Factors associated with long-term outcomes in adult congenital heart disease patients with infective endocarditis: a 16-year tertiary single-centre experience

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ORIGINAL ARTICLE

CONVENTIONAL VALVE OPERATIONS

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Factors associated with long-term outcomes in adult congenital heart disease patients with infective endocarditis: a 16-year tertiary single-centre experience

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Key question

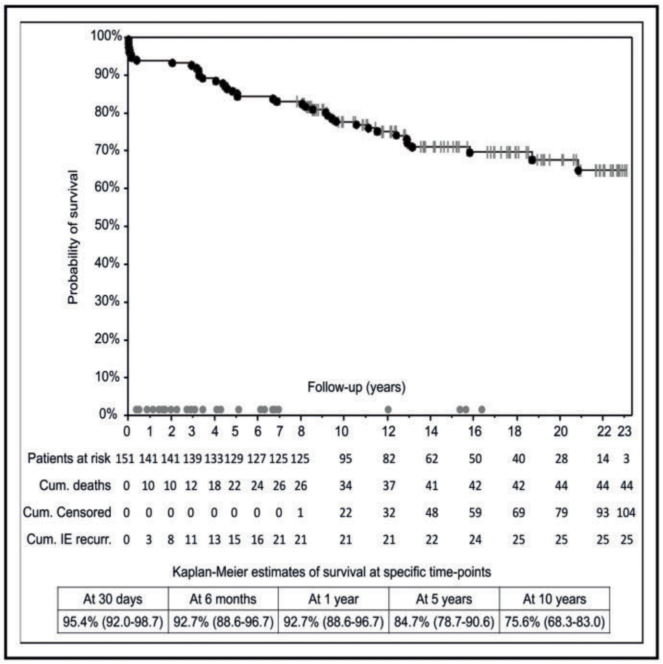
Which are the factors associated with long-term survival in ACHD patients with IE?

Key finding(s)

Complex ACHD and prosthetic valves were negatively while surgical treatment was positively associated with long-term survival.

Take-home message

Multidisciplinary approach and specialist perioperative care of ACHD IE patients can reduce mortality and improve functional status.



Abstract

OBJECTIVES: Studies concerning factors associated with long-term outcomes in adult congenital heart disease (ACHD) patients after infective endocarditis (IE) are scarce, while IE-related mortality in these patients remains a burden. We evaluated the factors associated with long-term survival in ACHD patients admitted for IE.

METHODS: We performed a retrospective single-centre study of all ACHD patients admitted for IE to a tertiary cardiothoracic centre between 1999 and 2015. Underlying ACHD, detailed echocardiographic and clinical data, surgical treatment and long-term follow-up were analysed.

RESULTS: We identified 151 ACHD patients admitted due to 176 episodes IE with 30-day, 6-month and 1-, 5- and 10-year survival of 95.4%, 92.7%, 92.7%, 84.7% and 75.6%, respectively. In a multivariable analysis, adjusted estimated probability of death was consistently higher after an IE episode among patients with complex as compared to simple/moderate ACHD: 10.6% vs 2.4% at 30 days, 15.0% vs 3.4% at 6 months and 1 year, 30.4% vs 7.8% at 5 years and 44.9% vs 13.1% at 10 years. Risk of death was higher among patients with prosthetic valve in comparison with those without (risk ratios 1.73–1.92). Surgical treatment was required in 76 (43.2%) episodes with 30-day mortality of 3.9%. Risk of death appeared to be lower than in the conservatively treated subgroup (risk ratios 0.71–0.78).

CONCLUSIONS: We demonstrated satisfactory long-term survival in ACHD patients who were treated for IE in a tertiary cardiothoracic centre. Early mortality tended to be lower in the surgically treated subgroup. Factors negatively associated with long-term survival were complex ACHD and presence of prosthetic valve.

Keywords: Adult congenital heart disease • Infective endocarditis • Survival • Outcomes • Surgery • Follow-up

ABBREVIATIONS

AKI	Acute kidney injury
ACHD	Adult congenital heart disease
CHD	Congenital heart disease
IE	Infective endocarditis
RR	Risk ratios
RRT	Renal replacement therapy

INTRODUCTION

The number of patients with congenital heart disease (CHD) surviving to adulthood is increasing, and the adult congenital heart disease (ACHD) population is the major substrate for infective endocarditis (IE) in younger patients [1]. ACHD patients with IE have a higher morbidity and mortality than those with structurally normal hearts and despite advances in antibiotic therapy, surgical techniques and perioperative care, IE remains a burden in this patient population [2–4]. Around 4% of admissions to tertiary ACHD centres relate to IE, with an associated mortality of 4–24%, reaffirming the potentially lethal nature of this condition [3, 5–8]. Several predictors of IE-associated mortality have been previously identified, including the development of an abscess and age [2, 9–11].

However, data concerning factors associated with long-term outcomes in ACHD patients after IE are scarce. Specifically, the growing number of ACHD patients with complex defects and/or previous surgery involving prosthetic material prompts the identification of factors associated with outcome. Based on these considerations, the primary aim of this study was to evaluate the factors associated with long-term survival among ACHD patients admitted for IE to a large tertiary ACHD centre over a 16-year study period. As a secondary objective, factors related to the perioperative outcomes of interest in the surgically treated subgroup of patients were investigated.

PATIENTS AND METHODS

Ethical statement

This study was approved by the Institutional Ethics Committee (Royal Brompton and Harefield Hospital, London, UK). The need to obtain informed consent was waived due to the retrospective analysis of de-identified data.

