ESC European Society of Cardiology

European Heart Journal (2023) **44**, 54–61
https://doi.org/10.1093/eurheartj/ehac618

CLINICAL RESEARCH
Congenital heart disease

Survival of patients with congenital ventricular septal defect

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Received 20 June 2022; revised 24 September 2022; accepted 13 October 2022; online publish-ahead-of-print 24 November 2022

See the editorial comment for this article 'Half a century of experience with congenital heart disease: what have we learned about ventricular septal defects?', by Anne Marie Valente and Michael D. Freed, https://doi.org/10.1093/eurheartj/ehac657.

Abstract

Aims The long-term survival of patients with isolated congenital ventricular septal defect (VSD) is not well described. The aim of this study was to describe the survival of a national cohort of patients with VSD compared with the general population.

Methods and results Using Danish nationwide medical registries, all patients diagnosed with congenital VSD ($n = 9{,}136$) in the period 1977–2018 were included. Patients with chromosomal abnormalities and concomitant congenital cardiac malformations other than atrial septal defect were excluded. Each patient was matched by birthyear and sex with ten controls from the general Danish population. Kaplan–Meier survival function and Cox proportional hazard regression were used to compute survival and mortality risk. Median follow-up was 22 years (interquartile range: 11–37). VSD patients displayed lower survival ($P<0.001$) yielding a hazard ratio (HR) for mortality of 2.7 [95% confidence interval (CI): 2.4–3.0] compared with matched controls. The adjusted HR for mortality among patients with unrepaired VSD was 2.7 (95% CI: 2.4–3.0) and 2.8 (95% CI: 2.1–3.7) for patients with surgically closed VSD. Stratified by era of VSD diagnosis, the HR for mortality was 3.2 (95% CI: 2.8–3.7) for unrepaired patients diagnosed before 1990 and 2.4 (95% CI: 2.0–2.7) for patients diagnosed later. Cardiac-related death was the commonest cause of death among unrepaired (30%) and surgically closed (65%) patients.

Conclusion Patients with VSD had lower survival compared with the general population. The HR for mortality was increased over 2.5-fold in patients with unrepaired defect (Eisenmenger syndrome excluded) and over 1.5-fold in patients with surgically closed defect (excluding surgical mortality).

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Structured Graphical Abstract

Key Question

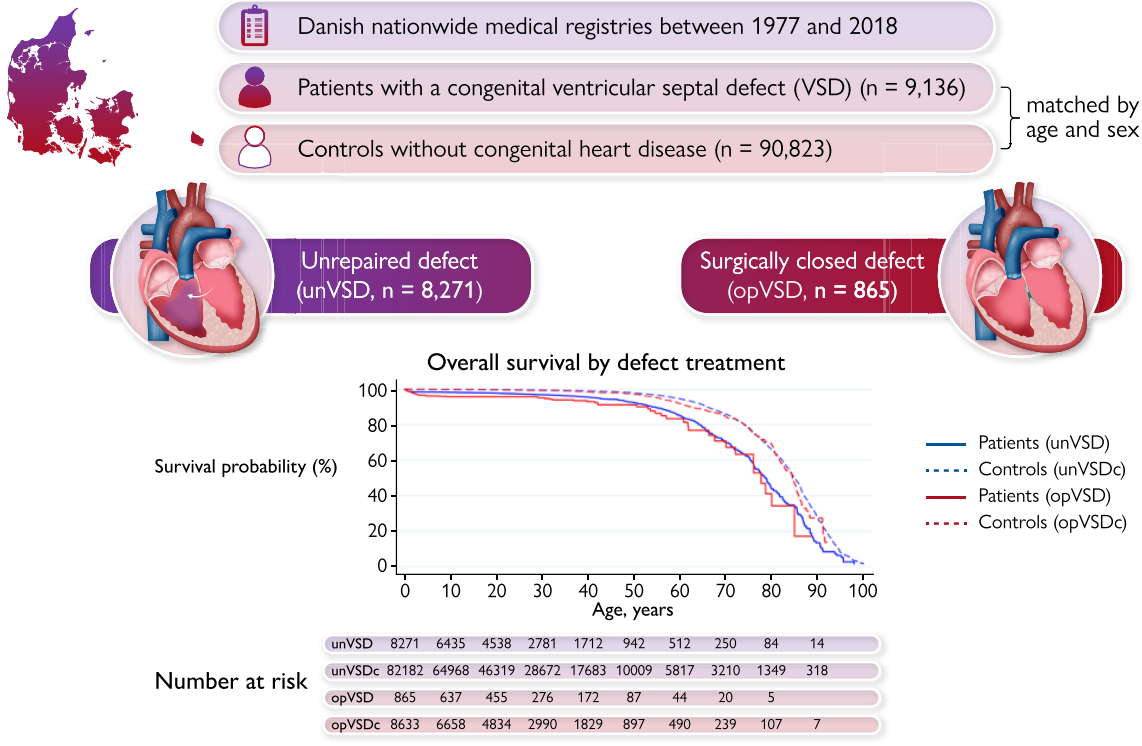
Do patients with ventricular septal defect, either unrepaired or surgically closed, have a survival rate comparable to that of the general population?

