The distribution and frequency of congenital heart disease in patients with known syndromes or non-specific dysmorphic features at Charlotte Maxeke Johannesburg Academic Hospital from 2010 to 2020

Author:

Dr. Avani Ashok Kashiram
MBBCh (WITS), DCH (SA), Dip HIV Man (SA)
Department of Paediatrics and Child Health
Registrar, Department of Paediatrics, WITS University
Johannesburg, South Africa
Email: avani.kashiram@gmail.com

Co-Authors:

Dr. Firoza Motara
MBBCh (WITS), FCPaeds (SA), MMed (WITS), Cert Cardio SA Paed
Department of Paediatrics and Child Health
Head of Paediatric Cardiology, Charlotte Maxeke Johannesburg Academic Hospital
Johannesburg, South Africa
Email: motaraf@hotmail.com

Prof Antoinette Cilliers
MBBCh, FCP (SA)
Department of Paediatrics and Child Health
Principal Specialist and Head of Paediatric Cardiology
Head of Paediatric Cardiology, Chris Hani Baragwanath Academic Hospital
Johannesburg, South Africa
Email: Antoinette.Cilliers@wits.ac.za

A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine in Paediatrics and Child Health

18 November 2024

Declaration

I, Avani Ashok Kashiram, declare that the contents of this MMed research report are my own independent efforts, with assistance from my supervisors. References to the work of other authors have been cited and acknowledged in accordance with academic standards. This research report is being submitted for the Degree of Master of Medicine in Paediatrics and Child Health at WITS University, Johannesburg. It has not been submitted to any other University previously.

Dr. Avani Ashok Kashiram

Signed on this day __*18*___ of____*November*____ 2024.

Dedication

To my husband and all my parents, whose unwavering support and encouragement have been invaluable throughout my academic pursuit. Your belief in me has fuelled my determination to reach this milestone. This MMed is dedicated to you with gratitude.

Acknowledgements

Dr. Kashiram extends sincere thanks to Prof. K. Thandrayen of Chris Hani Baragwanath Academic Hospital for her insightful mentorship and expert guidance with the statistical analysis of the data.

Table of Contents

Author Guidelines

This research report is in submissible format for the Cardiovascular Journal of Africa. Author guidelines are as documented below, and can be found on the following link: https://www.cvja.co.za/authors.php#:~:text=All%20submissions%20should%20be%20written,contacts%20for%20the%20corresponding%20author.

ARTICLE SUBMISSION

All categories of manuscripts for the Cardiovascular Journal of Africa must be submitted on-line to OJS. You will be assigned your own password and user name. This will allow complete interaction between the editor and authors. Internally, reviewers will be approached to review material in their field of expertise and assigned with similar interaction. All information will be entirely protected and confidential.

All submissions should be written in a clear and succinct manner, following the style of the Journal. Title page should include a descriptive title; authors' surname and forename, address of each author and full address, telephone, fax and e-mail contacts for the corresponding author. In text: tables and figures are either inserted as part of sentence, for example Table 1, or in parentheses, for example (Fig. 1). Each table should carry a descriptive heading.

OJS will clearly indicate which aspects of the submission must be supplied off-line (**download off-line document**). This must be provided to the Journal by mail (PO Box 1013, Durbanville, South Africa, 7551) or e-mail to **info@clinicscardive.com**

All images MUST be at or above intended display size, with the following image resolutions: Line Art 800 dpi, Combination (Line Art + Halftone) 600 dpi, Halftone 300 dpi Image files also must be cropped as close to the actual image as possible.

Preferred Image Format		**Alternative Image Format**	
Image Format	.tif	**Image Format**	.jpg
Image Width	Greater than or equal to intended display size	**Image Width**	Greater than or equal to intended display size
Colorspace	RGB	**Colorspace**	RGB
DPI	500+	**DPI**	500+
Alpha Channels	None	**Compression Quality**	Maximum
Layers	Flattened		

References numbered in the order of appearance in the text, according to Vancouver style. For articles: Author AB, Author C, Author M. The title of the article. Abbreviated journal title 1999; 14: 172–183. For book chapters: Author AB, Author CD. The title of the chapter. In: Editor A, Editor BC, ed. Title of the book, 2nd edn. Location: Publisher, 1999: 133 –139. DOI Numbers / PMID (Pubmed ID / PMC ID) must be added to all references to facilitate tagging for PubMed Central.

Original articles: Title page as above. Abstract (150 words) a short inclusive statement suitable for direct electronic abstracting, identifying the purpose of the study, key methods, the main results and the main conclusion. Keywords: maximum of six keywords for indexing. Introduction: concise description of background, sufficient for the non-specialist to appreciate the context of the work. Clear statement of the purpose of the study. Methods: a brief description of study design, procedures, analytical techniques and statistical evaluation. Results: a clear account of the study findings using quantitative language where possible and cross-referenced to tables and figures. Discussion: an interpretation of the study placed within the context of current knowledge, leading to specific conclusions where possible. Acknowledgements. References, figures and tables as above.

Journal Title Page

The distribution and frequency of congenital heart disease in patients with known syndromes or non-specific dysmorphic features at Charlotte Maxeke Johannesburg Academic Hospital from 2010 to 2020

Author:

Dr. Avani Ashok Kashiram
MBBCh (WITS), DCH (SA), Dip HIV Man (SA)
Department of Paediatrics and Child Health
Registrar, Department of Paediatrics, WITS University
Johannesburg, South Africa
Email: avani.kashiram@gmail.com
Tel no: 074 992 8264

Co-Authors:

Dr. Firoza Motara
MBBCh (WITS), FCPaeds (SA), MMed (WITS), Cert Cardio SA Paed
Department of Paediatrics and Child Health
Head of Paediatric Cardiology, Charlotte Maxeke Johannesburg Academic Hospital
Johannesburg, South Africa
Email: motaraf@hotmail.com
Tel no: 082 775 2580

Prof Antoinette Cilliers
MBBCh, FCP (SA)
Department of Paediatrics and Child Health
Principal Specialist and Head of Paediatric Cardiology
Head of Paediatric Cardiology, Chris Hani Baragwanath Academic Hospital
Johannesburg, South Africa
Email: Antoinette.Cilliers@wits.ac.za
Tel no: 083 343 5803

Abstract

Background

Congenital heart disease (CHD) is the most common birth defect globally, with approximately a third of cases having a genetic cause. However, there is paucity of South African data. A description of CHD associations in syndromic and dysmorphic patients follows.

Methods

A retrospective analysis of patient records at a Johannesburg tertiary hospital from 2010- 2020, which included patients with dysmorphism, genetic syndromes or major congenital abnormalities, aged birth to 16 years.

Results

Among 1024 participants, CHD was diagnosed in 37%(n=379), mostly acyanotic (82%). Predominant lesions were ventricular septal defect (31%, n=117) and atrioventricular septal defect (25%, n=93). Median age at diagnosis of CHD was 41 days. Genetic syndromes were diagnosed clinically or using molecular techniques, in 48%(n=493) of participants, predominantly trisomy 21 (27%, n=280). CHD was most frequent in trisomy 18 (94%). Documented deaths accounted for 7% (n=71) of the cohort, highest in cyanotic CHD.

Conclusion

This study shows a high incidence of CHD in children with syndromes, dysmorphism or isolated major congenital abnormalities, highlighting the need for CHD screening in these patients.

Keywords: paediatric, cardiology, congenital heart disease, genetic syndrome, congenital malformation

Introduction

Congenital heart disease (CHD) can be defined as "a structural abnormality of the heart or intrathoracic blood vessels that is of functional significance and occurs before birth"[1,2], but may present any time after birth, or not manifest symptoms at all. CHD is the most common major birth defect globally, occurring in 9 per 1000 live births [3] and 1 in 10 stillbirths., with the incidence estimated to be the same in developing and developed countries [4]. It is a key cause of heart failure in children and is the seventh leading cause of under-5 mortality in Africa [5]. An underlying genetic cause can be found in approximately one third of CHD patients [6]. Access to care in South Africa and the African continent is a major barrier, resulting in late presentation to a healthcare facility, as well as one third of patients not surviving beyond the neonatal period and half dying by the age of one year [7,8].

The global prevalence of CHD is increasing due to improved identification of patients through antenatal screening and diagnostics, for detecting previously undiagnosed mild subtypes [9]. This, combined with better survival and prognosis in high income countries (HICs) [2,5] has led to the rising global prevalence. In developing countries, CHD prevalence per capita is believed to be higher, likely due to a younger population mean age and a higher birth rate than developed countries [4], but may be underestimated due to limitation in resources, screening and access to care.