Population and study design

We performed an observational cohort study reviewing the institutional, prospectively maintained, database of all ACHD patients admitted with IE to the Royal Brompton Hospital (London, UK) between January 1999 and May 2015. All consecutive patients with IE episodes were analysed. For patients with recurrent IE episodes during the index period, characteristics were repeatedly recorded at each hospital admission (Fig. 1, upper panel). Patients were included if they were ≥16 years of age and had a diagnosis of CHD, as defined in the British cardiac society working party directive [12]. The ACHD patients were analysed according to the complexity of disease [13]. For the diagnostic classification of IE, the modified Duke criteria were used [14]. Criteria for surgery were followed according to the most recent European guidelines [15]. Conservative treatment was indicated according to the patients' comorbidities, anatomical characteristics, extent of IE and the virulence of the microorganism. It was advised if surgery was considered too high-risk due to comorbidities (pulmonary or renal disease, immunosuppression), if infection was responsive to initial antibiotic treatment or if the patient remained haemodynamically stable [15]. In addition, it was advised in the absence of IE-related complications such as periannular abscess, embolic episode, heart failure, right ventricular outflow obstruction and moderate-to-severe valve regurgitation or severe prosthetic valve dysfunction [15]. Anatomically, it was indicated in IE episodes without visible vegetation or involvement of aortic or mitral valve. In addition, surgical treatment was considered if more virulent microorganisms were detected (*Staphylococcus aureus*, fungi). Importantly, each decision was reviewed by the institutional multidisciplinary team [15].

Demographic, clinical, echocardiographic, intraoperative and postoperative data as well as laboratory parameters were extracted from our institutional electronic systems. To evaluate the risk factors for mortality in ACHD patients with IE, all IE episodes were considered. Date of hospital admission was considered time zero and patients were censored at the time of a new IE episode, death or end of follow-up (20 October 2021). Deaths were identified from the institutional electronic database, linked to the Office of National Statistics, which registers all UK deaths. Information on the cause of death was retrieved, when possible, from the medical records. If patients had recurrent endocarditis, each episode was included as a new episode. No Ethics Committee approval was required given that this analysis was retrospective and anonymized, and all patients who underwent surgical intervention provided informed consent.

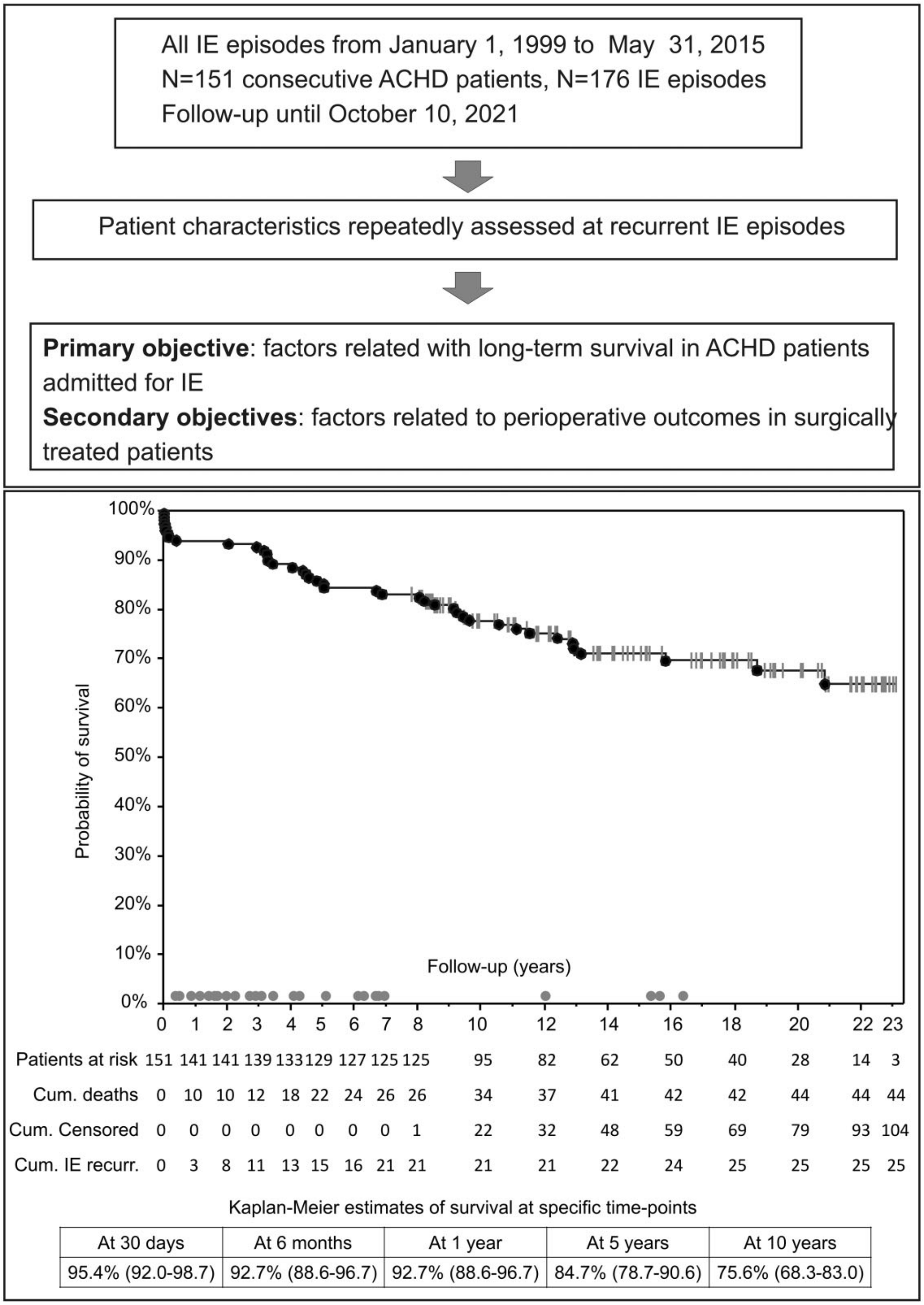


Figure 1: Upper panel: study outline. Lower panel: survival data after the first infective endocarditis episode recorded during the study period for 151 adult congenital heart disease patients: Kaplan–Meier product limit survival curve (black circles indicate deaths, ticks indicate censorings) and estimated survival at specific time points; number at risk, cumulative number of deaths and censorings (first censored time at 7.5 years) and cumulative number of recurrent infective endocarditis episodes (indicated by grey circles).