Key Finding

The survival of patients with ventricular septal defect was reduced, irrespective of treatment pathway. Patients with unrepaired and surgically closed defect both demonstrated an almost 3-fold higher hazard ratio for mortality than their matched peers, respectively.

Take Home Message

Even though deemed a 'simple' congenital heart disease, the diagnosis of ventricular septal defect comes with significant long-term consequences. Meticulous follow-up in specialized heart clinics is necessary to detect and possibly prevent or limit cardiovascular morbidity at an early stage.



Keywords Congenital heart disease • Ventricular septal defect • Survival • Long-term outcome

Introduction

Ventricular septal defect (VSD), the commonest congenital heart disease, is categorized as a 'simple' lesion with assumed negligible long-term risks when treated correctly in childhood. However, recent long-term studies have revealed significant cardiovascular morbidity, irrespective of whether surgical closure is performed, or patients are treated medically.[1–5] Consequently, clinical guidelines for adults with VSD have been modified towards a more vigilant follow-up strategy.[6,7] While it is now generally accepted that simple congenital heart diseases, such as VSD, are associated with an increased risk of long-term adverse cardiovascular outcomes, their impact on survival is less well known. Current data suggest that mortality up to 40 years after surgical closure is slightly higher than in the general population,[4,8,9] while long-term survival data on patients with unrepaired VSDs are undescribed. Using national medical registries, we report the survival of patients with isolated congenital VSD, unrepaired or surgically closed, compared to a matched cohort from the general population.

Methods

Study cohort and design

This nationwide cohort study is based on national medical registries in Denmark, which currently has a population of 5.8 million. The healthcare in Denmark is publicly funded, equally accessible for all citizens, and free of charge including all medical care for patients with congenital heart disease. Surgical treatment of patients with congenital heart disease is performed exclusively in public hospitals. Hospital data are collected in nationwide registries and linked to unique personal identification numbers provided for all citizens since 1968.

The Danish Civil Registration System (DCRS) was used to retrieve information on date of birth and date of death.[10] Data in DCRS are essentially complete and have high accuracy.[10] The Danish National Patient Registry (DNPR) was established in 1977 and contains information on all inpatient and outpatient hospital contacts in Denmark.[11] Data are updated yearly and include dates of admission and discharge, surgical data, and discharge diagnoses according to the International Classification of Diseases (ICD).[12] In Denmark the 8th edition of ICD was used until 1993 and replaced by the 10th edition. It is mandatory for all hospitals to report to the DNPR which reviews hospital data for missing codes, wrong digits, inaccuracies in personal identification numbers, and discrepancies between diagnosis and sex.[11] Thus, the DNPR is considered complete. All patients diagnosed with a congenital VSD in the period 1977–2018 were identified using the 8th (code: 74639) and the 10th (code: DQ21.0) edition of ICD. This cohort was supplemented by an external cohort of patients diagnosed with VSD (manually validated) prior to 1977. This cohort has been described elsewhere.[5] Patients diagnosed with chromosomal abnormalities or concomitant congenital cardiac malformations other than atrial septal defect (ASD) were excluded by using the ICD codes for these conditions. A detailed description of the ICD codes is embedded in the Supplementary material online, *Appendix Table S1 and S2*. Concomitant ASD was accepted in order to evaluate its effect on mortality in patients with VSD. All patients with an acute myocardial infarction diagnosis in the 8th or 10th edition of ICD prior to the VSD diagnosis were excluded. The ICD codes used for surgical procedures and comorbidities are embedded in Supplementary material online, *Appendix Table S3*. Up until 2016, surgical and transcatheter closure were performed in two hospitals with highly specialized cardiac teams, after which treatment was centralized to Copenhagen University Hospital.

To estimate the risk of mortality in the VSD population, each patient was matched by year of birth and sex with 10 controls without congenital heart disease and alive at the date of VSD diagnosis for the patient from the general Danish population. The DCRS[13] was used to identify the controls.

The study was approved by the Danish Data Protection Agency (j. no. 1-16-02-184-19). Delivered data were anonymized by replacing the personal identification number with a random code, performed by Denmark Statistics.

