TAPSE	16.0 ± 4.6	14.4 ± 3.1	0.08
Tricuspidal regurgitation velocity (m/s)	4.4 ± 0.7	4.2 ± 0.7	NS
Systolic pulmonary blood pressure (mmHg)	90.8 ± 25.7	98.1 ± 26.0	NS
Estimated mean pulmonary blood pressure (mmHg)	57.3 ± 16.4	64.5 ± 14.9	0.04
Pulmonary artery diameter (cm)	3.4 ± 4.0	2.9 ± 0.7	NS
Right heart catheterization			
Mean pulmonary artery pressure (mmHg)	61.6 ± 18.9	58.1 ± 19.6	NS
Mean right atrial pressure (mmHg)	8.5 ± 4.6	12.2 ± 5.2	< 0.05
Cardiac output (L/min)	4.5 ± 1.24	4.0 ± 1.5	NS
Cardiac index ($L/min/m^2$)	2.3 ± 0.7	2.1 ± 0.8	NS
Pulmonary artery wedge pressure (mmHg)	9.2 ± 3.9	7.9 ± 2.9	NS
Pulmonary vascular resistance (dynes*s/cm^5)	933.32 ± 499.1	1007.7 ± 208.4	NS
Systemic vascular resistance (dynes*s/cm^5)	1402.9 ± 149.1	1350.1 ± 116.5	NS
Mixed venous oxygen saturation (%)	69.9 ± 10.0	67.4 ± 18.7	NS

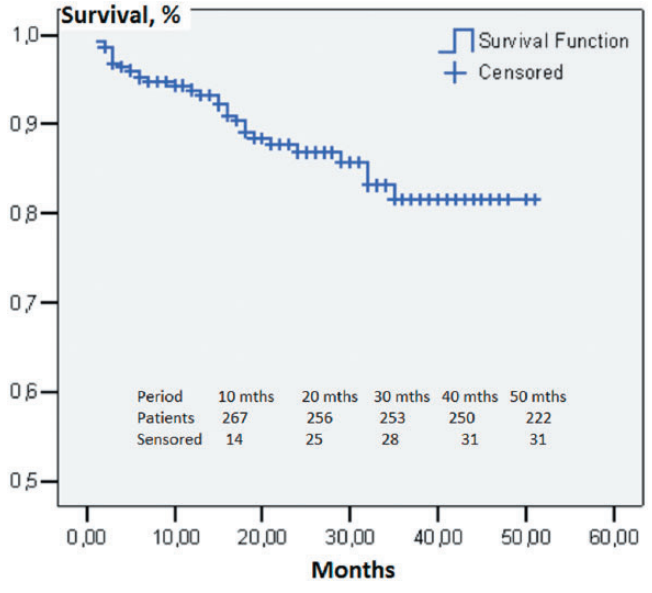

Fig. 1. Kaplan–Meier survival in overall study population.

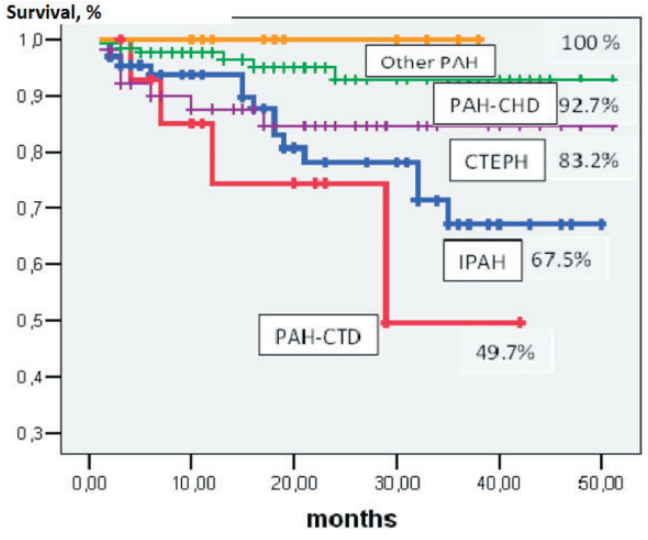

Fig. 2. Kaplan–Meier survival estimates for PH etiologic groups (unadjusted).

in our patients; however, they lost significance on multivariate Cox's regression analysis when the NT-proBNP level > 300 pg/mL was added in regression model (Table 6). EchoCG and RHC parameters did not preserve their significance in multivariate regression model.

