Cardiology in the Young

cambridge.org/cty

Outcomes in infective endocarditis among adults with CHD: a comparative national study

Ryan D. Byrne[1], Keila N. Lopez[2], Christopher R. Broda[1,2] and Stephen J. Dolgner[1,2]

[1]Adult Congenital Heart Program, Department of Pediatrics, Section of Cardiology, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA and [2]Department of Pediatrics, Section of Cardiology, Baylor College of Medicine/Texas Children's Hospital, Houston, TX, USA

Original Article

Cite this article: Byrne RD, Lopez KN, Broda CR, and Dolgner SJ (2024) Outcomes in infective endocarditis among adults with CHD: a comparative national study. *Cardiology in the Young* **34**: 2596–2605. doi: 10.1017/S1047951124026507

Received: 13 November 2023
Revised: 3 August 2024
Accepted: 29 August 2024
First published online: 10 October 2024

Keywords:
Infective endocarditis; adult CHD; mortality; surgery

Corresponding author:
Ryan D. Byrne; Email: ryan.byrne@bcm.edu

Abstract

Background: Given increased survival for adults with CHD, we aim to determine outcome differences of infective endocarditis compared to patients with structurally normal hearts in the general population. *Methods:* We conducted a retrospective cross-sectional study identifying infective endocarditis hospitalisations in patients 18 years and older from the National Inpatient Sample database between 2001 and 2016 using International Classification of Disease diagnosis and procedure codes. Weighting was used to create national annual estimates indexed to the United States population, and multivariable logistic regression analysis determined variable associations. Outcome variables were mortality and surgery. The primary predictor variable was the presence or absence of CHD. *Results:* We identified 1,096,858 estimated infective endocarditis hospitalisations, of which 17,729 (1.6%) were adults with CHD. A 125% increase in infective endocarditis hospitalisations occurred for adult CHD patients during the studied time period ($p < 0.001$). Adults with CHD were significantly less likely to experience mortality (5.4% vs. 9.5%, OR 0.54, CI 0.47–0.63, $p < 0.001$) and more likely to undergo in-hospital surgery (31.6% vs. 6.7%, OR 6.49, CI 6.03–6.98, $p < 0.001$) compared to the general population. CHD severity was not associated with increased mortality ($p = 0.53$). Microbiologic aetiology of infective endocarditis varied between groups ($p < 0.001$) with *Streptococcus* identified more commonly in adults with CHD compared to patients with structurally normal hearts (36.2% vs. 14.4%). *Conclusions:* Adults with CHD hospitalised for infective endocarditis are less likely to experience mortality and more likely to undergo surgery than the general population.

Introduction

The prevalence of patients with adult CHD continues to rise.[1] Increased life expectancy for patients living with complex cardiac anatomy has resulted in new and unique challenges, including management of complications such as infective endocarditis. Incidence of infective endocarditis in adults with CHD exceeds that of the general population[2,3] and can lead to multi-organ disease and death. In regional population-based and single-centre studies of infective endocarditis in adults with CHD, mortality rates ranged from 6% to 15%, and between one third and one half of such patients required surgical intervention.[4–6] Compared to other admission indications, hospitalisations due to infective endocarditis portend high acuity of illness for patients with adult CHD. In a study examining adults with tetralogy of Fallot, infective endocarditis-related admissions had higher in-hospital mortality, complications, and healthcare resource utilisation compared to admissions without infective endocarditis.[7]

Early mortality for infective endocarditis in the general population (patients with structurally normal hearts) is reported in the literature to be higher, ranging from 14.8% to 20.6%. [8–10] Management of infective endocarditis in adults varies institutionally, and the role and timing of a surgical approach are still debated.[11–13] The most recent American Heart Association/American College of Cardiology guidelines for the management of valvular heart disease recommend early surgery for those at greatest risk,[14] but notably, recommendations regarding surgery for infective endocarditis in adults with CHD are not addressed in these guidelines. Among patients with infective endocarditis in the general population, sex-related infective endocarditis outcome disparity has been commonly described [15,16]; however, associations between sociodemographics and infective endocarditis have not been evaluated in the adult CHD population.

In light of the rapidly growing adult CHD population in the United States, our study aims to determine outcome differences in infective endocarditis compared to patients with structurally normal hearts in the general population, including identifying factors that might contribute to dissimilarities. We will additionally explore associations of infective endocarditis with CHD

© The Author(s), 2024. Published by Cambridge University Press.

severity and patient sociodemographics within the adult CHD population to determine if there are any disparities in outcomes for this high-risk group.

Materials and methods

Study design and data source

We performed a retrospective cross-sectional study using the National Inpatient Sample database. This database is developed and maintained by the Healthcare Cost and Utilization Project and is sponsored by the Agency for Healthcare Research and Quality. The National Inpatient Sample database approximates a 20% stratified sample of discharges from community hospitals in over 45 participating states and, as was done in our study, can be weighted to provide national estimates. The dataset includes deidentified clinical and non-clinical elements such as International Classification of Diseases, Ninth and Tenth Revisions diagnosis and procedure codes, demographic characteristics, and expected payment source. The National Inpatient Sample, as well as other large United States databases in the paediatric population such as the Kids' Inpatient Database and Pediatric Health Information Systems database have been previously utilised to evaluate trends in infective endocarditis hospitalisations in various populations.[8,17–21] Given its public availability and the deidentified nature of the data, the Baylor College of Medicine Institutional Review Board deemed that this was not human subjects research.

Population selection and stratification

We identified hospitalisation discharges from 2001 to 2016 within the National Inpatient Sample that included diagnoses of infective endocarditis in patients 18 years or older using International Classification of Diseases codes. Associated CHD diagnosis, surgical procedure, microbiologic aetiology, and sociodemographic diagnosis codes were also identified. Details of diagnosis and procedural codes used are available in the supplemental material. Weighting was used to create national annual estimates, and these estimates were indexed to the United States population using census data.[22] Age groups were categorised as 18–44 years, 45–64 years, and 65+ years to facilitate comparisons due to large differences in age between adults with and without CHD. Due to non-linearity of age within our population, we elected to create age groups rather than utilise age as a continuous variable. The microbiologic aetiology of each infective endocarditis hospitalisation was identified when possible. Consistent with previous literature,[17] six groups of infective endocarditis microbiologic aetiologies were constructed: *Streptococcus*, *Staphylococcus*, Gram-negative bacteria, fungal, multiple organisms (more than one of the previous groups), and unknown organism. Due to its potential impact on outcome, a comparison of left-sided versus right-sided infective endocarditis was performed. International Classification of Diseases procedure codes, rather than diagnosis codes, were used to identify sidedness given diagnosis codes do not carry valve specificity. As such, sidedness analysis was limited to patients undergoing valve surgery. Left-sided lesions were defined as surgical intervention to the mitral or aortic valve. Right-sided lesions were defined as surgical intervention to the tricuspid valve, pulmonary valve, or to a right ventricle to pulmonary artery conduit. We additionally sought to investigate the comparative impact of drug abuse in adults with and without CHD given the opioid epidemic in the United States had a significant bearing on infective endocarditis during the study period. International Classification of Diseases Ninth and Tenth Revisions diagnosis codes for drugs of abuse were selected as has been previously identified in the literature.[23] Outcome measures were defined as in-hospital mortality and surgery for infective endocarditis.