Mortality and cause of death

The causes of death were obtained from the Danish Register of Causes of Death[14] which provides up to four diagnoses related to the death of the deceased person (including underlying cause of death, diagnoses related to the course of the death, and the direct cause of death). The cause of death was manually reviewed and the most likely cause was chosen in case of more than one diagnosis was reported. Perioperative mortality was defined as death occurring within 30 days after closure in or out of hospital.

Statistical analysis

Follow-up started at the time of birth (the index date) and continued until end of follow-up (31 December 2018) or death, whichever came first.

Survival rates were computed using Kaplan–Meier survival function and hazard ratios (HRs) for mortality were computed using Cox proportional hazard regression model. For patients with unrepaired VSD risk started at time of birth with underlying time scale being age, while risk started at time of defect closure with underlying time scale being years since closure for patients with closed VSD. Estimates were compared with the matched controls. For overall estimates, patients became at risk at the time of birth with underlying time scale being age. Estimates were stratified by era of diagnosis (<1990 or ≥1990), age at diagnosis (<18 or ≥18 years), closure of defect, era of closure (<1990 or ≥1990), and age at time at closure (<5 or ≥5 years). Truncated analysis was performed to compute risk of mortality in the adult VSD patient including patients alive at their 18th birthday and their matched controls. For the mortality analyses where Eisenmenger syndrome and perioperative mortality were excluded, patients together with their matched controls were censored if they fulfilled either criterion. Estimates were adjusted for a modified Charlson Comorbidity Index (CCI).[15,16] We excluded heart failure diagnoses from the CCI to avoid adjustment for intermediate steps between VSD and mortality. For the mortality analyses, six patients (with corresponding matched controls) and ten controls born before 1920 were excluded due to missing date of death. The assumption of proportional hazards was graphically verified by log minus log plots. Analyses were performed using STATA 16.1 (StataCorp. LP, College Station, TX, USA).

Results

In the national medical register, we identified 13 738 patients diagnosed with VSD. Of the total cohort of patients with VSD, 3660 (26.6%) were excluded due to concomitant congenital cardiac malformation and 692 (6.9%) were subsequently excluded due to chromosomal abnormalities. Of the remaining patients, 250 (2.6%) were excluded due to assumed postinfarction VSD leaving 9136 patients in the final VSD cohort.

Baseline characteristics

Median follow-up for the total cohort of patients was 22.1 years [interquartile range (IQR): 11.1–36.8] with a median age at diagnosis of 145 days (IQR: 8 days–5.5 years), where 5438 (59.5%) patients were diagnosed within first year of life. Demographics are presented in *Table 1*. The majority of patients ($n = 8271$) did not undergo defect closure. Of the VSD patients who had their defect closed ($n = 865$), eight patients received percutaneous transcatheter closure. Patients with closure before the age of 5 years ($n = 639$) had a median age at time of surgery of 252 days (IQR: 113 days–1.7 years), whereas those with late closure ($n = 226$) had a median age of 15 years (IQR: 6.9–37 years). We identified 22 patients with Eisenmenger syndrome, the majority (72%) received their VSD diagnosis before 1990. Of patients with concomitant ASD ($n = 1130$), 183 (16%) had surgical closure of their VSD.

Mortality

Survival of VSD patients was lower than in the general population (*Figure 1A*), irrespective of defect closure (*Figure 1B*). Mortality data for patients stratified by defect treatment, era of diagnosis and surgery, age at time of diagnosis and surgery, and for patients alive at 18 years of age are presented in *Table 2*.

Patients with unrepaired VSD displayed survival rates of 95% (95% CI: 95–96), 92% (95% CI: 91–93), 85% (95% CI: 83–87), 70% (95% CI: 66–74), and 44% (95% CI: 38–49) at 40, 50, 60, 70, and 80 years of age (*Figure 2A*). Patients diagnosed early (<18 years of age) displayed high HR for mortality while patients diagnosed late (≥18 years of age) did not. In a direct comparison, early VSD diagnosis was associated with increased HR for mortality compared with late diagnosis (HR: 1.5, 95% CI: 1.1–2.0).

Table 1 Baseline characteristics of patients with ventricular septal defect and matched controls from the general Danish population

