Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups

Alessandra Manes, Massimiliano Palazzini, Enri Leci, Maria L. Bacchi Reggiani, Angelo Branzi, and Nazzareno Galiè*

Institute of Cardiology, Bologna University Hospital, via Massarenti 9, Bologna 40138, Italy

Aims	This study compared the clinical, functional, and haemodynamic characteristics and current era survival of subgroups of patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD): Eisenmenger syndrome (ES); PAH-CHD associated with systemic-to-pulmonary shunts (SPs); PAH with small defects (SDs); and PAH after defect correction (CDs).
Methods and results	Data from consecutive PAH-CHD patients referred to our centre from 1 January 1998 to 31 May 2011 were collected. A contemporary group of idiopathic PAH patients was utilized for comparison. Treatment was per PAH guidelines, including combination therapy, with approved PAH-specific drugs. Survival was assessed with Kaplan–Meier analysis from the first invasive haemodynamic confirmation of PAH and compared across subgroups by log-rank test. Of 192 patients (mean age 41 ± 17 years; 61% female), 90 had ES (aged 41 ± 16 years); 48 SP (aged 47 ± 18 years); 10 SD (aged 25 ± 21 years); and 44 CD (aged 36 ± 17 years). Patients with ES had the highest baseline pulmonary vascular resistance and the lowest exercise capacity. Seventy-eight per cent were treated with approved PAH-specific drugs, and 44% were treated with combination therapy. Kaplan–Meier survival estimates (95% confidence interval) at 20 years for ES, SP, and CD were 87% (77–93%), 86% (60–96%), and 36% (12–72%, $P = 0.0001$ vs. ES; $P = 0.004$ vs. SP), respectively, and at 15 years for SD was 66% (16–91%, $P = 0.015$ vs. ES; $P = 0.016$ vs. SP). The survival of the 278 patients with idiopathic PAH appeared to be worse when compared with the PAH-CHD subgroups.
Conclusion	Relevant clinical, functional, haemodynamic, and survival differences were observed among subgroups. In particular, patients with CD and SD had the worst survival. These findings should be considered when planning medical or interventional treatment strategies in PAH-CHD patients.
Keywords	Congenital heart defects • Pulmonary arterial hypertension • Haemodynamics • Follow-up studies • Catheterization

Introduction

A large proportion of patients with congenital heart disease (CHD), in particular, those with relevant systemic-to-pulmonary shunts (SPs), if not treated very early in the course of the disease, develop pulmonary arterial hypertension (PAH).[1] The persistent exposure of the pulmonary vasculature to increased blood flow as well as increased pulmonary pressure results in the pulmonary obstructive arteriopathy that leads to the increase of pulmonary vascular resistance (PVR). If PVR approaches or exceeds systemic resistance, the shunt is reversed and the patient develops Eisenmenger syndrome.[2]

There are a multitude of very different clinical pictures of patients with PAH associated with CHD (PAH-CHD). However, four broad

clinical phenotypes have recently been defined[3,4]: Eisenmenger Syndrome, PAH associated with systemic-to-pulmonary shunts, PAH associated with small defects, and PAH after cardiac defect correction.

Eisenmenger syndrome[5] includes all systemic-to-pulmonary shunts due to large defects (post-tricuspid shunts are the most frequent) leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bi-directional shunt.[2] Cyanosis, erythrocytosis, and multiple organ involvement are present.

The patients with PAH associated with systemic-to-pulmonary shunts have moderate-to-large defects (pre-tricuspid shunts are the most frequent), the increase in PVR is usually mild-to-moderate, the systemic-to-pulmonary shunt is still largely present and no cyanosis is detectable at rest; in these cases, a late reversal of shunt (pulmonary-to-systemic) may be initiated by an increase in right atrial pressure due to right ventricular failure.

For patients with PAH with small defects (usually ventricular septal defects <1 cm and/or atrial septal defects <2 cm of effective diameter assessed by echocardiography),[6] the clinical picture is very similar to idiopathic PAH; in these cases, the relevance of the defect in the development of PAH is unclear.

In patients with PAH after cardiac defect correction (either percutaneous or surgical), PAH is either still present immediately after the interventions or has recurred several months or years after the procedure in the absence of significant post-operative residual congenital lesions or defects.

Although the demographic, clinical, haemodynamic, and prognostic characteristics of Eisenmenger Syndrome have previously been described,[7,8] the same cannot be said for the other three phenotypes, nor have these parameters been compared across all four phenotypes. In addition, it is not clear whether the survival benefit expected with the introduction of the new PAH medications[7] is uniform among different clinical subgroups. We present the comparative survival data of a large cohort of patients with PAH-CHD and classified according to the four clinical subgroups. As a comparator, a cohort of contemporary idiopathic PAH patients was utilized. The patients were diagnosed and treated with approved PAH-specific medications according to available guidelines.[6,9–11]

Methods

Study subjects

Data from consecutive patients (children ≤ 18 and adults >18 years, with and without Down syndrome) with PAH-CHD who were referred to the Institute of Cardiology, Ospedale S. Orsola-Malpighi, Bologna, Italy, have been prospectively collected in a dedicated database since 1998. Data from a contemporary group of idiopathic PAH patients were also consecutively collected in the same database. All patients or guardians of those aged ≤ 18 years gave signed consent to data being collected and utilized as per the ethical guidelines of the institute.