Data analysis

National estimates of the number of infective endocarditis discharges related to adult CHD were created, accounting for the complex weighting and stratification utilised in the National Inpatient Sample. Categorical variables were compared using a survey-weighted chi-square test. Continuous variables were compared using survey-weighted linear regression. Multivariable models for infective endocarditis mortality and surgery related to CHD status were created. Sociodemographic covariables included age group, sex (as defined in the National Inpatient Sample database), race/ethnicity, insurance type, and year. The statistical level for all comparisons was $p < 0.05$. Statistical analysis was performed using Stata/SE 15.0 and R version 3.6.1.

Adult CHD sub-analysis

Univariate and multivariable analyses within the adult CHD population were also performed to evaluate outcomes of mortality and surgery by disease complexity and patient sociodemographic predictor variables. CHD complexity was stratified by simple, complex, and unclassified as has been previously categorised in the literature.[24] Anatomic classification as delineated by the 2018 adult CHD guidelines [25] was not possible due to limitations of the International Classification of Diseases coding descriptions. The code for atrial septal defect/patent foramen ovale was excluded as an adult CHD diagnosis as it has been found to be highly non-specific and may not represent true CHD.[26] The organisation of disease complexity can be found in the supplemental material. Adult CHD subgroup analysis was performed within the studied time period of 2001 to 2014 using only International Classification of Diseases, Ninth Revision codes, as the transition to Tenth Revision codes did not allow for consistent disease severity categorisation. The adult CHD sociodemographic sub-analysis covariates included age group, sex, race/ethnicity, and insurance type.

Results

Patient demographics

We identified a total of 1,096,858 estimated hospital discharges in patients 18 years and older that included a diagnosis of infective endocarditis from 2001 to 2016. Patient demographics stratified by CHD status are summarised in Table 1. The number of estimated adult CHD infective endocarditis hospitalisations was 17,729 (1.6%). Over the studied time period, annual adult CHD infective endocarditis hospitalisations increased from 683 (1.3%) in 2001 to 1,805 (1.9%) in 2016 with a 125% increase in indexed hospitalisations from 0.32/100,000 adults to 0.72/100,000 adults ($p < 0.001$ for trend) Figure 1. No change in slope was detected pre- or post-2007 with the introduction of the American Heart Association guideline change regarding spontaneous bacterial endocarditis recommendations ($p = 0.33$). The number of hospitalisations for infective endocarditis in patients with structurally normal hearts increased from 53,549 in 2001 to 91,135 in 2016, corresponding to

https://doi.org/10.1017/S1047951124026507 Published online by Cambridge University Press

Table 1. Baseline characteristics

	Overall	Non-ACHD	ACHD	*P*
	N = 1,096,858	*N* = 1,079,129 (98.4%)	*N* = 17,729 (1.6%)	
Female	527,681 (48.1%)	522,607 (48.4%)	5,074 (28.6%)	<0.001
Age (years)				
Mean age (SEM)	64.2 (0.09)	64.5 (0.09)	45.2 (0.31)	<0.001
18–44	183,534 (16.7%)	174,221 (16.2%)	9,313 (52.5%)	<0.001
45–64	317,960 (29.0%)	312,153 (28.9%)	5,807 (32.8%)	
≥65	595,364 (54.3%)	592,755 (54.9%)	2,609 (14.7%)	
Race				
Non-Hispanic White	675,519 (61.6%)	664,286 (61.5%)	11,233 (63.3%)	<0.001
Non-Hispanic Black	137,945 (12.6%)	136,712 (12.7%)	1,233 (7.0%)	
Hispanic	71,420 (6.5%)	69,885 (6.5%)	1,535 (8.7%)	
Other or missing	211,974 (19.3%)	208,246 (19.3%)	3,728 (21.0%)	
Insurance type				
Government insurance	808,562 (73.7%)	801,402 (74.3%)	7,160 (40.4%)	<0.001
Private insurance	203,791 (18.6%)	195,656 (18.1%)	8,135 (45.9%)	
Other	84,505 (7.7%)	82,071 (7.6%)	2,434 (13.7%)	

ACHD = adult congenital heart disease; SEM = standard error of the mean.

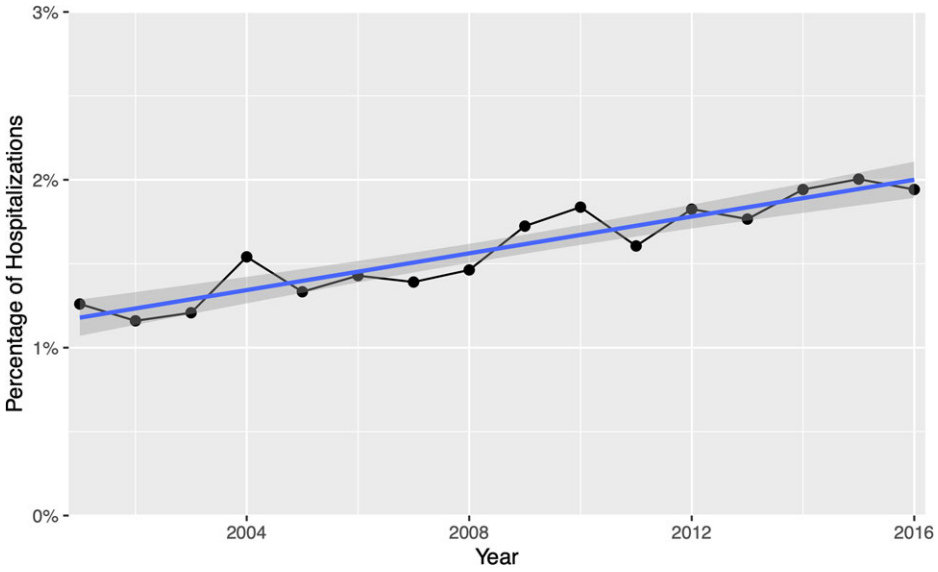


Figure 1. Percentage of infective endocarditis hospitalisations in patients with ACHD from 2001 to 2016. ACHD infective endocarditis hospitalisations in the United States increased from 683 (1.3%) in 2001 to 1,805 (1.9%) in 2016. Coincident with rising ACHD IE hospitalisations, the proportion of IE hospitalisations in non-ACHD patients decreased from 98.7% to 98.1%. ACHD = adult congenital heart disease; IE = infective endocarditits.