End points

Primary end points were determinants of long-term survival after an IE episode among ACHD patients. The time of origin was the date of hospital admission for the index IE episode, and patients were followed up until the date of death, October 2021 or until a recurrent IE episode (during the index period). In the case IE recurrence, patients were censored, a new set of baseline covariates were recorded and a new follow-up period was started. Secondary end points were factors related to early perioperative outcomes following surgical treatment of IE episodes, including acute kidney injury (AKI) requiring renal replacement therapy (RRT), and need for inotropic and/or vasopressor support. The KDIGO criteria were used to define AKI [16].

Data collection

Analysis of clinical data from an institutional prospectively maintained database on ACHD patients was performed. Any additional data were collected retrospectively from the electronic and archived hospital medical records. Patients' clinical data included demographics, underlying cardiac diagnosis, previous surgical interventions, presence and location of prosthetic valves and material and other comorbidities. Clinical characteristics regarding the IE episodes, microbiological and echocardiographic findings, complications and surgical treatment were analysed. IE-related complications that were analysed included heart failure, complete heart block, perivalvular abscess, moderate-to-severe valvular regurgitation, embolic event and cerebrovascular accident. Intraoperative and perioperative data, including blood transfusion, were recorded. In addition, intensive care unit admissions were classified as elective (postoperative care) or emergent (for patients who required immediate supportive care in intensive care unit or emergent surgical intervention).

Statistical analysis

We analysed patients' characteristics, need for surgery, AKI requiring RRT, need for inotropic and/or vasopressor support and long-term survival. To identify the predictors of survival, the main analysis was based on all recorded IE episodes and not per patient. Recurrent episodes were not considered as longitudinal covariates. Survival data were organized in the counting process mode. Patients who experienced >1 IE episode between January 1999 and May 2015 were censored at the repeated episode, and their demographic, clinical and episode-related characteristics were treated as repeatedly measured time-dependent covariates. The burden of previous IE episodes was accounted for as a time-dependent covariate. Survival was analysed by fitting Cox proportional hazard models with repeatedly measured explanatory variables and robust sandwich variance estimation where patient was treated as a cluster. As survival curves were generated for each potential explanatory variable, univariate survival analysis is summarized in Cox models with a single independent variable and probabilities of survival at specific time points. To identify independent predictors of survival, a multivariable Cox analysis was performed. Limitations of hazard ratios as measures of an effect of a treatment or exposure were considered, which are particularly likely in observational studies with long follow-up periods [17]. Therefore, considering the long follow-up period during which effects (hazard ratios) of the potential explanatory variables might have changed, we generated adjusted probabilities of event at specific time points and contrasted them with levels of potential predictors as ratios (relative risks) or differences (risk differences) of probabilities using the method of variance estimates recovery [17–19]. We generated (estimated) probabilities of death (1 - probability of survival) at post-IE episode time points that we considered informative: at 30 days, 6 months and 1, 5 and 10 years [18]. Since the potential explanatory variables of interest were categorial, we determined relative [risk ratios (RR)] and absolute (risk differences) differences between their levels. Confidence intervals were calculated by the method of variance estimates recovery [19]. To evaluate the factors related to perioperative outcomes in the surgically treated subgroup, generalized mixed models (binary distribution, logit link, profile likelihood estimation, compound symmetry structure of the R-side covariance matrix) were fitted. Statistical analyses were performed using SAS 9.4 for Windows software (SAS Inc., Cary, NC, USA) and package *Evalue* in R was used to evaluate sensitivity of estimates of interest to unmeasured confounding [20]. We considered age, complexity of ACHD, history of previous IE episodes (none/≥1), presence of prosthetic valves, presentation with IE complications (none/≥1) and type of treatment (surgical/conservative) in the case of survival, as explanatory variables. This was based on cross-tabulation of medical history, underlying cardiac diagnosis, index IE episode presentation and treatment-related data and on clinical rationale (Supplementary Material, Tables S1 and S2).

RESULTS

Characteristics of ACHD patients with IE episodes

We identified 151 ACHD patients (male $n = 105$ [69.5%]) with a total of 176 episodes of IE during the study period (Fig. 1, upper panel). Baseline characteristics and IE episodes are summarized in Tables 1–3 and Supplementary Material, Tables S1 and S2. In 47.2% of IE episodes, patients had a previous prosthetic valve implantation. More than a half (58.5%) of the episodes were valve-associated and 55.7% presented with at least 1 IE-related complication, most commonly moderate or severe valve regurgitation (30.7% of all episodes, Table 1 and Supplementary Material, Tables S1 and S2). Streptococci were identified in 77 (43.8%) episodes (Supplementary Material, Table S4). Echocardiography was positive for vegetations in 126 episodes with 53.2% (67/126 episodes) being left-sided IE (Table 3). Surgical treatment was required in 76 (43.2%) IE episodes (Table 1). Intraoperative characteristics of IE episodes in the surgical group are described in Supplemental Material (Supplementary Material, Tables S6–S8). In most of the cases where the IE episode was associated with at least 1 IE-related complication, surgical treatment was required (66/98, 67.3%), while it was required only in 12.8% (10/78) in uncomplicated episodes (Table 1). Characteristics of surgically and conservatively treated IE episodes are showed in Table 1. Surgically treated IE episodes were more frequent in simple ACHD (61.8%) and most of them had no history of previous IE (77.6%). Other characteristics of IE episodes according to CHD complexity, history of IE and presence of prosthetic material are described in Supplementary Material, Tables S1 and S2. The presence of prosthetic valves was more common in the complex ACHD (64.1%) and the prevalence of pre-existing prosthetic valves was higher with the increased number of previous IE episodes (Supplementary Material, Tables S1 and S2). Surgical treatment was more common in patients with simple lesions (47/75; 62.7%) than in patients with moderate (12/37; 32.4%) or complex (17/64; 26.6%) lesions.