In this retrospective study, all patients with clinically defined PAH,[6,9–12] i.e. mean pulmonary arterial pressure ≥ 25 mmHg at rest and pulmonary artery wedge pressure ≤ 15 mmHg as measured by right heart catheterization, were included. Pulmonary arterial hypertension was classified as being associated with CHD by the presence of a defect potentially leading to systemic-to-pulmonary shunt in accordance with current guidelines.[6,9–12] Patients with concomitant left heart disease defined by a left ventricular ejection fraction $\leq 45\%$ or a pulmonary wedge pressure ≥ 15 mmHg were excluded. Patients were categorized according to the four clinical subgroups as described in recent guidelines.[3,4] Data from 1 January 1998 to 31 May 2011 were analysed.

Date of diagnosis of PAH-CHD was established as the date of the first confirmatory right heart catheterization (even if performed elsewhere). For patients who underwent corrective procedures (interventional or surgical), the date of diagnosis was established as the date of the first confirmatory right heart catheterization after the procedure.

Upon referral to our centre, all patients underwent a complete assessment, including clinical history, physical examination, echocardiography, right heart catheterization, and 6-min walk test. These data were collected in a dedicated database along with the time between diagnosis of PAH and centre referral and subsequent follow-up data. Following referral to our centre, all the patients were uniformly treated according to the current guidelines and proposed treatment algorithms[6,9–13] with approved PAH-specific drugs. In Italy, epoprostenol, bosentan, iloprost, treprostinil, sildenafil, sitaxsentan, ambrisentan, and tadalafil were approved for PAH in September 1998, June 2002, September 2003, December 2004, October 2005, May 2008, December 2008, and September 2009, respectively; sitaxsentan was subsequently withdrawn in December 2010. Combination therapy of the approved drugs was also considered as per the current guidelines.[6,9–13]

Statistical analysis

Descriptive statistics are provided for subgroup comparisons, including number and percentage for categorical data and mean $\pm$ standard deviation (SD) for continuous variables.

The comparison of demographic, clinical, pathological, functional, and haemodynamic characteristics across the four clinical groups of PAH-CHD was performed by the χ^2 method or analysis of variance as appropriate. A P-value ≤ 0.05 was considered statistically significant. Statistical tests were two-sided.

For the survival analysis, all causes of mortality were included in the Kaplan–Meier analysis. Patients who underwent heart–lung or lung transplantation or were lost to follow-up were censored at the time of the operation or at the time of the last personal contact with our centre. Kaplan–Meier survival curves were assessed and compared with the log-rank test according to the clinical subgroups. One-, 5-, 10-, and 20-year survival was estimated for each of the PAH-CHD sub-populations; the date of the first confirmatory right heart catheterization establishing the presence of PAH-CHD or idiopathic PAH was considered to be the baseline from which survival was measured. A sensitivity analysis was conducted to assess the effect of a delay between diagnosis and referral on survival across the sub-populations by comparing the Kaplan–Meier survival curves of patients whose time between PAH diagnosis and referral was ≥ 5 years. Cox survival analyses, both univariate and adjusted for patient age at first confirmatory right heart catheterization, were performed as additional sensitivity analyses.

As the primary objective of the study was the comparison among the four PAH-CHD groups, we did not perform a statistical analysis comparing the survival of idiopathic PAH patients, with that of the PAH-CHD subgroups.

Statistical analyses were performed using the SAS software (version 9.1, SAS Institute, NC, USA).

Results

Study population

A total of 192 patients with PAH-CHD were included. Average age at the time of referral to our centre was 41 ± 17 years,

16 patients (9%) were children, 116 patients (61%) were females, 11 had Down syndrome (5.7%), and 1 had Kabuki syndrome. Average age at the time of the diagnostic right heart catheterization showing the presence of PAH was 33 ± 10 years.

Of the 192 PAH-CHD patients, 90 had Eisenmenger Syndrome, 48 had PAH associated with systemic-to-pulmonary shunts, 10 had small defects, and 44 had corrected defects. Demographic, clinical, pathological, functional, and haemodynamic characteristics at referral to our centre according to the clinical subgroups are shown in *Table 1*.

Age at referral to our centre was higher in patients with PAH associated with systemic-to-pulmonary shunts and lower in those with small defects. Female sex predominance was observed in all groups except for the patients with PAH after cardiac defect correction. The time between PAH diagnosis and referral to our centre (time from the first right heart catheterization diagnostic for PAH and the first contact) was longer in patients with the Eisenmenger Syndrome than the other subgroups (*Table 1*): mean $\pm$ SD was 15.9 ± 14.3 years in Eisenmenger Syndrome, 6.2 ± 10.0 years in PAH associated with systemic-to-pulmonary shunts, 3.4 ± 5.3 years in PAH associated with small defects, and 3.2 ± 5.3 years in PAH after cardiac defect correction ($P = 0.001$). Post-tricuspid, combined, and complex defects were predominant in patients with Eisenmenger Syndrome and in those with PAH after cardiac defect correction. The average age at the time of cardiac defect correction was 17.0 ± 16.3 years (median $= 11.0$ years). The average time between cardiac defect

Table 1 Demographic clinical, pathological, functional, and haemodynamic characteristics of 192 patients with pulmonary arterial hypertension associated with congenital heart disease, according to clinical subgroup, at referral to our centre

