TRANSTHORACIC ECHOCARDIOGRAPH IN A NEONATAL INTENSIVE CARE UNIT- INDICATIONS, YIELD AND SPECTRUM OF CONGENITAL HEART DISEASE IDENTIFIED. A RETROSPECTIVE DESCRIPTIVE CROSS-SECTIONAL STUDY

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DEDICATION

To Emefa, Yayra, Nunyuie and Esunyeh

Glory to the Lord

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OVERVIEW

Transthoracic echocardiography is readily available and routinely used in neonatal intensive care units in developed countries. In sub-Saharan Africa, however, there is limited availability and access. While the availability of echocardiography is improving, the absence of qualified paediatric cardiologists to perform them remains a challenge.

There is currently no consensus on the indications for echocardiography in newborns. The purpose of this study is to retrospectively investigate the indications and findings of transthoracic echocardiography in the neonatal intensive care unit at the Inkosi Albert Luthuli Central Hospital in Durban, over a 5-year period.

This retrospective, cross-sectional, observational study was done by searching through the database of the hospital for echocardiogram performed from 1st January 2015 to 31st December 2019. The demographic characteristic of the patients, the indications and findings of echocardiography was captured onto an excel data spreadsheet. Numerical and categorical data were obtained and analysed using Stata data analysis with a p value of <0.05 considered significant observation for categorical data.

From the study, it was observed that the overall positive yield of echocardiography for congenital heart defect was 51%. Over twenty indications for echocardiography were identified with respiratory distress being the commonest. Over thirty abnormalities were diagnosed over the period with patent ductus arteriosus, ventricular septal defect, atrioventricular septal defect, tetralogy of fallot and transposition of the great arteries being the top five most common diagnoses. The indications associated with a positive yield for congenital heart defect included cyanosis, murmur, and prior foetal ultrasound diagnosis of congenital heart defect (CHD).

The study summarises data on echocardiography in the neonatal unit over a period of 5 years. It provides information on the overall yield; the main indications for echocardiography; and prevalence and distribution of congenital heart defect over the study period.

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ABBREVIATIONS (IN ALPHABETICAL ORDER):

ALCAPA	Anomalous left coronary artery origin from pulmonary artery
ASD	Atrial Septal Defects
AS	Aortic stenosis
AVSD	Atrioventricular Septal Defects
CHD	Congenital Heart Defect
CCHD	Critical congenital Heart Defect
CoA	Coarctation of Aorta
DOB	Date of Birth
EA	Ebstein Anomaly
ECHO	Trans Thoracic Echocardiography
GIT	Gastrointestinal tract
HLHS	Hypoplastic left heart syndrome
IAA	Interrupted aortic arch
LI	Left isomerism
MS	Mitral stenosis
PAPVC	Partial Anomalous Pulmonary Venous Connection
PA/IVS	Pulmonary Atresia with Intact Ventricular Septum
PA/VSD	Pulmonary Atresia with Ventricular Septal Defect
PDA	Patent Ductus Arteriosus
PFO	Patent foramen ovale
RI	Right isomerism
SSA	Sub Saharan Africa
TA	Tricuspid Atresia
TAPVC	Total Anomalous Pulmonary Venous Connection
TOF	Tetralogy of Fallot
TrA	Truncus arteriosus
VSD	Ventricular Septal Defects

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CHAPTER 1
INTRODUCTION

1.1 LITERATURE REVIEW

Epidemiology:

Congenital Heart Defects (CHD) are defined as structural abnormalities of the heart and/or great vessels that are present at birth.[1] CHD are the commonest congenital birth defects worldwide and are a significant cause of morbidity and mortality in children. Despite regional variability of prevalence between 4/1000 to 50/1000 live births, the accepted global prevalence is eight (8) cases per 1000 live births. This represents approximately 1.35 million newborns each year with CHD. [2,3,4,5]

CHD data in Africa is gaining increasing attention. In recent **times** we have seen the publication of protocols for systematic review of articles on CHD across the world, including Africa.[6,7] In Nigeria the prevalence of CHD is estimated as 3.5 out of every 1000 live births.[8] In Ghana, the estimated burden of CHD is in the region of 372 per million of the population.[9] In Cameroon, the prevalence of CHD in hospital-based setting among children suspected of heart diseases is estimated to range between 9.9% and 13.1%.[10] In Tanzania, based on a birth of 2.1 million babies per year it is estimated that 16,800 infants per year might be born with congenital heart disease.[11] It is estimated that 12,000 children are born with CHD annually in South Africa.[9]

CHD Contribution to neonatal mortality:

CHD contributes significantly to neonatal and infant mortality.[12,13,14] It accounts for 3% of all infant deaths representing about 30 to 50% of infant mortality from congenital malformations worldwide and approximately 46% in developed countries like USA.[15] Approximately 70% of infant deaths attributable to congenital heart defects occur in the neonatal period. Some studies indicate that up to 4.2% of all neonatal deaths and 24.5% of neonatal deaths attributable to birth defects had congenital heart disease as an underlying cause.[16] These figures are expected to be higher in resource limited areas which include much of Sub-Saharan Africa (SSA).

Neonatal mortality rate is an important indicator of the quality of health care systems and an important component of the Millenium Development Goals (MDG) and now Sustainable Development Goals (SDG).[17] The World Health Organization (WHO) statement on newborn mortality on 28th of January 2022 stated that "In 2020, nearly half (47%) of all under-5 deaths occurred in the newborn period (the first 28 days of life). Sub-Saharan Africa has the highest neonatal mortality rate in the world (27 deaths per 1000 live births with 43% of global newborn deaths). Preterm birth; intrapartum-related complications; infections and birth defects are the leading causes of most neonatal deaths".[17] CHD plays a role in each of the stated leading cause of neonatal deaths. CHD is a risk factor for preterm delivery

and intrapartum complications of asphyxia; it increases the risk of infection, especially in the setting of increased pulmonary circulation and it is the commonest birth defect worldwide.[17]

The WHO statement in 2022 also added that "Children who die within the first 28 days of birth suffer from conditions and diseases associated with lack of quality care at or immediately after birth and in the first days of life".[17] It is therefore important that in addressing neonatal mortality rates, we improve the quality of care for neonatal CHD beginning with early screening and diagnosis.

Screening for congenital heart disease in the neonatal period:

Critical congenital heart defects (CCHD) represent the severest forms of CHD that require early intervention in the newborn period to avert mortality. Unfortunately, many of these babies appear healthy immediately **after birth** and may be sent home only to present 24 to 48 hours later, critically ill.[18,19] As with all screening modalities, newborn screening for CHD must be safe, cheap, easily accessible, and useable with high sensitivity and specificity.

The earliest suspicion of CHD is entertained during routine prenatal ultrasound scan. This is followed up by foetal echocardiography where a foetal diagnosis of CHD may be made. Prenatal ultrasound and foetal echocardiogram overall have a variable pick up rate for CHD.[20,21] The sensitivity and specificity are critically dependent on equipment and expertise which though established in many developed countries is not readily available in many developing countries. Where it is available, it is usually expensive. As a result, the first opportunity for many newborns in developing countries or resource limited centres for early screening of CHD is during the comprehensive newborn examination. This may or may not include pulse oximetry.

The comprehensive newborn cardiac examination typically involves assessment of appearance (colour), blood pressure, pulses, and auscultation of the precordium. Addition of pulse oximetry is a safe, inexpensive, and reliable screening tool especially for CCHD such as Hypoplastic left heart, Pulmonary atresia, Tetralogy of Fallot, Total anomalous pulmonary drainage, Transposition of the Great Vessels, Tricuspid atresia and, Truncus arteriosus. [22,23] In the absence of essential newborn examination and pulse oximetry by a trained person, a considerable number of healthy-looking newborns with CCHD are missed and sent home only to return in critical states soon after or later in infancy.

Physical examination on its own identifies less than 50% of congenital heart defects. However, pulse oximetry has been found to be specific and sensitive with a low false positive rate. Newborns who fail the pulse oximetry test for CHD are referred for further evaluation.[22] Risk factors for CHD are newborns who are sick, have murmurs, are cyanosed, have other congenital abnormalities, are syndromic, born to mothers with specific medical conditions (e.g. gestational diabetes, CHD etc.) and are exposed to

specific chemicals or medication (e.g. Anti-epileptic drugs; lithium etc.). These neonates undergo further history, examination, and investigations; namely, chest x-ray, electrocardiogram (ECG) and echocardiography. The most important diagnostic tool for CHD and CCHD is transthoracic echocardiography .[24.]

Paediatric Echocardiography and congenital heart disease:

Echocardiography has become the primary imaging tool in the diagnosis and assessment of congenital and acquired heart disease in infants, children, and adolescents.[24] Despite the significant progress in developed countries in diagnosing CHD, the same cannot be said in developing countries.[25,26]. In SSA, transthoracic echocardiography (TTE) is the ideal tool for cardiac assessment and considered the gold standard for diagnosing CHD. It is affordable, non-invasive, portable, and accurate in providing detailed anatomic, hemodynamic, and physiologic information about the paediatric heart.[24] In addition, it provides instantaneous and reproducible images at the point of care. Unfortunately, it remains difficult to access in most places.[27]

Echocardiography in the Neonatal unit:

Echocardiography has been a mainstay of neonatal intensive care units in developed countries.[37,38, 39, 40] Its use has evolved from the diagnosis of structural abnormalities and assessing pulmonary haemodynamics to more recent publications on their role in cardiopulmonary resuscitation[41]. It accounts for 78% of specific changes in clinical management[33]. Early diagnosis and intervention in CCHD in the neonatal period will potentially prevent up to 64% of neonatal deaths from CHD.[42]

Indication(s) for Paediatric echocardiography:

There have been numerous publications enumerating the indications for paediatric echocardiography across all age groups.[28] Most paediatricians agree with performing echocardiography for new-borns with cardiorespiratory symptoms, chromosomal abnormalities, and congenital non-cardiac anomalies [29,30,31].

Identifying indications for an echocardiogram is a major step in guiding the diagnosis and management of patients.[8] A recent position statement in 2020 by the Cardiovascular Imaging Department of the Brazilian society of cardiology and the Interamerican Society of Cardiology provides a comprehensive evidence-based indication for echocardiography. [32]

In the neonatal unit, echocardiography is performed to diagnose structural heart defects, evaluate cardiac function and pulmonary haemodynamic study (including pulmonary hypertension). [33] The combination of background clinical information and physical examination findings determine the appropriate indications for echocardiography in the neonatal period.

The indications for echocardiography in the neonatal period include family history of cardiac defect; antenatal diagnosis of CHD or arrhythmia; maternal drug, toxin or infection exposure; maternal chronic disease (e.g._SLE, pre-gestational diabetes); non cardiac malformation; cardiorespiratory symptoms (cyanosis, heart failure, shock, hypoxia, hypotension, arrhythmia) with or without murmur; asymptomatic murmur etc. [32]. With increasing research into and knowledge of the systemic disease and their relationship with cardiovascular disorders in the newborn, the pool of indications continue to expand. That notwithstanding, it is important that every unit comes up with a unit-based list of indications based on the epidemiology of cardiac pathology in the unit.[34] This will enhance the detection of CHD, improve efficiency in the utilisation of the service and improve the overall yield of echocardiography.

