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Risk Factors for Recoarctation and Mortality in Infants Submitted to Aortic Coarctation Repair: A Systematic Review.

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Margarida Queirós da Silva Dias

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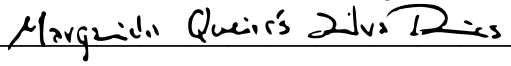

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DESIGNAÇÃO DA ÁREA DO PROJECTO

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Risk Factors for Recoarctation and Mortality in Infants Submitted to Aortic Coarctation Repair: a Systematic Review

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COORIENTADOR (se aplicável)

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	X
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☐

Faculdade de Medicina da Universidade do Porto, 12/03/2020

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Risk Factors for Recoarctation and Mortality in Infants Submitted to Aortic Coarctation Repair: A Systematic Review.

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Abstract

Background: Aortic coarctation is a common congenital heart defect that often requires correction at a young age. Currently, success is defined by the achievement of a durable repair with low morbidity and mortality. We sought to systematically review the literature on risk factors for recoarctation and mortality in infants submitted to aortic arch coarctation repair under 1 year of age.

Methods: PubMed and Scopus were searched for studies reporting risk factors for recoarctation and mortality from January 1989 to August 2019.

Results: Among the 1038 retrieved articles, 18 met the inclusion criteria, with a total of 2891 patients. The extracted risk factors for recoarctation were comprehensively summarized in the following categories: demographic variables, associated anomalies, clinical and repair variables and morphometric variables. Younger age and lower weight were weak determinants of need for reintervention, while smaller aortic arch was a strong predictor of recoarctation. While balloon angioplasty is a clear risk factor for arch restenosis, the chosen surgical technique is not a strong risk factor. Associated minor cardiac anomalies and lower weight at surgery were important risk factors for death.

Conclusion: Younger and smaller infants are at increased risk for adverse outcomes when submitted to aortic arch coarctation repair. This is particularly important when associated with smaller arch morphology. Strategies to improve the management of these patients may play a key role in improving their outcomes. Notably, surgical technique was not a strong predictor of recoarctation and mortality, suggesting that the choice of one over the other should be tailored.

Keywords: Aortic coarctation, Coarctation repair, Recoarctation, Reintervention, Mortality, Risk factor.

Introduction

Coarctation of the aorta is a common congenital heart defect typically characterized by narrowing of the aortic isthmus near the ductus arteriosus. It can range from a discrete coarctation to a long segment of arch hypoplasia[1]. Aortic coarctation can occur as an isolated defect, but frequently it appears associated with other cardiac malformations[2].

Patients that present for initial aortic coarctation repair are often very young (frequently under 1 year of age) and can have critical clinical conditions[3]. With advances in surgical strategies, this defect is commonly repaired at diagnosis at this early age, with good short-term and long-term outcomes[4-8]. Different surgical techniques have been defined[1], and some centers have also described percutaneous interventions for infants with native coarctation[9-11]. In young patients with native aortic coarctation not associated with other major cardiac defects, end-to-end anastomosis and extended end-to-end anastomosis are the most frequently used techniques[3]. Regardless of the technique used, nowadays, surgery success is defined by the achievement of a durable repair with low morbidity[12].

There have been several studies evaluating risk factors for adverse outcomes after surgical intervention, including recoarctation, although the literature is often conflicting and inconclusive, especially regarding the influence of child weight and surgical strategy on the rate of reinterventions[7,8,13,14]. Other possible risk factors identified in individual studies include anatomical and morphological characteristics of the aortic arch, preoperative care, and age at time of the intervention[12,14,15]. Nevertheless, a comprehensive analysis of the evidence to determine the risk factors conclusively lacks in the literature. Conducting a systematic review is a paramount method to summarize and aggregate findings from individual studies, and, in clinical settings, it is vital for the assessment of risk factors that influence the decision-making process.

In this study, we aim to pool available data and attempt a large-scale examination of the existing studies to define the risk factors associated with recoarctation and mortality after surgical repair of coarctation of the aorta in neonates and infants until 1 year of age.

Materials and methods

Search Strategy

We conducted a systematic literature review that followed the PRISMA guidelines[16]. PubMed and Scopus electronic databases were searched for articles published between January 1989 and August 2019 using the following query: (“Mortality”[Mesh] OR reintervention[Text Word] OR reop*[Text Word] OR recurrent[Text Word] OR recoarctation[Text Word] OR surgical repair[Text Word] OR coarctation repair[Text Word] OR surgical treatment of aortic coarctation[Text Word]) AND (“Aortic Coarctation"[Mesh] OR aortic coarctation[Text Word] OR coarctation of the aorta[Text Word]) AND (“Risk”[Mesh:NoExp] OR “Risk Factors”[Mesh] OR “Risk Assessment”[Mesh:NoExp] OR risk factor*[TIAB] OR predictive[TIAB]). No restrictions concerning language or publication status were applied.

Additionally, we conducted manual searches of reference lists from all included articles. No search of conference literature, gray literature, and unpublished literature was undertaken.

Eligibility Criteria

The databases were searched independently by two authors that evaluated identified studies for inclusion based on Title and Abstract, according to the eligibility criteria. When a study could not be excluded on this basis or in case of disagreement, the full text was reviewed, and the two independent reviewers discussed it until a consensus was reached.

The study was eligible for inclusion if it examined risk factors for recoarctation or mortality and met the following criteria: (1) patients were submitted to surgical or percutaneous repair of aortic coarctation until 1 year of age, and (2) patients with isolated aortic coarctation or associated with minor congenital heart defects, without associated complex congenital heart defects. The outcome of interest was the occurrence of recoarctation, reintervention for recurrent arch obstruction, or related mortality. Articles published more than 30 years ago were excluded considering the great technical advances recognized in pediatric cardiac surgery. Also, reviews, letters, conference papers, editorials, and nonhuman studies were excluded.

Data Collection and Quality Assessment

Data from studies were extracted independently to a previously prepared spreadsheet, and both reviewers discussed the data for consistency. The retrieved data were summarized in the following: first author's name, year of publication, study design, sample size, sample characteristics (sex, age, weight, associated anomalies), repair strategy, follow-up time, reintervention or recoarctation rate, mortality rate, reported endpoints, risk factors identified and respective adjusted effect size, confidence interval, p-value, and method of analysis. When data were missing from the articles, the corresponding authors were contacted to retrieve more information.

