The prevalence, characteristics and outcomes of anomalous left coronary artery from the pulmonary artery at the Chris Hani Baragwanath Academic Hospital over a 28-year period

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A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics

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DECLARATION

I, Anjali-Larisha Chhiba, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the Department of Paediatrics and Child Health, Faculty of Health Sciences, at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signature: ______________________________

Date: __16th___ day of ____June_____ 2021

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LIST OF ABBREVIATIONS

ALCAPA:	Anomalous left coronary artery from the pulmonary artery
CHBAH:	Chris Hani Baragwanath Academic Hospital
CXR:	Chest X-ray
LVEF:	Left ventricular ejection fraction
ECG:	Electrocardiogram
CTR:	Cardiothoracic ratio
LCA:	Left coronary artery
CT:	Computerized tomography
DIACA:	Direct reimplantation of the anomalous coronary artery onto the aorta
IQR:	Interquartile ranges
WITS:	University of the Witwatersrand
HIV:	Human Immunodeficiency Virus
PDA:	Patent ductus arteriosus
ICU:	Intensive care unit
ARCAPA:	Anomalous right coronary artery from the pulmonary artery

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The prevalence, characteristics and outcomes of anomalous left coronary artery from the pulmonary artery at the Chris Hani Baragwanath Academic Hospital over a 28-year period

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ABSTRACT

Background Anomalous left coronary artery from the pulmonary artery (ALCAPA) accounts for 0.25-0.5% of congenital cardiac disease. ALCAPA results in myocardial ischaemia and a dilated cardiomyopathy which can be reversed post-surgical correction. We describe the presenting clinical features, diagnostic findings and post-operative outcomes, including the improvement of the left ventricular function, in patients presenting to a Southern African tertiary care centre.

Methods A retrospective analysis of patients with ALCAPA over a 28-year period at the Chris Hani Baragwanath Academic Hospital (CHBAH).

Results A total of 38 patients (24 (63.2%) females; median age at diagnosis of 4.6 months (IQR: 3.2 to 9.1 months)) were included. The symptoms and clinical features on presentation were nonspecific. Cardiomegaly on chest X-ray (CXR) was present in 84.2% of patients. Deep Q waves in leads I and aVL was the most prevalent finding on electrocardiography. ST segment depression and T wave inversion occurred in the lateral and inferior diaphragmatic leads. LVEF significantly improved from (38.8±6.3)% to (57.5±9.1)% post-surgical correction (p-value=0.0004) by the first follow up (at a median of 1.3 months). The early mortality rate was 21.6%.

Conclusion The symptoms at presentation are nonspecific and predominantly respiratory. A high index of suspicion by clinicians with a focus on the common electrocardiographic features is crucial in the diagnosis of ALCAPA.

INTRODUCTION

Anomalous left coronary artery from the pulmonary artery (ALCAPA), is a result of a poorly understood disruption in the embryological development of the coronary arteries. ALCAPA is a rare congenital cardiac defect accounting for 0.25-0.5% of congenital cardiac disease and occurring approximately once per 300 000 live births.[1] An early diagnosis of ALCAPA requires the recognition of a constellation of clinical signs and electrocardiogram (ECG) features.

The clinical findings of ALCAPA are nonspecific and thus necessitates a high clinical index of suspicion. The commonest presenting clinical symptoms and signs found in the literature include dyspnoea, feeding intolerance, failure to thrive, irritability and the presence of a cardiac murmur.[1-4] Patients may initially be asymptomatic due to a high pulmonary artery pressure supplying the myocardium, albeit at a lower oxygen saturation.[3] As the pulmonary resistance decreases, the pulmonary artery pressure decreases and results in a coronary steal phenomenon with subsequent myocardial ischaemia.[3] The presence of a collateral blood supply between the right and left coronary arteries is protective and may influence the timing of presentation as well the presenting clinical manifestations.

The current consensus regarding chest X-ray (CXR) findings is unclear. While cardiomegaly on CXR has been found in patients with ALCAPA,[3, 5] a study by Levitas et al., demonstrated a normal cardiothoracic ratio (CTR) on CXR to be a common finding.[6] More importantly, electrocardiographic findings aid in the diagnosis of ALCAPA. These comprise a sinus tachycardia, abnormal deep Q waves (especially in leads I and aVL), ST segment changes (with ST segment elevation or depression) and T wave inversion.[1, 2, 7] A later electrocardiographic sign, indicating absent muscle contraction secondarily to myocardial infarction, is an abnormal R wave progression in the chest leads localized to the affected region.[8]

The diagnosis of ALCAPA is confirmed non-invasively by echocardiography with the left coronary artery (LCA) seen originating from the pulmonary artery. The right coronary artery becomes the dominant coronary artery and may be dilated. Colour Doppler can be used to show collateral blood supply, flow from the right coronary artery to the LCA (which is the equivalent of a right to left shunt), as well as retrograde flow from the LCA into the pulmonary artery.[9] Echocardiography can also show the effects of myocardial ischaemia and infarction on the left ventricle and the mitral valve, by the presence of left ventricular dilatation, ventricular dysfunction and mitral regurgitation.[2, 9] An increased echogenicity of the anterolateral papillary muscle and the adjacent myocardium is in keeping with fibrosis and infarction. [9]

Cardiac catheterization and angiography can assist in the diagnosis of ALCAPA in instances when the coronary arteries are not clearly visualized on echocardiography.[4] It aids in delineating the coronary artery anatomy and its origin, the identification of retrograde blood flow from the LCA to the pulmonary artery and the presence of collateral blood flow from the right coronary artery.[1, 2, 4, 10] With improved precision of echocardiography and other less invasive diagnostic modalities such as computerized tomography (CT) scans there is a decreased need of cardiac catheterization and angiography in confirming the diagnosing of ALCAPA.

Surgical management is the definitive treatment for ALCAPA. Direct reimplantation of the anomalous coronary artery onto the aorta (DIACA) is the most frequent method used.[1, 7, 10-12] A less common surgical intervention is the Takeuchi procedure which includes a pulmonary arteriotomy, the creation of an aortopulmonary window and the use of the pericardium to reconstruct the pulmonary artery.[10]

Excellent postoperative outcomes have been found in patients with ALCAPA across various studies.[10, 11, 13] A study by Kanoh et al., with a long term follow up of over 16 years, showed normalization of the left ventricle and mitral valve function post-surgical repair over time.[11] Early mortality rates post-surgery ranged between zero and 16% with far less late mortality and a reported survival rate of 86-100% of patients ten years post-surgical repair.[13]

There is a paucity of available data regarding the clinical presentation, diagnostic findings and outcomes of ALCAPA in our South African paediatric population. South Africa is a low to middle income developing country with a large diverse population, many of whom rely on peripheral hospitals for medical services. These secondary care institutes are required to make an appropriate assessment before referring patients to specialist services, thus emphasising the importance of clinical and electrocardiographic knowledge in the recognition of ALCAPA.

MATERIALS AND METHODS

Data collection

A retrospective analysis of all paediatric patients diagnosed with ALCAPA at the Chris Hani Baragwanath Academic Hospital (CHBAH) between January 1991 and December 2018 was conducted. Patients were identified using the electronic Paediatric Cardiology database, which was used in conjunction with cardiac paper records to obtain the required information. Each patient was allocated a study number to ensure that patient identifiers were not included in the data collection. There were 38 patients who fulfilled the criteria for inclusion in the study. This included all paediatric patients (≤ 14 years of age) diagnosed with ALCAPA (with or without additional cardiac lesions) who either presented to CHBAH or were referred from the surrounding hospitals. Patients with other coronary artery anomalies were excluded.

The demographic data, presenting symptoms and clinical features, the initial diagnosis and the CXR features were noted. ECG findings were evaluated according to the definitions available in the literature.[1, 14] The rate, rhythm and axis of each ECG was measured and analysed according to age-specific norms. Abnormal Q waves were defined as being more than 25% of the R wave height in the same lead or more than 3mm in lead one or more than 2mm in lead aVL, as well as being more than 0.03 seconds in duration.[1, 14] ST segment depression was defined as being more than 1mm below the baseline for more than 0.08 seconds duration.[14] T wave inversion and the leads in which the various ECG changes were observed was documented.

The available echocardiographic findings were captured. The left ventricular ejection fraction (LVEF) was defined as normal within the range of 56-78% (with a mean ejection fraction of 66%).[14] The right coronary artery diameter was interpreted based on the mean body surface area-based normal values.[14] The available cardiac catheterization and angiographic findings were captured.

The method and timing of surgical repair was noted. Post-surgical data captured included the duration of follow up, time to being asymptomatic, normalization of the LVEF and the resolution of mitral regurgitation. Other outcomes such as death (pre-, intra- or post-operatively) and the loss to follow up was noted. Early mortality was considered to be within 30 days of the operation.

