Systematic Review/Meta-analysis

The Ross Procedure in Children and Infants: A Systematic Review With Pooled Analyses

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ABSTRACT

Background: The Ross procedure is a surgical option for congenital aortic stenosis that involves replacing the diseased aortic valve with a pulmonary autograft. Little is known about outcomes in children, particularly those younger than 1 year.
Methods: A systematic review with pooled analyses was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Inferred individual patient data were extracted from life tables. The primary end points were early ($\leq$30 days) and late (>30 days) mortality rates following the Ross procedure

RÉSUMÉ

Contexte : L'intervention de Ross est une option chirurgicale visant à corriger une sténose aortique congénitale. Elle consiste à remplacer une valve aortique pathologique en utilisant la propre valve pulmonaire du patient (autogreffe pulmonaire). Les résultats de cette intervention ont été peu étudiés chez les enfants, en particulier chez les enfants de moins d'un an.
Méthodologie : Une revue systématique avec analyses des données groupées a été menée en respectant les critères PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*). Les

The Ross procedure, also known as the pulmonary autograft procedure, is the only surgical option for congenital aortic stenosis in children that allows the diseased aortic valve to be replaced by a living valve substitute.[1] A pulmonary autograft provides numerous advantages: potential for growth in children, avoidance of anticoagulation therapy, and near-optimal haemodynamics.[2] These qualities distinguish it from other available options for aortic valve replacement by prosthetic substitutes, be they biological or mechanical. However, a major risk is transforming univalve into bivalve disease. Furthermore, the impact of reinterventions on the initially healthy right ventricular outflow tract (RVOT) is not to be neglected.[1] There is a paucity of large-scale data on paediatric outcomes following the Ross procedure, particularly among infants. Prior systematic reviews provided important insights[3,4] but were limited by analyses that relied on pooled person-time approaches, which carry the potential to overestimate risks with shorter follow-up durations. Moreover, no prior systematic review has specifically addressed outcomes in

patients younger than 1 year. We conducted a systematic review using extracted individual patient data, time-to-event analyses, and metaregression to study early- and long-term mortality associated with the Ross procedure, along with freedom from surgical reintervention. We specifically addressed age at surgery in metaregression analyses and conducted subgroup analyses in infants.

Materials and Methods

Search strategy

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5] An experienced librarian performed electronic searches of the PubMed, Embase, and MEDLINE databases for eligible studies published between January 2000 and May 2022 in humans. The search strategy, which is provided in Supplemental Appendix S1, encompassed all languages. Search terms included aortic valve replacement, autograft, Ross procedure, Ross operation, and children. All titles and abstracts of identified studies were screened by 2 independent investigators, who then reviewed full-text publications for potentially eligible studies. In case of disagreement, a consensus was negotiated. Secondary sources of data were sought by searching Google Scholar and by cross-

in children. Secondary end points were freedom from reintervention for the right ventricular outflow tract and pulmonary autograft. These end points were assessed in the overall population of children. Sensitivity analyses were performed in subgroups younger than 1 year of age (infants) and in noninfant children.

Results: A total of 25 studies on 2737 patients met inclusion criteria. The pooled early survival rate was 96.0% (95% confidence interval [CI]: 95.1%-96.8%) overall and 86.8% (95% CI: 82.1%-90.3%) among infants. Pooled overall 10-year survival, freedom from pulmonary autograft reintervention, and freedom from right ventricular outflow tract reintervention rates were 91.1%, 90.2%, and 79.7%, respectively. Corresponding pooled rates in infants were 79.3%, 87.1%, and 51.2%. Mortality was significantly higher among infants compared with noninfant children (hazard ratio: 3.38, 95% CI: 2.44-4.68; $P < 0.001$). In metaregression analyses, younger age was strongly associated with poorer survival and higher reintervention rates.

Conclusions: Modest survival and autograft reoperation rates were observed following the Ross procedure in children. Surgery in infancy was strongly associated with poorer survival and higher reintervention rates.

données dérivées de patients individuels ont été tirées de tables de survie. Les principaux critères d'évaluation étaient les taux de mortalité précoce ($\leq$ 30 jours) et tardive ($>$ 30 jours) à la suite de l'intervention de Ross réalisée chez des enfants. Les critères d'évaluation secondaires étaient l'absence de nouvelle intervention pour la chambre de chasse du ventricule droit et pour l'autogreffe pulmonaire. Ces paramètres ont été évalués pour l'ensemble de la population pédiatrique. Des analyses de sensibilité ont été réalisées dans des sous-groupes de patients âgés de moins d'un an (nourrissons) et d'enfants plus âgés.

Résultats : Au total, 25 études portant sur 2 737 patients répondaient aux critères d'inclusion. Les taux de survie précoce étaient de 96,0 % (intervalle de confiance [IC] à 95 %; 95,1 à 96,8 %) dans l'ensemble des patients et de 86,8 % (IC à 95 %; 82,1 à 90,3 %) chez les nourrissons. Le taux de survie globale à 10 ans, d'absence de nouvelle intervention pour l'autogreffe pulmonaire et d'absence de nouvelle intervention pour la chambre de chasse du ventricule droit étaient respectivement de 91,1 %, de 90,2 % et de 79,7 % (données groupées). Les taux correspondant pour le sous-groupe composé de nourrissons étaient de 79,3 %, de 87,1 % et de 51,2 % (données groupées). La mortalité était significativement plus élevée chez les nourrissons comparativement aux enfants plus âgés (rapport des risques instantanés : 3,38, IC à 95 % : 2,44 à 4,68; $p < 0,001$). Dans les analyses de métarégression, le jeune âge était fortement corrélé à un taux de survie plus bas et à des taux plus élevés de nouvelles interventions.