Limited data exist for South Africa, with Hoosen et al. [10] reporting a CHD prevalence of 0.6-0.8 per 1000 live births, and an annual incidence of approximately 11 000. In Nigeria, a low-middle income country (LMIC), CHD prevalence ranges from 6.6 to 28.8 per 1000 live births, with 15% occurring in syndromic infants [11]. Prognosis, especially of severe or critical subtypes,

in LMICs is poorer due to socioeconomic and healthcare infrastructure challenges, leading to many patients not surviving to diagnosis. Despite being classified as an upper-middle income country by the World Bank, South Africa's vast income inequity affects access to care, resulting in the country not aligning with CHD trends in other high-middle income countries (HMICs)[5]. A lack of routine cardiac examination in primary healthcare facilities and absent universal newborn pulse oximetry screening for critical CHD result in many critical subtypes being missed and patients often presenting in extremis [10]. The South African Department of Health does not have an official policy regarding screening newborns for critical CHD.

CHD is multifactorial, with genetic, epigenetic, and environmental factors playing a role in embryological cardiac development. Precursor cells (which later develop into multiple other

organs) outside the cardiac tube form the basis of the pathophysiology of associations between extracardiac abnormalities and genetic syndromes [12]. The Baltimore Washington Infant Study [13] highlighted that genetic morphogenic pathways shape cardiac phenotypes, thus associating specific cardiac lesions to certain syndromes.

Congenital cardiac lesions are frequently associated with extra-cardiac abnormalities [2], resulting in a high incidence of CHD in syndromic patients. Studies in Lagos and Uganda emphasize the importance of cardiac and genetic screening in syndromic patients, with Ekure et al. [14] finding that 72% of patients with congenital malformations had CHD, and Namuyonga et al. [8] demonstrating a high likelihood of positive genetic test results in children with CHD.

Genetic syndromes associated with CHD include: aneuploidy (10% of cases) [6], copy number variants like 22q11.2 deletion syndrome (22q11.2DS) and Williams syndrome (12%) [15], and single gene disorders such as Kabuki, Noonan and Alagille syndromes (3-5%) [16]. The following is known about CHD prevalence in specific syndromes, and their most commonly associated cardiac lesions [11,16,17]:

- Trisomy 21 (T21): 40-50% have CHD- 45-62% atrioventricular septal defect (AVSD), 35% ventricular septal defect (VSD)
- Trisomy 18 (T18): 60-80% have CHD- 76-94% VSD, 77-88% patent ductus arteriosus (PDA)
- 22q11.2 DS: 70-81% have CHD- 20% Tetralogy of Fallot (TOF), 13% interrupted aortic arch (IAA), 13-43% septal defects.
- 22q11.2DS is the most prevalent chromosomal abnormality in patients with conotruncal lesions, warranting testing for this genetic abnormality in all such patients. Conotruncal lesions include: TOF, pulmonary atresia with VSD, double outlet ventricles, truncus arteriosus, transposition of great vessels (TGV) and interrupted aortic arch with VSD [18].
- VACTERL association: 73% have CHD- 30% VSD [19,20].
- Patients with isolated anorectal malformations (ARM) have a 10-30% incidence of CHD [20].

Rationale and Potential Uses of Current Study

There is paucity of data addressing epidemiology, environmental and genetic associations with CHD in South Africa, and correlations with international data have yet to be established. The PROTEA project [5] aims to assess the epidemiology and genetics of CHD in South Africa, and preliminary results found marked differences between South African and global prevalence of certain subtypes of CHD, with mild subtypes being lower and severe subtypes being higher than international estimates [5].

Knowledge about genotype-cardiac phenotype correlation, as well as CHD associations with major extracardiac malformations is crucial for prognostication and management of patients, particularly in regions where access to timely echocardiography may be limited. This understanding plays a role in management protocols and policymaking.

The aim of this study is to describe and categorise the frequency of CHD in association with genetic syndromes and isolated major congenital abnormalities at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and to compare findings to global literature.

This study also aims to highlight the need for cardiac screening in dysmorphic and syndromic patients. South African epidemiological data in this regard can guide future research on aetiology and genetic risk factors of CHD and help to plan future healthcare provision for CHD in under-resourced countries such as ours.

Methods

Study Design and Setting

Data were collected from the CMJAH paediatric cardiology database for this retrospective, descriptive study. CMJAH is a public sector tertiary hospital in Johannesburg, South Africa. It is a major referral centre for hospitals and clinics in Johannesburg and the Paediatric Cardiology Unit receives approximately 2500 referrals annually. The unit undertakes cardiac catheterization procedures on site and refers all patients needing cardiac surgery to the Nelson Mandela Children's Hospital (NMCH) for cardiothoracic intervention. All dysmorphic patients referred to CMJAH paediatric cardiology for CHD evaluation have a full physical examination and echocardiogram.

Study Population

The study included live born patients from birth to 16 years old at diagnosis, with dysmorphic features (as identified by the referring physician), isolated major congenital abnormalities or identifiable syndromes, who were seen at CMJAH paediatric cardiology from 1 January 2010 to 31 December 2020. The cohort included inpatients, outpatients and referrals from the genetics service and cluster hospitals. All patients meeting these criteria were included, irrespective of the presence or absence of CHD.

Data Collection and Analysis

Clinical and demographical information of patients was obtained from the CMJAH paediatric cardiology database using filters: "syndromes, dysmorphic, limb abnormalities, cleft lip and palate, choanal stenosis/atresia, exomphalos, hydrocephalus, ear abnormalities, eye abnormalities, skin abnormalities, anorectal malformation, omphalocele, marfanoid, oesophageal atresia, tracheo-oesophageal fistula, and situs inversus". Additional information was gathered using paper-based clinical records obtained from the Paediatric Cardiac Clinic. Patients seen at CMJAH cardiology have a transthoracic echocardiogram (TTE) performed at the first visit, using standardised views with ultrasound machines equipped with paediatric cardiac software programs. Standard 2D, M-mode and doppler studies are undertaken.

Data were entered into a Microsoft Excel spreadsheet (Microsoft Corp., USA) and then analysed using Statistica (Version 14.0.0.15, TIBCO Software). Continuous variables were described by means and standard deviations (if normally distributed) and medians and interquartile ranges (if non-normally distributed). Categorical variables were described according to percentages and frequencies of the cohort. The Chi Square test and Fisher's exact test were used to compare categorical variables, and unpaired t-tests and Wilcoxon rank sum tests were used for parametric and non-parametrically distributed continuous variables. A variable was considered statistically significant if P values were <0.05.

Definitions

Syndromes

The study classified patients as having dysmorphic features based on abnormal physical findings identified by the referring physician or paediatric cardiologist during physical examination. Extracardiac abnormalities and genetic syndromes were classified according to guidelines from the European Surveillance of Congenital Anomalies (EUROCAT) system [21]. Patients were categorised into four groups: confirmed syndrome, suspected syndrome (based on characteristic phenotypic features), dysmorphic features not fitting a specific syndrome, or isolated major congenital abnormalities that may be part of a syndrome. Where dysmorphic features were listed in patient records, these were grouped as per EUROCAT groupings, or documented as unknown if features were not documented in patient records.

A VACTERL association was diagnosed in patients with "three or more of the following abnormalities: vertebral, anorectal, cardiac, oesophageal atresia/tracheo-oesophageal fistula, renal/urinary and limb" [20]. If a patient had an isolated anorectal malformation (ARM), but no other documented malformations, they were grouped separately as having an isolated major congenital abnormality.

Major congenital abnormalities included in the study were those frequently forming part of a syndrome or association, and were ARM, central nervous system, craniofacial (including cleft lip and palate and choanal atresia, ear and eye abnormalities) or limb abnormalities, oesophageal atresia and tracheo-oesophageal fistula, omphalocele and situs inversus.

Syndromes analysed were those most associated with cardiac lesions based on review of literature, namely, Trisomies 21, 13 and 18, Williams, Noonan, Turner, Marfan and 22q11.2 deletion syndromes and VACTERL association. Less common syndromes were classified as "other". With regards to T21, patients were classified as "confirmed T21" or "phenotypic T21" in cases where lab confirmation was not attained.