Factors associated with long-term survival

On patient basis ($N = 151$), shortest/longest censored times were 93.7/277.3 months (median 182.4); and respective failure times

Table 1: Main characteristics of adult congenital heart disease patients and infective endocarditis episodes (overall, by the presence of infective endocarditis-related complications and type of treatment)

	IE episodes	IE-related complications		Type of treatment	
		≥1	None	Surgical	Conservative
N episodes	176	98	78	76	100
Patient characteristics					
Age (years)	36 (SD: 12)	37 (SD: 12)	35 (SD: 12)	37 (SD: 13)	36 (SD: 12)
Gender, male	125 (71.0)	75 (76.5)	50 (64.1)	62 (81.6)	63 (63.0)
Simple ACHD	75 (42.6)	55 (56.1)	20 (25.6)	47 (61.8)	28 (28.0)
Moderate ACHD	37 (21.0)	21 (21.4)	16 (20.5)	12 (15.8)	25 (25.0)
Complex ACHD	64 (36.4)	22 (22.4)	42 (53.9)	17 (22.4)	47 (47.0)
History of prosthetic valves	83 (47.2)	44 (44.9)	39 (50.0)	38 (50.0)	45 (45.0)
IE episode characteristics					
Valve-associated episode	103 (58.5)	57 (58.2)	46 (59.0)	53 (69.7)	50 (50.0)
No complications	78 (44.3)	–	–	10 (13.2)	68 (68.0)
≥1 complication	98 (55.7)	–	–	66 (86.8)	32 (32.0)
Heart failure	20 (11.4)	20 (20.4)	–	14 (18.4)	6 (6.0)
Complete heart block	3 (1.7)	3 (3.1)	–	2 (2.6)	1 (1.0)
Perivalvular abscess	21 (11.9)	21 (21.4)	–	20 (26.3)	1 (1.0)
Moderate-to-severe valve regurgitation	54 (30.7)	54 (55.1)	–	44 (57.9)	10 (10.0)
Embolic episode[a]	26 (14.8)	26 (26.5)	–	12 (15.8)	14 (14.0)
CVA	16 (9.1)	16 (16.3)	–	12 (15.8)	4 (4.0)
Cyanosis at presentation	22 (12.5)	9 (9.2)	13 (16.7)	4 (5.3)	18 (18.0)
Microorganism					
Staphylococci[b]	29 (16.5)	22 (22.5)	7 (9.0)	16 (21.1)	13 (13.0)
Streptococcus viridans	10 (5.7)	4 (4.1)	6 (7.7)	4 (5.3)	6 (6.0)
Enterococci	3 (1.7)	2 (2.0)	1 (1.3)	1 (1.3)	2 (2.0)
HACEK organism	8 (4.6)	5 (5.1)	3 (3.8)	4 (5.3)	4 (4.0)
Others[c]	85 (48.3)	44 (44.9)	41 (52.6)	35 (46.1)	50 (50.0)
Negative culture	22 (12.5)	10 (10.2)	12 (15.4)	9 (11.8)	13 (13.0)
Unavailable	19 (10.8)	11 (11.2)	8 (10.3)	7 (9.2)	12 (12.0)
Treatment type					
Surgical treatment	76 (43.2)	66 (67.3)	10 (12.8)	–	–
Conservative treatment	100 (56.8)	32 (32.7)	68 (87.2)	–	–
Elective ICU admission[d]	66 (37.5)	58 (59.2)	8 (10.3)	66 (86.8)	0
Emergent ICU admission	16 (9.1)	13 (13.3)	3 (3.8)	7 (9.2)	9 (9.0)

Data are presented as count (%) or mean (SD).

[a]Pulmonary, coronary, cerebral, splenic or peripheral (limbs);.

[b]*S. aureus* or coagulase negative *Staphylococci*.

[c]For further details please see Supplementary Material, Table S3.

[d]Postoperative ICU admission.

ACHD: adult congenital heart disease; CVA: cerebrovascular accident; HACEK: *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*; ICU: intensive care unit; IE: infective endocarditis; SD: standard deviation.

were 3 days/250.3 months (median 59.3) resulting in overall median follow-up time of 153.3 months (Q1–Q3 102.6–223.4). In our cohort of 151 patients, estimated survival at 30 days and 1, 5 and 10 years after the first IE episode was 95.4%, 92.7%, 84.7% and 75.6%, respectively (Fig. 1, lower panel). On IE episode basis (*N* = 176), shortest/longest censored times (censoring also at repeated IE episode) were 4.9/277.3 months (median 163.5). Overall median follow-up time (including failure times) was 141.4 months (Q1–Q3 81.7–214.6). Simple and moderate ACHD patients with IE were associated with better survival in comparison with complex ACHD, and patients without prosthetic valves demonstrated better survival when compared to those with prosthetic valves (Fig. 2A–C). History of IE or IE-related complications was not related to survival (Fig. 2D and E). Furthermore, long-term survival appeared slightly better in patients who underwent surgical treatment than in those medically managed (Fig. 2F).