Yield of Paediatric echocardiography:

Despite limited studies, the yield of abnormal findings for paediatric echocardiography is generally considered high with abnormalities of structure and/or function being identified between 33% to about 70% of echocardiograms.[33,34,35] Studies carried in some urban outpatient clinics in SSA have reported similar rates.[11,10,36.] There have been no documented studies on the yield of echocardiography in a neonatal care unit in SSA. This could be because paediatric echocardiography services in the neonatal unit is still in the early stage in most parts of the continent. It can however be deduced that if the overall yield of paediatric echocardiography in detecting CHD is high then it should be higher in the neonatal unit which manages symptomatic and high-risk babies for CHD and CCHD. To bridge this knowledge gap, it has become important to establish bedside neonatal echocardiography services in neonatal units in the region to facilitate early diagnosis and documentation of the findings onto a data system. This will provide better understanding of the pattern of indication for echocardiography and diagnosis (and yield) of CHD and CCHD in our neonatal intensive care units.

1.2 RATIONALE FOR THE STUDY

The Inkosi Albert Luthuli Central Hospital (IALCH) is a specialised referral centre in the province of KwaZulu-Natal(KZN). The neonatal unit receives newborns from high-risk pregnancies requiring specialised care as well as newborns transferred from elsewhere requiring specialised neonatal services. The paediatric cardiology unit has had at least one qualified paediatric cardiologist performing or supervising the performance of echocardiograms in the neonatal unit. All information pertaining to the echocardiogram performed is entered into a central database system. The neonatal unit is partitioned into three clinical areas i.e. intensive care unit, isolation unit and high dependency unit. The unit has a general-purpose ultrasound that is used by the paediatric cardiology team to perform echocardiography. Requests for echocardiography is usually made by the neonatal team. The request comes in the form of brief clinical information and the indication(s) for echocardiogram. The paediatric cardiology team reviews the request and performs the study at the most opportune time based on the urgency and working schedule of the team. Upon completion of the study, a report is generated onto the hospital system and the relevant clinical management discussed with the neonatal team.

The indications for echocardiography in neonates are not well defined. In addition, the findings and impact on patient management has not been investigated. As a result of this, scarce specialised resource may not be providing targeted service to neonates who really need it while clinicians may be overwhelmed providing services with no clinical benefit. A better understanding of the indications for echocardiography and the outcome will help to refine the criteria for which echocardiography is requested. This will facilitate efficient utilisation of critical resources (both human and logistics).

1.3 STATEMENT OF PROBLEM/ RESEARCH QUESTION

Which indications for echocardiography are associated with a positive yield for congenital heart defects in the neonatal unit?

1.4 AIMS

To determine the indications for echocardiography associated with a positive yield for congenital heart defects in the neonatal intensive care unit over a 5-year period.

1.5 OBJECTIVES

1. To describe the primary indications of echocardiography performed over a 5-year period.
2. To describe the findings of echocardiography performed over a 5-year period.

CHAPTER 2
METHODOLOGY

2.1 SCOPE OF PROJECT

This a retrospective descriptive cross-sectional study using data from the 1st of January 2015 to 31stDecember 2019.

2.2 STUDY DESIGN

Study location:

The study was conducted at the Inkosi Albert Luthuli Central Hospital making use of electronic stored data base system.

Study population:

Neonates admitted to the neonatal unit who had an echocardiogram performed between the period 1st January 2015 to 31st December 2019. This will include both preterm and term neonates.

Sampling strategy:

This was a retrospective chart review of data entered into the Paediatric cardiology data base of the hospital. This data was inputted by a member of the paediatric cardiology team after the echocardiogram was performed. A simple search of the paediatric cardiology record for echocardiography performed in the neonatal unit over the study period was done. The clinical notes of each of the identified patients were reviewed manually to confirm the indication and findings of the echocardiography performed. These were then captured onto an excel spread sheet.

Sample size:

A total of 1010 patients were identified from the initial search. Unfortunately, 4 patients had incomplete data inputted into the system which could not be traced. The data of all 1006 patients (representing 99.6% of the total) were captured and analysed.

Inclusion criteria: All echocardiograms, with complete data, done in the neonatal intensive care unit over the study period were included in the study. All diagnosed cases of PDA (pathological or physiological) were included.

Exclusion criteria: All follow-up echocardiograms performed for the same indication and diagnosis in the same patient were excluded from the study. A follow-up echocardiogram refers to all subsequent studies performed for the same initial indication. e.g. if the initial indication for an echo was respiratory distress and the diagnosis is PDA, all follow up echocardiography study to monitor the size of the PDA were excluded.

2.3 DATA CAPTURE

Using a simple excel spread sheet, relevant details of all primary echocardiography studies done within the study period were captured.

Data was captured onto an excel spreadsheet. The data captured include:

- Hospital number
- Date of birth
- Mode of delivery
- Gestational age
- Gender
- Echocardiography: Date of request; Date study was done
- Primary indication for echocardiography
- Outcome of echocardiography study
- Clinical state of patient at the time of echocardiography
- Other significant echocardiography findings

2.4 STATISTICAL ANALYSIS

Software:

The statistical data analysis was conducted in R Statistical computing software of the R Core Team, 2020, version 3.6.3. The results were presented in the form of descriptive and inferential statistics.

Descriptive statistics:

Where applicable, the descriptive statistics of numerical measurements were summarized as the minimum, maximum, quartiles, interquartile range, means, standard deviation and the coefficient of variation. On the other hand, the categorical variables were described as counts and percentage frequencies where pie, simple and multiple bar charts were also used to visually display the categorical variables.

Two independent groups:

Depending on the distribution of the numerical variables between two independent groups, mean or median differences were assessed using either t-test or Wilcoxon respectively.

Test for independence:

To determine the association between categorical variables, a Chi-Square Test was used and when the distribution of the cross tabulations contained an expected value of less than five, a Fisher's exact test was applied. In the case of significant difference between the Chi-Square or Fisher exact test, a row wise paired z-test was used as a post hoc analysis following the omnibus tests (Chi-Square or Fisher exact test).

Significance level:

All the inferential statistical analysis tests will be conducted at 5% levels of significance.

Summary: The strength of the analysis is premised on the fact that 99.6% of available data in the population were analysed. "Positive Yield" for this study is defined as an abnormal finding on Echocardiogram. Data analysis was done with the assistance of a statistician.

2.5 LIMITATIONS TO THE STUDY

1. This is a retrospective study. This means that any incorrectly entered data or missing data will affect the results of the study and the conclusions.

2. In the absence of standardised indication for echocardiography, the primary data identifier is the patient hospital identity number which is captured once. This means that patients who had echocardiography done at various times for different indications had only the initial echocardiogram analysed. To address this limitation, future studies should be prospective and use the indications for echocardiography as the primary data identifier. This will ensure analysis of every indication for echocardiography in the population.

3. The lack of consensus on the definition of patent ductus arteriosus (PDA) in the neonatal period and especially in preterm neonates may have led to the inclusion of physiologic PDA amongst the diagnosis of CHD. Excluding all preterm infants and PDA in the study omits a critical patient population in the neonatal period. In this study, this cohort has been included in the analysis. In this study "PDA" is considered an "abnormal finding" and not a CHD due to reasons outlined.

2.6 ETHICAL CONSIDERATION

There was no direct or telephonic contact with patients or their caregiver or staff of the neonatal unit throughout the study. The study did not have any influence on ongoing patient management and duties of staff. Confidentiality was maintained as far as possible by ensuring that all data with categorical patient identifiers i.e., name, address, and telephone number remain with the researcher and were not available to the public or third party. In addition, access to electronic patient data was restricted by password and monitored by the hospital information technology unit.

The protocol of this study was reviewed and approved by the UKZN Biomedical Research Ethics Committee (Protocol reference number: BREC/00005961/2023). Site approval was also obtained from the Provincial research committee of KwaZulu-Natal, Department of Health Directorate, and the Inkosi Luthuli Central Hospital management. No external funding was sourced for the study and no financial benefit has been accrued from conducting the study.

The findings of the study will be made available to the Department of Health Directorate, KwaZulu-Natal Province; the Inkosi Albert Luthuli Central Hospital; Paediatric department; Paediatric cardiology unit and Neonatal Intensive care unit.

CHAPTER 3
RESULTS AND ANALYSIS

3.1 Table 1: Demographic characteristics

	Overall (N=1006)
Gender	
Male	546 (54.3%)
Female	458 (45.5%)
Indeterminate	2 (0.2%)
Age at time of ECHO in days	
Median(Q1-Q3)	4.00(2.00-11.0)
n(Min-Max)	1006(0-160)
Age at time of ECHO	
0-7 days	624 (62.0%)
8-14 days	136 (13.5%)
15-21 days	54 (5.4%)
21-28 days	42 (4.2%)
>28 days	150 (14.9%)
Gestation	
Preterm	520 (51.7%)
Term	486 (48.3%)
Delivery mode	
Normal vaginal delivery	444 (44.1%)
Caesarean section	557 (55.4%)
Emergency Caesarean section	5 (0.5%)

Table 1 shows a summary of the demographic characteristics of the patients. Data from a total of 1006 patients were extracted and analysed. Majority of the patients were male (54.3%). 0.2% of the patients had indeterminate gender at the time of ECHO. The median age at the time of ECHO was 4 days with 1st quartile age of 2 days and 3rd quartile age of 11 days. The maximum age was 160 days and a minimum of 1 day. Majority of the ECHOs were done in the first week of life (62.0%) with the least number done from the 3rd to the 4th week (4.2%). 14.9% of ECHOs were done after 28 days (these are patients who had remained in the neonatal unit after the neonatal age). More patients were delivered preterm+ (51.7%) and were mainly delivered via Caesarean section (55.9%).+ *Preterm is defined as babies born alive before 37 weeks of pregnancy are completed (WHO)*