a 45% increase in the number of indexed hospitalisations from 25.22/100,000 adults to 36.56/100,000 adults. Despite this increase in absolute number of non-adult CHD infective endocarditis hospitalisations, due to the relatively higher rise in adult CHD infective endocarditis hospitalisations, the proportion of infective endocarditis hospitalisations in the general population decreased from 98.7% to 98.1% over the studied time period. Adult CHD patients with infective endocarditis were younger than those with infective endocarditis in the general population (mean age 45.2 years vs. 64.5 years, $p < 0.001$). Race/ethnicity and insurance type were also significantly different between the groups ($p < 0.001$) with non-adult CHD patients more likely to be non-Hispanic Black (12.7% vs. 7.0%) and have governmental insurance (74.3% vs. 40.4%). Adults with CHD were more likely to have private insurance (45.9% vs. 18.1%).

Infective endocarditis mortality and valve surgery

In-hospital infective endocarditis mortality was lower in adults with CHD compared to the general population (5.4% vs. 9.5%, respectively, $p < 0.001$) Figure 2. Over the studied time period, the mortality rate decreased significantly in patients with structurally

https://doi.org/10.1017/S1047951124026507 Published online by Cambridge University Press

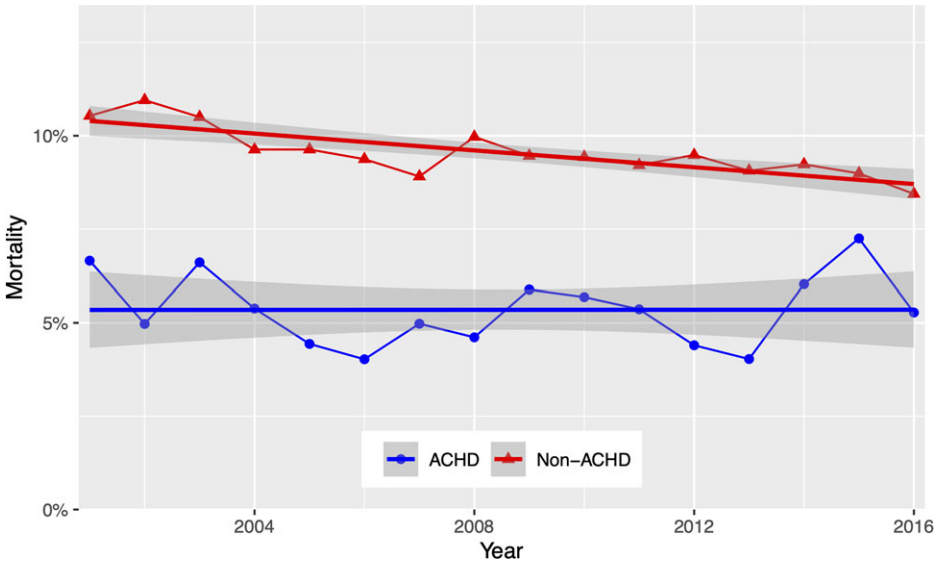


Figure 2. Comparative in-hospital infective endocarditis mortality by ACHD status from 2001 to 2016. In-hospital infective endocarditis mortality was significantly lower for patients with ACHD compared to non-ACHD patients from 2001 to 2016. Note that annual mortality rates remained similar among ACHD patients while mortality rate significantly decreased in non-ACHD patients. ACHD = adult congenital heart disease.

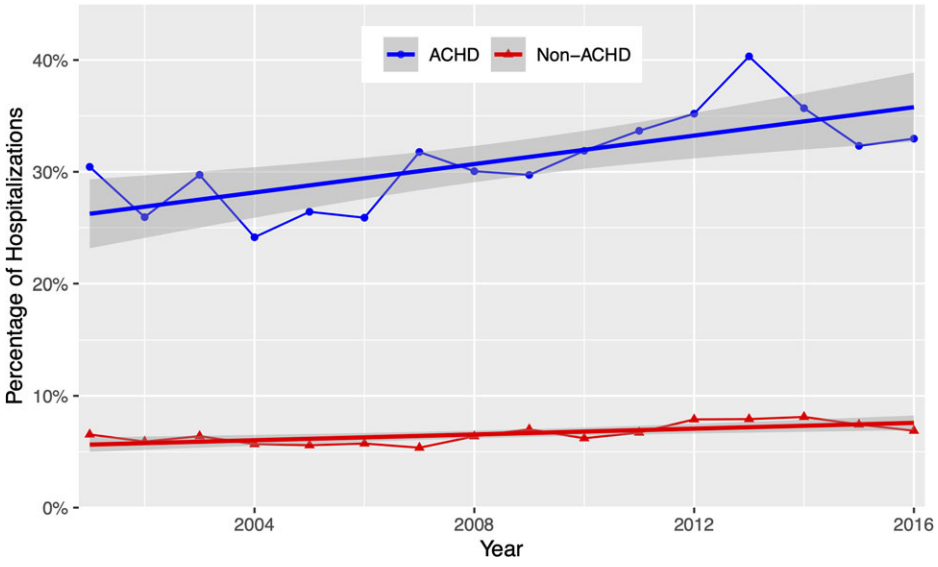


Figure 3. Comparative in-hospital infective endocarditis surgery by ACHD status from 2001 to 2016. In-hospital infective endocarditis surgery was significantly more common for patients with ACHD compared to non-ACHD patients from 2001 to 2016. Annual surgery rates for infective endocarditis significantly increased for both ACHD and non-ACHD patients. ACHD = adult congenital heart disease.

normal hearts, from 10.5% in 2001 to 8.4% in 2016 ($p < 0.001$), but did not change significantly among adults with CHD ($p = 0.75$). Patients with adult CHD were significantly more likely than the general population to undergo surgery during their infective endocarditis hospitalisation (31.6% vs. 6.7%, $p < 0.001$) Figure 3. Over the studied time period, the infective endocarditis surgery rate increased in adults with CHD, from 30.4% to 33.0% ($p < 0.001$), as well as in patients with structurally normal hearts (6.5% to 6.9%, $p < 0.001$). Given the age difference between the cohorts, analyses of mortality and surgery were performed stratified by age group Figure 4. Mortality generally increased with older age in both groups. Compared to adults with CHD, mortality was higher for the general population in the younger and middle-aged groups ($p = 0.003$ and $p < 0.001$, respectively) but was not significantly different in the oldest age group (9.6% for adults with CHD vs. 10.1% for the general population, $p = 0.68$). Overall rates of surgery were lowest in the oldest age group, with surgery consistently performed more often among adults with CHD across all age groups ($p < 0.001$ for each group).