In a multivariable analysis, adjusted estimated probability of death was consistently higher after an IE episode in patients with complex ACHD as compared to simple/moderate ACHD: 10.6% vs 2.4% at 30 days, 15.0% vs 3.4% at 6 months and 1 year, 30.4% vs 7.8% at 5 years and 44.9% vs 13.1% at 10 years (Fig. 3). This resulted in relative risks between 4.52 (95% CI 0.89–29.3) at 30 days and 3.43 (95% CI 1.97–6.82) at 10 years and corresponding absolute risk differences. The width of the confidence intervals reduced with time due to the increasing cumulative number of events (death), but all estimates appeared fairly resistant to unmeasured confounding. There appeared a numerical tendency of a greater mortality risk among patients with prosthetic valve in comparison with those without (RR 1.73–1.92) and in complicated IE episode when compared to non-complicated episode (RR 1.50–1.66), but with considerable uncertainty as per wide confidence intervals. In addition, the risk tended to be lower in the surgical subgroup of patients as compared to the conservatively treated subgroup (RR 0.71–0.78), even if no obvious association could be demonstrated, and it was not associated with the history of IE episodes (Fig. 3).

Table 2: Underlying cardiac diagnosis in adult congenital heart disease patients requiring admission for infective endocarditis

Underlying cardiac diagnosis	*N* (%)
Simple ACHD	75 (42.6)
Isolated bicuspid aortic valve	37 (21)
Isolated aortic valve disease (aortic stenosis and regurgitation)	7 (4)
Isolated mitral valve disease	4 (2.3)
Isolated patent foramen ovale	2 (1.1)
Isolated atrial septal defect	3 (1.7)
Repaired atrial septal defect without residual defect	1 (0.6)
Isolated ventricular septal defect (unrepaired)	20 (11.4)
Other (Marfan's syndrome)	1 (0.6)
Moderate complexity ACHD	36 (20.5)
Tetralogy of Fallot	14 (8)
Ventricular septal defect with associated anomaly	14 (8)
Coarctation of the aorta	3 (1.7)
Atrioventricular septal defect	2 (1.1)
Subvalvular or supravalvular aortic stenosis	2 (1.1)
Sinus of Valsalva aneurysm	1 (0.6)
Severe complexity ACHD	65 (36.9)
Pulmonary atresia	17 (9.7)
Transposition of the great arteries without ventricular septal defect	11 (6.3)
Congenitally corrected transposition of the great arteries	9 (5.1)
Double-outlet right ventricle	9 (5.1)
Eisenmenger syndrome	6 (3.4)
Single ventricle	6 (3.4)
Transposition of the great arteries with ventricular septal defect	4 (2.3)
Truncus arteriosus	3 (1.7)

ACHD: adult congenital heart disease.

Table 3: Location of the vegetations detected on echocardiogram

Location of vegetations	*N* (%)
Native aortic valve	39 (22.2)
Tricuspid aortic valve	28 (15.9)
Bicuspid aortic valve	11 (6.3)
Prosthetic aortic valve	11 (6.3)
Native mitral valve	16 (9.1)
Prosthetic mitral valve	1 (0.6)
Native pulmonary valve	6 (3.4)
Prosthetic pulmonary valve	23 (13.1)
Homograft pulmonary conduit	8 (4.5)
Native tricuspid valve	14 (7.9)
VSD	14 (7.9)
VSD patch	7 (4.0)
Atrioventricular valve	2 (1.1)
Truncal valve	1 (0.6)
Pulmonary artery band	2 (1.1)
RVOT	2 (1.1)
Baffle	1 (0.6)

RVOT: right ventricular outflow tract; VSD: ventricular septal defect.

Factors related to perioperative outcomes in the surgical subgroup

Seventy-six IE episodes were surgically treated in 74 patients (2 patients underwent surgery twice) (Table 4). Underlying CHD was predominantly simple (47/76, 61.8%; Table 1) and previous history of IE was present in less than a quarter of the patients (a total of 22.4%, 14.5% with 1 and 7.9% with 2–4 previous IE; Supplementary Material, Tables S1 and S2). In addition, 38 (50%) IE episodes were observed in patients with prosthetic valves, 53 (69.7%) were valve-related and 66 (86.8%) presented with complications (Table 1). RRT was needed in 14 (18.4%), inotropic support in 41 (53.9%) and vasopressor support in 43 (56.6%) cases (Table 5 and Supplementary Material, Table S5). Perioperative inotropic support was required more often in patients with complex ACHD (70.6%) in comparison with those with moderate (50.0%) and simple (48.9%) ACHD (Table 5 and Supplementary Material, Table S5). However, RRT and vasopressor support appeared similarly distributed across subsets in respect to CHD complexity, presence of prosthetic valves, history of IE or IE-related complications (Table 5 and Supplementary Material, Table S5). Within this limited sample, adjusted analysis did not indicate that any of these factors was related to the need for RRT, inotropic or vasopressor support (Supplementary Material, Fig. S1). However, the need for inotropic support was more common when the underlying CHD was complex (adjusted probability 75%) as compared to simple/moderate ACHD (∼50%).

Three surgically treated IE episodes had a fatal early outcome on postoperative days 5, 11 and 21 (adjusted survival estimate 96.6% at 30 days, Fig. 2F). Adjusted cumulative risk of 30-day mortality was estimated at 3.9% (Fig. 3).

