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Incidence and prognosis of critical congenital heart disease in neonates at Charlotte Maxeke Johannesburg Academic Hospital

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2018

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Incidence and prognosis of critical congenital heart disease in neonates at Charlotte Maxeke Johannesburg Academic Hospital

Student: **Tshiamo Mogajane**

Student Number: **1322005**

Degree: **MMED in Paediatrics**

Supervisors: **Prof DE Ballot**

Dr F Motara

Submitted: **November 2016**

DECLARATION

I, Tshiamo Mogajane declare that this research report is my own work. The report is being submitted for the degree of Masters of Medicine in the branch of Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

T. Mogajane

28 October 2016

DEDICATION

I thank my parents for their endless support in my quest to complete this research report.

ACKNOWLEGMENTS

I wish to thank my research supervisors Prof Ballot and Dr Motara for their expert guidance during the process. I would also like to acknowledge all the staff that assisted with the collection of data in the neonatal unit at Charlotte Maxeke Johannesburg Academic Hospital.

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LIST OF ABBREVIATIONS

ASD	Atrial septal defect
AS	Aortic stenosis
BW	Birth weight
Coarc	Coarctation of the aorta
CHB	Congenital heart block
DORV	Double outlet right ventricle
EA	Ebstein's anomaly
ECD	Endocardial cushion defect
GA	Gestational age
HRV	Hypoplastic right heart
HLV	Hypoplastic left heart
IAAH	Interrupted aortic arch
PA	Pulmonary atresia
PS	Pulmonary stenosis
SV	Single ventricle
SVT	Supraventricular tachycardia
Truncus	Truncus arteriosus
TAPVD	Total anomalous pulmonary venous drainage
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot
VSD	Ventricular septal defect.

Incidence and prognosis of critical congenital heart disease in neonates at Charlotte Maxeke Johannesburg Academic Hospital

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ABSTRACT

Background: A significant number of neonates with congenital heart disease present with a life-threatening illness in the neonatal period where survival depends on timely diagnosis, management and referral.

Objectives: To determine the incidence and prognosis of critical congenital heart disease in neonates admitted to Charlotte Maxeke Johannesburg Academic Hospital, and to compare it with international data.

Method: This was a retrospective, descriptive study of neonates with critical and non-critical congenital heart disease admitted to Charlotte Maxeke Johannesburg Academic Hospital between 01 January 2006 and 31 December 2014.

Results: There were 284 neonates diagnosed with congenital heart disease during the study period - 133 with critical congenital heart disease (8.2 per 1000 neonatal admissions) and 151 with non-critical congenital heart disease (9.3 per 1000 neonatal admissions). The mortality rate for neonates with critical congenital heart disease was 61/133 (45.9%).

Conclusion: Critical congenital heart disease is not commonly diagnosed in neonates, however the mortality rate is high. Increased awareness and screening programs may improve early diagnosis and allow timeous intervention.

BACKGROUND

Congenital heart disease (CHD) is one of the most common congenital anomalies [1]. The prevalence of CHD varies across populations and also over time [2]. These variations are in part due to the quality of data captured, such as completeness of diagnosis (prenatal and postnatal), and registration of cases, amongst other issues. Europe has a common database for CHD, comprised of population-based surveys that form part of the European Surveillance of Congenital Anomalies (EUROCAT) [2]. Data on CHD in low to middle income countries (LMICS), especially Africa is scarce, and studies often do not include indigenous inhabitants. The estimated global prevalence of CHD is 8 per 1000 live births [1]. Africa has the lowest reported birth prevalence of CHD (1.9 per 1000 live births) with the prevalence in South Africa estimated to be 0.6-0.8 per 1000 live births [1] [3]. This estimate may be due to under reporting, as many patients with CHD in Africa are missed [4].

Critical congenital disease (CCHD) comprises cyanotic CHD and left-sided obstructive lesions which may present with or without cyanosis [5] (See Table 1). Survival of neonates with CCHD depends on timely diagnosis, management and referral [3]. These cardiac lesions require surgery or catheterization in the neonatal period to avoid death or severe morbidity [6]. The global incidence of CCHD is reported to be 2 – 3 per 1000 live births [4]. The incidence of CCHD is constant worldwide, but is thought to be underestimated in countries where prenatal ultrasound screening is not uniformly practiced [4]. Early diagnosis of CCHD relies on antenatal fetal anomaly screening and neonatal examination. In South Africa, most of the CCHD are not diagnosed before birth owing to limited antenatal screening for CCHD [4].

Normal neonatal examination does not exclude serious or life threatening cardiovascular malformations. About one third of babies with signs and symptoms of CHD are only diagnosed by 6 weeks of age and 57% by 3 months [7]. If every baby with signs and symptoms of CHD had an echocardiogram, half of them could have been diagnosed by 6 weeks and 76% by 3 months [7]. Routine neonatal echocardiography is, however, not feasible in South Africa due to resource constraints [8].