Discussion

This study is the first analysis of the Ukrainian register of PH patients who were treated and followed in the only referral center between June 2014 and July 2018. Ukrainian PH treatment realities are: few approved specific drugs (only iloprost and sildenafil); patients are not supported

Table 4. Predictors of death on stepwise binary logistic regression analysis.

Characteristics	OR (95% CI); significance
WHO functional class IV	6.34 (2.25–17.9); $P < 0.001$
Ascites	5.65 (2.5–12.8); $P < 0.001$
HR at admittance	1.04 (1.02–1.07); $P = 0.002$
HR at admittance $\geq$ 100 beats per min*	3.07 (1.18–7.94); $P = 0.021$
HR on treatment	1.06 (1.02–1.10); $P < 0.001$
HR on treatment $\geq$105 beats per min*	12.9 (1.14–46.9); $P = 0.039$
Office systolic blood pressure on treatment	NS
Office systolic blood pressure on treatment $\leq$ 100 mmHg*	3.34 (1.34–8.29); $P = 0.009$
6MWT at admittance	NS
6MWT at admittance $\leq$ 349 m*	2.39 (1.03–5.55); $P = 0.042$
6MWT on treatment	NS
6MWT on treatment $\leq$ 340 m*	5.45 (1.49–19.9); $P = 0.01$
NT-proBNP	1.01 (1.01–1.08); $P = 0.03$
NT-proBNP > 300 pg/mL*	5.26 (1.52–18.2); $P = 0.009$
Right atrium square	1.05 (1.01–1.09); $P = 0.008$
Right atrium square $\geq$ 22 cm^2*	3.6 (1.31–9.94); $P = 0.013$
Right ventricular square in diastole (cm^2)	1.12 (1.04–1.22); $P = 0.005$
Right ventricular square in systole (cm^2)	1.12 (1.03–1.23); $P = 0.012$
Mean right atrial pressure at RHC	1.13 (1.03–1.24); $P = 0.009$
Mean right atrial pressure at RHC $\geq$ 10 mmHg*	3.44 (1.19–9.98); $P = 0.023$

*Value was evaluated by stepwise analysis
6MWT, 6-min walking test; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RHC, right heart catheterization; HR, heart rate.

Table 5. Predictors of death on univariate Cox's proportional hazards analysis.

	Univariate analysis (OR (95% CI); significance)
WHO functional class IV	4.94 (2.12–11.48); $P = 0.001$
Presence of ascites	4.52 (2.21–9.24); $P = 0.001$
CTD etiology of PAH	3.07 (1.07–8.87); $P = 0.037$
CHD etiology of PAH	0.28 (0.11–0.68); $P = 0.005$
HR on treatment $\geq$ 105 beats per min	7.85 (1.83–33.69); $P = 0.006$
Office systolic BP $\leq$ 100 mmHg	2.78 (1.26–6.1); $P = 0.011$
6 MWT on treatment $\leq$ 340 m	3,47 (1.01–12.35); $P = 0.05$
NT-proBNP > 300 pg/ml	4.98 (1.49–16.6); $P = 0.009$
Right atrium square $\geq$ 22 cm^2	14.2 (1.92–104.89); $P = 0.009$
Right ventricular square in diastole	1.08 (1.03–1.14); $P = 0.004$
Right ventricular square in systole	1.08 (1.02–1.11); $P = 0.011$
Mean pressure in right atrium per each 1-mmHg increase	1.02 (1.02–1.19); $P = 0.021$

permanently by specific therapy (the government support program only started in summer 2016 and sometimes therapy might be stopped because of obstacles in the supporting process). However, our data demonstrated that the long-term survival of PH patients with PAH or CTEPH is in line with published data from other countries: 93.3%, 86.8%, and 81.5% at one, two, and three years, respectively.[11–17] The Portuguese study by Marques-Alvesa et al. reported a one-year survival rate of 95% and a three-year survival rate of 77%.[11] In the REVEAL register, these were 85% and 68%, respectively.[12] Similar data were found in the French register: 88% and 65%, respectively. The large

Table 6. Multivariate predictors of death on Cox's proportional hazards analysis in all PH patients.