Table 4: Surgical procedures

Type of surgical procedure	*N* (%)
Left-sided surgical procedure	
Isolated aortic valve replacement	18 (23.7)
Aortic valve and root replacement	11 (14.5)
Isolated mitral valve repair	2 (2.6)
Isolated truncal valve replacement	1 (1.3)
Right-sided surgical procedure	
Isolated pulmonary valve replacement	8 (10.5)
Isolated RV–PA conduit replacement	6 (7.9)
Isolated tricuspid valve replacement	1 (1.3)
Combined valvular procedure	16 (21.1)
Isolated pacemaker/ICD extraction	5 (6.6)
Other procedures	8 (10.5)

ICD: implantable cardioverter defibrillator; RV-PA: right ventricle-pulmonary artery.

DISCUSSION

We investigated a large cohort of 151 ACHD patients to evaluate factors associated with long-term survival after each IE episodes, as well as factors related to perioperative outcomes in the surgically treated patients. Our results indicate a lower early IE-related mortality (4.6% at 30 days) than previously reported, but within the broad range of 2–24%; though IE-related mortality remains somewhat higher among patients with complex CHD (8.3% at 30 days) [3, 9, 10]. Our early mortality rate reflects a high proportion of prosthetic valves (47.2%) and complicated IE episodes, common in large tertiary ACHD referral centres with complex cases.

While IE in general cardiac populations is associated with high in-hospital mortality (up to 30%), in ACHD patients relatively

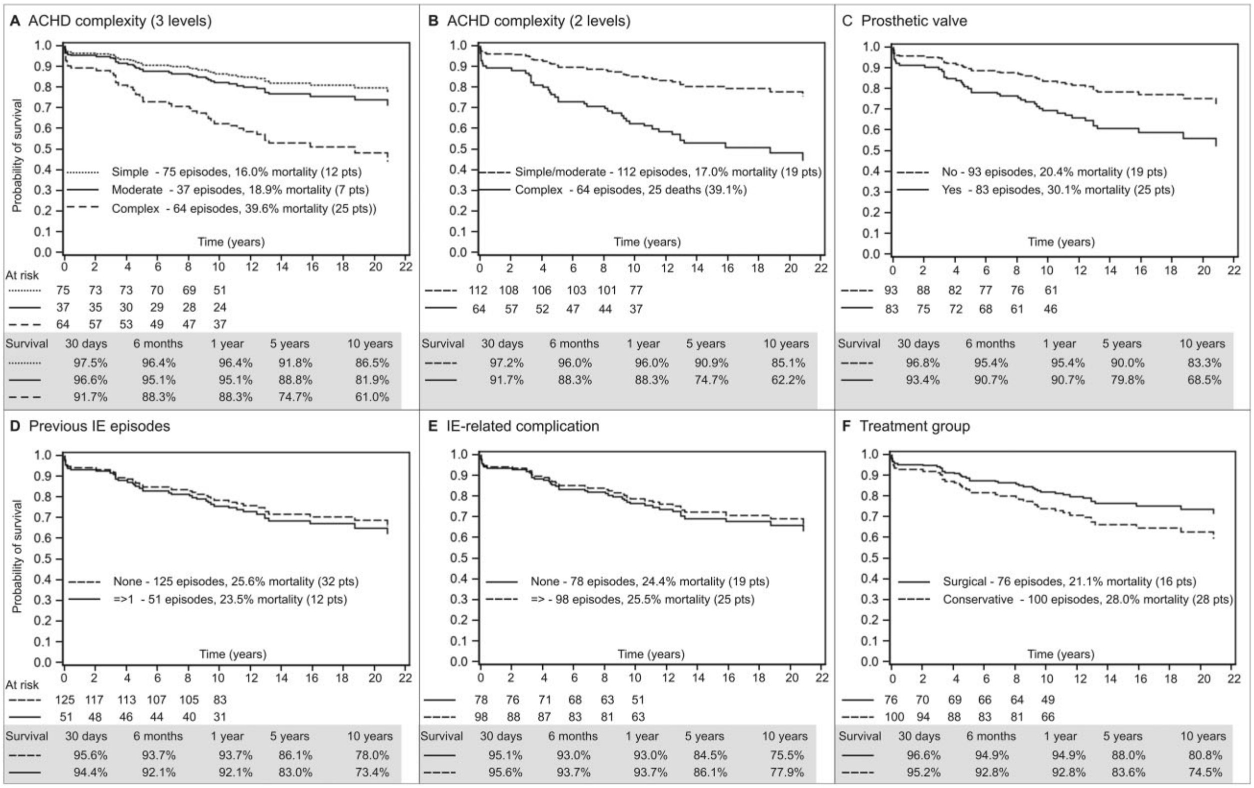


Figure 2: Survival times (unadjusted) across different subsets of 176 infective endocarditis (IE) episodes—by complexity of adult congenital heart disease, presence of prosthetic valves, history of previous IE, IE-related complications and type of treatment. Total deaths are depicted over the entire follow-up period; numbers at risk up to 10 years and estimated survival at specific time points.

lower mortality rates are observed due to various factors including younger age, higher proportion of right-sided IE and management by multidisciplinary teams [2]. van Melle *et al.* [21] performed a large contemporary cohort of CHD patients included in a prospective international study in which they analysed the independent factors associated with all-cause mortality during the follow-up of 700 days. As compared to non-CHD patients, CHD patients with IE had a better outcome in terms of all-cause mortality, despite the presence of more advanced disease at admission [21]. Recent evidence emphasized that patients with left-sided IE have worse outcome than patients with right-sided IE [22]. Interestingly, the incidence of left-sided IE in our cohort (53.2%) was even higher than in previous reports [10, 23]. Moore *et al.* [9] reported a relatively high IE-related early mortality (15% within 3 months of admission). In their series, cerebral emboli and AKI were associated with the higher mortality. Our 1-year mortality (7.3%) was lower than that described in previous studies [11]. Mylotte *et al.* [11] reported a mortality of 8.8% within 1 year of IE diagnosis in ACHD patients without prosthetic valves. Similarly, Kuijpers *et al.* [10] reported an IE-related and 1-year mortality of 16% and 19% in their nationwide cohort of ACHD patients. They noted valve-containing prosthetics, multiple defects and previous IE were associated with greater risk of IE. Tutarel *et al.* [3] recently found only development of an abscess to significantly predict in-hospital mortality.