Data analysis

All data was captured on a Microsoft Excel spreadsheet and analysed using STATA (MP 13) software. Continuous variables were presented as medians and interquartile ranges (IQR) and categorical variables described using frequencies and percentages. These were compared using a Fisher's exact bivariate analysis, dividing the patients into an infant (patients less than 12 months of age) and a non-infant group (patients more than 12 months of age). The associations between multiple variables and the LVEF at presentation were assessed using a univariate regression analysis. A paired samples *t*-test was used to compare pre- and post-surgical correction LVEFs.

A Fisher's exact test was used to compare the group of patients who survived to those who demised (pre- and post-surgery), as well as to compare the outcomes over two decades (the 1990s and the 2000s). A chi-square test analysis was not feasible due to the small sample size. It became apparent that a multiple of the expected frequencies in the respective categories consisted of values less than five. A p-value less than 0.05 was considered statistically significant.

Ethical consideration

The University of the Witwatersrand (WITS) Faculty Graduate Studies Committee, the WITS Human Research Ethics Committee (clearance certificate number: M190741) and the necessary medical authorities at the CHBAH all granted permission to access the study data and conduct this study.

RESULTS

A total of 38 patients were diagnosed with ALCAPA between January 1991 and December 2018 at the CHBAH. This constituted 0.45% of the 8387 patients with congenital cardiac defects seen by the Paediatric cardiology unit over this time period.

Patient demographics

The median age of diagnosis was 4.6 months (IQR: 3.2 to 9.1 months), with 24 (63.2%) female and 14 (36.8%) male patients. Of the patients, 37 (97.4%) were black and one patient (2.6%) caucasian, which is reflective of the race demographic seen at the CHBAH. Using standard World Health Organization (WHO) weight-for-length charts according to age, 16 (51.6%) patients with available anthropometry plotted values within the normal range, three (9.7%) patients were wasted and 12 (38.7%) patients were severely wasted on presentation. There were 25 (65.8%) patients who presented to the CHBAH on initial presentation. The remainder 13 (34.2%) patients were referred from other medical facilities – of which, 10 (26.3%) patients were from peripheral district hospitals.

Details at presentation

The majority of patients, 31 (81.6%), had no pre-existing medical conditions at the time of presentation. There were three (7.9%) patients who presented with previous cardiac diagnoses (two patients with a diagnosis of myocarditis and one patient with an anterior mitral valve leaflet prolapse) and one (2.6%) patient had Trisomy 21. Of the patients, 10 (26.3%) were Human Immunodeficiency Virus (HIV) exposed, with two (5.3%) patients being HIV positive and on treatment. There was one (2.6%) patient on tuberculosis treatment at presentation.

The frequency of the various presenting symptoms and clinical features at presentation are tabulated in *Table I*. The most frequent symptoms on presentation were dyspnoea in 26 (68.4%), a history of a cough in 16 (42.1%) and a history of poor feeding in seven (18.4%) patients. The most common clinical features were a displaced apex beat and respiratory distress both occurring in 20 (52.6%), followed by hepatomegaly in 17 (44.7%) patients.

All of the patients in our study had an alternative initial diagnosis, which is reflective of the non-specific presentation of ALCAPA. The most common initial diagnosis proposed was a lower respiratory tract infection in 27 (71.1%) of the patients. This was followed by dilated cardiomyopathy and myocarditis, both diagnosed in eight (21.1%) patients. Less common diagnoses included other cardiac defects in five (13.2%) (these included a congenital cardiac defect as a diagnosis, a patent ductus arteriosus (PDA), an anterior mitral valve leaflet prolapse and a left coronary ostial stenosis), sepsis and congestive cardiac failure in two (5.3%) and gastroenteritis in one (2.6%) of the 38 patients.

CXR findings

Of the patients, 32 (84.2%) had cardiomegaly reported on the initial CXR, with the remaining six (15.8%) having a normal CTR. The median CTR was 70% (IQR: 61 to 70%). The most prevalent additional CXR findings included pulmonary congestion in 10 (26.3%), followed by biventricular enlargement in five (13.2%) and bronchopneumonic changes in four (10.5%) patients.

ECG findings

Table II illustrates the important ECG manifestations of ALCAPA. Of the 34 patients with available ECGs at diagnosis, 29 (85.3%) had a normal heart rate for age, four (11.8%) had a tachycardia and one (2.9%) patient had a bradycardia. All of the ECGs showed sinus rhythm. The majority of the patients, 24 (70.6%), had a normal axis for age, seven (20.6%) had a left axis with the remaining three (8.8%) having a rightward axis for age. Deep Q waves (fulfilling the defined criteria) were present in 32 (94.1%) of the ECGs.

Abnormal Q waves occurred most frequently in a combination of leads I and aVL in 31 (96.9%) patients, with five (15.6%) of these patients additionally having abnormal Q waves in the limb leads. ST segment depression occurred in eight (23.5%) of the 34 patients, most frequently in lead aVF in four (50.0%) patients, followed by lead II in three (37.5%) and lead aVL in two (25.0%) patients. Inverted T waves occurred in 21 (61.8%) patients, most frequently in the lateral and inferior diaphragmatic leads. Of the 83 episodes of abnormal T wave inversion across the 34 ECGs analysed, 37 (44.6%) occurred in the lateral leads: I, aVL, V5 and V6, and 32 (38.6%) in the inferior diaphragmatic leads: II, III and aVF. Additional ECG findings included left ventricular hypertrophy in 17 (50.0%) and biventricular hypertrophy in four (11.8%) patients.

Echocardiography findings

Of the 37 patients who had echocardiography studies, the LCA was visualized originating from the pulmonary artery in 32 (86.5%) patients. The LVEF was measured in 36 patients and was decreased in 33 (91.7%) patients, with a median LVEF of 34.0% (IQR: 23.5 to 43.5%). Mitral regurgitation was present in 27 (73.0%) patients, with majority being graded as mild. An increased echogenicity of the papillary muscles and adjacent endocardium was noted for 26 (70.3%) of the 37 patients with echocardiography studies.

Measurement of the right coronary artery diameter was documented for 19 (51.4%) of the patients, with 18 (94.7%) being dilated. Collateral blood flow between the right and left coronary arteries was visualized in two (5.4%) patients. Retrograde blood flow from the LCA to the pulmonary artery was evident in 16 (43.2%) patients. Other findings included a PDA and a patent foramen ovale. The echocardiographic findings are summarized in *Table III*.

Cardiac catheterization and angiographic findings

There were 19 (50.0%) patients who had a cardiac catheterization and angiography performed. In 18 (94.7%) patients the LCA was visualized originating from the pulmonary artery. In 16 (84.2%) retrograde blood flow from the LCA to the pulmonary artery was evident, with 10 (52.6%) patients showing the presence of collateral blood supply from the right coronary artery. Additional and these findings are summarized in *Table IV*.

Analysis of the diagnostic findings showed that only the echocardiographic visualization of the LCA originating from the pulmonary artery and the presence of left ventricular dilatation were statistically significant when comparing the infant and non-infant groups, with p-values of 0.037 and 0.042 respectfully. Analysis of the LVEF and various selected variables (as depicted in *Table V)* showed that only anthropometry of the severely wasted category was statistically significant with a p-value of 0.048.

Surgical correction

Of the 38 patients, 30 (78.9%) underwent surgical correction for ALCAPA, with 27 (90.0%) patients undergoing DIACA and in the remaining 3 (10.0%) patients a tunnel was created from the LCA to the aorta. The median number of days to repair from the diagnosis of

ALCAPA was 27 days (IQR: 12 to 51 days), with a median age of repair of 5.7 months (IQR: 3.7 to 11.6 months).

Post-surgical follow up findings

For the 30 patients who underwent surgical repair, 19 (63.3%) had available follow up findings. The median months of first follow up post-surgical repair was 1.3 months (IQR: 0.9 to 1.9 months). At this first follow up, 18 (94.7%) patients were asymptomatic and one (5.3%) patient was tachypnoeic. A cardiac murmur was found in 4 (21.1%) patients and two (10.5%) patients had other complications –a right brachial plexus injury in one patient and a right hemiplegia secondary to a left cerebral infarct in the other. Both of these patients had a long intensive care unit (ICU) stay post surgery. The median time to being asymptomatic was 1.4 months (IQR: 0.9 to 2.0 months).

Of the 18 (94.7%) patients with echocardiography findings at the first follow up post surgery, 11 (61.1%) showed normal LVEFs, 10 (90.9%) of whom initially had a decreased LVEF. The remaining seven (41.2%) patients had decreased LVEFs at the first follow up post-surgery. The median LVEF was 61% (IQR: 39 to 74%) at the first follow up. The LVEF significantly improved from (38.8±6.3)% pre-surgical correction to (57.5±9.1)% post-surgical correction (p-value=0.0004).