Many neonates with CCHD are not diagnosed at birth, and late diagnosis of CCHD is associated with increased hospitalization and costs [9]. Late detection of CCHD is defined as diagnosis after the birth hospital discharge and approximately 23% of infants with CCHD are diagnosed late [9]. Late detection of CCHD is significantly associated with more hospital admissions (52%), longer duration of hospitalization (18%), and higher inpatient costs during infancy (35%) [9]. Improved screening for CCHD might help save cost in inpatient care during infancy. Early detection of CCHD is however not associated with a lower mortality for patients with significant CHD [9].

Table 1. Critical cyanotic heart lesions and left-sided obstructive lesions

List of Critical cyanotic congenital heart lesions
Tetralogy of Fallot
Transposition of great arteries
Hypoplastic right heart
Tricuspid atresia
Truncus arteriosus
Double outlet right ventricle
Single ventricle
Total anomalous pulmonary venous return

List of left-sided obstructive lesions
Hypoplastic left heart
Aortic stenosis
Coarctation of aorta
Interrupted aortic arch

The one year survival for infants with CCHD has been improving over time, yet the mortality remains high. One year survival for infants with CCHDs improved from 67.4% (1979-1993) to 82.5% (1994-2005) [10]. Late diagnosis (diagnosis after birth hospital discharge) was also associated with improved one year survival [9]. One year survival was 71.7% for neonates with CCHD diagnosed within the first day of life, and was 82.5% for neonates with CCHD diagnosed after the first day of life ($p < .001$) [10]. This difference in mortality is likely due to more severe conditions being present among infants with CCHD that is detected early in the neonatal period [10]. Some infants with CCHD may not require corrective surgery in early infancy based on the severity of their cardiac lesions [5].

This study aims to describe the incidence and outcome of neonates presenting with CCHD at CMJAH over a 9 year period.

METHODS

This was a retrospective, descriptive study of all neonates with CCHD who were admitted to CMJAH between 01 January 2006 and 31 December 2014. CMJAH is a tertiary hospital with a cardiology and cardiac surgery service. There is a cluster of regional hospitals and midwife clinics which refer neonates to CMJAH for tertiary services.

Participants

Inclusion criteria:

All neonates (<28 days of life) who were admitted to CMJAH (neonatal and general paediatric wards) with a critical congenital cardiac defect were eligible for inclusion in the study. Critical congenital heart disease was defined as a group of heart defects that cause serious, life-threatening symptoms and requires intervention within the early neonatal period or first year of life [4]. Neonates diagnosed with a CHD that was non-critical (non-CCHD) were also included in the study, but analyzed separately. Neonates with dysrhythmias (notably congenital heart block) were also included in the non-critical CHD group.

Exclusion criteria:

Neonates diagnosed with patent ductus arteriosus (PDA) only were excluded from the study, as the presence of a PDA varies with gestational age and can depend on changing physiology (such as fluid overload and sepsis). Neonates assessed by a paediatric cardiologist, but without a confirmed cardiac diagnosis were excluded. Neonates referred directly to the cardiothoracic unit from other hospitals were also excluded.

For the purpose of the study, chromosomal abnormalities were defined as confirmed trisomy 13, trisomy 18 and trisomy 21. Neonates who were dysmorphic but did not have a chromosomal diagnosis were analyzed with the group as having no chromosomal abnormality. Chromosomal analysis was not done routinely but requested at the discretion of the attending physician, based on clinical assessment. There was no record of clinically dysmorphic babies who did not have a chromosome analysis done.

Database

Data from the study was retrieved from the CMJAH neonatal database, as well as from the paediatric cardiology database. The REDcap neonatal database is used for the purpose of clinical audit [11]. Information is collected for each patient on discharge from the neonatal unit at CMJAH. Data is managed using REDcap (Research Electronic Data Capture), hosted by the University of the Witwatersrand [11]. Patient records from the paediatric cardiology department are also stored on an electronic database. Accuracy of data captured on the databases is checked at several stages of the data collection process. Data collected from the databases included: age at presentation, gestational age, birth weight, ethnicity, cardiac diagnosis (obtained by echocardiography or cardiac catheterization), surgical treatment, and survival to hospital discharge.

