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Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality

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Aims The population of adults with congenital heart disease (ACHD) is growing and ageing. Limited information about the diagnostic spectrum of this emerging population, its resource utilization at tertiary ACHD centres, and especially about prognostic parameters is available.

Methods and results Retrospective cohort study on all ACHD patients ≥60 years of age under active follow-up. All-cause mortality was the primary outcome measure. Out of a total population of 7315 ACHD patients, 375 [190 females (50.7%), mean age 64.8 ± 5.9 years] fulfilled the inclusion criteria. During a median follow-up of 5.5 (IQR 3.1–8.6) years, 55 of the 375 patients died. The number of interventions ($P = 0.0006$), the number and length of hospitalization ($P < 0.0001$), and the number of outpatient clinic visits ($P < 0.0001$) were significantly higher in patients ≥60 compared with patients aged between 20 and 60 years. Patients ≥60 years of age with moderate or severe congenital heart defects had worse survival prospects than their age- and gender-matched comparison population. On multivariate Cox analysis, coronary artery disease [hazard ratio (HR): 5.04; 95%CI: 1.88–13.51, $P = 0.0014$], symptoms of heart failure (HR: 2.36; 95%CI: 1.05–5.29, $P < 0.05$), NYHA class (HR: 1.96; 95%CI: 1.18–3.26, $P < 0.01$), and moderate to severe reduction in systemic ventricular systolic function (HR: 1.90; 95%CI: 1.20–2.99, $P < 0.001$) were the strongest prognostic factors.

Conclusion There is a growing number of elderly ACHD patients with high mortality rates and a higher utilization of healthcare resources compared with younger patients. Acquired morbidities, such as coronary artery disease, seem to be key determinants of outcome in this older population in conjunction with the underlying congenital heart disease.

Keywords Adult congenital heart disease • Outcome • Coronary artery disease

Introduction

The population of adults with congenital heart disease (ACHD) is increasing and ageing.[1] Mortality due to congenital heart disease has shifted away from the infant and childhood period towards adulthood, with a steady increase of age at death.[2] As survival rates of patients with congenital heart disease continue to improve and patients with this condition live longer, the demand for ACHD services is likely to grow.[3,4] Indeed, we have recently reported increasing hospital admissions for ACHD over the age of 65 in England between 1994 and 2004.[3] It is estimated that this patient group of ACHD accounts for around 7–10% of all ACHD patients.[5] Despite this, however, limited information about the spectrum of this emerging population, its resource utilization affecting tertiary ACHD centres and especially about prognostic parameters is available. It is possible that prognostic markers established in younger ACHD cohorts may not be directly applicable to older ACHD patients, where acquired heart and other conditions are likely to gain importance. The only available study so far assessing prognostic factors in older ACHD patients was published by Afilalo *et al.*[5] It is a population-based

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Table 1 Baseline characteristics

	All	Dead	Alive	*P*-value
Age	64.8 ± 5.9	65.4 ± 6.7	64.7 ± 5.7	0.99
Female, *n* (%)	190 (51)	23 (42)	167 (52)	0.149
Complexity of heart defect, *n* (%)				0.115
Simple	165 (44.0)	17 (30.9)	148 (46.3)	
Moderate	174 (46.4)	30 (54.5)	144 (45.0)	
Complex	28 (7.5)	7 (12.7)	21 (6.6)	
Other	8 (2.2)	1 (1.8)	7 (2.2)	
NYHA class, *n* (%)				< 0.0001
I	163 (53.3)	9 (20.9)	154 (58.6)	
II	85 (27.8)	14 (32.6)	71 (27.0)	
III	58 (19.0)	20 (46.5)	38 (14.4)	
Ventricular function, *n* (%)				0.004
Normal	295 (88.9)	32 (80)	263 (90.1)	
Mild	23 (6.9)	2 (5)	21 (7.2)	
Moderate	9 (2.7)	4 (10)	5 (1.7)	
Severe	5 (1.5)	2 (5)	3 (1.0)	