	Hazard ratio		
	Regression 1	Regression 2	Regression 3
WHO functional class IV	NS	-	-
Presence of ascites	2.43 (95% CI = 1.09–5.46); $P = 0.031$	2.17 (95% CI = 1.01–4.89); P=0.05	2.39 (95% CI = 1.05–5.48); $P = 0.039$
Office systolic BP $\leq$ 100 mmHg	2.5 (95% CI = 1.07–5.83); $P = 0.034$	2.35 (95% CI = 1.01–5.5); $P = 0.048$	NS
CHD etiology of PH	0.31 (95% CI = 0.10–0.92); $P = 0.035$	NS	-
CTD etiology of PH	NS	-	-
HR on treatment $\geq$ 105 bpm	NS	-	-
NT-proBNP > 300 pg/mL		3.69 (95% CI = 1.07–12.7); $P = 0.038$	3.1 (95% CI = 1.07–10.66); $P = 0.05$
Right atrium square $\geq$ 22 cm^2			NS
Mean pressure in right atrium per each 1-mmHg increase			NS

Giessen Pulmonary Hypertension Registry published one- and three-year survival rates of 88.2% and 72.2% for 685 PAH patients, respectively.[18] The Spanish and Danish registers reported similar findings.[16,17] Overall, event-free survival was 84%, 72%, and 64% for years 1, 2, and 3 in the Swiss register.[19]

Baseline characteristics of our patient population showed the majority of patients (74%) were young women (mean age = 43.8 ± 14.2 years). The most common cause of PH was PAH-CHD (48.4%), similar to the Portuguese[11] and Chinese[20] registers, but higher than the French (11.3%),[13] Scottish (23%),[17] Giessen (13.3%),[18] and Czech (21%) registers.[14] Most of our PAH-CHD patients had uncorrected systemic-to-pulmonary shunts or Eisenmenger syndrome. That was possible because of a lack of organizations for pediatric cardiac diagnostic help and the poor education of the Ukrainian population (some parents refused to give their informed consent for surgery). A high prevalence of patients with uncorrected CHD could partly explain the higher survival rate of our patients at three years compared with studied populations in other countries. Some studies demonstrated better survival in PAH-CHD patients than in IPAH patients or those with other forms of PAH.[10,11,18,21] Manes et al. reported that the estimated Kaplan–Meier survival at 20 years for patients with Eisenmenger syndrome and systemic-to-pulmonary shunts was 87% and 86%, respectively.[21] The worst survival was observed in patients with PAH after defect surgery or with small defects. Improved survival in patients with uncorrected CHD may be explained by preservation of right ventricular function as the absence of remodeling after birth and sustained right ventricular hypertrophy.[22]

We had a low percentage of PAH-CTD patients in our register: only 5.3% compared with the French (15.3%),[13] Giessen (21.2%),[18] Scottish (29.7%),[17] and Portuguese (24.6%)[11] registers. There seems to be inertia in Ukrainian rheumatologists when referring CTD patients with suspicion on PH to specialized centers. Our data demonstrated worst survival in PAH-CTD among all other etiology forms of PAH. At three years, estimated survival was only 49.7%. It confirms the data from other studies.[11,18,23] In the analysis by Launay et al., the unadjusted risk of death for PAH associated with systemic scleroderma compared with IPAH was 2.9.[24] In our study it was similar: 3.07.

Unadjusted factors associated with mortality in our overall population of patients were: poor functional status (functional class IV); presence of ascites; exercise limitation (6MWT distance); etiology of PAH; higher HR and lower office systolic blood pressure on treatment; and right atrium and ventricular hemodynamic function (high level of NT-proBNP, right atrium and right ventricular enlargement, higher right atrium pressure). Almost the same factors affecting survival were reported in other trials.[3,4,9,11–13] The male sex was not associated with death in our common patient groups as in other trials. It may be explained by the lack of statistical power due to the low male rate among patients with a higher risk of death: IPAH (14.7%) and PAH-CTD (6.6%). But among 10 IPAH male patients, six died at the end of study, while of the 37 men in the PAH-CHD group, only three died. A level of NT-proBNP > 300 pg/mL and presence of ascites at first visit were the most powerful and independent predictors of death in multivariant Cox's proportional hazard analysis. They could be evaluated as markers of right heart failure. As the prognostic role of NT-proBNP was proved in some other studies,[25–27] the prognostic role of ascites was not assessed before.