Cardiac Lesions

Cardiac lesions were categorised according to standards outlined in the International Classification of Diseases (ICD-11) [22]. To facilitate data analysis, patients with multiple cardiac lesions were assigned a single diagnosis reflecting the most significant lesion according to the classification standards and hierarchy of the New England Regional Infant Cardiac Program [23] (Appendix A). The hierarchy categorised lesions into 21 broad diagnostic groups of commonly encountered lesions, and a group "other" for rarely encountered lesions. A comprehensive list of all lesions and their frequencies in patients with multiple lesions is available in the supplemental data, (Appendix B)

Lesion presence from the database was recorded as either "present" or "absent", and functional significance was evaluated in cases of uncertainty, where the attending cardiologist's opinion and the full echocardiogram report were reviewed. Echocardiographic findings deemed clinically insignificant by the paediatric cardiologists, namely: peripheral pulmonary stenosis (PPS) with right ventricular outflow gradient <25mmHg or that resolved on follow-up, or patent ductus arteriosus (PDA) that was only present during the neonatal period (28 days) were re-classified as having a "normal heart" (meaning no CHD) for the purposes of the data analysis in the study.

Compliance with Ethical Standards

Approval to conduct this study was granted by the University of Witwatersrand Human Research Ethics Committee (Medical) ref. no. M220842. Patients were assigned study numbers only known to the lead author, and confidentiality was maintained throughout data collection by excluding personal identifiers from the Excel database, which was used to collect the data used for analysis. This Excel database was password protected and stored offline on the lead author's computer.

Results

Patient Characteristics

A total of 1024 patients (55.7%, n=570 male, 44.2%, n=453 female, and one patient with ambiguous genitalia); median age at diagnosis of CHD 41 days (IQR 6-296 days)) seen at CMJAH from 01 January 2010 to 31 December 2020 were included in this study. Demographic and clinical characteristics of the enrolled patients are outlined in table 1 and table 2.

Table 1: Age characteristics of the study cohort

Variable	**Total N = 1024**		**Normal Heart (No CHD) N = 645**		**Acyanotic CHD N = 311**		**Cyanotic CHD N = 68**	
AGE AT FIRST PRESENTATION/CONSULT								
	n/%	**Median days (IQR)**	**n/%**	**Median days (IQR)**	**n/%**	**Median days (IQR)**	**n/%**	**Median days (IQR)**
All Ages [a]	**1024**	41 (6-296)	**645**	27 (6-300)	**311**	106 (10-302)	**68**	11 (3-199)
0-28 days (neonates) [a]	480/ 46.9%	6 (3-10)	325/ 50.4%	6 (4-10)	115/ 37%	7 (3-13)	40/ 58.8%	4 (2-8)
29 – 89 days 1mo-3mo	106/ 10.4%	56 (39-71)	66/ 10.2%	59 (37-75)	34/ 10.9%	47 (39-65)	6/ 8.8%	54 (49-67)
90-364 days (3mo-1yr)	219/ 21.4%	211 *[7 months]* (145-265)	107/ 16.6%	211 *[7 months]* (138-263)	101/ 32.5%	210 *[7 months]* (156-268)	11/ 16.2%	220 *[7.3 months]* (125-277)
365 – 1825 days (1 year- <5 years)	131/ 12.8%	714 *[1.9 years]* (468-1252)	75/ 11.6%	801 *[2.2 years]* (481-1305)	45/ 14.5%	658 *[1.8 years]* (456-1099)	11/ 16.2%	713 *[1.9 years]* (411-1182)
1826 – 4745 days (5 years- <13 years)	70/ 6.8%	2973 *[8.1 years]* (2246-3766)	58/ 9%	3024 *[8.2 years]* (2246-3766)	12/ 3.9%	2927 *[8 years]* (2303-3731)	0	-
4746 – 5840 days (13 years- <16 years)	18/ 1.8%	5274 *[14.4 years]* (4944-5487)	14/ 2.2%	5262 *[14.4 years]* (4944-5644)	4/ 1.3%	5274 *[14.4 years]* (5002-5368)	0	-
AGE AT DEATH								
	n/%	**Median (IQR) Total**	**n/%**	**Median (IQR) Normal Heart**	**n/%**	**Median (IQR) Acyanotic CHD**	**n/%**	**Median (IQR) Cyanotic CHD**
All Ages	**71/ 6.9%**	67 (14-388)	**9/ 1.4%**	127 (19-388)	**41/ 13.2%**	76 (17-358)	**21/ 30.9%**	24 (9-227)
0-28 days (neonates)	27/ 38%	12 (6-17)	3/ 33.3%	14 (12-19)	13/ 31.7%	14 (10-17)	11/ 52.4%	9 (3-15)
29 – 89 days (1mo-3mo)	12/ 16.9%	58 (45-68)	1/ 11.1%	68	8/ 19.5%	59 (45-72)	3/ 14.3%	50 (46-57)
90-364 days (3mo-1yr)	14/ 19.7%	248 *[8.2 months]* (227-274)	2/ 22.2%	231 *[7.7 months]* (127-335)	10/ 24.4%	255 *[8.5 months]* (239-274)	2/ 9.5%	208 *[6.9 months]* (190-227)
365 – 1825 days (1 year- <5 years)	15/ 21.1%	705 *[1.9 years]* (485-1029)	3/ 33.3%	1143 *[3.1 years]* (388-1636)	8/ 19.5%	636 *[1.7 years]* (525-764)	4/ 19%	874 *[2.4 years]* (621-1010)
1826 – 4745 days (5 years- <13 years)	2/ 2.8%	2330 *[6.4 years]* (2324-2337)	0	-	1/ 2.4%	2337 *[6.4 years]*	1/ 4.8%	2324 *[6.4 years]*
4746 – 5840 days (13 years- <16 years)	1/ 1.4%	4850 *[13.3 years]*	0	-	1/ 2.4%	4850 *[13.3 years]*	0	-

[a] *Denote variables with a p value <0.05 for acyanotic vs cyanotic CHD*

Table 2: Demographic and clinical characteristics of the study cohort

	Total N = 1024 n (%)	**Normal Heart (No CHD) N = 645 n (%)**	**Acyanotic CHD N = 311 n (%)**	**Cyanotic CHD N = 68 n (%)**
SEX				
Male	570 (55.7%)	374 (58.0%)	157 (50.5%)	39 (57.3%)
Female	453 (44.2%)	270 (41.9%)	154 (49.5%)	29 (42.7%)
Ambiguous	1 (0.1%)	1 (0.1%)	0	0
NUMBER OF LESIONS				
All lesions [a]				
0	645 (62.9%)	645 (100.0%)	0	0
1	285 (27.8%)	0	234 (75.0%)	51 (76.1%)
2 [a]	73 (7.1%)	0	66 (21.1%)	7 (10.4%)
3 [a]	14 (1.3%)	0	8 (2.6%)	6 (8.8%)
≥4 [a]	7 (0.6%)	0	3 (0.9%)	4 (5.9%)
ASSOCIATED SYNDROMES				
Isolated major congenital abnormality	264 (25.8%)	246 (38.1%)	14 (4.5%)	4 (5.9%)
Diagnosed Syndrome [a]	493 (48.1%)	202 (31.3%)	252 (81.0%)	39 (57.4%)
Dysmorphic, unknown features	133 (13.0%)	112 (17.4%)	14 (4.5%)	7 (10.3%)
Dysmorphic, features identified [a]	134 (13.1%)	85 (13.2%)	31 (10.0%)	18 (26.5%)

[a] *Denote variables with a p value <0.05 for acyanotic vs cyanotic CHD*

Most patients presented during the neonatal period (46.9%; n=480), while adolescents aged 13-16 years old (n=18) represented the least common age group for presentation. Patients with cyanotic CHD presented earlier compared to children with acyanotic heart disease (11 vs 106 days (p=0.008)).

Table 3 outlines the distribution of the1024 in the cohort based on their follow-up to cardiology. CHD was absent in 62.1% (n=636), and these patients were subsequently discharged from follow-up. Seventy-one patients (6.9%) died and 237 (23.1%) were lost to follow-up. The majority of those lost to follow-up were initially assessed during the neonatal period (45.5%) and were not subsequently seen again. Among the group lost to follow-up, 76.8% (n=182) had an identified syndrome and 86.9% (n=206) had acyanotic CHD.

Amongst the 71 documented patient deaths within the cohort, 38% (n=27) were in the neonatal group, of which three did not have underlying CHD. Acyanotic CHD (13.2%, n=41) predominated over cyanotic CHD (30.9%, n=21) amongst the overall known deaths, however, the highest proportion of deaths occurred in patients with cyanotic CHD. Overall, nine patients that died within the cohort did not have underlying CHD.