Normalization of the LVEF occurred at a median of six months (IQR: 2 to 10 months) post-surgical correction of ALCAPA. A Kaplan-Meier analysis depicted in *Figure 1* shows the time to normalization of the left ventricular function (from the available LVEF data) post-surgical correction.

Mild mitral regurgitation was present in 12 (66.7%) patients. Mitral regurgitation was initially present in 14 (77.8%) of the 18 patients, with six (50.0%) of these patients showing moderate to severe mitral regurgitation pre-surgical correction. Additional post-surgical follow up findings are summarized in *Table VI.*

Mitral regurgitation resolved at a median of six months (IQR: 3 to 9.5 months) post-surgical correction. The median number of months of follow up post-surgery, taking into account the latest follow up of patients, was 121.3 months (IQR: 61.1 to 173.9 months).

Outcomes

Outcomes are shown in *Figure 2*. Of the patients, 12 (31.6%) continue to be followed up at the Paediatric Cardiology Clinic and two (5.3%) patients have been transferred to adult cardiology. There were 11 (28.9%) patients who were lost to follow up, and eight (21.1%) patients who demised post surgery within 30 days (with three patients demising post-surgery on the day of surgery). The median number of days post-surgery to patient demise was 0.5 days (IQR: 0 to 10.5 days). There were three (7.9%) patients who demised prior to surgery and two patients (5.3%) who absconded prior to surgery. A Fisher's Exact test demonstrated no significant difference in outcomes between patients in the infant versus the non-infant group (p-value 0.383).

A schematic overview of the diagnostic findings and outcomes for the patients included in this study are illustrated in *Figure 3*.

Additional analysis

A bivariate analysis of the survival group versus the non-survival group showed no statistically significant differences with regards to the demographics, diagnostic findings and the age of repair (*Table VII*). The median LVEF at diagnosis was 39% (IQR: 30 to 41%) in the survival group versus 31% (IQR: 23 to 40%) in the non-survival group.

A review of the patient cohort over two decades – the 1990s and the 2000s, showed no statistically significant differences in the diagnostic modalities between the two groups. Mitral regurgitation was diagnosed more frequently in the 2000s group (p-value of 0.001), possibly due to the availability of improved echocardiographic colour Doppler technology. The patients in the 2000s group were repaired sooner at a median of 18.5 days (IQR: 9.5 to 46.5 days) versus the 1990s group which were repaired at a median of 42 days (IQR: 18 to 51 days) post diagnosis. There were no significant differences in outcomes between the two groups (p-value 0.126).

DISCUSSION

ALCAPA is a rare congenital cardiac condition accounting for approximately 0.5% of all cases of congenital cardiac defects.[1] This is similar to the incidence of ALCAPA in our CHBAH cohort of 0.45% of all congenital cardiac defects documented in the study period. Due to the lack of specificity of the clinical manifestations of ALCAPA there is a possibility of underdiagnosis if missed on the initial presentation of patients. In a study by Zheng et al., 78.3% of the patients had an alternative initial clinical diagnosis, [1] as compared to 100% of the patients in our study.

Patients with ALCAPA initially tolerate the origin of the LCA from the pulmonary artery due to the relatively higher pressure in the pulmonary artery in the early neonatal period.[10] Once the pulmonary vascular resistance and the pulmonary arterial pressures decline, the LCA may instead be supplied blood by the collaterals from the right coronary artery and this may result in a "coronary steal" into the pulmonary artery.[1] This may explain the young median age of 4.3 months at the time of presentation - after the drop in physiological pulmonary hypertension of the newborn.

A study by Zheng et al., with a cohort of 23 patients, showed significant differences in the radiographic, electrocardiographic and echocardiographic findings between an infant and non-infant group, with the presence of an increased CTR, significant Q waves and T wave inversion being more prevalent in the infant group, as well as a lower LVEF and more severe left ventricular dilatation than in the non-infant group.[1] In our analysis, the echocardiographic visualization of the LCA originating from the pulmonary artery and the presence of left ventricular dilatation found in the infant group were statistically significant. Older patients may have poorer echocardiographic acoustic windows that may mitigate against good visualisation of the LCA origin and older patients at presentation are likely to have developed good collateral blood flow and therefore may have less left ventricular dysfunction and dilatation.

The most frequent symptoms on initial presentation were dyspnoea, cough and poor feeding, which are comparative to the available literature on ALCAPA.[1-4] The most common signs occurring in our study cohort on initial presentation were a displaced apex beat, respiratory distress and hepatomegaly. These non-specific signs and symptoms led to an initial diagnosis of a lower respiratory tract infection in the majority of patients (71.1%).

An interesting case illustrating the diversity of the presenting symptoms in our cohort, was that of a patient with confirmed Trisomy 21 with a large PDA and severe reversible pulmonary hypertension diagnosed on cardiac catheterization. During attempted surgical ligation of her PDA her blood pressure decreased significantly after the PDA was clamped. The surgery was abandoned and Eisenmenger's syndrome was suspected. A repeat cardiac catheterization and angiography showed reversible pulmonary hypertension but a chance observation on review of the pulmonary angiogram showed the LCA originating from the main pulmonary artery. It is most likely that the perfusion of the LCA was dependent on the high pulmonary pressures and during ligation of the PDA, the pulmonary pressures dropped, resulting in reduced perfusion of the LCA which caused myocardial ischaemia. She subsequently successfully underwent a PDA closure and DIACA of the ALCAPA.

Previous studies show conflicting findings regarding CXR findings, with small studies by Brotherton et al. and Holst et al. demonstrating cardiomegaly on CXR in the majority of patients with ALCAPA.[3, 5] In our cohort, 84.2% of patients had cardiomegaly on CXR, with a median CTR of 70%. While this is a non-specific finding, it is important as it may prompt further investigation.

Myocardial ischaemia ensues in the late neonatal and infant period when the pulmonary pressures decline.[3] Consequently, ischaemic changes become evident on the ECG in patients with ALCAPA. The majority of the patients in the study cohort (94.1% of the patients with ECGs) had deep Q waves particularly in leads 1 and aVL. In the study by Zheng et al., deep Q waves were more prevalent in the infant group compared to the non-infant group.[1] The latter group had more non-specific ECG findings which may be explained by the development of collateral circulation in this group.[1] In our study, deep Q waves were prevalent across all age groups and ischaemic changes were observed in the lateral and inferior diaphragmatic leads as evidenced by T wave inversion and ST segment depression.

In a study by Kurup et al.,[15] increased echogenicity of the anterolateral papillary muscle and the adjacent myocardium due to fibrosis and ischaemia was a useful finding contributing to the diagnosis of ALCAPA and was seen in 70% of our study patients. Ischaemia of the myocardium in the distribution of the left coronary artery also results in left ventricular dysfunction, left ventricular dilatation, a decrease in the LVEF and mitral regurgitation caused by annular dilatation and /or ischaemia of the papillary muscles.[1, 9] The median LVEF in the study cohort of patients was 34% which is lower compared to other studies.[1, 16]

This may be attributed to our study having more infant patients who, according to the literature, are more likely to present with left ventricular dysfunction.[9, 11]

Analysis of various variables and their relationship to LVEF, found no significant correlation for the majority except for the severely wasted anthropometric category which was associated with a statistically significant decrease in LVEF. Poor feeding as a result of heart failure and a low LVEF could explain why there is a correlation between wasting and a low LVEF.

Cardiac catheterization and angiography confirmed the diagnosis of ALCAPA in several patients where the diagnosis was not clear on echocardiography. A study by Li et al., showed a 100% accuracy using invasive coronary angiography and coronary CT angiography to confirm the diagnosis compared to 90.9% using transthoracic echocardiography.[17] The accuracy of diagnosis using echocardiography was 86.5% versus 94.7% using cardiac catheterization and angiography in the study cohort. Due to the limitations imposed by two-dimensional imaging in the diagnosis of ALCAPA, the progression to other less invasive and lower risk diagnostic modalities such as multi-slice CT angiography and cardiac magnetic resonance has occurred.[18]

The majority of the patients in our cohort had surgical correction with DIACA, which is the surgical option most employed by congenital heart surgeons with good outcomes. Most patients recover left ventricular function, as evidenced by an improvement in the LVEF, as well as show an improvement in the severity of mitral regurgitation post-surgical correction.[9] From the study cohort, patients showed normalization of their reduced LVEF over time (median of 6 months). Mitral regurgitation improved from moderate and severe to mild with complete resolution at a median of six months post-surgery. The majority of the patients were asymptomatic by the first follow up visit.

Several patients experienced complicated post-operative ICU admissions. One patient developed a right hemiplegia following a left cerebral infarct and another was documented to have a right brachial nerve palsy. Two patients in the study cohort required a left ventricular assistant device and demised shortly after surgery.