Conclusions : Des taux modestes de survie et de réopération d'autogreffe ont été observés après la procédure de Ross chez les enfants. La chirgurgie pendant la petite enfance était fortement associée à une survie plus faible et à des taux de réintervention plus élevés.

checking references from articles of interest. In the event of multiple publications with overlapping study populations, the most recent report was retained.

Inclusion criteria and quality assessment

All studies evaluating outcomes (ie, survival, RVOT, and pulmonary autograft reinterventions) of the Ross procedure in children (<18 years) were included. Studies were required to (1) have extractable data from Kaplan-Meier (KM) curves, including time points at which events or censoring occurred, survival probabilities, and the number at risk at various time points; (2) be conducted exclusively in children; and (3) have no more than a low or moderate risk of bias as assessed by the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS I) tool. The ROBINS I tool was specifically developed to assess risk of bias in nonrandomized studies.[6] Case reports, small case series (<20 patients), review articles, and letters to the editor were excluded. Studies pertaining only to the Ross-Konno procedure were likewise excluded. Among included studies that contained an amalgam of patients with both Ross and Ross-Konno procedures, the subgroup with Ross-Konno procedures was excluded whenever the data permitted. The study was registered on PROSPERO (CRD42022320085). As a protocol deviation, ROBINS I was employed to assess risk of bias instead of the Newcastle-Ottawa Scale in order to align the study with recommendations from the Cochrane Collaboration (https://methods.cochrane.org/robins-i).

Patient consent was not required for this retrospective meta-analysis on deidentified data.

End points

The primary end points were early ($\leq$30 days) and late (>30 days) mortality rates following the Ross procedure in children. Secondary end points were freedom from reintervention for the RVOT and pulmonary autograft. These end points were assessed in the overall population of children. Sensitivity analyses were performed in subgroups of patients younger than 1 year (infants) and in noninfant children.

Data extraction and statistical analysis

Data extraction from each available KM curve was performed using the methodology described by Guyot et al.[7] In the same manner, censored information was extrapolated from censoring marks on the KM graphs. Each KM curve was digitized using digitalization software (Digitizelt, Braunschweig, Germany). A KM data reconstruction algorithm developed in R software (version number 2.15.1; R Foundation for Statistical Computing, Vienna, Austria) was used to derive individual patient data. Derived KM curves were graphically verified against the original ones, and only those with accuracies $\geq$98% were accepted. Once validated, the KM data from the various studies were stored together in the study database.

A time-to-event approach was then used to assess overall survival, freedom from first surgical or percutaneous RVOT reintervention, and freedom from autograft reintervention.

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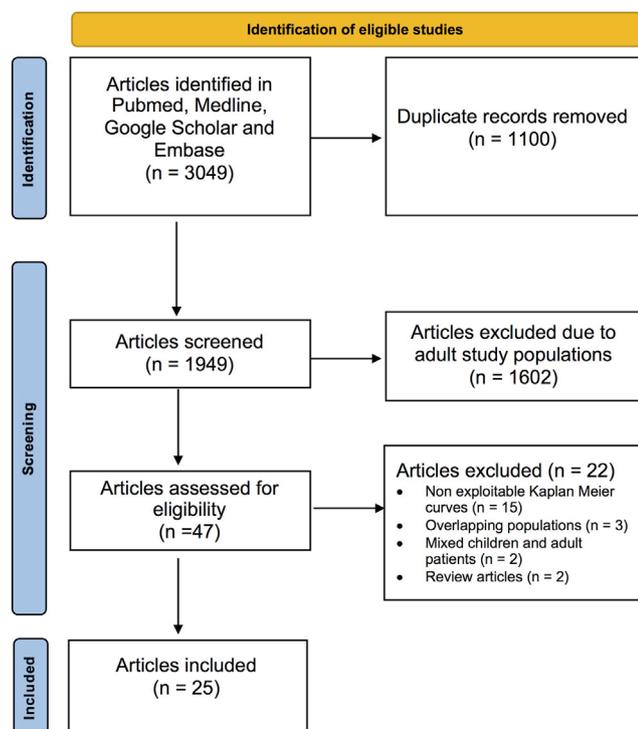
Figure 1. Flow chart of the literature search.

Log-rank tests were applied for group comparisons. Proportionality assumptions for hazard ratios (HR) were assessed by introducing the interaction term log(time*group) in the model. Study outcomes were then derived for each study at each time point. Heterogeneity was examined using Cochran's Q test as well as the I^2 statistic, and random effect models were used to assess the combined outcomes using at-risk numbers as weights. Sensitivity analyses for primary and secondary end points were performed by excluding the 2 studies that included more than 1 patient (ie, 5 and 11 patients) with infective endocarditis. Metaregression analyses were used to investigate potential determinants of study outcomes (log-transformed). All tests were 2-sided, and the threshold for significance was set at 0.05. No adjustment for multiple comparisons was made. Analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC).