NYHA, New York Heart Association; *P*-value is for comparison between patients who died and those that are alive (Mann–Whitney *U* test was used for continuous and χ^2 test for categorical variables)

cohort study using the Quebec Congenital Heart Disease Database and International Classification of Diseases codes. While including a large number of patients coming into contact with the healthcare system—therefore inclusive of patients not under active tertiary care—by necessity, this type of analysis lacks in-depth patient information. For example, clinical data such as patients' functional capacity or information on ventricular function was missing in this report.[5] Our current study, in contrast, takes a tertiary ACHD centre perspective, aiming to evaluate the burden of disease, clinical spectrum as well as predictors of outcome in adults with congenital heart disease over 60 years of age, currently seen at a single, large supra-regional ACHD centre.

Methods

This is a retrospective cohort study, including all patients under active follow-up at our centre who were ≥60 years of age at any point between January 2000 and March 2012. The time-point of inclusion was the date of the 60th birthday or the first visit after the year 2000 if a patient was already 60 years old in the year 2000. January 2000 was chosen as this represents the point when our electronic data was established, thus allowing us to identify all eligible patients. Out of 7315 patients registered at the ACHD centre at the Royal Brompton Hospital (6390 of whom are under active follow-up and were included in the survival analyses), 375 fulfilled the inclusion criteria (*Tables 1* and *2*). Patients undergoing percutaneous aortic valve replacements were not included in this study. The primary endpoint of the study was all-cause mortality. Deaths were identified from the hospital database, linked to the Office of National Statistics which registers all UK deaths. Information on the cause of death was retrieved from the medical records. If the cause of death was not available from the medical records, we contacted family care practitioners to obtain further information on the cause of death. As this was a retrospective analysis of data collected for routine clinical care and administrative purposes, individual informed consent was not required (UK National Research Ethics Service guidance). The study was locally registered and approved.

Table 2 Underlying diagnosis

Diagnosis	*n* (%)
Predominantly mild lesions	
Shunt lesions	210 (56.0)
Valve disease	41 (10.9)
Moderate complexity lesions	
Tetralogy of Fallot	45 (12.0)
Coarctation of the aorta	32 (8.5)
Ebstein's anomaly	10 (2.7)
Complex lesions	
Eisenmenger	12 (3.2)
ccTGA	10 (2.7)
Complex other	7 (1.9)
Other	
Marfan syndrome	8 (2.1)

ccTGA, congenital corrected transposition of the great arteries; complex other: double inlet left ventricle, double-chambered right ventricle, tricuspid atresia, Fontan.

Clinical data

Demographic data, as well as information on medical and surgical history were retrieved for all patients from hospital records. Complexity of cardiac lesions was classified according to the Bethesda classification.[6]

Symptomatic status was assessed according to the New York Heart Association classification (NYHA). Systemic ventricular function was graded semiquantitatively as normal, mildly, moderately, or severely impaired based on the results of routine transthoracic echocardiograms, or other advanced imaging modalities where available, as described previously.[7] In patients with a systemic left ventricle and a biventricular anatomy, it was graded according to current recommendations (mildly impaired ventricular function corresponding to an ejection fraction below ~55%, moderately impaired <45%, and severely impaired <30%, respectively).[8] For the purpose of this study, coronary artery disease was only diagnosed if it was proved by coronary angiogram or if there was a history of percutaneous coronary intervention or aorto-coronary bypass surgery. Dementia was diagnosed according to the guidelines of the National Institute of Health and Clinical Excellence of the UK.[9] Cyanosis was defined as a resting oxygen saturation of <90%. Renal dysfunction was diagnosed according to clinical practice guidelines.[10] Pulmonary hypertension was diagnosed according to recent European guidelines.[11] History of arrhythmia encompasses any type of supraventricular or ventricular arrhythmia requiring therapy. Lung disease includes any form of lung disease (asthma, chronic obstructive lung disease, emphysema, etc.) and patients with diabetes include both insulin-dependent and non-insulin-dependent cases. The number of hospitalizations, length of hospital stay, number of outpatient visits, number of interventions and operations were calculated based on administrative data and expressed per 100 patient years (years of follow-up) for our study group. In addition, this data was compared with the data of all other ACHD patients under our care during the same time period with an age between 20 and 40 years, and 40 and 60 years, respectively.