The median LVEF in patients who demised pre- and post-operatively was 31%. The study by Zhang et al. showed that a low LVEF prior to surgery can help to identify probable high risk patients who may do poorly in the immediate post-operative period; however, even patients with a lower LVEF were found to have satisfactory recovery in the midterm follow up period.[10] This finding is replicated in our cohort, with patients with very low initial LVEFs of 24 and 29% doing well post-surgical correction with good recovery of their reduced left ventricular function.

An improvement in LVEF post-surgery does not preclude subclinical residual myocardial damage and perfusion deficits, as demonstrated by the late post-surgical MRI findings in a study by Alexi-Meskishvili et al.[19] Continued follow up post-surgical correction is therefore required. One of the study patients presented with chest pain eight years post-surgery. A cardiac perfusion scan was planned but the patient did not return for the procedure and was lost to follow up.

A study by Naimo et al. showed an early mortality of 0-16% for patients with ALCAPA post-surgery and late mortality being rare with an overall survival of 86-100% at 10 years.[13] Zhang et al. showed an early mortality rate of 7.7% and a much lower late mortality rate of 3.8%.[10] In our study, the early mortality rate was 21.6% which is far higher than in other studies.[10, 13, 20] This may be attributed to various factors such as a delay in the initial diagnosis, delays in transfer to a cardiac centre from other centres due to transport difficulties, delays in surgical correction due to long waiting lists or delays in attempts to optimize patients for open heart surgery.

In contrast to ALCAPA, anomalous right coronary artery from the pulmonary artery (ARCAPA) is extremely rare with an even lower incidence of 0.002% and is often an incidental finding.[18] Patients with ARCAPA occasionally present with symptoms of myocardial ischaemia when coronary steal occurs from the LCA to the right coronary artery.[18] One patient with ARCAPA was diagnosed during the study period. The patient was a nine-month-old male with no previous medical history who presented with failure to thrive, dyspnoea and poor feeding. The CXR showed cardiomegaly and the ECG demonstrated poor right ventricular forces. Echocardiography disclosed a possible ARCAPA associated with a decreased LVEF of 46% and moderate mitral regurgitation. ARCAPA was confirmed on cardiac catheterization and angiography. The patient underwent surgical reimplantation of the right coronary artery onto the aorta. His left ventricular function took approximately 67.4 months to recover post-surgery which is considerably longer than the patients with ALCAPA.

While our study showed no statistical difference in the diagnosis and outcomes of patients between the first and second decades, an increased awareness of ALCAPA, early diagnosis and advances in the surgical process and intensive care should positively impact patients' outcomes in our setting.

Limitations

A small sample size was a major limitation of our study, however, given the rarity of this condition, the findings do compare well with other large studies. As this was a retrospective analysis, we relied on the information retrieved from the Paediatric Cardiology electronic database and the hospital records. Therefore, unavailable data could not be accounted for. There was a major loss to follow up of patients, the cause of which is multifactorial in our setting and may be attributed to transport difficulties created by financial constraints, patient demise or patients returning to other provinces or countries of origin. Consequently, the loss to follow up placed a limitation on the post-surgical outcome and survival analyses.

CONCLUSION

ALCAPA is a rare congenital cardiac condition which requires timeous diagnosis and surgical correction for improved clinical outcomes. Due to the non-specific presenting symptoms and clinical manifestations, a high index of suspicion by clinicians is crucial in prompting further investigations such as an ECG which has features commonly occurring in patients with ALCAPA. This is important in our setting where a large proportion of our population rely on the peripheral hospitals for medical services, making the clinical and electrocardiographic recognition of ALCAPA vital for a prompt referral to a tertiary centre for early management and improved outcomes for our patients.

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation and gratitude to Professor Antoinette Cilliers for her guidance and valuable expertise in this research endeavour. A special thank you to Professor Kebashni Thandrayen for her advice regarding the statistical analyses. Last but not least, my gratitude goes to each participant and their families within the study who have enabled us to broaden our understanding and knowledge of ALCAPA within our setting and thereby contribute to the assessment and management of future patients.

FIGURES

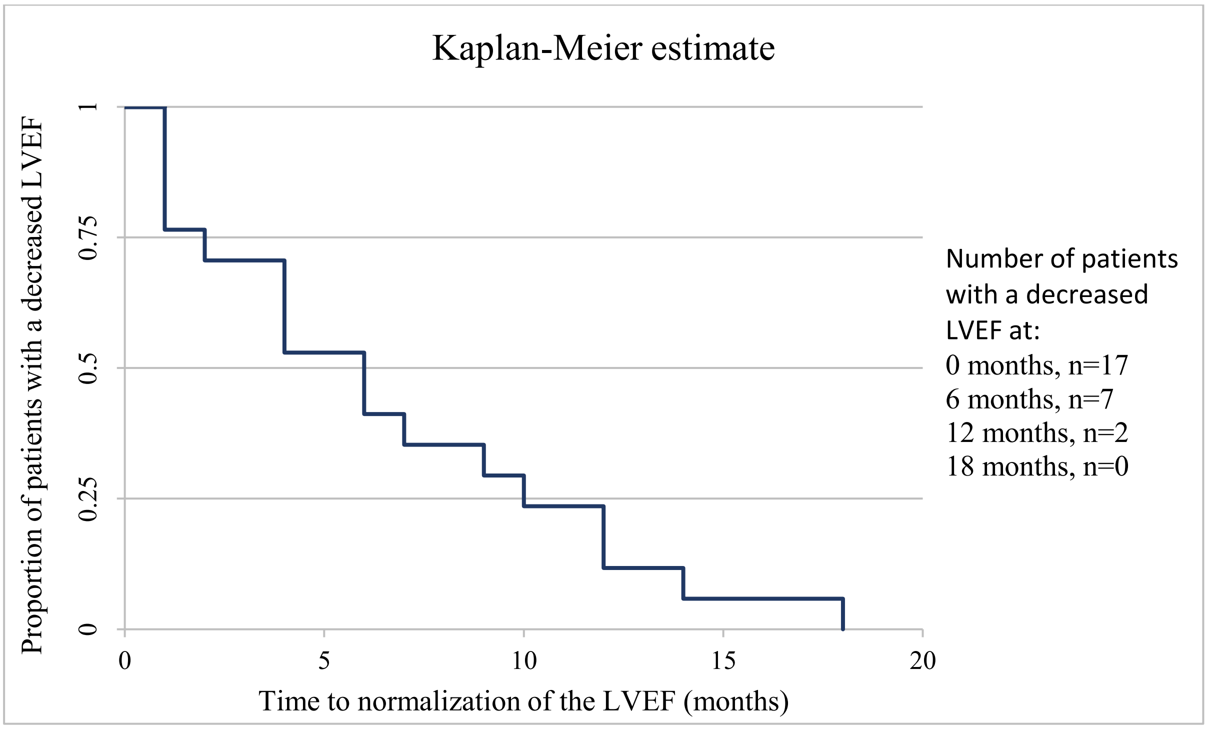

Figure 1 *Illustrating the time to normalization of the LVEF following the surgical reimplantation of the LCA*

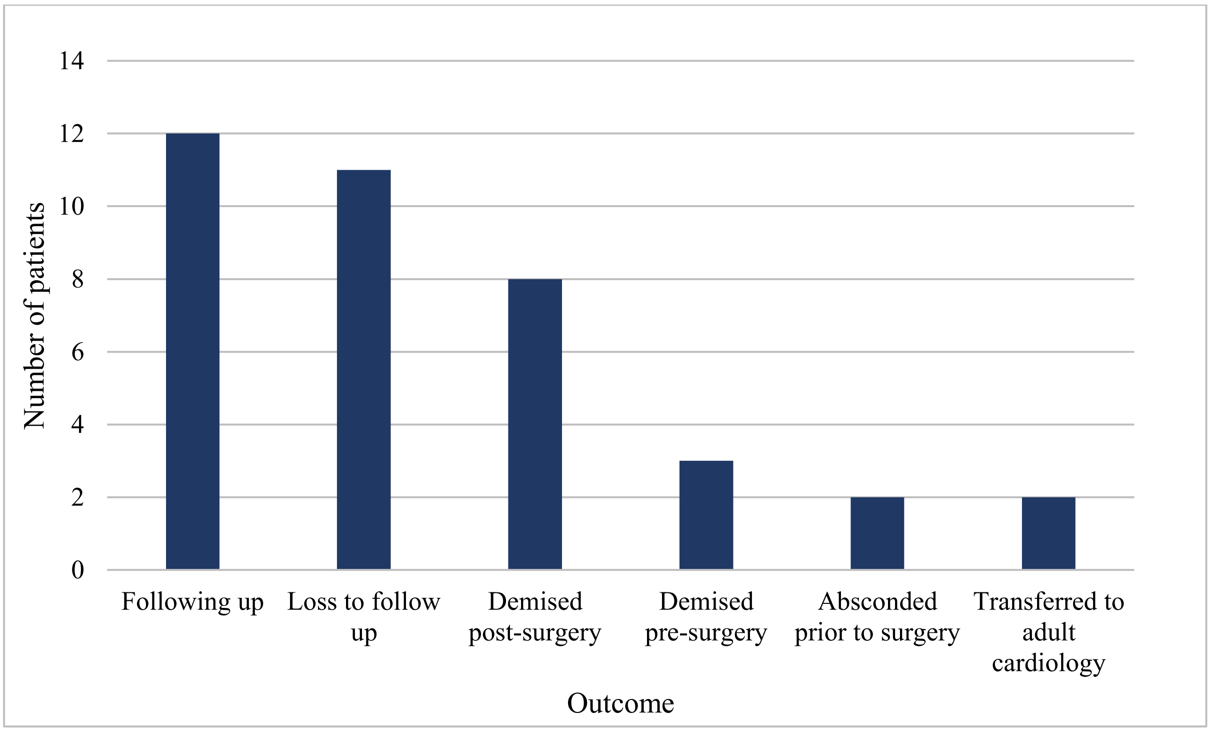

Figure 2 *Illustrating the outcomes of the patients diagnosed with ALCAPA at the CHBAH from 1991 to 2018*

