ORIGINAL RESEARCH ARTICLE

Hospitalisations for heart failure predict mortality in pulmonary hypertension related to congenital heart disease

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ABSTRACT

Objective Despite the progress in the management of patients with adult congenital heart disease (ACHD), a significant proportion of patients still develop pulmonary hypertension (PH). We aimed to highlight the rate of the complications in PH-ACHD and the predicting factors of cumulative mortality risk in this population.

Methods Data were obtained from the cohort of the national registry of ACHD in Greece from February 2012 until January 2018.

Results Overall, 65 patients receiving PH-specific therapy were included (mean age 46.1±14.4 years, 64.6% females). Heavily symptomatic (New York Heart Association (NYHA) class III/IV) were 53.8% of patients. The majority received monotherapy, while combination therapy was administered in 41.5% of patients. Cardiac arrhythmia was reported in 30.8%, endocarditis in 1.5%, stroke in 4.6%, pulmonary arterial thrombosis in 6.2%, haemoptysis in 3.1% and hospitalisation due to heart failure (HF) in 23.1%. Over a median follow-up of 3 years (range 1–6), 12 (18.5%) patients died. On univariate Cox regression analysis history of HF hospitalisation emerged as a strong predictor of mortality (HR 8.91, 95% CI 2.64 to 30.02, p<0.001), which remained significant after adjustment for age and for NYHA functional class.

Conclusions Long-term complications are common among patients with PH-ACHD. Hospitalisations for HF predict mortality and should be considered in the risk stratification of this population.

INTRODUCTION

Life expectancy of patients with congenital heart disease has increased, shifting the mortality burden from childhood to adulthood.[1–4] Consequently, cardiologists have to manage the complications of adult congenital heart disease (ACHD), such as pulmonary hypertension (PH). In the current era, the early detection and surgical management of congenital heart disease have contributed to the reduction in the incidence of Eisenmenger syndrome (ES); yet, the incidence in other types of PH-ACHD, such as complex ACHD, PH in closed defects and segmental PH is likely to increase.[5–8]

In the past, patients with PH-ACHD were considered to have better survival rates compared with patients with idiopathic pulmonary arterial hypertension (PAH).[9] However, data from Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) registry showed that PAH-ACHD have a similar prognosis in patients with idiopathic PAH.[10] Furthermore, median survival of patients with ES in Euro Heart Survey was reported to be diminished by 20 years compared with the general population and indeed the 3-year mortality among patients with ES in Multi-centre Study on Eisenmenger (MUSE) study was 25.3%.[11 12] According to recent data, heart failure (HF) is the leading cause of death,[13] although PAH-specific therapy which is widely used in PH-ACHD, has improved their survival.[14–16]

In the context of adult Congenital Heart disease registry—A registry from HeLLENic CardioloGy SociEty (CHALLENGE) registry, we aimed to highlight the rate of long-term complications in patients with PH-ACHD and the predicting factors of cumulative mortality risk in this population.

METHODS

Baseline data were obtained from the initiation of the Greek national registry of ACHD (February 2012) until January 2018. Seventeen ACHD centres participated in this registry nationwide. The CHALLENGE registry conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The methods that were used to collect the data for the CHALLENGE registry have been previously described.[17]

Out of the total population, we only included the patients who were under PH-specific therapy (PAH and segmental PH). Right heart catheterisation had been performed at least once in their lifetime and precapillary PH was defined as mean pulmonary arterial pressure ≥25 mm Hg with pulmonary arterial wedge pressure ≤15 mm Hg.[18] We excluded from the analysis patients with ACHD with postcapillary PH as well as Fontan patients who were receiving PH-specific therapy in whom the definition of PH and the indication for potential commencement of PH-specific therapies differ. The rest were classified according to the anatomical

diagnosis as pretricuspid defect (atrial septal defect), post-tricuspid defect (ventricular septal defect, patent ductus arteriosus or aortopulmonary window, atrioventricular septal defect), complex (univentricular heart, transposition of the great arteries and common arterial trunk) and segmental PH (pulmonary hypertension diagnosed with right heart catheterisation in discrete lung areas such as patients with pulmonary atresia and major aortopulmonary collateral arteries). Patients with PAH were also classified into the four categories of PAH-ACHD according to the European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines on Diagnosis and Treatment of PH[18]: ES, PAH associated with prevalent systemic to pulmonary shunts, PAH with small/coincidental defects and PAH after correction. At baseline assessment, patients were reviewed for the administered therapy, including PH-specific therapy, other medical therapy for cardiac reasons and oxygen therapy as well as for history of complications, such as arrhythmia, endocarditis, stroke, pulmonary artery thrombosis and hospitalisation for HF. Survival status, date and cause of death were reported by the research investigators of the participating ACHD centres.