Statistical analysis

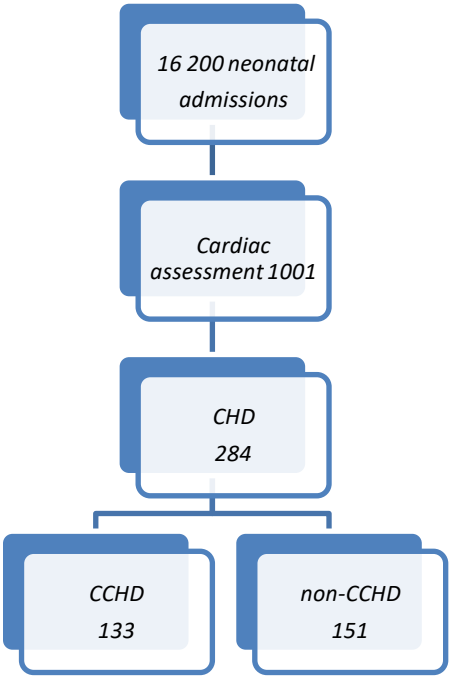
Data collected was entered into a Microsoft Excel spreadsheet (Microsoft, USA), and imported into a statistical software package SPPS version 23 (IBM, USA). Categorical variables were described using frequencies and percentages. Continuous variables had a normal distribution, so were described using mean and standard deviation. Neonates with CCHD were compared with those with non-critical CHD, with regard to characteristics and survival to hospital discharge. Patients who were discharged home and those who were transferred out of hospital were grouped together as survivors for the purpose of analysis. Categorical variables were compared using Chi Square analysis and continuous variables using unpaired tests. A p value of 0.05 was considered to be statistically significant.

Ethics

Ethics approval for the study was obtained from the Human Research Ethics Committee of the University of Witwatersrand: clearance certificate number M151001.

RESULTS

Figure 1. Total number of neonates at each stage of the study



A total of 1001/16 200 (6.2%) neonates admitted at CMJAH were referred for cardiac assessment. There were 133 neonates with CCHD (46.8%) (8.2/1000 neonatal admissions) and 151 with non CCHD (53.2%) (9.3/1000 neonatal admissions). Characteristics of neonates with CCHD and non CCHD are shown in Table 2-3.

Gestational age, birth weight, and outcome were only available in 19 patients. There was no significant difference in birth weight between survivors and non-survivors ((2.4kg (SD 0.7) vs 2.7 kg (SD 0.8) p=0.3). Similarly there was no difference in gestational age between survivors and non-survivors (35.5 weeks (SD 2.6) vs 37 weeks (SD 3.2) p=0.3).

Table 2. Characteristics of neonates with CCHD at CMJAH

Cardiac diagnosis	**No of patients**	**Surgical management**	**Died**	**Chromosomal abnormalities**
CCHD	(n=133), n (%)	(n=44), n (%)	(n=61), n (%)	(n=4)
Coarc	18 (13.5)	11 (61)	5/18 (28)	0
HLH	15 (11.3)	0 (0)	15/15 (100)	0
TOF	19 (14.3)	5 (26)	4/19 (21)	2
PA	22 (16.5)	6 (27)	10/22 (45)	0
TAPVD	2 (1.5)	0 (0)	0/2 (0)	0
DORV	9 (6.8)	0 (0)	2/9 (22)	1
Truncus	1 (0.8)	0 (0)	0/1 (0)	0
TGA	8 (6.0)	5 (63)	4/8 (50)	0
TA	17 (12.8)	7 (41)	9/17 (53)	0
EA	2 (1.5)	2 (100)	2/2 (100)	0
SV	5 (3.7)	1 (20)	2/5 (40)	0
IAA	9 (6.8)	5 (56)	6/9 (67)	1
Complex cyanotic CHD	6 (4.5)	2 (33)	2/6 (33)	0

Table 3. Characteristics of neonates with non CCHD at CMJAH

Cardiac diagnosis	No of patients	Surgical management	Died	Chromosomal abnormalities
Non-CCHD	(n=151), n (%)	(n=8), n (%)	(n=11), n (%)	(n=42)
VSD	75 (49.7)	4 (5.3)	3/75 (4)	13
ECD	35 (23.2)	4 (11.4)	6/35 (17.1)	22
ASD	34 (22.5)	0 (0)	2/34 (5.9)	7
CHB	7 (4.6)	0 (0)	0/7 (0)	0

Table 4. Characteristics of neonates with CCHD compared with neonates with non-CCHD with respect to cardiac surgery and survival to hospital discharge at CMJAH

	CCHD (n=133), n (%)	non-CCHD (n=151), n (%)	P value
Surgical intervention	44 (33)	8 (5.3)	< 0.05
Survival to hospital discharge	72 (54)	140 (92.7)	< 0.05

Neonates with CCHD

A significant number of neonates admitted at CMJAH with a CHD had CCHD 133/284 (46.9%). They were predominantly male (61%). The majority was diagnosed in the early neonatal period (within the first 7 days of life) 83/133 (62%). A significant number of neonates with CCHD died during the study period 61/133 (45.8%, p <0.05), as compared with neonates with non-CCHD. Only 44/133 (33%) neonates had surgery for their cardiac defects. In those children with CCHD, surgery was significantly associated with survival – 30/41 (73.1%) of those who had surgery

survived compared to 16/68 (23.9%) of those who did not have surgery (p<0.001). Outcome was unknown in 24 cases. There were 4/133 (3%) neonates diagnosed with a chromosomal abnormality. All of the neonates with CCHD diagnosed with a chromosomal disorder had either trisomy 13 or 18 respectively.