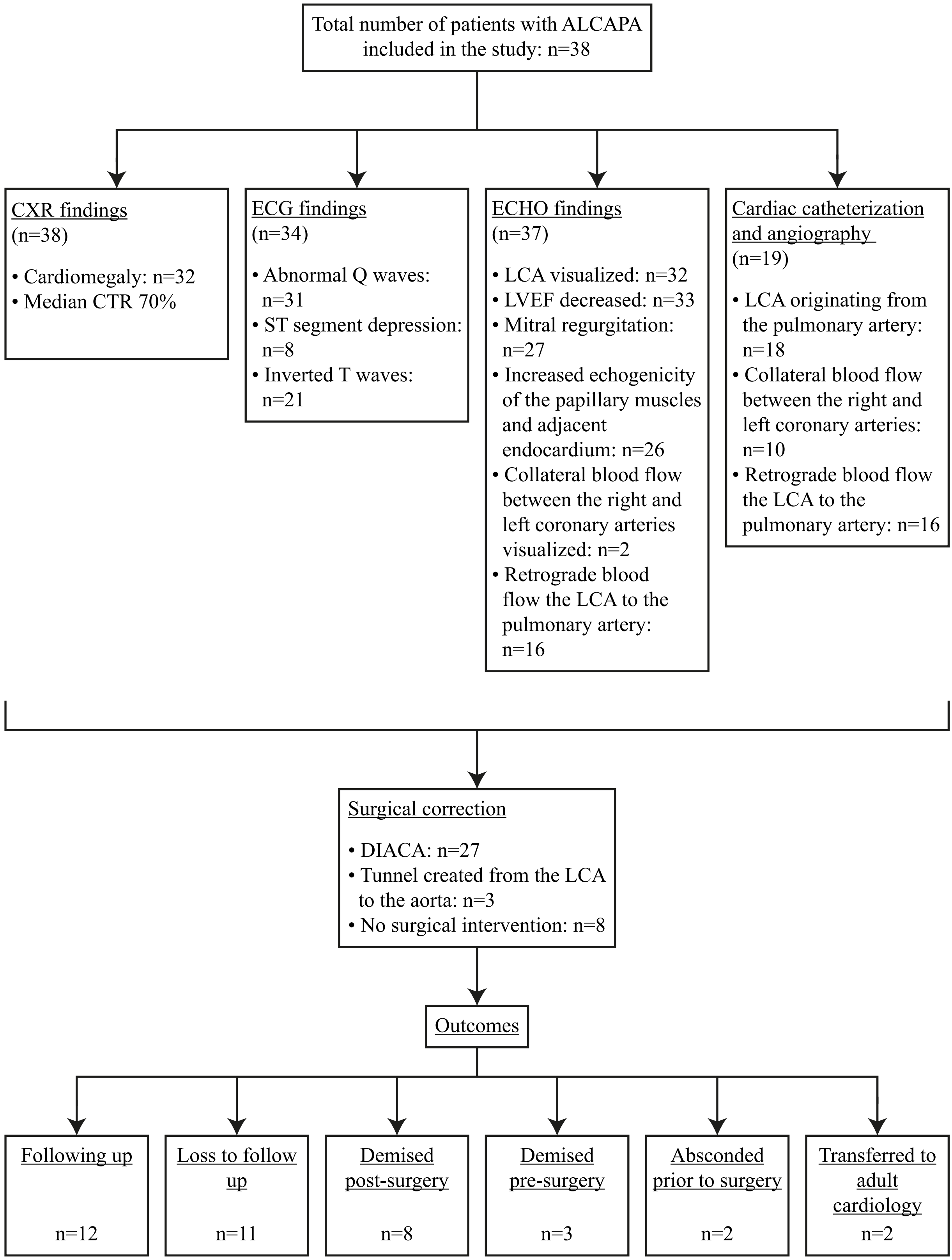

Figure 3 *Schematic overview of the diagnostic findings and outcomes in the patients included*

TABLES

***Table I** The presenting symptoms and clinical features in the 38 patients with ALCAPA at the CHBAH (1991-2018)*

Variable	Number of patients (% of the total number of patients, n=38)	**Variable**	Number of patients (% of the total number of patients, n=38)
Presenting symptom		Clinical feature	
Dyspnoea	26 (68.4)	Displaced apex beat	20 (52.6)
Cough	16 (42.1)	Respiratory distress	19 (50.0)
Poor feeding	7 (18.4)	Hepatomegaly	17 (44.7)
Gastroenteritis	6 (15.8)	Irritability	11 (28.9)
Diaphoresis	4 (10.5)	Cardiac murmur	8 (21.1)
Fever	3 (7.9)	Tachycardia	7 (18.4)
Cyanosis	2 (5.3)	Tachypnoea	7 (18.4)
Inconsolability	2 (5.3)	Hypotension	4 (10.5)
Shortness of breath	2 (5.3)	Crepitations	2 (5.3)
Fatigue	1 (2.6)	Gallop rhythm	2 (5.3)

***Table II** The electrocardiographic manifestations of ALCAPA*

Variable	Number of patients (% of the total number of ECGs analysed, n=34)
Presence of deep Q waves	32 (94.1)
Leads I and aVL	31 (96.9)
Leads I, aVL and limb leads	5 (15.6)
ST segment depression	8 (23.5)
Lead aVF	4 (50.0)
Lead III	3 (37.5)
Lead aVL	2 (25.0)
Inverted T waves	21 (61.8)
Left ventricular hypertrophy	17 (50.0)
Biventricular hypertrophy	4 (11.8)

Table III *The echocardiographic manifestations of ALCAPA*

Variable	Number of patients (% of the total number of patients with echocardiographic findings, n=37)
LCA visualized originating from the pulmonary artery	32 (86.5)
LVEF	36 (97.3)
Decreased	33 (91.7)
Normal	3 (8.3)
Median LVEF = 34.0%, IQR: 23.5 to 43.5%	
Mitral regurgitation	27 (73.0)
Mild	14 (51.9)
Mild-moderate	1 (3.7)
Moderate	7 (25.9)
Moderate-severe	4 (14.8)
Severe	1 (3.7)
Increased echogenicity of the papillary muscles and adjacent endocardium	26 (70.3)
Right coronary artery diameter	19 (51.4)
Dilated	18 (94.7)
Normal	1 (5.3)
Other echocardiographic findings	
Presence of collateral blood flow between the right and left coronary arteries	2 (5.4)
Presence of retrograde blood flow from the LCA to the pulmonary artery	16 (43.2)

Table IV *The cardiac catheterization and angiographic findings in patients with ALCAPA*

Variable	Number of patients (% of the total number of patients with cardiac catheterization and angiography, n=19)
LCA visualized originating from the pulmonary artery	18 (94.7)
Retrograde blood flow evident from the LCA to the pulmonary artery	16 (84.2)
Presence of collateral blood flow from the right coronary artery	10 (52.6)
Additional findings	
Visibly dilated right coronary artery	4 (21.1)
Left ventricular dysfunction	1 (5.3)
Left ventricular hypertrophy	1 (5.3)
PDA and severe pulmonary hypertension	1 (5.3)

Table V *A univariate analysis for the variables listed and the LVEF at diagnosis*

Variable	**Coefficient (95% Confidence Interval)**	**p-value**
Age in months	0.20 (-0.62-0.47)	0.13
Gender	8.81 (-1.35-18.97)	0.09
Anthropometry		
Wasted	-12.98 (-32.00-6.04)	0.17
Severely wasted	-11.65 (-23.19-0.10)	0.05
CTR on CXR	-0.53 (-1.21-0.15)	0.12
Abnormal Q waves on ECG	-7.40 (-29.69-14.88)	0.50
ST depression on ECG	-1.84 (-14.27-10.60)	0.77
Inverted T waves on ECG	-1.32 (-12.18-9.53)	0.81
Mitral regurgitation on echocardiography	-5.30 (-17.10-6.51)	0.37
Retrograde blood flow from the LCA to the pulmonary artery on cardiac catheterization and angiography	-4.19 (-30.50-22.12)	0.74
Presence of collateral blood flow from the right coronary artery to the LCA on cardiac catheterization and angiography	-0.63 (-17.32-16.07)	0.94

