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Outcomes in neonatal critical and non-critical aortic stenosis: a retrospective cohort study

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2022-324189).

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Received 28 March 2022
Accepted 5 January 2023
Published Online First 19 January 2023

To cite: Olofsson CK, Hanseus K, Ramgren JJ, *et al*. *Arch Dis Child* 2023;**108**:398–404.

ABSTRACT

Objective To compare long-term survival, reinterventions and risk factors using strict definitions of neonatal critical and non-critical valvular aortic stenosis (VAS).

Design A nationwide retrospective study using data from patient files, echocardiograms and the Swedish National Population Registry.

Setting and patients All neonates in Sweden treated for isolated VAS 1994–2018. We applied the following criteria for critical aortic stenosis: valvular stenosis with duct-dependent systemic circulation or depressed left ventricular function (fractional shortening ≤27%). Indication for treatment of non-critical VAS was Doppler mean gradient >50 mm Hg.

Main outcome measures Short-term and long-term survival, aortic valve reinterventions need of valve replacements, risk factors for reintervention and event-free survival.

Results We identified 65 patients with critical VAS and 42 with non-critical VAS. The majority of the neonates were managed by surgical valvotomy. Median follow-up time was 13.5 years, with no patients lost to follow-up. There was no 30-day mortality. Long-term transplant-free survival was 91% in the critical stenosis group and 98% in the non-critical stenosis group (p=0.134). Event-free survival was 40% versus 67% (p=0.002) in the respective groups. Median time from the initial treatment to reintervention was 3.6 months versus 3.9 years, respectively (p=0.008).

Conclusions Critical VAS patients had significantly higher need for reintervention during the first year of life, lower event-free survival and lower freedom from aortic valve replacement at age ≥18 years, compared with neonates with non-critical stenosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neonatal valvular aortic stenosis is usually managed by surgical valvotomy or by catheter intervention. Varying definitions of critical aortic stenosis causes heterogenous groups, and outcomes are therefore difficult to compare. Few complete national cohorts exist, and reports of long-term outcome after treatment are rare.

WHAT THIS STUDY ADDS

⇒ We used a strict definition of critical valvular aortic stenosis in a complete national cohort. Significantly higher event-free survival was found in neonates treated for non-critical valvular aortic stenosis in comparison with those treated for a critical aortic stenosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings stress the importance of discriminating between critical and non-critical valvular aortic stenosis when studying outcome after treatment during in the neonatal period.

INTRODUCTION

Isolated valvular aortic stenosis (VAS) represents 3%–5% of congenital heart disease, with a wide spectrum of severity. In the most severe form, critical neonatal VAS presents with a hypoplastic aortic annulus, severely dysplastic valve leaflets, left ventricular dysfunction and duct dependent systemic circulation with fatal outcome in the absence of treatment.[1] There is no generally accepted definition of critical VAS. In the literature, the definitions includes: age at intervention, <30 days[2 3] or <3 months[4–7]; anatomic features such as duct dependency[8 9]; functional features such as depressed left ventricular function[10]; ongoing pharmacological treatment with prostaglandin or inotrope support[11 12]; or as a combination of criteria.[1 13–15]

Another group of neonates with VAS present in good clinical condition with a heart murmur, and the indication for treatment in the neonatal period is a significant gradient across the aortic valve. The term non-critical VAS is sometimes used to describe congenital VAS after the neonatal period. Our hypothesis is that non-critical VAS exists also in neonates and that this group has a different and more benign prognosis after treatment compared with critical VAS patients.

Valvotomy, surgical or by catheter intervention, is the first-hand treatment in the neonatal period. Data for comparison of treatment methods derive from single-centre reports[2–5 8 10–13 16 17] and a few multicentre studies.[9 14 15 18] However, comparison of outcome after neonatal treatment of VAS is complicated by the varying definition of critical VAS. Centres are usually dedicated to surgical valvotomy (SAV) or balloon aortic valvotomy (BAV) as initial treatment, but some use both methods at the discretion of the paediatric cardiologist or surgeon. The aim of this study was to compare short-term and long-term outcomes after treatment of patients with critical and non-critical VAS in the neonatal period.