Statistical analysis

Continuous variables were given as mean±SD when distributed normally and as median with range otherwise. Discrete data were presented as counts and percentages. For intergroup comparisons, analysis of variance, X^2 test and Fisher's exact test were used as appropriate. As a result of the relatively small number of outcome events, we focused on univariable and bivariable Cox regression analyses. History of hospitalisations for HF was tested alongside other associated univariable parameters ($p \leq 0.10$) as pairwise comparisons. Kaplan-Meier survival curve was used to illustrate survival prospects according to HF hospitalisation. Two-tailed p values ≤0.05 were considered to be statistically significant. Statistical analysis was performed with the use of SPSS V.22.0 (SPSS, Chicago, Illinois, USA) and Rstudio V.3.3.2.

RESULTS

Of the 2399 patients, who were included in CHALLENGE registry, 68 patients (2.8%) were under PH-specific therapy. Three patients with Fontan circulation were excluded. The baseline characteristics of the remaining 65 patients and the differences based on anatomical diagnosis are displayed in table 1. Mean age was 46.1±14.4 years and two-thirds were female. Almost half had a post-tricuspid defect and were in New York Heart Association (NYHA) class III/IV. Of patients with PAH (n=57), 40 suffered from ES, 13 from left-to-right shunt, 1 from small/coincidental defect and 3 had PAH after correction. Nine patients (13.8%) suffered from Down syndrome, of whom five had atrioventricular septal defect, three had ventricular septal defect and one had ventricular septal defect and patent ductus arteriosus.

Out of the total, 73.8% had undergone a right heart catheterisation before the initiation of PH-specific therapy. The majority (90.8%) were treated with endothelin receptor antagonists, followed by phosphodiesterase type 5 inhibitor (49.2%), while 6.2% were under prostanoids (two treprostinil, one selexipag and one unknown). A proportion of 41.5% of patients were in combination therapy (35.3% were in double and 6.2% in triple therapy) and almost two-thirds of them were heavily symptomatic (NYHA class III/IV). Most patients received sequential combination therapy, while a female patient aged 50 years with severe PH-ACHD due to left-to-right shunt, in NYHA class III with a history of hospitalisation for right HF, received upfront double oral combination therapy. With regard to the rest cardiac pharmacotherapy, half (50.8%) were under diuretics, one-third (32.3%) were under oral anticoagulation therapy and 30.8% under anti-arrhythmic drugs.

At baseline assessment, the most common complication (30.8%) among patients with PH-ACHD was arrhythmia, mainly atrial fibrillation (20%), followed by ventricular arrhythmia (4.6%) (mainly non-sustained ventricular tachycardia), atrial flutter (4.6%) and complete heart block/insertion of pacemaker (3.1%). Almost one-quarter of patients were hospitalised due to HF (23.1%), while pulmonary thrombosis, stroke, haemoptysis and endocarditis were also occasionally reported (table 2). Patients with a history of HF hospitalisation had a mean age of 56.5±15.6 years, were mainly women (73.3%), heavily symptomatic (86.7% in NYHA class III/IV) and 46.7% had a history of arrhythmia. Regarding anatomical diagnosis, five patients had a pretricuspid shunt, five had post-tricuspid shunt, three had complex ACHD and two had segmental PH.

Over a median follow-up of 3 years (1–6 years), corresponding to 263 patient-years, 12 (18.5%) patients died, giving an average mortality rate of 4.5% per patient-year. The main cause of death was right HF (table 2). At univariable analysis, mortality was predicted by HF hospitalisation (HR 8.91, 95% CI 2.64 to 30.02, p<0.001), age (HR 1.04, 95% CI 1.01 to 1.08, p=0.03) and advanced NYHA class (HR 9.74, 95% CI 1.26 to 75.52, p=0.029) (figure 1). Figure 2 shows the Kaplan-Meier surviving curves of the patients with