Table VI *Post-surgery follow up findings*

Variable	Number of patients (% of the total number of patients with post-surgical correction follow up findings, n=19)
Symptoms at the first follow up	
Asymptomatic	18 (94.7)
Tachypnoeic	1 (5.3)
Median months until asymptomatic was 1.37 (IQR: 0.9 to 2 months)	
Echocardiographic findings at the first follow up	18 (94.7)
LVEF (median LVEF of 58% (IQR: 39 to 74%))	18 (100)
Normal	11 (61.1)
Decreased	7 (38.9)
Normalization of LVEF occurred at a median of 6 months (IQR: 2 to 10 months)	
Mitral regurgitation	12 (66.7)
Grade: mild	12 (100)
Resolution of mitral regurgitation occurred at a median of 6 months (IQR: 3 to 9.5 months)	
Other	
Left ventricular dilatation	3 (16.7)
Pericardial effusion	1 (5.6)
Mild pulmonary regurgitation	1 (5.6)
Aortic regurgitation	1 (5.6)
Residual PDA	1 (5.6)

***Table VII** A Bivariate analysis of the demographic and diagnostic findings in the survival versus the non-survival groups*

Variable	**Survival group** Number of patients (% of the total number of patients for the variable stated)	**Non-survival group** Number of patients (% of the total number of patients for the variable stated)	**p-value**
Demographic	n=14	n=11	
Age: Infant Non-infant	11 (78.6) 3 (21.4)	11 (100.0) 0 (0.0)	0.23
Gender: Female Male	 9 (64.3) 5 (35.7)	 8 (72.7) 3 (27.3)	1.00
Anthropometry: Normal Wasting Severely wasted	 6 (42.9) 5 (35.7) 1 (7.1)	 3 (27.3) 4 (36.4) 1 (9.1)	1.00
Radiographic findings	n=14	n=11	
Presence of cardiomegaly	13 (92.9)	9 (81.8)	0.57
ECG findings	n=13	n=10	
Rate: Normal Tachycardic	11 (84.6) 2 (15.4)	8 (80.0) 2 (20.0)	1.00
Axis: Normal Right Left	8 (61.5) 2 (15.4) 3 (23.1)	9 (90.0) 0 (0.0) 1 (10.0)	0.41
Abnormal Q waves	12 (92.3)	10 (100.0)	1.00
ST segment depression	2 (15.4)	3 (30.0)	0.62
Inverted T waves	9 (69.2)	6 (60.0)	0.69
Echocardiographic findings	n=13	n=11	
LCA visualized originating from the pulmonary artery	12 (92.3)	10 (90.9)	1.00
Decreased LVEF	13 (100.0)	9 (90.0)	0.44
Presence of left ventricular dilatation	9 (69.2)	7 (63.6)	1.00
Presence of mitral regurgitation	9 (69.2)	6 (54.5)	0.68
Dilated right coronary artery	6 (46.2)	5 (45.5)	1.00

Cardiac catheterisation and angiography	n=6	n=4	
Retrograde blood flow from the LCA to the pulmonary artery	5 (83.3)	3 (75.0)	1.00
Collateral blood flow from the right coronary artery to the LCA	3 (50.0)	2 (50.0)	1.00

QUESTIONS FOR THE SA HEART JOURNAL

1) Which of the following is correct?
    a. ARCAPA is more common than ALCAPA
    b. The diagnosis of ALCAPA requires echocardiography
    c. ALCAPA is a common congenital cardiac defect
    d. ALCAPA is often misdiagnosed
2) Which electrocardiographic features are the commonest in ALCAPA?
    a. ST segment depression in leads I and aVL
    b. T wave inversion in leads V1 to V3
    c. Deep Q waves in leads I and aVL
    d. A sinus tachycardia
3) Which of the following is false?
    a. The surgical correction of ALCAPA ensures normal myocardial perfusion long term
    b. ALCAPA results from a disruption in the embryological development of the coronary arteries
    c. The presence of collateral blood supply from the right to the left coronary artery is protective
    d. The left ventricular ejection fraction improves post-surgical correction of ALCAPA

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APPENDIX A:
AUTHOR GUIDELINES FOR THE SA HEART JOURNAL

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Disclosures

Authors must declare all financial disclosures and conflicts of interest in the cover letter and on the title page of the manuscript.

Ethics

All studies must be in compliance with institutional and international regulations for human and animal studies such as the Helsinki declaration (2008) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects) and the South African MRC ethics guidelines (https://www.samrc.ac.za/research/ethics/guideline-documents). Human studies require ethics committee approval and informed consent which must be documented in your manuscript. Animal studies require ethics committee approval and must conform to international guidelines for animal research. Compliance with these requirements must be documented in your manuscript.

Content

1. Title page: It should contain the title of the manuscript, the names of all authors in the correct sequence, their academic status and affiliations. If there are more than 4 authors, the contribution of each must be substantiated in the cover sheet. The main author should include his/her name, address, phone, fax and email address.
2. Authors are solely responsible for the factual accuracy of their work.
3. Articles should be between 3 000 and 5 000 words in length.
4. A 200-word abstract should state the main conclusions and clinical relevance of the article.
5. All articles are to be in English.
6. Abbreviations and acronyms should be defined on first use and kept to a minimum.
7. Tables should carry Roman numeral, I, II etc., and figures Arabic numbers 1, 2 etc.
8. 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]

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.

Online media
Perreault, L. (2019). Obesity in adults: Role of physical activity and exercise. UpToDate. Retrieved January 12, 2020, from https://www.uptodate.com/contents/obesity-in-adults-role-of-physical-activity-and-exercise

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10. 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 MS Word or PowerPoint document. 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 and table must have a separate self-explanatory legend.
11. Remove all markings such as patient identification from images and radiographs before photographing.
12. Include 3 challenging questions on the content of the manuscript relating to the key messages. The questions will be included in a questionnaire for CPD accreditation purposes. Please supply each question with a choice of 4 - 5 possible answers of which only one is correct (multiple correct answers not allowed) and highlight the correct answer. Please do not supply questions with a simple yes/no option.

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The manuscript should be submitted online on the SA Heart® Journal open access platform https://tinyurl.com/y9prlopt. Follow further instructions on this website.

APPENDIX B:
RESEARCH PROTOCOL

THE PREVALENCE, CHARACTERISTICS AND OUTCOMES OF ANOMALOUS LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY AT THE CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL OVER A 28-YEAR PERIOD

INTRODUCTION

Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA) is caused by a poorly understood disruption in the embryological development of the coronary arteries. Consequently, the left coronary artery originates from the pulmonary artery instead of the aorta. It is a rare congenital cardiac defect accounting for 0.25% to 0.5% of congenital heart disease (1). ALCAPA is also known as Bland-White-Garland Syndrome, as its first clinical description was given by Bland, White and Garland in 1933 (2).

Due to an initially high pulmonary artery pressure, patients are usually asymptomatic at birth as there is enough blood supply reaching the myocardium; albeit at a lower oxygen saturation (3). As the neonatal physiology changes over time, the pulmonary artery pressure decreases and blood flows with a lower pressure to perfuse the myocardium (4). This predisposes the myocardium supplied by the left coronary artery to myocardial ischaemia (4).

As pulmonary resistance decreases, pulmonary artery pressure decreases further and this leads to the coronary steal phenomenon; whereby retrograde flow from the high pressure left coronary artery to the pulmonary artery occurs (3). This contributes to myocardial ischaemia and in time patients develop an anterolateral myocardial infarction associated with a dilated cardiomyopathy (4). Poor coronary perfusion causes direct papillary muscle ischaemia and left ventricular dysfunction and dilatation which is associated with annular dilatation of the mitral valve; both of which cause mitral regurgitation (5).

Collateral blood supply between the right and left coronary arteries may develop which aid in perfusion of the left ventricular myocardium (4). A large study by Langa et al. showed that collateral blood supply, which is protective, was evident in patients more than one year of age (6). The presence of collateral blood supply impacts the time of presentation of patients as well as the clinical manifestations they present with.

There are a few publications from tertiary care institutions describing the clinical presentation, radiological findings, management and postoperative outcome of patients with ALCAPA. The studies are however small and this is likely due to the low incidence of ALCAPA (2, 3, 4, 7). These studies took place in low- and middle-income countries. No publications describing ALCAPA in the paediatric population have emanated from Southern Africa to date.