3.2 Figure 1: Indications for echocardiography (I)

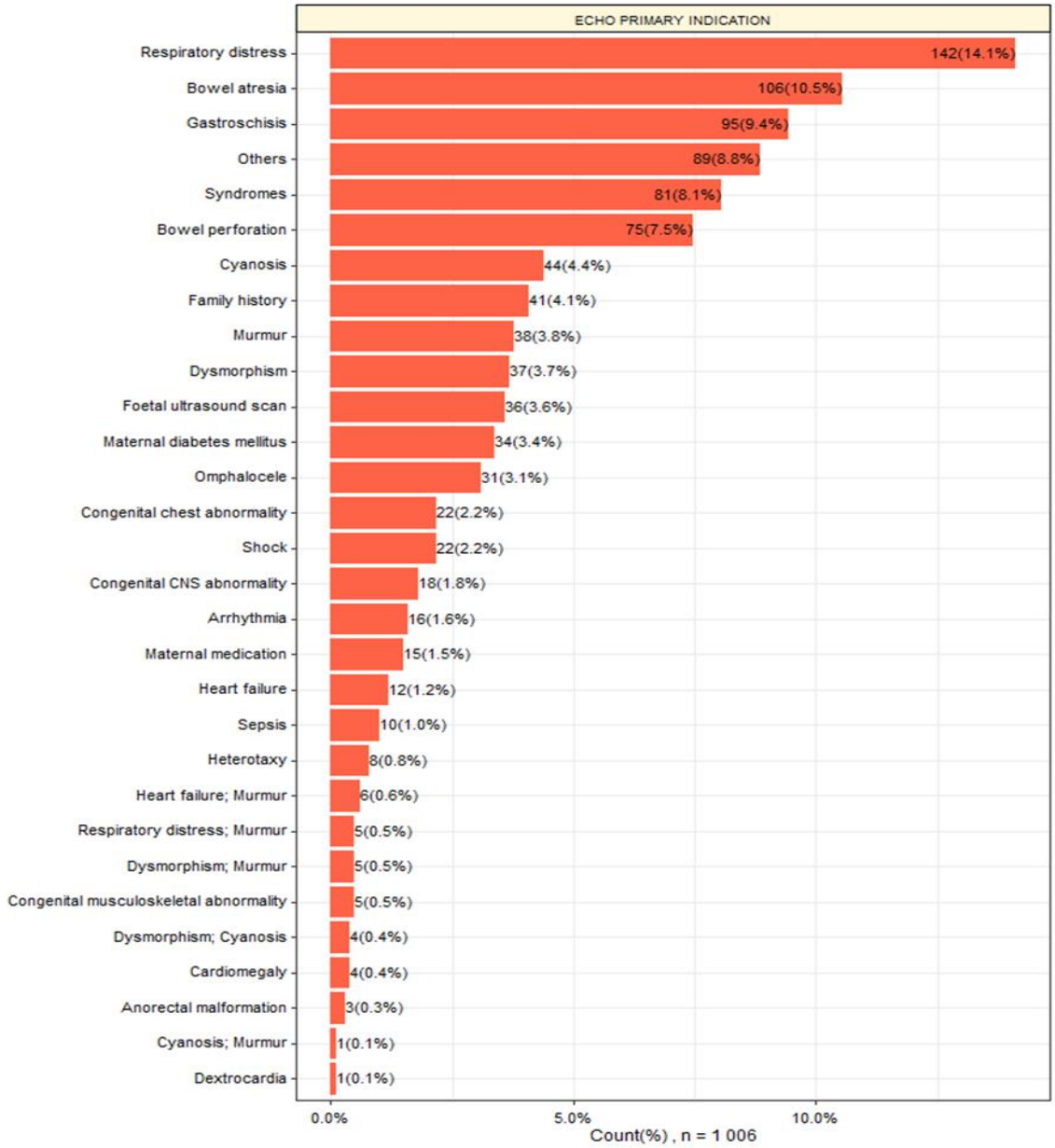

Figure 1 shows the indications for ECHO requested by the neonatal unit. The most common indication for echocardiography was respiratory distress (14.1%) with the remaining top 5 common causes being bowel atresia*(10.5%); gastroschisis (9.4%); Others** (8.8%); and syndromes (8.1%). The five least common indications include Dysmorphism with cyanosis (0.4%); cardiomegaly (0.4%); Anorectal malformation (0.3%); cyanosis with murmur (0.1%) and Dextrocardia (0.1%). Maternal factors include maternal diabetes (3.5%) and maternal medications known to cause congenital heart defects (1.5%).

** Bowel atresia includes oesophageal atresia; duodenal atresia and jejunal atresia. ** Others include embolised PICC line; conjoint twins; inborn error of metabolism; Thrombo-embolic phenomenon; multiple gestation; neonatal seizures; intra cranial bleed etc. ***NB: Foetal ultrasound aka "abnormal foetal ultrasound"*

3.3 Figure 2: Indication for echocardiography (II)

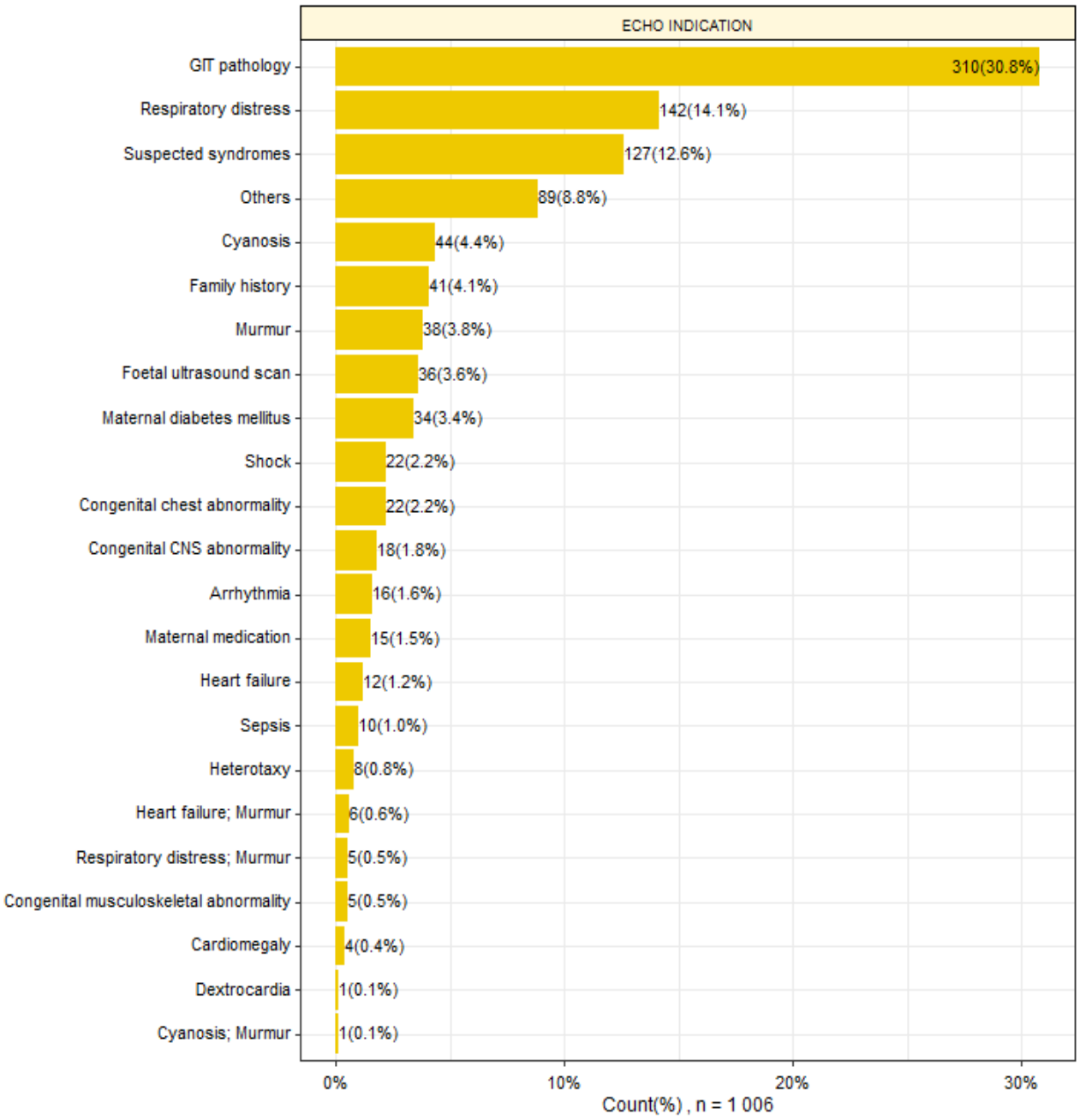

Figure 2 shows the indications for echocardiography which are analysed and grouped together All gastrointestinal pathologies from figure 1 collated and labelled as "GIT pathologies" (i.e. bowel atresia, gastroschisis, bowel perforation and anorectal malformation). Similarly, "syndromes" and "dysmorphism" from figure 1 are collated and labelled as "Suspected syndrome". The top five indications for echocardiography based on these changes are - GIT pathologies (30.8%); respiratory distress (14.1%); Suspected syndromes (12.6%); Others (8.8%) and Cyanosis (4.4%).

3.4 Figure 3: Outcome of echocardiograph for abnormal findings

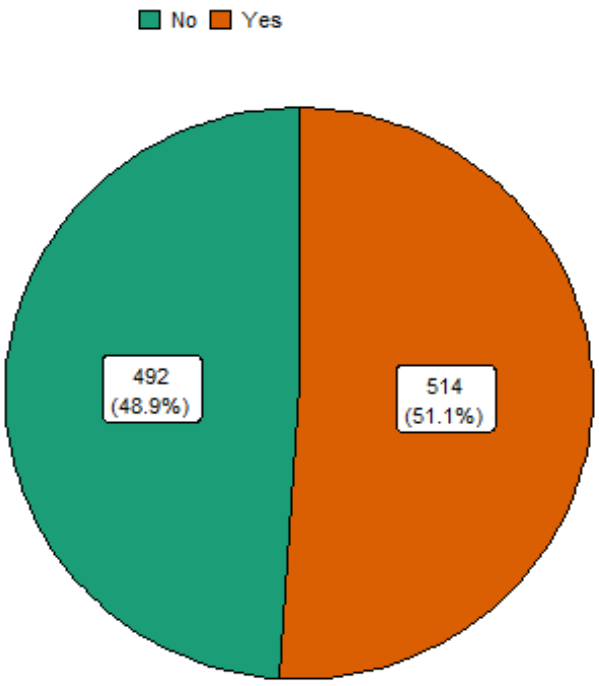

Figure 3 shows the outcome (Yield) of echocardiography. An almost equal number had normal (48.9%) and abnormal findings (51.1%) on echocardiography.

3.5 Figure 4: Distribution of abnormal findings

Figure 4 shows the distribution of CHD diagnosed on ECHO. The most frequent abnormal finding was PDA (55.5%) followed by VSD only (6.4%), VSD with PDA (3.95%); AVSD (3.9%); and Univentricular heart (3.7%) (top five defects). The least common defects where Common atrium, AP window and TAPVC each with a frequency of 0.2%.

3.6 Table 2: Indications for echocardiography and Outcome of echocardiography

Abnormal finding	No (N=492)	Yes (N=514)	p-value	Overall (N=1006)
ECHO primary indication			Chisq., p<0.001	
Respiratory distress	67 (13.6%)	75 (14.6%)	1.000	142 (14.1%)
Murmur	8 (1.6%)	30 (5.8%)	**0.012**	38 (3.8%)
Cyanosis	3 (0.6%)	41 (8.0%)	**<0.001**	44 (4.4%)
Arrhythmia	6 (1.2%)	10 (1.9%)	1.000	16 (1.6%)
Syndromes	32 (6.5%)	49 (9.5%)	1.000	81 (8.1%)
Dysmorphism	19 (3.9%)	18 (3.5%)	1.000	37 (3.7%)
Shock	9 (1.8%)	13 (2.5%)	1.000	22 (2.2%)
Heart failure	2 (0.4%)	10 (1.9%)	1.000	12 (1.2%)
Cardiomegaly	2 (0.4%)	2 (0.4%)	1.000	4 (0.4%)
Sepsis	7 (1.4%)	3 (0.6%)	1.000	10 (1.0%)
Dextrocardia	1 (0.2%)	0 (0.0%)	1.000	1 (0.1%)
Heterotaxy	0 (0.0%)	8 (1.6%)	0.231	8 (0.8%)
Family history	26 (5.3%)	15 (2.9%)	1.000	41 (4.1%)
Foetal ultrasound scan	3 (0.6%)	33 (6.4%)	**<0.001**	36 (3.6%)
Gastroschisis	63 (12.8%)	32 (6.2%)	**0.011**	95 (9.4%)
Omphalocele	17 (3.5%)	14 (2.7%)	1.000	31 (3.1%)
Anorectal malformation	2 (0.4%)	1 (0.2%)	1.000	3 (0.3%)
Congenital chest abnormality	16 (3.2%)	6 (1.2%)	0.897	22 (2.2%)
Congenital musculoskeletal abnormality	4 (0.8%)	1 (0.2%)	1.000	5 (0.5%)
Congenital CNS abnormality	15 (3.0%)	3 (0.6%)	0.104	18 (1.8%)
Bowel atresia	77 (15.7%)	29 (5.6%)	**<0.001**	106 (10.5%)
Bowel perforation	43 (8.7%)	32 (6.2%)	1.000	75 (7.5%)
Heart failure; Murmur	1 (0.2%)	5 (1.0%)	1.000	6 (0.6%)
Dysmorphism; Murmur	0 (0.0%)	5 (1.0%)	1.000	5 (0.5%)
Dysmorphism; Cyanosis	0 (0.0%)	4 (0.8%)	1.000	4 (0.4%)
Cyanosis; Murmur	0 (0.0%)	1 (0.2%)	1.000	1 (0.1%)
Respiratory distress; Murmur	0 (0.0%)	5 (1.0%)	1.000	5 (0.5%)
Maternal diabetes mellitus	20 (4.1%)	14 (2.7%)	1.000	34 (3.4%)
Maternal medication	9 (1.8%)	6 (1.2%)	1.000	15 (1.5%)
Others	40 (8.1%)	49 (9.5%)	1.000	89 (8.8%)

Table 2 compares the indication and findings of echocardiography. Using a P value of 0.05, the indications that significantly predict an abnormal finding (Yes) on echocardiography were murmur; cyanosis; abnormal foetal ultrasound and bowel atresia.