PATIENTS AND METHODS

We included all neonates (<30 days) treated for isolated VAS between 1 January 1994 and 31 December 2018 in a national, retrospective study. Paediatric heart surgery, including aortic valve catheter interventions, is centralised to the Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, and the Pediatric Heart Center at Skåne University Hospital, Lund, since 1994,[19] ensuring complete nationwide coverage of all neonates treated for VAS in the present study. Patients were identified in surgical and catheter registries and data collected from patient files at the two centres, referring hospitals and the Swedish Registry of Congenital Heart Disease. The current cohort of neonates with critical aortic stenosis was in part included in a previous study.[13] Survival was cross-checked against the Swedish Population Registry as of October 2019.

Indications for treatment were: (a) critical VAS with duct-dependent systemic circulation and/or depressed left ventricular function with fractional shortening (LVFS) ≤27% or (b) non-critical AS with Doppler mean gradient >50 mm Hg. A right to left shunt across the ductus arteriosus, with or without a reversed blood flow in the aortic arch, was defined as duct-dependent systemic circulation. Patients with associated cardiac malformations requiring treatment were excluded. Only patients primarily assigned to biventricular repair were included. The preferred initial treatment in both institutions is SAV, that is, commissurotomy including thinning of dysplastic leaflets and shaving off noduli. Primary BAV was performed during a limited period (2000–2006) in one centre. In the early era, two premature babies were treated with closed transventricular valvotomy.

Duct-dependency, left ventricular function, Doppler-derived gradients, aortic valve regurgitation and presence of left ventricular endocardial fibroelastosis (EFE) were evaluated with echocardiography. Preoperative echocardiograms were re-examined for classification of critical versus non-critical VAS and to systematically assess EFE, graded as not present, focal or extensive. If the echocardiogram was not retrieved or not reviewed in detail due to poor quality in older registrations, data were collected from the patient file. The postprocedural echocardiograms were obtained before hospital discharge. Description of leaflet morphology was obtained from the surgical reports or, if no surgery was performed, from the echo report.

Statistical analysis

IBM SPSS statistical software, version 27 was used for data analysis. Categorical variables are reported as absolute numbers and percentages. Continuous variables are expressed as either mean±SD or median and range. Student's t-tests were performed to compare continuous variables and χ^2 tests or independent-samples Mann-Whitney U tests for categorical variables. Survival and freedom from events were analysed with the Kaplan-Meier method and log-rank test. Proportional hazards regression model was used for risk factor analysis of reintervention and aortic valve replacement (AVR). Variables with $p<0.1$ in the univariable analysis were included in a multivariable regression model. Duct dependency and left ventricular function were included as clinically relevant variables in the multivariable model for critical VAS, as was aortic annulus z-score in the multivariable model for non-critical VAS. The association between size of aortic valve and event-free survival in duct-dependent patients was examined in an adjusted logistic regression model. For all tests, $p<0.05$ was considered statistically significant.

RESULTS

We identified 107 neonates (21% girls) with isolated valvular VAS treated during the 24-year study period. After review of echocardiograms and reports, 65 patients fulfilled our criteria for critical VAS based on duct dependency (n=12), duct dependency and depressed left ventricular function (n=28) or depressed left ventricular function (n=25). The remaining 42 patients were classified as non-critical VAS. All medical records were retrieved. No patients were lost to follow-up. Median follow-up time was 13.5 years (1.3–25.7). Demographic variables are presented in table 1.

Echocardiographic, Doppler and catheter data are presented in table 2. EFE was found only in patients with critical VAS. Extensive EFE was present in 13 patients, all with severe left ventricular dysfunction at presentation, and focal EFE was seen in 24 cases.

The initial procedure was SAV (n=95), BAV (n=8), closed transventricular valvotomy (n=2), or primary Ross procedure (n=2). Figure 1 shows flowcharts with an overview of all interventions.

From 2006, all echocardiographic studies are complete (digital storage). Between 1994 and 2005 (analogue storage) left ventricular measurements were incomplete in 15 cases. Peak aortic gradient was missing in two cases and calculation of mean aortic gradient was missing in five cases, all in cases with severely depressed left ventricular function. In five cases, the preoperative echocardiogram was not retrieved (data collected from patient files).

Mortality

There were no deaths in the first 30 days after surgery. Long-term transplant-free survival was 91% in critical VAS patients and 98% in non-critical patients (p=0.134) (figure 2A). Median

Table 1 Patient characteristics

	Non-critical aortic stenosis	Critical aortic stenosis	P value
Patients (n)	42	65	
Gestational age, median (range), weeks	40 (35–42)	39 (26–42)	0.022*
Gender, male/female	33/9	52/13	0.858†
Birth weight, mean (SD), kg	3.6 (0.66)	3.3 (0.76)	0.01‡
Age at diagnosis, median (range), days	2 (0–20)	1 (0–7)	0.315*
Age at first treatment, median (range), days	8 (1–26)	5 (0–26)	0.004*
Follow-up time, median (range), years	14.6 (1–26)	13.0 (1–26)	0.314*

*Independent-samples Mann-Whitney U test.
†χ^2 test.
‡Independent-samples t-test.

Table 2 Echocardiographic and catheter-derived data before and after primary intervention

	Non-critical (n=42)	Critical (n=65)	P value
LVEDd, cm	1.71 (0.29)	1.94 (0.46)	*0.005*
LVEDd, z-score	−1.25 (1.43)	0.05 (2.30)	*0.001*
IVSd, cm	0.50 (0.12)	0.48 (0.15)	*0.611*
IVSd, z-score	1.53 (1.27)	1.04 (1.28)	*0.095*
LVPWd, cm	0.40 (0.11)	0.46 (0.13)	*0.26*
LVPWd, z-score	0.93 (1.48)	2.12 (1.37)	*<0.001*
LVFS, % (median, range)	39 (28–58)	24 (5–53)	*<0.001*
LVFS <28%, n (%)	0	47(78)	*<0.001*
Aortic annulus, mm	7.37 (1.15)	6.37 (1.02)	*<0.001*
Aortic annulus, z-score	0.3 (1.53)	−0.97 (1.49)	*<0.001*
Peak aortic gradient, mm Hg	101 (25)	42 (22)	*<0.001*
Residual peak aortic gradient, mm Hg	39 (18)	42 (22)	*0.478*
Mean aortic gradient, mm Hg	55 (13)	44 (21)	*0.004*
Residual mean aortic gradient, mm Hg	24 (9.3)	25 (13)	*0.781*
Peak aortic jet velocity, m/s	5.0 (0.58)	4.2 (1.08)	*0.000*
Residual peak aortic jet velocity, m/s	3.0 (0.77)	3.1 (0.8)	*0.459*
Catheter derived gradients			
Catheter gradient at BAV, mm Hg	60 (15)	67 (42)	*0.849*
Residual catheter gradient, mm Hg	38 (87)	33 (21)	*0.747*
Aortic regurgitation after intervention, n (%)			
None	13 (31)	23 (35)	
Trivial	18 (43)	33 (51)	
Mild	4 (10)	7 (11)	
Moderate	0	0	
Severe	0	0	

Values represent mean (SD), except where otherwise stated.
BAV, balloon aortic valvotomy; IVSd, interventricular septum end-diastole; LVEDd, left ventricular end-diastolic dimension; LVFS, left ventricular fractional shortening; LVPWd, left ventricular posterior wall end-diastole.

follow-up time was 13.5 years (1–26). The deaths in the critical AS group occurred at 2 months (caused by septicaemia and heart failure before hospital discharge), at 10 months (pneumonia and heart failure), at 2 years (ventricular failure after reoperation) and at 21 years (endocarditis in a biological aortic valve prosthesis). They were all males born with duct-dependent systemic circulation, poor left ventricle function and extensive EFE with mean aortic annulus z-score below −1.6 at presentation. Causes of death are accounted for in detail in a previous study.[13] In the non-critical AS group, a 3-year-old boy was found dead in bed; cause of death could not be determined. In addition, in the group of critical VAS two patients had heart transplants at the age of 1 and 15 years, and two patients were converted to univentricular palliation.

Reinterventions

The main indications for reintervention were Doppler mean or invasive gradient >50 mm Hg or significant aortic regurgitation. For evaluation of aortic regurgitation, magnetic resonance tomography was also used.

Aortic valve reintervention was required in 58% of the critical VAS patients and 33% of the non-critical VAS patients. Kaplan-Meier curves for freedom from reintervention demonstrated a statistically significant difference between the groups (figure 2B; p=0.008), with a median time to reintervention of 3.6 months (0–17.3 years) in the critical VAS group compared with 3.9 years (0–14) in the non-critical VAS group (online supplemental table 1)

Freedom from reintervention in the critical VAS group were 63%, 58%, 52%, 45% and 42%, and in the non-critical VAS group 86%, 81%, 71%, 67% and 67% at 1, 5, 10, 15 and 20 years, respectively. In both groups, the most common indication for a reintervention was residual stenosis.

Aortic valve replacement

AVR was required in 35% of the critical VAS patients, with one-third needing repeated replacements (figure 1). Median age at AVR was 7.22 years (0.02–17.27). The first replacement was Ross (n=10), biological prosthesis (n=3), mechanical prosthesis (n=5) or homograft in the aortic root position (n=5). In the non-critical VAS group, 26% required AVR at median 7.53 years (0.01–14.39), either Ross (n=10) or biological prosthesis (n=1). The difference between groups in freedom from AVR did not reach statistical significance (figure 2C; p=0.092). However, in patients aged ≥18 years at follow-up, freedom from valve replacement was 2/15 (8%) in the critical VAS group and 6/9 (67%) in the non-critical group (p=0.004).

Event-free survival

Event-free survival, that is, freedom from death, heart transplantation, conversion to single ventricle palliation, or any reintervention, was 40% in the critical VAS group and 67% in the non-critical group (figure 2D; p=0.002).

Risk factor analysis

Risk factors for transplant-free survival, reintervention and AVR are summarised in online supplemental tables 2A,B and

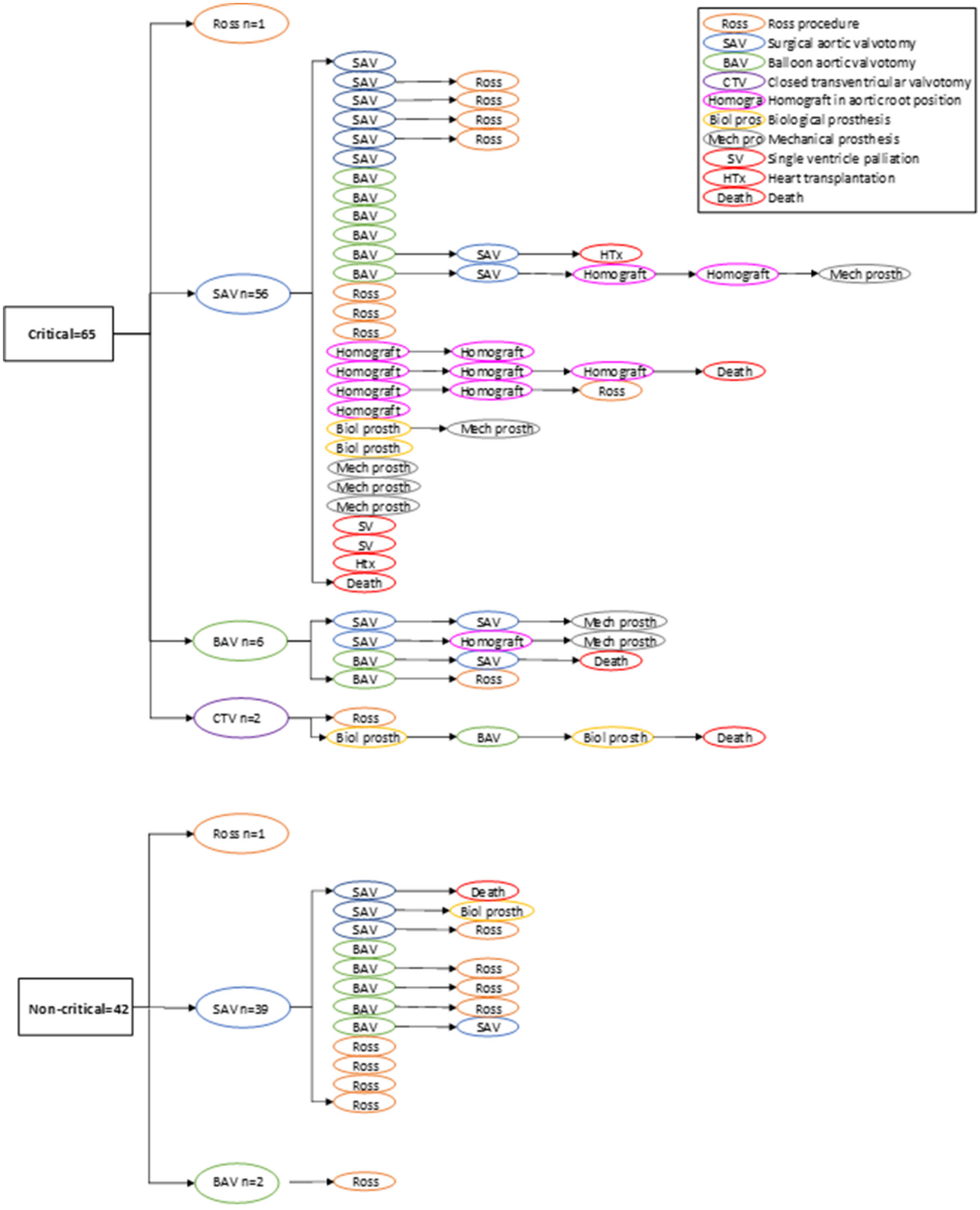

Figure 1 Flow chart of all interventions and mortality in the critical and non-critical aortic stenosis groups.

3. Smaller aortic annulus z-score and higher residual gradient at hospital discharge were risk factors for reintervention, while small aortic annulus and presence of any aortic regurgitation after first treatment were independent risk factors for AVR in critical VAS patients. Higher residual gradient was a risk factor for reintervention in non-critical VAS patients. In the whole

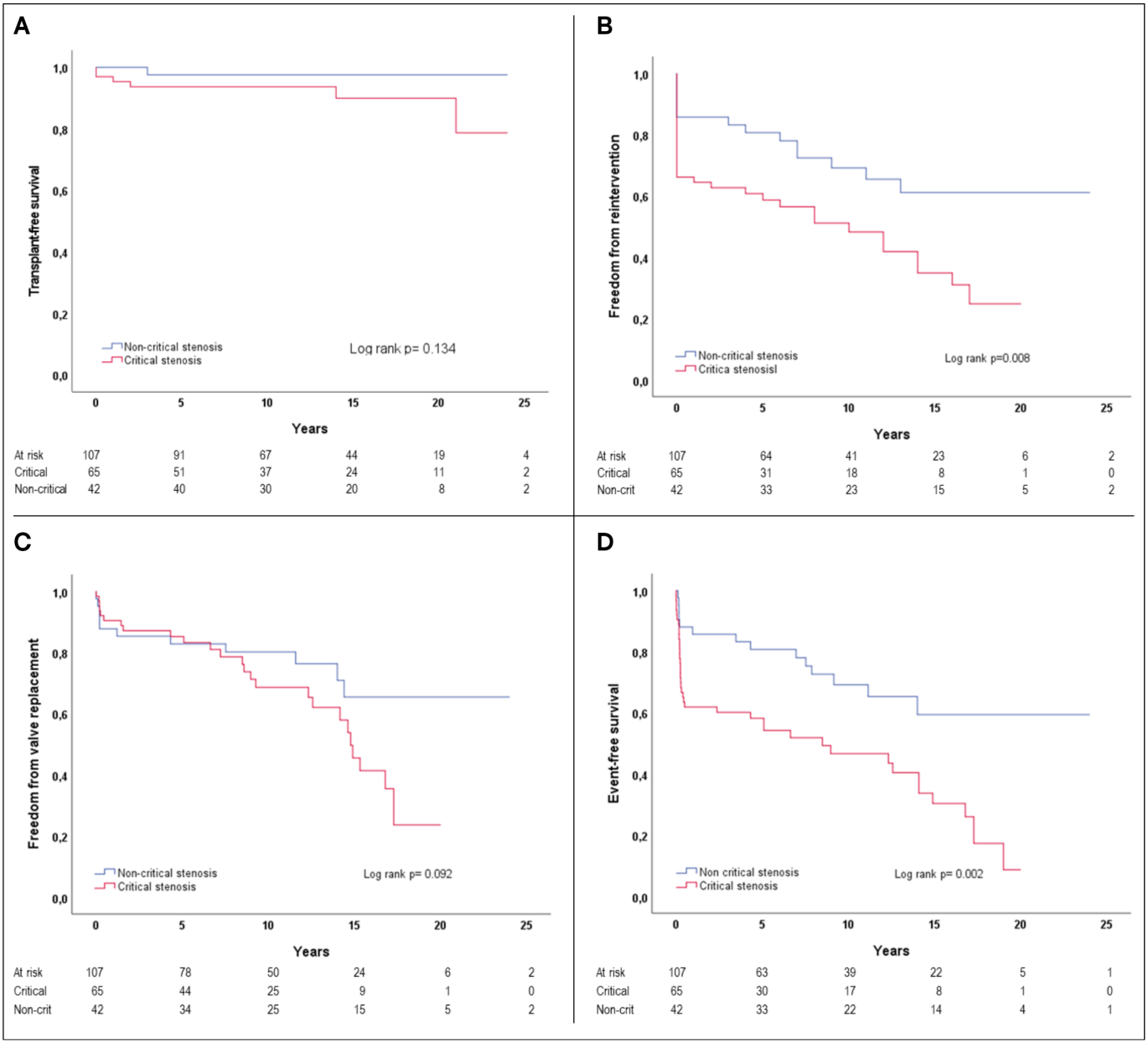

Figure 2 (A–D) Kaplan-Meier curves of critical and non-critical valvular aortic stenosis. (A) Transplant-free survival. (B) Freedom from reintervention. (C) Freedom from aortic valve replacement. (D) Event-free survival.

cohort, the aortic annulus z-score and residual gradient remained risk factors for reintervention. Valve leaflet morphology was not associated with a significant risk of reintervention or aortic valve replacement. These results were confirmed in a regression model including all patients with critical and non-critical aortic stenosis as covariates (online supplemental table 3).

Table 3 presents a logistic regression model for size of aortic valve annulus as an effect modifier of event-free survival in duct-dependent patients adjusted for left ventricular function.

DISCUSSION

Patients with isolated critical VAS versus non-critical VAS stenosis have different outcomes after treatment in the neonatal period. Based on outcome and risk factor analysis, two groups can be clearly distinguished by their clinical and echocardiographic appearance before treatment, as well as by the differences in the need for reinterventions, AVR and event-free survival after treatment. In the present study, SAV was the initial treatment in 90% of the cases, including neonates with duct dependency and/or in poor condition with severe heart failure, with no 30-day mortality. Long-term transplant-free survival was 91% in the critical and 98% in the non-critical VAS group as compared with 90% in a contemporary study of neonates by Vergnat *et al*[3] with a median follow-up time of 13 years. In our study, the critical VAS group had a high need of reintervention during the first year of life (figure 2B, table 3). A similar finding of high need of early reinterventions in neonates treated for critical VAS was reported by Hickey *et al*.[9] The finding of significant difference in reintervention rate is important, as time to reintervention is often an argument used when comparing treatment methods. During the first 10 years of life, we found similar rates of AVR in both groups. However, at ≥18 years of age 13/15 patients born with critical VAS and 3/9 born

Table 3 Odds ratio for event-free survival after first intervention in duct-dependent patients, adjusted for fractional shortening, with size of aortic valve annulus as effect modifier

Aortic valve annulus (mm)	Adjusted OR
5	0.15
5.5	0.25
6	0.44
6,5	0.74
6.775	**1**
7	1.27
7.5	2.18
8	3.72
8.5	6.37

Bold value shows the size of the aortic valve annulus when the OR is 1.
OR, Odds ratio.

with non-critical AS had had an AVR (figure 2C). This can be compared with the study by Vergnat *et al* reporting AVR, at median 5.9 years of age, in 31/97 late survivors in a mixed cohort of neonates with critical and non-critical VAS after treatment with SAV or BAV.[3] The difference between the groups in the present study is summarised in the event-free survival rate of 40% in the critical VAS group compared with 67% in the non-critical group at the end of follow-up in our study (figure 2D).