Neonates with non-CCHD

There were 151/284 (53.2%) neonates diagnosed with CHD that was non-critical. The majority was male (56%). Most were diagnosed in the late neonatal period (after the first 7 days of life, but before the first 28 days of life) 86/151 (57%). A total of 11/151 (7.3%) died during the study period. There were 8 neonates with non-CCHD (5.3%) who had surgery for their cardiac defect (VSD 4, ECD 4). A significant number of neonates with non-CCHD were diagnosed with a chromosomal disorder 42/151 (27.8%, p <0.05), as compared with neonates CCHD. The majority had trisomy 21 21/42 (50%).

DISCUSSION

Early diagnosis of CCHD relies on antenatal fetal anomaly screening and clinical examination. In South Africa, most CCHD are not diagnosed before birth, owing to the limited antenatal screening for CCHD [4]. The majority of newborns, mainly at midwife birth units and peripheral hospitals, do not get to be examined by members of paediatric staff. Thus neonates with CHD, especially CCHD at peripheral health centers are often missed.

Examination of all newborn babies by a trained member of paediatric staff can help identify neonates with congenital disease [12]. The incidence of CHD is higher when all neonates are carefully examined by full-time members of paediatric staff, who actively looked for evidence of

CHD. The incidence of CHD at a tertiary paediatric hospital in South Africa was reported to be 8.6 per 1000 live births, when all neonates were examined by a full time member of paediatric staff (compared with 5.3 per 1000 live births when only some neonates were examined) [12]. A significant number of the neonates with CHD (30%) were discovered after neonatal discharge [12]. Thus it is highly recommended that all newborn infants be routinely examined by trained member of paediatric staff, not only soon after delivery, but also at the time of postnatal check of the mother. Pulse oximetry can also be used to screen for CCHD, on all newborns prior to neonatal discharge. Pulse oximetry screening is an effective, noninvasive, and inexpensive tool allowing for early diagnosis of CCHD [4].

The use of pulse oximetry to screen for neonates with CCHD can help identify patients that require cardiac surgery early, and thus reduce the morbidity and mortality from CCHD [13]. In the absence of early detection, patients with CCHD are at risk for serious complications or death within the first days, or weeks of life [13]. The mortality rate was high amongst neonates with CCHD (46%), compared with approximately 25% reported in international literature [10]. Only 33% of neonates with CCHD had surgery for their cardiac defect. With appropriate care, the prognosis for patients with CCHD is excellent, with at least 85% expected to survive to adulthood [3].

Neonates diagnosed with coarctation of the aorta, had the most number of cardiac surgeries 11/18 (61%). The mortality rate for these patients was low 5/18 (28%), compared with neonates with other types CCHD in the present study. The mortality rate of neonates who undergo coarctation repair is very low, but the mortality of neonates with a birth weight of less

than 2.5kg is 24%, which is similar to the mortality rate in the current study [14]. In the local context, neonates with coarctaion of the aorta would therefore be preferred surgical candidates over neonates with more complex cardiac abnormalities. Pulmonary atresia was the most commonly diagnosed CCHD (16.5%), and the mortality rate for pulmonary atresia was high (43%). Hypoplastic left heart syndrome contributed significantly to the high mortality for neonates with CCHD 15/61 (25%). Patients with hypoplastic heart disease have a poor prognosis in the local context where neonatal cardiac surgery and heart transplantation is not feasible. Neonates with hypoplastic left heart in the current study all died, however, surgery is not offered to neonates with this condition in the study setting, as outcomes are poor with or without surgery.

Advances made in the developed world in diagnostic options, as well as surgical and interventional management of CCHD have not been replicated in Africa. Every year 3000 children die or remain disabled from their congenital heart conditions in South Africa, as paediatric cardiac services are unable to meet the high patient demand [3]. There is a shortage of paediatric cardiologists in South Africa, with only 24 practising in the country in 2008. This is far less than the international recommendation, that South Africa should have at least 88 paediatric cardiologists. Paediatric cardiothoracic surgeons are also scarce, with only 12 practicing in the country in 2008, and patient load of approximately 4500 children with CHD who required surgical intervention [3]. Another bottleneck that contributes to the high morbidity and mortality in patients with CCHD is the lack of theatre availability and

postoperative intensive care, which requires highly specialized medical and nursing management [3].

A significant number of neonates with non-CCHD had a chromosomal disorder (28%), compared to those with CCHD (3%). It is not known how many non-dysmorphic neonates with a CHD had a chromosomal abnormality in the study setting. Chromosomal analysis was not routinely done on patients diagnosed with CHD. Only some of the neonates with a CHD had chromosomal analysis done based on the clinicians clinical assessment. It is therefore possible that in the absence of comprehensive genetic testing, genetic abnormalities were under reported in the current study. Approximately 12% of infants with CHD have a chromosomal abnormality, Hartman et al [15]. CHD most likely to be associated with a chromosomal abnormality were interrupted aortic arch, atrioventricular septal defect, and double outlet right ventricle. The most common chromosomal abnormalities observed in international literature were trisomy 21 (52.8%), trisomy 18 (12.8%), and 22q11.2 deletion 12.2%) [15]. For neonates with CCHD who had chromosomal analysis done in the study setting, trisomy 13 and 18 were the only chromosomal abnormalities detected in this subset of patients. For neonates with non-CCHD 50 percent had trisomy 21 and the remaining 50 percent had either trisomy 13 or 18 respectively. Antenatal screening for congenital anomalies should be encouraged, as termination of pregnancy could be offered where anomalies associated with a high mortality are detected [5]. Clinicians should have a low threshold to test for chromosomal abnormalities in infants with CHD, especially those with certain types of CHDs [15].

It is possible that prematurity could account for the high mortality rate in neonates with CCHD. Unfortunately birth weight and gestational age were unavailable in the majority of patients.

However, in those for whom this information was present, there was no difference in gestational age or birth weight between survivors and non-survivors.

CONCLUSION

Relatively few neonates were diagnosed with CCHD at CMJAH, compared with that reported in international literature, which reflects under diagnosis of neonates with congenital heart disease. This may be improved with a low cost intervention such as the use of neonatal pulse oximetry which is effective to screen for CCHD [4]. South Africa is a resource limited country with a shortage of medical staff and equipment. There is a shortage of nursing staff that would be relied upon for routine pulse oximetry screening for CCHD [4]. There is also a limited supply of pulse oximetry machines to screen for all neonates. In addition, the majority of neonates are discharged early (within 6 hours of birth) from health centers. Antenatal ultrasonography can also be used as an alternative screening tool for CCHD [4]. However only a few people are skilled to be able to detect significant congenital heart disease using antenatal ultrasonography in South Africa, and in other low income countries. Visible cyanosis on first examination of the newborn by medical staff can help identify patients with critical congenital heart disease. Most of the newborns are first examined by nursing staff trained in the care of the newborn to identify clinical signs, including cyanosis, that require further medical care. Neonates with clinical features suggestive of congenital heart disease can be referred for an echocardiogram.

LIMITATIONS

This was a retrospective descriptive study of an existing database for neonates with CHD. The study relied on accuracy and completeness of data capture. Some of the information captured on the database was incomplete. Many of the neonates were referred in from outlying hospitals and did not have information on birth weight and gestational age. A significant number neonates were lost to follow up, thus their outcome could not be accurately determined. Also other confounding factors, such as the presence of comorbidity, could have contributed to the high mortality amongst neonates with CCHD. Accurate figures for live births and neonatal admissions were not available, so an accurate incidence could not be established. A prospective national database for CHD with accurate birth records is required to determine the actual incidence of CHD.

FUNDING

The researcher incurred all the expenses of the research project. The cost of the research project was negligible.

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Appendix 1: Instructions for authors

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Autumn 2013
Volume 10 • Number 2

sa heart

Instructions for authors

1. A cover sheet is to be submitted with each manuscript. It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. The main author should include his/her name, address, phone, fax and e-mail address.

2. Articles should be the original, unpublished work of the stated author. All materials submitted for publication are assumed to be submitted exclusively for publication in this journal. Written permission from the author or copyright holder must be submitted with previously published figures, tables or articles.

3. Authors are solely responsible for the factual accuracy of their work.

4. Articles should be between 3 000 and 5 000 words in length.

5. A 200-word abstract should state the main conclusions and clinical relevance of the article.

6. All articles are to be in English.

7. Abbreviations and acronyms should be defined on first use and kept to a minimum.

8. Tables should carry Roman numeral, I, II etc., and illustrations Arabic numbers 1, 2 etc.

9. References should be numbered consecutively in the order that they are first mentioned in the text and listed at the end in numerical order of appearance. Identify references in the text by Arabic numerals in superscript after punctuation, e.g. …trial. [13]

10. The following format should be used for references:

    Articles

    Kaplan FS, August CS, Dalinka MK. Bone densitometry observation of osteoporosis in response to bone marrow transplantation. *Clin Orthop* 1993;**294**:73-8. (If there are more than six authors, list only the first three followed by *et al.*)

    Chapter in a book

    Young W. Neurophysiology of spinal cord injury. In: Errico TJ, Bauer RD, Waugh T (eds). *Spinal Trauma*. Philadelphia: JB Lippincott; 1991: 377-94.

11. Please submit two copies of the article, one to the Guest Editor and a second to the Editor directly (afd@sun.ac.za) or via the secretary of the South African Heart Association (erika@saheart.org).

12. Articles are to be submitted by e-mail. The text should be in MS Word. Pages should be numbered consecutively in the following order wherever possible: Title page, abstract, introduction, materials and methods, results, discussion, acknowledgements, tables and illustrations, references.

13. Where possible all figures, tables and photographs must also be submitted electronically. The illustrations, tables and graphs should not be imbedded in the text file, but should be provided as separate individual graphic files, and clearly identified. The figures should be saved as a 300 dpi jpeg file. Tables should be saved in a PowerPoint document or also as a 300 dpi jpeg. If photographs are submitted, two sets of unmounted high quality black and white glossy prints should accompany the paper. Figures and photographs should be of high quality with all symbols, letters or numbers clear enough and large enough to remain legible after reduction to fit in a text column. Each figure must have a separate self-explanatory legend.

14. Remove all markings, such as patient identification, from radiographs before photographing.

Appendix 2: Ethics clearance certificate

R14/49 Dr Tshiamo Mogajane

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151001

NAME: (Principal Investigator)	Dr Tshiamo Mogajane
DEPARTMENT:	Paediatrics Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Prevalence and Outcome to Discharge of Critical Congenital Heart Disease in Neonates at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	30/10/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Ballot
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/10/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3: Protocol

Incidence and prognosis of critical congenital heart defects in neonates at Charlotte Maxeke Academic Hospital

Paul Mogajane, MBchB

Student number: 11140/82548/0044

Research supervisor:

Prof Ballot

Dr Motara

Background:

Congenital heart disease (CHD) is one of the most common congenital anomalies. Advances in paediatric care have resulted in an increased detection of patients born with CHD. With the improvement in medical knowledge and technology, many more babies are surviving, contributing to an increased prevalence of CHD. The introduction of echocardiography into clinical practice in the 1970's has also greatly contributed to an increase in the CHD birth prevalence. The estimated global prevalence of CHD is 8 per 1,000 live births (1). The prevalence of CHD varies across populations and also over time. These variations are in part due to data completeness and capture, such as completeness of the diagnosis (prenatal and postnatal) and registration of cases, amongst other issues. Europe has a common database for CHD, comprised of population-based surveys that form part of the European Surveillance of Congenital Anomalies (EUROCAT) (2). Whereas data about CHD in Africa and developing

countries is scarce, and studies often do not include the indigenous inhabitants (1). Africa has the lowest reported birth prevalence of CHD (1.9 per 1,000 live births) with the prevalence in South Africa estimated to be 0.6-0.8 per 1,000 live births (3). This estimate might be under reporting the true prevalence in Africa as many patients with CHD are missed.

Untreated CHD has considerable consequences and costs. Africa has lagged behind international acceptable standards in the management of CHD as many of these children go untreated. Every year in South Africa over 3000 children die or remain disabled from their congenital heart condition due to resource constraints. Survivors of CHD without surgical intervention require repeated hospital admissions and frequent follow-up visits (3). This places a significant financial and emotional burden on already impoverished caregivers and families. With the advancement of paediatric care, many more children are surviving to reach adulthood. The prevalence of CHD in the adult population is estimated to be 4 per 1,000 adults. As the survival rate of patients with CHD is expected to rise, producing large numbers of adults with congenital heart disease, more resources would be required to manage these patients. Adults with CHD require long term medical care, with its associated high costs (1). This poses medical, social, and economic challenges. Thus more adult cardiologists may need to be trained to deal with an increasing population of adults with CHD. Another important consideration is that for patients with CHD that require surgical repair, outcomes at older ages are often less favourable than at younger ages. Thus a high early detection rate, and surgical repair of patients with CHD, will result in better outcome (4). The birth prevalence of CHD differs between the different geographical areas. Worldwide ventricular septal defect (VSD) is the most commonly reported CHD subtype (5). In Africa the second most commonly reported CHD subtype is transposition of

the great arteries followed by atrial septal defect (ASD) (6). Whereas ASD is the second most common CHD in Europe, America and Asia, followed by patent ductus arteriosus. However a significant difference in the birth prevalence of the subtypes of CHD was noted between Asia, and Europe and America. There is a higher birth prevalence of pulmonary outflow tract obstruction defects in Asia (pulmonary stenosis and tetralogy of Fallot), and a lower birth prevalence of left ventricular outflow tract obstruction (coarctation of the aorta and aortic stenosis). Whereas Europe and North America reported a higher birth prevalence of left ventricular obstructive defects, and a lower birth prevalence of right ventricular out-flow tract lesions. No scientific explanation could be found to account for this difference in the birth prevalence of CHD subtypes in Asia, and North America and Europe. However genetics could account for the difference in the birth prevalence of CHD subtypes in the different continents (1)