Characteristic	Eisenmenger syndrome	PAH with systemic-to-pulmonary shunt	PAH with small defects	PAH after defect correction	P-value
Patients, *n* (%)	90 (47)	48 (25)	10 (5)	44 (23)	N/A
Age (years)	41 ± 16	47 ± 18	25 ± 21	36 ± 17	0.0002
Female sex, *n* (%)	56 (63)	34 (71)	6 (60)	20 (45)	0.08
PAH diagnosis to referral,[a] *n* (%)					
≥ 0 to <1 year	29 (33)	29 (60)	6 (60)	26 (59)	<0.001
≥ 1 to <5 year	2 (2)	4 (8)	1 (10)	8 (19)	
≥ 5 year	59 (65)	15 (31)	3 (30)	10 (22)	
Type of the defect, *n* (%)					
Atrial septal defect	10 (11)	22 (46)	4 (40)	12 (27)	0.0001
Ventricular septal defect	36 (40)	10 (21)	5 (50)	18 (41)	0.106
Patent ductus arteriosus	15 (17)	0	0	3 (7)	0.009
Partial APVR-isolated	0	3 (6)	0	0	0.035
Partial APVR + atrial septal defect	3 (3)	10 (21)	0	3 (7)	0.004
Other combined[b]	11 (12)	2 (4)	1 (10)	2 (5)	0.393
Complex[c]	15 (17)	1 (2)	0	6 (13)	0.058
6-min walk distance (m)	367 ± 108	420 ± 128	406 ± 130	415 ± 136	0.0661
Borg dyspnoea score	5 ± 3	4 ± 3	4 ± 2	5 ± 3	0.0961
WHO functional class, *n* (%)					
Class I	5 (5)	4 (8)	0	2 (5)	0.641
Class II	23 (26)	20 (42)	4 (40)	16 (36)	
Class III	61 (68)	24 (50)	6 (60)	26 (59)	
Class IV	1 (1)	0	0	0	
Mean right atrial pressure	7 ± 4	7 ± 3	5 ± 2	10 ± 6	<0.0001
Mean pulmonary artery pressure (mmHg)	80 ± 20	52 ± 19	67 ± 34	64 ± 18	<0.0001
Pulmonary vascular resistance (dyn/s/cm⁵)	1904 ± 940	721 ± 743	1078 ± 650	1182 ± 693	<0.0001
Systemic cardiac index (L/min/m²)	2.5 ± 1.3	2.2 ± 0.7	2.3 ± 0.9	2.6 ± 1.0	0.3594

All data are presented as means $\pm$ SD unless otherwise stated.
PAH, pulmonary arterial hypertension; APVR, anomalous pulmonary venous return; WHO, World Health Organization; N/A, not applicable.
[a]Time from the first right heart catheterization diagnostic for pulmonary arterial hypertension and referral to our centre.
[b]Any combination of defects other than APVR with atrial septal defect.
[c]Atrioventricular defects or univentricular pathophysiology.

Table 2 Medication of 192 patients with pulmonary arterial hypertension associated with congenital heart disease, according with clinical subgroup (at the end of follow-up)

Medication, n (%)	Eisenmenger syndrome	PAH with systemic-to-pulmonary shunt	PAH with small defects	PAH after defect correction	P-value
Digitalis	23 (26)	7 (15)	4 (40)	13 (30)	0.211
Diuretics	45 (50)	25 (52)	3 (30)	33 (75)	0.013
Oral anticoagulant treatment	40 (44)	24 (50)	7 (70)	30 (68)	0.045
Long-term oxygen therapy	26 (29)	3 (6)	0	5 (11)	0.001
PAH approved medications					
Monotherapy	27 (30)	11 (23)	2 (20)	5 (11)	0.121
Endothelin receptor antagonists	15 (17)	13 (27)	1 (10)	5 (11)	0.205
Phosphodiesterase type-5 inhibitors	0	0	3 (30)	2 (5)	0.000
Prostanoids	29 (32)	8 (17)	3 (30)	26 (59)	0.0001
Combination therapy	29 (32)	8 (17)	3 (30)	26 (59)	0.0001

PAH, pulmonary arterial hypertension.

correction and the first right heart catheterization diagnostic for PAH was 16.6 ± 11.2 years (median = 16.9 years). Nine patients (20.5%) among the 44 with PAH after cardiac defect correction had a residual shunt which was mild in 6 cases and moderate in 3. Patients with Eisenmenger Syndrome showed the worst exercise capacity, functional capacity, and haemodynamics.

Among the 11 patients with Down syndrome, 8 had Eisenmenger Syndrome, 2 had PAH associated with systemic-to-pulmonary shunts, and 1 had a corrected defect.

Medical treatment of patients at the end of the follow-up according to the clinical subgroups is shown in *Table 2*. A larger number of patients with PAH after cardiac defect correction were treated with diuretics and a smaller number of patients with Eisenmenger Syndrome were treated with oral anticoagulant medication compared with the other groups. In the overall population, 150 (78%) patients were treated with approved PAH-specific medications, 66 (34%) of whom were treated with combination therapy. A larger number of patients with PAH after cardiac defect correction were treated with combination therapy compared with the other groups. A larger number of patients with PAH after cardiac defect correction were treated with combination therapy compared with the other groups. All 11 patients with Down syndrome were treated with approved PAH-specific medications.

As comparator arm, we used data from 278 patients with idiopathic PAH, which were included in our prospective database from 1 January 1998 to 31 May 2011. The average age at the time of referral to our centre was 50 ± 20 years, 27 patients (10%) were children and 159 patients (57%) were females. In this population, 262 (94%) patients were treated with approved PAH-specific medications, 66 (45%) of whom were treated with combination therapy.

Survival analysis

In the overall observation period (mean ± SD = 172 ± 160 months) of patients with PAH-CHD, 43 deaths occurred: 21 were due to heart failure, 16 were sudden cardiac death, 2 were due to

haemoptysis, 2 due to pneumonia, 1 due to cerebral haemorrhage, and 1 was unknown. Among the 11 patients with Down syndrome, there was 1 death. Four patients underwent double lung or heart–lung transplantation. Ten patients (5.2%) were lost to follow-up. Six patients (6/90 = 6.6%) in the Eisenmenger Syndrome group, two (2/48 = 4.2%) in the PAH associated with the systemic-to-pulmonary shunt group, zero in the PAH associated with the small defects group, and two (2/44 = 4.5%) in the corrected defect group.