Results

Literature search

A flowchart for study inclusion is shown in Figure 1. A total of 3049 potential studies were identified for screening. A first-level screening of titles and abstracts yielded 47 articles for full-text review. Among these, 2 review articles were excluded, 15 had no extractable KM curves, 2 reported a mixed population of adults and children, and 3 had overlapping study populations. One study[8] had an overlapping population with a more recent study[9] on RVOT and pulmonary autograft reintervention outcomes but not on survival and was, therefore, included in the assessment of the latter outcome. Overall, 25 observational studies with a total of 2737 patients were included.[9-28] By design, all included

studies had a ROBINS I score in the low or moderate risk of bias category (Supplemental Table S1).

Study characteristics

Characteristics of included studies are summarized in Table 1. All studies were retrospective, and most were from single centres. The median study size was 80 (interquartile range: 44-124) patients, with a median follow-up time of 7.0 (interquartile range: 5.2-10.1) years. The studies included a preponderance of boys (median: 71%). Main indications for the Ross procedure were mixed congenital aortic valve disease (median: 46%), congenital aortic stenosis (median: 30%), and congenital aortic insufficiency (median: 20%). Infective endocarditis was a rare indication mentioned in 4 studies, 2 of which included 1 patient each. In the majority of cases, the aortic valve was bicuspid (median: 61%).

Overall outcomes

A total of 2210 children from 22 studies were included in analyses of early and late mortality after the Ross procedure. The overall pooled early survival rate was 95.8% (95% confidence interval [CI]: 94.9%-96.6%). Pooled survival rates at 5, 10, and 15 years were 93.2% (95% CI: 92.1%-94.2%), 91.1% (95% CI: 89.7%-92.3%), and 90.1% (95% CI: 88.5%-91.5%), respectively.

A total of 2083 children from 19 studies were included in the analysis of pulmonary autograft reintervention. Freedom from autograft reintervention 5, 10, and 15 years after the Ross procedure was 96.0% (95% CI: 94.9%-96.8%), 90.2% (95% CI: 88.5%-91.8%), and 79.0% (95% CI: 75.9%-81.8%), respectively. A total of 1868 children from 18 studies were included in the analysis of RVOT reinterventions. Freedom from RVOT reintervention at 5, 10, and 15 years was 92.1% (95% CI: 90.6%-93.3%), 79.7% (95% CI: 77.2%-81.9%), and 63.5% (95% CI: 59.9%-66.9%), respectively. Rates for all primary and secondary end points remained similar in sensitivity analyses that excluded studies having more than 1 patient with infective endocarditis (Supplemental Table S2). Heterogeneity between studies for 5-year survival ($P < 0.001$; $I^2 = 62\%$), freedom from pulmonary autograft reintervention ($P < 0.001$; $I^2 = 59\%$), and freedom from RVOT reintervention ($P < 0.001$; $I^2 = 66\%$) was moderate to substantial.

Metaregression

Factors potentially associated with survival, autograft reintervention, and RVOT reintervention that were assessed in metaregression analyses are listed in Table 2. Strong associations between younger age at surgery and higher mortality ($P < 0.001$) and RVOT reintervention ($P = 0.002$) were observed, with no association between age at surgery and pulmonary autograft reintervention rate (Fig. 2). Boy vs girl, aortic stenosis, aortic insufficiency, mixed aortic valve disease, bicuspid aortic valve, and median year of the study period were not statistically significantly associated with mortality, pulmonary autograft, or RVOT reintervention.

Early and late survival according to subgroups (Fig. 3A)

A total of 1945 patients were included in subgroup analyses of children over 1 year of age (ie, noninfant children).
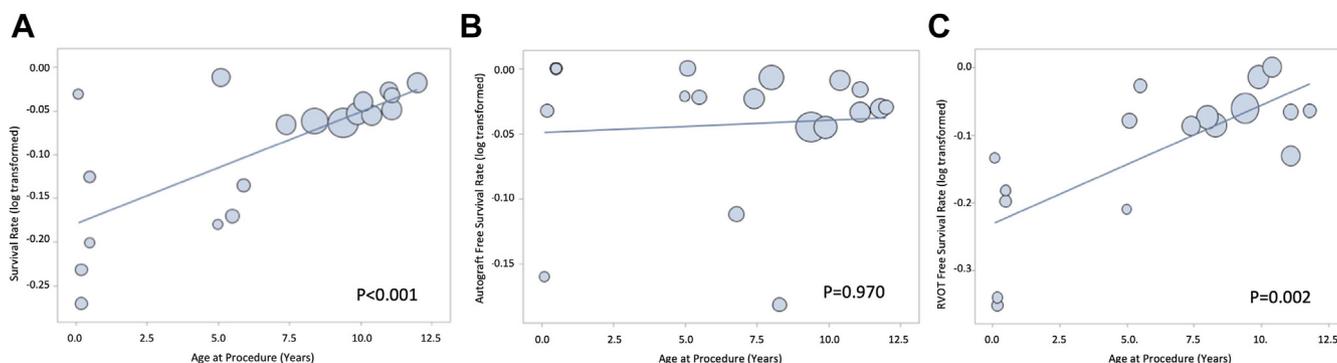
Figure 2. Age-dependent metaregression model on (**A**) 5-year survival, (**B**) 5-year autograft reintervention, and (**C**) 5-year right ventricular outflow tract (RVOT) reintervention.