Considering that this review was based mainly on observational studies, we used the Quality Assessment Tools, developed by the National Heart, Lung and Blood Institute from the National Institute of Health, to assess the quality of the included articles[17]. Although not entirely validated, this 14-criteria form has been widely used to evaluate the internal validity and risk of bias of observational studies in systematic reviews and meta-analysis. Two of the reviewers assessed all studies and evaluated the 14 criteria independently. The quality of the studies was then graded as "Good", "Fair", or "Poor", according to the potential for bias and the ability of the study to accurately assess an association between exposure and outcome. If there were discrepancies between the two authors, the data were discussed to reach a consensus.

Results

Literature Search Results

We identified 365 articles from PubMed and 673 from Scopus, amounting to a total of 1038 titles. *Figure 1* depicts the flowchart of the selection process. After removing duplicates, we scanned 795 titles and abstracts, selecting 57 for full-text analysis. The reference lists of these full-text articles provided 10 added studies. After assessing the full text of the included 67 articles, we excluded 59 of them for not meeting all inclusion criteria. Finally, 18 studies were included in the systematic review for qualitative synthesis[9,12-14,18-31].

Study characteristics

The studies characteristics and clinical parameters, along with the main results of the included studies, are summarized in *Tables 1, 2, 3, 4*. Thirteen[9,12-14,19-22,24-27,29] of the included studies were rated as "Good" and five studies[18,23,28,30,31] as "Fair" according to the Quality Assessment Tools (this evaluation is summarized in *Online Resource 1*). We included 18 studies that recruited a total of 2891 patients from eight different countries. The follow-up duration ranged from 0 to 360 months.

Around 61% of patients were male. The weight of the patients at the intervention ranged between 0.8 and 10.4 kg, and approximately 34.4% had a ventricular septal defect associated. Other associated minor anomalies, such as bicuspid aortic valve, were also reported in some of the studies in variable percentages *Table 2.*

The most common surgery strategies were the following: end-to-end anastomosis in 27.8%; extended-end-to-end anastomosis in 25.6%; subclavian flap aortoplasty in 7.8%; balloon angioplasty in 6.2%; patch aortoplasty in 4.8%; combined surgical strategies were used in 3.4%, and less than 1% of patients had another type of repair performed. Regarding surgical strategy, a thoracotomy was performed in 70% of patients, with only 21.7% being submitted to a sternotomy; the remaining 8% had a percutaneous approach to perform angioplasty.

Crude rates of reintervention for recoarctation of the aorta in the included studies were calculated by dividing the number of patients requiring the reintervention by the total number of patients included and ranged from 5.9 to 46.6% in 16 of the

studies. The rate of procedure-related mortality was calculated by dividing the number of deaths by the total number of patients included in the 18 studies and ranged from 0 to 22.4%. Patients lost to follow-up were excluded from these calculations. The total recoarctation rate in the combined population of this study was 11.9% and the procedure-related mortality was 3.8%.

Factors Associated with Recoarctation

Table 5 summarizes the results from statistical tests of risk factors for recoarctation of the aorta, in the following categories: demographic variables, associated anomalies, clinical and intervention variables, morphometric variables. A complete description of these risk factors is given below.

Demographic Variables

The effect of age at time of intervention was examined in six studies[12-14,18,19,24]; only two studies found a significant association between younger age at repair and recoarctation: Exp(B)=0.98 (p=0.034)[12] and OR=1.06 (p=0.05)[14], respectively.

Also, eight studies[12-14,18,19,24,28,29] assessed the effects of weight before surgery on the outcome, with only two studies showing a significant association between low weight at repair and arch restenosis: OR=0.016 (p=0.047)[28] and OR=1.97 (p<0.0001)[18]. In addition, Gorbatykh et al.[18] noted that the weight was not a significant risk factor when included on a multivariable model with the different surgical strategies. Moreover, lower birthweight[29] and smaller body length at surgery[22] were both considered risk factors.

Notably, no studies found a significant association between prematurity or time of diagnosis of the coarctation – pre or postnatal – with recoarctation[12-14,19,29].

Associated Anomalies

A positive association between recoarctation and aortic arch hypoplasia was shown in only two studies: OR 2.864 (p=0.001)[22] and OR 1.31 (p=0.0047)[18]; interestingly, Gorbatykh et al.[18] found that the arch hypoplasia was not a significant

risk factor for recoarctation when included in a multivariable model with different surgical strategies: OR=0.92 (p=0.06).

Remarkably, the presence of other cardiac defects was not proven to be statistically related with the occurrence of recoarctation [12,14,19,31].

Clinical and Intervention Variables

Prostaglandins infusion prior to surgery was assessed in three studies[12-14], with only Lehnert et al.[12] establishing a significantly positive relation with recoarctation: Exp(B)=1.53 (p=0.0043). Conversely, no study found a documented patent arterial duct to be a significant risk factor[12,13,20,24]. The need for inotropes prior to surgery and the type of suture used were also associated with recoarctation[13,29].

The type of coarctation repair strategy were evaluated in eight articles[9,12,18-20,25,27,30]: two positively associated patch aortoplasty [19,25], while Gorbatykh et al.[18] established in a multivariable model both direct end-to-end anastomosis and oblique anastomosis as risk factors for recoarctation, but not reverse aortoplasty: OR=2.82 (p<0.001), OR 1.42 (p=0.045), and OR=0.66 (p=0.36), respectively. Also, extended end-to-end repair anastomosis was found to be risk factors in the analysis by Truong et al.[29] Particularly, repair performed by balloon angioplasty was a significant risk factor for recoarctation in the three studies that explored this type of repair [9,20,27].

Postoperative peak doppler velocity, post-intervention systolic gradient and residual coarctation on the pre-discharge echocardiography were also identified as significantly associated risk factors for recoarctation in three studies [19,24,27,29].

Morphometric Variables

Three studies[14,19,24] assessed the risk of the diameter of the coarctation, with two[19,24] of them showing a positive correlation between smaller diameter and the occurrence of restenosis of the aortic arch.

The morphometric variables of the aorta were analyzed in seven studies[13,14,18,19,24,26,29]. Notably, McElhinney et al.[14] found that while ascending aortic arch diameter was a risk factor for restenosis, when indexed to weight,

this relation diminished. Contrarily, a smaller transverse arch diameter remained a risk factor even when indexed to weight: OR=3.0 (p=0.001) and OR=7.9 (p=0.04), respectively. Moreover, Burch et al.[13] also demonstrated that the risk of recoarctation decreased per 1 mm increase in transverse aortic arch diameter: RR=0.57 (p=0.04).

Truong et al.[29] also established the increase in the descending aorta diameter, indexed to weight, as a protective factor: HR=0.14 (p=0.04).

The remaining studies[18,24,26] were unable to demonstrate arch morphometry as a significant risk factor for recoarctation of the aorta.