In the overall population, 1-, 5-, 10-, and 20-year survival rates were 99% [95% confidence interval (CI), 96–100%], 91% (95% CI, 85–94%), 85% (95% CI, 78–90%), and 77% (95% CI, 68–84%), respectively (*Figure 1*).

In patients with Eisenmenger Syndrome, 1-, 5-, 10-, and 20-year survival rates were 99% (95% CI, 92–100%), 93% (95% CI, 85–97%), 89% (95% CI, 79–94%), and 87% (95% CI, 77–93%), respectively (*Figure 2*).

In patients with PAH associated with systemic-to-pulmonary shunts, 1-, 5-, 10-, and 20-year survival rates were 100%, 93% (95% CI, 76–98%), 93% (95% CI, 76–99%), and 86% (95% CI, 60–96%), respectively (P = 0.799 vs. Eisenmenger Syndrome) (*Figure 2*).

In patients with PAH associated with small defects, 1-, 5-, 10-, and 15-year survival rates were 100%, 88% (95% CI, 39–98%), 88% (95% CI, 39–98%), and 66% (95% CI, 16–91%), respectively (P = 0.015 vs. Eisenmenger Syndrome and P = 0.016 vs. PAH associated with systemic-to-pulmonary shunts) (*Figure 2*). In this group, 20-year data were not available for the small sample size.

In patients with PAH after cardiac defect correction, 1-, 5-, 10-, and 20-year survival rates were 98% (95% CI, 85–100%), 83% (95% CI, 66–92%), 65% (95% CI, 43–80%), and 36% (95% CI, 12–62%), respectively (P = 0.0001 vs. Eisenmenger Syndrome and P = 0.004 vs. PAH associated with systemic-to-pulmonary shunts) (*Figure 2*).

The difference in survival across the four clinical subgroups of PAH-CHD was also apparent in 87 patients who had a delay of ≥5 years between PAH diagnosis and referral to our centre (*Figure 3*).
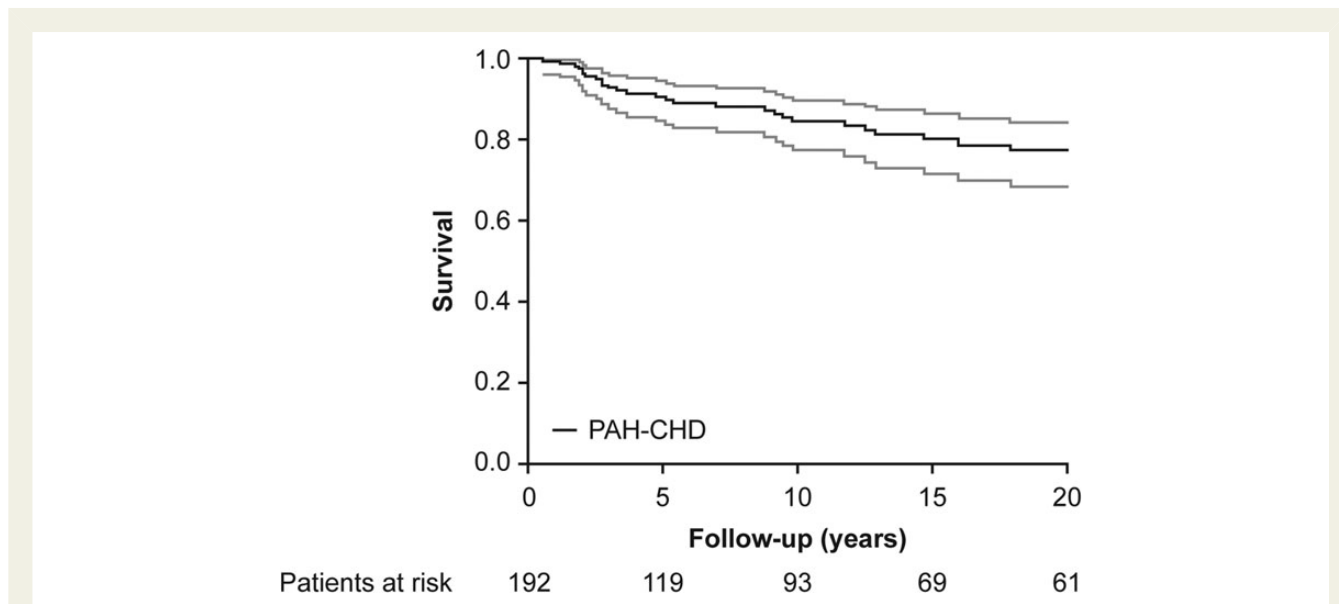
Figure 1 Kaplan–Meier survival curve (with 95% confidence intervals) of 192 patients with pulmonary arterial hypertension associated with congenital heart disease. PAH-CHD indicates pulmonary arterial hypertension associated with congenital heart disease.
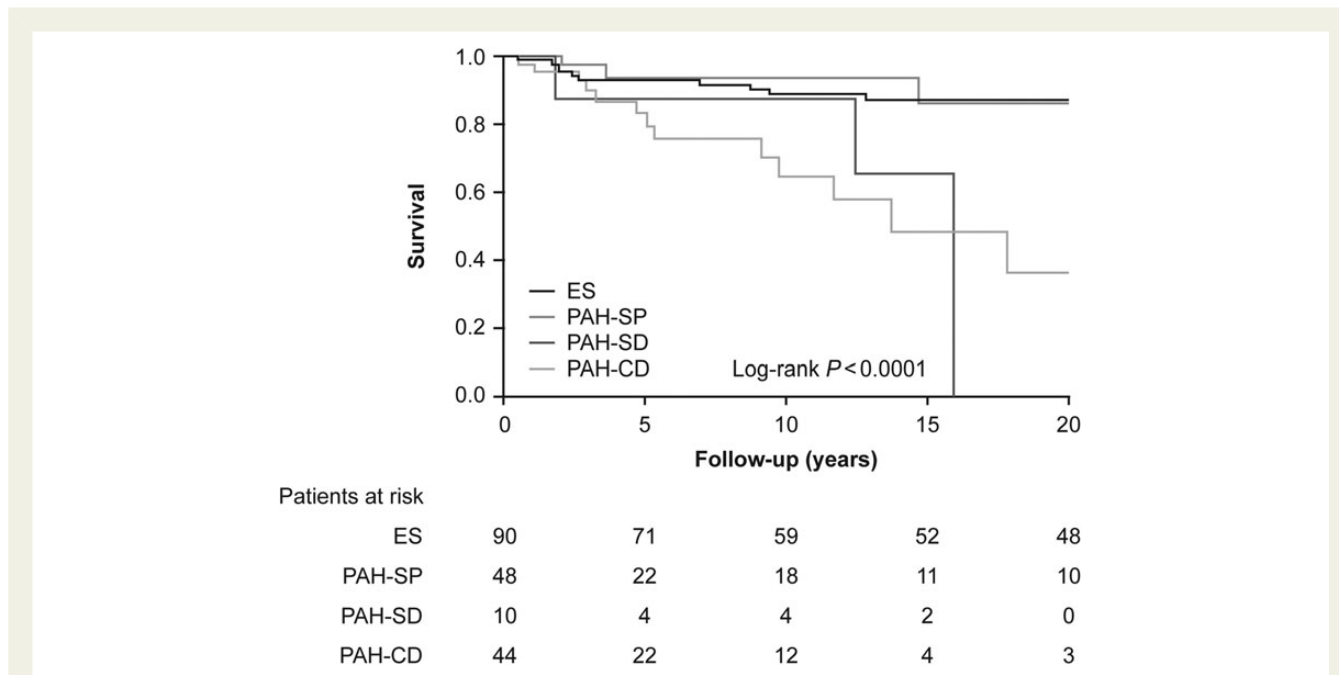