Statistical analysis

Statistical analyses were performed using MedCalc version 12.3.0.0 (MedCalc Software, Mariakerke, Belgium) and R package version 2.15.0. Continuous variables are presented as mean ± standard deviation or median (interquartile range), whereas categorical variables are presented as number (percentage). Comparison between groups was performed using the Fisher's test or Mann–Whitney *U* test for continuous and χ^2 test for categorical variables. Univariate Cox proportional-hazards analysis was used to assess the association between variables and all-cause mortality. Significant parameters ($P < 0.05$) were subsequently included in a multivariate Cox regression model in a stepwise fashion. Kaplan–Meier curves and log-rank tests were used to compare survival (all-cause mortality) for severity of congenital heart defect, NYHA class, and systemic ventricular function. Relative survival was assessed using custom made R code based on a non-parametric method reported by Finkelstein *et al.*[12] Relative survival was compared with the general population (2007–2009 interim life tables) after excluding UK non-residents.[13] All tests were performed two-sided and for all analyses, a *P*-value < 0.05 was considered statistically significant. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Demographic and baseline characteristics of the study population are presented in *Table 1*. The number of elderly patients (≥60 years of age) with ACHD at our centre was increasing steadily during the study period as shown in *Figure 1A*. While in 2000, only 37 patients over the age of 60 were under regular follow-up, this number increased to 320 in the year 2011 (an increase of 864%). Out of the 375 patients, 130 (34.7%) were referred to our service after their 60th birthday. *Figure 1B* illustrates the change in the number of patients with simple, moderate complexity, and complex heart defects over the study period. It shows that patients with simple defects are still dominating; however, there was also an approximately six- to seven-fold increase in the number of patients with heart defects of at least moderate complexity. Simple defects comprised mainly left-to-right shunt lesions as well as valvular heart disease (*Table 2*). Out of the 210 patients with a shunt lesion, 139 (66.2%) had an atrial-septal defect. The majority of these patients ($n = 123$) underwent ASD closure (75.6% percutaneously) either before (25.2%) or after their 60th birthday (74.8%). Other shunt lesions (anomalous pulmonary venous return, ventricular septal defects, atrioventricular septal defects, patent arterial duct, and sinus venosus defects) were present in 71 patients (33.8%). These were closed in 54 patients (in 7.4% percutaneously and 92.6% surgically; 51.9% before the 60th birthday). In only 17 patients, the shunt