Recognition of ALCAPA depends on the recognition of a constellation of clinical signs and electrocardiographic features. Zheng et al. demonstrated that infant patients (less than one year of age) with ALCAPA presented commonly with dyspnoea, feeding intolerance, diaphoresis and failure to thrive (2). In a recent study in 2017 by Guzeltas et al., with patients presenting between one month and 10 years of age, it was found that 60% of patients presented with a murmur, 40% of patients presented with shortness of breath and 30% of patients were asymptomatic (8).

Episodes of colic or irritability associated with diaphoresis or pallor warranted further investigation in a study on infants with ALCAPA by Brotherton and Philip in 2008 (4). In this small study, they also emphasized a history of poor feeding and failure to thrive in patients presenting in congestive cardiac failure and only one patient in this study had a cardiac murmur (4). The presenting signs and symptoms vary slightly between studies and different age groups. A high index of suspicion is key for clinicians to make the diagnosis.

The common finding on chest radiography was cardiomegaly in a study by Brotherton and Philip, which showed cardiomegaly present in 80% of patients (4). In a small study by Holst et al. in 2015, of seven infants, three (43%) were noted to have cardiomegaly on chest radiography (3). A study by Levitas et al. contradicted previous studies by concluding that a normal cardiac size on chest radiography was a common finding in patients with ALCAPA (9). The current consensus regarding chest radiographic findings is unclear.

Specific electrocardiographic features have been demonstrated in studies on ALCAPA and it is an important bedside diagnostic tool which is available in most primary and secondary health care facilities. For example in a study by Weigand et al., ST segment changes were regarded as noteworthy if there was at least a 1mm elevation or depression of the segment from baseline or at least 10% of the combined R and S wave amplitude (10). Q waves were important if they were at least 25% of the R wave height or at least 20 milliseconds in duration (10). In this study, interpretable electrocardiograms showed 78% of patients having T wave inversion, 89% of patients having abnormal Q waves in at least one lead and 44% revealed ST segment changes (10).

Most recently, a study by Guzeltas et al. showed that 70% of patients with ALCAPA had deep Q waves in leads I, AVL and V6, with a sinus tachycardia in 50% of patients and T wave inversion in leads V5 to V6 in 20% of cases (8). In the study by Zheng et al., the main electrocardiographic features were abnormal Q waves and T wave inversion in leads I, AVL and V4 to V6 (2). These studies demonstrate the similarity in some electrocardiographic parameters in patients with ALCAPA.

ALCAPA can be confirmed in most cases by a skilled echocardiographer non-invasively. When necessary, a definitive diagnosis can also be made on angiography in the cardiac catheterization theatre. It is important to note that echocardiographic features vary with age and collateral blood supply visible on colour Doppler imaging using echocardiography may only become evident over time (5).

Patients presenting in infancy usually have not developed collateral blood supply to the left myocardium. Consequently there is reduced myocardial perfusion as blood shunts from the left coronary artery to the pulmonary artery as the pulmonary vascular resistance decreases (5). This left to right shunt can be demonstrated echocardiographically using colour Doppler which shows retrograde flow of blood from the left coronary artery into the pulmonary artery.

The coronary artery steal of blood away from the myocardium results in left ventricular dysfunction and dilatation which is associated with a reduced left ventricular ejection fraction and mitral regurgitation (5). The right coronary artery becomes the dominant artery in patients with ALCAPA and appears dilated on echocardiography.

Echocardiographic parameters for the assessment of the effects of myocardial ischaemia and infarction on the left ventricle and the mitral valve have been documented in patients with ALCAPA. In a study by Patel et al., left ventricular dysfunction was defined by a left ventricular ejection fraction of less than 45%, mitral insufficiency was assessed based on the width of the vena contracta (the narrowest flow region of the regurgitant jet), whereby 1mm was trivial, 1-3mm was mild, 3-6mm was moderate and more than 6mm was assessed as severe mitral regurgitation (5). Right coronary artery dilatation was dependant on age; more than 2mm was regarded as dilated in infants, more than 3mm in children 1-6 years of age and more than 4mm in children older than 6 years of age (5).

Similar findings were reported by Guzeltas et al., where 90% of patients with ALCAPA were shown on echocardiography to have varying degrees of left ventricular dilatation, mitral regurgitation and collateral blood flow (8). In addition, 80% of patients demonstrated a dilated right coronary artery and only 40% of patients had retrograde diastolic flow towards the pulmonary artery (8).

A recent study by Kanoh et al demonstrated more severe impairment of the left ventricular ejection fraction in infants as compared to older patients (11). This finding was similar to the study by Zheng et al., where it was found that the infant group demonstrated much lower left ventricular ejection fractions, and a greater frequency of left ventricular dilatation and mitral insufficiency as compared to the noninfant group (2). They also showed a higher right coronary artery to aortic root diameter ratio in the noninfant group of patients with coronary artery collaterals evident in the interventricular septum in both groups in this study (2).

The study by Zhang et al. divided patients with ALCAPA into two groups depending on their left ventricular ejection fraction (7). Patients with left ventricular ejection fractions less than 50% were found to be of younger age, had a lower weight, had intercoronary collateral dysplasia and a lower right coronary artery to aortic root diameter ratio (7). These findings are in keeping with other studies which demonstrate poorer myocardial viability and less collateral coronary supply in infants.

Surgical management which is the definitive treatment for ALCAPA, has evolved over the years and includes the following; DIACA is the “Direct reimplantation of the anomalous coronary artery onto the aorta” (7). The Takeuchi procedure involves creating a pulmonary arteriotomy, a transverse flap of pulmonary artery tissue and an aortopulmonary window (7). Pericardium is then used to reconstruct the pulmonary artery (7). This technique is usually used if the left coronary ostium is at an exceptional distance from the aorta (6). A less common procedure involves ligating the left coronary artery at its origin with or without Coronary Artery Bypass Grafting (CABG) (7). DIACA is the method most frequently used for the surgical correction of ALCAPA in the modern era (2, 7, 10-12).

Excellent postoperative outcomes have been found in patients with ALCAPA across various studies (7, 11, 13). Even in patients with severe myocardial infarction, there was satisfactory recovery of myocardial function in midterm follow up (median length of seven years) after a dual coronary arterial system was successfully restored (7).

In the study by Kanoh et al, a longer follow up of 16 years found that outcomes were remarkable, with left ventricular ejection fractions normalizing and mitral valve function improving post-surgical correction of ALCAPA (11). They did however also emphasize that myocardial damage can remain for a long period post-surgery, thus necessitating the need for long term follow up of patients (11).

Early mortality in patients with ALCAPA ranged between zero and 16% (13). Late mortality was found to be rare with survival reported in 86% to 100% of patients at 10 years post-surgical correction (13). A study by Naimo et al. stated an overall survival of 98% at 20 years post-surgery in patients with ALCAPA (13). Early diagnosis and surgical management are key in patients with ALCAPA.

The incidence of ALCAPA may be under reported if the diagnosis is missed. In the study by Zheng et al., 78% of patients were initially diagnosed incorrectly (2). In a study by Levitas et al., nine patients were misdiagnosed at presentation, and on subsequent electrocardiograms all nine patients had electrocardiographic findings suggestive of ALCAPA (9).

There is a paucity of data regarding the clinical presentation, findings and outcomes of South African children with ALCAPA. It is important for the medical fraternity to be aware of this congenital cardiac condition to ensure early diagnosis and surgical correction with improved outcomes for our patients. South Africa is a low to middle income country with a large diverse population. There are economic challenges and resource constraints in the health sector with majority of patients not having any private medical aid funding. With South Africa being a resource-constrained country, it is likely that the time to surgical management and the post-operative outcomes for patients with ALCAPA may differ from the studies from resource replete countries.

In South Africa peripheral hospitals serve majority of our population and unfortunately do not always have specialist services available. The information gained from studies assessing the clinical and diagnostic features in a local setting will contribute to setting guidelines for the diagnosis of children and adults with ALCAPA. This will lead to appropriate treatment being instituted early and improved outcomes for patients.

AIM

To describe the prevalence, characteristics and outcomes of children with ALCAPA presenting to a Southern African tertiary care centre namely the Chris Hani Baragwanath Academic Hospital over a 28-year period.

OBJECTIVES

In children diagnosed with ALCAPA at the Chris Hani Baragwanath Academic Hospital over a 28-year period, to describe the:

1) Prevalence
2) Clinical, radiographic and electrocardiographic features
3) Echocardiographic, cardiac catheterization and angiographic features
4) Surgical treatment and the 1-year and 5-year survival outcomes post diagnosis

METHODS

Study design

This study is an observational study with a retrospective analysis of paediatric patients diagnosed with ALCAPA over the last 28 years at the Chris Hani Baragwanath Academic Hospital in Soweto.