	VSD unrepaired (*n* = 8271)	Controls (*n* = 82 190)	VSD closed (*n* = 865)	Controls (*n* = 8633)
Female sex, *n* (%)	4368 (52.8)	43 381 (52.8)	384 (44.4)	3836 (44.4)
Median follow-up, years	22.1 (11.2–36.5)	22.8 (11.7–37.3)	21.0 (9.4–36.2)	22.1 (11.2–37.3)
Diagnosis/closure <1990, years	40.1 (34.3–47.8)	40.7 (35.3–49.2)	39.9 (34.5–46.4)	40.7 (36.7–47.5)
Diagnosis/closure ≥1990, years	17.6 (9.1–26.1)	17.7 (9.2–25.9)	16.7 (8.1–25.2)	17.3 (8.5–25.4)
Median age at VSD diagnosis, days	155 (6–6.1 years)	–	–	–
Diagnosis <1990, years	3.0 (39 days–12.6)	–	–	–
Diagnosis ≥1990, days	92 (4–3.8 years)	–	–	–
Median age at surgical VSD closure, years	–	–	1.2 (151 days–5.4)	–
Closure <1990, years	–	–	4.5 (1.9–8.5)	–
Closure ≥1990, days	–	–	283 (115–3.0 years)	–
Comorbidities				
Arrhythmia, *n* (%)	343 (4.2)	1154 (1.4)	62 (7.2)	141 (1.6)
Systemic hypertension (mmHg), *n* (%)	340 (4.1)	2442 (3.0)	40 (4.6)	237 (2.8)
Ischaemic cerebrovascular disease, *n* (%)	117 (1.4)	784 (<1)	5 (<1)	86 (1.0)
Chronic pulmonary disease, *n* (%)	150 (1.8)	962 (1.2)	16 (1.9)	106 (1.2)
Diabetes, *n* (%)	150 (1.8)	1221 (1.5)	16 (1.9)	125 (1.5)
Heart failure, *n* (%)	265 (3.2)	623 (<1)	147 (17.0)	60 (<1)
Infectious endocarditis, *n* (%)	100 (1.2)	39 (<1)	57 (6.6)	8 (<1)
Ischaemic heart disease, *n* (%)	304 (3.7)	1504 (1.9)	35 (4.0)	144 (1.7)
Pulmonary arterial hypertension, *n* (%)	72 (<1)	59 (<1)	20 (2.3)	6 (<0.1)

Data are presented as absolute numbers with percentage of total numbers and as median with interquartile range, P_{25}–P_{75}. VSD, ventricular septal defect.

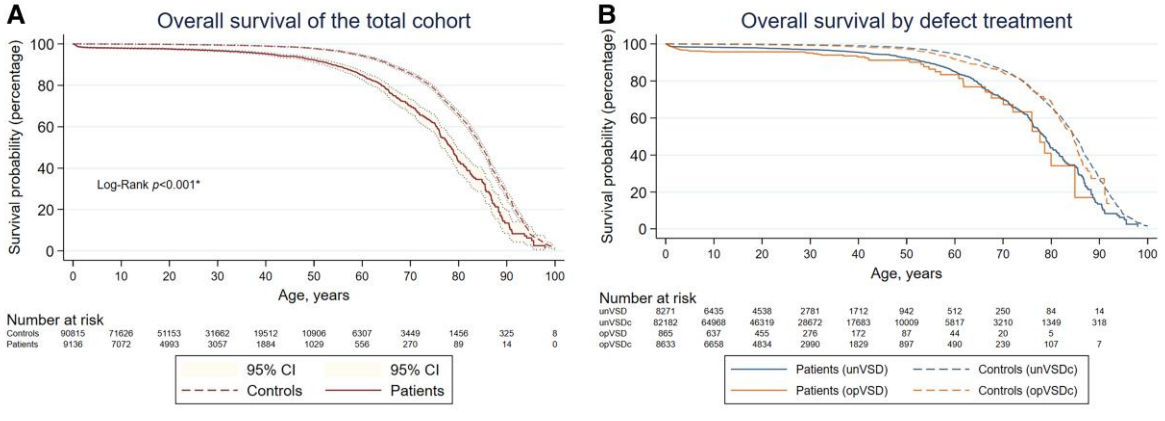


Figure 1 Overall survival in years from birth of patients with a congenital VSD compared with controls matched by age and sex (*A*). Overall survival in years from birth of patients with a congenital VSD stratified by defect treatment and compared with controls matched by age and sex (*B*). unVSD = Patients with unrepaired VSD; opVSD = Patients with surgically corrected VSD; unVSDc = Controls to patients with unrepaired VSD; opVSDc = Controls to patients with surgically corrected VSD. VSD, ventricular septal defect. *Level of significance between patients and controls.