Outcome differences persisted in multivariable analysis. Compared to the general population, adult CHD status was associated with a decrease in the odds of infective endocarditis in-hospital mortality (OR 0.54, 95% CI 0.47–0.63, $p < 0.001$), and adult CHD status was associated with much higher odds of undergoing surgery for infective endocarditis (OR 6.49, 95% CI 6.03–6.98, $p < 0.001$).

Outcome analysis related to anatomic complexity within the adult CHD cohort alone was subsequently performed. Table 2 demonstrates infective endocarditis mortality and surgery within adults with CHD stratified by disease severity. Those with complex CHD did not have increased mortality compared to patients with simple disease (OR 1.01, 95% CI 0.68–1.49, $p = 0.96$). However, the odds of a patient with complex disease undergoing valve surgery were lower in comparison with those that had simple CHD (OR 0.68, 95% CI 0.56–0.83, $p < 0.001$).

Mortality for those who underwent surgery compared to those medically managed was not statistically different within either the adult CHD cohort (5.1% vs. 5.5%, $p = 0.55$) or in the general

https://doi.org/10.1017/S1047951124026507 Published online by Cambridge University Press

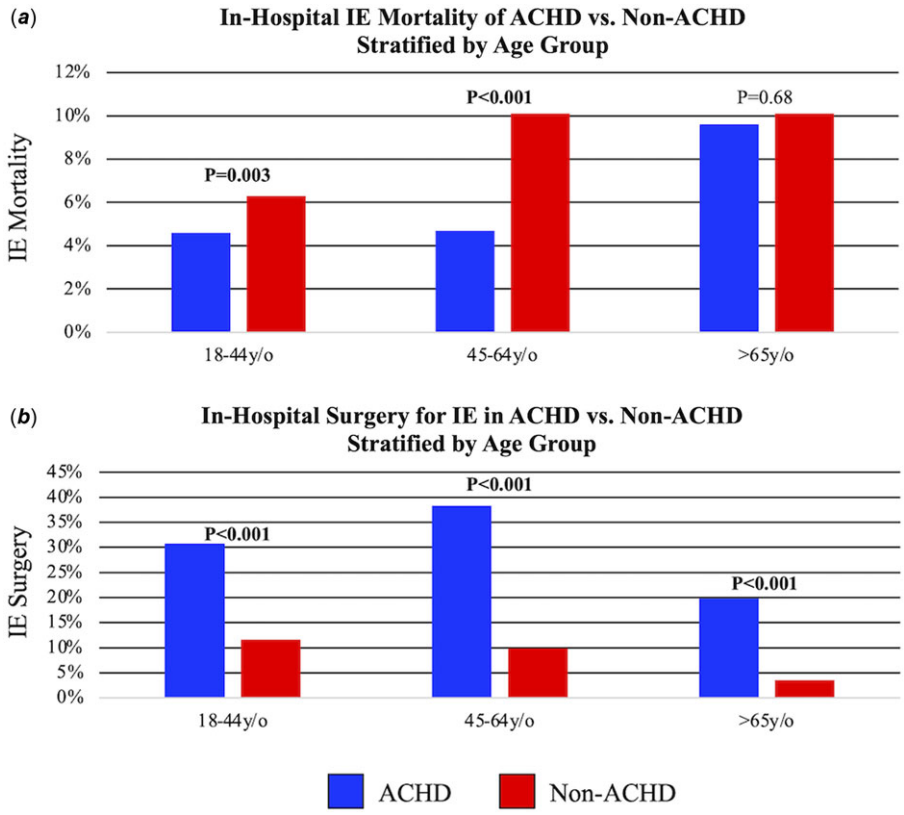


Figure 4. In-hospital infective endocarditis mortality and surgery stratified by age group. Due to the age difference between the ACHD and non-ACHD cohorts, we performed an analysis of mortality and surgery stratified by age group. (***a***) Mortality was significantly higher in the oldest age groups compared to the youngest age groups in both ACHD and non-ACHD. Mortality was significantly lower for patients with ACHD compared to non-ACHD except for in the oldest age group where no difference was found. (***b***) Rates of surgery for infective endocarditis were significantly higher for ACHD compared to non-ACHD across all age groups. ACHD = adult congenital heart disease; IE = infective endocarditis.

Table 2. Univariate and multivariable sub-analysis of mortality and surgery for patients with ACHD stratified by disease severity

ACHD infective endocarditis mortality			
Overall ***N*** **= 14,241**	**Disease severity**		
	Simple ***N*** **= 8,787**	**Complex** ***N*** **= 4,044**	**Unspecified** ***N*** **= 1,410**
739 (5%)	433 (4.9%)	239 (5.9%)	67 (4.7%)
	REF	OR = 1.01 95% CI: 0.68–1.49 *P* = 0.96	OR = 0.86 95% CI: 0.48–1.53 *P* = 0.60
ACHD infective endocarditis surgery			
Overall ***N*** **= 14,269**	**Disease severity**		
	Simple ***N*** **= 8,810**	**Complex** ***N*** **= 4,049**	**Unspecified** ***N*** **= 1,410**
4,477 (32%)	3,213 (36.5%)	1,006 (24.9%)	257 (18.2%)
	REF	OR = 0.68 95% CI: 0.56–0.83 *P* < 0.001	OR = 0.42 95% CI: 0.30–0.58 *P* < 0.001

ACHD = adult congenital heart disease; REF = reference.
*Differences in mortality and surgical overall cohorts are due to missing data.

population (9.9% vs. 9.5%, $p = 0.10$). Interaction analysis between adult CHD status and surgery for infective endocarditis was negative ($p = 0.36$).