Factors Associated with Mortality

The risk factors for mortality were assessed in four of the included studies[12,21,23,25]. Table 6 illustrates the summarized results. The effect of weight was studied in three studies [12,21,23] but only Lehnert et al.[12] and Curzon et al.[21] found a positive association between weight <2.5 kg and the risk of intervention-related or cardiac death.

One particular study[25] focused on associated cardiac anomalies as potential factors that increased mortality. In fact, Quaegebeur et al.[25] showed that the presence of ventricular septal defects, concomitant with the type of aortic arch repair, was a significant risk factor for death. Furthermore, Lehnert et al.[12] established the presence of ventricular septal defects as a risk factor for mortality in these patients (in this study, death occurred in five patients that had concomitant closure of the septal defect and coarctation repair and in one patient requiring pulmonary banding).

Discussion

The present systematic review was based mainly on observational studies and explored the risk factors for recoarctation and mortality in infants submitted to repair of coarctation of the aorta under 1 year of age. This large qualitative study included 2891 individuals retrieved from 18 different studies. A broad range of risk factors was analyzed, including demographics, morphometric, clinical, and intervention variables, as well as associated cardiovascular anomalies.

Younger age, lower weight, and prematurity have been thought as risk factors for adverse outcomes in these patients. In this review, six studies[12-14,18,19,24] analyzed the effect of age as a potential risk factor for recoarctation, but only two studies[12,14] showed that younger age at repair minimally increased the risk of restenosis of the aorta in multivariable analysis. These findings suggest that age at repair may not be a strong determinant of recoarctation or death as previously assumed. Of the eight studies[12-14,18,19,24,28,29] addressing weight as a possible risk factor, only two[18,28] demonstrated that lower weight at repair was a risk factor for recoarctation, and Gorbatykh *et al.[18]* noted that this was not a significant factor when adjusting for surgical strategy. However, two studies[12,21] have found an association of weight at repair <2.5 kg with up to a 2.65-fold increase[21] in mortality. Low weight at intervention is classically viewed as a potential risk factor. This is reinforced by our systematic review, which showed that weight <2.5 kg is indeed a risk factor for mortality and recoarctation, although the evidence supporting the former is weak. Regarding prematurity, five studies[12-14,19,29] addressed this as a potential risk factor, but none was able to demonstrate a significant association with recoarctation. Also, smaller length[22] and lower birth weight[29] were pointed as risk factors in two individual studies, but no other study addressed these factors.

Notably, no study found a relationship between time of diagnosis – prenatal or postnatal – and adverse outcomes, even though some literature had previously suggested that a prenatal diagnosis improved outcome, with lower required doses of prostaglandins and decreased mortality rates[32,33].

Seven studies[12-14,18,19,26,29] evaluated the association between recoarctation and aortic arch morphometry. Two studies[18,22] showed that the hypoplastic aortic arch was a significant risk factor but presented conflicting results. Hager et al.[22] showed that the odds of developing recoarctation or death when hypoplastic arch is present are 2.9 to 1, whereas Gorbatykh et al.[18] demonstrated that this was not a determinant factor when added to a multivariable regression model with the different types of surgical strategy. Interestingly, McElhinney et al.[14] found that a smaller transverse arch diameter was related to increased recoarctation, and its effect increased when indexed to weight. Moreover, Burch et al.[13] concluded that per 1-mm increase in the transverse arch diameter the risk for recoarctation diminished 43%. This

evidence supports the assumption that hypoplastic aortic arch is an important risk factor for the reintervention and should be taken into account when choosing the repair strategy.

On the other hand, possible residual arch obstruction, ascertain by postoperative peak doppler velocity flow[27,29], or increased discharge systolic blood pressure gradient[19] were significant risk factors for recoarctation. This residual obstruction of the aortic arch, while possibly related to a technical failure to address the obstruction, may also be associated with underappreciated arch hypoplasia.

Minor associated cardiac defects, such as small ventricular defects, bicuspid aortic valve, and left superior vena cava, were addressed as potential risk factors in seven studies[12-14,19,20,24,31], but none found a significant increase in recoarctation rates, although Quaegebeur et al.[25] demonstrated that the presence of ventricular septal defects or aortic valve stenosis was associated with increased mortality.

Lehnert et al.[12] was the only study that found a positive relation between recoarctation and prostaglandin infusion before surgery. Moreover, it was also noted that, in patients receiving prostaglandins, extended end-to-end anastomosis led to fewer reinterventions compared to end-to-end anastomosis. This might be explained by difficult in ascertain the margins to be resected, which results from changes in morphology of the aortic isthmus with the reopening of the ductus arteriosus. In fact, although the exact etiology of the recoarctation is yet to be fully understood, the role played by residual ductal tissue seems to be crucial[34].

Regarding surgical technique, the literature has pointed to extended end-to-end anastomosis as the better alternative to avoid recoarctation due to a more extensive resection, preservation of the subclavian artery and oblique anastomosis[4,6,35]. However, the results of this systematic review are somewhat conflicting. Six studies[12,14,18,19,25,30] addressed the type of surgery strategy with future need for reintervention, but only two [19,25] of those associated patch aortoplasty with recurrent coarctation and Gorbatykh et al.[18] even assessed an increased risk when an oblique anastomosis was performed. Although several studies have been conducted to compare different surgical strategies[4,6-8,36], these findings suggest that none is universally superior to another, and the choice of one over the other should be tailored.

The three studies that compared coarctation repair by percutaneous balloon angioplasty to surgical repair[9,20,27] agreed that this technique significantly increased the risk for recoarctation and need for reintervention. Usually, this technique is viewed as a palliative treatment in low-weight newborns with immature systems and organs because it allows stabilization and growth until surgery[37]. Balloon angioplasty with stenting is the repair strategy of choice in adults[1], but in younger individuals, it brings an important challenge: the placement of a stent is usually not feasible due to the continuous somatic growth of the vessels at this age. Recently, some studies have investigated the prospect of introducing breakable stents in infants: introduced at a small diameter, the stents have properties that allow subsequent unlimited expansions in line with arch growth, which may reduce the incidence of restenosis and favor this technique in selected patients[11,38,39].

This systematic review has several strengths. It is the first systematic review to comprehensively explore risk factors for recoarctation of the aorta and mortality in infants submitted to coarctation repair under 1 year of age. A strict search strategy was followed, using PRISMA guidelines to screen two databases, PubMed and Scopus. Moreover, based on the Quality Assessment Tools developed by the National Heart, Lung and Blood Institute from the National Institute of Health, all the included studies were rated as “Good” or “Fair”, which suggested a low risk of bias. Finally, the included publications involved different populations and cardiothoracic surgery departments from eight countries across the world to warrant the applicability the findings and to investigate an extensive range of risk factors for recoarctation and mortality in young infants.