Table 2 All-cause mortality in patients with unrepaired and closed ventricular septal defect, respectively, and corresponding matched controls from the general population

	VSD unrepaired				VSD closed			
	Number of death events/ total number of patients (%)	Mortality rate per 10 000 person-years		Hazard ratio (95% CI)	Number of death events/ total number of patients (%)	Mortality rate per 10 000 person-years		Hazard ratio (95% CI)
		Patients	Controls			Patients	Controls	
All patients	516/8271 (6.2)	24.3	11.6	2.7 (2.4–3.0)	62/865 (7.2)	41.4	12.4	3.3 (2.5–4.5)
				2.7 (2.4–3.0)[a]				2.8 (2.1–3.7)[a]
Diagnosis <1990	289/1853 (15.6)	37.4	17.5	3.2 (2.8–3.7)	–	–	–	
Diagnosis ≥1990	227/6418 (3.5)	16.8	7.9	2.4 (2.0–2.7)	–	–	–	
Early diagnosis	206/7008 (2.9)	14.6	2.4	6.1 (5.1–7.2)	–	–	–	
Late diagnosis	310/1263 (24.5)	43.4	29.5	2.0 (1.8–2.2)	–	–	–	
Surgery <1990	–	–	–		37/210 (17.6)	58.4	13.3	4.3 (3.0–6.3)
Surgery ≥1990	–	–	–		25/655 (3.8)	29.0	11.6	2.5 (1.6–3.9)
Early surgery	–	–	–		33/639 (5.2)	32.7	2.9	11.1 (6.8–18.0)
Late surgery	–	–	–		29/226 (12.8)	59.3	32.7	1.8 (1.2–2.7)

Risk of mortality for patients with either an unrepaired or a surgically closed ventricular septal defect compared with their matched controls. Risks are stratified by era of diagnosis or era of surgically closure, age at time of diagnosis, and age at closure of defect. Early and late diagnosis defined as diagnosis before and after the age of 18 years, respectively. Early and late surgery defined as surgery before and after 5 years of age, respectively. CI, confidence interval; VSD, ventricular septal defect.
[a]Adjusted for modified Charlson Comorbidity Index.

Patients with surgically closed VSD displayed survival rates of 94% (95% CI: 92–96), 93% (95% CI: 91–95), 90% (95% CI: 87–93), and 89% (95% CI: 86–92) at 10, 20, 30, and 40 years after surgical closure (*Figure 2B*). Early surgical closure (<5 years of age) was associated with a high HR that was not seen in patients with late closure (≥5 years of age), presented in *Table 2*. Patients with early closure had a perioperative mortality of 4.5% ($n = 29$) while the corresponding figure for those with late closure was 2.5% ($n = 6$). The majority of perioperative deaths ($n = 25$) occurred before 1990. Direct comparison between patients with early vs. late closure revealed increased HR for mortality when the VSD was closed early (HR: 3.2, 95% CI: 2.0–5.0).

Patients with unrepaired VSD alive at 18 years of age displayed HR for mortality of 2.0 (95% CI: 1.8–2.2) compared with the comparison cohort. Correspondingly, patients with surgically closed VSD displayed HR for mortality of 1.5 (95% CI: 1.02–2.2). Graphical illustration is embedded in the Supplementary material online, *Appendix Figure S1*.

The HR for mortality in patients with unrepaired VSD and concomitant ASD was 3.2 (95% CI: 2.4–4.3). Correspondingly, patients with surgically closed VSD and concomitant ASD displayed HR of 3.5 (95% CI: 1.8–6.9).

The survival of patients with unrepaired VSD diagnosed in the modern era was superior to that of the prior era but still lower than that of the general population (*Figure 2C*). Similar era effect was seen for patients with surgical closed VSD (*Figure 2D*).

In order to mimic the contemporary mortality of VSD patients and thus provide a better understanding of the outcome of patients managed in the modern era, we excluded perioperative mortality and patients with Eisenmenger syndrome. The HR for mortality in patients with unrepaired defect with Eisenmenger syndrome excluded was 2.6 (95% CI 2.4–2.9) [HR adjusted for CCI was 2.6 (95% CI: 2.4–2.9)]. The HR for mortality in patients with closed defect with Eisenmenger syndrome and perioperative mortality excluded was 1.7 (95% CI: 1.1–2.5) [HR adjusted for CCI was 1.3 (95% CI: 0.9–2.0)]. In an additional attempt to mimic the contemporary mortality of VSD patients, we only included patients managed after 1990 (Eisenmenger syndrome and perioperative mortality excluded) revealing HR for mortality of 2.4 (95% CI: 2.0–2.7) for patients with unrepaired defect and 1.8 (95% CI: 0.9–3.3) for patients with closed defect. Furthermore, early closure (<5 years of age) in the contemporary era was associated with an HR for mortality of 1.9 (95% CI: 0.7–5.0) while late closure (≥5 years of age) was associated with a HR for mortality of 1.6 (95% CI: 1.1–2.6), see Supplementary material online, *Appendix Figure S2-S4* for graphical illustrations.