Infective endocarditis microbiologic aetiology

A comparison of overall incidence in microbiologic aetiology as well as the incidence in patients who experienced mortality and those who underwent surgery during their hospitalisation is shown in Figure 5. A significant difference in overall infective endocarditis microbiology between patients with and without adult CHD was identified ($p < 0.001$). *Streptococcus* was the most identified cause of infective endocarditis in adults with CHD (36.2%) but was identified in only 14.4% of infective endocarditis in adults with structurally normal hearts. Comparatively, *Staphylococcus* was the most identified aetiology in patients

https://doi.org/10.1017/S1047951124026507 Published online by Cambridge University Press

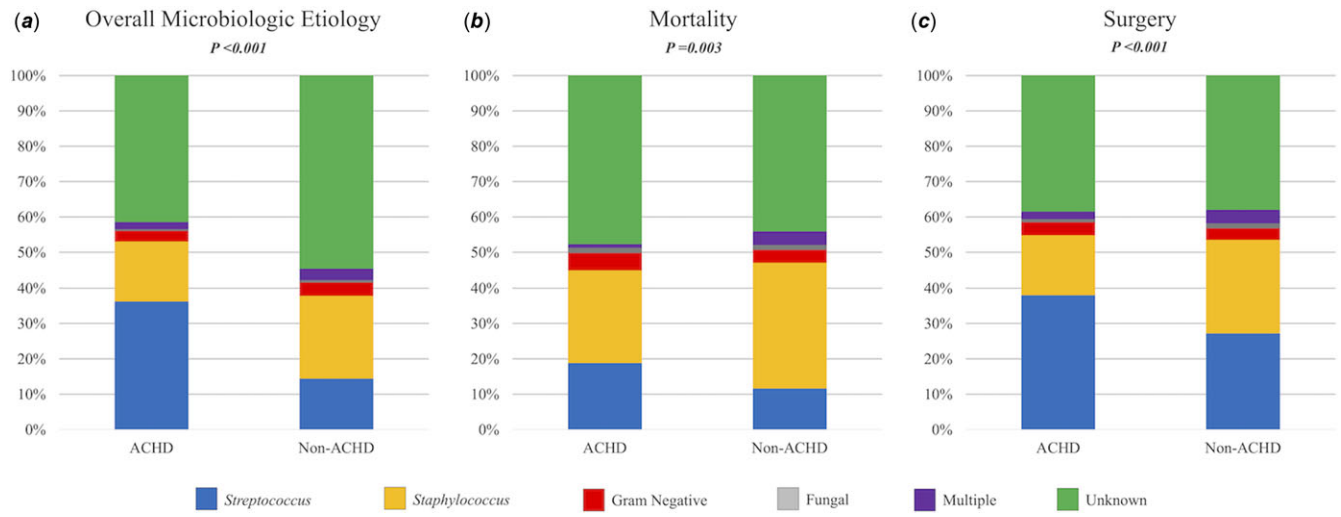


Figure 5. Proportion of microbiologic aetiology within ACHD and non-ACHD cohorts. Panel (***a***) represents the overall percentages of microbiologic aetiology within each cohort, while panels (***b*** and ***c***) represent the proportion of microbiologic aetiologies of patients who experienced mortality and surgery, respectively. Significant differences were found between the ACHD and non-ACHD cohorts within each comparison, most notable for a larger proportion of *Streptococcus* in ACHD in both the overall (***a***) and surgery (***c***) comparisons and a larger percentage of *Staphylococcus* in both the ACHD and non-ACHD cohorts who experienced mortality (***b***). ACHD = adult congenital heart disease.

without CHD (23.4%) but was the infectious pathogen in only 16.8% of infective endocarditis in adults with CHD. Microbiologic aetiology in a large proportion of infective endocarditis hospitalisations within both groups remained unknown (41.4% and 54.5% in adults with and without CHD, respectively). In those who died, a significant difference in infective endocarditis aetiology was found between adults with CHD and the general population ($p = 0.003$) with *Staphylococcus* identified more often compared to *Streptococcus* for both adults with CHD (26.2% vs. 18.8%) and in the general population (35.4% vs. 11.6%). For those managed surgically in either group, *Streptococcus* was the most commonly isolated organism, which was noted in higher proportions in adults with CHD (38.0% vs. 27.2%, $p < 0.001$).

Left- versus right-sided infective endocarditis

In patients who underwent valve surgery for infective endocarditis, a comparison of involvement of the left, right, or both sides of the heart was performed. Left-sided infective endocarditis was more common by a sizeable margin in adults with and without adult CHD (87.0% and 86.1%, respectively) compared to right-sided infective endocarditis (4.7% and 7.7%, respectively $p < 0.001$). In the general population, a significant difference in mortality related to sidedness of infective endocarditis was detected with 6.2% in right-sided infective endocarditis, 10.2% in left-sided infective endocarditis, and 13.0% when both left and right sides were affected ($p < 0.001$). When the structurally normal group was stratified by age group, mortality rates were lower across the board for the youngest group (4.1%, 5.7%, and 6.9% for right, left, and both sides, respectively, $p = 0.05$) and considerably higher in the oldest age group (17.0%, 14.9%, 18.4% for right, left, and both sides, respectively, $p < 0.001$). Within the adult CHD cohort, there was no significant difference in mortality related to infective endocarditis sidedness, including when stratified by age groups.

Drugs of abuse and infective endocarditis

Among adults with CHD and infective endocarditis, 774 (4.4%) were related to drugs of abuse compared to 54,844 (5.1%) in those without CHD ($p = 0.07$). Within the adult CHD group, no difference in mortality was seen among patients with drugs of abuse-related infective endocarditis compared to infective endocarditis unrelated to drug abuse (7.1% vs. 5.3%, respectively, $p = 0.35$). Similarly, no significant difference in infective endocarditis surgery was observed related to drugs of abuse in patients with adult CHD (38.6% vs. 31.3%, $p = 0.07$).

Adult CHD sociodemographic sub-analysis

We then compared outcomes for infective endocarditis among adults with CHD by sex, race/ethnicity, and insurance type. Table 3 summarises a multivariable analysis of these demographic characteristics for both infective endocarditis mortality and in-hospital surgery. There were no noted differences in mortality between female and male patients (5.4% vs. 5.1%, $p = 0.80$). In multivariable analysis, female sex was associated with lower odds of undergoing surgery in comparison with male sex (OR 0.60, 95% CI 0.49–0.73, $p < 0.001$). Of the non-Hispanic White patients, 5.1% died compared to 6.7% in the non-Hispanic Black and 4.2% in the Hispanic populations ($p = 0.68$). Rates of surgery were also similar between the race/ethnicity groups ($p = 0.97$). Likewise, in multivariable analysis, no difference in odds of mortality or undergoing surgery was identified by race/ethnicity. In univariate analysis, mortality was significantly higher for those with governmental insurance compared to private insurance (7.6% vs. 3.3%, $p < 0.001$), and surgery occurred less often in patients with governmental insurance than private insurance (26.6% vs. 33.4%, $p < 0.001$). On multivariable analysis, there was a significantly higher odds of mortality for patients with governmental insurance (OR 2.16, 95% CI 1.44–3.26, $p < 0.001$), but no

https://doi.org/10.1017/S1047951124026507 Published online by Cambridge University Press

Table 3. Multivariable sub-analysis of outcome by sex, race/ethnicity, and insurance type in ACHD infective endocarditis