Table 3: Follow-up outcomes by syndrome diagnosis and CHD classification

TOTAL: N = 1024				
	Death (n=71)	**Discharged from follow-up (No CHD)** (n=636)	**Lost to follow-up** (n=237)	**Continued follow-up** (n=80)
Syndrome diagnosis (based on clinical diagnosis or molecular testing)				
Diagnosed Syndrome (n)	46	199	182	66
No genetic diagnosis (n)	25	437	55	14
CHD Classification				
Acyanotic CHD (n)	41	0	206	64
Cyanotic CHD (n)	21	0	31	16
No CHD (n)	9	0	0	0

Cardiac Abnormalities

A total of 379 (37.0%) patients had cardiac abnormalities, with acyanotic CHD (n=311, 82.1%) predominating over cyanotic CHD (n=68, 17.9%) (Table 1). The most common acyanotic lesions were septal defects- VSD (30.8%), followed by AVSD (24.5%), and the most common cyanotic lesion was Tetralogy of Fallot (TOF) (7.1%).

Most patients had one lesion, predominantly acyanotic CHD (n=234, 75.0%). In patients with multiple lesions, those with four or more lesions were more likely to have cyanotic CHD (p=0,0064).

CHD associated with syndromes

Syndromes were diagnosed in 493 children (48.1%) (Table 2), either through clinical diagnosis by a skilled paediatrician or geneticist, or by using molecular techniques. Trisomy 21 (T21) was the most common syndrome identified (27.2%, n=280) in the total cohort (Table 4). Figure 1 illustrates the distribution of cardiac lesion subtypes in patients with CHD who have syndromic presentations and those with isolated major congenital abnormalities.

Table 4: CHD subtypes associated with specific syndromes

	T21 **N = 280** n (%)	**Phenotypic T21** **N = 41** n (%)	**T18** **N = 31** n (%)	**T13** **N = 12** n (%)	**22q11.2DS** **N = 13** n (%)	**VACTERL** **N = 56** n (%)	**[a] Other Syndromes** **N = 101** n (%)	**Dysmorphic** **N = 226** n (%)	**[b] Isolated major congenital abnormality** **N = 264** n (%)
***Normal heart** **n = 645**	101 (36.1%)	29 (70.7%)	2 (6.5%)	4 (33.3%)	1 (7.7%)	39 (69.6%)	55 (54.5%)	168 (74.3%)	246 (93.2%)
***Total with lesion(s)** **n = 379**	**179** (63.9%)	**12** (29.3%)	**29** (93.5%)	**8** (66.7%)	**12** (92.3%)	**17** (30.4%)	**46** (45.5%)	**58** (25.7%)	**18** (6.8%)
Ventricular septal defect **n = 117**	49 (17,5%)	6 (14.6%)	21 (67.7%)	2 (16.7%)	1 (7.7%)	7 (12.5%)	8 (7.9%)	15 (6.6%)	8 (3.0%)
Atrioventricular septal defect **n = 93**	82 (29.3%)	3 (7.3%)	3 (9.7%)	-	-	-	2 (2%)	1 (0.4%)	2 (0.8%)
Patent ductus arteriosus **n = 40**	30 (10.7%)	-	1 (3.2%)	-	-	1 (1.8%)	5 (5%)	3 (1.3%)	-
Tetralogy of Fallot **n = 27**	5 (1.8%)	2 (4.9%)	-	-	5 (38.5%)	1 (1.8%)	5 (5%)	8 (3.5%)	1 (0.4%)
Atrial septal defect **n = 24**	10 (3.6%)	1 (2.4%)	-	-	-	3 (5.4%)	2 (2%)	6 (2.7%)	2 (0.8%)
Double outlet right ventricle **n = 18**	-	-	1 (3.2%)	2 (16.7%)	2 (15.4%)	1 (1.8%)	2 (2%)	9 (4.0%)	1 (0.4%)
Right ventricular outflow tract obstruction **n = 10**	-	-	-	-	-	-	8 (7.9%)	2 (0.9%)	-
Left ventricular outflow tract obstruction **n = 10**	-	-	1 (3.2%)	-	1 (7.7%)	-	3 (3%)	5 (2.2%)	-
Hypoplastic left ventricle **n = 6**	-	-	-	1 (8.3%)	-	-	1 (1%)	4 (1.8%)	-
Pulmonary atresia + ventricular septal defect **n = 6**	-	-	-	1 (8.3%)	1 (7.7%)	2 (3.6%)	1 (1%)	-	1 (0.4%)
Mitral valve abnormality **n = 6**	1 (0.4%)	-	-	-	-	-	4 (4%)	1 (0.4%)	-
Complex cyanotic lesion(s) **n = 5**	1 (0.4%)	-	1 (3.2%)	-	-	-	1 (1%)	1 (0.4%)	1 (0.4%)
Anomalous pulmonary venous drainage **n = 4**	-	-	-	-	-	1 (1.8%)	1 (1%)	1 (0.4%)	1 (0.4%)
Heterotaxy **n = 4**	-	-	-	2 (16.7%)	-	1 (1.8%)	-	-	1 (0.4%)
Coarctation of aorta **n = 3**	-	-	-	-	-	-	2 (2%)	1 (0.4%)	-
Truncus arteriosus **n = 2**	-	-	-	-	2 (15.4%)	-	-	-	-
Tricuspid Atresia 1c **n = 2**	1 (0.4%)	-	-	-	-	-	-	1 (0.4%)	-
Other CHD **n = 2**	-	-	1 (3.2%)	-	-	-	1 (1%)	-	-

***N = 1024 patients; 645 with structurally normal hearts and 379 with cardiac lesions (distribution detailed in table)**

***[a]* <u>Other</u> <u>Syndromes:</u> Alagille,** Beckwith-Wiedemann, congenital rubella, CHARGE, Cornelia de Lange, Crouzon, fetal alcohol, Golden Hare, Kabuki, Kleinfelter, **Marfan, Noonan,** Pierre-Robin, Prader-Willi, Sotos and Treacher-Collins, **Turner, Williams** syndromes. <u>Rare syndromes:</u> Reubenson Taybi, Peter Plus, Wolf-Hirschhorn, 2p deletion, Trisomy 14, Apert, Duplication 21q22.3, STAC 3 disorder, Partial monosomy 21, Ellis Van Creveld, Cat eye, 15q deletion, 7p22.1 microduplication, 9p Deletion, 7q22.3q31.1 deletion, 21q monosomy, 22q13.33 duplication and 22q11 duplication syndromes.

***[b]* Isolated congenital abnormality:** Anorectal malformation, craniofacial abnormality, limb abnormality, omphalocoele, oesophageal atresia, tracheo-oesophageal fistula.