However, there are some important limitations to our systematic review. First, the retrieved studies were heterogeneous regarding the definition of the potential risk factors, adjusted covariates, and sample size; as such, the comparison of the studies was challenging. However, although we did not acquire sufficient studies to perform a meta-analysis for the relationship between the different risk factors for recoarctation and mortality due to heterogeneity of methodology, we still managed to identify key factors. Second, considering the limited number of studies that analyzed some risk factors, the accuracy and validity of the relationship between these factors and the outcome may also be questionable. Importantly, while most studies were rated as “Good” using the

Quality Assessment Tools, indicating a low risk of bias and good ability to draw associative conclusions about the effects of the exposure, significant publication bias was noted in most of the included studies. Most studies did not report all nonsignificant results or reported only the associated p-values. Additionally, the included studies were mostly observational, retrospective and monocentric, with only one clinical trial and one prospective multicentric observational cohort. Hence, the conclusions of this review are subjected to observational bias, and the body of evidence should be taken accordingly.

In conclusion, this study analyzed and identified the risk factors for recoarctation and mortality in infants under 1 year of age submitted to coarctation repair. Notably, we demonstrated that the most determining factors for recoarctation were related to smaller aortic arch and balloon angioplasty, while mortality was strongly associated with lower weight at repair. Moreover, this systematic review established the ambiguity of the methodology in this field, which greatly influences the comparability of findings and condensation of the scientific evidence.

In the future, more extensive, prospective and multicentric cohorts are required for a clear understanding of the many involved factors, which is vital for patient's management.

Author Contributions

MD and JM designed the study. MD and JM worked equally in study selection, data collection and assessed the quality of included studies. MD drafted the manuscript. MD, JM, ALM and AB revised the manuscript. All authors reviewed and approved the final manuscript.

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Compliance with Ethical Standards

Ethical Approval

This study did not require ethical approval.

Conflict of Interest

The authors declare that they have no conflict of interest.

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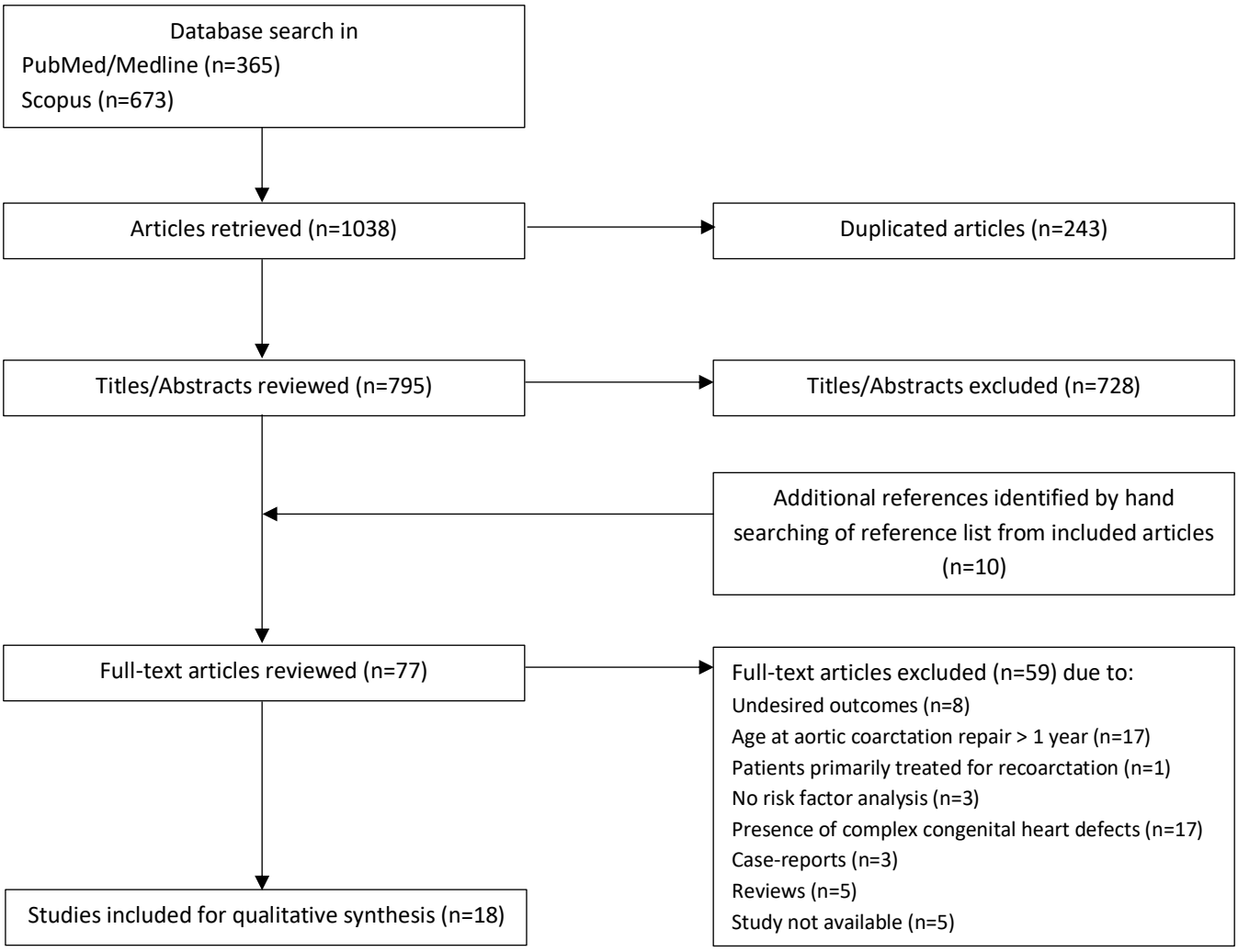

Figure 1. Flowchart of the systematic review of risk factors with recoarctation and mortality in infants submitted to aortic coarctation repair under 1 year of age.