	Mortality	Surgery
Sex		
Male	REF	REF
Female	OR 0.86 (95% CI 0.58–1.28, $P = 0.46$)	OR 0.60 (95% CI 0.49–0.73, $\mathbf{P < 0.001}$)
Race/ethnicity		
Non-Hispanic White	REF	REF
Non-Hispanic Black	OR 1.18 (95% CI 0.65–2.13, $P = 0.54$)	OR 1.12 (95% CI 0.81–1.57, $P = 0.49$)
Hispanic	OR 0.77 (95% CI 0.39–1.53, $P = 0.46$)	OR 1.03 (95% CI 0.74–1.43, $P = 0.85$)
Other or missing	OR 1.05 (95% CI 0.71–1.55, $P = 0.82$)	OR 1.04 (95% CI 0.85–1.27, $P = 0.72$)
Insurance type		
Private insurance	REF	REF
Governmental insurance	OR 2.16 (95% CI 1.44–3.26, $\mathbf{P < 0.001}$)	OR 1.01 (95% CI 0.83–1.23, $P = 0.95$)
Other	OR 1.55 (95% CI 0.91–2.65, $P = 0.11$)	OR 1.23 (95% CI 0.97–1.56, $P = 0.08$)

ACHD = adult congenital heart disease; REF = reference.

significant difference was noted in the odds of undergoing surgery (OR 1.01, 95% CI 0.83–1.23, $p = 0.95$).

Discussion

Utilising a United States national inpatient database from 2001 to 2016, we compared outcomes of infective endocarditis between adults with and without CHD. The proportion of infective endocarditis-related adult CHD hospitalisations has increased significantly from 1.3% in 2001 to 1.9% in 2016. Though their hearts are more anatomically complex, adults with CHD experienced less in-hospital infective endocarditis mortality than the general population. Among adult CHD patients, no significant mortality difference was noted between simple and complex disease, further emphasising the limited impact of cardiac anatomic complexity on infective endocarditis outcome. Alternatively, factors identified in our study such as younger age in adults with CHD and a difference in microbiologic aetiology between those with and without CHD may play a larger role. Surgery during an infective endocarditis hospitalisation was significantly more common among adults with CHD; however, surgery did not confer a survival advantage in either cohort.

Increasing adult CHD infective endocarditis hospitalisations

We identified a 125% increase in indexed infective endocarditis hospitalisations for the adult CHD population from 2001 to 2016, a trend similar to previously reported National Inpatient Sample data describing an increase in all-cause adult CHD hospitalisations over a similar time period.[24] It is important to note that this trend does not necessarily signify an increasing rate of infective endocarditis among adults with CHD, but rather may be more attributable to a growing adult CHD population that now comprises a larger relative percentage of the overall United States population.[1,27] This finding highlights the importance of specialised providers and qualified medical centres familiar with the management of infective endocarditis among adult CHD populations. Notably, referral to specialised adult CHD centres has been associated with a significant reduction in mortality for this complex group of patients.[28]

Outcome differences and contributing factors

Comparatively lower in-hospital mortality related to infective endocarditis was identified in adults with CHD compared to the general population in the United States, offering an American perspective that demonstrates similar outcomes as recent studies from Europe.[29,30] We believe this mortality difference is likely multifactorial, though perhaps one key factor is the difference in microbiologic aetiology in patients with CHD. *Streptococcus*, which has been consistently identified as the leading causative pathogen of infective endocarditis in the CHD population,[4,17,31] was also the most commonly identified cause of infective endocarditis in our adult CHD cohort. This is perhaps related to an increased burden of dysplastic and/or prosthetic valvular tissue in adults with CHD that increases the likelihood of transient bacteraemia from oral flora to adhere and proliferate. In contrast, *Staphylococcus* was the most commonly isolated organism in our cohort of adults without CHD, and it has also previously been demonstrated to predominate in patients with infective endocarditis and structurally normal hearts in the general population.[8,10,20,32] Historically, infective endocarditis outcome parallels microbiologic aetiology. *Streptococcus* is associated with lower in-hospital mortality in patients with structurally normal hearts,[32] and similar favourable outcomes have been identified when *Streptococcus* is isolated in CHD patients with infective endocarditis following Melody valve placement.[33] Conversely, *Staphylococcus* has been associated with increased infective endocarditis related complications and mortality in both populations.[10,31,32,34–37] In our study, *Staphylococcus* was the most commonly isolated organism in patients who died in either group and was particularly prominent in patients without CHD who experienced mortality, where it was identified over three times as frequently as *Streptococcus*.

https://doi.org/10.1017/S1047951124026507 Published online by Cambridge University Press

As has been previously argued,[5,29] early detection and intervention likely also play a significant role in the infective endocarditis adult CHD mortality difference. In a study of infective endocarditis in the general population, Thuny et al.[9] postulated that high mortality rates may be due to delayed identification and late referral to institutions experienced in infective endocarditis management including capabilities of early surgery. In patients with CHD, infective endocarditis is often an early consideration with any indication of fever or with the onset of other systemic symptoms, particularly in the context of changing cardiac valve function.

Given risk factors of left-sided infective endocarditis such as thromboembolism and heart failure, we additionally considered the impact of left- versus right-sided infective endocarditis involvement on mortality. The large majority of infective endocarditis was left-sided in patients with and without CHD, which is similar to previously reported data.[30] Given our sidedness analysis was limited to patients undergoing surgical valve intervention, this data likely reflects a proclivity to surgically treat infective endocarditis that is left-sided. Infective endocarditis sidedness was similar between each group with only a modest difference in right-sided involvement driving statistical significance and is unlikely to meaningfully impact overall mortality. Compared to right-sided infective endocarditis, left-sided disease conferred an increase in mortality in the structurally normal group, likely related to age and potentially due to delayed detection resulting in development of complications associated with left-sided infective endocarditis as previously noted.

The United States opioid epidemic imparted considerable influence during the time period of our study, though its impact related to infective endocarditis affected both adults with and without CHD similarly given comparable rates in each group. In adults with CHD, drug abuse also did not convey significance in infective endocarditis outcome as no differences in mortality or surgery were demonstrated related to drug abuse.

The difference in rates of surgery during an infective endocarditis hospitalisation between adults with and without CHD is notable and may suggest a predilection for surgical management of infective endocarditis in CHD patients. Surgery for infective endocarditis in adults with CHD in our study occurred in nearly one third of patients, which is similar to previously reported surgical rates for adult CHD infective endocarditis.[5,29] Those with transcatheter Melody valves with infective endocarditis have even higher reported rates of surgical intervention (44%).[38] One possible explanation for this management paradigm is the necessity for a more aggressive approach in instances of haemodynamically compromising infective endocarditis complications such as right ventricular outflow tract obstruction within conduits or transcatheter pulmonary valves.[33,38] Another possibility is the influence of surgical familiarity for the management of patients with CHD. Institutions accustomed to frequent application of surgical or transcatheter intervention for patients with CHD may also be more apt to consider a surgical approach for complications such as infective endocarditis.