The pooled early survival rate was 96.0% (95% CI: 95.1%-96.8%). Survival rates at 5, 10, and 15 years were 94.8% (95% CI: 93.7%-95.6%), 91.3% (95% CI: 89.9%-92.5%), and 90.2% (95% CI: 88.7%-91.6%), respectively. Among the 265 patients included in the predefined subgroup of infants, the pooled early survival rate was 86.8% (95% CI: 82.1%-90.3%). Pooled infant survival rates at 5 and 10 years were 81.0% (95% CI: 75.7%-85.3%) and 79.3% (95% CI: 73.4%-84.0%), respectively. Mortality was significantly higher among infants compared with noninfant children (HR: 3.38, 95% CI: 2.44-4.68; $P < 0.001$).

Reinterventions according to subgroups (Fig. 3)

Freedom from autograft reintervention in noninfant children at 5, 10, and 15 years of follow-up after the Ross procedure was 96.0% (95% CI: 94.9%-96.9%), 90.3% (95% CI: 88.5%-91.9%), and 78.5% (95% CI: 75.3%-81.4%), respectively. The corresponding 5- and 10-year freedom from pulmonary autograft reintervention rates among infants were 95.0% (95% CI: 88.2%-97.9%) and 87.1% (95% CI: 76.7%-93.0%), respectively. Differences among the 2 age categories were not statistically significant (HR: 0.80, 95% CI: 0.42-1.50; $P = 0.481$).

Freedom from RVOT reintervention in noninfant children at 5, 10, and 15 years of follow-up after the Ross procedure was 94.2% (95% CI: 92.8%-95.3%), 82.4% (95% CI: 79.9%-84.6%), and 66.8% (95% CI: 63.0%-70.3%), respectively. The corresponding pooled 5- and 10-year freedom from RVOT reintervention rates in infants were 73.4% (95% CI: 65.5%-79.7%) and 51.2% (95% CI: 41.0%-60.6%), respectively. The rate of RVOT reintervention was significantly higher among infants (HR: 3.82, 95% CI: 2.94-4.96; $P < 0.001$).

Discussion

The Ross procedure is a recognized option for the treatment of congenital aortic stenosis that incorporates a pulmonary autograft.[10] A randomized trial in adults reported a highly significant survival benefit associated with the Ross procedure when compared with an aortic homograft.[11] However, the surgical technique is complex and associated with a long learning curve that has been estimated to be between 75 and 100 cases.[12] This factor, along with valid concerns about transforming univalve into bivalve disease, likely contributes to the low rate of adoption of this procedure.[10] This systematic review specifically focused on children undergoing the Ross procedure for whom outcomes are less well established. The main findings include the following: (1) early mortality in children was <5%; (2) the 15-year survival rate was 90%; (3) reintervention rates were substantial with, for example, over one-third of children requiring RVOT reintervention by 15 years of follow-up; and (4) outcomes were significantly worse for children who had the Ross procedure as infants, particularly with regard to overall survival and RVOT reintervention.

Unlike prior systematic reviews that pooled mortality and reinterventions without accounting for differences in follow-up duration,[4,13] the present analysis incorporated time-to-event methodology. Not accounting for differences in follow-up when calculating rates can produce inaccurate estimates in the context of marked heterogeneity in follow-up durations. Assuming that risks are constant over time carries the potential to overestimate mortality rates, especially when follow-up is brief. Moreover, time-to-event methodology provides more accurate estimates of freedom from reintervention rates. In addition, the method of extracting individual patient data allows for long-term assessments that were not possible with the methodology used in prior systematic reviews. Plotting survival curves confirmed a 2-tiered risk function for overall survival with higher perioperative mortality followed by gradual attrition beyond a few months, which was most striking in infants. In contrast, the RVOT reintervention rate was reasonably constant over time.

Some studies included in 2 prior meta-analyses had no extractable survival curves and were, therefore, excluded from the current analysis. Although this criterion carries the potential to introduce selection bias, the results were nevertheless consistent with Moroi et al's analysis.[4] Our methodology further allowed heterogeneity to be assessed between studies and metaregression to explore associations between study characteristics and outcomes. As all studies included patients operated on before the year 2000, conclusions should be extrapolated with caution to more recent cohorts.

Overall, early and late mortality rates in children after the Ross procedure seemed reasonable. However, infants experienced significantly higher mortality rates. Smaller prior studies reported 30.7%[14] and 23.3%[15] hospital mortality rates after the Ross procedure in infants. Young age (<1 year) has