3.7 Table 3: Demographic characteristics and Outcome of echocardiography

Abnormal findings	No (N=492)	Yes (N=514)	p-value	Overall (N=1006)
Demographic characteristic				
Gender			Chisq., p = 0.160	
Male	278 (56.5%)	268 (52.1%)		546 (54.3%)
Female	214 (43.5%)	244 (47.5%)		458 (45.5%)
Indeterminate	0 (0.0%)	2 (0.4%)		2 (0.2%)
Age at time of ECHO in days			Ranksum	
Median(Q1-Q3)	5.00(2.00-11.0)	3.00(1.00-11.0)	0.002	4.00(2.00-11.0)
n(Min-Max)	492(0-160)	514(0-102)		1006(0-160)
Age at time of ECHO			Chisq., p = 0.240	
0-7 days	296 (60.2%)	328 (63.8%)		624 (62.0%)
8-14 days	77 (15.7%)	59 (11.5%)		136 (13.5%)
15-21 days	30 (6.1%)	24 (4.7%)		54 (5.4%)
21-28 days	18 (3.7%)	24 (4.7%)		42 (4.2%)
>28 days	71 (14.4%)	79 (15.4%)		150 (14.9%)
Gestation			Chisq., p = 0.240	
Preterm	245 (49.8%)	275 (53.5%)		520 (51.7%)
Term	247 (50.2%)	239 (46.5%)		486 (48.3%)
Delivery mode			Chisq., p = 0.074	
Normal vaginal delivery	235 (47.8%)	209 (40.7%)		444 (44.1%)
Caesarean section	255 (51.8%)	302 (58.8%)		557 (55.4%)
Emergency Caesarean section	2 (0.4%)	3 (0.6%)		5 (0.5%)

Table 3 compares the demographic characteristic of patients and abnormal findings on echocardiography. Using a p value < 0.05, none of the demographic characteristic could significantly predict the outcome of echocardiography.

3.8 Figure 5: Comparing Distribution of abnormal findings in preterm and term neonates

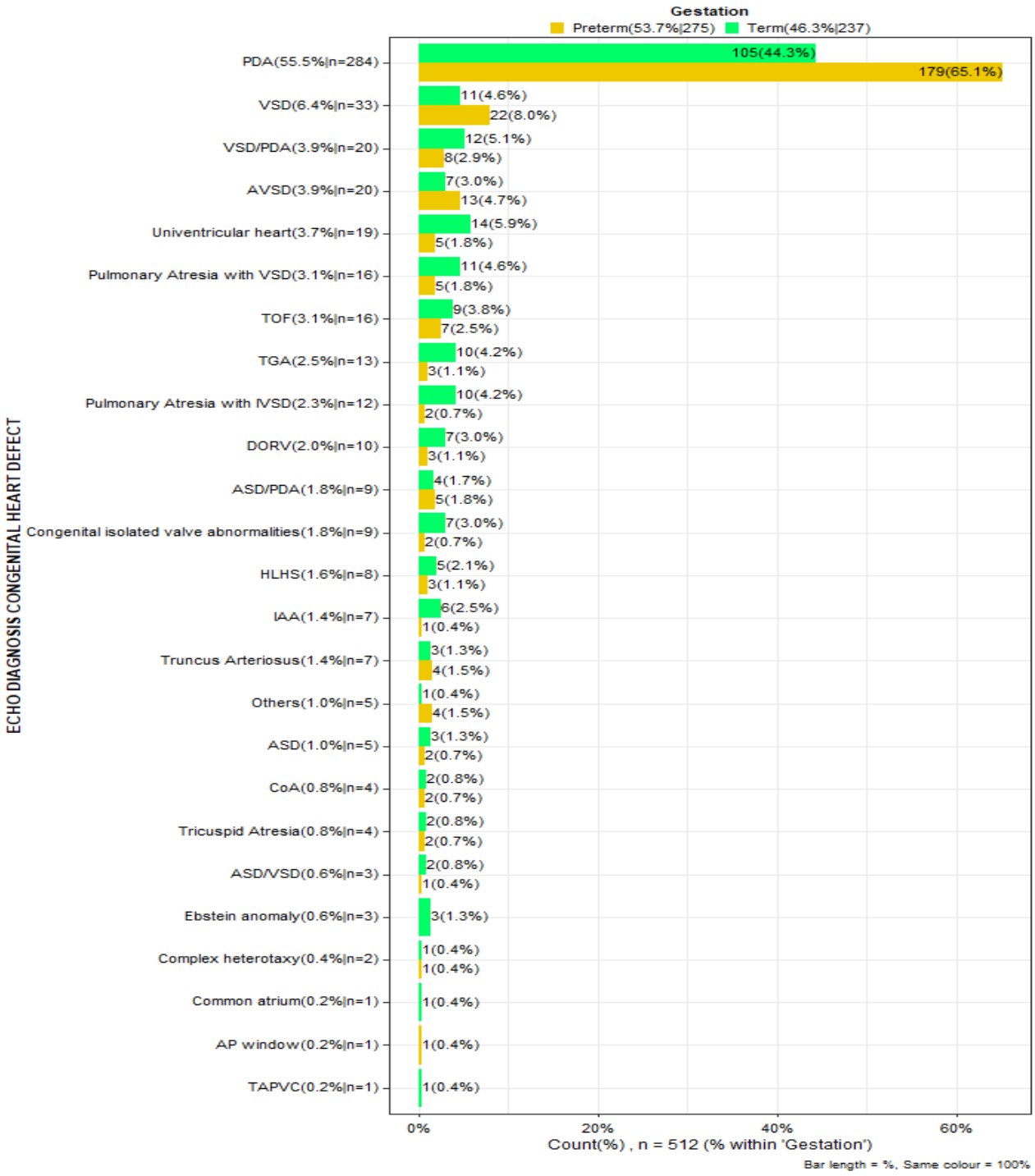

Figure 6 shows the distribution of abnormal finding amongst preterm and term neonates. The most frequent abnormal finding for both term and preterm neonates is PDA. The most frequent acyanotic congenital heart defect for preterm and term neonates is PDA, followed by ventricular septal defect(VSD). The most frequent cyanotic congenital heart defect for preterm and term neonates were Tetralogy of Fallot (TOF) and univentricular heart, respectively.

3.9 Figure 6: Distribution of CHD (excluding PDA)

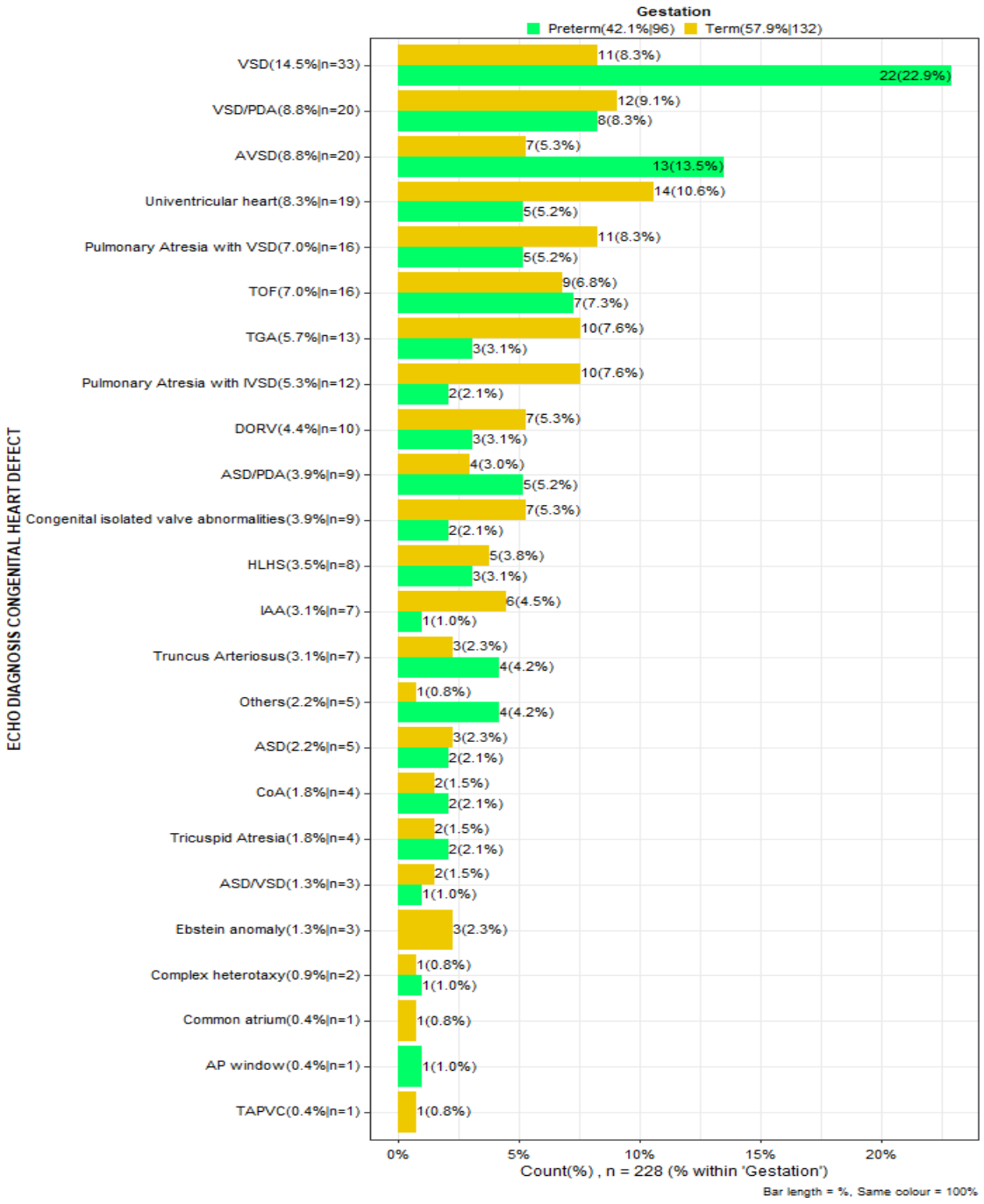

Figure 6 shows the distribution of abnormal findings on echocardiography excluding isolated PDA from the analysis. Amongst the preterm neonates, the most frequent acyanotic and cyanotic CHD were VSD and TOF, respectively. Amongst the term neonates, the most frequent acyanotic and cyanotic CHD respectively were VSD and univentricular heart.