In our study, the 6MWT distance $\leq$ 340 m was a predictor of death on univariate hazard analysis, but not in multivariate analysis, while in the Giessen registry report it also

preserved significance in multivariate analysis. In the MAESTRO trial, macitentan therapy was not associated with improving 6MWT results in a general study population, but it was among patients at the referral center.[28] The one of possible explanation for this is that patients and medical staff are more trained for providing this test in referral centers. With more training the results are more accurate. We included in the database values that were obtained at the beginning of our study when we were not as well trained. That is why some objective parameters (NT-proBNP and ultrasound signs of ascites) were more significant for prognosis than the subjective parameters of the 6MWT.

Hemodynamic parameters did not achieve statistical significance as predictors of mortality in multivariate Cox's analysis, which could be explained by the lack of statistical power of our study population. However, unadjusted survival analysis demonstrated a high association of right atrium size $\geq 22\,cm^2$ (OR = 14.2; $P = 0.009$) and higher right atrium pressure (OR = 1.02; $P = 0.021$) with poor prognosis. In Raymond et al.'s study during the mean follow-up period of 36.9 ± 15.4 months, pericardial effusion ($P = 0.003$) and right atrium area index (> median) were predictors of mortality in IPAH patients.[5] Austin et al. found that a right atrial area $> 18\,cm^2$ was associated with poor survival in univariate analysis, but not in multivariate analysis.[29] Unlike RAP, it preserved its statistical significance on multivariate analysis. A RAP > 15 mmHg was a powerful predictor of death in a Thai study for patients with systemic-to-pulmonary shunts.[30] In our study, we found that mRAP ≥ 10 mmHg was associated with an increased death rate (OR = 3.44; $P < 0.023$) on stepwise binary logistic regression analysis, but not on other analyses.

Study limitations

The main limitations of our study were: (1) small sample size which did not allow us to find more statistical powerful predictors of death on multivariate Cox's analysis; (2) we had a higher proportion of patients with uncorrected CHD than in other trials, which could impact on the death rate in the overall population, but the etiology subgroup survival analysis showed that the three-year survival rate for our IPAH patients (67.5%) was almost similar to other reports or lower (75% in Thenappan et al.'s study,[23] 69% in the Swiss study (60% IPAH),[19] 76.2% in the Giessen PH Registry,[18] and 75% in the Portuguese study[11]). This numeric lower survival of our patients could be explained by problems with treatment (no choice of drugs, no permanent treatment); (3) at baseline, we did not have complete RHC data: some patients came with acceptable values from other centers, but these data were not complete (without PAWP or cardiac output values, etc.). This missing information was not entered in the database and could not be analyzed. That is one reason why RHC data (e.g. cardiac output) were not associated with prognosis in our study; (4) the threshold for our analysis was a PVR > 300 dynes*s/cm^5, which is higher than the standard 240 dynes*s/cm^5. This threshold may also affect comparisons with other registry studies, but the mean PVR in our study was comparable with it in other registers; (5) some patients joined our register after having already taken specific therapy and we did not analyze how long this therapy was and did not provide a separate evaluation of survival for newly diagnosed patients; and (6) the data reflected work from only one referral center in Ukraine and the results of treatment might be different from the rest of the PH Ukrainian population.

Conclusion

This study is the first single-center Ukrainian PH population report. Overall, one-, two-, and three-year survival was 93.3%, 86.8%, and 81.5%, respectively, and it differed between etiology PH subgroups. These data are almost similar to the data of centers from other countries. In the global PH population, the presence of ascites and higher levels of NT-proBNP were strong independent predictors of death. We need more findings and should provide new long-term nationwide register studies for better care for PAH patients in modern conditions until new specific therapies become available in Ukraine.

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Conflict of interest

The author(s) declared that there is no conflict of interest.

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