Table 1. Baseline study characteristics

First author	Year of publication	Number of patients	Infants, n (%)	Study period	Study location	Boys, n (%)	AS, n (%)	AI, n (%)	ML, n (%)	IE, n (%)	BAV, n (%)	Median age (y)	Mean follow-up (y)
Bansal	2015	85	0 (0)	1992-2012	Los Angeles, USA	53 (62)	25 (29)	21 (25)	39 (46)	0 (0)	—	5.1	5.0
Binsalamah	2020	98	NA	1995-2018	Houston, USA	69 (70)	16 (16)	18 (18)	64 (65)	5 (5)	53 (54)	6.8	3.8
Bové*	2021	110	11 (10)	1991-2019	Brussels, Ghent, Belgium	82 (75)	50 (45)	16 (15)	44 (40)	0 (0)	—	10.4	10.1
Brancaccio	2014	55	13 (24)	1993-2012	Roma, Italy	39 (71)	14 (25)	8 (15)	31 (56)	0 (0)	15 (27)	5.9	5.5
Brown et al	2016	115	NA	1993-2015	Indianapolis, USA	—	15 (13)	16 (14)	84 (73)	0 (0)	85 (74)	11.0	7.8
Charitos et al	2012	263	NA	1988-2011	Luebeck, Germany	187 (71)	49 (19)	46 (17)	154 (59)	0 (0)	149 (56)	8.0	6.9
Cleveland (<1 y)	2022	58	58 (100)	1993-2020	Los Angeles, USA	37 (64)	26 (45)	15 (26)	17 (29)	0 (0)	—	0.2	6.7
Donald et al	2020	110	0 (0)	1995-2018	Melbourne, Australia	93 (66)	39 (28)	27 (20)	63 (45)	11 (8)	66 (47)	7.4	8.9
Donald et al (<1 y)	2020	30	30 (100)	1995-2018	Melbourne, Australia	—	—	—	—	—	—		
Elder*	2013	34	28 (82)	1991-2010	New York, USA/Monaco	26 (77)	12 (35)	4 (12)	18 53)	0 (0)	—	0.5	10.6
Elkins	2001	178	11 (6)	1986-2001	Oklahoma City, USA	128 (72)	38 (21)	37 (21)	102 (57)	1 (0.6)	157 (88)	9.9	5.2
Fernandez	2021	32	NA	1997-2017	Cordoba, Spain	21 (66)	—	—	—	—	—	11.8	15.0
Frigiola	2010	95	NA	1994-2008	Milan, Italy	79 (83)	17 (18)	22 (23)	56 (59)	0 (0)	50 (56)	12.0	7.0
Horer	2010	152	NA	1988-2006	Munich, Germany	109 (72)	31 (20)	36 (24)	85 (56)	0 (0)	97 (64)	10.1	6.1
Kadner	2008	52	15 (29)	1993-2004	Paris, France	34 (65)	31 (60)	—	—	—	27 (52)	5.0	3.6
Kallio et al	2015	51	13 (26)	1994-2009	Helsinki, Finland	31 (61)	33 (65)	9 (20)	9 (18)	0 (0)	34 (67)	5.5	4.8
Lo Rito (<1 y)	2014	22	22 (100)	1991-2011	Birmingham, UK	15 (68)	13 (59)	7 (32)	2 (9)	0 (0)	14 (64)	0.5	10.8
Luciani et al	2014	305	37 (12)	1990-2012	Verona, Italy	185 (61)	109 (36)	103 (34)	93 30)	0 (0)	171 (56)	9.4	8.7
Luxford (<1 y)	2022	35	35 (100)	1995-2018	Sydney, Australia	28 (80)	33 (94)	1 (3)	0 (0)	1 (3)	25 (71)	0.1	4.1
Martin	2019	63	8 (13)	1990-2018	Quebec, Canada	51 (81)	29 (46)	19 (30)	15 (24)	0 (0)	41 (65)	11.1	20.5
Mookhoek (<1 y)*	2015	76	76 (100)	1990-2013	The Netherlands/Germany	60 (79)	50 (66)	12 (16)	14 (18)	0 (0)	44 (58)	0.2	3.6
Nakayama	2021	44	NA	1993-2019	Tokyo, Japan	33 (75)	14 (32)	13 (30)	17 (68)	0 (0)	24 (55)	8.3	14.9
Nelson (<1 y)	2015	44	44 (100)	1991-2013	Ann Arbor, USA	29 (66)	21 (48)	3 (7)	20 (45)	0 (0)	29 (66)	—	9.8
Nelson	2015	196	0 (0)	1991-2013	Ann Arbor, USA	140 (71)	39 (20)	40 (20)	117 (60)	0 (0)	145 (74)	—	—
Schlein	2021	124	13 (11)	1991-2020	Vienna, Austria	88 (71)	17 (14)	44 (35)	63 (51)	0 (0)	79 (64)	11.1	12.1
Sievers	2010	200	NA	1988-2008	Luebeck, Germany	141 (71)	45 (23)	57 (29)	90 (45)	0 (0)	114 (57)	8.4	—
Vricella	2021	69	NA	1996-2018	Chicago, USA	—	8 (12)	12 (17)	49 (71)	0 (0)	—	12.0	9.4

AI, aortic insufficiency; AS, aortic stenosis; BAV, bicuspid aortic valve; IE, infective endocarditis; ML, mixed lesion; NA, not available.

* The 3 multicentre studies included patients from 2, 2, and 6 centres, respectively.

Table 2. Metaregression analyses exploring factors potentially associated with survival and reintervention for the pulmonary autograft or right ventricular outflow tract (RVOT) in the first 5 years of follow-up