One of the main strengths of our study is that provides evidence about factors associated with long-term survival, while several previous studies investigated only predictors of in-hospital mortality [3]. We demonstrated that long-term survival (10 years) was 75.6%, particularly in the setting of simple or moderate ACHD, absence of prosthetic valves and surgically treated IE episodes. Importantly, the proportion of patients with complex ACHD who developed IE episode (36.4%) was in line with other studies [2]. History of IE and presence of IE-related complications did not influence survival. In our study, surgical treatment was required in 43.2% of IE episodes, which is slightly higher than in some previous reports [3, 24]. Interestingly, surgical candidates had predominantly simple ACHD (81.6%) with no history of IE (77.6%) and more commonly had valve-associated IE episode (43.4%). As expected, they more often presented with IE-related complications such as moderate-to-severe valve regurgitation (57.9%), perivalvular abscess (26.3%) and heart failure (18.4%). Importantly, our adjusted cumulative risk of death at 30 days postoperatively was only 3.9%. Thus, early postoperative survival might be related to timely diagnosis, treatment by experienced multidisciplinary teams, excellent surgical outcomes and a relatively higher proportion of patients with simple CHD.

Interestingly, the most frequent causative microorganisms in our study were *Streptococci*, which is in line with several other studies [2, 3, 9, 25], while a few reports identified *Staphylococci* [10, 26, 27]. As our follow-up includes patients from before and after the change in guidelines for antibiotic prophylaxis, we are unable to draw specific conclusions. Still, further studies might be needed to clarify any concerns related to the increase in the incidence of *Staphylococci*.

Limitations

Limitations are inherent to the retrospective observational study design and its restriction to a single institution, which was

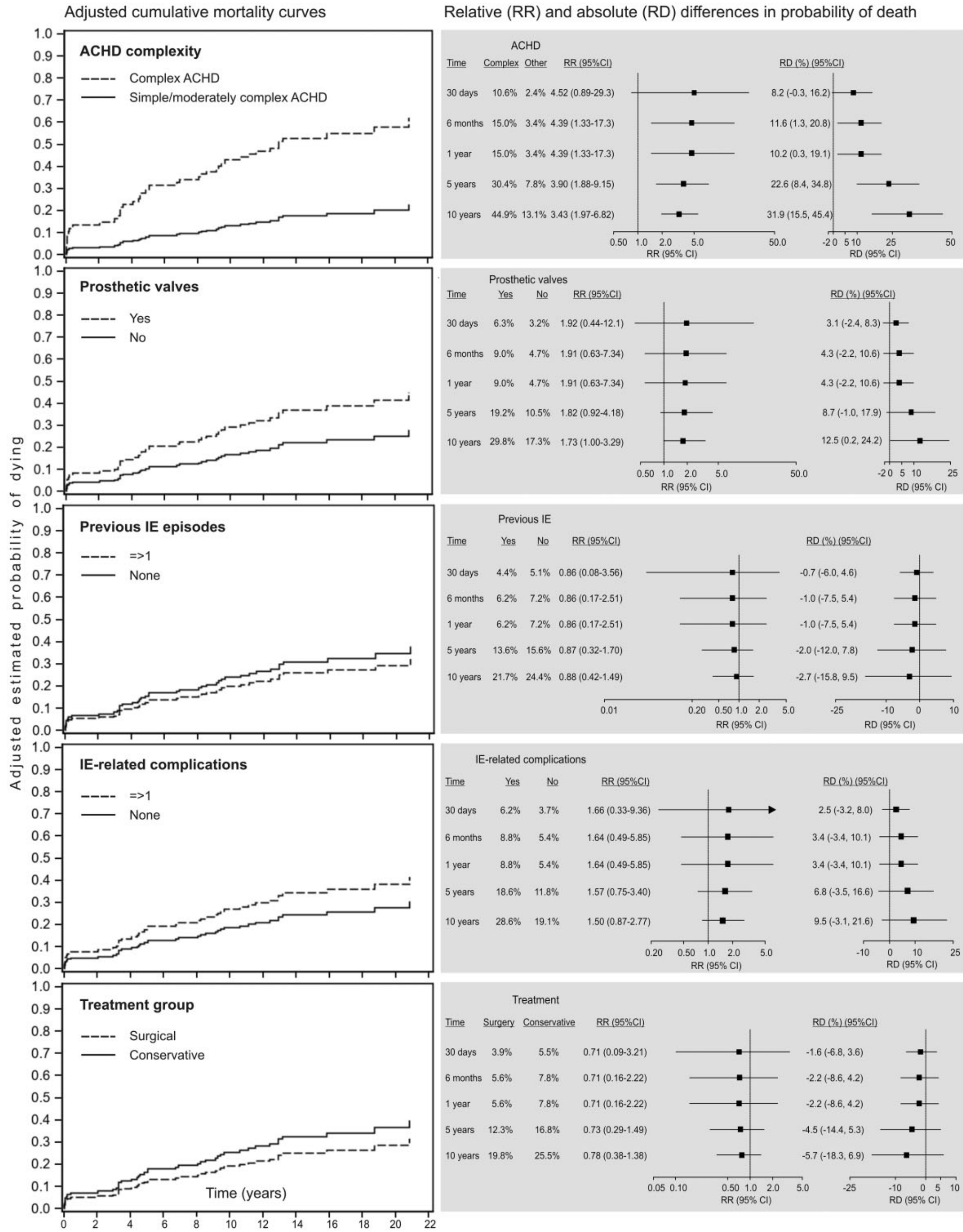


Figure 3: Multivariable analysis of survival after 176 infective endocarditis (IE) episodes with independent variables: age (older age was associated with higher mortality risk), complexity of adult congenital heart disease, presence of prosthetic valves, history of previous IE, IE-related complications and type of treatment. Left panels: adjusted cumulative mortality curves. Right panels: estimated adjusted risk of death at specific time points and relative (relative risk) and absolute (risk difference) risk differences.