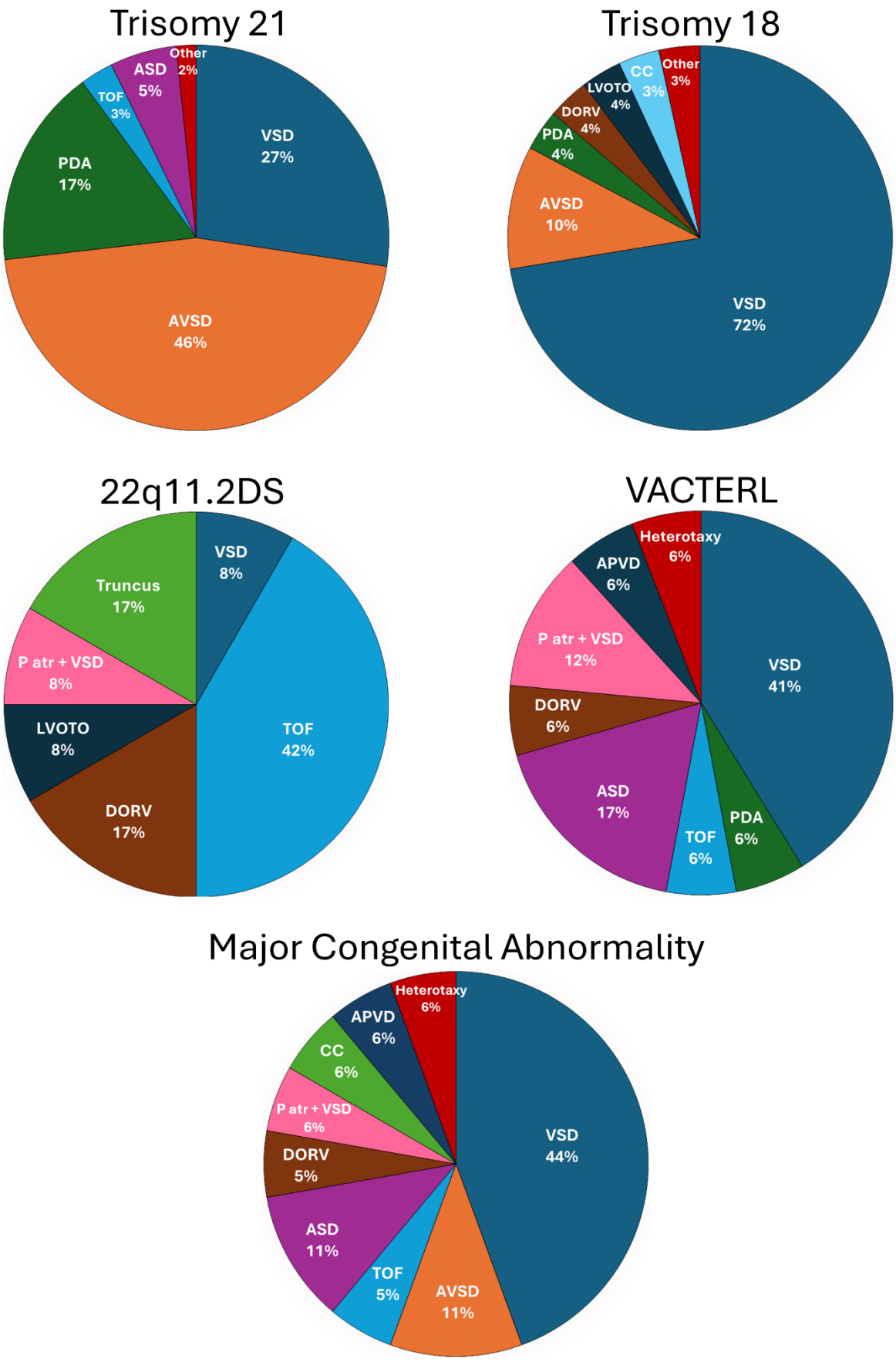

Figure 1: Proportion (%) of CHD subtypes per syndrome

APVD: Anomalous pulmonary venous drainage, **ASD:** atrial septal defect, **AVSD:** atrioventricular septal defect, **CC:** complex cyanotic lesions, **DORV:** double outlet right ventricle, **LVOTO:** left ventricular outflow tract obstruction, **Other:** rare CHD subtypes, **P atr + VSD:** pulmonary atresia with ventricular septal defect, **PDA:** patent ductus arteriosus, **TOF:** tracheo-oesophageal fistula, **Truncus:** truncus arteriosus, **VSD:** ventricular septal defect

Among 397 individuals with CHD, 179 (47.1%) had T21, making it the most frequently encountered syndrome in this group, followed by 58 (15.3%) with “dysmorphic” features (patients without a clinically identifiable or molecularly confirmed syndrome diagnosis), and 29 (10.4%) with trisomy 18 (T18) (Table 4). Patients with T18 had the highest proportion (93.5%) of cardiac lesions within a particular syndrome, with the predominant lesion within this group being VSD (n=21, 67.7%). Of all AVSD cases, 88.2% occurred in T21 cases. AVSD was also the most common cardiac lesion in T21 patients (29.3%, n=82), followed by VSD (17.5%, n=49).

Majority of patients with T18 (n=23, 74%) presented during the neonatal period. Deaths were documented in nine of these patients, seven of which occurred during the neonatal period.

Despite a relatively small sample size in 22q11DS (n=13), 92.3% had CHD, with conotruncal lesions such as TOF (n=5) and truncus arteriosus (n=2) predominating. Other syndromes that had a high percentage of patients with CHD were trisomy 13 (T13) (66.7%). Small sample sizes for other syndromes commonly associated with CHD such as Alagille (n=3), Williams (n=5), Turner (n=8), Marfan (n=7) and Noonan (n=5) limited the ability to establish genotype-cardiac phenotype correlations, despite some syndromes having CHD frequencies of up to 80%.

Congenital rubella syndrome was found in eight patients, six of which had CHD- all acyanotic lesions, namely PDA (n=3), VSD (n=2) and peripheral pulmonary stenosis (PPS)(n=1).

There were 264 (25.7%) patients with isolated major congenital abnormalities such as ARM, craniofacial abnormality, limb abnormality, omphalocele, oesophageal atresia and tracheoesophageal fistula. These patients were screened by cardiology as part of workup for syndromes such as VACTERL. CHD was found in 6.8% (n=18) of these patients, the most prevalent lesion being AVSD (n=8). Of the 104 patients referred to cardiology with ARM, five patients (4.5%) had CHD. Thirty percent of patients with suspected VACTERL association had CHD, with a predominance of acyanotic (n=12) over cyanotic (n=5) CHD. VSD (41%) was the predominant lesion found within this group. Other major congenital abnormalities documented in the VACTERL group of patients included genitourinary, tracheo-oesophageal fistula and skeletal abnormalities. Patients diagnosed with isolated tracheo-oesophageal fistula (n=57) had a CHD frequency of 7%, all of which had acyanotic CHD.

Associated non-cardiac malformations

In dysmorphic patients not diagnosed with a specific syndrome (n=226; 22.1%), abnormalities included craniofacial (n=32, 14.2%), marfanoid features (n=14, 6.2%), limb (n=12, 5.3%%) and central nervous system (n=10, 4.4%). Notably, in 136 patients classified as “dysmorphic” on the database, specific features were not documented in either clinical records or the cardiology database. Among 14 patients with marfanoid features without confirmed Marfan syndrome, 13 had no cardiac abnormalities, and one had a mitral valve abnormality (mitral valve prolapse).

Discussion

In this retrospective descriptive study of 1024 children with dysmorphic features, genetic syndromes (clinically diagnosed or confirmed through molecular testing) and isolated major congenital abnormalities, we report that 37.0% had associated CHD (Table 1), with acyanotic CHD being more common than cyanotic CHD. Children with syndromes are more likely to have CHD, especially T21, T18, 22q11.2DS, and VACTERL. The syndrome with the highest frequency of CHD was T18, followed by 22q11.2DS (Table 4). The most common syndrome in this cohort was T21. The predominant lesion in patients with CHD was VSD (30.8%).

Our study represents pioneering CHD research from South Africa. The PROTEA study, a larger prospective study in Cape Town [5], enrols echocardiographically confirmed CHD cases, and aims to establish the country's first genotyped and phenotyped registry and biorepository of CHD patients. Preliminary results identified marked differences in early results between South African and global prevalence rates of certain subtypes of CHD. Currently, comprehensive data addressing CHD in South and Southern Africa remains limited.

Understanding the association between extra-cardiac malformations, genetic syndromes, and CHD is crucial for patient care and prognostication of outcomes, particularly in the context of a resource-limited country such as South Africa, where access to specialised care such as paediatric cardiology and cardiothoracic surgery is limited. Knowledge of genotype-cardiac phenotype correlations inform effective management, recurrence risk assessment, and healthcare policy. This knowledge empowers healthcare providers to tailor interventions and support systems effectively to optimise care for CHD patients.

When analysing and comparing prevalence data, it is essential to account for variability arising from different inclusion criteria for congenital malformations and a broad interpretation of what is classified as significant congenital heart disease and what constitutes "dysmorphism".

Patient Characteristics

This study reported a predominance of acyanotic CHD (82%). These findings are similar to a Nigerian study looking at the preliminary results of a CHD registry (including syndromic and non-syndromic CHD) [11], that found a predominance of acyanotic CHD (76%) compared to cyanotic CHD (23%). In a study of infants with genetic syndromes and major congenital malformations in Lagos [14], a much higher prevalence of CHD was detected as compared to our study (73% vs 37%). Patients in the Lagos study had clinically or molecularly confirmed

syndrome diagnoses, which are strongly associated with CHD, whereas our study also included undiagnosed dysmorphic patients, who were found to have a lower association with CHD, potentially explaining the lower CHD prevalence in our cohort.

Predominant CHD subtypes in our study were VSD (31%), AVSD (25%) and PDA (11%), in contrast to the PROTEA study [5] which reported VSD (20%), ASD (11%), PDA (11%), and AVSD (7%). Reasons for this could be that the PROTEA study is not limited to syndromic children as ours is, accounting for higher percentages lesions such as AVSD (associated with T21) in our study. Both our study and the PROTEA study found TOF in 7% of patients.