Cause of death

Cardiac-related death was the commonest cause of death accounting for approximately a third of the deaths in patients with unrepaired defects and two-thirds of the deaths in surgically corrected patients (*Table 3*). One third of the cardiac-related deaths were of ischaemic origin in both patient groups. Heart failure was the most frequent non-ischaemic cause of death among unrepaired patients while ischaemic heart disease was the most frequent cause among surgically closed patients. In both groups, some causes of deaths were reported as 'VSD'. It is unknown to what extent this covers heart failure, pulmonary arterial hypertension, malignant arrhythmia, and sudden cardiac death.

Discussion

This is the largest, population-based study, with the longest follow-up, of patients with congenital VSD. It includes 9136 patients and

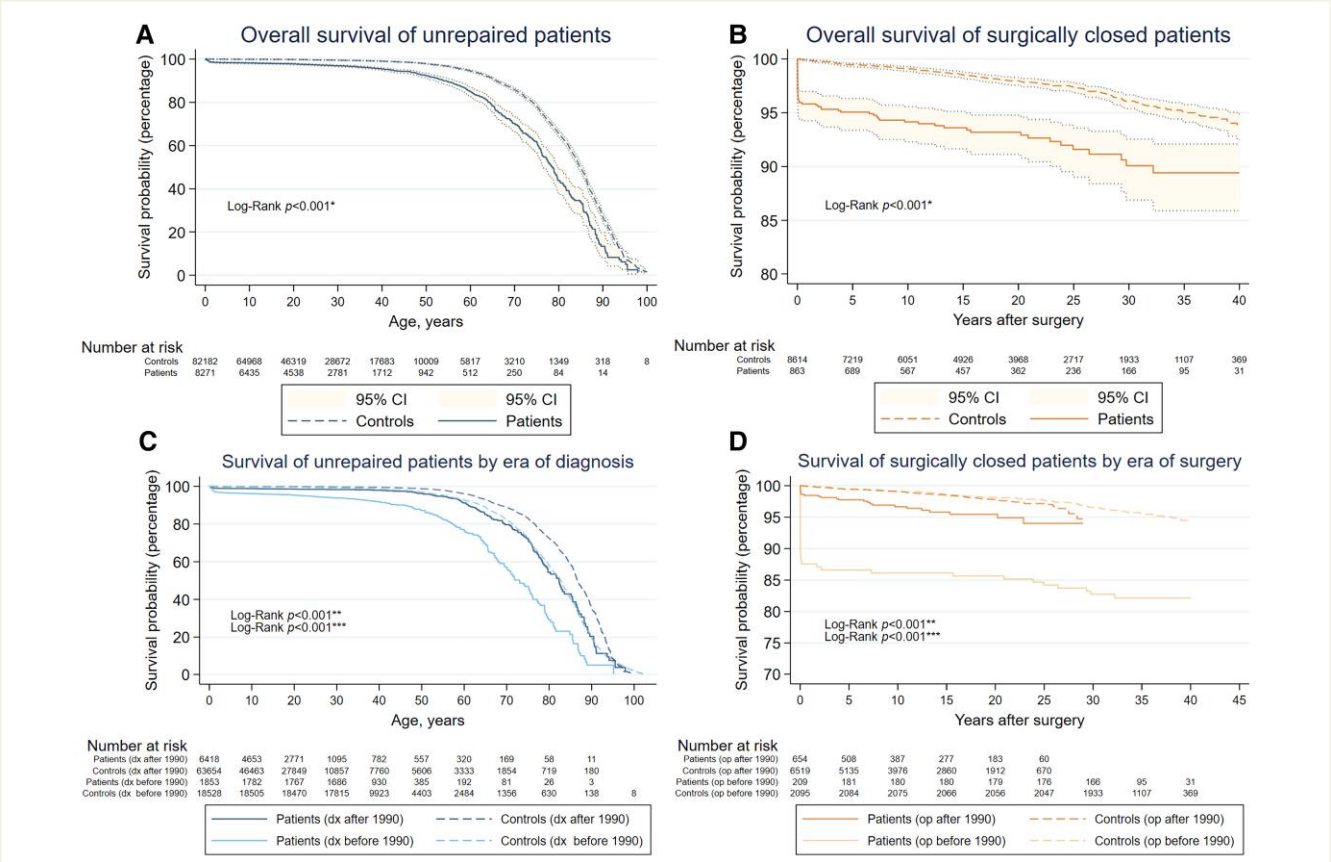


Figure 2 Overall survival of patients with a congenital VSD stratified by treatment. Survival in years from birth of patients with unrepaired VSD compared with controls matched by age and sex (*A*). Survival in years from defect closure of patients with a surgically closed VSD compared with controls matched by age and sex (*B*). Survival in years from birth of patients with unrepaired VSD stratified by era of diagnosis (before or after 1990) compared with controls matched by age and sex (*C*). Survival in years from defect closure of patients with a surgically closed VSD stratified by era of closure (before or after 1990) compared with controls matched by age and sex (*D*). DX, diagnosis; OP, operation; VSD, ventricular septal defect. *Level of significance between patients and controls. **Level of significance between patients and controls managed in past eras (before 1990). ***Level of significance between patients and controls managed in the modern era (after 1990).