Normal neonatal examination does not exclude serious or life threatening cardiovascular malformations. About half of the babies noted to have a murmur in the early neonatal period have a structural heart disease. Wren et al found that about one third of the babies with signs and symptoms of CHD were only diagnosed by 6 weeks of age and 57% by 3 months. However if every baby with signs and symptoms of CHD had an echocardiogram, half of them could have been diagnosed by 6 weeks and 76% by three months. Thus early referral of babies with signs and symptoms of CHD for cardiology assessment and echocardiography is encouraged (7). However this is not feasible in our setting in South Africa, due to resource constraints. There is a shortage of paediatric cardiologists in South Africa. Only 24 paediatric cardiologists were practicing in South Africa in 2008, half of them in the private sector. This is far less than the

international recommendation, that South Africa should have at least 88 paediatric cardiologists. Paediatric cardiothoracic surgeons are also scarce, with only 12 practicing in the country. This is insufficient to successfully manage the high patient load, as every year in South Africa approximately 4500 children with CHD require surgical intervention. Another major deterrent to adequate care is the lack of theatre availability and postoperative intensive care, which requires highly specialized medical and nursing management (3)

More recently, use of pulse oximetry is more practical and feasible in screening for critical congenital heart disease (CCHD). These are CHD requiring surgery or catheterization before 1 year. Low oxygen saturation indicates hypoxemia, an early clinical sign of CCHD. Additional testing, repeat pulse oximetry and echocardiogram, is needed following an abnormal pulse oximetry screen to determine whether CCHD are present. However pulse oximetry screening for CCHD is not routinely done in South Africa. This is important as approximately 20% of CHD present with life-threatening illness in the neonatal period where survival depends on timely diagnosis, management and referral (8). There is a lack of information on babies presenting with a life threatening (critical) CHD in the neonatal period in South Africa.

Aim

The study aims to determine the incidence and prognosis of neonates presenting with critical congenital heart disease (CCHD) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 2006 to 2014.

Objectives

- To determine the incidence of critical congenital heart disease (CCHD) in neonates admitted during the first 28 days of life to CMJAH between 01 January 2006 to 31 December 2014.
- To compare the incidence of CCHD at CMJAH to the rest of Africa and the world.
- To describe the different cardiac anomalies in patients with CCHD at CMJAH.
- To establish how many infants with CCHD have chromosomal disorders.
- To determine the survival to discharge of neonates with CCHD at CMJAH.

Method

This was a retrospective study describing newborn infants with CCHD at CMJAH. Patient information will be obtained from the CMJAH neonatal database, ward admissions registers and Paediatric Cardiology unit consult register. Cardiac anomalies (diagnosis) will be obtained from the Paediatric Cardiology unit register.

Inclusion criteria:

All neonates (<28 days of life) who were admitted to CMJAH (neonatal and general paediatric wards) between 01/01/2006 and 31/12/2014 with the diagnosis of CCHD will be eligible for

inclusion in the study. Patients with dysrhythmias (notably congenital heart block) will be included in the study.

Exclusion criteria:

Patients with the diagnosis of persistent pulmonary hypertension of the newborn (PPHN), patent ductus arteriosus (PDA) and myocarditis will be excluded from the study. This is because PPHN is not primarily a cardiac defect, whereas the presence of PDA varies with gestational age and can depend on changing physiology, such as fluid overload and sepsis.

Data collection

Demographic and clinical characteristics and survival to hospital discharge will be obtained for each patient. The data collection sheet is included in Appendix A. Records will be identified and allocated a data number. The key to patient identification and data numbers will be kept separately by the primary investigator.

Statistical analysis

Data will be described using standard statistical methods. Categorical variables will be reported using frequencies and percentages. The distribution of continuous variables will be examined and either mean and standard deviation or the median and interquartile range will be used to describe these variables as appropriate. If there are sufficient numbers in each diagnostic category, the outcome to hospital discharge will be compared between the categories. The annual incidence will be compared between different years. Chi square analysis will be used for both these comparisons.

Timing

	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May
Literature review and preparation of the protocol														
Protocol assessment														
Ethics application														
Collection of data														
Data analysis														
Writing up thesis														

Funding

The researcher will incur the expenses of the research project. A personal computer will be utilized for data analysis. It is anticipated that the cost of the research project will be negligible.

Ethics

The research proposal will be submitted to the ethics committee of the University of Witwatersrand, for approval, prior to commencement of the study. Data used in the study will treated with confidentiality. The identifying markers of the patient obtained from the database, used for analysis, will be omitted. Identifying markers will be delinked using codes. Accessibility to the CMJAH database is restricted. Data retrieved from the database will be captured onto a personal computer of the primary investigator, which requires a code for access. As this is a retrospective record review study, informed consent from the patient is not required. Furthermore there will be no direct interaction with the patients, whose data will be analysed in the study. However consent will be obtained from the chief Executive Officer of CMJAH, for the proposed study.