Our study reports most patients presenting during the neonatal period, with patients with cyanotic CHD presenting earlier than those with acyanotic CHD. The group of patients with cyanotic CHD presenting for the first time as toddlers or preschoolers could be accounted for by TOF being the most regularly observed cyanotic lesion, a lesion where children can have variable degrees of cyanosis and thus can be recognized late.

Late presentation is multifactorial in our setting where there is limited access to medical care, with predominantly nurse-run primary health care, where only a few doctors may conduct neonatal examination and well-child visits. Paediatric cardiology is a specialist service, relying on timely referrals from various levels of care. The lack of a neonatal pulse oximetry screening program contributes to missed diagnoses of critical cyanotic CHD, and often families only present with the child once multi-organ dysfunction manifests [7]. In a study of CHD (not limited to syndromic patients) in Nigeria [4], 58% of patients presented in infancy, while only 32% of our patients were first seen as infants. On literature review, data regarding age at presentation was limited.

The highest mortality was during the neonatal period, consistent with Rossouw's commentary on CHD in Africa [7], even among patients without cardiac lesions. This can be explained by various other factors contributing to neonatal mortality, such as prematurity and its associated complications. Further studies and analyses would be required to look at the factors contributing to death in syndromic patients, across all age groups. The number of deaths in our study is likely underestimated due to the large number of patients lost to follow-up, and the uncertainty of the outcome of these children. A systematic analysis of the global burden of CHD [24] found a mortality of 42.1 per 100 000 infants less than 1 year, and an age standardised mortality of 1.5 per 100 000 due to CHD in Southern Sub-Saharan Africa. Mortality data for CHD in South Africa are limited, but findings from our study suggest that there is a high mortality amongst syndromic and dysmorphic children.

Syndromes associated with CHD

A genetic syndrome was diagnosed in 48.1% of the cohort. The most common syndrome was T21 (27%), with 64% of these patients having CHD, exceeding the 40-50% reported in the literature [4,16,17]. Within T21, AVSD was the most frequent defect (29.3%) followed by VSD (17.5%), which again differs from other studies reporting 45-62% and 35% respectively. Ekure et al [4] found similar associations with syndromes, but different frequencies of lesions, namely: T21 most commonly having AVSD (57%), followed by septal and ductal defects (grouped together forming 30%). A review of the literature about T21 and CHD [25] found that the types of CHD varied greatly between sources analysed, and the authors found no clear consensus on types of lesions directly associated with T21. The frequency of TOF in T21 (1.8%) was in keeping with known literature [26].

Trisomy 18 carries a poor prognosis, with a high incidence of CHD largely contributing to mortality. The frequency of CHD in the study population was higher than documented in the literature (93.5% vs 60-80%) [17], but only nine deaths were recorded, as the remaining patients were lost to follow-up.

Congenital Rubella Syndrome still has a burden of disease in our setting, due to Rubella vaccination not yet being part of South Africa's routine expended programme of immunisation. It is an optional vaccination in the private sector. The patients with congenital rubella syndrome in this study had CHD distribution similar to that found in the literature in other developing countries such as Nigeria [4].

Another important syndrome commonly associated with CHD is 22q11.2DS. Sixty-three patients seen during the period 2010-2020 had conotruncal lesions, with 11 (17.4%) of these being diagnosed as having 22q11DS. This is in keeping with findings by Goldmuntz et al [18], who found that 17.9% of patients with conotruncal lesions have underlying 22q11.2DS. Digilio et al [27] found that 82% of patients with 22q11.2 DS had CHD, majority of whom had conotruncal lesions. This is lower than our study findings of 92.3% of patients with 22q11.2DS having CHD. This higher prevalence may reflect selection bias, as our undiagnosed dysmorphic patients could include unidentified cases of 22q11.2DS. Digilio et al [27] found TOF in 26% and pulmonary atresia with VSD in 24% of patients with 22q11.2DS. The difference in our findings could be limited to access to care, with more severe lesions like pulmonary atresia being missed before reaching healthcare, while other lesions such as TOF may only become apparent later in life depending on the severity of the right ventricular outflow obstruction.

In a prospective study [28] about 22q11.2DS conducted at Red Cross War Memorial Children's Hospital in Cape Town, South Africa, six patients with CHD were identified, with VSD being the most common lesion. While the sample size is limited for direct comparison, given the similar resource setting, it is anticipated that these patients would exhibit a comparable distribution of lesions to those in our study.

All patients born with anorectal malformations as well as those with tracheo-oesophageal fistulae are referred for screening echocardiograms due to an awareness of the VACTERL association. A retrospective analysis of patients born with ARM at a hospital in Italy [20] showed a similar trend, but a much higher incidence of CHD (most common defect VSD) in patients with VACTERL(73%), and isolated ARM (16%) compared to our cohort. A study in USA [19] also found similar results, with patients with VACTERL having a 67% incidence of CHD, and VSD being the most common lesion. Our study found that there was a higher frequency of CHD (30%) in patients with multiple congenital abnormalities as part of VACTERL association, rather than those with isolated anorectal malformations or tracheo-oesophageal fistulae (4.5% and 7% respectively). This supports the supposition that syndromic children are more likely to have CHD, compared to non-syndromic children with isolated major congenital abnormalities. Although the frequency of CHD in both isolated ARM and tracheo-oesophageal fistula was low in our cohort, it remains higher than that of the general population, highlighting the importance of cardiac screening in these patients., The frequency of ARM and trachea-oesophageal fistula and CHD in patients with VACTERL association is reportedly very high, up to 90% in some cases [19].

The group with the lowest proportion of CHD in the cohort were those with an isolated congenital abnormality. These patients are sent for cardiac screening to rule out the possibility of having CHD as another associated abnormality. The rate of CHD in this group (n=18/264, 6.8%) is higher than that of the general population (9 out of 1000 live births worldwide, 0.9% [3], justifying the need for screening these patients despite a relatively low frequency of CHD compared to syndromic patients.

Regarding genetic testing in South Africa, Kromberg et al. [29] noted that despite advancements in types of testing, access remains limited, primarily available in academic centres and the National Health Laboratory Service (NHLS), which operates with only 10% of the required staff. The private sector offers genetic testing in four of the nine provinces. Testing is available for most common genetic conditions but is only available at a tertiary level of care in the public

sector. Recent literature searches have not yielded publications regarding current laboratory genetic services in South Africa.

Currently, patients in our setting are referred from the Genetics Clinic to the Cardiology Clinic for screening on a case-by-case basis, based on having a syndrome commonly associated with CHD, or the presence of multiple congenital abnormalities. Referral pathways are in place for provinces that do not have a clinical genetics service. Genetic testing is performed by either quantitative fluorescence polymerase chain reaction (QF-PCR) for aneuploidy syndromes, micro-array analysis for copy number variants in dysmorphic patients not fitting a particular syndrome, or those with multiple congenital abnormalities. Testing for single gene defects is limited to requests by clinical geneticists. The turnaround times for genetics test results varies between three days to three months, depending on the type of testing, and are accessible to patients within the state sector in Johannesburg.

Strengths

The strengths of this study include comprehensive data collection analysing a large patient cohort over a 10-year period, as well as the broad inclusion criteria including genetically undiagnosed dysmorphic patients. As one of the first of its kind in South Africa, it provides novel insights into syndromic CHD and forms a baseline for further detailed studies.

The strong referral system between genetics and cardiology at CMJAH facilitated a considerable number of referrals to paediatric cardiology, strengthening the comprehensiveness of the data. The diverse patient population at CMJAH and its referral hospitals enabled the analysis of a varied patient group.

Furthermore, the database used in the study was compiled through a multidisciplinary approach, providing a holistic view of CHD in syndromic patients.

Weaknesses and Limitations

Due to the retrospective nature of the study, information available relied on the accurate capture of information into the CMJAH paediatric cardiology database and patient records, without the ability to re-examine patients to obtain missing information. Some files of deceased patients were not accessible, leading to patients being classified as “dysmorphic with non-specified features” and potentially missing syndromes and important associations. A sizeable group of patients were lost to follow-up, leaving their survival outcomes and genetic diagnoses unknown. Small sample sizes for certain syndromes limited the ability to draw conclusions for these.

Bias may have occurred with inter-observer variability, as only patients deemed clinically dysmorphic by the attending doctor would have been referred to paediatric cardiology. The clinical misdiagnosis of a dysmorphic patient may have resulted in a pool of patients not being included in the study. The use of screening checklists could be introduced to improve clinical detection of dysmorphic babies and those at risk of having CHD prior to discharge.
These limitations could largely be overcome by a multi-centre prospective study of this nature, including a multidisciplinary team to aid in comprehensive assessment and diagnosis of syndromes and CHD.