CHAPTER 4
DISCUSSION

4.1 Indications for echocardiography:

There were 30 indications identified for echocardiography in this study. The most stated indication for echocardiography (figure 1) was respiratory distress (14.1%). This is consistent with the well documented observation that the commonest clinical symptom in the neonatal unit is respiratory distress. Cardiovascular clinical features of cyanosis (4.4%) and murmur (3.8%) were amongst the most common indications. When all the GIT pathologies i.e. gastroschisis, omphalocele, anorectal malformation, bowel perforation and bowel atresia were collated and labelled as "GIT pathologies" (figure 2), it became the most common indication (30.8%) followed closely by respiratory distress.

The most likely reason for the over representation of non-cardiovascular congenital abnormalities and GIT pathologies is that neonates were specifically referred to the study location (IALCH-NICU) from every public facility in the province for the management of these defects. The least common indication were patients with combined clinical features of cyanosis and murmur (1%) as well as dextrocardia (1%).

Overall, the indications identified in the study appeared appropriate and consistent with numerous published indications for echocardiography in the neonatal unit in developed countries. These include recently published works by the American Society of Echocardiography (ASE) [35,41]; European Association of Echocardiography (EAE) and the Association for European Paediatric Cardiologists (AEPC) [43,44,45] . This is also reported in many other publications.[20,46]

These publications also emphasised the importance of periodical review of the indications for echocardiography in the neonatal unit, a position consistent with the general protocol and guidelines for echocardiography published by the Paediatric Cardiac Society of South Africa (PCSSA) in 2007 [47]. A major limitation, however, is the lack of standardised indications for echocardiography from the IALCH-NICU. Standardising indications based on the findings of this study would facilitate more accurate information for future audits in this population.

4.2 Yield from Echocardiography:

This study was conducted in a neonatal unit in SSA. To my knowledge this in the first of its kind devoted to the yield in the neonatal period compared to others like Billa et al which looked at the yield from birth to 18 years with the lowest age range of 0 to 3 months and a positive yield for abnormal findings from echocardiography of 34%. [49]

The overall positive yield for abnormal echocardiography over the study period was 51%. This is comparable to other published data. The yield of abnormal findings for paediatric echocardiography is considered high with abnormalities of structure and/or function being identified between 33 to 70% .[33,34,35] Studies carried out in some urban outpatient clinics in SSA have reported similar range of rates. [10,11,36]

The study site is a quaternary referral centre which accepts ill babies. These babies usually have a high suspicion for CHD. This invariably results in a low threshold for requesting echocardiography with a resultant high positive yield. Furthermore, the availability of foetal ultrasound during the antenatal period has resulted in early diagnosis of suspected CHD. These babies are admitted to the neonatal unit soon after delivery and are mandated to have a cardiac evaluation including echocardiography. This will invariably increase probability of an abnormal finding. From Table 2, 92% of neonates with abnormal foetal ultrasound had an abnormal finding on echocardiography. The lack of standardised indication to scrutinise the request for echocardiography may have contributed to the high percentage of echocardiography with normal findings. This cohort will need to be studied further.

The most common indication for echocardiography was respiratory distress (table 2). However, only 53% of these patients had a positive yield (abnormal finding) for echocardiography compared to 92% for patients with abnormal foetal ultrasound. It can be inferred that improving clinical examination of patients with respiratory distress to sift out those unlikely to have CHD as well as encouraging the performance of foetal ultrasound in high-risk pregnancies will result in an improved overall positive yield for echocardiography in the neonates. At present a comprehensive foetal anomaly scan is not part of routine antenatal care within the public service in South Africa.[51] Should this become standard of care, the diagnosis of neonatal congenital heart disease is likely to improve significantly.

This study provides useful information on the efficiency of the echocardiography service being provided in the neonatal unit. However, it is important to note that both normal and abnormal echocardiography findings are useful in making critical clinical management decisions that will potentially save lives and reduce the cost of care. In some studies, the impact of echocardiography has been reported to contribute as much as 78% to specific changes in clinical management[33] . However, the impact of echocardiography on the management of neonates in this cohort was not the objective of this study.

4.3 Distribution of congenital heart defects:

A total of 25 different CHDs were identified in the study (figure 4). These included left to right shunt heart defects (ASD, VSD and AVSD); left ventricular out flow tract lesions (COA; HLHS; IAA); cyanotic congenital heart defects (TOF; PA with VSD; PA with IVS; TA; Truncus arteriosus; EA; TAPVC;) and univentricular heart anatomy. The most common CHD identified were VSD, AVSD,

univentricular heart and TOF (inclusive of PA with VSD). With the exception of PDA which had a very high prevalence of 50% compared to the widely published 5-10% in the general population, the data is consistent with many published data on the distribution of CHD in the paediatric age group worldwide.[11,34,36.] In SSA, the distribution is largely consistent with the recently published results of the PartneRships in cOngeniTal hEart disease (PROTEA) project, a prospective Southern African Multicentre CHD registry and biorepository.[50]

The distribution of CHD (figure 5) was significantly skewed by the diagnosis of PDA constituting more than 50% of CHD. This is inclusive of both preterm and term neonates. Most patients were preterm. The prevalence of PDA in preterm neonates is documented as between 20% to 60% depending on the population and diagnostic criteria. [48] This may explain the high prevalence of PDA in this study population. When the preterm and term neonates were separated, the prevalence of PDA remained the highest amongst the term babies. (figure 6).

The definition of PDA in the neonatal period is known to be controversial and often centre or research dependent. The difference between a physiologic and pathologic PDA is usually based on age at which the PDA was diagnosed, its haemodynamic significance and natural history. It is widely defined as the failure of the ductus arteriosus to close within 72 hours after birth with majority occurring within 24 hours. The evidence for this is not strong. The easiest way to resolve the physiologic vs pathologic ductus arteriosus would be if it were possible to see how many needed to be closed or had PDA present on subsequent visits. This, however, was outside the scope of the study. Another factor skewing the high frequency of PDA is that some of these patients may have been referred for PDA closure specifically. It is not clear from the data what criteria for a diagnosis of PDA was employed for the data entry at the time of echocardiography. It is for this reason that in this study all PDAs are considered an abnormal finding on echocardiography (not necessarily a CHD) and are analysed together as one variable.

From figure 6, when PDA and preterm are excluded from the analysis, the most common acyanotic CHD amongst term neonates is VSD and the most common cyanotic CHDs are univentricular heart, TOF and TGA. This is also consistent with the distribution of CHDs in the neonatal period[11,34,36]

Several studies identified TGA as the commonest cyanotic CHD in the neonatal period. In this study it was the third behind univentricular heart and TOF. This is consistent with the work by Antke et al in Tanzania. [11,34,] It is a well-known fact that neonates with TGA appear normal **at birth** and are subsequently discharged only to present weeks later in an acute cyanotic state when the patent foramen ovale (PFO) or PDA becomes more restrictive. A high index of suspicion and good clinical assessment including pulse oximetry is critical in the early diagnosis of TGA.

4.4 Indication (s) associated with significant yield for congenital heart defects:

Using a p value <0.05, the probability of identifying a CHD was high when the indication for echocardiography were cyanosis, murmur, and abnormal foetal ultrasound diagnosis (table 2). Conversely, the probability of not identifying a CHD was higher in patients with gastroschisis or bowel atresia (Table 2). No demographic characteristics was associated with a significant difference in the probability of a positive or negative yield for CHD (table 1).

Respiratory distress and heart failure as stand-alone indications showed no significant difference in the outcome of echocardiography i.e. there was an almost equal number of patients with or without CHD and any observed difference was due to chance. However, when combined with "murmur" there is a significant difference in the outcome of echocardiography with most patient having a diagnosis of CHD. This means that clinical evaluation of murmur in the neonatal period increases the probability of CHD on echocardiography. This observation is made solely on analysis of secondary data generated from individual primary data rather than from actual patients with respiratory distress, heart failure and a murmur and therefore its clinical application must be made cautiously.

The designation of positive and negative yield for CHD is to inform the magnitude of clinical suspicion and not to dismiss the outcomes entirely no matter how small the yield. For example, majority of patients with non- cardiac congenital abnormalities (58.9%) had structurally normal hearts (table 2). Despite this, the 41.1% of patient with abnormal echocardiograms for this indication represent a significant number clinically. Similarly, in table 2, majority of patients with gastroschisis (66.3%) had a normal echocardiogram. However, the 33.7% that had abnormal echocardiograms represent a clinically significant number.

CHAPTER 5
CONCLUSION

This study is unique in that it studied indications for, and outcomes of echocardiography compared to other studies on paediatric echocardiography in SSA that studied only the outcomes of paediatric echocardiography. Furthermore, this study was conducted amongst in-patients in the neonatal intensive care unit compared to other studies conducted at the outpatient department (OPD). [10,11,36] Conclusions are drawn on analysis with p valves of <0.05.

The overall positive yield for abnormal finding on echocardiography in the neonatal unit of the IALCH over the study period was 51%. Although this is consistent with the widely published range of 30-70%, it can be higher with improved clinical evaluation and indication especially since this is not a "normal" population of neonates but a cohort of mostly ill neonates.[33]

The commonest primary indication for echocardiography was respiratory distress. There was however no significant difference in the outcomes of echocardiography i.e. an almost equal number of them either had normal or abnormal finding on echocardiography. Any observed difference is entirely due to chance.

However, secondary analysis with combined respiratory distress, murmur and heart failure showed that a considerable number had abnormal findings on echocardiography. Any future protocol for targeted neonatal echocardiography in the neonatal unit must stress the need to evaluate neonates with respiratory distress thoroughly to identify additional features of heart failure and murmur. This will improve the yield of discovering abnormal findings on echocardiography whilst redirecting attention to other causes of respiratory distress.

Primary indications with a significant number of abnormal findings on echocardiography are cyanosis, murmur and suspected CHD on foetal ultrasound scan. This means that patients with these characteristics should have a lower threshold for obtaining an echocardiography even if physical examination with pulse oximetry initially is normal.

Conversely, when the indication is gastroschisis or bowel atresia a significant number had normal findings on echocardiography. On secondary analysis, the combined indication of "GIT pathologies" and "non-cardiac abnormalities" also had a considerable number with normal findings on echocardiography. Although these patients should have a higher threshold for obtaining echocardiography, a thorough clinical examination with pulse oximetry should suffice in most cases.

The commonest abnormality on echocardiography was PDA (55.5%). This is not surprising considering almost 49.8% of the patients were preterm in whom the ductus arteriosus physiologically takes a longer time to close compared to term babies. Additionally, for both term and preterm babies, the distinction

between physiologic and pathologic PDAs was not as clear as highlighted previously. The most common CHD is VSD which is closely followed by other acyanotic CHD, AVSD and ASD. The most common cyanotic CHDs were univentricular heart, TOF and TGA.

There were significant limitations to the study. Key amongst these was the absence of standardised indication for echocardiography as well as the challenge of distinguishing between significant and non-significant echocardiographic abnormalities in certain cases. It is my recommendation that the Paediatric cardiology unit of IALCH completes the process of standardising the indications for echocardiography.

Areas for future research include investigating the impact of echocardiography in critical clinical decision making; investigating the accuracy of echocardiography in the diagnosis of functional abnormalities such as pulmonary hypertension and ventricular dysfunction in critically ill neonates; and investigating the challenges of targeted neonatal echocardiography screening by neonatologists in the intensive care unit.

CHAPTER 6
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CHAPTER 7
APPENDIX

Appendix I – Final approved Protocol

Title: Transthoracic Echocardiography in a Neonatal intensive care unit- Indications and Positive Yield. A retrospective descriptive cross-sectional study.

By: Dr. Della Adzosii, Paediatric cardiology fellow. Student Number: 221117240

Supervisor: Dr. Ebrahim Hoosen

1. Introduction/ Background:

A congenital heart defect (CHD) is a structural abnormality of the heart and/or great vessels that is present at birth.[1] CHD are the commonest congenital birth defects worldwide and are a significant cause of morbidity and mortality. Despite regional variability of a prevalence of between 4-50/1000 live births; the accepted global prevalence is eight (8) cases per 1000 live births. [2,3] This represents approximately 1.35 million newborns with CHD each year.[4,5]

CHD data in Africa is gaining more attention, as highlighted by recent articles .[6, 7] A review in 2013 estimated that 12,000 children are born with CHD in South Africa annually.[8]

CHD contributes significantly to neonatal and infant mortality[9, 10, 11] and accounts for 3% of all infant deaths representing about 30 to 50% of infant mortality from congenital malformations worldwide.[12] Furthermore, approximately 70% of infant deaths attributable to congenital heart defects occur in the neonatal period.

Sub-Saharan Africa has the highest neonatal mortality rate in the world (27 deaths per 1000 live births) with 43% of global newborn deaths [13] Preterm births; intrapartum-related complications; infections and birth defects are the leading causes of most neonatal deaths.[13] A close look at the common causes of newborn deaths highlights the impact of congenital heart disease on each of them. CHD is a risk factor for preterm delivery and intrapartum asphyxia; it increases the risk of infection (especially with those that increase pulmonary circulation).[13]

The January 2022 World Health Organization (WHO) statement on newborn mortality mentions that "Children who die within the first 28 days of birth suffer from conditions and diseases associated with lack of quality care at or immediately after birth and in the first days of life".[13] It is therefore important that in addressing neonatal mortality rates, we improve the quality of care for neonatal CHD beginning with early screening and diagnosis.

Critical congenital heart disease (CCHD) represents the severest forms of congenital heart disease that require early intervention in the newborn period to avert mortality. Unfortunately, many of these babies appear healthy at first and may be sent home only to present 24 hours to 48 hours later critically ill.[14, 15] Screening for CCHD is necessary for timeous intervention. Like with all screening modalities, newborn screening for CHD must be safe, cheap, easily accessible, and useable with high sensitivity and specificity. The relatively low prevalence of CCHD means that any screening tool must me extremely accurate

The first opportunity for many newborns in developing countries or resource poor centres for early screening of CHD are the comprehensive newborn examination and pulse oximetry. In the absence of essential newborn examination and pulse oximetry by a trained person, a considerable number of healthy-looking newborns with CHD are missed and sent home only to die suddenly, return critically ill or be identified after the optimal opportunity for intervention has passed. Many centres, including those in developing countries, have adopted essential newborn screen with pulse oximetry as routine protocol. Such a programme, however, is only effective if it is followed by 2D echocardiography.[16]

Many centres in South Africa still lack the equipment, skill, and work force to provide complementary echocardiography following a positive pulse oximetry screen. Where it is available, training and service provision is often not guided by recommended standards of performance including appropriate indications for use. [17]

Echocardiography is routinely and easily available in neonatal intensive care units in developed countries.[18, 19, 20, 21]. In South Africa however, there is limited availability and access. While the availability of echocardiography is improving, the availability of qualified paediatric cardiologists remains a challenge, even in well-resourced

environments.[22] Training of other role players such as neonatologists to perform initial screening or "targeted" studies is a solution in some settings.[23, 24] In South Africa and the developing world, access to echocardiography is even more severely constrained and criteria for performing echocardiography need to be reviewed to ensure that patients on one hand have appropriate diagnoses made while on the other hand limited resources are not strained or abused. There is currently limited consensus on the indications for echocardiography in newborns, and while some general guidelines and protocols exist in developed countries, there is none for limited resource environments.

For development of such guidelines, evaluation and review of current practice would play a key role in identifying inefficiencies that require addressing.[25]

2. Purpose of the study:

Neonatal care units around the world have advanced in developing guidelines for the training and performance of neonatal echocardiogram by a neonatologist. This study will determine the clinical scenarios that are strongly related to a positive yield from neonatal echocardiography and provide initial information towards the development of local guidelines.

2.1. Research Question

What indications for Echocardiography in the neonatal period are associated with a high Positive yield?

2.2. Aim:

1. To determine the indications associated with a Positive Yield from Transthoracic echocardiograph performed at the Inkosi Albert Luthuli Central Hospital Neonatal intensive care.

2.3. Objectives:

1. To describe the primary indications and the outcome of echocardiography performed in a neonatal unit by performing a retrospective chart review.

2. To further determine which indications that are related to a positive yield for congenital heart disease.

3. Methodology:

3.1 Study location

Inkosi Albert Luthuli Central Hospital

3.2. Study setting

The Inkosi Albert Luthuli Central Hospital is the referral centre for specialized services for the province of KwaZulu-Natal. The neonatal unit receives newborns at IALCH from high-risk pregnancies requiring specialized care as well as newborns transferred from elsewhere requiring specialized neonatal services not available elsewhere. The unit has a general-purpose ultrasound used by the paediatric cardiology team to perform an echocardiogram over the study period, the paediatric cardiology unit has had at least one qualified paediatric cardiologist performing or supervising the performance of echocardiograms in the neonatal unit. All information pertaining to the echocardiogram performed is entered into a central database system.

3.3 Scope of Project

This a retrospective descriptive cross-sectional study.

1. Study population:

   Neonates admitted to the neonatal unit who had an echocardiogram performed between the period 1st January 2015 to 31st December 2019. This will include both preterm and term neonates.

2. Sampling strategy:

   This will be a retrospective chart review.

3. Sample size:

   The echocardiography database will be surveyed for the period 1st January 2015 to 31st December 2019 to identify all new echocardiogram studies performed in the neonatal unit. This is estimated to be one thousand over the period. A new echocardiogram study is the first echocardiogram performed for the neonate in the neonatal unit for a specific indication.

4. Sampling method:

   Using a simple excel spread sheet, relevant detail of all first-time echocardiography studies done within the study period will be captured.

5. Inclusion criteria:

   All neonates in the unit who had an echocardiogram done over the study period will be included in the study.

6. Exclusion criteria

   All follow-up echocardiograms for the same indication in the same patient will be excluded from the study. A follow-up echocardiogram refers to all subsequent studied performed for the same initial indication.

4. **Data Entry:**

Data will be entered into an Excel spreadsheet. Data to be collected will include:

1. Hospital number
2. Date of birth
3. Mode of delivery
4. Gestational age
5. Gender
6. Date of request for Echocardiogram
7. Primary indication
8. Date of Echocardiogram study
9. Outcome of Echocardiogram study
10. Clinical state at the time of Echocardiogram
11. Other findings of note

Appendix 1 shows the flow chart for the data extraction

5. **Statistical analysis:**

Data will be analyzed using Stata v13 statistical software, and a p-value of <0.05 will be considered statistically significant. Descriptive statistics will be calculated using the mean with standard deviation and frequency distributions. Categorical variables will be analyzed using the Chi-square test/ Fisher's test, while multivariable analysis will be done using logistic regression. "Positive Yield" for this study is defined as an echocardiogram diagnosis of a significant structural abnormality.

6. **Study duration:**

The study will commence once full ethics approval is obtained. This is estimated to be complete by the end of July 2023. It will take about 3 months to collect data, 1 month to analyze and present the data and 2 months to complete the final work. It is expected to be completed by 30th March 2024.

7. **Limitations to the study:**

The study is retrospective and only data already recorded can be obtained. Where indications are not clearly stated in a predefined format, the researcher will have to review the patient folder in detail to arrive at the most likely indication. This will introduce an element of observer bias.

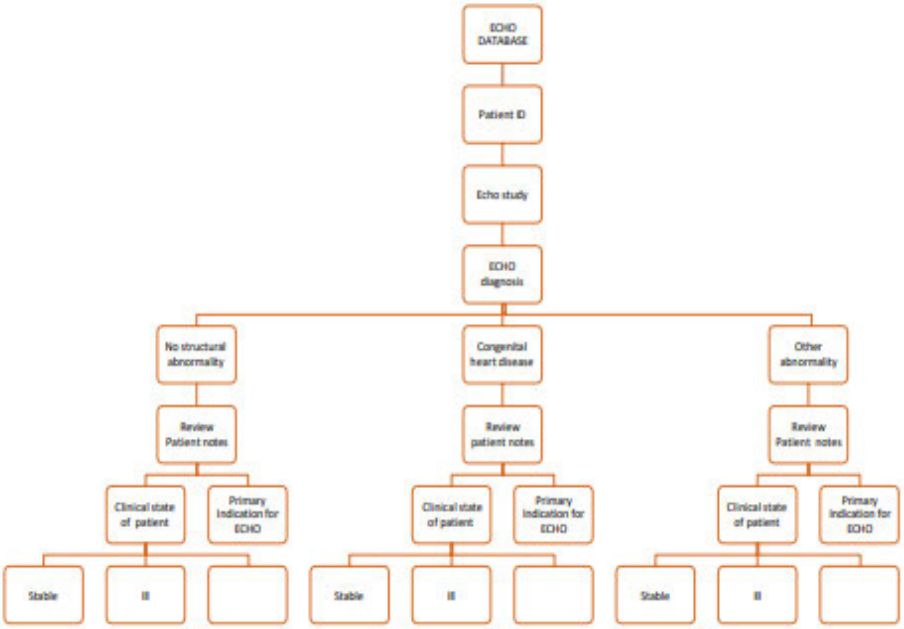
8. **Ethical consideration:**

The study will have no influence on patient management and should not affect the institution, the patients, or their caretakers. Confidentiality will be maintained as far as possible by ensuring that all data with patient identifiers i.e., name, address, the telephone and hospital numbers remain with the researcher and are not available to the public or third party. In addition, access electronic patient data is restricted by password and monitored by the Hospital IT unit.

9. **Budget: No budget required**

Appendix 1

Figure 1- Flow chart for Data extraction from Echo data base and patient notes



Reference:

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Appendix II: Ethical approval letter from BREC/Post graduate office

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

14 December 2023

Dr Della Adzosii (221117240)
School of Clinical Medicine
Medical School

Dear Dr Adzosii,

Protocol reference number: BREC/00005961/2023
Project title: Transthoracic echocardiograph in a Neonatal Intensive Care Unit- Indications, Yield and spectrum of congenital heart disease identified. A retrospective descriptive cross-sectional study.
Degree: MMedSc

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 14 December 2023. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 14 December 2023. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on RIG on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 13 February 2024.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za

Appendix III – Hospital Approval letter 1

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

NKOSI ALBERT LUTHULI CENTRAL HOSPITAL
Private Bag X03, Mayville, 4058
00 Vusi Mzimela (Bellair) Road, Mayville,4091
Tel: 031 240 1059 Fax: 031 240 1005 Email: Ursula.john@ialch.co.za
OFFICE OF THE MEDICAL MANAGER

Reference: BREC 000059612023
Enquiries: Medical Management

2 October 2023

Dr D Adzosii (221117240)
School of Clinical Medicine
Medical School

Dear Dr Adzosii

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Transthoracic echocardiograph in a Neonatal Intensive Care Unit-Indications, Yield and spectrum of congenital heart disease identified. A retrospective descriptive cross-sectional study.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted]

Dr L P Mtshali
Medical Manager

GROWING KWAZULU-NATAL TOGETHER

Appendix IV: Hospital Approval Letter 2

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Physical Address 800 Vusi Mzimela Road, Mayville - 4058
Postal Address: Private bag X03 Mayville – 4058
Tel: 031 240 1124 Fax: 031 240 1005 Email: linda.mtshali@ialch.co.za
www.kznhealth.gov.za

DIRECTORATE:
OFFICE OF THE MEDICAL MANAGER
INKOSI ALBERT LUTHULI CENTRAL HOSPITAL

Reference: BREC00005961/2023
Enquiries: Dr L P Mtshali

2 October 2023

Dr D Adzosii (221117240)
School of Clinical Medicine
Medical School

Dear Dr Adzosii

Re: Approved Research: Ref No: BREC/00005961/2023:Transthoracic echocardiograph in a Neonatal Intensive Care Unit-Indications, Yield and spectrum of congenital heart disease identified. A retrospective descriptive cross-sectional study.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above-mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

- The application is an online process by logging on to: HTTP://NHRD.HEALTH.GOV.ZA and follow the steps as indicated on the Provincial Health Research page.