Table 1 Baseline characteristics of the patients with PH-ACHD

	All	Post-tricuspid	Pretricuspid	Complex	Segmental	P values
	n=65	n=33 (50.8%)	n=12 (18.5%)	n=12 (18.5%)	n=8 (12.3%)	
Age	46.1±14.4	44.7±14.8	56.2±16.8	40.1±9.5	44.5±8.4	0.043
Males	23 (35.4%)	13 (39.4%)	5 (41.7%)	2 (16.7%)	3 (37.5%)	0.51
NYHA class III/IV	35 (53.8%)	14 (42.4%)	7 (58.3%)	8 (66.7%)	6 (75%)	0.26
Down syndrome	9 (13.8%)	8 (24.2%)	1 (8.3%)	0	0	
PH pharmacotherapy						
ERA	59 (90.8%)	31 (93.9%)	12 (100%)	9 (75%)	7 (87.5%)	0.15
PDE5i	32 (49.2%)	16 (48.5%)	6 (50%)	6 (50%)	4 (50%)	1
Prostanoids	4 (6.2%)	2 (6.1%)	1 (8.3%)	1 (8.3%)	0	
Combination therapy	27 (41.5%)	14 (42.4%)	6 (50%)	4 (33.3%)	3 (37.5%)	0.86
Oxygen therapy	15 (23.1%)	7 (21.2%)	2 (16.7%)	2 (16.7%)	4 (50%)	0.27

ACHD, adult congenital heart disease; ERA, endothelin receptor antagonist; n, number; NYHA, New York Heart Association; PH, pulmonary hypertension; PDE5i, phosphodiesterase 5 inhibitor.

Table 2 Complication rates among patients with PH-ACHD

	n=65
Arrhythmias	20 (30.8%)
Endocarditis	1 (1.5%)
Stroke	3 (4.6%)
Pulmonary thrombosis	4 (6.2%)
HF hospitalisation	15 (23.1%)
Haemoptysis	2 (3.1%)
Cause of death	12 (18.5%)
RHF	6 (9.2%)
Sepsis	2 (3.1%)
Arrhythmia	1 (1.5%)
Sudden death	1 (1.5%)
Massive pulmonary haemorrhage	1 (1.5%)
Unknown	1 (1.5%)

ACHD, adult congenital heart disease; HF, heart failure; n, number; PH, pulmonary hypertension; RHF, right heart failure.

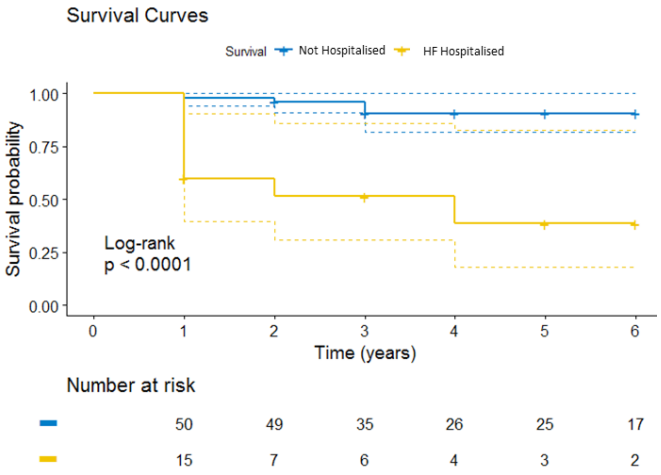

Figure 2 Kaplan-Meier curves for patients being (yellow line) or not (blue line) hospitalised for HF. HF, heart failure.

and without a history of HF hospitalisation. The association between history of hospitalisation for HF and mortality remained significant even after adjustment for age (age-adjusted HR 7.35, 95% CI 2.00 to 27.05, p=0.003) and for NYHA class (NYHA-adjusted HR 5.85, 95% CI 1.66 to 20.58, p=0.006). Of the 15 patients who were hospitalised for HF decompensation, 8 died within a median time of 14 months (3 days–38 months) after the index hospitalisation. Five patients died of right HF, one of arrhythmia, one of sepsis and one of massive pulmonary haemorrhage.

After excluding the eight patients with segmental PH, due to their different pathophysiology, mortality was still predicted by history of hospitalisation for HF (HR 10.61, 95% CI 2.70 to 41.75, p=0.001), age (HR 1.04, 95% CI 1.01 to 1.09, p=0.028) and advanced NYHA class (HR 8.84, 95% CI 1.12 to 69.88, p=0.039). History of hospitalisation for HF was associated with death in these patients when adjusted for age (age-adjusted HR 8.68, 95% CI 2.04 to 36.89, p=0.03) and for NYHA class (NYHA-adjusted HR 7.08, 95% CI 1.70 to 29.43, p=0.007).