Variables	Number of studies	Number of patients	Median (Q1-Q3)	R^2	P value
5-year overall survival (log-transformed)					
Age at surgery (y)	19	1279	7.4 (0.5-10.4)	0.481	<0.001
Boys (%)	19	1387	71 (65-77)	0.014	0.64
Aortic stenosis (%)	20	1453	36 (22-54)	0.209	0.84
Aortic insufficiency (%)	20	1453	21 (15-28)	0.002	0.043
Mixed lesion (%)	19	1438	45 (24-56)	0.229	0.039
Bicuspid aortic valve (%)	16	1250	64 (56-67)	0.062	0.35
Follow-up time (y)	19	1299	7.0 (5.2-10.1)	0.068	0.32
Median year of enrolment	20	1453	2000 (1997-2002)	0.007	0.74
5-year freedom from RVOT reintervention (log-transformed)					
Age at surgery (y)	17	1037	7.4 (0.5-9.9)	0.474	0.002
Boys (%)	18	1160	70 (65-75)	0.002	0.86
Aortic stenosis (%)	17	1130	45 (29-59)	0.038	0.98
Aortic insufficiency (%)	17	1130	20 (15-30)	0.001	0.46
Mixed lesion (%)	16	1119	43 (21-52)	0.026	0.54
Bicuspid aortic valve (%)	13	963	64 (56-66)	0.137	0.21
Follow-up time (y)	18	1160	8.8 (5.0-10.8)	0.001	0.96
Median year of enrolment	18	1160	2001 (1997-2003)	0.019	0.59
5-year freedom from autograft reintervention (log-transformed)					
Age at surgery (y)	18	1080	7.7 (5.0-10.4)	0.001	0.97
Boys (%)	18	1161	69 (65-75)	0.001	0.98
Aortic stenosis (%)	18	1121	36 (21-48)	0.039	0.50
Aortic insufficiency (%)	18	1121	20 (15-30)	0.028	0.43
Mixed lesion (%)	17	1110	45 (29-57)	0.021	0.58
Bicuspid aortic valve (%)	13	911	64 (55-66)	0.007	0.79
Follow-up time (y)	19	1196	8.9 (5.0-10.8)	0.001	0.88
Median year of enrolment	19	1196	2001 (1999-2004)	0.010	0.69

previously been proposed as a risk factor for mortality.[16,17] Consistently, a recent study in neonates (<30 days of age) reported high levels of early (24%) and late (43%) mortality after the Ross procedure.[3] Although outcomes have improved over time,[18] several studies including an analysis using the Society for Thoracic Surgeons Congenital Heart Disease Database[18] and a recent meta-analysis[19] in children reported significant associations between low-volume centres (defined as <4 cases/y in the Society for Thoracic Surgeons study) and higher mortality, particularly among neonates.[16,17]

A few prior studies that did not specifically target children compared early and late mortality associated with the Ross technique when compared with mechanical or biological aortic valve replacement. Alsoufi et al[20] reported superior early (P < 0.001) and late (P = 0.009) survival with the Ross procedure when compared with mechanical valves. A similar conclusion was reached by Brown et al[21] when the comparator group had mechanical valves or aortic allografts (P = 0.017). Similarly, a large study from the UK national database confirmed better survival with the Ross procedure compared with mechanical and biological aortic valves.[22] In this article and others, survival after the Ross procedure approximated that of the general population.[22,23] Others have reported that the Ross procedure had no impact on restricting activities of daily living or on quality of life.[9,24]

In our meta-analysis, freedom from autograft reintervention was satisfactory (eg, approximately 90% at 10 years), which likely reflects the growth qualities of the autograft.[25] A higher autograft reintervention point prevalence rate of 19.2% was reported in a recent meta-analysis that included studies of the Ross-Konno procedure and had a follow-up that ranged from 5 days to 23 years.[19] Results have been inconsistent across studies as to whether the Ross procedure is associated with fewer or

more reinterventions than other options for aortic valve replacement.[22,26] Reintervention rates did not favour the Ross procedure in Alsoufi et al's study.[20] This was thought to be driven by the inclusion of patients with rheumatic fever, which is associated with a particularly high rate of pulmonary autograft reintervention.[27] On the whole, the notion that the Ross procedure should be avoided owing to an excess of reinterventions when compared with mechanical aortic valves has largely been refuted. Mechanical valves are also associated with the additional morbidity that results from anticoagulation.

Reasons underlying the higher rate of pulmonary autograft reintervention in infants remain uncertain. One hypothesis implicates the immunoinflammatory response of an immature aortic annulus to a bulky pulmonary valve graft.[28] The histologic constitution of the pulmonary valve with its lower content of elastic tissue[29] may also contribute to progressive dilation when subjected to the higher systemic pressures.[30] For this reason, Yacoub et al[10] recommended strict blood pressure control in the first 6 postoperative weeks to facilitate valve adaptation to its new environment. Newer implantation techniques such as including the valve in a prosthetic tube appear to have improved durability.[9]

The "Achilles' heel" of the Ross procedure remains the high rate of reintervention on the initially healthy RVOT. A significantly higher rate of RVOT reintervention was observed in infants for speculative reasons. The highly developed immune system in infants could potentially lead to pulmonary homograft dysfunction.[31] The lack of growth potential of the substitute used for RVOT reconstruction may also play a role. This has prompted some authors to advocate oversizing the homograft when possible to delay reintervention.[28] Except in North American countries, pulmonary homografts are difficult to obtain, especially for small sizes, due to a lack of