First author	Year	Country	Study Design	Quality assessment	Sample size (N)	Follow-up time (months)		Study endpoints
						Median	Range	
Lehnert**[12]**	2019	France	Retrospective cohort	Good	530	90.8	3-191.8	Reintervention for recurrent obstruction Mortality
Ramachandran**[26]**	2018	US	Retrospective cohort	Good	102	72	-	Reintervention for recurrent obstruction Long-time success
Sen**[27]**[b]	2018	India	Retrospective cohort	Good	75	BA: 6 SR: 6	BA: 6-68 SR: 6-42	Reintervention for recurrent obstruction
Adamson**[19]**	2017	US	Retrospective cohort	Good	68	14.4	3.1-24.3	Recoarctation at 2 years post-surgery
Gorbatykh**[18]**[a]	2017	Russia	Retrospective cohort	Fair	114	37	13	Recoarctation
Soynov**[28]**	2017	Russia	Randomized trial	Na	54	25	21-30	Primary endpoint: freedom from residual arterial hypertension Secondary endpoints: freedom from reoperation due to recoarctation or anastomotic aneurysm; elastic properties of the aortic wall and aortic arch shape
Tulzer**[30]**	2016	Austria	Retrospective cohort	Fair	183	75.6	2.4-217.9	Reintervention for recurrent obstruction Mortality
Truong**[29]**	2014	US	Retrospective cohort	Good	84	12.3	0.5-71.9	Recoarctation
Kalfa**[23]**	2014	Canada	Retrospective cohort	Fair	105	-	-	Mortality
Chiu**[20]**[a]	2013	Taiwan	Retrospective cohort	Good	88	114	62.1	Reintervention for recoarctation CV complications
Burch**[13]**	2009	US	Retrospective cohort	Good	167	57.6	0-141.6	Recurrent obstruction requiring reintervention Survival
Hager**[22]**	2009	Germany	Retrospective cohort	Good	191	156	0-360	Composite endpoint: death + reintervention because of restenosis + current restenosis
Karamlou**[19]**	2009	Canada	Retrospective cohort	Fair	36	-	-	Recoarctation Mortality Aortic arch growth
Liang**[24]**[a]	2009	Taiwan	Retrospective cohort	Good	18	488	33.5	Recoarctation
Curzon**[21]**	2008	US	Retrospective cohort	Good	594	-	-	Mortality
Fiore**[9]**[b]	2005	US	Retrospective cohort	Good	57	BA: 34.5 SR: 32	-	Recoarctation Mortality Aneurysm formation
McElhinney**[14]**	2001	US	Retrospective cohort	Good	103	24	5-111.6	Primary endpoint: reintervention for recurrent obstruction Secondary endpoint: death and intervention for obstruction of the aortic valve and/or subvalvular left ventricular outflow tract
Quaegebeur**[14]**	1994	US	Prospective cohort	Good	322	13.3	0.01-32.4	Mortality Reintervention for recurrent obstruction

Table 1. Baselines characteristics of studies included in the systematic review and meta-analysis.
NA nonapplicable, *N* number.
[a] Follow-up time expressed in mean and respective standard deviation.
[b] Studies present the data divided by groups (BA: Balloon angioplasty group; SR: Surgical repair group).

First author	Year	Male (%)	Age at 1st repair (days)				Weight at 1st repair (kg)				AAH (%)	VSD (%)	Thoracotomy (%)	Sternotomy (%)
			Mean	±SD	Median	Range	Mean	±SD	Median	Range				
Lehnert**[12]**	2019	58.7	13	1.6	-	-	3.2	0.75	-	-	30.4	41.9	87	13
Ramachandran**[26]**	2018	-	-	-	12	2-375	-	-	3.3	1.1-9.8	-	-	100	0
Sen**[27]**[b, c]	2018	73.3	-	-	BA: 1.3 SR: 1.2	BA: 0.18-10 SR: 0-12	3.8	1.7	-	-	46.7	-	0	100
Adamson**[19]**[c]	2017	67.6	20.9	20.8	-	-	3.3	0.9	-	-	-	8.8	69	31
Gorbatykh**[18]**	2017	-	6.1	3.8			6.4	3.5	-	2.5-10.4	14.9	-	100	0
Soynov**[28]**[a]	2017	64.8	-	-	MRA: 63.9 EEEA: 67.6	MRA: 9-96 EEEA: 21-94	-	-	MRA: 3.9 EEEA: 4.5	MRA: 3.2–4.2 EEEA: 3.2–5.1	100	-	100	0
Tulzer**[30]**	2016	57.9	-	-	15	6.5-50	-	-	3.4	2.8-4.2	100	28.4	60.7	39.3
Truong**[29]**	2014	62	-	-	12	1-85	-	-	3.4	1.18-5.9	-	21.4	100	-
Kalfa**[23]**	2014	-	-	-	-	-	-	-	-	-	61.9	38.1	-	-
Chiu**[20]**[c]	2013	59.1	1.3	0.96	-	-	3.5	0.7	-	-	63.6	69.3	NA	NA
Burch**[13]**	2009	48	-	-	16	1-85	-	-	3.4	0.8-6	-	37.1	100	0
Hager**[22]**	2009	63.4	-	-	41	3-352	-	-	-	-	28.8	0	-	-
Karamlou**[31]**	2009	-	-	-	11	2-69	2.	0.3	-	-	-	50	83.3	16.7
Liang**[24]**	2009	83.3	84	93	-	21-330	4	1.9	-	2.1-8.0	-	33.3	NA	NA
Curzon**[21]**	2008	-	-	-	-	-	-	-	-	-	-	-	-	-
Fiore**[9]**[b]	2005	61.4	BA: 8.8 SR: 7.7	-	-	-	BA: 3.6 SR: 3.4	-	-	-	-	50.9	100	0
McElhinney**[14]**	2001	61	-	-	18	1-90	-	-	3.3	1.0-6.4	-	18	100	0
Quaegebeur**[25]**	1994	-	-	-	6	0-23	-	-	2.97	1.6-4.0	1.2	47.5	-	-
TOTAL		61	-	-	-	-	-	-	-	-	-	34.4	70	21.7

Table 2. Baseline characteristics of study participants, including age, weight, associated anomalies and surgical repair approach.
NA Surgical approach not applicable because repair strategy was percutaneous balloon angioplasty, *SD* standard deviation, *AAH* aortic arch hypoplasia, *VSD* ventricular septal defect.
[a] Study presented the data divided by groups (MRA: modified reverse aortoplasty; EEEA: extended end-to end anastomosis).
[b] Studies present the data divided by groups (BA: Balloon angioplasty group; SR: Surgical repair group).
[c] Studies present the data divided by groups and mean values were calculated.