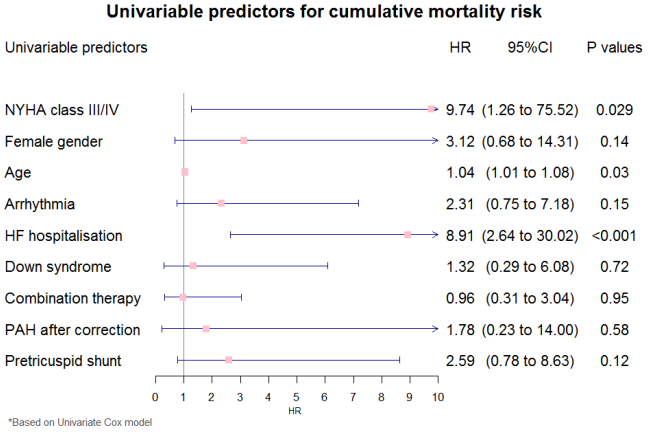

Figure 1 Determinants of cumulative mortality risk. HF, heart failure; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension.

DISCUSSION

In total, 3% of the patients with ACHD who were enrolled in the CHALLENGE registry were receiving PH-specific treatment. The morbidity rate in these patients with PH-ACHD was high, since almost one-third experienced cardiac arrhythmia and one-quarter hospitalisation for HF. Patients who had a history of hospitalisation for HF had a ninefold increased mortality risk.

A proportion of 18.5% of the patient cohort died during a 3-year follow-up period. The survival of patients with PAH-ACHD has improved with the administration of PAH targeted therapy.[14 19] However, the prognosis of these patients is still worse compared with the rest of the ACHD population and immortal time bias was the reason that survival rates of these patients might have been overestimated in the past.[11 14 20] This is also in line with data from the MUSE study, in which 25.3% of the patients with ES died in a 3-year follow-up period.[12]

HF is now the leading cause of death in a contemporary cohort of ES patients with ES, while peri-procedural and haemoptysis-induced deaths have been reduced.[13] This was also the case in our mixed PH-ACHD cohort, where 50% of the patients died due to right HF. Steps forward have been noted in the medical care of patients with ES, such as endocarditis prophylaxis and iron supplementation when needed along with the avoidance of pregnancy and phlebotomies, as well as careful logistical planning of non-cardiac surgery.[21 22] However, the optimal management of these patients is yet to be defined. For instance, it is still unknown if drugs which are traditionally used for left-sided HF can be safely and effectively used in the setting of a cyanotic patient with PH and right HF.

Recent data from the Prostacyclin (PGI 2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) and Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) studies showed an increasing relevance of hospitalisations for worsening of PAH as a risk factor for subsequent mortality.[23] Consequently, preventing these events seems to be of high importance and intensive treatment approach could help towards this direction. This is in agreement with the data that advocate earlier use of combination therapy, especially in a subset of patients who are at high risk.[24 25]

This study is limited mainly by the small sample size and the post hoc nature of the analyses, since this registry was not

designed to specifically enrol patients with PH-ACHD. Therefore, useful data, such as natriuretic peptides levels, functional capacity, echocardiography and recent full haemodynamic data are missing. In addition, the cohort is heterogeneous with the inclusion of a mix of patients with segmental PH. Nevertheless, subgroup analysis of the PH population provided consistent findings. The aforementioned reasons might explain the lack of a significant association between shunt location and mortality, which has previously been reported in the ES community.[26 27] Finally, as per the study design we could not isolate patients with PH-ACHD who were not under PH-specific therapy.

CONCLUSIONS

Prognosis of patients with PH-ACHD remains dismal. Patients who were hospitalised for HF had a ninefold risk of death, indicating that an admission to the hospital for HF decompensation is of great significance when risk stratifying these patients.

Key messages

What is already known on this subject?

- Pulmonary hypertension (PH) is a common and severe complication of congenital heart disease, which carries a dismal prognosis.

What might this study add?

- Patients with a history of hospitalisation for heart failure had a ninefold risk of death.

How might this impact on clinical practice?

- Hospitalisation for heart failure should be taken into account in the risk stratification of patients with PH and patients with adult congenital heart disease.

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Contributors All authors have participated in the work. All enrolled the patients from the different ACHD centres and collected the required data. DN reviewed the literature, organised and wrote the various sections of the paper along with the author GG. All authors have reviewed critically and edited the final version.

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