importantly includes mortality data for patients with unrepaired VSD. Our findings are novel and provide important information regarding the natural and unnatural history of VSD. First, overall, VSD patients displayed an almost three-fold increased all-cause mortality when compared with the general Danish population (*Structured Graphical Abstract*). Second, the survival of patients with unrepaired defects was significantly lower compared with their corresponding matched controls even with Eisenmenger syndrome excluded. Similarly, survival 40 years after surgical closure of VSD, excluding surgical mortality, was lower compared with matched controls. Third, patients with unrepaired defects and early VSD diagnosis (within the first 18 years of age) had a substantial risk of mortality. Fourth, cardiac-related death was the commonest cause of death in both unrepaired and surgically closed patients, albeit with different underlying cardiovascular causes.

Mortality

The overall survival of VSD patients was clearly lower than that of their peers. When broken down by era, there was evident improvement in survival for patients diagnosed or surgically closed after 1990 compared with before, yet the risk of mortality for those was still almost two-fold the mortality of the general comparison cohort. While the impact of improved pre-, peri-, and postoperative care over time is intuitive in surgically treated patients, the improved survival of unrepaired patients diagnosed after 1990 is less easy to explain. It is possible that patients with smaller VSD are being diagnosed more frequently with the more readily available echocardiography. This is supported by the three-fold increase in diagnoses in the ~30 years since 1990, compared with the 30 years prior. Even so, there was still a significant mortality burden in those with unrepaired defects. This finding is important as there are no data on long-term survival of patients with unrepaired VSD. The pattern of mortality is also intriguing. Inspecting our survival plots, survival for unrepaired VSD patients overlaps with the control population until the 4th decade of life, after which the survival curves diverge. This might explain why others have reported survival rates similar to healthy peers, as in prior studies patients have only been followed into their 30s,[17] 40s,[18] and 50s.[19] That said, in a cohort of patients with isolated VSD (92% unrepaired) diagnosed between 1963 and 1973 and alive at 15 years of age, Videbæk *et al.*[5] reported all-cause mortality almost double that of the general Danish population. Patients that contributed to these data are included in our study and constitute ~6% of our cohort.

Table 3 Causes of death in patients with ventricular septal defect

	VSD unrepaired ($n = 8271$)	VSD closed ($n = 865$)
Total number of deaths	**516 (6.2)**	**62 (7.2)**
Cardiac, total	**153 (30)**	**40 (65)**
Cardiac, non-ischaemic		
Heart failure	26 (17)	4 (10)
Arrhythmia	6 (3.9)	–
Valve pathology	11 (7.2)	1 (2.5)
Cardiomyopathy	6 (3.9)	4 (10)
Endocarditis	4 (2.6)	1 (2.5)
VSD	39 (25)	18 (45)
Cardiac other	15 (9.8)	2 (5.0)
Cardiac, ischaemic		
Ischaemic heart disease	46 (30)	10 (25)
Non-cardiac, total	**348 (67)**	**21 (34)**
Chronic pulmonary disease	12 (3.4)	1 (4.8)
Infection	44 (13)	1 (4.8)
Pneumonia or influenza	26 (7.5)	1 (4.8)
Kidney, liver and gastrointestinal disease	15 (4.3)	2 (9.5)
Neoplasm	61 (18)	5 (24)
Pulmonary embolism	10 (2.9)	–
Stroke	7 (2.0)	2 (9.5)
Vascular or hematological	19 (5.5)	–
Other	154 (44)	9 (43)
Unknown	**15 (2.9)**	**1 (1.6)**

Data are reported as absolute numbers with percentages. 'Cardiac', 'non-cardiac', and 'unknown' causes of death are presented as percentage of total numbers of death. Each specific cause of death within the categories 'cardiac' and 'non-cardiac' are presented as percentage of the total number of deaths within each category. Unknown: Found dead or no specific cause reported.
Other: causes of death not specified in the table.
VSD, ventricular septal defect.

In the current study, early diagnosis, before the age of 18 years, was associated with a higher mortality compared with late diagnosis, which could be explained by the fact that the majority of patients with symptomatic lesions are detected early due to heart failure and failure to thrive, and so by inference are the larger defects. Nonetheless, VSD patients diagnosed beyond the age of 18 years still have a late hazard for mortality that is almost two-fold that of the comparison cohort.