First author	Year	Recoarctation rate (%)	Risk factors for recoarctation	Statistical method	Effect size measure
Lehnert**[12]**	2019	11.5	Prematurity; postnatal diagnosis; left superior vena cava; mitral valve size <-2SD; VSD; bicuspid aortic valve; hypoplastic transverse aorta (<3 mm); arterial duct open before surgery; dilatation in emergency before surgery; **PGE1 infusion at surgery**; weight at surgery <2.5 kg; **age at surgery <15 days**; sternotomy; type of surgical strategy; type of aortic arch repair; left subclavian conservation; extracorporeal circulation	Univariable and multivariable[d] Cox proportional hazard regression	Exp(B)
Ramachandran**[26]**[c]	2018	5.9	Echography arch dimensions; age at surgery; weight at surgery; surgical complications; PGE1 infusion; outpatient vs inpatient before surgery	Multivariable proportional hazards regression	-
Sen**[27]**[a]	2018	34.7	Balloon angioplasty in neonates	Chi-squared test	-
			Residual coarctation on the pre-discharge echocardiogram	Univariate analysis	
Adamson**[19]**	2017	22	Male sex; prenatal diagnosis; EGA (weeks); age at diagnosis (days); genetic syndrome; bicuspid aortic valve; bovine trunk; aberrant subclavian; patent ductus arteriosus; small septal defects; posteriorly malaligned VSD; small left sided structures; age at surgery (days); weight at surgery (kg); sternotomy (CPB); **patch aortoplasty**; cross-clamp time (min); CPB time (min); immediate SBP gradient; paradoxical hypertension; laryngeal nerve injury: phrenic nerve injury; length of hosp. stay (days); discharge SBP gradient; ascending arch diameter; ascending arch z score; transverse arch diameter; transverse arch z score; coarctation diameter; **coarctation index <0.7**; doppler CW peak velocity; diastolic flow continuation in the abdominal aorta	Univariable and multivariable[d] logistic regression	OR
Gorbatykh**[18]**	2017	13.2	Age at surgery <1 month; weight at surgery <3kg; body surface area <0.3m^2; distal aortic arch z-score; PGE1 infusion before surgery; hypoplasia of the aortic arch; oblique anastomosis under the aortic arch; direct anastomosis; reversible aortoplasty	Multivariate Cox regression	
Soynov**[28]**[a]	2017	5.6	Low weight before surgery	Multivariable Cox regression	OR
Tulzer**[30]**	2016	6	EEEA with thoracotomy	Univariate analysis	-
Truong**[29]**	2014	8.0	Prenatal diagnosis; prematurity (gestational age<37 weeks); birth weight; distal ascending aorta z-score; proximal arch z-score; distal arch z-score; descending aorta diameter, indexed; aortic root z-score; **ST junction z-score**; proximal ascending aorta z-score; weight at surgery (kg); suture material (prolene vs. polydioxanone); duration of intensive care unit stay; arm/leg systolic blood pressure gradient ≥20 mmHg; inotropes; **postoperative peak Doppler flow velocity**	Univariable and multivariable[d] Cox proportional hazards model	HR
Kalfa**[23]**	2014	-	NA	-	-
Chiu**[20]**[a]	2013	46.6	Balloon angioplasty; patent ductus arteriosus	Multivariate logistic regression	-
Burch**[13]**	2009	10.8	Cross-clamp time (per min increase); **suture type (polypropylene vs polydioxanone)**; EGA (<37 weeks); PGE1 infusion at surgery; ductus arteriosus (closed vs open); **female sex**; absolute transverse arch diameter (per 1-mm increase); age at repair (per 10-d increase); weight at surgery (per 1-kg increase)	Multivariable Cox regression	RR
Hager**[22]**[b]	2009	23	Hypoplastic aortic arch; body length at surgery	Multivariable Cox regression	OR
Karamlou**[31]**	2009	13.9	VSD	Multivariate logistic regression	-
Liang**[24]**	2009	44.4	Age (months); weight (kg); PGB (mmHg); PGA (mmHg); MPAP (mmHg); CoA diameter (mm); follow-up (months); PGA ≥10 mmHg; sex (M/F); associated PDA; CoA diameter ≤3 mm; age ≤1 month	Student's t-test and Fisher's exact test	Mean/ Frequency
Curzon**[21]**	2009	-	NA	-	-
Fiore**[9]**[a]	2005	83	Balloon angioplasty	Kaplan-Meier analysis	-
McElhinney**[14]**	2001	15.4	**Age (continuous)**; age <2 weeks; weight (continuous); weight <2 kg; premature birth; male sex; valvular aortic stenosis; bileaflet aortic valve; ventricular septal defect; abnormal mitral valve apparatus; left superior caval vein; common brachiocephalic trunk; syndromes/multiple noncardiac anomalies; ascending aorta diameter (absolute); ascending aorta diameter indexed to weight; **transverse arch diameter (absolute)**; transverse arch diameter indexed to weight; aortic isthmus diameter (absolute); aortic isthmus diameter indexed to weight; transverse arch/ascending aorta	Univariable and multivariable[d] Cox proportional hazard regression	

			diameter ratio; isthmus/ascending aorta diameter ratio; isthmus/transverse arch diameter ratio; symptoms of coarctation present; diagnosis by fetal echocardiogram; newborn diagnosis and admission; alprostadil infusion; repair by subclavian flap angioplasty; repair by end-to-end anastomosis		
Quaegebeur**[25]**	1994	7.0	Patch graft	Multivariable hazard function regression	-

Table 3. Recoarctation rates and risk factors studied in the systematic review, with respective statistical method analysis.
NA nonapplicable, *VSD* ventricular septal defect, *PGE1* prostaglandin E1, *CPB* cardiopulmonary bypass, *SBP* systolic blood pressure, *CW* continuous wave, *EEEA* extended end-to-end anastomosis, *ST* sinotubular, *EGA* end gestational age, *PGB* pressure gradient before balloon angioplasty, *PGA* pressure gradient after balloon angioplasty, *MPAP* mean pulmonary artery pressure, *CoA* coarctation of the aorta, *PDA* patent ductus arteriosus, *OR* odds ratio, *RR* relative risk, *HR* hazard ratio.
[a] Studies present the data divided by groups and mean values were calculated.
[b] Study has composite primary outcome for recoarctation + mortality.
[c] Study outcome is long-term success, defined by freedom of reintervention and mortality.
[d] Bold-text risk factors were inserted in multivariable models.