Study population

The patients included in this study are all paediatric patients diagnosed with ALCAPA in the Paediatric Cardiology department at Chris Hani Baragwanath Academic Hospital between 1991 and 2018.

Inclusion criteria

- All paediatric patients (less than 18 years of age) diagnosed with ALCAPA

- Patients who presented to Chris Hani Baragwanath Academic Hospital as well as patients referred from surrounding hospitals
- Patients with other congenital cardiac conditions in addition to ALCAPA

Exclusion criteria

- Patients with other congenital coronary artery anomalies

All patients meeting the inclusion criteria will be used in this study.

We have an estimated 37 patients diagnosed with ALCAPA on the Paediatric Cardiology electronic database at the Chris Hani Baragwanath Academic Hospital between 1991 and 2018.

This is a reasonable number of patients as it is larger than the sample size of most studies on ALCAPA which have been conducted to date.

<u>Study procedure</u>

The Paediatric Cardiology database and the Cardiology files of the patients in this study will be accessed with permission from the Hospital Chief Executive Officer (See appendix A), the Head of the Paediatric Department, Professor Velaphi (see appendix B) and the Head of the Paediatric Cardiology Department, Professor Antionette Cilliers (see appendix C)

An application to the University of the Witwatersrand Human Research Ethics Committee (Medical) will be made.

Ethical clearance from the Human Research Ethics Committee (Medical) has been granted to Professor Cilliers for the use of the Paediatric Cardiology electronic database for research (see appendix D).

Each study participant’s file will be allocated a study number to ensure that all data captured will be done so anonymously and only linked to the study number and not to the patient’s identity details.

Patient records will remain on the hospital premises at all times as data capturing will be done on site. Password protected software will be used for data capturing and storage under the study number. These measures will ensure that there is maximum patient confidentiality at all times.

<u>Data collection</u>

A data collection sheet (see appendix E), will be used to collect the necessary data for each patient in the study.

Details of the following will be collected for each patient:

- Demographic characteristics: Age at diagnosis, gender, race, weight and height, hospital accessed and existing medical conditions
- Symptoms and clinical features at presentation
- Chest radiographic findings at presentation
- Initial diagnosis
- Chest electrocardiographic findings
- Echocardiographic findings
- Cardiac catheterization and angiography findings if applicable
- Method of surgical management of the patient
- Time to surgical correction after the diagnosis was made
- Post-operative clinical and echocardiographic outcomes at the first and latest follow up
- Time of normalization of cardiac function

The possible symptoms at presentation and the clinical features which appear on the data collection sheet are based on findings in the available literature on ALCAPA.

The possible electrocardiogram and echocardiogram findings which appear on the data collection sheet have been determined using definitions in the study by Zheng et al, as well as the textbook: *Pediatric Cardiology for Practitioners* by Myung K Park which discusses the electrocardiographic and echocardiographic findings in paediatric patients (2, 14).

Data will be entered onto a Microsoft Excel spreadsheet for interpretation and analysis.

<u>Data analysis</u>

Statistical analysis:

Means with standard deviations and medians with ranges will be used for continuous variables. Frequencies and percentages will be used for categorical variables.

Chi-squared and Fischer exact tests will be used for analysis of categorical variables.

Paired-samples *t*-test will be used to compare pre- and post-surgical correction echocardiographic findings.

ETHICAL CONSIDERATIONS

<u>Risks to patients:</u>

This study poses no risk to the patients involved as it is a retrospective review of data. By using the measures previously described there will be no loss of confidentiality for patients.

<u>Benefits to patients:</u>

There is no direct benefit to the patients involved in this study.

Informed consent:

As this is a retrospective study, informed consent will not be required directly from the study participants as there are no risks to the patients. In addition, information will be collected anonymously with no patient identification details included.

The STROBE Criteria for observational studies will be adhered to in this study and missing data will be accounted for at all stages

Study costs

This is a retrospective study and thus no costs will be incurred to the participants. Study participants will also not receive payment in any form.

LIMITATIONS

Being a retrospective study, the main limitation will be the inability to gather all the necessary information for each patient as this relies on the information already present in the files.

All the investigations may not have been done for all the patients in the study or they may be unavailable.

There may be discrepancies in the available echocardiographic findings depending on the time of diagnosis of patients as more recently the echocardiographic machines offer better precision compared to earlier times.

TIMELINE

	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May
Literature review																								
Preparing protocol																								
Protocol assessment																								
Ethics application																								
Collecting data																								
Data analysis																								
Writing up - thesis																								
Submission and marking																								

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PROTOCOL APPENDIX

DATA COLLECTION SHEET (Part 1)

DATA COLLECTION SHEET			Study No.:
Age at diagnosis		Gender M F	Date of dx
Race	B W C I	Weight	Height
Hospital	CHBAH Other (including date of transfer):		
Existing medical conditions			
Symptoms at presentation	☐ poor feeding ☐ diaphoresis with feeding ☐ inconsolability ☐ dyspnoea ☐ other:	Clinical features at presentation	☐ failure to thrive ☐ irritabilty ☐ distress ☐ cardiac murmer Type: ☐ other:
Intial diagnosis			
Chest radiographic findings	☐ cardiomegaly CTR: ☐ lung fields: ☐ other:		
ECG findings	☐ Rate: ☐ Rhythm: ☐ Axis: <u>Abnormal Q waves:</u> ☐ > 25% of R wave height Leads: ☐ > 0.03 sec Leads: <u>ST segment:</u> ☐ elevation >1mm for >0.08sec Leads: ☐ depression >1mm for >0.08sec Leads: ☐ <u>Inverted T waves:</u> Leads: Other abnormal findings:	ECHO findings	☐ left coronary artery visualized coming off the pumonary artery ☐ presence of left ventricular dilatation ☐ left ventricular ejection fraction : ☐ mitral regurgitation present Severity: ☐ Right coronary artery width: ☐ Aortic root diameter: ☐ collateral blood flow evident ☐ retrograde flow from left coronary artery to pulmonary artery

DATA COLLECTION SHEET (Part 2)

<table>
<tr><td>Cardiac Cath and angiographic findings</td><td colspan="4">☐ Left coronary artery originating from the pulmonary artery
☐ Evidence of retrograde flow from the left coronary artery to the pulmonary artery
☐ Presence of collateral blood flow
☐ Available pressures:
Pulmonary artery pressure (s/d/m) :
Aortic pressure (s/d/m) :

Other findings:</td></tr>
<tr><td>Method of surgical repair</td><td colspan="2"></td><td>Months post diagnosis & date</td><td></td></tr>
<tr><td>First follow up</td><td colspan="4">No. of months post repair & date:</td></tr>
<tr><td>Post operative clinical outcomes at first follow up</td><td>☐ Asymptomatic
☐ Symptoms & signs at follow up:

Complications:</td><td colspan="2">Post operative ECHO findings</td><td>☐ LVEF:

☐ Mitral regurgitation present
Severity:

Other important findings:</td></tr>
<tr><td>Frequency of follow ups</td><td colspan="4"></td></tr>
<tr><td>Normalization of cardiac function</td><td colspan="4">No. of months post repair when patient aymptomatic:

No. of months post repair when ECG normal (if available):

No. of months post repair when LVEF normalized:

No. of months post repair when MR resolved:</td></tr>
<tr><td>Latest follow up</td><td colspan="4">No. of months post repair & date:</td></tr>
<tr><td>Post operative clinical findings at latest follow up</td><td>☐ Asymptomatic
☐ Symptoms & signs at follow up:

Complications:</td><td colspan="2">ECHO findings at long term follow up</td><td>☐ LVEF:

☐ Mitral regurgitation present
Severity:

Other important findings:</td></tr>
<tr><td>Other outcomes</td><td colspan="4">☐ Passed away while awaiting surgery
☐ Passed away intraop
☐ Passed away post surgery No. of months post op:
☐ Absconded prior to surgery
☐ Loss to follow up</td></tr>
</table>

APPENDIX C:
ETHICS CLEARANCE

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R49 Dr A Chhiba

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190741

NAME: Dr A Chhiba
(Principal Investigator)

DEPARTMENT: School of Clinical Medicine
Department of Paediatrics and Child Health
Medical School
University

PROJECT TITLE: *The prevalence, characteristics and outcomes of anomalous left coronary artery from the pulmonary artery at the Chris Hani Baragwanath Academic Hospital over a 28 year period*

DATE CONSIDERED: 2019/07/26

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Professor A Cilliers

APPROVED BY: Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2019/08/02

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **«Missing mail merge field»** and therefore reports and re-certification will be due in the month of **«Missing mail merge field»** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

16 March 2021
Date

APPENDIX D:
PLAGIARISM DECLARATION

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Anjali-Larisha Chhiba (Student number: 303105) am a student registered for the degree of Masters of Medicine in Paediatrics in the academic year 2021.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: ______________ Date: 16 March 2021

APPENDIX E:
TURNITIN REPORT

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