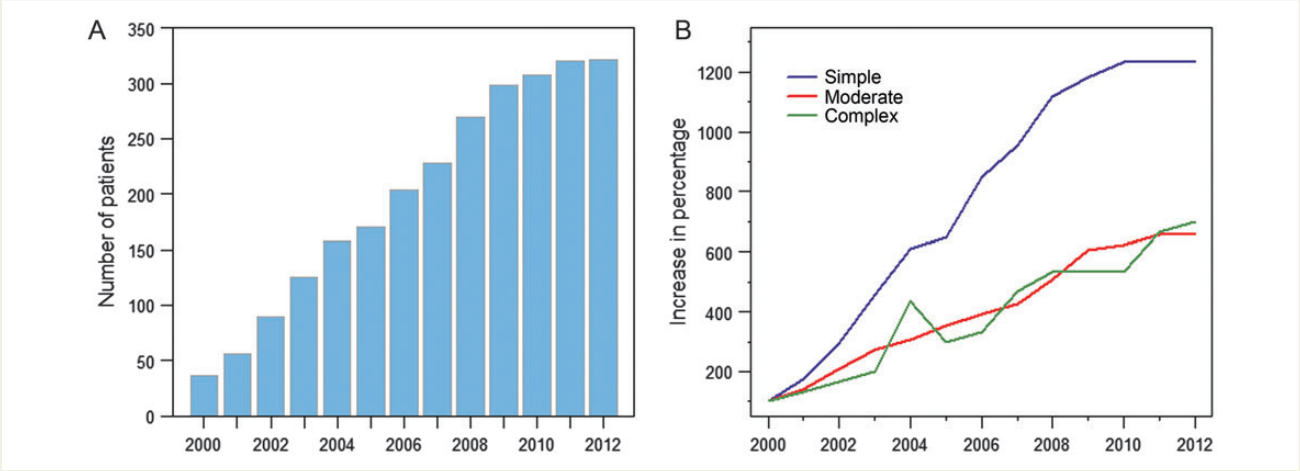

Figure 1 Number of patients ≥60 years of age under follow-up. (*A*) Overview over the whole cohort. (*B*) Relative number of patients stratified by the complexity of congenital heart defect (year 2000 is indexed as 100%). There was a 12-fold increase of patients with simple defects, and a six- to seven-fold increase in patients with moderate–severe complexity.

defect was not closed. In 10 patients, the defect was small and haemodynamically not significant, in five cases an intervention was offered but refused by the patient and two patients had major co-morbidities and were therefore deemed unsuitable for interventional or surgical treatment. *Tables 1 and 2* provide further information on the distribution of complexity of the underlying heart defect and the specific diagnosis of patients with moderate or complex heart lesions. The majority of patients were in NYHA class I, with only 19% of patients reporting symptoms compatible with NYHA class III. In this ambulatory patient population, no patient was in NYHA class IV at baseline assessment. In 25 patients (10 out of these with Eisenmenger syndrome), cyanosis was present.

Comparing healthcare utilization between elderly and younger patients, it emerged that the number of interventions per 100 patient years was significantly higher in the age group over 60 compared with the age group of 20–60. Similarly, the number of hospitalizations and the cumulative length of hospital stay were higher in this age group as was the number of outpatient clinic visits (*Table 3*). The only exception was, as expected, the number of cardiac surgeries which was significantly lower in the elderly.

Over a median follow-up period of 5.5 (IQR 3.1–8.6) years, 55 (14.6%) elderly patients died. The cause of death was cardiac in 22 patients (heart failure in 21, myocardial infarction in one), multi-organ failure in three patients, cerebrovascular accident in two patients, and non-cardiac in 12 patients (six of those due to cancer). In 15 cases, death was directly attributable to the underlying congenital heart defect (heart failure in 13, multi-organ failure in two). In 16 cases, no information regarding the cause of death was available. *Table 1* illustrates that patients who died during follow-up were in a worse NYHA functional class and had more impaired systemic ventricular function at baseline.

Patients $\geq$60 years of age had significantly worse survival prospects compared with younger patients in absolute terms (log-rank $P < 0.0001$) as shown in *Figure 2*. When assessing relative survival, however, a different picture emerged: patients below the age of 60 had worse relative survival prospects than expected for an age- and gender-matched sample from the general population [302 observed deaths vs. 49.7 expected deaths, standardized mortality ratio (SMR) 6.05, 95% confidence interval (CI) 5.21–7.03, $P < 0.0001$] while this was not the case for elderly patients and their reference population (55 observed deaths vs. 44.3 expected deaths, SMR 1.03, 95% CI 0.76–1.40, $P = 0.82$). In fact, relative survival prospects of elderly patients as a group were not significantly different from expected survival in the reference population. This is mainly due to the predominance of elderly patients with simple lesions (44%) who had similar survival prospects to their reference population (SMR 0.70, $P = 0.06$). However, elderly patients with moderate or complex disease had significantly worse than expected outcome (SMR 1.89 ($P = 0.002$), and 2.91 ($P = 0.01$), respectively). *Figure 3* illustrates the association between complexity of the underlying congenital heart defect, NYHA class, and systemic ventricular function with mortality in elderly patients.

Univariate and multivariate Cox proportional-hazard analyses were performed to identify predictors of all-cause mortality in patients $\geq$60 years of age. On univariate analysis, the following parameters were tested but emerged as being non-significant: age, gender, arterial hypertension, previous cerebrovascular accident, dementia, renal dysfunction, and history of smoking. Significant univariate predictors of all-cause mortality (*Table 4*) were included into the multivariate Cox analysis. Coronary artery disease [hazard ratio (HR): 5.04; 95% CI: 1.88–13.51, $P = 0.0014$], symptoms/signs of heart failure (HR: 2.36; 95% CI: 1.05–5.29, $P < 0.05$), NYHA functional class (HR: 1.96; 95% CI: 1.18–3.26, $P < 0.01$), and systemic ventricular function (HR: 1.90; 95% CI: 1.20–2.99, $P < 0.001$) emerged as independent predictors of mortality (*Table 4*).