Yours faithfully

[redacted]

Dr L P Mtshali
Medical Manager

Appendix V: Provincial Health Research Committee Approval

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:

Health Research & Knowledge Management

NHRD Ref: KZ_202310_036

Dear Dr D Adzosii
(UKZN)

Approval of research

1. The research proposal titled **'Transthoracic Echocardiography in a Neonatal intensive care unit- Indications and Positive Yield. A retrospective descriptive cross-sectional study'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. ***Kindly liaise with the facility manager BEFORE your research begins.***
      This is to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Mr. X Xaba on 033-395 2805.

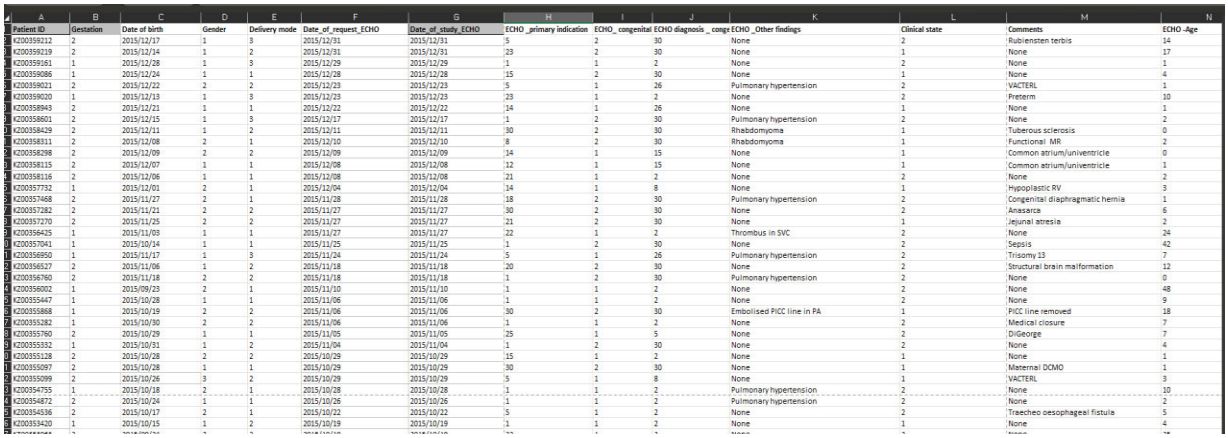
Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Provincial Health Research Committee
Date: 31/10/2023

GROWING KWAZULU-NATAL TOGETHER

Appendix VI: Data collection Excel spreadsheet



	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	Patient ID	Gestation	Date of birth	Gender	Delivery mode	Date_of_request_ECHO	Date_of_study_ECHO	ECHO _primary indication	ECHO_ congenital	ECHO diagnosis _ congen	ECHO _Other findings	Clinical state	Comments	ECHO -Age
2	KZ00359212	2	2015/12/17	1	3	2015/12/31	2015/12/31	5	2	30	None	2	Rubiensten terbis	14
3	KZ00359219	2	2015/12/14	1	2	2015/12/31	2015/12/31	23	2	30	None	1	None	17
4	KZ00359161	1	2015/12/28	1	3	2015/12/29	2015/12/29	1	1	2	None	2	None	1
5	KZ00359086	1	2015/12/24	1	1	2015/12/28	2015/12/28	15	2	30	None	1	None	4
6	KZ00359021	2	2015/12/22	2	2	2015/12/23	2015/12/23	5	1	26	Pulmonary hypertension	2	VACTERL	1
7	KZ00359020	1	2015/12/13	1	3	2015/12/23	2015/12/23	23	1	2	None	2	Preterm	10
8	KZ00358943	2	2015/12/21	1	1	2015/12/22	2015/12/22	14	1	26	None	1	None	1
9	KZ00358601	2	2015/12/15	1	3	2015/12/17	2015/12/17	1	2	30	Pulmonary hypertension	2	None	2
10	KZ00358429	2	2015/12/11	1	2	2015/12/11	2015/12/11	30	2	30	Rhabdomyoma	1	Tuberous sclerosis	0
11	KZ00358311	2	2015/12/08	2	1	2015/12/10	2015/12/10	8	2	30	Rhabdomyoma	1	Functional MR	2
12	KZ00358298	2	2015/12/09	2	2	2015/12/09	2015/12/09	14	1	15	None	1	Common atrium/univentricle	0
13	KZ00358115	2	2015/12/07	1	1	2015/12/08	2015/12/08	12	1	15	None	1	Common atrium/univentricle	1
14	KZ00358116	2	2015/12/06	1	1	2015/12/08	2015/12/08	21	1	2	None	2	None	2
15	KZ00357732	1	2015/12/01	2	1	2015/12/04	2015/12/04	14	1	8	None	1	Hypoplastic RV	3
16	KZ00357468	2	2015/11/27	2	1	2015/11/28	2015/11/28	18	2	30	Pulmonary hypertension	2	Congenital diaphragmatic hernia	1
17	KZ00357282	2	2015/11/21	2	2	2015/11/27	2015/11/27	30	2	30	None	2	Anasarca	6
18	KZ00357270	2	2015/11/25	2	2	2015/11/27	2015/11/27	21	2	30	None	1	Jejunal atresia	2
19	KZ00356425	1	2015/11/03	1	1	2015/11/27	2015/11/27	22	1	2	Thrombus in SVC	2	None	24
20	KZ00357041	1	2015/10/14	1	1	2015/11/25	2015/11/25	1	2	30	None	2	Sepsis	42
21	KZ00356950	1	2015/11/17	1	3	2015/11/24	2015/11/24	5	1	26	Pulmonary hypertension	2	Trisomy 13	7
22	KZ00356527	2	2015/11/06	1	2	2015/11/18	2015/11/18	20	2	30	None	2	Structural brain malformation	12
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26	KZ00355868	1	2015/10/19	2	2	2015/11/06	2015/11/06	30	2	30	Embolised PICC line in PA	1	PICC line removed	18
27	KZ00355282	1	2015/10/30	2	2	2015/11/06	2015/11/06	1	1	2	None	2	Medical closure	7
28	KZ00355760	2	2015/10/29	1	1	2015/11/05	2015/11/05	25	1	5	None	2	DiGeorge	7
29	KZ00355332	1	2015/10/31	1	2	2015/11/04	2015/11/04	1	2	30	None	2	None	4
30	KZ00355128	2	2015/10/28	2	2	2015/10/29	2015/10/29	15	1	2	None	1	None	1
31	KZ00355097	2	2015/10/28	1	1	2015/10/29	2015/10/29	30	2	30	None	1	Maternal DCMO	1
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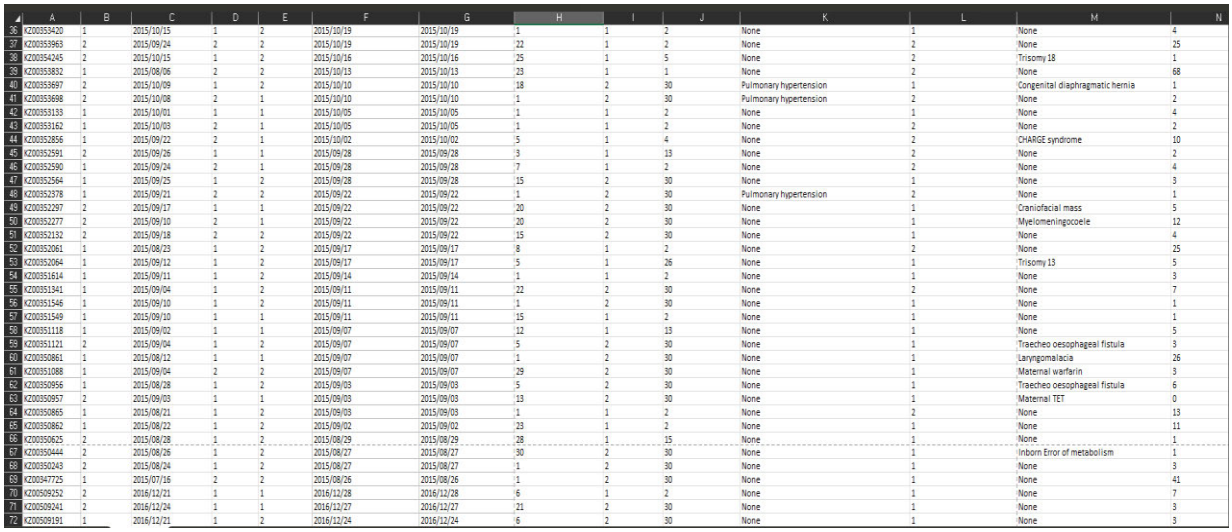
33	KZ00354755	1	2015/10/18	2	1	2015/10/28	2015/10/28	1	1	2	Pulmonary hypertension	2	None	10
34	KZ00354872	2	2015/10/24	1	1	2015/10/26	2015/10/26	1	1	2	Pulmonary hypertension	2	None	2
35	KZ00354536	2	2015/10/17	2	1	2015/10/22	2015/10/22	5	1	2	None	2	Traecheo oesophageal fistula	5
36	KZ00353420	1	2015/10/15	1	2	2015/10/19	2015/10/19	1	1	2	None	1	None	4