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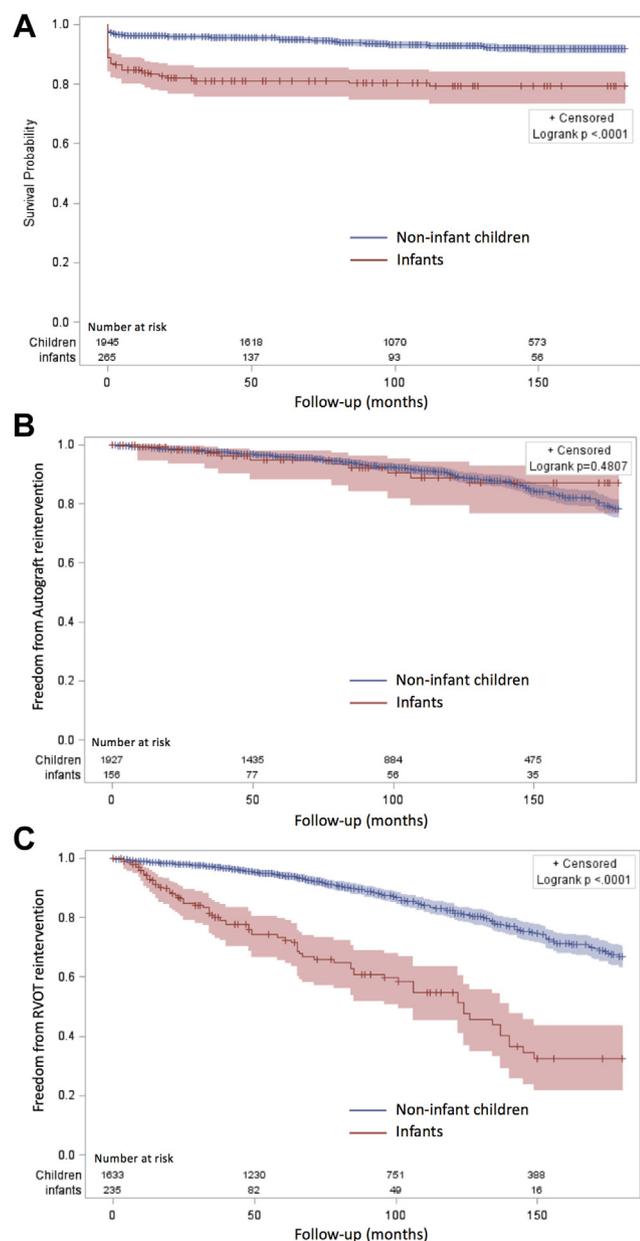
Figure 3. (**A**) Kaplan-Meier survival curves for children (>1 year) and for the subgroup of infants (<1 year) after a Ross procedure. (**B**) Freedom from pulmonary autograft reintervention after the Ross procedure in children and in the subgroup of infants. (**C**) Freedom from right ventricular outflow tract (RVOT) reintervention after the Ross procedure in all children and in the subgroup of infants.

donors, forcing centres to use xenografts instead. Our findings are consistent with a study by Sharabiani et al[22] that identified age <1 year as a significant risk factor for RVOT reintervention. The advent of the transcatheter pulmonary valve has added an important tool to the therapeutic arsenal,[32] providing further rationale to delay the initial Ross procedure when feasible. This delay could help overcome anatomic size-related limiting factors.

It should be acknowledged that children who undergo the Ross procedure as infants may have a multitude of different factors that prompt earlier intervention and drive poorer outcomes. Meta-regression analyses based on aggregate patient data have limitations in singling out these features. Our analyses showed a strong association between age at surgery and mortality and RVOT reintervention. For younger children (eg, <5 years), decisions on when to intervene should be made on a case-by-case basis. An approach that attempts to delay the Ross procedure to allow for growth would require a rigorous assessment of safety and efficacy prior to adoption.[29]

Limitations

In the absence of randomized trials, this meta-analysis was based on observational studies with their inherent limitations. Only studies with a ROBINS I low or moderate risk of bias and exploitable KM curves were included. Most studies that were excluded for nonevaluable KM curves were small such that the resulting selection bias is unlikely to be substantial. Meta-regression analyses were limited to univariable associations owing to the limited statistical power. Thresholds for significance were set at 0.05 and not adjusted to account for multiple comparisons, as customary for exploratory analyses. Other potential sources of bias that could impact individual studies include immortal time bias (ie, lower likelihood of including patients who died subsequent to the Ross procedure) and patient channelling bias (due to performing the Ross procedure in patients with varying baseline prognoses). The index date was defined as the date of the procedure. The meta-analysis captures procedures largely performed in the early 2000s and does not reflect the substantial improvements in techniques and perioperative care that have since occurred. Outcomes may also differ among patients with the Ross procedure performed at different stages of disease progression. Adjustments for potential confounders are limited by the lack of individual patient data on covariates. Finally, the median follow-up was 7 years such that longer-term outcomes were not assessed. Large multicentre studies based on detailed individual patient data, such as the creation of an international paediatric Ross registry, could help overcome many of these limitations.

Conclusions

In this systematic review with individual data pooling and metaregression of Ross procedures performed in children, modest mortality and autograft reoperation rates were observed. However, a greater than 3-fold higher risk of mortality was noted in infants. Over one-third of the overall cohort and half of the infants required reoperation for RVOT dysfunction at 10 years, highlighting the importance of this complication. Further studies are required to determine if an approach of delaying the Ross intervention beyond infancy when deemed safe and feasible translates into improved outcomes.

Ethics Statement

The research reported in this meta-analysis conforms to the ethical guidelines outlined in the Declaration of Helsinki.

Patient Consent

The authors confirm that patient consent does not apply to this article. The meta-analysis is based on published de-identified aggregate data.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Ross DN. Replacement of aortic and mitral valves with a pulmonary autograft. *Lancet*. 1967;2:956–958.

2. El-Hamamsy I, Poirier NC. What is the role of the Ross procedure in today's armamentarium? *Can J Cardiol*. 2013;29:1569–1576.

3. Rajab TK, Zorrilla-Vaca A, Kavarana MN, Mokashi S, Sainathan S. Ross operation in neonates: a meta-analysis. *Ann Thorac Surg*. 2022;113:192–198.