Figure 2 Kaplan–Meier survival curve of 192 patients with pulmonary arterial hypertension associated with congenital heart disease categorized according to the four clinical subgroups. Eisenmenger Syndrome, Eisenmenger syndrome; PAH-systemic-to-pulmonary shunt, pulmonary arterial hypertension associated with systemic-to-pulmonary shunt; PAH-SD, PAH with small defect; PAH-cardiac defect, PAH after cardiac defect correction.

Cox survival analyses confirmed the difference across the four clinical subgroups of PAH-CHD. Both in the univariate model ($P = 0.05$) or in the model adjusted for patient age at first confirmatory right heart catheterization ($P = 0.0003$).

In the group of patients with idiopathic PAH (mean $\pm$ SD follow-up $= 57 \pm 55$ months), 1-, 5-, 10-, and 15-year survival rates were 90% (95% CI, 93−86%), 63% (95% CI, 56−69%), 46% (95% CI, 38−54%), and 38% (95% CI, 27−49%), respectively.
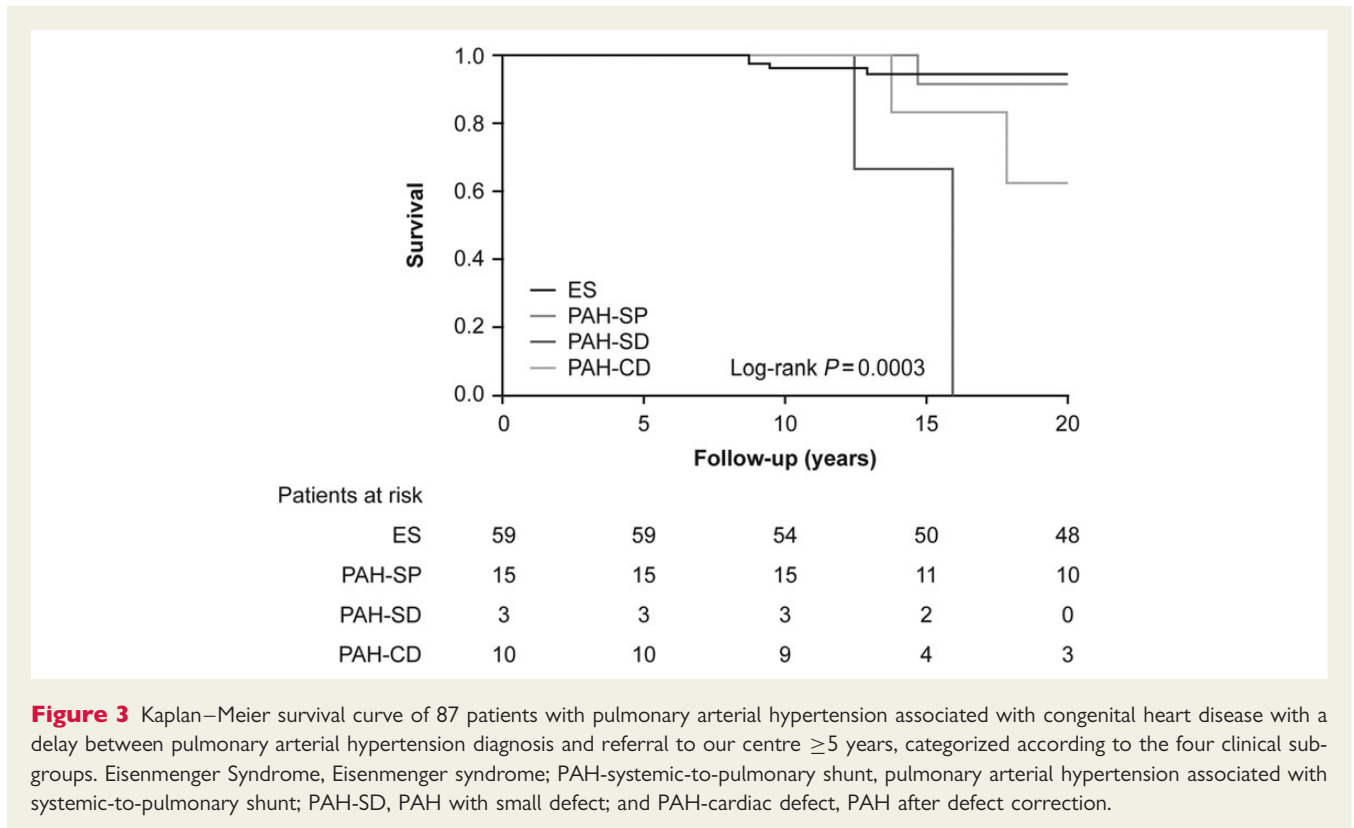
Figure 3 Kaplan–Meier survival curve of 87 patients with pulmonary arterial hypertension associated with congenital heart disease with a delay between pulmonary arterial hypertension diagnosis and referral to our centre ≥5 years, categorized according to the four clinical subgroups. Eisenmenger Syndrome, Eisenmenger syndrome; PAH-systemic-to-pulmonary shunt, pulmonary arterial hypertension associated with systemic-to-pulmonary shunt; PAH-SD, PAH with small defect; and PAH-cardiac defect, PAH after defect correction.

Discussion

These data from a single-centre cohort are the first of their kind as they enable a direct comparison of the survival of patients with different phenotypes of PAH-CHD. Our data clearly show that patients with PAH after cardiac defect correction have a far worse outcome than any other type of PAH-CHD. While it has been suspected for some time and reported, although not uniformly, in children[14,15] that this is the case, these are the first long-term data to support this notion in a predominantly adult patient population.

The overall survival rate of the PAH-CHD patients in this study (Figure 1) confirms the good outcome observed in other contemporary PAH-CHD datasets of patients with Eisenmenger Syndrome.[7,16] Five-year survival was 93% in Eisenmenger Syndrome patients in our study, compared with 91% after 5 years of follow-up in the Diller et al.study[16] and a 95% 5-year survival rate in the Dimopoulos et al.[7] study.

Our data, when compared with that of other PAH aetiologies, such as idiopathic or associated conditions, also confirm that the long-term prognosis in the overall PAH-CHD patient population is the best out of all the PAH aetiologies. Five-year survival of patients with PAH-CHD in our study was 91% compared with 63% in the contemporary group of 278 idiopathic PAH patients in which the same treatment strategy was used, and compared with 3-year survival rates of 70% for idiopathic, heritable, or anorexigen-associated PAH[17] and 56% for PAH associated with connective tissue disease,[18] from other series. However, patients with PAH-CHD are a heterogeneous population as reported in

the clinical classification specific to this population[3,4,6] and, therefore, it is unlikely that they follow a similar disease course. By analysing data from patients as per the four described phenotypes of PAH-CHD, we have shown different clinical, functional, exercise, and haemodynamic characteristics as well as diverse patterns of survival across these four groups.

Eisenmenger syndrome

Patients with Eisenmenger Syndrome had the longest time between diagnosis and referral to our centre, a predominance of post-tricuspid shunts (85.5%) as well as the worst clinical, exercise, and functional characteristics and the highest increase of PVR among the four clinical subgroups (Table 1). However, survival was similar in patients with Eisenmenger Syndrome to those with PAH associated with systemic-to-pulmonary shunts and significantly better than for patients with small defects or corrected defects. The survival curves of patients with Eisenmenger Syndrome compared with those with small or corrected defects start to diverge in 2–5 years after the first diagnosis of PAH, but the largest difference is observed after 10–12 years. Data from the Registry to Evaluate Early And Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) have shown in paediatric patients with PAH-CHD that, initially, there is no survival difference in patients with unrepaired and repaired defects (2-year survival estimated as 86 ± 7 vs. 85 ± 5%).[15] However, longer term follow-up (up to 5 years) of patients in the British PAH paediatric registry[13] shows worst survival in children with repaired defects compared with those with Eisenmenger

Syndrome.[14] The reasons for the discrepancy between the worst functional characteristics associated with the highest increase of PVR of Eisenmenger Syndrome patients and the better survival may include the presence of a cardiac defect which allows a pulmonary-to-systemic shunt. The increase of pulmonary-to-systemic shunt and the reduction of systemic blood oxygenation on exercise may explain the lower exercise capacity of these patients.[19] However, pulmonary-to-systemic shunt may maintain adequate systemic flow and pressure contributing to the longer survival. In addition, Eisenmenger Syndrome patients may have a better right ventricular function due to the early development of PAH which is responsible for the maintenance of the foetal type of right ventricular hypertrophy.[20] We did not directly assess the right ventricular function in our patients, but indirect evaluation may be obtained by the comparison of the loading conditions: right atrial pressure and PVR may be considered as surrogates for the pre-load and after-load of the right ventricle, respectively. In our series, Eisenmenger Syndrome patients had by far the highest mean pulmonary artery pressure and PVR (after-load) while maintaining an average right atrial pressure (pre-load) close to normal limits (*Table 2*). This may support the hypothesis of better right ventricular contractility in this subgroup of patients.

Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts

This group was characterized by an older age, a relatively short time between diagnosis and referral to our centre, a large predominance of pre-tricuspid shunts (72.3%), and the lowest level of PVR compared with the other groups. The survival was very similar to that of the Eisenmenger Syndrome group even if the reasons to explain this relatively good outcome may be different, including delayed and less-severe pulmonary vascular disease (which nevertheless was still at a severe enough stage to be a contraindication for cardiac defect correction). The delayed onset of pulmonary vascular disease is confirmed by the older age of this group and the predominance of pre-tricuspid shunts may support the hypothesis of a less-severe pulmonary vascular disease.

Pulmonary arterial hypertension associated with small defects

The patients with PAH associated with small defects were only 5% of the overall PAH-CHD population of this study. They were the youngest and had a predominance of post-tricuspid shunts (60.0%). In these cases, the influence of the congenital defect in the induction and progression of pulmonary vascular disease is unclear and a diagnosis of idiopathic PAH with a concomitant congenital defect may be proposed. The presence of a common underlying cause for these two conditions has never been established. Interestingly, the survival of patients with PAH associated with small defects appears to be far better when compared with that of 'classical' idiopathic PAH patients,[17] In our study, the 15-year survival was 66% for PAH associated with small defects and 38% for those with idiopathic PAH. In contrast, the 15-year survival of the small defects group was worse compared with the survival of patients with Eisenmenger Syndrome (87%) and with systemic-to-pulmonary

shunts (86%). The reason why the patients with PAH associated with small defects have an intermediate survival between patients with idiopathic PAH and patients with PAH and larger uncorrected defects is unclear. Possible explanations include the favourable prognostic influence of the small defects, which may allow a pulmonary-to-systemic shunt in the advanced stages, limiting the progressive reduction of the systemic output. This mechanism, which may explain the better survival compared with idiopathic PAH patients, may not be sufficient to reach the more favourable prognosis of patients with larger defects and larger shunts.

Pulmonary arterial hypertension after cardiac defect correction

The patients in this group were characterized by an intermediate age, time between diagnosis and referral to our centre, increase of PVR among the groups, and by a predominance of post-tricuspid shunts (72.7%) similar to that in the Eisenmenger Syndrome patients. The reasons for the initiation and progression of PAH in these subjects include a delayed correction of the defects especially if the pulmonary vascular disease had already developed. In our series, the defects were corrected at a relatively late age (median age at correction was 11.0 years), and the presence of PAH was detected after a median of 16.9 years from cardiac defect correction. The 44 patients of this group underwent surgery in multiple centres and it is not retrospectively possible to identify the operability criteria used in each individual centre at the time the correction was performed. In addition, in the majority of patients, the pre-operative right heart catheterization was either not performed (operability based on echocardiographic parameters) or not available, and the pre-operative values of pulmonary arterial pressure and PVR were unknown.

The influence of residual defects after the correction on the development of PAH is unclear. However, residual shunts were present only in one-fifth of our cases and they were small in size in two-thirds of cases.

The reasons for the worse prognosis of these patients compared with patients with Eisenmenger Syndrome are unclear and include the lack of a possible pulmonary-to-systemic shunt in the case of elevation of PVR or impaired adaptation of the right ventricle to an increasing after-load when this starts after the first months/years of life. This last hypothesis may be confirmed by a higher value of right atrial pressure (pre-load) despite lower PVR (after-load) in patients with corrected defects compared with the Eisenmenger Syndrome patients of our study (*Table 2*).

As discussed, an increase in mortality rate in paediatric CHD patients with post-operative PAH compared with paediatric Eisenmenger Syndrome patients has already been reported.[14] However, in this series, PAH was likely to be a relatively early complication after cardiac defect correction (average age of children was 6.9 years) compared with our patient population in which PAH was detected very late after correction (*Table 1*). In the Euro Heart Survey on adult CHD, a better survival of corrected and uncorrected CHD patients with PAH compared with Eisenmenger Syndrome patients was reported.[21] However, in this study, the definition of PAH was questionable (systolic pulmonary arterial pressure ≥40 mmHg or qualitatively defined as 'abnormal'), and

it is possible that some patients in this series did not have PAH classified by the criteria of the current guidelines.[6]

In the subgroup of patients with Down syndrome, who were all treated with PAH-specific medications, we did not observe an excess of mortality compared with the other patients.

The different survival observed among patients with PAH associated with the different CHD clinical subgroups cannot be attributed to a different treatment strategy. On the contrary, a larger percentage of the patients with PAH with small or corrected defects were treated with approved PAH-specific drugs compared with the other two groups.

Limitations

This is a retrospective analysis of a prospectively collected database in a specialist PAH centre and, as such, there are a number of inherent limitations.

Patient population is selected by referral to centre and, therefore, there may be a selection bias. In particular, as a specialist centre, we may only have the more severe patients referred to us. However, this will affect all four groups and so will not affect the intragroup survival comparisons.

We started our survival analysis from the first diagnosis of PAH by right heart catheterization to minimize referral bias. We observed a mean delay of 6–17 years across groups between the first diagnosis of PAH by right heart catheterization and referral to our centre (Table 1). This means a variable treatment gap between diagnosis and referral, which may have an effect on survival. However, patients with Eisenmenger Syndrome who had the best survival rate also had by far the largest referral delay (Table 1), supporting the hypothesis that the survival difference we observed could have been even larger without referral heterogeneity. In addition, the difference in survival across the clinical subgroups of PAH-CHD was confirmed in the 87 patients who had a delay of ≥5 years between PAH diagnosis and referral (Figure 3). Another potential bias is the 'immortal time bias',[22] which arises from the very nature of an observational cohort study. In our study, as well as in other series,[7,14,15,17,21] the bias arises as only patients who remain alive after diagnosis (i.e. diagnostic right heart catheterization) up to referral and first assessment are included. However, in this study, the bias will have affected all four clinical subgroups and the intragroup survival comparisons will not have been influenced. In fact, in 87 patients with the largest delay between PAH diagnosis and referral to our centre, the survival difference was confirmed. A final limitation is related to the small size of some of the groups, in particular, the small defects group had only 10 patients.