minimized by prospective data collection and inclusion of all consecutive patients. We could not account for non-cardiac comorbidities or other treatments as potentially relevant baseline or post-baseline confounders. Furthermore, it is possible that some IE episodes among our ACHD population remained under-reported. However, we collected detailed clinical information including echocardiograms with exact location of IE. Additionally, there is a potential selection bias regarding all ACHD patients treated for IE at our centre over the study period. Apart from ACHD complexity and gender, other potential predictors of outcomes changed over time in patients with recurrent IE episodes; therefore, we opted to consider all IE episodes, each of them with new values of covariates, thus avoiding misclassification bias. Although deaths were identified from the hospital database, linked to the Office of National Statistics, which registers all UK deaths, it is possible that some patients might have been

Table 5: Cross-tabulation of characteristics of surgically treated (N = 76) infective endocarditis episodes (overall, by the complexity of adult congenital heart disease, presence of prosthetic valves and infective endocarditis-related complications)

	ACHD complexity			Prosthetic valves		IE-related complications	
	Simple	Moderate	Complex	No	Yes	None	≥1
N	47	12	17	38	38	10	66
Age	40 (SD: 13)	33 (SD: 9)	30 (SD: 10)	39 (SD: 13)	34 (SD: 12)	26 (SD: 9)	38 (SD: 13)
Simple ACHD	–	–	–	32 (84.2)	15 (39.5)	0	47 (71.2)
Moderate ACHD	–	–	–	0	12 (31.6)	2 (20.0)	10 (15.2)
Complex ACHD	–	–	–	6 (15.8)	11 (28.9)	8 (80.0)	9 (13.6)
No previous IE	42 (89.4)	7 (58.3)	10 (58.8)	36 (94.7)	23 (60.5)	6 (60.0)	53 (80.3)
≥1 previous IE	5 (10.6)	5 (41.7)	7 (41.2)	2 (5.3)	15 (39.5)	4 (40.0)	13 (19.7)
Prosthetic valves	15 (31.9)	12 (100)	11 (63.7)	–	–	8 (80.0)	30 (45.5)
No IE-related complications	0	2 (16.7)	8 (47.1)	2 (5.3)	8 (21.1)	–	–
≥1 IE-related complication	47 (100)	10 (83.3)	9 (52.9)	36 (94.7)	30 (78.9)	–	–
Admitted to ICU[a]	45 (95.7)	12 (100)	16 (94.1)	36 (94.7)	37 (97.4)	9 (90.0)	64 (97.0)
Elective ICU admission	42 (89.4)	10 (83.3)	14 (82.4)	33 (86.8)	33 (86.8)	8 (80.0)	58 (87.9)
Emergent ICU admission	3 (6.4)	2 (16.7)	2 (11.8)	3 (7.9)	4 (10.5)	1 (10.0)	6 (9.1)
Renal replacement therapy	8 (17.0)	3 (25.0)	3 (17.6)	6 (15.8)	8 (21.0)	2 (20.0)	12 (18.2)
Inotropic support	23 (48.9)	6 (50.0)	12 (70.6)	19 (50.0)	22 (57.9)	7 (70.0)	34 (51.5)
Vasopressor support	28 (59.6)	6 (50.0)	9 (52.9)	22 (57.9)	21 (55.3)	4 (40.0)	39 (59.1)

Data are presented as count (%) or mean (SD). Data for the entire surgically treated subgroup are listed in Table 1.
[a]The rest of the patients transferred to the recovery unit.
ACHD: adult congenital heart disease; ICU: intensive care unit; IE: infective endocarditis; SD: standard deviation.

living elsewhere or might have died outside of the UK and were lost to follow-up. Another potential selection bias is that each treatment decision was reviewed on our multidisciplinary team meetings and the best treatment was proposed for each patient on a benefit–risk balance. Therefore, patients with complex CHD were likely more often considered for conservative treatment based on increased risk of surgery. Finally, our cohort comprises an adult population and therefore our results cannot be extrapolated to children.

CONCLUSION

Our data demonstrated 75.6% long-term survival in ACHD patients treated for IE in a tertiary cardiothoracic centre. Furthermore, surgically treated patients experienced slightly lower early IE-related mortality, although they more frequently had only simple CHD. However, patients with complex CHD were more often considered for conservative treatment due to increased risk of surgery based on multidisciplinary team decision. Factors negatively associated with long-term survival were complex ACHD and presence of prosthetic valve. A multidisciplinary approach and specialist care in the perioperative and critical care of this challenging population are likely to reduce mortality and improve functional status.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Alessandra Verzelloni Sef: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing—original draft. **Siân I. Jaggar:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing—review & editing. **Vladimir Trkulja:** Conceptualization; Formal analysis; Methodology; Software; Validation; Writing—review & editing. **Rafael Alonso-Gonzalez:** Conceptualization; Data curation; Investigation; Methodology; Supervision; Validation; Writing—review & editing. **Davorin Sef:** Conceptualization; Formal analysis; Methodology; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **Marko I. Turina:** Conceptualization; Methodology; Supervision; Validation; Writing—review & editing.

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