4. Moroi MK, Bacha EA, Kalfa DM. The Ross procedure in children: a systematic review. *Ann Cardiothorac Surg*. 2021;10:420–432.

5. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;160:1–36.

6. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:4–10.

7. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012;12:9.

8. Sievers HH, Stierle U, Charitos EI, et al. Major adverse cardiac and cerebrovascular events after the Ross procedure: a report from the German-Dutch Ross registry. *Circulation*. 2010;122(suppl 1):S216–S223.

9. Charitos EI, Takkenberg JJM, Hanke T, et al. Reoperations on the pulmonary autograft and pulmonary homograft after the Ross procedure: an update on the German Dutch Ross Registry. *J Thorac Cardiovasc Surg*. 2012;144:813–823.

10. Yacoub MH, El-Hamamsy I, Sievers HH, et al. Under-use of the Ross operation—a lost opportunity. *Lancet*. 2014;384:559–560.

11. El-Hamamsy I, Eryigit Z, Stevens LM, et al. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. *Lancet*. 2010;376:524–531.

12. Bouhout I, Ghoneim A, Poirier N, et al. Impact of the learning curve on early outcomes following the Ross procedure. *Can J Cardiol*. 2017;33:493–500.

13. Takkenberg JJM, Klieverik LMA, Schoof PH, et al. The Ross procedure: a systematic review and meta-analysis. *Circulation*. 2009;119:222–228.

14. Kallio M, Pihkala J, Sairanen H, Mattila I. Long-term results of the Ross procedure in a population-based follow-up. *Eur J Cardiothorac Surg*. 2015;47:e164–e170.

15. Donald JS, Wallace FRO, Naimo PS, et al. Ross operation in children: 23-year experience from a single institution. *Ann Thorac Surg*. 2020;109:1251–1259.

16. Tan Tanny SP, Yong MS, d'Udekem Y, et al. Ross procedure in children: 17-year experience at a single institution. *J Am Heart Assoc*. 2013;2:1–9.

17. Luciani GB, Lucchese G, Carotti A, et al. Two decades of experience with the Ross operation in neonates, infants and children from the Italian Paediatric Ross Registry. *Heart*. 2014;100:1954–1959.

18. Rowe G, Gill G, Zubair MM, et al. Ross procedure in children: the Society of Thoracic Surgeons Congenital Heart Surgery Database Analysis. *Ann Thorac Surg*. 2023;115:119–125.

19. Tohme S, Jiang S, Farooqi K, et al. Ross procedure in neonate and infant populations: a meta-analysis review. *World J Pediatr Congenit Hear Surg*. 2023;13:759–769.

20. Alsoufi B, Al-Halees Z, Manlhiot C, et al. Mechanical valves versus the Ross procedure for aortic valve replacement in children: propensity-adjusted comparison of long-term outcomes. *J Thorac Cardiovasc Surg*. 2009;137:362–370.e9.

21. Brown JW, Patel PM, Ivy Lin JH, et al. Ross versus non-Ross aortic valve replacement in children: a 22-year single institution comparison of outcomes. *Ann Thorac Surg*. 2016;101:1804–1810.

22. Sharabiani MTA, Dorobantu DM, Mahani AS, et al. Aortic valve replacement and the Ross operation in children and young adults. *J Am Coll Cardiol*. 2016;67:2858–2870.

23. Takkenberg JJM, Kappetein AP, Van Herwerden LA, et al. Pediatric autograft aortic root replacement: a prospective follow-up study. *Ann Thorac Surg*. 2005;80:1628–1633.

24. Mokhles MM, Körtke H, Stierle U, et al. Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. *Circulation*. 2011;123:31–38.

25. Chester AH, El-Hamamsy I, Butcher JT, Latif N, Bertazzo S, Yacoub MH. The living aortic valve: from molecules to function. *Glob Cardiol Sci Pract*. 2014;2014:52–77.

26. Ruzmetov M, Vijay P, Rodefeld MD, Turrentine MW, Brown JW. Evolution of aortic valve replacement in children: a single center experience. *Int J Cardiol*. 2006;113:194–200.

27. Alsoufi B, Manlhiot C, Fadel B, et al. Is the Ross procedure a suitable choice for aortic valve replacement in children with rheumatic aortic valve disease? *World J Pediatr Congenit Hear Surg*. 2012;3:8–15.

28. Yacoub M, El-Hamamsy I. The Ross operation in infants and children, when and how? *Heart*. 2014;100:1905–1906.

29. McElhinney DB, Lock JE, Keane JF, Moran AM, Colan SD. Left heart growth, function, and reintervention after balloon aortic valvuloplasty for neonatal aortic stenosis. *Circulation*. 2005;111:451–458.

30. Wisneski AD, Matthews PB, Azadani AN, et al. Human pulmonary autograft wall stress at systemic pressures prior to remodeling after the Ross procedure. *J Heart Calve Dis*. 2014;23:377–384.

31. Aranda Granados PJ, Concha Ruiz M, Casares Mediavilla J, et al. Incidence and clinical impact of pulmonary homograft dysfunction after the Ross procedure. *Rev Española Cardiol*. 2004;57:29–36.

32. Bonhoeffer P, Boudjemline Y, Saliba Z, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. *Lancet*. 2000;356:1403–1405.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Pediatric and Congenital Heart Disease* at https://www.cjcpc.ca// and at https://doi.org/10.1016/j.cjcpc.2024.02.004.