Appendix A

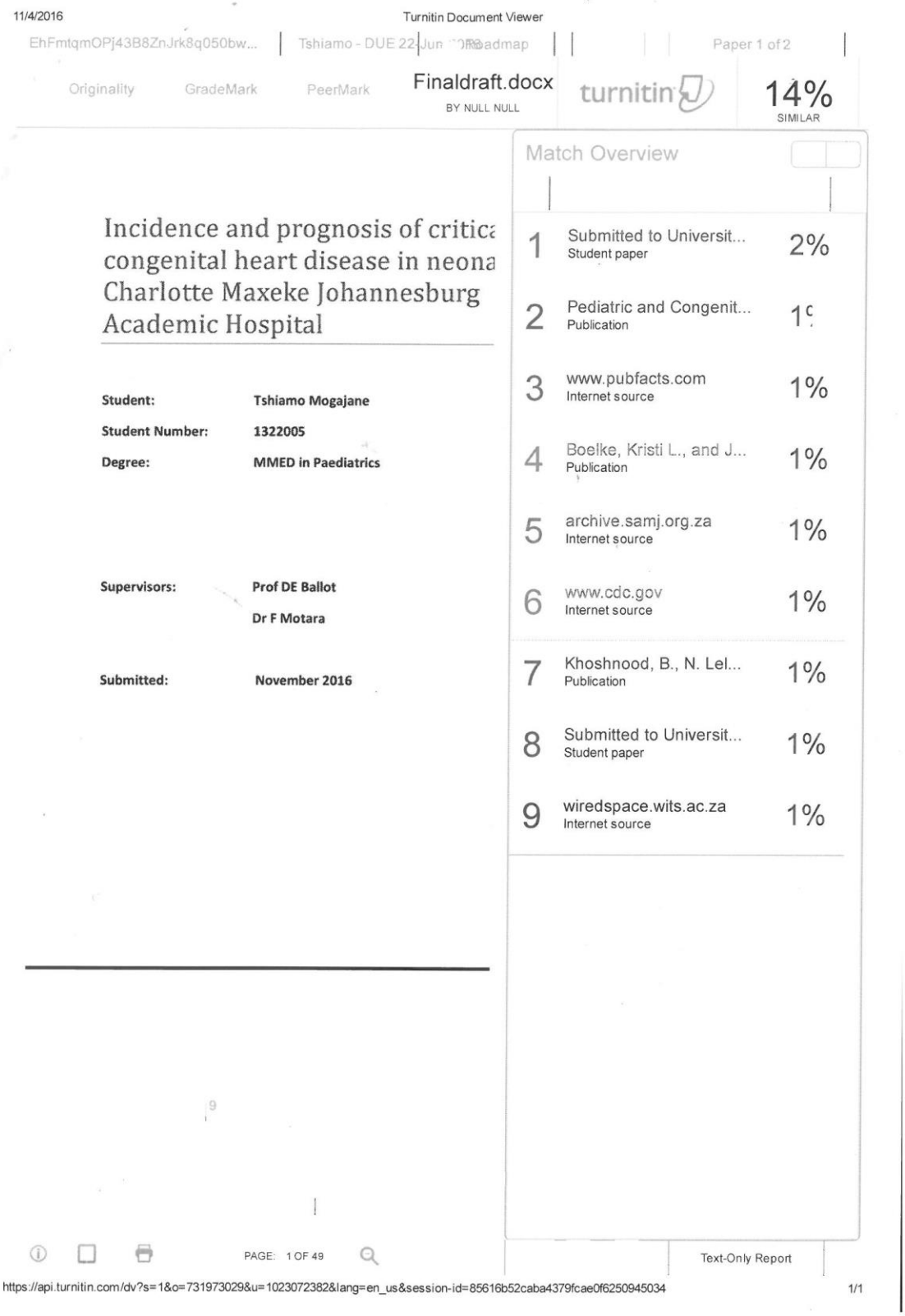
Study number:			
Demographics		**Place of birth**	
Age at presentation		CMJAH (20)	
0-7 days (1)		Other hospitals (21)	
8-20 days (2)		Clinic (22)	
Ethnicity		BBA (23)	
White (3)		**Mechanical ventilation**	
Coloured (4)		Yes (24)	
Indian (5)		No (25)	
Black (6)		**Echocardiographic findings**	
Gestational age		VSD (26)	
< 28 weeks (7)		ASD (27)	
28-30 weeks (8)		PDA (28)	
31-34 weeks (9)		PS (29)	
35-37 weeks (10)		TOF (30)	
> 37 weeks (11)		Coarc (31)	
Birth weight (12)		TGA (32)	

800-999 (13)		Aos (33)	
1000-1499 (14)		Other (34)	
1500-1999 (15)		**Investigations and treatment**	
2000-3999 (16)		Cardiac catheterization (35)	
>4000 (17)		Operation (36)	
Chromosomal disorder		Medical management (37)	
Yes (18)		**Outcome**	
No (19)		Survival to hospital discharge (38)	
		Died (39)	

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Appendix 4: Turnitin report



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Student: Tshiamo Mogajane

Student Number: 1322005

Degree: MMED in Paediatrics

Supervisors: Prof DE Ballot

Dr F Motara

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