Contribution to body of knowledge

This study has provided data about CHD and associated genetic syndromes and has highlighted similarities but also important differences in a South African population that is vastly diverse and lacks data in this subject, when compared to other data. It has highlighted the importance of cardiac screening in all dysmorphic children, regardless of whether they have a confirmed genetic diagnosis or not.

Conclusion

This study describes a series of dysmorphic and syndromic patients at a single site in South Africa. It provides a description of the clinical epidemiology of CHD in syndromic South African children over a 10-year period and highlights important associations between CHD and certain syndromes. The CHD prevalence of 37% within this cohort highlights the need for early referral of all newborns with dysmorphic features and major congenital abnormalities for genetic and cardiac screening to facilitate early diagnosis and appropriate management, optimising outcomes for children and families. The presence of CHD impacts on morbidity and mortality in these patients and is an important factor for prognostication and planning future healthcare provision for these patients.

The reported frequency of congenital cardiac lesions in South Africa appears lower than that of HICs, likely due to an underestimation of the true prevalence in our population, as many patients may demise before diagnosis by a paediatric cardiologist. Although cardiac findings for common syndromes align with literature, the authors were unable to establish correlations for less common syndromes. The findings of the study suggest that syndromic patients and patients with major congenital abnormalities require vigilant screening for CHD, and a high index of clinical suspicion. Further investigation and analysis are warranted in understanding the burden of CHD and other major congenital abnormalities in South Africa to inform healthcare planning and management of these patients in a limited-resource setting like ours.

Establishing effective provincial or national registries and conducting population-based studies in public health settings in LMICs is crucial for accurate assessment of CHD prevalence and categorization, especially in at-risk populations such as those with genetic syndromes and congenital malformations.

Recommendations

Sample sizes for certain syndromes such as Williams and Noonan were limited in out cohort, therefore, multicentre studies looking specifically at rarer syndromes may assist in characterising important associations with these syndromes and CHD in our population. Prospective studies of patients with dysmorphism without a recognizable syndrome may allow for comprehensive documentation of specific dysmorphic features to draw correlations between these phenotypic features and CHD. Additionally, a study looking specifically at isolated major congenital abnormalities without dysmorphic features would also be important to characterise the association with CHD and these abnormalities.

Implementation of standardised screening protocols developed through collaboration between clinical genetics and paediatric cardiology departments will optimise prompt and appropriate referral pathways for primary care physicians and paediatricians. Improved knowledge of genotype-cardiac phenotype correlations will empower clinicians to detect these patients and manage and refer appropriately.

A national pulse oximetry screening programme, as well as improvement of knowledge and skills of primary care practitioners in delivery wards and integrated management of childhood illness (IMCI) clinics is crucial for early detection and referral of these high-risk patients. These measures may significantly improve CHD detection rates, and survival in vulnerable populations.

Additionally, scaling up a registry such as the one established in the PROTEA project nationally will enable characterisation of CHD in the South African population. This enlarged database will facilitate inter-institutional patient tracking (especially in cases of loss of follow-up) and provide a robust platform for paediatric cardiology and genetics research.

Lastly, at health system level, strengthening genetic and paediatric (general and cardiology) services in the state healthcare sector in South Africa will facilitate earlier diagnosis of syndromic patients, and screening and management of associated complications, such as CHD. These systemic improvements are fundamental to advancing both clinical care and research capabilities within the health care sector.

Acknowledgments

Dr. Kashiram extends sincere thanks to Prof. Kebashni Thandrayen of Chris Hani Baragwanath Academic Hospital for her insightful mentorship and expert guidance with the statistical analysis of the data.

Conflict of interest

The authors declare that they have no conflict of interest or financial disclosure related to this study.

Author contributions

Dr Kashiram was the principal author, responsible for data collection, data analysis and composition of study findings. Dr Motara provided access to and assisted with the paediatric cardiology database and interpretations of echocardiogram findings for patients. Prof Cilliers and Dr Motara provided technical cardiology knowledge and guidance on the study design, data management, as well as final editing of this study.

Funding Sources

This study was self-funded by the principal author, Dr Kashiram.

Bibliography

1. Grech V, Gatt M. Syndromes and malformations associated with congenital heart disease in a population-based study. Int J Cardiol. 1999; 68:151–6.

2. Saacks N, Spracklen T, Eales J, Shaboodien G, Keavney B, Zühlke L. The genetics of congenital heart disease: The role of advanced genomic approaches. SA Heart [Internet]. 2021 [cited 2024 Aug 4];18. Available from: https://www.journals.ac.za/index.php/SAHJ/article/view/4886

3. van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJM, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011; 58:2241–7.

4. Ekure EN, Kalu N, Sokunbi OJ, Kruszka P, Olusegun-Joseph AD, Ikebudu D, et al. Clinical epidemiology of congenital heart disease in Nigerian children, 2012-2017. Birth Defects Res. 2018; 110:1233–40.

5. Aldersley T, Lawrenson J, Human P, Shaboodien G, Cupido B, Comitis G, et al. PROTEA, A Southern African Multicenter Congenital Heart Disease Registry and Biorepository: Rationale, Design, and Initial Results. Front Pediatr. 2021; 9:763060.

6. Duarte VE, Singh MN. Genetic syndromes associated with congenital heart disease. Heart Br Card Soc. 2023; heartjnl-2023-323126.

7. Rossouw B. Congenital heart disease in Africa threatens Sustainable Development Goals. South Afr J Crit Care Off J Crit Care Soc. 2021;37.

8. Namuyonga J, Lubega S, Aliku T, Omagino J, Sable C, Lwabi P. Pattern of congenital heart disease among children presenting to the Uganda Heart Institute, Mulago Hospital: a 7-year review. Afr Health Sci. 2020; 20:745–52.

9. Tankeu AT, Bigna JJR, Nansseu JRN, Aminde LN, Danwang C, Temgoua MN, et al. Prevalence and patterns of congenital heart diseases in Africa: a systematic review and meta-analysis protocol. BMJ Open. 2017;7: e015633.

10. Hoosen EGM, Cilliers AM, Hugo-Hamman CT, Brown SC, Lawrenson JB, Zuhlke L, et al. Paediatric cardiac services in South Africa. South Afr Med J Suid-Afr Tydskr Vir Geneeskd. 2011; 101:106–7.

11. Ekure EN, Bode-Thomas F, Sadoh WE, Orogade AA, Otaigbe BE, Ujunwa F, et al. Congenital Heart Defects in Nigerian Children: Preliminary Data from the National Pediatric Cardiac Registry. World J Pediatr Congenit Heart Surg. 2017; 8:699–706.

12. Calcagni G, Unolt M, Digilio MC, Baban A, Versacci P, Tartaglia M, et al. Congenital heart disease and genetic syndromes: new insights into molecular mechanisms. Expert Rev Mol Diagn. 2017; 17:861–70.

13. Ferencz C, Rubin JD, McCarter RJ, Brenner JI, Neill CA, Perry LW, et al. Congenital heart disease: prevalence at livebirth. The Baltimore-Washington Infant Study. Am J Epidemiol. 1985; 121:31–6.

14. Ekure EN, Animashaun A, Bastos M, Ezeaka VC. Congenital heart diseases associated with identified syndromes and other extra-cardiac congenital malformations in children in Lagos. West Afr J Med. 2009; 28:33–7.

15. Duarte VE, Singh MN. Genetic syndromes associated with congenital heart disease. Heart. 2023;1–7.

16. Hopkins MK, Dugoff L, Kuller JA. Congenital Heart Disease: Prenatal Diagnosis and Genetic Associations. Obstet Gynecol Surv. 2019; 74:497–503.

17. Lin AE, Santoro S, High FA, Goldenberg P, Gutmark-Little I. Congenital heart defects associated with aneuploidy syndromes: New insights into familiar associations. Am J Med Genet C Semin Med Genet. 2020; 184:53–63.

18. Goldmuntz E, Clark BJ, Mitchell LE, Jawad AF, Cuneo BF, Reed L, et al. Frequency of 22q11 deletions in patients with conotruncal defects. J Am Coll Cardiol. 1998; 32:492–8.

19. Cunningham BK, Hadley DW, Hannoush H, Meltzer AC, Niforatos N, Pineda-Alvarez D, et al. Analysis of cardiac anomalies in VACTERL association. Birt Defects Res A Clin Mol Teratol. 2013; 97:792–7.