Discussion

The current study shows an exponential increase in the number of patients under follow-up at tertiary ACHD centres who reach 60 years and beyond. This increase is likely to continue as the survival prospects of patients with heart defects, of even moderate or complex severity, continue to improve. Elderly ACHD patients are afflicted by substantial morbidity, frequently requiring hospital admissions or interventions, and thus, utilizing more healthcare resources. Acquired morbidities like coronary artery disease appear to be of greater importance in defining outcome in older compared with younger ACHD patients in conjunction with the underlying congenital heart defect.

Table 3 Number of hospitalization, outpatient visits, interventions, and operations per age group

	Age group			
	20–40 years	**40–60 years**	**> 60 years**	***P*-value***
Patients at risk[a]	3252	2260	375	
Hospitalizations [*n*/100 patient-years]	9.49	14.07	16.40	<0.0001
Hospitalizations days [*n*/100 patient-years]	70.92	102.80	141.67	<0.0001
Outpatient visits [*n*/100 patient-years]	122.46	145.09	159.44	<0.0001
Interventions [*n*/100 patient-years]	1.94	2.88	3.11	0.0006
Surgeries [*n*/100 patient-years]	2.15	2.25	1.23	0.0001

[a]As of March 2012.
*Comparisons are made between patients > 60 years of age vs. patients <60 years of age.

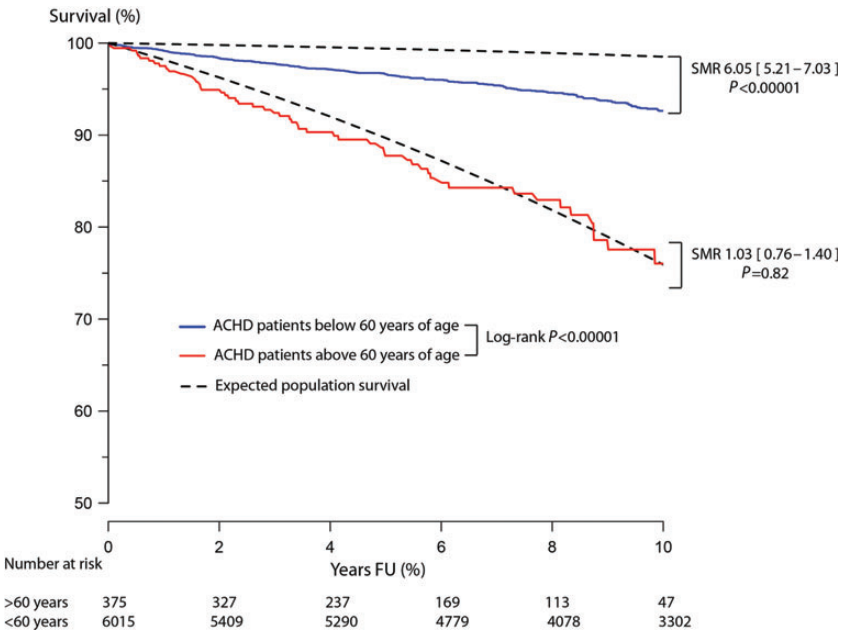

Figure 2 Relative survival of patients above and below 60 years of age. SMR = standardized mortality rate (observed/expected number of deaths) compared with an age- and gender-matched sample from the general population. For further details on the methodology used see text. The dotted line represents the expected survival curve for an age- and gender-matched sample from the general UK population.

