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The prognosis of common arterial trunk from a fetal perspective: A prenatal cohort study and systematic literature review

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Abstract

Objective: The limited number of large fetal cohort studies on common arterial trunk (CAT) impedes prenatal counseling at midgestation. This study evaluates the prognosis of CAT from a fetal perspective.

Method: Fetuses with a prenatally diagnosed CAT were extracted from the PRECOR registry (2002–2016). We evaluated fetal and postnatal survival and the presence of additional morbidity at last follow-up. Literature databases were searches systematically for additional cases.

Results: Thirty-eight cases with a prenatal diagnosis of CAT were identified in our registry, of which 18/38 (47%) opted for pregnancy termination (TOP). Two cases resulted in spontaneous intrauterine demise (10%, 2/20), six cases demised postnatally (33%, 6/18), leaving 60% (12/20) alive, after exclusion of TOP, at a mean age of six (range: 2–10 years).

Additional morbidity was found in 42% (5/12) of survivors, including 22q11.2 deletion syndrome, Adams-Oliver syndrome and intestinal atresia, whereas 8% (1/12) had developmental delay. The remaining 30% (6/12) of survivors appeared isolated with normal development. All of whom six required replacement of the initial right ventricle to pulmonary artery conduit. Additionally, we reviewed 197 literature cases on short-term outcome.

Conclusion: The risk of fetal and neonatal demise, as well as significant morbidity amongst survivors, should be included in prenatal counseling for CAT.

Key Points

What's already known about this topic?

- Postnatal cohort studies have reported generally good postoperative results for common arterial trunk (CAT)

- Prenatal counseling relies primarily on these selected cohorts, due to the lack of prenatal follow-up studies

What does this study add?

- A large cohort study evaluating outcome of fetal CAT beyond the neonatal period and with regard to the presence of genetic diagnoses, extracardiac malformations and neurodevelopment
- The first systematic literature review on short-term outcome following a prenatal diagnosis of CAT

1 | INTRODUCTION

Common arterial trunk (CAT), also known as truncus arteriosus, is a rare congenital heart defect (CHD) that accounts for approximately 1% of fetuses diagnosed with a CHD.[1] It is characterized by a single arterial trunk, overriding the interventricular septum, which provides blood to the systemic and pulmonary circulation and coronary arteries. To describe the anatomical variations between CAT cases, three classification systems have been reported to date.[2–4]

Prenatal detection rates for conotruncal anomalies, including CAT, have increased substantially over the past years.[5–8] A prenatal diagnosis provides the opportunity for genetic analysis and advanced ultrasound examination, given its association with genetic syndromes and (extra-) cardiac malformations.[9–11] This is essential, as it enables parents to make an informed decision whether to continue the pregnancy and provides the opportunity for delivery in a specialized facility. Despite these clear benefits, evidence stating that a prenatal diagnosis would influence neonatal mortality and morbidity, is scarce.[12–17]

Parental counseling for fetuses with a CAT is, however, primarily based on postnatal cohort studies, due to the lack of large studies on prenatally detected cases. The majority of these postnatal cohorts focus on postoperative results or neonatal outcome, which may only reflect a selected population of CAT cases.[18–20] To provide evidence on the prognosis of CAT from a fetal perspective and improve prenatal counseling at midgestation, this study will focus on outcome of *fetuses* with a prenatal diagnosis of CAT. A systematic analysis of the literature is performed to assemble evidence from currently available studies.

2 | METHODS

All fetuses and neonates with a diagnosis of a CHD in the region Amsterdam-Leiden (40,000 births/year) are referred to a tertiary care center. Since 2002 these centers have together collected all CHD cases in our population-based registry "PRECOR." Data collection for this registry has explicitly been described before.[21] We used this registry to identify all fetuses with a prenatal diagnosis of CAT from 2002 to 2016. The standard midtrimester anomaly scan was introduced as part of the Dutch national screening program in 2007. Our cohort has reported one of the highest prenatal detection rates since, including a 85% prenatal detection rate for CAT,[21] which has only increased over time. As the majority of prenatally detected cases in this cohort originate from 2007–2016, we expect that our cohort is representative for all fetuses with CAT.

Postnatal echocardiography and postmortem reports were assessed to ascertain the diagnosis in all cases. If pregnancy was terminated or spontaneous intrauterine fetal demise (IUFD) occurred without parental consent for autopsy, cases were not excluded to avoid selection bias.

The fetal ultrasound databases were evaluated for data on structural malformations, genetic testing and pregnancy outcome. Patient records were studied to assess postnatal mortality (age at) surgery, neurodevelopment at postsurgical outpatient consultations and verify the extracardiac malformations (ECMs) detected with prenatal ultrasound.

Patient characteristics and respective outcome parameters will be presented for each case individually. This study has been approved by the Leiden University's medical ethics committee.

2.1 | Systematic review

Our systematic review of the literature is reported following the PRISMA statement[22] and has been submitted for registration in the PROSPERO database on 11 September 2019. We explored the PubMed, Embase, Web of Science, Academic Search Premier, and Cochrane Library databases for articles on outcome of fetal CAT in September 2019. The entire search strategy is enclosed as supplementary material (Appendix S1).

Criteria for inclusion in the systematic review were; (1) case series (≥3 cases minimum) ór cohort studies (any number of CAT cases) that report on (2) pregnancy or postnatal outcome of (3) prenatally diagnosed case(s) with CAT. Fetal studies focusing on cohorts with 22q11.2 deletion syndrome (DS) were not considered eligible for inclusion to avoid a potential selection bias. If information on pregnancy outcome was missing from the abstract or full-text, authors were contacted for additional information to enable inclusion of these studies in the review.

Two researchers (Amber v Nisselrooij (AvN), Lotta Herling and Monique Haak (LH)) independently screened the literature search results for eligible articles. Discordances were discussed and, if necessary, a third reviewer (MH) was consulted. The same authors (AvN, LH) studied the full-text of selected articles to extract data on pregnancy and postnatal outcome in fetuses with a prenatal diagnosis

of CAT. Pregnancy outcome was considered our primary outcome, as most studies focused on perinatal parameters. Secondary parameters included: neonatal surgery, neonatal mortality (<28 days of age), survival at the end of the study period and the presence of a genetic diagnosis or additional malformations. If multiple studies reported on the same cases, the most eligible study was chosen.

The Quality in Prognostic Studies (QUIPS) tool[23] was used to evaluate the quality of selected articles was evaluated [AvN and LH, independently] and identify major risks of bias. This assessment was merely used for interpretation of results and did not determine inclusion in the review.

Descriptive statistics were used to display the results of all included articles separately, with regard to pregnancy outcome, postnatal course and the presence of additional morbidity. To estimate the prognosis of fetal CAT in a large cohort of prenatally diagnosed fetuses, we attempted to summarize the raw data from all included articles and combine these with our own original data, when possible.

3 | RESULTS

We identified 43 fetuses with a prenatal diagnosis of CAT in the PRECOR registry. Consent for autopsy was obtained in 30% (6/20) of demised fetuses, which all confirmed the prenatal diagnosis. Postnatal echocardiography confirmed the diagnosis in 78% (18/23) of liveborn cases, resulting in an 83% (24/29) overall diagnostic accuracy. After exclusion of these five misdiagnosed cases with pulmonary atresia and a ventricular septal defect (PA-VSD), 38 cases were included in this study. The majority of fetuses originated from 2007–2016 (87%, 33/38).

3.1 | Structural malformations

Fetuses with CAT had additional morbidity in 61% (23/38) of the cases, involving genetic syndromes (39%, 15/38) and/or structural ECMs (53%, 20/38). Karyotyping or aneuploidy testing was performed in all cases (38/38), whereas some received additional testing for genetic syndromes as well: 39% (15/38) FISH for 22q11.2 DS, 39% (15/38) chromosome microarray analysis and 18% (7/38) exome sequencing, respectively. Although 22q11.2 DS (21%, 8/38) was diagnosed particularly often, less common syndromes, such as CHARGE, Adams-Oliver and Cri-du-Chat syndrome, were also found in a significant proportion of fetuses (18%, 7/38). The ECMs diagnosed on prenatal ultrasound were all confirmed postnatally, and none of the fetuses that appeared isolated on prenatal ultrasound showed ECMs after birth.

Additional cardiac anomalies were present prenatally in 37% (14/38) of all fetuses with CAT. These mainly comprised truncal valve regurgitation (moderate to severe) or stenosis (21%, 8/38) and interruption of the aortic arch (IAoA; 8%, 3/38). Other significant CHDs, including polyvalvular disease (3%, 1/38), anomalous pulmonary venous return (3%, 1/38), mitral valve stenosis (3%, 1/38) and unroofed coronary sinus (3%, 1/38), all occurred in nonisolated cases (Table 1).

Isolated CAT cases (39%, 15/38), without a (prenatally suspected) genetic diagnosis or ECMs, presented with significant prenatal truncal valve regurgitation or stenosis in 33% (5/15) or an interrupted aortic arch in 7% of cases (1/15), respectively. However, the majority (60%, 9/15) did not show other significant cardiac anomalies (right aortic arch or aberrant right subclavian artery not considered; Table 1).

3.2 | Termination of pregnancy

Parents opted for pregnancy termination (TOP) in 47% (18/38) of cases with a prenatally diagnosed CAT, of which 5% (2/38) comprised selective multifetal pregnancy reductions. The majority of terminated cases had additional morbidity (72%, 13/18) or significant truncal valve regurgitation (11%, 2/18) and only 17% (3/18) appeared isolated. The proportion of TOPs for CAT decreased over time: from 57% in 2002%–2009% to 41% in 2010–2016.

3.3 | Mortality

IUFD occurred in 10% (2/20) of continuing pregnancies. The remaining 90% (18/20) resulted in a liveborn neonate at a median gestational age of 39 weeks (Table 1). Four neonates (22%, 4/18 liveborns) died within the first week of life. Two had spontaneous preterm prelabor rupture of membranes (PPROM) and were not actively treated after birth. Both of whom had a very poor prognosis and expected quality of life, based on the combination of (extreme) prematurity and significant additional morbidity (case 22 and 24). The remaining two were actively treated, but died either pre- or postoperatively. The first (case 23) comprised a case with CHARGE syndrome and multiple congenital anomalies that was delivered at 34 weeks of gestation due to PPROM. She died the first day despite ventilation and intubation. The second case (case 21) with 22q11.2 DS and IAoA underwent surgery at day 7, but died the same day due to severe postoperative complications.

We encountered two infant deaths (11%, 2/18 liveborns) at 5 and 18 months of age. One infant (case 25) was born dysmature at 31 weeks of gestation and had a complex CAT with an atrioventricular septal defect, severe left atrioventricular valve incompetence and mild-to-moderate truncal valve regurgitation. She underwent banding of the pulmonary arteries at 3 weeks of age (body weight: 1900 g) and presented with poor right ventricular function at 5 months of age. Although corrective surgery was planned immediately, a cardiac arrest occurred during preoperative preparations and she eventually died of multiorgan failure. The second case (case 26) with CAT type 2, complicated by bilateral pulmonary artery stenosis, received corrective surgery and replacement of the Gore-Tex patch with a pulmonary homograft at 16 months of age. Two months later, the child suddenly deteriorated at home and a cardiac arrest followed shortly after, most likely provoked by a respiratory tract infection causing increased right ventricular pressures.

TABLE 1 Outcome and associated anomalies in 38 cases with a prenatal diagnosis of CAT

					Outcome				Associated anomalies		
Case	Sex	GA dx	Birth year	CAT conf.	Pregnancy	GA at birth	Age at surgery	Devel. delay	Cardiac, prenatal	Extracardiac, prenatal	Genetic diagnosis
1	F	19 + 0	2003	–	TOP	–	–	–	0	Cleft lip	22q11.2 DS
2	M	20 + 5	2006	+	TOP	–	–	–	0	MCA[a]	0
3	M	20 + 3	2006	+	TOP	–	–	–	0	0	22q11.2 DS
4	M	18 + 3	2006	–	TOP	–	–	–	0	MCA[b]	MODY type 3
5	M	20 + 4	2007	–	TOP	–	–	–	0	0	0
6	F	19 + 6	2007	–	TOP	–	–	–	RAA, PLSVC, ARSA	MCA[c]	0
7	F	21 + 5	2008	+	TOP	–	–	–	0	MCA[d]	0
8	M	20 + 1	2008	–	TOP	–	–	–	RAA	Cleft lip-palate	0
9	M	19 + 6	2008	–	TOP	–	–	–	Truncal valve regurg.	0	22q11.2 DS
10	M	19 + 5	2009	+	TOP	–	–	–	0	0	0
11	F	21 + 5	2009	–	TOP	–	–	–	0	0	0
12	F	20 + 6	2010	+	TOP	–	–	–	Truncal valve regurg., fibroelastosis	MCA[e]	Trisomy 9 mosaicism
13	M	19 + 1	2010	–	TOP	–	–	–	Polyvalvular disease	Cerebellar hypoplasia, Rocker bottom feet	Trisomy 13
14	F	20 + 0	2014	–	TOP	–	–	–	Truncal valve regurg./stenosis	0	0
15	F	21 + 0	2015	–	TOP	–	–	–	Truncal valve stenosis	0	22q11.2 DS
16	M	20 + 2	2016	–	TOP	–	–	–	Truncal valve regurg.	0	0
17	F	19 + 4	2009	–	MFPR	–	–	–	0	Abnormal aspect kidney + Urethral dilatation	PTHSL1
18	M	18 + 3	2014	–	MFPR	–	–	–	0	sIUGR (gratacos 3), SUA	0
19	M	20 + 3	2008	–	IUFD (29 + 0)		–	–	Truncal valve regurg.	Fetal hydrops	0
20	F	17 + 5	2009	+	IUFD (29 + 5)		–	–	Truncal valve regurg., IAoA	Fetal hydrops	0
21	M	20 + 5	2005	+	NND (day 7)	40 + 3	7	–	IAoA type B *[RAA]*	0	22q11.2 DS
22	M	21 + 0	2007	+	NND (day 1)	35 + 3 (PPROM)	–	–	0	IUGR	Cri-du-Chat syndrome
23	F	19 + 1	2011	+	NND (day 1)	34 + 1 (PPROM)	–	–	APVR	MCA[f]	CHARGE syndrome
24	F	17 + 1	2014	+	NND (day 4)	28 + 4 (PPROM)	–	–	MS, PLSVC, enlarged CS	IUGR	0

(Continues)

TABLE 1 (Continued)

					Outcome				Associated anomalies		
Case	Sex	GA dx	Birth year	CAT conf.	Pregnancy	GA at birth	Age at surgery	Devel. delay	Cardiac, prenatal	Extracardiac, prenatal	Genetic diagnosis
25	F	16 + 5	2016	+	InfD (5 months)	31 + 5	22	–	RAA *[AVSD]*	MCA[g]	0
26	M	20 + 5	2015	+	InfD (1.5 years)	39 + 6	8	+	0	0	0
27	F	21 + 0	2007	+	Alive (4 years)	39 + 2	14	+	0	0	22q11.2 DS
28	F	34 + 1	2008	+	Alive (10 years)	38 + 1	96	0	0 *[RAA]*	MCA[h]	Adams-Oliver syndrome
29	M	20 + 2	2009	+	Alive (9 years)	40 + 1	16	+	*0*	MCA[i]	22q11.2 DS
30	M	21 + 1	2009	+	Alive (9 years)	39 + 1	13	0	0	0	0
31	F	22 + 3	2009	+	Alive (8 years)	39 + 3	18	0	RAA	0	0
32	F	20 + 4	2011	+	Alive (8 years)	37 + 0	11	0	IAoA type B	0	0
33	F	20 + 5	2011	+	Alive (7 years)	39 + 6	22	0	RAA	0	0
34	M	22 + 1	2012	+	Alive (6 years)	39 + 0	36	+	0	Bilateral hydronephrosis	22q11.2 DS
35	M	20 + 4	2014	+	Alive (4 years)	41 + 3	9	+	RAA	0	0
36	M	26 + 3	2015	+	Alive (4 years)	37 + 2	13	0	Truncal valve stenosis	0	0
37	M	19 + 1	2016	+	Alive (2 years)	37 + 2	125	0	Unroofed CS, PLSVC	Intestinal atresia	0
38	M	20 + 2	2016	+	Alive (3 years)	41 + 0	14	0	0	0	0

Note: Data presented between "[ ]" include associated anomalies that were not detected before birth. Outcome is assessed at last follow-up visit. Age at surgery reported in days.

Abbreviations: APVR, anomalous pulmonary venous return; ARSA, aberrant right subclavian artery (arteria lusoria); CS, coronary sinus; Devel., delay developmental delay (present at last follow-up visit); InfD, Infant death; IAoA, interrupted aortic arch; IUFD, intrauterine fetal demise; IUGR, intrauterine growth restriction; MCA, multiple congenital anomalies; MFPR, multifetal pregnancy reduction; MODY, Maturity-Onset Diabetes of the Young; MS, mitral valve stenosis; NND, neonatal death (< 28 days); PLSVC, persistent left superior vena cava; PPROM, preterm prelabor rupture of membranes; PTHSL1, Pitt-Hopkins-like syndrome-1; TOP, termination of pregnancy; RAA, right aortic arch; regurg., regurgitation; sIUGR, selective IUGR; VSDs, ventricular septal defects; 22q11.2 DS, 22q11.2 deletion syndrome; 0, not present; + , present, – , no information,

Cases with multiple congenital anomalies (MCA):

[a]*Cheilognathopalatoschisis, diaphragmatic hernia, radial aplasia with ulnar shortening right, bilateral flexion contracture of the wrist, bilateral oligodactylia (two* fingers and one thumb right hand, absent right foot), rocker-bottom foot left, thoracic kyphosis, hypospadias, possibly a diaphragmatic hernia with short ribs.

[b]Holoprosencephaly, bilateral renal agenesis, single umbilical artery, oligohydramnios.

[c]Multicystic dysplastic unilateral kidney, abdominal cyst, single umbilical artery, (uncertainty on diaphragmatic hernia).

[d]Abnormal sacral spine, dislocated/abnormal location kidneys, single umbilical artery, (oligohydramnios).

[e]Spina bifida (L3/L4 to sacrum), hydrochephaly, unilateral renal agenesis, unilateral foot deformity (or deviation), single umbilical artery, signs of fetal decompensation.

[f]Unilateral schisis, unilateral renal agenesis, single umbilical artery.

[g]Hemivertebra, rib malformation, polydactyly, unilateral club foot, single umbilical artery, absent growth at 31 + 5 due to maternal factors (preeclampsia, HELLP, placental insufficiency with abnormal peripheral Dopplers).

[h]Bilateral asymmetric dysplasia of feet with unilateral equinovarus deformity, bilateral flexion contracture wrist, IUGR with brain-sparing (increased end-diastolic flow MCA).

[i]Abnormal head shape, abnormal shape ear.

3.4 | Prenatal counseling

The classification by Collett & Edwards[2] was used to describe the type of CAT in 75% of cases (15/20). The CAT was classified type I in 27% (4/15) and type II in 73% (11/15) of fetuses. Fetuses with CAT type I and II showed a relatively similar survival rate (75%, 3/4 vs. 63%, 7/11) and probability to present with additional malformations (75%, 3/4 vs. 73%, 8/11).

Fetuses with additional morbidity (nonisolated) showed a 50% (5/10) mortality risk (TOPs not included), including all early neonatal deaths (40%, 4/10) and one infant death (10%, 1/10). All of whom had significant other cardiac anomalies, whereas none of the nonisolated survivors did.

Isolated cases had a 30% (3/10) probability of fetal (20%, 2/10) or postnatal demise (10%, 1/10). Significant truncal valve regurgitation was found in both IUFD fetuses, but in none of the survivors. The presence of an IAoA alone, apart from prenatal truncal valve regurgitation, was not associated with fetal or neonatal mortality. All isolated CAT survivors required replacement of the initial right ventricle to pulmonary artery (RV-PA) conduit (6/7) or RV-PA patch (1/7) and 43% (3/7) up to four surgical re-interventions, due to pulmonary stenosis or insufficiency (cardiac catheterizations not considered).

After exclusion of pregnancy terminations, 60% of fetuses with CAT (12/20) were alive at last follow-up visit (mean: 6 years, range: 2–10). Half of these survivors had a genetic diagnosis, significant ECMs or developmental delay, leaving 50% (6/12) isolated with normal development. This means that only 30% (6/20) of continuing pregnancies and a prenatal diagnosis of CAT were alive without additional morbidity or signs of developmental delay at 6 years of age (Figure 1).

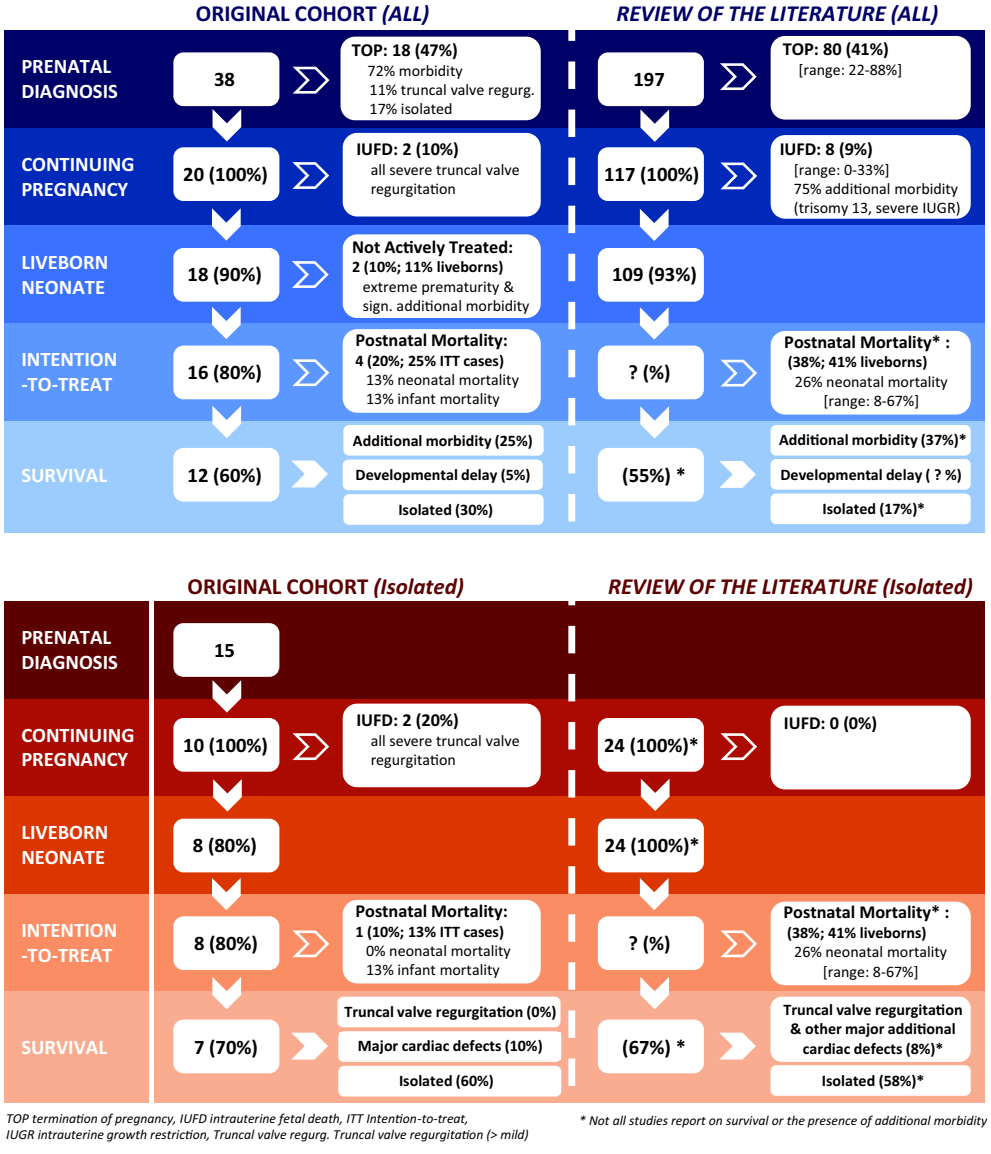

FIGURE 1 Outcome of (isolated) fetuses after a prenatal diagnosis of common arterial trunk; ITT, intention-to-treat; IUFD, intrauterine fetal death; IUGR, intrauterine growth restriction; TOP, termination of pregnancy; Truncal valve regurg., truncal valve regurgitation (>mild). * Not all studies report on survival or the presence of additional morbidity [Colour figure can be viewed at wileyonlinelibrary.com]

3.4.1 | Systematic review

Our literature search identified 546 potentially relevant articles, of which 70 were assessed for eligibility based on title and abstract and 13 eventually met the inclusion criteria (Figure 2).[5–7,24–33] Five studies focuses on CAT specifically,[6,7,24,30,31] whereas the remaining eight included other cardiac defects as well.[5,25–29,32,33] Altogether, these studies described 197 fetuses with a prenatal diagnosis of CAT.

3.5 | Additional morbidity

The available data on outcome and presence of additional morbidity in fetuses with CAT is reported for each study separately, and combined, in Table 2. A genetic syndrome was found in 30% (44/148) of all fetuses with CAT, which varied between 13% and 39% in large cohorts. Structural ECMs, such as holoprosencephaly, cleft lip, renal agenesis and esophageal or duodenal atresia, were present in 36% (61/170) of CAT cases. Associated cardiac anomalies were reported in five studies (39% of cases, 37/95).[7,28,30,32,33]

3.6 | Outcome

Forty-three percent of pregnancies (100/235, range 22%–88%) was terminated. IUFD occurred in 6% of continuing pregnancies (8/135, range 0%–13% in larger cohorts), which means 94% (127/135) resulted in a liveborn neonate.

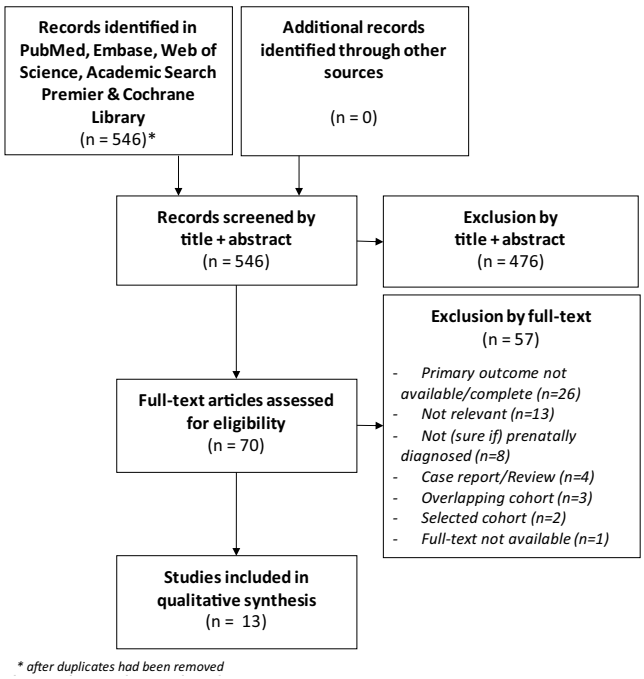

FIGURE 2 Flowchart systematic review of the literature. * after duplicates had been removed

The probability of neonatal death, reported in nine of the 14 available cohorts (including ours), appeared 28% (20/72) in liveborn neonates. Surgery was performed in 76% (63/83) of neonates, because 20% (17/83) died preoperatively and 4% (3/83) were awaiting surgery. The study by Morgan et al.[31] only described the proportion of cases that underwent primary biventricular repair, which is the preferable surgical option for the correction of CAT in the majority of cases. As they did not specify the proportion of cases that died preoperatively, were awaiting surgery or received alternative surgery, these cases were not included in the calculated proportion of cases that underwent surgery in all studies together. After exclusion of pregnancy terminations, 55% (50/91) of CAT fetuses were alive at the time each study was reported, based on the 10 studies that described survival.

3.7 | Prenatal counseling

In seven studies mortality was related to the presence of additional morbidity.[5,7,24-26,28,30] Genetic syndromes or ECMs were found in 75% of deceased cases (IUFD or neonatal death) versus 31% of surviving cases. Four studies reported on mortality for isolated CAT and its relation to associated cardiac anomalies.[7,24,28,30] These studies together showed a postnatal mortality of 33% (8/24) (all with intention-to-treat). Prenatal truncal valve regurgitation or major additional cardiac defects were present in 63% (5/8) of demised cases compared to 13% (2/16) of survivors (data not presented). If data from our cohort were included as well, this was 64% (7/11) in nonsurvivors and 9% (2/23) in survivors, respectively.

To conclude, 54% (36/67) of CAT fetuses with complete data survived, of which 37% (25/67) occurred isolated and 17% (11/67) had additional morbidity (mainly genetic syndromes; Figure 1, Appendix S2).

3.8 | Quality assessment

The QUIPS tool[23] was used to identify major risks of bias for each of the 13 studies (Appendix S3). Most studies (10/13) scored low to moderate risk of bias on all six domains. Hafner et al.[29] scored high risk of bias on "outcome measurement", because outcome was not clearly defined, not measured similarly in all patients and incomplete for pregnancy outcome. However, after we had contacted the authors, they supplied us with complementary data. Lee et al.[30] and Traisrisilp et al.[33] scored high risk of bias on "study attrition," because a significant proportion of cases were lost-to-follow-up or the number of cases excluded due to incomplete postnatal follow-up was not stated.

4 | DISCUSSION

Our study shows a considerable risk of mortality in fetuses diagnosed with CAT. Demise mainly occurs during pregnancy or shortly after birth in cases with truncal valve incompetence or complications as a

TABLE 2 Review of results on pregnancy outcome, postnatal course and additional mortality derived from included articles

Author, year	Study-period	*N.*	Confirmation of diagnosis	Pregnancy outcome			Neonatal outcome		Survival		Associated anomalies		
				TOP	IUFD	Livebirth	Surgery	NND	All	*TOP excl.*	Genetic diagnosis	*N* tested	Structural anomalies
Allan et al.,[26] 1984	<1984	1	Yes (100%)	0% (0/1)	0% (0/1)	100% (1/1)	-	0% (0/1)	0% (0/1) alive; (1 InfD at 4 mo)	0% (0/1) alive	0% (0/1)	-	0% (0/1) ECMs
Paladini et al.,[32] 1996	1990–1994	6	Yes (100%)	50% (3/6)	0% (0/6)	50% (3/6)	33% (1/3); (1 *awaiting*)	67% (2/3) (1 NNDpr, 1 NNDpo)	17% (1/6) alive and awaiting surgery	33% (1/3)	17% (1/6): Trisomy 18	100% (6/6); karyo	17% (1/6) ECMs0% (0/6) associated CVAs
Hafner et al.,[29] 1998	1992–1996	3	Yes	67% (2/3)	0% (0/3)	33% (1/3)	-	-	-	-	33% (1/3): Aneuploidy (47 +fragment)	100% (3/3); karyo	33% (1/3) ECMs: spina bifida; *unknown for aneuploidy case*
Tometzki et al.,[25] 1999	1985–1997	3	Yes (100%)	33% (1/3)	33% (1/3)	33% (1/3)	100% (1/1)	0% (0/1)	33% (1/3) survival > 28 days;	50% (1/2)	67% (2/3): Trisomy 13, CHARGE syndrome	-	33% (1/3) ECMs: bilateral anophthalmos; *unknown for T13/ CHARGE cases*
Duke et al.,[24] 2001	1990–1999	17	Yes (100%)	24% (4/17)	0% (0/17)	76% (13/17)	62% (8/13)	54% (7/13) (5 NNDpr, 2 NNDpo)	29% (5/17) alive; (1 InfD > 3 months)	38% (5/13)	18% (3/17): 22q11.2 DS (3)	71% karyo, 59% 22q11.2 (FISH)	24% (4/17) ECMs: 1 hydrocephaly, 3 MCA
Volpe et al.,[7] 2003	1993–2002	23	Yes (100%)	35% (8/23)	9% (2/23)	57% (13/23)	62% (8/13)(2 awaiting)	- (3 prD,2 poD[d])	35% (8/23) alive; (2 awaiting surgery)	53% (8/15)	35% (8/23): 22q11.2 DS (6), Trisomy 13, Trisomy 22	96% karyo, 83% 22q11.2 (FISH)	43% (10/23) ECMs: 4/10 MCA30% (7/23) associated CVAs
Galindo et al.,[5] 2009	1990–2005	13[a]	Yes (100%)	38% (5/13)	0% (0/13)	62% (8/13)	75% (6/8)	38% (3/8); (2 NNDpr,1 NNDpo)	23% (3/13) alive; (2 InfDpo)	38% (3/8)	31% (4/13): Trisomy 13 (2), 22q11.2 DS (2)	-	54% (7/13) ECMs
Swanson et al.,[6] 2009	1992–2007	38	Yes, partly (only livebirths)	45% (17/ 38)	5% (2/38)	50% (19/38)	89% (17/19)	11% (2/19) (2 NNDpr, 4 poD[d])	34% (13/38) alive to 60 days;	62% (13/21)	-	-	32% (12/38) ECMs
Bourdial et al.,[27] 2012	2002–2007	16	Yes (not all fetal deaths)	88% (14/ 16)	0% (0/16)	22% (2/16)	-	-	-	-	25% (4/16): 22q11.2 DS (4)	-	-
Lee et al.,[30] 2013	2003–2012	12[b]	Yes (100%)	33% (4/12)	0% (0/12);	67% (8/12)	88% (7/8)	25% (2/8)(1 NNDpr, 1 NNDpo)	50% (6/12) alive after surgery;	75% (6/8)	17% (2/12): unbalanced translocation, inversion	100% karyo, 75% 22q11.2 (FISH)	17% (2/12) ECMs67% (8/12) associated CVAs
Traisrisilp et al.,[33] 2015	2004–2013	8[c]	Yes (100%)	75% (6/8)	0% (0/8)	25% (2/8)	-	-	-	-	13% (1/8): Trisomy 13	88% karyo	25% (2/8) ECMs75% (6/ 8) associated CVAs

(Continues)

TABLE 2 (Continued)

Author, year	Study-period	N.	Confirmation of diagnosis	Pregnancy outcome			Neonatal outcome		Survival		Associated anomalies		
				TOP	IUFD	Livebirth	Surgery	NND	All	*TOP excl.*	Genetic diagnosis	*N* tested	Structural anomalies
Gómez et al.,[28] 2016	2006–2013	8	Yes (100%)	88% (7/8);	0% (0/8)	12% (1/8);	100% (1/1)	0% (0/1)	13% (1/8) alive at 10 MoL.	100% (1/1)	38% (3/8): Trisomy 13 (2), Triploïdy	100% karyo/FISH for 22q11	50% (4/8) ECMs: 1 holoprosencephaly, 3 MCA25% (2/8) associated CVAs
Morgan et al.,[31] 2019	1990–2014	49	Uncertain	22% (11/49)	2% (1/49)	76% (37/49)	*73% (27/37) primary BVR*	-	-	-	-	-	-
Original data*This study*	2002–2016	38	Yes (63%)	47% (18/38)	5% (2/38)	47% (18/38)	83% (15/18)	22% (4/18)(3 NNDpr, 1 NNDpo)	32% (12/38) alive after surgery(2 InfDpo at 5 & 18 mo)	60% (12/20)	39% (15/38): 22q11.2 DS (8), Aneuploidy (2), other genetic diagnosis (5)	100% karyo/FISH for 22q11	45% (17/38) ECMs37% (14/38) associated CVAs
All included studies		**235**		**43%** (100/235) *[22%–88%]*	**3%** (8/235) *[0%–33%]*	**54%** (127/235) *[22%–76%]*	**76%** (64/84) *[62%–89%]*	**28%** (20/72) *[11%–67%]*	**31%** (50/159) *[17%–50%]*		**30%** (44/148) *[17%–67%]*		**36%** (61/170) ECMs**39%** (37/95) associated CVAs
All included studies (TOP excl.)		**135**			6% (8/135) [0%–50%]	94% (127/135) [50%–100%]	70% (64/91) [53%–88%]	26% (20/77) [8%–67%]		**55%** (50/91) *[33%–75%]*			

Note: Data are presented as % (*n*) or % (*n*) or % (*n*) [range]. Proportions reported for individual studies that are based on $n = 1$, are not taken into account in the range.

Abbreviations: BVR, biventricular repair; CVAs, cardiovascular anomalies; ECMs, extracardiac malformations; InfD, infant death; IUFD, intrauterine fetal demise; Karyo, karyotyping; MCA, multiple congenital anomalies; NND, neonatal death (<28 days of life); po postoperatively; poD postoperative death (age at time of death unknown); pr, preoperatively; prD, preoperative death (age at time of death unknown); mo., months of age; TOP, termination of pregnancy; 22q11.2 DS, 22q11.2 microdeletion syndrome.

[a]Assessment of (neonatal) outcome/associated defects related to all common arterial trunk (CAT) with definitive postnatal diagnosis (including those with different prenatal dx).

[b]Assessment of associated defects related to postnatal confirmed CAT cases (excluding two fetal deaths without autopsy: 1 TOP, 1 IUFD).

[c]Only CAT type II and III was eligible for inclusion in this study.

[d]Not stated whether there were neonatal deaths amongst the cases that died pre- or postoperatively (Volpe. 2003), only that it happened <30 days after surgery (Swanson. 2009).

Bold values represent a sum of all studies together

result of a genetic syndrome, in particular when delivered prematurely. Sixty percent of continuing pregnancies with intention-to-treat, calculated from midgestation, were alive after surgery and only 30% of cases showed no signs of additional morbidity or developmental delay at the age of six.

This is the first large cohort study that evaluates postnatal outcome, with regard to additional morbidity and neurodevelopment, in fetuses diagnosed with CAT. A systematic analysis of the literature to assemble evidence from currently available studies has to our knowledge never been performed either. First of all, we encountered a 10% IUFD risk in continuing pregnancies, which was slightly higher compared to the literature. This might be due to an underrepresentation of IUFD cases in reported studies, as some studies merely focus on cases with confirmation of the diagnosis on postnatal echocardiography or autopsy,[5,24,28,30] which can often not be performed after fetal demise. We expect that our findings approach the true risk of IUFD, as comparable results have been reported by two similar cohort studies.[6,7]

Although the vast majority of continuing pregnancies appeared to result in a liveborn neonate, there remained a considerable risk of postnatal mortality (30%). Half of these cases did not undergo surgery, which all involved complex CAT cases with (extreme) prematurity. Active treatment after birth was not initiated in the majority of these preoperative deaths, as the prenatally expected prognosis and quality of life was poor. The postnatal mortality rate in all included studies combined appeared slightly higher, but still comparable.[5–7,24,30,32] Unfortunately most of these cohorts merely mention case-specific, rather than general, causes for postnatal mortality and did not focus on potential prognostic factors apart from truncal valve pathology. Large postnatal cohorts that describe the outcome of CAT often solely include cases that underwent surgery.[9,10,34–37] This is important for prenatal counseling, because this selection explains why postnatal cohort studies overestimate the overall survival; these studies report 1-year survival rates between 79% and 89%, which is comparable to the 1-year postoperative survival of 87% in our cohort. From a fetal perspective, however, only 60% of reported fetuses with CAT were alive 6 years after surgery.

The presence of additional morbidity has shown to be an important predictor for mortality, as genetic syndromes or ECMs were found in 75% of nonsurvivors (IUFD and neonatal deaths) compared to 31% of survivors. Premature birth, which occurred only in cases with additional morbidity, appeared equally important, as none of those that delivered prematurely survived until corrective surgery could be performed. In term neonates, the risk of postnatal mortality was still slightly higher in those with genetic syndromes or significant ECMs compared to those with isolated CAT and favorable cardiac anatomy. As it is likely that additional morbidity is directly related to preterm birth, and might reflect the more severely affected cases, we believe both aspects should be considered to estimate the prognosis. In isolated cases the presence of prenatal truncal valve regurgitation (greater than mild) was particularly associated with fetal and postnatal mortality. The finding that major additional cardiac anomalies (other than IAoA), beside truncal valve regurgitation, are a risk factor for postnatal mortality in isolated CAT, was not confirmed in our cohort.[7,24,30] Thus, despite the fact that most postnatal cohorts solely report on the need for truncal valve repair or additional cardiac defects as risk factors for mortality,[9,34,37] these data show that genetic syndromes and significant ECMs are also important to consider.

The prognosis of fetal CAT is, however, not only influenced by the considerable risk of postnatal mortality, but significant morbidity among survivors as well. Genetic syndromes associated with neurodevelopmental delay or (postoperative) complications, such as 22q11.2 deletion and Adams-Oliver syndrome, were found in a third of fetuses that survived and have a significantly negative impact on the quality of life of these children. If advanced techniques, such as exome sequencing, are applied to rule out these genetic syndromes, counseling regarding the prognosis can be more specific and more optimistic, especially in isolated cases. This is important, as the proportion of isolated cases at midgestation increased over time, due to advances in prenatal detection of CAT. Accurate diagnosis of CAT at midgestation has, however, proven to remain a challenge, as a small proportion appeared to have a PA-VSD after birth.[5–7,24]

An important limitation of the literature review is the fact that prenatally diagnosed cases with CAT originated from a long time-period (1990–2016) and studies mainly focused on short-term perinatal outcome. This complicates objective comparison of outcome data, as prenatal detection rates, surgical techniques and postnatal care management have changed significantly over time. Besides that, previous studies barely report on postnatal outcome beyond the neonatal period nor the presence of significant morbidity or developmental delay amongst survivors. In four of the 13 included studies,[27,29,31,33] data on postnatal course or survival were not even complete for all cases, which represent 32% of reported fetuses. As the vast majority originated from the large cohort by Morgan et al.[31] the authors were contacted and verified that all available data had been reported. Additionally, most studies did not perform genetic testing in all CAT cases[7,24,33] or did not report the proportion tested.[6,25–27,29,31,32] Lastly, the presence of additional morbidity could not always be directly related to outcome, because it had either been described for all CAT cases together[6,32] or the article lacked information on the postnatal course entirely.[27,29,33] Although this restricted our systematic review almost exclusively to short-term neonatal parameters, such an overview has never been presented before. Furthermore, it stresses the importance of large cohort studies with sufficient data on outcome and prognosis from a fetal perspective to improve prenatal counseling for CAT.

5 | CONCLUSION

The survival rate for prenatally diagnosed CAT is low and depends highly on the presence of additional morbidity and occurrence of premature birth. As genetic syndromes, ECMs and developmental delay are present in half of the cases that do survive, microarray analysis with sequential exome sequencing should be considered in these cases. Large prospective cohort studies, that include extensive

genetic testing for all cases, are needed to assess the prognosis with morbidity-free survival more precisely.

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CONFLICT OF INTEREST STATEMENT

The authors declare certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or nonfinancial interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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