Dissecting the risk of mortality in surgically closed patients, our data show a 30-year survival after surgical VSD closure of 90% which is in line with previously published papers showing 40-year survival rates of 86%,[4] 81%,[8] and 79%,[9] respectively. Raissadati *et al.*[8] demonstrated a 50-year survival of 77% after surgical VSD repair. Our data suggest that VSD patients surgically managed in the modern era present with similar survival and risk of mortality as the general population. However, with limited follow-up only until their 4th decade of life we are unable to conclude that their long-term outcome is unproblematic thereafter since the mortality rate for unrepaired patients increases at around 50–60 years of age. Furthermore, early closure of VSD before the age of 5 years was associated with substantial mortality while those closed late seems to have a mortality risk comparable with the general population. This is not unexpected given that older patients will likely have smaller, hemodynamically less significant defects.

It is difficult to define which VSD patients that have a favourable long-term outcome. Theoretically, the increased mortality might be a result of the development of VSD-related complications. Our data on causes of death are supportive in this regard. In patients with unrepaired outlet and less frequently perimembranous defect, there is a risk of prolapse of the right coronary cusp resulting in progressive aortic regurgitation which ultimately might lead to left ventricular dysfunction and heart failure. Arrhythmias, in patients with surgically closed defect in particular, also constitute a possible problem that may occur with advancing age as well as infective endocarditis, which constitute a significant risk of mortality if reoperation is required. Meticulous follow-up in specialized adult congenital heart disease clinics is necessary to detect and possibly prevent or limit cardiovascular morbidity at an early stage.

Cause of death

Cardiac-related death was the commonest cause of death, accounting for approximately a third of the deaths in patients with unrepaired defects and two-thirds of the deaths in surgically corrected patients, considerably higher than for the general Danish population (15%).[20] One third of the cardiac-related deaths were of ischaemic origin both among patients with unrepaired and surgically closed defect. Heart failure was common in both groups, but the underlying hemodynamic substrate may differ we suspect. Again, our dataset does not allow us to stratify heart failure for its different phenotypes, but it is possible that left-to-right shunts increase with time as left ventricular compliance changes with aging (as for ASD) in those with unrepaired defects, while the effects of prior surgery, e.g. intraoperative myocardial damage, residual interventricular conduction defects and ventricular dyssynchrony, may all take their toll in the long term. In this regard, our data are hypothesis-generating, and no matter the underlying cause, the impact on mortality justifies detailed research investigations targeting these potentially modifiable substrates for heart failure in patients with congenital VSD. What is also clear from our data is that VSDs may be simple to correct, but they do not age with simplicity, and it is perhaps misleading to categorize VSD as a 'simple' congenital heart lesion. Not only may this give patients, their families, and carers a 'false sense of security', but it has implications for the recognition of this lesion as something that requires both diligent longitudinal follow-up and focussed research in the future in order to modify the lifetime risk for these patients.

Limitations

Type and size of defect, Qp/Qs ratio, pulmonary artery pressure, ventricular function, and details of indications for surgery are not included in the national medical registries and are therefore unavoidable deficiencies. Furthermore, prevalence of spontaneous closure of defects is unknown. The cause of death registered in the Danish Register of Causes of Death are only as precise as what the doctor interprets and enters in the death certificate. The cause can be registered as

most likely, when autopsy is not performed, but ailments such as VSD are obviously not a valid cause of death but rather the underlying cause likely to cover heart failure, pulmonary arterial hypertension, sudden cardiac death, or any other VSD-related complication.

The validity of the surgical procedures in the DNPR has not been systematically investigated. However, as the ICD codes for surgical procedures ares always entered by the surgeon after the intervention in combination with standardized and stringent reporting of codes from hospital to the DNPR, we suggest that the validity of the surgical procedures is high, independent of era. Finally, prior to 1990 some patients will have died without a diagnosis and others will be alive undiagnosed, and patients surviving until the introduction of the Danish medical registries in 1977 represent a selected group of survivors, leading to a potential underestimation of mortality. The net effect of these weaknesses might explain part of the improved survival across eras but does not fundamentally undermine our conclusions.

Conclusion

Patients with VSD have increased late mortality compared with that of the general Danish population. Patients with unrepaired and surgically closed defect both demonstrated an almost three-fold higher risk of mortality than their matched peers.

Survival improved for both unrepaired and surgically closed patients in the modern era, but contemporary cohorts still show increased mortality. These novel findings suggest that even though deemed a 'simple' congenital heart defect the diagnosis comes with significant long-term consequences. Thus, the most common of cardiac defects is deserving of a better understanding of the complex factors that can lead to a major increase in lifetime mortality.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

This work was supported by the Novo Nordic Foundation [NNFSA170030576].

Conflict of interest: None declared.

Data availability

The data underlying this article cannot be shared publicly in accordance with the directive from the central authority on Danish Statistics, Statistics Denmark.

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