Adult CHD infective endocarditis sociodemographic outcome disparities

Significant sex and insurance differences were identified within the adult CHD infective endocarditis group, adding to the growing number of outcome disparities among vulnerable patient populations. In our study, women with adult CHD and infective endocarditis were less likely to undergo surgery. Our data is consistent with the literature,[15,16] which has identified lower rates of valve surgery in women with structurally normal hearts and infective endocarditis despite improved in-hospital and 1 year mortality for those who are surgically managed. One possible explanation for these findings might be an avoidance of surgery in women who are pregnant when diagnosed with infective endocarditis.

In our adult CHD cohort, those with governmental insurance had significantly higher mortality rates. Similar outcomes in insurance disparities have been identified in the paediatric population following congenital heart surgery.[39] As the adult CHD population continues to grow, ensuring access to care is paramount. National health policies such as the Affordable Care Act lower uninsured rates in adults with CHD,[40] demonstrating one strategy of reducing underinsurance as a barrier to care. Additional system-level mechanisms of reducing disparity within heart centres include social determinants of health screening to assist in understanding access to medications and adult CHD physicians, broad implementation of implicit bias training to ensure equal recognition and treatment of all patients with infective endocarditis regardless of sociodemographic characteristics, centre-based quality improvement initiatives including timely and adequate imaging studies, as well as increasing awareness and education of the signs and symptoms of infective endocarditis, particularly to lower socio-economic status communities.

Limitations

Despite the large size of our overall population derived from utilisation of a national database from 2001 to 2016, this study has several limitations. Inherent limitations exist with retrospective data collection which can only provide association as opposed to causality. The deidentified nature of the National Inpatient Sample database creates the possibility that some infective endocarditis hospitalisations are readmissions as opposed to newly diagnosed cases, potentially overestimating the true incidence of infective endocarditis in the United States.

Generalisability within this dataset is dependent on reliable International Classification of Diseases coding, which may not be consistent across institutions. Coding errors have been identified in CHD,[26] and the current dataset may include inaccuracies in regard to presence of CHD and congenial heart disease complexity. For instance, the code for "non-rheumatic mitral valve insufficiency" may be utilised if the valve pathology is due to acquired valve degeneration or from a congenital aetiology, and non-trivial overlap likely exists. This limits our ability to identify patients, particularly in the non-adult CHD group, that may be at higher risk for mortality or surgery related to infective endocarditis such as those with acquired degenerative valve disease. Furthermore, International Classification of Diseases codes for history of prosthetic valve disease are likely under-coded in patients with adult CHD, limiting the comparative utility of this variable between the non-adult CHD and adult CHD groups.

An additional limitation of International Classification of Diseases coding includes an inability to identify less common microbiologic organisms such as the *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella* group. Such a limitation has been acknowledged previously[17] and may

https://doi.org/10.1017/S1047951124026507 Published online by Cambridge University Press

account for a larger proportion of patients with unknown microbiologic aetiologies in our cohort. Given the heterogeneity of adult CHD anatomy, valve specificity does not always accurately denote a left-sided mitral and aortic valve and right-sided tricuspid and pulmonary valve, limiting our sidedness comparison and its impact on mortality. Inclusion of analyses to determine the impact of genetic syndromes such as 22q11 deletion was considered; however, we believe under-coding and/or inconsistent coding of such inherited disorders during inpatient admissions likely limits the reliability of this data. Institutional variability in the management of infective endocarditis such as empiric antimicrobial selection and varying thresholds for surgical intervention may affect outcome. Finally, complexity of surgical intervention may vary from simple valve debridement to more complex valve or conduit resections/replacements and could impact surgical outcome.

Conclusion

Utilising a large United States inpatient database, an increase in adult CHD infective endocarditis hospitalisations indexed to the United States population was identified between 2001 and 2016. Adults with CHD had significantly lower in-hospital infective endocarditis mortality than the general population. One key factor likely contributing to this disparity is the difference in microbiologic aetiology between the groups. Surgery was performed in adult CHD infective endocarditis hospitalisations at a significantly increased rate than that of the general population, likely signalling a more aggressive approach to infective endocarditis management in the CHD group. Finally, disparities in outcomes among patients who are female and have governmental insurance within the adult CHD cohort require further investigation, particularly surrounding access to high-quality adult CHD care.

These data better inform both adult congenital and non-adult congenital cardiologists regarding how infective endocarditis epidemiology and outcome differ between these groups and should encourage early consideration and treatment of infective endocarditis across all patient populations, even in the absence of cardiac anatomic complexity.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951124026507

Acknowledgements. None.

Financial support. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Competing interests. None.