First author	Year	Mortality rate (%)	Risk factors for mortality	Statistical method	Effect size measure
Lehnert**[12]**	2019	3.6	Presence of VSD; weight at surgery <2.5kg	Multivariable Cox proportional hazard regression	Exp (B)
Ramachandran**[26]**[b]	2018	0	Echography arch dimensions; age at surgery; weight at surgery; surgical complications; use of prostaglandin; outpatient vs inpatient before surgery	Multivariable proportional hazards regression	-
Sen**[27]**	2018	2.7	NA	-	
Adamson**[19]**	2017	0	NA	-	-
Gorbatykh**[18]**	2017	0	NA	-	-
Soynov**[28]**	2017	3.7	NA	-	-
Tulzer**[30]**	2016	0.54	NA	-	-
Truong**[29]**	2014	0	NA	-	-
Kalfa**[23]**	2014	2.8	Weight <2.5kg in hypoplastic arch repaired by sternotomy	Cochran Mantel-Haenszel	-
Chiu**[20]**	2013	0	NA	-	-
Burch**[13]**	2009	1.8	NA	-	-
Hager**[22]**[a]	2009	2.6	Hypoplastic aortic arch; body length at surgery	Multivariable Cox regression model	OR
Karamlou**[19]**	2009	22.2	No risk factor associated with mortality was found	Multivariable analysis	-
Liang**[24]**	2009	0	NA	-	-
Curzon**[21]**	2008	3.5	Weight <25kg	Univariate analysis	RR
Fiore**[9]**	2005	0	NA	-	-
McElhinney**[14]**	2001	0	NA	-	-
Quaegebeur**[14]**	1994	15	Age (days) at repair and multiplicity of VSDs; single, moderate-sized or large VSD; size of VSDs and multiplicity of VSDs; multiplicity of VSDs; MV anomaly (with/out other anomalies of LV-Ao); subaortic narrowing and no mitral valve anomaly; aortic valve stenosis, isolated; aortic valve stenosis and LV hypoplasia; severe noncardiac anomalies; EEEA repair proximal to LCC artery, and VSD; extension of patch graft prox. to LSA, and moderate/large VSD; repair of CoA with PT band and presence of VSD	Multivariable hazard function regression	Coefficient ± SD

Table 4. Mortality rates and risk factors studied in the articles systematically reviewed.
NA nonapplicable, *VSD* ventricular septal defect, *MV* mitral valve, *LV* left ventricle, *EEEA* extended end-to-end anastomosis, *LCC* left common carotid, *LSA* left subclavian artery, *CoA* coarctation of the aorta, *PT* pulmonary trunk, *OR* odds ratio, *RR* relative risk, *SD* standard deviation.
[a] Study has composite primary outcome for recoarctation + mortality.
[b] Study outcome is long-term success, defined by freedom of reintervention and mortality.

Risk factor category	First author	Year	Statistical analysis	Risk factor for recoarctation	Effect size	CI95%	p-value	Effect measure
Demographic variables	Lehnert[12]	2019	Multivariable analysis	Age at surgery <15 days	-	-	0.032	Exp(B)
	McElhinney[14]	2001	Multivariable analysis	Age at surgery	1.06	1.00-1.11	0.05	OR
	Truong[29]	2014	Univariable analysis	Birth weight	0.38	0.16-0.93	0.03	HR
	Soynov[28]	2017	Univariable analysis	Weight at surgery (kg)	0.016	0.001-0.51	0.047	OR
	Gorbatykh[18]	2017	Multivariable analysis	Weight <3kg	1.97	1.59-2.45	<0.0001	OR
	Burch[13]	2009	Multivariable analysis	Sex (female vs male)	2.77	1.05-7.30	0.04	RR
	Hager[22][b]	2009	Multivariable analysis	Body length at surgery	0.923	0.560-0.970	0.001	OR
Associated anomalies	Hager[22][b]	2009	Multivariable analysis	Hypoplastic aortic arch	2.864	1.581-5.186	0.001	OR
	Gorbatykh[18]	2017	Multivariable analysis	Hypoplastic aortic arch	1.31	1.08-2.75	0.0047	OR
Clinical and repair variables	Lehnert[12]	2019	Multivariable analysis	PGE1 infusion before surgery	-	-	0.0072	Exp(B)
	Truong[29]	2014	Univariable analysis	Inotropes	5.57	1.08-28.89	0.04	HR
	Burch[13]	2009	Multivariable analysis	Suture type (polypropylene vs polydioxanone)	3.31	1.21-8.59	0.014	RR
	Adamson[19]	2017	Multivariable analysis	Patch aortoplasty	9.36	1.57-54.66	0.014	OR
	Quaegebeur[14][a]	1994	Univariable analysis	Patch aortoplasty	-	-	0.002	-
	Gorbatykh[18]	2017	Multivariable analysis	Direct anastomosis	2.82	0.82-1.89	<0.001	OR
	Gorbatykh[18]	2017	Multivariable analysis	Oblique anastomosis	1.42	1.07-2.23	0.045	OR
	Tulzer[30]	2016	Univariable analysis	EEEA with thoracotomy	-	-	<0.05	-
	Sen[27]	2018	Univariable analysis	Balloon angioplasty in <1 month (vs surgical repair)	-	-	0.007	Frequency
	Chiu[20]	2013	Univariable analysis	Balloon angioplasty (vs surgical repair)	-	-	<0.05	-
	Fiore[9]	2005	Univariable analysis	Balloon angioplasty (vs surgical repair)	-	-	<0.05	-
	Truong[29]	2014	Univariable analysis	Duration of intensive care unit stay	1.31	1.1-1.54	<0.01	HR
	Truong[29]	2014	Multivariable analysis	Postoperative peak doppler velocity flow	1.13	1.04-1.23	<0.01	HR
	Sen[27]	2018	Univariable analysis	Residual coarctation on the pre-discharge echocardiography	-	-	0.04	-
	Adamson[19]	2017	Univariable analysis	Discharge SBP gradient	-	-	0.04	-
	Liang[24]	2009	Univariable analysis	PGA (mmHg)	-	-	0.012	Mean
Morphometric variables	Adamson[19]	2017	Multivariable analysis	Coarctation index <0.7	33.8	5.7-199.5	0.0001	OR
	Liang[24]	2009	Univariable analysis	CoA diameter ≤3mm	-	-	0.013	Frequency
	McElhinney[14]	2001	Univariable analysis	Ascending arch diameter (absolute)	2.1	1.14-3.8	0.02	OR
	Truong[29]	2014	Univariable analysis	Proximal ascending aorta z-score	2.99	1.19-7.53	0.02	HR
	Truong[29]	2014	Univariable analysis	Descending aorta diameter, indexed	0.14	0.02-0.89	0.04	HR
	Truong[29]	2014	Multivariable analysis	ST junction z score	4.19	1.47-11.95	<0.01	HR
	McElhinney[14]	2001	Multivariable analysis	Transverse arch diameter (absolute)	3.0	1.54-6.0	0.001	OR
	McElhinney[14]	2001	Univariable analysis	Transverse arch diameter indexed to weight	7.9	2.0-31.4	0.04	OR
	Burch[13]	2009	Univariable analysis	Transverse arch diameter (per 1-mm increase)	0.57	0.34-0.96	0.04	RR
	McElhinney[14]	2001	Univariable analysis	Transverse arch/ascending aorta diameter ratio	20.2	1.11-491	0.02	OR

Table 5. Identified risk factors for recoarctation according to the studies included in the systematic review.
CI confidence interval, *PGE1* prostaglandin E1, *EEEA* extended end-to-end anastomosis, *SBP* systolic blood pressure, *PGA* pressure gradient after balloon angioplasty, *CoA* coarctation of the aorta, *ST* sinotubular, *OR* odds ratio, *RR* relative risk, *HR* hazard ratio.
[a] Study used a confidence interval of 70%.
[b] Study has composite primary outcome for recoarctation + mortality.