The results of this study confirm that there are relevant clinical, functional, and haemodynamic differences among clinical subgroups of patients with PAH-CHD. In addition, an important heterogeneity in survival among groups is observed: patients with Eisenmenger Syndrome and with systemic-to-pulmonary shunts have a better long-term survival compared with subjects with small or corrected defects. These findings should be considered when planning medical or interventional treatment strategies in patients with PAH-CHD.

Acknowledgements

Funding

Conflict of interest: N.G. reports serving as a consultant and receiving payment for lecture fees from Actelion Pharmaceuticals Ltd, Pfizer, GlaxoSmithKline, Eli Lilly, and Bayer Schering Pharma. The other authors report no conflict of interests.

References

1. Adatia I, Kothari SS, Feinstein JA. Pulmonary hypertension associated with congenital heart disease: pulmonary vascular disease: the global perspective. *Chest* 2010;**137**(6 Suppl):52S–61S.
2. Beghetti M, Galiè N. Eisenmenger syndrome: a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;**53**:733–740.
3. Galiè N, Manes A, Palazzini M, Negro L, Marinelli A, Gambetti S, Mariucci E, Donti A, Branzi A, Picchio FM. Management of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. *Drugs* 2008;**68**:1049–1066.
4. Simonneau G, Robbins I, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;**54**:S43–S54.
5. Eisenmenger V. Die angeboren defects des kammerscheidewand des herzen. *Z Klin Med* 1897;**32**:1–28.
6. Galiè N, Hoeper M, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G; ESC Committee for Practice Guidelines (CPG). Guidelines on diagnosis and treatment of pulmonary hypertension: the Task Force on Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and of the European Respiratory Society. *Eur Heart J* 2009;**30**:2493–2537.
7. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ, Gatzoulis MA. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. *Circulation* 2010;**121**:20–25.
8. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, Stone S. Eisenmenger's syndrome: factors relating to deterioration and death. *Eur Heart J* 1998;**19**:1845–1855.
9. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J; Task Force. Guidelines on diagnosis and treatment of pulmonary arterial hypertension: the Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004;**25**:2243–2278.
10. Badesch BD, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, McLaughlin VV; American College of Chest Physicians. Medical therapy for pulmonary arterial hypertension. ACCP evidence-based guidelines for clinical practice. *Chest* 2004;**126**:35S–62S.
11. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J, Harrington RA, Anderson JL, Bates ER, Bridges CR, Eisenberg MJ, Ferrari VA, Grines CL, Hlatky MA, Jacobs AK, Kaul S, Lichtenberg RC, Lindner JR, Moliterno DJ, Mukherjee D, Pohost GM, Rosenson RS, Schofield RS, Shubrooks SJ, Stein JH, Tracy CM, Weitz HH, Wesley DJ. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *Circulation* 2009;**119**:2250–2294.

12. Nomenclature Committee. Nomenclature and classification of pulmonary hypertension. In: Rish S ed. *Primary Pulmonary Hypertension: Executive Summary from the World Symposium-Primary Pulmonary Hypertension.* Geneva, Switzerland: World Health Organization; 1998, pp. 25–27.

13. Baumgartner H, Bonhoeffer P, De Groot NMS, De Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJM, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, Swan L, Andreotti F, Beghetti M, Borggrefe M, Bozio A, Brecker S, Budts W, Hess J, Hirsch R, Jondeau G, Kokkonen J, Kozelj M, Kucukoglu S, Laan M, Lionis C, Metreveli I, Moons P, Pieper PG, Pilossoff V, Popelova J, Price S, Roos-Hesselink J, Uva MS, Tornos P, Trindade PT, Ukkonen H, Walker H, Webb GD, Westby J. ESC Guidelines for the management of grown-up congenital heart disease. *Eur Heart J* 2010;**31**:2915–2957.

14. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001–2006. *Heart* 2009;**95**:312–317.

15. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term PAH disease management. *Circulation* 2012;**125**:113–122.

16. Diller GP, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, Uebing A, Harries C, Goktekin O, Gibbs JS, Gatzoulis MA. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case–control study. *Eur Heart J* 2006;**27**:1737–1742.

17. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaïci A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jaïs X, Montani D, Souza R, Simonneau G. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010;**122**:156–163.

18. Hachulla E, Carpentier P, Gressin V, Diot E, Allanore Y, Sibilia J, Launay D, Mouthon L, Jego P, Cabane J, de Groote P, Chabrol A, Lazareth I, Guillevin L, Clerson P, Humbert M; ItinérAIR-Sclérodermie Study Investigators. Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinérAIR-Sclérodermie study. *Rheumatology* 2009;**48**:304–308.

19. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation* 2005;**112**:828–835.

20. Hopkins WE. The remarkable right ventricle of patients with Eisenmenger syndrome. *Coron Artery Dis* 2005;**16**:19–25.

21. Engelfriet PM, Duffels MGJ, Moller T, Boersma E, Tijssen JG, Thaulow E, Gatzoulis MA, Mulder BJ. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. *Heart* 2007;**93**:682–687.

22. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008;**167**:492–499.