20. Moras P, Zarfati A, Bagolan P, Conforti A, Toscano A, Iacobelli BD. Anorectal malformations (ARM) and VACTERL association and severity of congenital heart diseases (CHD): Experience of 396 consecutive patients in a tertiary center. Pediatr Neonatol. 2024; 65:381–5.

21. EUROCAT. EUROCAT Guide 1.4: Instruction for the registration of congenital anomalies [Internet]. Central Registry, University of Ulster; 2013. Available from: https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/Full_Guide_1_4_version_28_DEC2018.pdf

22. World Health Organisation. International Classification of Diseases, Eleventh Revision (ICD-11) [Internet]. 2022. Available from: https://icd.who.int/browse/2024-01/mms/en#2004408087

23. Talner CN. Report of the New England Regional Infant Cardiac Program, by Donald C. Fyler, MD, Pediatrics, 1980;65(suppl):375-461. Pediatrics. 1998; 102:258–9.

24. Zimmerman MS, Smith AGC, Sable CA, Echko MM, Wilner LB, Olsen HE, et al. Global, regional, and national burden of congenital heart disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Child Adolesc Health [Internet]. 2020 [cited 2024 Aug 4]; 4:185–200. Available from: https://linkinghub.elsevier.com/retrieve/pii/S235246421930402X

25. Santoro SL, Steffensen EH. Congenital heart disease in Down syndrome – A review of temporal changes. J Congenit Cardiol [Internet]. 2021; 5:1. Available from: https://doi.org/10.1186/s40949-020-00055-7

26. Fahed AC, Gelb BD, Seidman JG, Seidman CE. Genetics of congenital heart disease: the glass half empty. Circ Res. 2013; 112:707–20.

27. Digilio M, Marino B, Capolino R, Dallapiccola B. Clinical manifestations of Deletion 22q11.2 syndrome (DiGeorge/Velo-Cardio-Facial syndrome). Images Paediatr Cardiol. 2005; 7:23–34.

28. De Decker R, Bruwer Z, Hendricks L, Schoeman M, Schutte G, Lawrenson J. Predicted v. real prevalence of the 22q11.2 deletion syndrome in children with congenital heart disease presenting to Red Cross War Memorial Children's Hospital, South Africa: A prospective study. South Afr Med J Suid-Afr Tydskr Vir Geneeskd. 2016;106: S82-86.

29. Kromberg JGR, Sizer EB, Christianson AL. Genetic services and testing in South Africa. J Community Genet. 2013; 4:413–23.

30. nhlsadmin. Type Of Tests [Internet]. National Health Laboratory Service. [cited 2024 Aug 10]. Available from: https://www.nhls.ac.za/diagnostic-services/type-of-tests/

Appendix A: Hierarchical classification of cardiac lesions (adapted from the New England Regional Infant Cardiac Program [23])

Categorical Hierarchy	Categorical Diagnosis
01	Heterotaxias
02	Single ventricle
03	Hypoplastic left ventricle
04	Tricuspid atresia
05	Truncus arteriosus
06	Double-outlet right ventricle
07	D-transposition of great arteries
08	L transposition of great arteries
09	Endocardial cushion defects (now atrioventricular septal defect)
10	Total anomalous pulmonary venous return
11	Pulmonary atresia with intact ventricular septum
12	Tetralogy of Fallot
13	Coarctation of aorta
14	Ventricular septal defect
15	Aortic stenosis
16	Pulmonary stenosis
17	Myocardial disease
18	Atrial septal defect (secundum)
19	Patent ductus arteriosus
20	No significant heart disease
21	Lung disease
22	Other

Appendix B: Detailed echocardiographic findings for study participants from the CMJAH paediatric cardiology database

Multiple lesions are listed and separated by commas.

Lesion description	**Patient count of lesion description (n=)**
Normal heart	611
Atrioventricular septal defect (AVSD)	87
Ventricular septal defect (VSD)	68
Patent ductus arteriosus (PDA)	38
PDA *(during neonatal period only)*	25
Tetralogy of Fallot (TOF)	24
VSD, PDA	21
Atrial septal defect (ASD), VSD	16
ASD	15
Double outlet right ventricle (DORV)	14
Peripheral pulmonary stenosis (PPS) *(during neonatal period only)*	7
ASD, PDA	7
PPS	5
Pulmonary atresia with VSD (P atr + VSD)	5
ASD, VSD, PDA	5
Valvar aortic stenosis (LVOT-valvar)	4
Mitral valve (MV) prolapse, ballooning MV	3
Hypoplastic left ventricle (Hypo LV)	3
AVSD, PDA	3
Congenital mitral insufficiency (Cong MI)	2
Coarctation of aorta (CoA)	2
Valvar pulmonary stenosis (RVOT- Valvar PS)	2
Tricuspid atresia type 1c	2
PDA, PPS	2
Partial anomalous pulmonary venous drainage (PAPVD)	2
Truncus arteriosus (Truncus)	2
Left pulmonary artery (LAP) stenosis (RVOT- LPA Stenosis)	2
ASD, PPS	2
VSD, PPS (neonatal)	2
Hypertrophic obstructive cardiomyopathy (LVOT- HOCM)	2
DORV, transposition of great vessels (TGV), supravalvar pulmonary stenosis (RVOT- supra)	1
DORV, AVSD, heterotaxy- dextroposition	1
VSD, Redundant tricuspid valve (TV)	1
Hypo LV, Bicuspid aortic valve (Bicusp AV), CoA, Parachute MV	1
DORV, TGV	1
AVSD, ASD	1

VSD, Interrupted Arch (LVOT- Int Ao)	1
Hypo LV, LVOT- Int Ao	1
DORV, ASD, VSD	1
Bicusp AV, Abnormal pulmonary valve (Abn PV)	1
RVOT- Valvar PS, cong MI	1
Arch abnormality, Valvar aortic stenosis (LVOT-valvar)	1
TOF, PDA	1
AVSD, CoA	1
Heterotaxy- dextrocardia, ASD	1
MV prolapse	1
Heterotaxy- dextrocardia, VSD	1
ASD, PAPVD	1
Hypoplastic left heart syndrome (HLS), Mitral atresia, aortic stenosis, CoA, PDA, VSD	1
ASD, VSD, PDA (neonatal), PPS	1
DORV, ASD, VSD, Right Aortic arch	1
P Art + VSD, Absent LPA, major aortopulmonary collateral arteries (MAPCAS)	1
DORV, CoA	1
ASD, VSD, PDA, Abnormal PV	1
S vent, AVSD, pulmonary atresia (PA), TGV, PDA	1
Dilated aortic root	1
TOF, AVSD, PS	1
Double outlet left ventricle (DOLV)	1
TOF, RVOT-LPA stenosis	1
DOLV, TGV, VSD, ASD	1
DORV, VSD, PDA	1
PDA (neonatal), ASD, total anomalous pulmonary venous drainage (TAPVD)	1
VSD, Dilated aortic root	1
PDA (neonatal), patent foramen ovale (PFO)	1
VSD, LVOT- Bicusp AV, LVOT-Int Ao	1
PDA, AVSD	1
VSD, PDA, MV cleft	1
ASD, VSD, CoA	1
Heterotaxy- dextroposition	1
PDA, RVOT- Valvar PS	1
Pentalogy of Fallot	1
Grand Total	**1024**

Appendix C: WITS Postgraduate Committee approval to conduct study.

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

29 September 2022
Person No: 359546
PAG

Dr AA Kashiram
25 David Draper Road
Bruma
2026
South Africa

Dear Dr Avani Kashiram

Master of Medicine in Paediatrics: Approval of Title

We have pleasure in advising that your proposal entitled *The distribution and frequency of congenital heart disease in patients with known syndromes or non-specific dysmorphic features at Charlotte Maxeke Johannesburg Academic Hospital from 2010 to 2020* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix D: WITS Human Research Ethics Committee (Medical) approval to conduct study

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:	Dr A Kashiram School of Clinical Medicine Department of Paediatrics and Child Health Medical School University
	E-mail: avani.kashiram@gmail.com
CC:	Supervisor: Dr F Motara and Professor A Cilliers <motaraf@hotmail.com> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252
	E-mail: Iain.Burns@wits.ac.za
DATE:	2020/10/10
REF:	R14/49
PROTOCOL NO:	**M220842** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*The distribution and frequency of congenital heart disease in patients with known syndromes or non-specific dysmorphic features at Charlotte Maxeke Johannesburg Academic Hospital from 2010 to 2020*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps