Nigerian Medical Journal
NIGERIA MEDICAL ASSOCIATION
Print ISSN 0300-1652, E-ISSN 2229-774X

Review Article

The variability in pattern, presentation, and outcomes in the management of congenital corrected transposition of the great artery (ccTGA): A Systematic Review and Meta-analysis.

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Abstract

Background: Congenitally corrected transposition of the great arteries (ccTGA) is a rare congenital heart disease with varying regional reports in management approach. The meta-analysis is aimed to document various regional differences in the pattern, presentation, and outcomes in the management of congenitally corrected transposition of the great artery(ccTGA)

Methodology: Search engines for published articles on ccTGA were used in the meta-analysis. This includes PubMed, Google Scholar, Web of Science, Medline, and Africa journal online. Articles published between 2001 and 2024 were recruited of which the last search was done in August 2024. Selected articles were highlighted and screened by means of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Statistical heterogeneity was assessed with the I^2 statistics.

Results: Fifty-one full articles were screened from the initial four hundred and eighty citations. A total of 37 studies were further excluded from the 51 studies after further screening for incomplete data, case reports, non-English language reportage, and studies from autopsy findings. The resultant 14 studies were presented in PRISMA. The statistical significance was observed as evidenced by the significance heterogeneity identified in the selected studies.

Conclusion: The review had shown that children with ccTGA presented with varying features with some chromosomal correlates. Management options are directed towards a high index of suspicion, early intervention, and prompt surgical care to avert the numerous complications that follow the disease.

Keywords: *ccTGA; Meta-Analysis; Children; Complex; Heterogeneity.*

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How to cite: Chinawa JM, Chinawa AT, Uwaezuoke NA, Igoche PD. The variability in pattern, presentation, and outcomes in the management of congenital corrected transposition of the great artery(ccTGA): A Systematic Review and Meta-analysis. Niger Med J 2024; 65 (6):851-864.https://doi.org/10.60787/nmj.v65i6.655.

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Introduction:

Congenital heart disease (CHD) is a cardiac anomaly seen especially at the time of birth or in utero.[1] The prevalence of CHDs was noted to be 8.07 per 1000 live births. In Southeast Nigeria, a prevalence rate of 0.22% has been documented, with a notable increasing trend over the past decade. [2,3]

Congenitally corrected transposition of the great arteries (ccTGA) is a rare heart disease that contributes less than 1% of all congenital heart disease.[1] It is a unique congenital heart lesion in that despite the anatomical malformation, there is a physiologically normal blood flow without any shunting or mixing of blood.[4] The techniques and indications for surgical correction have experienced lots of evolution with varied reports on management approaches.[4]

Children with ccTGA present as an isolated combination of atrioventricular and ventriculo-arterial discordance, the great vessels may be L-malposed with the aorta lying left and anterior to the main pulmonary artery.[5-6]

Surgical surgical intervention is the treatment of choice especially for those with symptoms of RV dysfunction and moderate to severe tricuspid regurgitation. There is a high level of controversy in the management of children with ccTGA who are asymptomatic with preserved RV function and normal tricuspid valve function since some of them had a favorable prognosis with attendant risks and long-term complications associated with surgical intervention.[7]

The mortality rate is high for children with symptoms who had no surgical intervention. Heart failure is the frequently reported cause of death. [8] This may result from the inability of the morphological right ventricle to withstand systemic workload over time.[8-12] There is no known pharmacological intervention that improves survival in children with systemic right ventricular dysfunction. The prevalence of sudden death from ccTGA is reported as high as 17.1%. This is higher than the 10.3% reported in an Australian study.[7]

There are different regional practices and varying reports on clinical presentations, investigations, and management of children with CCTGA. This may lead to varied outcomes, resulting in differences in morbidity and mortality rates. Furthermore, studies on ccTGA are primarily focused on the adult population, while the limited studies on children are fragmented and lack synchronization.

The meta-analysis is aimed to document various regional differences in the pattern, presentation, and outcomes in the management of congenitally corrected transposition of the great artery(ccTGA). The systematic review and meta-analysis are very important because they reviewed the different regional and country approaches to the management of children with ccTGA, and highlighted the varying symptoms, clinical features, rhythmic abnormalities, and surgical outcomes in all the included countries of study. The meta-analysis also attempted to present pooled gender and socio-demographic correlates of children with ccTGA from different regions.

Methodology

Study participants

This study included children aged 1 day to nineteen years. Only studies that reported pattern of presentation, surgical outcome of ccTGA, and diagnosis of ccTGA using echocardiography alone were included.

Search strategy

Methods: Search engines for published articles on ccTGA were used in the meta-analysis. This includes PubMed, Google Scholar, Web of Science, Medline, and Africa journal online. Articles published between 2001 and 2024 were recruited, of which the last search was done in August 2024. Children under the age of 19 years were included in the search. A manual search was used to screen for other articles not seen from the search engines above. Selected articles were highlighted and screened by means of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Statistical heterogeneity was assessed with the I^2 statistics.

Keywords such as ccTGA, children, syndromic and clinical outcomes, surgical outcomes and complications, and investigations were used during the study.

Selection of studies

Children who fulfilled the inclusion criteria were enrolled in the study. They include: (1) Those aged 1 day to 19 years who had ccTGA, (2) Epidemiology: Documented age and gender prevalence of ccTGA (2) Reported outcome on surgical intervention, (3) Lesions and morphology associated with ccTGA such as ventricular septal defect (VSD), pulmonary stenosis (PS), atrial septal defect (ASD), and ccTGA with intact septum. (4) Chromosomal and syndromic correlates and associated situs solitus or inversus. Articles with children more than 19 years of age, review articles, case series, case reports, work with a mixture of children and adults, letters to the editor, and duplicated studies were excluded. Two researchers reviewed the literature search and if there is any bias, it shall be resolved with a third researcher. In the case of a misplaced article, the researchers will communicate with the corresponding author. The epidemiology, clinical correlates, gender and age correlates, and management options from the study that fulfilled the inclusion criteria were ascertained.

Data Extraction

Socio-demographic data and other epidemiological facts and outcomes of treatment were documented in the included study. The studies were conducted in all the continents except the African and South American continents. The studies from the South American continent were excluded because they were studies from the adult population while that from one African country (Kenya) was excluded because it was a case report. The spread of the authors, the study site, sample size, summary of the included studies, and their major findings were assessed for heterogeneity using forest plots. The highest number of studies was in Asia and Europe with thirteen and eleven publications respectively. All the studies were conducted between 2001 and 2024.

Risk of Bias Assessment

The risk of bias assessment was used to reduce errors and the risk of bias during the study selection. Differences between the reviewers were resolved through interactive sessions and if necessary, a third reviewer may be needed if there are any disagreements with the two previous reviewers. With respect to the sample size (SS) and the prevalence (p) of ccTGA, the precision (C) or margin of error for each included study was estimated using the following formula:

$SS=z2\times p\times(1-p)/d2,$

Z= the value fixed at 1.96 across studies (corresponding to 95% confidence interval). The desirable margin of error is less than and equal to 5% (0.05)

Ethical Approval and Consent to participate

Ethical approval was obtained from the Health Research Ethics Committee of the University of Nigeria Teaching Hospital.

Statistical analysis

The pooled mean prevalence was analyzed with IBM SPSS version 20 software. The pooled mean age, gender, sample size, and duration of the study were estimated using the student t-test. A meta-analysis of the mean age from the different studies was carried out using the meta package in R. The analysis methods used in this meta-analysis included standard techniques for combining and evaluating study results while accounting for potential heterogeneity. These methods ensure that the final conclusions drawn from the meta-analysis are statistically sound and reflective of the variability present across the included studies. The p-value less than 0.05 indicates that the heterogeneity noted is statistically significant.

Results:

Fifty-one full articles were screened from the initial four hundred and eighty citations. A total of 37 studies were further excluded from the 51 studies after further screening for incomplete data, case reports, non-English language reportage, and studies from autopsy findings. The 14 studies were presented in PRISMA as seen in Figure 1. Statistical significance was observed as evidenced by significance heterogeneity identified in the selected studies. The model of the Mean raw (MRAW) column was used to present the pooled mean age and gender. Statistical heterogeneity was assessed with the I^2 statistics.

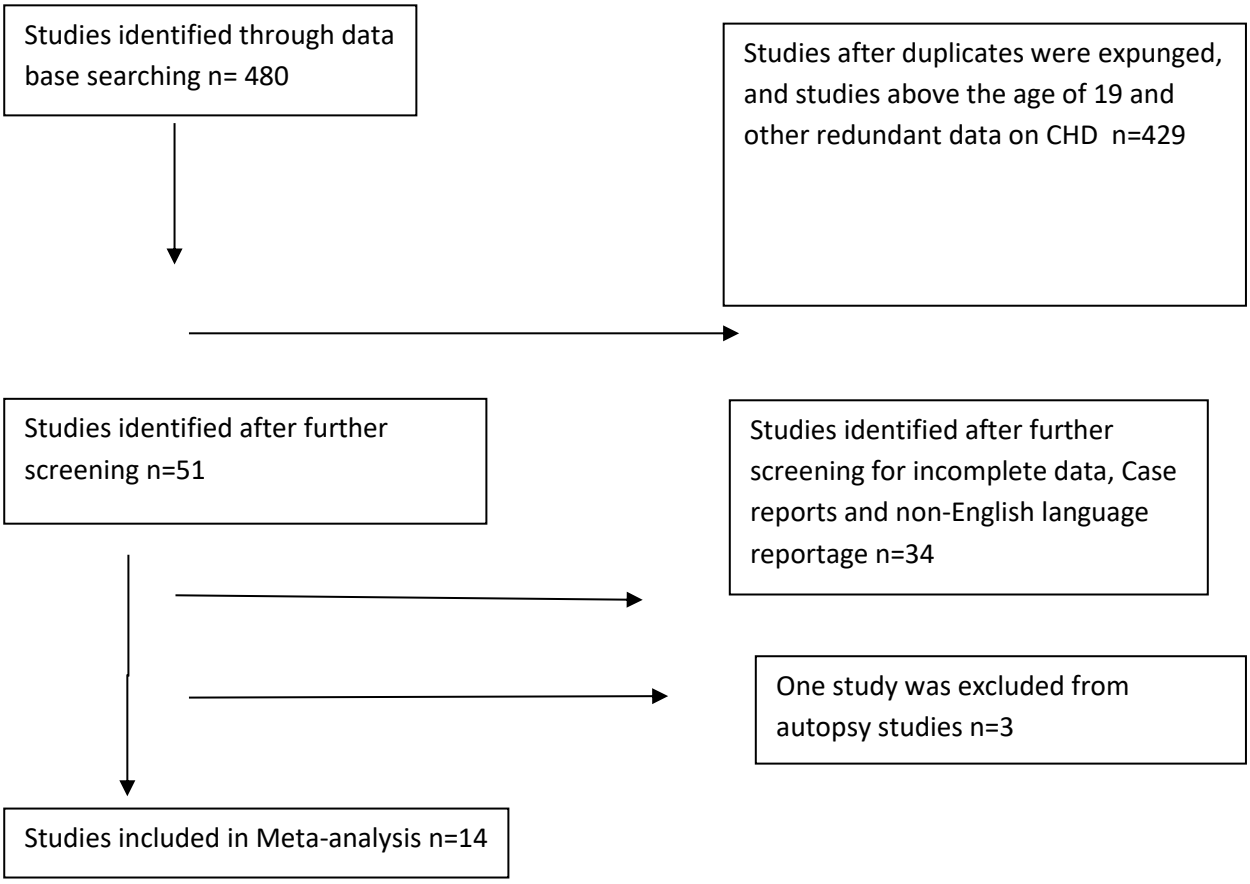

Figure 1: PRIMA flow chart for included studies

Table 1: Socio-demographic, mortality, and outcome of included studies.

Author and yr of study	City/location	Mean Age (months)	Sample size	Mortality	Mean Follow up(yrs)
Weixler et al [13] 2020	Netherland	21.6	25	0	NA
He et al[14] 2022	China	64.8	270	19	4.2
Rebecca [15] et al 2020	Italy	18	85	5	NA
Gerardo [16] et al 2005	Italy	98.3	102	NA	NA
Benjamin [17] et al 2019	USA	58.8	91	57	NA
Shagun et al [18] 2017	USA	15	15	0	5.5
Sachin et al[19] 2016	India	122.7	23	1	3.3
Jennifer et al[20] 2012	Australia	0.03	15	1	NA
Vladimir et al [21] 2012	Netherlands	34.8	6	1	4.5
Vincent et al [22]2021	USA	14.1	8	0	NA
Bin et al[23] 2014	China	37.3	14	3	NA
Xiaomin [24] et al 2021	China	31.2	90	9	5.1
Sen et al[25] 2017	China	64.8	31	1	3.3
Taner et al [26]2020	Turkey	30	120	2	4.4

Table 1 shows the socio-demographic variable of the included studies.

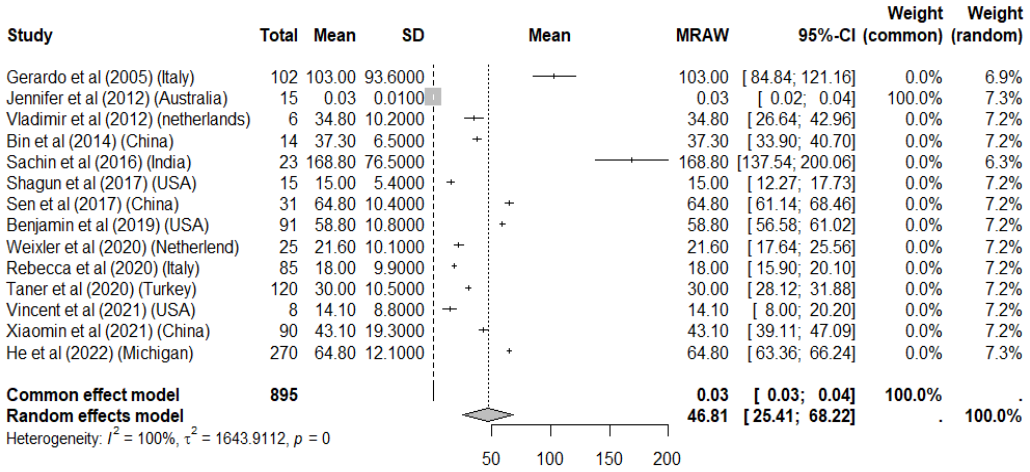

Figure 2: Shows the heterogenicity of the various studies

Heterogeneity: As shown in figure 2, the analysis shows very high heterogeneity (I^2 = 99.9%), suggesting that the effects observed across studies are not consistent and may be influenced by different factors.

Common vs. Random Effects Models: The significant difference between the common effect model (mean = 0.0318) and the random effects model (mean = 46.8150) underscores the importance of considering study variability. The random effects model, which accounts for this variability, suggests a much higher combined effect.

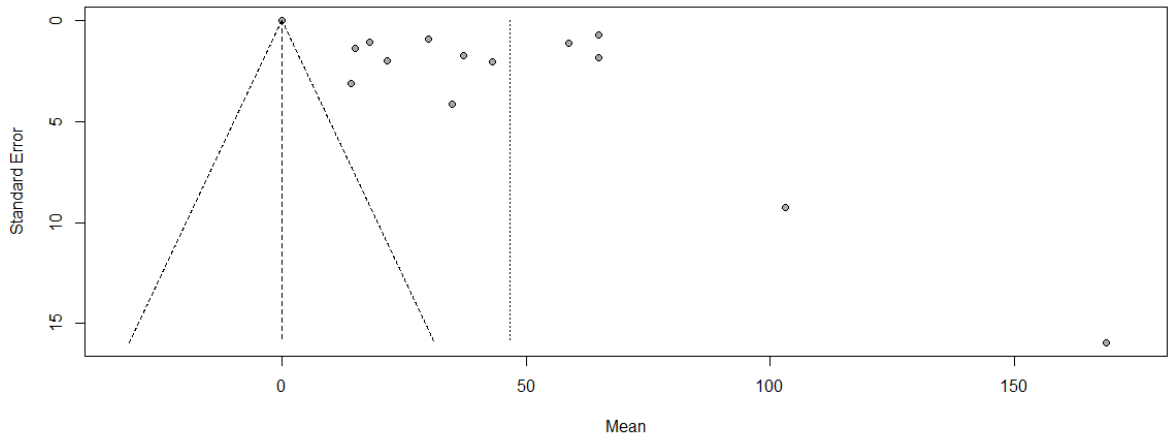

Figure 3: The funnel plot for the studies shows a high heterogeneity among the different studies

Discussion

The meta-analysis indicates that while individual studies report different mean effects, there is substantial variability between them.[13-26] The random effects model provides a more realistic combined estimate given the high heterogeneity. Similarly, the analysis for the prevalence showed substantial variability due to the significant heterogeneity.

Prevalence Values

The prevalence of ccTGA has not been documented in several studies.[13-27] Most work focuses more on surgical techniques and post-operative events. However, the few studies that cited prevalence studies noted varying outcomes. For instance, Weixler [13] et al noted a prevalence value of 0.05%, while Paladini et al [16] in Italy, documented a value of 0.02 per 1000 live births, Kumar et al[17] in the USA noted a prevalence of 0.03 per 1000 in their reportage. However, Obongonyinge et al[28] in Uganda documented ccTGA to have occurred in 14% of children with CHD while Jennifer et al [20] in Australia and Wallis et al in Florida, USA documented prevalence values of 0.02 to 0.03 per 1000, 0.02 to 0.03 per 100 and, 1/33,000 respectively. Besides, Amaral et al [29] in Brazil documented the prevalence rate of ccTGA as 0.5% of cases of children with CHD. The varying prevalence rates obtained from different authors above could be related to differences in the country of study, duration of the studies, racial differences, or possibly differences in sample size used in the study. The minimum age of presentation from the study is 1 day and the maximum age was 19 years. It is important to note that some children may have ccTGA that may go unnoticed till the adult age.[29-31] Early diagnosis of children with ccTGA can be done in utero and this is a crucial step in early diagnosis. This may help to identify any complications before pregnancy to improve outcomes and enable early intervention.[30]

Prenatal Diagnosis of ccTGA

Banjoko, et al [31] in the United Kingdom and Jenniferet al [20] in Melbourne, Australia have all reported cases of prenatal diagnosis of ccTGA. The prenatal diagnosis of ccTGA is very challenging. Double discordance is a very important criterion in the diagnosis of ccTGA in utero. [32] Most children with ccTGA are diagnosed immediately after birth. However, some can remain symptom-free and undiagnosed for several years. Osakada et al [33] in their reportage, noted a case of congenitally corrected transposition of the great arteries (ccTGA) that was first diagnosed in an 88-year-old man.

Clinical features and Electrocardiogram findings in ccTGA

The clinical manifestation in children with ccTGA depends on the severity of associated cardiac lesions. Our entries noted syncopal attacks and various degrees of heart blocks. [13-27] Long-term survival with ccTGA is wildly reported, with attendant morbidity. For instance, Beauchesne et al [34] in a cohort of 44 children a over 12-year period noted that more than half of the children with ccTGA presented with features of mitral and tricuspid regurgitation after a long period of follow-up.

Graham et al [35] also noted lower episodes of heart failure in children with ccTGA without associated lesions compared with those with associated lesions. [36,37] Children with ccTGA may present with various degrees of conduction abnormalities. Re-entrant AV tachycardia and sick sinus syndrome, ventricular tachycardia, and atrial flutter are other documented conducting abnormalities in ccTGA. [38-40]

Bradycardia and various degrees of AV heart block have been reported in the current meta-analysis, For instance, Rebecca et al [15] in Italy, Shuhei et al [41] in Japan, Abdelrehim et al [42] in Bangladesh, and Claudia-Andreea et al [43] in Bucharest, Romania have all reported various degrees of bradycardia in their series.

Consanguinity

Familial recurrence of ccTGA is very rare. The meta-analysis showed only 1 report on consanguinity or familial cases of ccTGA. [44] Gerardo et al [16] in Rome, Italy identified consanguinity in the parents of three probands. They conducted large clinical case series over a seven-year period, with a large sample size of 102 patients. The authors reported that children with ccTGA had no affected relatives when compared with 15% of families with congenital heart disease.[45]

Situs inversus in ccTGA

The systematic review also noted several structural defects and other associations in children with ccTGA such as ventricular septal defect, atrial septal defect, patent ductus ateriosus, and pulmonary artery stenosis. However, the most intriguing of them is the situs inversus. Taner et al in Istanbul, Turkey, He et al in China[14], Vincent et al [22] in Fort Worth, Texas, Gerardoet al [16] in Rome, Italy and Claudia-Andreea et al [43] in Romania have all documented situs inversus in children with ccTGA in their reports, with various clinical scenarios. For instance, Taner et al, [26] noted a prevalence of situs inversus in children with ccTGA as 17.5%, with 9.5% presenting with severe tricuspid regurgitation and 28.5% of them presenting with pulmonary atresia. Total situs inversus is an uncommon occurrence in children with ccTGA.[46-50] The haemodynamics seen in situs inversus, especially the alterations in cardiac output, could pose a serious problem during atrial switch surgery. Children with ccTGA and situs inversus may develop ventricular arrhythmia and cardiomyopathy post-operation.[49-51]

Commotio-Cordis: A rare abnormality in ccTGA

Commotio cordis is a very rare but catastrophic clinical scenario that can happen after a sudden fall from a blunt injury to the chest. Shuhei et al [41] in Toyama-shi, Japan noted a transient complete atrioventricular (AV) block after a mild chest blow (*commotio cordis*) with a transient loss of consciousness in a 2-year-old female child who had ccTGA. They noted first-degree AV block and ST abnormalities. The child improved subsequently with residual pathological Q-waves.

Genetic Syndromes and Extra-cardiac Malformations

Corrected congenital transformation of the great artery is seldom associated with genetic syndromes. The meta-analysis only reported one syndromic association. Munaf et al [52] noted a case of Marfanoid habitus in a 15-year-old child who also had dextrocardia. A very remote percentage of children with ccTGA could show features of Turner, Williams, Noonan, Downs, or Marfan syndromes. DiGeorge/Velocardiofacial Syndrome may be associated sporadically with del22q11, CHARGE, and VACTERL syndromes in children with ccTGA. [53,54] Tuberous sclerosis is a rare extra-cardiac manifestation. [55]

It is crucial to note that TGAs and ccTGA may not be seen as features of cardiac defect of del22q11 syndrome, a genetic defect well known in cono-truncal anomalies.[56] Children with ccTGA and TGA had only a 1% chance of having del22q11.[57-61] ccTGA has also been rarely implicated in children with asplenia syndrome (right isomerism). [57-65]

Management options

Various management options have been documented by several authors from different regions in the systematic review. Those who presented with ductal-dependent lesions could benefit from parenteral prostaglandin. [66-67] Symptomatic children who presented with associated shunt lesions with hemodynamic instability will benefit from intra-cardiac repair.[68] The post-operative complications noted in the meta-analysis are worsening tricuspid regurgitation and complete heart block. [68-70] Several authors have noted the use of pacemakers after surgery. For instance, Termignon et al [71] documented 33% of his series who require pacemaker post-operation.

The closure of associated structural defects was seen in the meta-analysis. It is important to note that VSD repair could worsen AV valve regurgitation and may cause severe right ventricular dysfunction in children with ccTGA [71] Dysplastic, or friable tricuspid valve may need a repair or replacement especially when there is severe tricuspid regurgitation, and ventricular dysfunction.[72]

Double switch procedure could be lifesaving in associated large ventricular septal defect and pulmonary stenosis. This has been reported by several authors in the systematic review. [72] Double switch manoeuvre may be difficult in chordal mal-attachment of the mitral valve.

Children with a large ventricular septal defect and pulmonary outflow obstruction may benefit from the right ventricular to right pulmonary artery baffle (Rastelli) procedure.[73] In addition, those with regressed left ventricles will benefit from the Senning procedure. [74] Weixler et al[18] in the Netherlands, Shagun et al in the USA, Jennifer et al in Melbourne, Australia, Vladimir et al in Leiden, Netherlands, Nedam et al in Bosnia and Herzegovina, had all reported Ratelli operation as a surgical option for ccTGA with the pulmonary obstructive lesion.[73-75]

Arterial switch operation (ASO) is the surgical option of choice.[77] For ASO to take precedence, the pressure of the left ventricle should be at least near-systemic pressures, the left ventricular mass index should be normal, and the left ventricle should not be regressed.[77]

The regressed left ventricle could be handled with pulmonary artery banding (PAB) before a definitive repair. Banjoko, et al United Kingdom also reported PAB in a day-old neonate who had surgery 12 months

later. The meta-analysis reported post-operative complications such as pulmonary venous obstruction, atrial arrhythmias, and caval obstruction in children with PAB.[78]

Mortality rates

Mortality rates have been reported to be low if surgery is done. Studies by Weixler et al, He et al, Vladmir et al, Bin et al, and Sen et al, reported varying mortality rates across different geographic locations and at follow-up periods.[14,18,20,21,25.] The causes of death in their reports are mainly post-operative complications such as rhythmic disorders, severe right ventricular dysfunction, and sudden death.

Regional differences in the diagnosis and management of ccTGA.

The meta-analysis indicates that while individual studies report different mean effects and regional differences, there is substantial variability between them. The random effects model provides a more realistic combined estimate given the high heterogeneity.

Limitation

This study is limited by the heterogeneity in the sample size, age at presentation, and country of study. Furthermore, the meta-analysis did not include molecular genetics in children with ccTGA. This was due to the paucity of studies in the included criteria.

Conclusion

The review had shown that children with ccTGA presented with varying features with some chromosomal correlates. Management options are directed towards a high index of suspicion, early intervention, and prompt surgical care to avert the numerous complications that follow the disease.

Competing Interest: The authors declare that they have no competing interests.
Funding: This study was not funded by any organization. We bore all the expenses that accrued from in study.

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