Risk factor category	First author	Year	Statistical analysis	Risk factor for mortality	Effect size	CI95%	p-value	Effect measure
Demographic variables	Quaegebeur[14][a]	1994	Multivariable analysis	Age (days) at repair and multiplicity of VSDs	-0.33	±0.071	<0.0001	Coefficient
	Lehnert[12]	2019	Multivariable analysis	Weight at surgery <2.5kg	-	-	0.037	Exp(B)
	Curzon[21]	2008	Univariable analysis	Weight <2.5kg	2.65	1.12-6.24	<0.01	RR
	Hager[22][b]	2009	Multivariable analysis	Body length at surgery	0.923	0.560-0.970	0.001	OR
Associated anomalies	Lehnert[12]	2019	Multivariable analysis	VSD	-	-	0.001	Exp(B)
	Quaegebeur[14][a]	1994	Multivariable analysis	Single, moderate-sized or large VSD	1.16	±0.47	0.01	Coefficient
	Quaegebeur[14][a]	1994	Multivariable analysis	Size of VSDs and multiplicity of VSDs	-3.9	±1.48	0.009	Coefficient
	Quaegebeur[14][a]	1994	Multivariable analysis	Multiplicity of VSDs	6.6	±1.57	<0.0001	Coefficient
	Quaegebeur[14][a]	1994	Multivariable analysis	MV anomaly (with/out other anomalies of LV-Ao)	3.7	±0.43	<0.0001	Coefficient
	Quaegebeur[14][a]	1994	Multivariable analysis	Subaortic narrowing and no mitral valve anomaly	3.8	±0.58	<0.0001	Coefficient
	Quaegebeur[14][a]	1994	Multivariable analysis	Aortic valve stenosis, isolated	1.94	±0.67	0.004	Coefficient
	Quaegebeur[14][a]	1994	Multivariable analysis	Aortic valve stenosis and LV hypoplasia	3.2	±0.79	<0.0001	Coefficient
	Quaegebeur[14][a]	1994	Multivariable analysis	Severe noncardiac anomalies	1.17	±0.54	0.03	Coefficient
	Hager[22][b]	2009	Multivariable analysis	Hypoplastic aortic arch	2.864	1.581-5.186	0.001	OR
Clinical and repair variables	Quaegebeur[14][a]	1994	Multivariable analysis	EEEA repair proximal to LCC artery, and VSD	1.45	±0.56	0.009	Coefficient
	Quaegebeur[14][a]	1994	Multivariable analysis	Extension of patch graft prox. to LSA, and moderate/large VSD	1.87	±0.47	<0.0001	Coefficient
	Quaegebeur[14][a]	1994	Multivariable analysis	Repair of CoA with PT band and presence of VSD	-1.55	±0.67	0.02	Coefficient

Table 6. Identified risk factors for mortality according to the studies included in the systematic review.
VSD ventricular septal defect, *MV* mitral valve, *LV-Ao* left ventricle – aorta, *EEEA* extended end-to-end anastomosis, *LCC* left common carotid, *LSA* left subclavian artery, *CoA* coarctation of the aorta, *PT* pulmonary trunk.
[a] Study used a confidence interval of 70%, and the confidence interval is given by the standard deviation.
[b] Study has composite primary outcome for recoarctation + mortality.

Anexo 1: Submission Guidelines for Pediatric Cardiology

Title Page

The title page should include:

- The name(s) of the author(s)
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Always use footnotes instead of endnotes.

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Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

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Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].
2. This result was later contradicted by Becker and Seligman [5].
3. This effect has been widely studied [1-3, 7].

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Apêndice 1: Online Resource 1

Author	Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality rating
Lehnert[12]	2019	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	NR	✓	Good
Ramachandran[28]	2018	✓	✓	✓	✓	X	✓	✓	✓	✓	NA	✓	NA	NR	✓	Good
Sen[29]	2018	✓	✓	✓	✓	✓	✓	X	✓	✓	NA	✓	NA	NR	✓	Good
Adamson[21]	2017	✓	✓	✓	✓	X	✓	✓	✓	✓	NA	✓	NA	✓	✓	Good
Gorbatykh[20]	2017	✓	✓	✓	✓	X	✓	✓	X	✓	NA	✓	NA	NR	✓	Fair
Soynov[30]	2017	✓	✓	NR	NR	NR	✓	✓	✓	✓	✓	✓	X	✓	✓	Fair
Tulzer[32]	2016	✓	✓	✓	✓	X	✓	✓	X	✓	NA	✓	NA	X	✓	Fair
Truong[31]	2014	✓	✓	✓	✓	X	✓	✓	✓	✓	NA	✓	NA	✓	✓	Good
Kalfa[25]	2014	✓	✓	✓	✓	X	✓	✓	X	✓	NA	✓	NA	NR	✓	Fair
Chiu[22]	2013	✓	✓	✓	✓	X	✓	✓	X	✓	NA	✓	NA	✓	✓	Good
Burch[15]	2009	✓	✓	✓	✓	X	✓	✓	✓	✓	NA	✓	NA	✓	✓	Good
Hager[24]	2009	✓	✓	✓	✓	X	✓	✓	X	✓	NA	✓	NA	✓	✓	Good
Karamlou[21]	2009	✓	✓	✓	✓	X	✓	✓	X	✓	NA	✓	NA	NR	✓	Fair
Liang[26]	2009	✓	✓	✓	✓	X	✓	✓	✓	✓	NA	✓	NA	NR	✓	Good
Curzon[23]	2008	✓	✓	✓	✓	X	✓	✓	✓	✓	NA	✓	NA	NR	✓	Good
Fiore[9]	2005	✓	✓	✓	✓	X	✓	✓	X	✓	NA	✓	NA	✓	✓	Good
McElhinney[16]	2001	✓	✓	✓	✓	X	✓	✓	✓	✓	NA	✓	NA	✓	✓	Good
Quaegebeur[16]	1994	✓	✓	✓	✓	X	✓	✓	✓	✓	NA	✓	NA	✓	✓	Good

Online Resource 1 - Summary for quality assessment of studies included in the systematic review using the Quality Assessment Tools – National Heart, Lung and Blood Institute, National Institute of Health.
NA nonapplicable, NR not reported.