The number of ACHD patients over the age of 60 is increasing. We saw a nearly nine-fold increase in patient numbers between 2000 and 2012 (*Figure 1A*). This clearly reflects the success of congenital cardiac surgery and congenital cardiology over recent decades. However, the cohort of patients studied in the current study is noteworthy: many patients did not receive surgical or interventional treatment in childhood, or therapy was limited to palliative measures. Those patients, who were operated, received surgical treatment in the pioneering years of congenital cardiac surgery and cardiac surgery in general. Some of the employed surgical techniques have been abandoned since, leading to a changing and dynamic profile of sequelae and evolving spectrum of long-term complications in contemporary ACHD cohorts.[14] Furthermore, most patients nowadays are operated in infancy receiving reparative and not palliative procedures with better peri-operative care.[15–17] With ever increasing surgical expertise and earlier normalization of the circulation therefore, the spectrum of patients surviving to old age is likely to include more complex patients in the future.[1,18] Therefore, the spectrum of elderly patients presenting to tertiary centres is likely to change over the next years and this may also positively affect survival prospects in this emerging patient group. Additionally, this might also lead to a changed spectrum regarding the causes of death. Some of the patients included here also represent selected cases of natural survival to old age, despite having moderate or complex underlying congenital heart defects, often only reported anecdotally.[19] In addition, it is not unusual to diagnose some forms of simple cardiac defects in late adult life and this is especially true for simple shunt lesions such as atrial-septal defects.[20–22] The availability of interventional treatment options more recently may have also lead to increasing referral rates of patients with secundum ASDs to tertiary centres and this could—at least in part—explain the considerable increase in patients with simple lesions observed in our study.

The current study shows that elderly ACHD patients are high utilizers of ACHD services (*Table 3*). This is particularly so for hospitalizations and non-surgical interventions. This in turn, reflects inherent morbidity but also progress made in interventional techniques. The increased tendency to refer elderly patients for tertiary care and interventional procedures is also based on recent evidence confirming symptomatic relief and haemodynamic improvement following interventional procedures in patients over 60 years of age.[23,24] We contend that as the number of elderly ACHD patients increases, along with the complexity of the underlying defects, the burden on ACHD services will rise considerably. This has obvious implications on health care planning both in terms of appropriate facilities and for training of professionals with relevant expertise.[25,26]

Despite a relative predominance of simple lesions compared with younger individuals, ACHD patients ≥60 years of age had significantly worse survival prospects on average in the current study. Although, this could partly be attributed to the effects of older age (as illustrated by the lower standardized mortality rate compared with younger patients), it highlights the need for risk stratification to identify patients who may likely benefit from special medical attention. In addition, elderly patients with underlying heart defects of at least moderate complexity had significantly worse survival prospects compared with their reference population.

In our study in elderly patients (≥60 years of age) with congenital heart disease, coronary artery disease as an acquired comorbidity