In the critical VAS group, a smaller aortic valve annulus was an independent risk factor for reinterventions and valve replacement. McCrindle *et al*[15] described a small aortic valve annulus diameter as an incremental risk factor for death. However, Vergnat *et al* did not find size of aortic valve to be an independent risk factor for reintervention or AVR. These differences might be created by differences in definition of critical VAS, where the present study and McCrindle *et al* used a similar definition (duct-dependent systemic circulation and/or depressed left ventricular function), in contrast to Vergnat *et al*, who included all neonates with treatment before 30 days of age. In the present study, size of aortic valve was not an independent risk factor in the non-critical group, where residual gradient after initial treatment was the most important risk factor limiting event-free survival.

Our results suggest that size of the aortic valve annulus is a more important risk factor for reintervention and AVR than valve leaflet morphology. The importance of aortic annulus size was further analysed in a logistic regression model (table 3). The results suggest, for example, that an annulus diameter of 6 mm, in duct-dependent neonates, gave an OR of 0.44 for event-free survival, while an annulus of 7 mm gave an OR of 1.27 for event-free survival. Agreement between echocardiographic and intraoperative assessment of leaflet arrangement have been described as low[3] and determining valve morphology by reviewing old echocardiograms is challenging. Conflicting reports describe the influence of leaflet morphology on treatment outcome. Loomba *et al*, Petit *et al* and Siddiqui *et al* found no such association, in contrast to Hraska *et al*, Moninder *et al* and Vergnat *et al*, who found trileaflet morphology associated with better outcome.[2 3 12 16 20 21] In our risk factor analysis, where leaflet morphology was determined at the surgeon's discretion, we found no association with bicuspid or tricuspid leaflet arrangement, time to reintervention or AVR.

Results after treatment of critical or neonatal VAS are reported from many centres. Despite the number of publications and debates, it is not clear whether SAV[6 8 13 16 22 23] or BAV,[10–12 18 24] as primary intervention, offers the best short-term and long-term outcomes. Because of differences in definition, outcomes and surgical preference, studies are hard to compare. Reports from centres offering both SAV and BAV[2–4 9 14 15 17] often lack information about why patients are offered one treatment or the other. As Baram *et al* and Alexiou *et al* point out, the decision to intervene with a catheter or surgical procedure is at the discretion of the team or treating physician and not determined by a protocol.[4 23] This introduces a possibility of patient selection or referral bias, undermining the validity in comparison of the two treatment methods. Randomised controlled studies are lacking and difficult to accomplish, but the validity of the comparisons would increase if inclusion criteria were defined more rigorously. This would allow differences in outcome to be traced back to the chosen treatment method and not confused with differences related to subgroup differences in the patient material.

A limitation of the present study is that, although it describes a complete national cohort of consecutively collected cases, the number of patients and events is still rather small. This might preclude the possibility of finding statistically significant associations (type 2 errors), despite the inclusion of all eligible patients and complete data over a 24-year period as no patient was lost to follow-up.

CONCLUSIONS

There was no 30-day mortality. Long-term transplant-free survival was 91% in critical VAS patients and 98% in non-critical patients. Patients with critical VAS had a significantly higher need for reintervention during the first year of life, lower event-free survival and lower freedom from AVR at ≥18 years of age, compared with patients with non-critical VAS. This finding stresses the importance of using a strict definition of critical VAS when comparing outcome after treatment in the neonatal period.

Acknowledgements We would like to thank Niclas Olofsson and Erling Englund for support with the statistical analysis.

Contributors CKO, JS and KH contributed to conception and design of the work. CKO, JS, KH, JJR and MJS contributed to the data collection. CKO and JS contributed analysis and interpretation of data and drafting the article. All coauthors have critically read and revised the manuscript. JS is garantor.

Funding This study was financed by grants from the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement (SU 2018-04267) and from the Department of Research and Development, Västernorrland County Council.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethics Review Board of Western SwedenID 518-16, T1123-17. Informed consent was not required according to the ethics review board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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