	A	B	C	D	E	F	G	H	I	J	K	L	M	N
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38	KZ00354245	2	2015/10/15	1	2	2015/10/16	2015/10/16	25	1	5	None	2	Trisomy 18	1
39	KZ00353832	1	2015/08/06	2	2	2015/10/13	2015/10/13	23	1	1	None	2	None	68
40	KZ00353697	2	2015/10/09	1	2	2015/10/10	2015/10/10	18	2	30	Pulmonary hypertension	1	Congenital diaphragmatic hernia	1
41	KZ00353698	2	2015/10/08	2	1	2015/10/10	2015/10/10	1	2	30	Pulmonary hypertension	2	None	2
42	KZ00353133	1	2015/10/01	1	1	2015/10/05	2015/10/05	1	1	2	None	1	None	4
43	KZ00353162	1	2015/10/03	2	1	2015/10/05	2015/10/05	1	1	2	None	2	None	2
44	KZ00352856	1	2015/09/22	2	1	2015/10/02	2015/10/02	5	1	4	None	2	CHARGE syndrome	10
45	KZ00352591	2	2015/09/26	1	1	2015/09/28	2015/09/28	3	1	13	None	2	None	2
46	KZ00352590	1	2015/09/24	2	1	2015/09/28	2015/09/28	7	1	2	None	2	None	4
47	KZ00352564	1	2015/09/25	1	2	2015/09/28	2015/09/28	15	2	30	None	1	None	3
48	KZ00352378	1	2015/09/21	2	2	2015/09/22	2015/09/22	1	2	30	Pulmonary hypertension	2	None	1
49	KZ00352297	2	2015/09/17	1	1	2015/09/22	2015/09/22	20	2	30	None	1	Craniofacial mass	5
50	KZ00352277	2	2015/09/10	2	1	2015/09/22	2015/09/22	20	2	30	None	1	Myelomeningocoele	12
51	KZ00352132	2	2015/09/18	2	2	2015/09/22	2015/09/22	15	2	30	None	1	None	4
52	KZ00352061	1	2015/08/23	1	2	2015/09/17	2015/09/17	8	1	2	None	2	None	25
53	KZ00352064	1	2015/09/12	1	2	2015/09/17	2015/09/17	5	1	26	None	1	Trisomy 13	5
54	KZ00351614	1	2015/09/11	1	2	2015/09/14	2015/09/14	1	1	2	None	1	None	3
55	KZ00351341	1	2015/09/04	1	2	2015/09/11	2015/09/11	22	2	30	None	1	None	7
56	KZ00351546	1	2015/09/10	1	2	2015/09/11	2015/09/11	1	2	30	None	1	None	1
57	KZ00351549	1	2015/09/10	1	1	2015/09/11	2015/09/11	15	1	2	None	1	None	1
58	KZ00351118	1	2015/09/02	1	1	2015/09/07	2015/09/07	12	1	13	None	1	None	5
59	KZ00351121	2	2015/09/04	1	2	2015/09/07	2015/09/07	5	2	30	None	1	Traecheo oesophageal fistula	3
60	KZ00350861	1	2015/08/12	1	1	2015/09/07	2015/09/07	1	2	30	None	1	Laryngomalacia	26
61	KZ00351088	1	2015/09/04	2	2	2015/09/07	2015/09/07	29	2	30	None	1	Maternal warfarin	3
62	KZ00350956	1	2015/08/28	1	2	2015/09/03	2015/09/03	5	2	30	None	1	Traecheo oesophageal fistula	6
63	KZ00350957	2	2015/09/03	1	1	2015/09/03	2015/09/03	13	2	30	None	1	Maternal TET	0
64	KZ00350865	1	2015/08/21	1	2	2015/09/03	2015/09/03	1	1	2	None	2	None	13
65	KZ00350862	1	2015/08/22	1	2	2015/09/02	2015/09/02	23	1	2	None	1	None	11
66	KZ00350625	2	2015/08/28	1	2	2015/08/29	2015/08/29	28	1	15	None	1	None	1
67	KZ00350444	2	2015/08/26	1	2	2015/08/27	2015/08/27	30	2	30	None	1	Inborn Error of metabolism	1
68	KZ00350243	2	2015/08/24	1	2	2015/08/27	2015/08/27	1	2	30	None	1	None	3
69	KZ00347725	1	2015/07/16	2	2	2015/08/26	2015/08/26	1	2	30	None	1	None	41
70	KZ00509252	2	2016/12/21	1	1	2016/12/28	2016/12/28	6	1	2	None	1	None	7
71	KZ00509241	2	2016/12/24	1	1	2016/12/27	2016/12/27	21	2	30	None	1	None	3
72	KZ00509191	1	2016/12/21	1	2	2016/12/24	2016/12/24	6	2	30	None	1	None	3

73	KZ00509054	2	2016/12/21	1	2	2016/12/22	2016/12/22	5	2	30	None	1	Dandy walker malformation	1
74	KZ00509140	1	2016/12/19	2	2	2016/12/22	2016/12/22	25	1	6	Pulmonary hypertension	2	None	3
75	KZ00509028	2	2016/12/20	1	1	2016/12/21	2016/12/21	16	2	30	None	1	None	1
76	KZ00508879	2	2016/12/18	1	2	2016/12/21	2016/12/21	6	2	30	None	1	None	3
77	KZ00508761	1	2016/11/08	2	1	2016/12/20	2016/12/20	1	1	29	None	2	Aortic arch abnormality	42
78	KZ00508833	1	2016/11/29	2	1	2016/12/19	2016/12/19	22	1	2	None	2	None	20
79	KZ00508820	2	2016/12/15	2	2	2016/12/15	2016/12/16	21	1	2	None	2	Duodenal atresia	1
80	KZ00508552	2	2016/12/11	1	2	2016/12/13	2016/12/14	21	1	21	None	2	Jejunal atresia	3
81	KZ00508555	1	2016/12/13	2	1	2016/12/13	2016/12/14	14	2	30	None	1	None	1
82	KZ00508536	1	2016/12/12	2	2	2016/12/13	2016/12/14	6	2	30	None	2	Extra uterine pregnancy	2
83	KZ00508451	2	2016/11/30	1	2	2016/12/14	2016/12/14	6	2	30	None	2	None	14
84	KZ00507965	1	2016/11/09	2	2	2016/12/06	2016/12/08	22	2	30	None	2	None	29
85	KZ00507958	1	2016/12/04	2	1	2016/12/05	2016/12/08	16	2	30	None	2	None	4
86	KZ00507948	1	2016/12/03	1	2	2016/12/08	2016/12/08	15	2	30	None	1	None	5
87	KZ00507416	2	2016/11/25	1	1	2016/11/28	2016/11/28	15	2	2	None	1	None	3
88	KZ00507453	2	2016/11/25	1	1	2016/11/27	2016/11/28	5	1	11	None	2	Trisomy 18	3
89	KZ00507425	1	2016/11/22	2	2	2016/11/28	2016/11/28	1	2	30	None	2	None	6
90	KZ00507369	1	2016/11/14	2	2	2016/11/24	2016/11/25	22	1	2	None	2	None	11
91	KZ00506936	1	2016/11/19	2	1	2016/11/20	2016/11/20	22	2	30	None	2	None	1
92	KZ00506961	2	2016/11/20	2	1	2016/11/20	2016/11/21	1	1	2	Pulmonary hypertension	2	None	1
93	KZ00506780	1	2016/10/19	1	1	2016/11/16	2016/11/17	1	1	2	None	2	None	29
94	KZ00506460	1	2016/11/09	2	2	2016/11/14	2016/11/16	22	2	30	None	2	None	7
95	KZ00506476	2	2016/11/07	1	1	2016/11/12	2016/11/12	7	1	18	None	2	None	5
96	KZ00506304	1	2016/10/18	2	1	2016/11/10	2016/11/10	8	1	26	None	2	None	23
97	KZ00506101	2	2016/10/31	1	1	2016/11/08	2016/11/08	8	2	30	Vein of galen	2	None	8
98	KZ00505838	1	2016/10/28	2	2	2016/11/02	2016/11/03	2	1	17	None	2	None	6
99	KZ00505813	2	2016/11/02	1	2	2016/11/02	2016/11/02	14	1	26	None	2	None	0
100	KZ00505632	2	2016/10/31	1	1	2016/11/01	2016/11/02	2	1	2	None	1	None	2
101	KZ00505489	1	2016/10/28	1	2	2016/10/28	2016/10/29	13	1	2	None	1	None	1
102	KZ00505201	1	2016/09/28	2	2	2016/10/27	2016/10/27	8	1	2	None	2	None	29
103	KZ00505345	2	2016/10/26	2	2	2016/10/26	2016/10/27	15	1	2	None	1	None	1
104	KZ00505141	2	2016/10/22	1	1	2016/10/25	2016/10/27	19	2	30	None	1	None	5
105	KZ00505003	1	2016/10/18	2	2	2016/10/25	2016/10/27	22	2	30	None	1	None	9
106	KZ00505146	2	2016/10/23	2	1	2016/10/25	2016/10/26	1	1	2	None	2	None	3
107	KZ00504341	1	2016/09/24	2	2	2016/10/26	2016/10/26	1	1	4	Pulmonary hypertension	2	None	32
108	KZ00504246	1	2016/10/06	2	2	2016/10/26	2016/10/26	3	1	20	None	2	None	20

Appendix VII – Codes for data input

CODED FOR DATA ENTRY INTO EXCEL

Patient ID: No coding **Date of Birth [DOB]:** Date format-DDMMYYYY

Maturity at birth: Coded

1. Preterm
2. Term

Gender: Coded

1. Male
2. Female
3. Indeterminate

Mode of Delivery: Coded

1. Normal Vaginal Delivery (NVD)
2. Elective Caesarean Section
3. Emergency Caesarean Section

ECHO-Primary indication [Primary indication for echocardiogram as clearly stated or deduced from patient notes]: **Coded**

1. Respiratory distress/Prolonged ventilation
2. Murmur
3. Cyanosis
4. Arrhythmia
5. Syndrome/Multiple congenital abnormalities/ARM
6. Dysmorphism
7. Shock
8. Heart failure
9. Cardiomegaly
10. Sepsis
11. Dextrocardia
12. Heterotaxy
13. Family History of Congenital Heart Disease
14. Foetal scan diagnosis of Congenital Heart Disease
15. Gastrochisis
16. Omphalocoele
17. Anorectal malformation
18. Congenital chest abnormality (including Congenital diaphragmatic hernia)
19. Congenital musculoskeletal abnormality
20. Congenital CNS abnormality
21. Bowel atresia
22. Bowel perforation
23. Heart failure and murmur
24. Dysmorphism and murmur
25. Dysmorphism and cyanosis
26. Cyanosis and murmur
27. Respiratory distress and Murmur
28. Maternal Diabetes
29. Maternal Medication
30. Others e.g. Not specified; Maternal arrhythmia; BOH; CHD on screening ECHO; IEM;

ECHO-DOR [Date echocardiogram was requested for patient]: Date format-DDMMYYYY

ECHO-DOS [Date echocardiogram was done for patient]: Dated format-DDMMYYYY

ECHO-OUTCOME [Outcome of Echocardiogram performed]: Coded

1. Congenital Heart Disease
2. No structural abnormality
3. Other abnormality

ECHO-CHD specified [Specific Congenital Heart Disease identified on Echocardiogram]: Coded

1. Ventricular Septal Defect (VSD)
2. Patent Ductus Arteriosus (PDA)
3. Atrial Septal Defect (ASD)
4. Atrioventricular Septal Defect (AVSD)
5. Tetralogy of Fallot (TET)
6. Transposition of the Great Arteries (TGA)
7. Truncus Arteriosus (TA)
8. Tricuspid Atresia
9. Total Anomalous Pulmonary Venous Drainage (TAPVD)
10. Partial Anomalous Pulmonary Venous Drainage (PAPVD)
11. Double Outlet Right Ventricle (DORV) unspecified
12. AP window
13. Complex heterotaxy
14. Common atrium
15. Univentricular Heart
16. Hypoplastic Left Heart Syndrome (HLHS)
17. Coarctation of the Aorta (CoA)
18. Interrupted Aortic Arch (IAA)
19. Pulmonary Atresia with Intact Ventricle Septum (PA/IVS
20. Pulmonary Atresia with Ventricular Septal Defect (PA/VSD)
21. Congenital isolated Valve abnormalities (Mitral valve, Tricuspid valve, Aortic valve, Pulmonary valve)
22. Ebstein's anomaly (EA)
23. Supramitral valve ring (SMR)
24. Cor triatriatum
25. Anomalous origin of the Left coronary artery from the Pulmonary artery (ALCAPA)
26. VSD/PDA
27. ASD/VSD
28. ASD/PDA
29. OTHERS
30. Not applicable

ECHO- Other Findings [Other findings other than Congenital Heart Defects]: No coding

ECHO- Clinical state [Clinical state of child at the time of Echocardiogram]: Coded

1. Stable
2. ill

Thank you