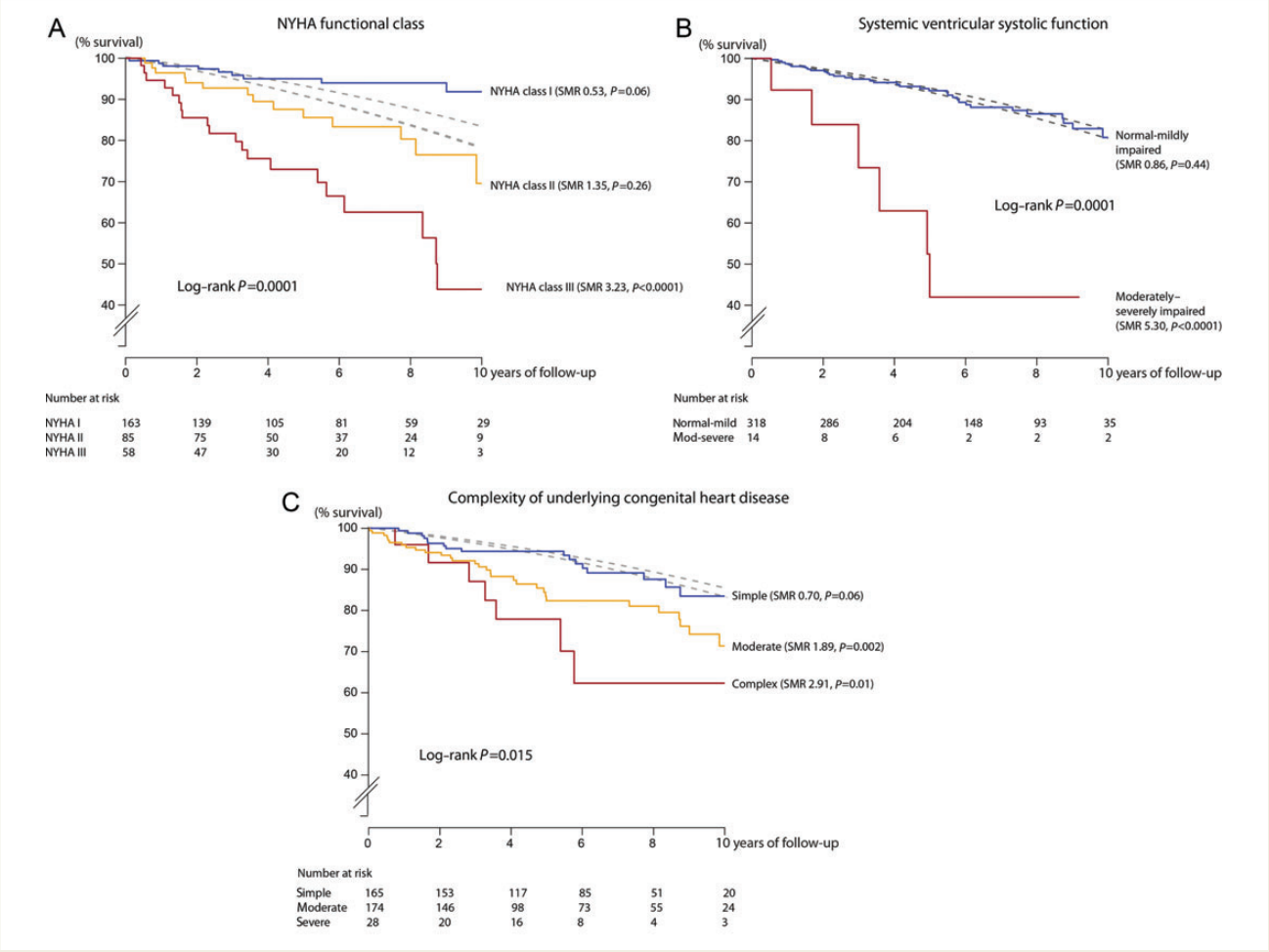

Figure 3 Kaplan-Meier curves for elderly adults with congenital heart disease patients stratifying patients by New York Heart Association class, systemic ventricular function, and complexity of congenital heart defect. The dotted line represents the expected survival curve for an age- and gender-matched sample from the general UK population. (*A*) NYHA class (dotted lines: upper for NYHA I, lower two overlapping lines for NYHA II and III, respectively). (*B*) Systemic ventricular function (dotted lines: upper for moderately–severely impaired, lower for normal–mildly impaired). (*C*) Complexity of congenital heart defect (dotted lines: upper for complex, lower for moderate).

emerged as a significant predictor of mortality in addition to the underlying congenital heart disease (*Table 4*). Sudden cardiac death and heart failure are not uncommon in the ACHD population in general,[27,28] however, this is normally not related to ischaemic heart disease. In fact, a recent publication has demonstrated that none of the studied ACHD patients under the age of 40 from our institution had significant coronary artery disease.[29] With increasing age, however, acquired heart disease clearly becomes relevant. Afilalo *et al.*[5] recently reported the results of a population based study of ACHD patients over the age of 65. The authors identified dementia, gastrointestinal bleeding, and chronic kidney failure as main predictors of mortality. In their study, severity and type of congenital heart defect seemed to have no impact on mortality. However, the aforementioned comorbidities were only present in a small number of their patients (1–2%). In contrast, our study highlights the importance of both—acquired coronary artery disease and underlying congenital heart disease—on outcome in this population. The apparent disparity between the studies is probably explained by the different methodologies employed. The study by Afilalo *et al.*[5] is based on records from administrative databases that contain International Classification of Diseases codes. This leads to a large sample size at the expense of in-depth clinical information. For example, information regarding functional status (NYHA class) and ventricular function was not available to the authors.[5] In contrast, our study is based on hospital records of a single centre allowing for a more detailed analysis of clinical risk factors. Furthermore, due to a concentration of ACHD patients with more severe heart disease at tertiary centres, the current study includes a larger number of patients with lesions of higher complexity.

Coronary artery disease emerged as a significant predictor of outcome in our study. This is of importance since it has been reported that the prevalence of significant coronary artery disease in ACHD patients is similar to that in the general population.[29] Furthermore, it has been shown that ~80% of ACHD patients studied had at least one cardiovascular risk factor.[30] Therefore, our findings also emphasize the importance of primary cardiovascular prevention in

Table 4 Univariate and multivariate predictors of all-cause mortality

Variable	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Cyanosis	5.22 (2.69–10.13)	<0.0001		
NYHA functional class	2.78 (1.91–4.05)	<0.0001	1.96 (1.18–3.26)	<0.01
Symptoms/signs of heart failure requiring treatment	3.04 (1.76–5.25)	0.0001	2.36 (1.05–5.29)	<0.05
Ventricular function	2.10 (1.44–3.06)	0.0001	1.90 (1.20–2.99)	<0.001
Pulmonary hypertension	3.20 (1.56–6.55)	0.0016		
History of arrhythmia	2.28 (1.29–4.05)	0.0046		
Complexity of heart defect	1.82 (1.20–2.74)	0.0047		
Lung disease	2.65 (1.30–5.42)	0.0078		
Diabetes	2.81 (1.20–6.57)	0.018		
Cancer	3.47 (1.09–11.05)	0.0364		
Coronary artery disease	2.02 (1.02–4.00)	0.0448	5.04 (1.88–13.51)	0.0014

Ventricular function was assessed semiquantitatively as described in the Methods section.
HR, hazard ratio; NYHA, New York Heart Association.

ACHD patients irrespective of age as well as the fact that every physician taking care of this challenging patient group should be adequately trained in the proper evaluation and treatment of coronary artery disease.

Limitations of the study

We focused on patients under follow-up at a tertiary ACHD centre. Therefore, it is possible that our study sample may not represent the pattern of ACHD existing in the community. Due to the retrospective nature of the study, the heterogeneity of the underlying population, and the limited number of deaths within each diagnostic subgroup, we were unable to study prognostic markers for specific lesions. Future studies focusing on specific lesions, utilizing advanced cardiac imaging, contemporary biomarkers, and possibly cardiopulmonary exercise testing may provide specific insights. Furthermore, we only considered systolic ventricular function for the current study. Diastolic dysfunction is likely to be present in a considerable proportion of patients but was not assessed due to the retrospective nature of the study. This aspect also requires further attention in future studies. Resource utilization was judged based on the number of procedures and days spent in hospital adjusted for length of the follow-up period. To formally calculate costs, this quantity would have to be multiplied by the respective unit costs. As older patients (with higher prevalence of co-morbidities on average) are generally more costly to treat compared with younger individuals, we contend that this formal analysis would only strengthen the association between older age and increased resource use. Despite all efforts, including contacting the primary care physicians of the patients who died, it was not possible to obtain further information regarding the cause of death in 16 of the 55 patients. One could assume that at least a subset of these patients died suddenly, which is known to be one of two major causes of death in ACHD patients.[31–33] This assumption is supported by the fact that some of the patients had been seen in our clinic shortly before their death and were found to be in stable condition without signs of heart failure or evidence of other malignant non-cardiac conditions.

In conclusion, the number of elderly patients with congenital heart disease is increasing dramatically. As ACHD patients age, acquired medical conditions especially coronary artery disease become highly relevant in determining outcome in these patients. Nonetheless, the underlying congenital heart disease still accounts for a significant proportion of the mortality. Our data, thus, support the importance of cardiovascular risk stratification not only in elderly, but also in younger patients to modify the risks for acquired heart disease later in life as well as a multidisciplinary team approach including general, congenital, and interventional (coronary) cardiologists in older ACHD patients.

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Conflict of interest: none declared.

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