References

1. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation 2014; 130: 749–756.
2. Verheugt CL, Uiterwaal CS, van der Velde ET et al. Turning 18 with congenital heart disease: prediction of infective endocarditis based on a large population. Eur Heart J 2011; 32: 1926–1934.
3. Baumgartner H, Bonhoeffer P, De Groot NM et al. ESC guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 2010; 31: 2915–2957.
4. Moore B, Cao J, Kotchetkova I, Celermajer DS. Incidence, predictors and outcomes of infective endocarditis in a contemporary adult congenital heart disease population. Int J Cardiol 2017; 249: 161–165.
5. Tutarel O, Alonso-Gonzalez R, Montanaro C et al. Infective endocarditis in adults with congenital heart disease remains a lethal disease. Heart 2018; 104: 161–165.
6. Mylotte D, Rushani D, Therrien J et al.Incidence, predictors, and mortality of infective endocarditis in adults with congenital heart disease without prosthetic valves. Am J Cardiol 2017; 120: 2278–2283.
7. Egbe AC, Vallabhajosyula S, Akintoye E, Connolly HM. Trends and outcomes of infective endocarditis in adults with tetralogy of fallot: a review of the national inpatient sample database. Can J Cardiol 2019; 35: 721–726.
8. Bor DH, Woolhandler S, Nardin R, Brusch J, Himmelstein DU. Infective endocarditis in the U.S., 1998–2009: a nationwide study. PLoS One 2013; 8: e60033.
9. Thuny F, Di Salvo G, Belliard O et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation 2005; 112: 69–75.
10. Cabell CH, Jollis JG, Peterson GE et al. Changing patient characteristics and the effect on mortality in endocarditis. Arch Intern Med 2002; 162: 90–94.
11. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? Circulation 2010; 121: 1141–1152.
12. Lalani T, Chu VH, Park LP et al. In-hospital and 1-year mortality in patients undergoing early surgery for prosthetic valve endocarditis. JAMA Intern Med 2013; 173: 1495–1504.
13. Funakoshi S, Kaji S, Yamamuro A et al. Impact of early surgery in the active phase on long-term outcomes in left-sided native valve infective endocarditis. J Thorac Cardiovasc Surg 2011; 142: 836–842 e831.
14. Otto CM, Nishimura RA, Bonow RO et al.ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. Circulation 2020; 143: e72–e227.
15. Bansal A, Cremer PC, Jaber WA, Rampersad P, Menon V. Sex differences in the utilization and outcomes of cardiac valve replacement surgery for infective endocarditis: insights from the national inpatient sample. J Am Heart Assoc 2021; 10: e020095.
16. Sambola A, Fernandez-Hidalgo N, Almirante B et al. Sex differences in native-valve infective endocarditis in a single tertiary-care hospital. Am J Cardiol 2010; 106: 92–98.
17. Dolgner SJ, Arya B, Kronman MP, Chan T. Effect of congenital heart disease status on trends in pediatric infective endocarditis hospitalizations in the United States between 2000 and 2012. Pediatr Cardiol 2019; 40: 319–329.
18. Sakai Bizmark R, Chang RR, Tsugawa Y, Zangwill KM, Kawachi I. Impact of AHA's 2007 guideline change on incidence of infective endocarditis in infants and children. Am Heart J 2017; 189: 110–119.
19. Bates KE, Hall M, Shah SS, Hill KD, Pasquali SK. Trends in infective endocarditis hospitalisations at United States children's hospitals from 2003 to 2014: impact of the 2007 American heart association antibiotic prophylaxis guidelines. Cardiol Young 2017; 27: 686–690.
20. Pant S, Patel NJ, Deshmukh A et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. J Am Coll Cardiol 2015; 65: 2070–2076.
21. Mori M, Brown KJ, Bin Mahmood SU, Geirsson A, Mangi AA. Trends in infective endocarditis hospitalizations, characteristics, and valve operations in patients with opioid use disorders in the United States: 2005–2014. J Am Heart Assoc 2020; 9: e012465.
22. Compiled from 1990 to 1999 bridged-race intercensal population estimates (released by NCHS on 1997/1926/2004); revised bridged-race 2000-2009 intercensal population estimates (released by NCHS on 1910/1926/2012); and bridged-race Vintage 2015. United States Department of Health and Human Services (US DHHS) CfDCaPC, National Center for Health Statistics (NCHS). Bridged-Race Population Estimates, United States. July 1st resident population by state, county, age, sex, bridged-race, and Hispanic origin, 2010-2015. postcensal population estimates (released by NCHS on 1996/1928/2016). Available on CDC WONDER Online Database, http://wonder.cdc.gov/bridged-racev2015.html, Accessed 1996/1998/2021.
23. Schranz AJ, Fleischauer A, Chu VH, Wu LT, Rosen DL. Trends in drug use-associated infective endocarditis and heart valve surgery, 2007 to 2017: a study of statewide discharge data. Ann Intern Med 2019; 170: 31–40.

https://doi.org/10.1017/S1047951124026507 Published online by Cambridge University Press

24. Agarwal S, Sud K, Menon V. Nationwide hospitalization trends in adult congenital heart disease across 2003–2012. J Am Heart Assoc 2016; 5: e002330.
25. Stout KK, Daniels CJ, Aboulhosn JA et al. AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol 2018; 73: e81–e192, 2019.
26. Rodriguez FH, 3rd Ephrem G, Gerardin JF, Raskind-Hood C, Hogue C, Book W. The 745.5 issue in code-based, adult congenital heart disease population studies: relevance to current and future ICD-9-CM and ICD-10-CM studies. Congenit Heart Dis 2018; 13: 59–64.
27. Gilboa SM, Devine OJ, Kucik JE et al. Congenital heart defects in the United States: estimating the magnitude of the affected population in 2010. Circulation 2016; 134: 101–109.
28. Mylotte D, Pilote L, Ionescu-Ittu R et al. Specialized adult congenital heart disease care: the impact of policy on mortality. Circulation 2014; 129: 1804–1812.
29. Maser M, Freisinger E, Bronstein L et al.Frequency, mortality, and predictors of adverse outcomes for endocarditis in patients with congenital heart disease: results of a nationwide analysis including 2512 endocarditis cases. J Clin Med 2021; 10: 5071.
30. van Melle JP, Roos-Hesselink JW, Bansal M et al. Infective endocarditis in adult patients with congenital heart disease. Int J Cardiol 2022; 370, 178–185.
31. Cahill TJ, Jewell PD, Denne L et al. Contemporary epidemiology of infective endocarditis in patients with congenital heart disease: a UK prospective study. Am Heart J 2019; 215: 70–77.
32. Murdoch DR, Corey GR, Hoen B et al.Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the international collaboration on endocarditis-prospective cohort study. Arch Intern Med 2009; 169: 463–473.
33. Abdelghani M, Nassif M, Blom NA et al. Infective endocarditis after melody valve implantation in the pulmonary position: a systematic review. J Am Heart Assoc 2018; 7: e008163.
34. Mir T, Uddin M, Qureshi WT, Regmi N, Tleyjeh IM, Saydain G. Predictors of complications secondary to infective endocarditis and their associated outcomes: a large cohort study from the national emergency database (2016–2018).. Infect Dis Ther 2022; 11: 305–321.
35. Selton-Suty C, Celard M, Le Moing V et al. Preeminence of staphylococcus aureus in infective endocarditis: a 1-year population-based survey. Clin Infect Dis 2012; 54: 1230–1239.
36. Marques A, Cruz I, Caldeira D et al. Risk factors for in-hospital mortality in infective endocarditis. Arq Bras Cardiol 2020; 114: 1–8.
37. Kim JH, Lee HJ, Ku NS et al. Infective endocarditis at a tertiary care hospital in south Korea. Heart 2021; 107: 135–141.
38. Davtyan A, Guyon PW, El-Sabrout HR et al. Selective valve removal for melody valve endocarditis: practice variations in a multicenter experience. Pediatr Cardiol 2022; 43: 894–902.
39. Chan T, Pinto NM, Bratton SL. Racial and insurance disparities in hospital mortality for children undergoing congenital heart surgery. Pediatr Cardiol 2012; 33: 1026–1039.
40. Salciccioli KB, Salemi JL, Broda CR, Lopez KN. Disparities in insurance coverage among hospitalized adult congenital heart disease patients before and after the affordable care act. Birth Defects Res 2021; 113: 644–659.

https://doi.org/10.1017/S1047951124026507 Published online by Cambridge University Press