A STUDY ON THE OUTCOME OF PATIENTS WITH DOWN SYNDROME WITH CONGENITAL HEART DISEASE

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ABSTRACT

Backgrounds:

Congenital heart defect (CHD) is the most common defect associated with Down syndrome (DS). Studies conducted in Asian countries reported ventricular septal defect (VSD) instead of atrioventricular septal defect (AVSD) as the most common congenital heart defect among Asian children with Down Syndrome.

Objectives: To study the outcome of children with DS, to identify the distribution of CHD types in DS and the risk factors associated with poor outcome among patients with DS and CHD.

Method: A retrospective, observational, cohort study conducted at two tertiary centres; University Malaya Medical Centre (UMMC) and Hospital Sultanah Aminah Johor Bahru (HSAJB) between 1st January 2005 to 31st December 2015 in children who are clinically diagnosed with DS. Patients from UMMC were identified from the Paediatric Cardiology and Genetic database in UMMC and patients from HSAJB are selected from Paediatric Cardiology Clinical Information System (PCCIS) and Jabatan Pendaftaran Negeri Johor. Medical records were reviewed for demographics, clinical characteristics, associated medical condition, 2D-echocardiography and chromosomal results. Parents were also contacted via phone call to gather missing information.

Results: A total of 754 patients with DS were included in the study whereby 634 from HSAJB and 120 from UMMC. 420 (55.7%) patients had CHD and 334 (44%) had normal heart. Most common CHD was VSD in 138 (32.9%) followed by patent ductus arteriosus (PDA) in 125 (29.8%) and AVSD in 77 (18.4%). A total of 207 (40.9%) patients with CHD required surgical treatment. There were total of 131 (17.5%) deaths in which, 95 (29%) patients with CHD compared to 10.8% (36) patients without CHD died. A total of

38 (40%) patients died prior to surgery with reducing trend in the number from 2013 to 2015. Fifteen patients (16%) died after surgery. The number of patients who died after surgery was relatively low with less than 5 patients each year. Highest mortality was in AVSD patients (n=34, 44%) and 20 of them were treated conservatively. Survival probabilities for patients with CHD was 79% up to 1 year of age and 75% up to 10 years. AVSD has the poorest survival outcome when compared to other CHD types, with only 60% survived to 1 year and 54% to 10 years. There were 2 significant factors that are associated with death for the patients with DS and CHD. Patients with severe CHD had a 3.117 higher likelihood to die compared to the mild and moderate patients (95% CI 1.741- 5.581, $p<0.001$). The presence of primary persistent pulmonary hypertension is also poor survival indicator (OR: 2.606, 95% CI 1.452-4.677).

Conclusion:

The prevalence of CHD in DS was 56% in this study, highlighting the importance of cardiac screening for children with DS. VSD is the commonest CHD followed by PDA and AVSD. The severity of the CHD and the presence of PPHN carries poor prognosis for the survival of the children with DS. It is important to refer children with DS and CHD for early surgery before pulmonary hypertension occurs.

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LIST OF ABBREVIATIONS

Abbreviation	Full Text
ASD	Atrial Septal Defect
AVSD	Atrioventricular Septal Defect
CHD	Congenital Heart Defect
CRF	Case Report Form
CoA	Coarctation of Aorta
DORV	Double Outlet
DS	Down Syndrome
LVOT	Left Ventricular Outflow Obstruction
MREC	Malaysian Research Ethic Committee
NMRR	National Medical Research Registry
PAVSD	Pulmonary atresia with Ventricular Septal Defect
PAIVS	Pulmonary atresia with Intact Ventricular Septum
PCCIS	Paediatric Cardiology Clinical Information System
PDA	Patent Ductal Arteriosus
PHT	Pulmonary Hypertension
PPHN	Persistent Pulmonary Hypertension of Newborn
PS	Pulmonary Stenosis
RVOT	Right Ventricular Outflow Tract
TA	Tricuspid Atresia
TAPVD	Total Anomalous Pulmonary Venous Drainage
TGA	Transposition of Great Arteries
TOF	Tetralogy of Fallot
VSD	Ventricular Septal Defect

CHAPTER 1: INTRODUCTION & LITERATURE REVIEW

Introduction

Down syndrome (DS) is the most common syndrome causing intellectual disability, affecting 1/700 live births. It was first described in 1862 and in late 1950's, trisomy 21 was identified as the cause of the DS. In United States of America, the prevalence of DS has risen by 30% between the year of 1979 to 2003.[1]

Hoe TS and Boo NY reported in 1989, the incidence of DS among Malaysian babies delivered in Maternity Hospital Kuala Lumpur was 1:959[2], lower than various studies from Japan, Sweden and Egypt which reported an incidence of between 1:555 to 1:850 livebirths.[3,4,5] The single centre study which was conducted over 18-month period, found 36 Downs babies from 34,522 livebirths.

Congenital heart disease (CHD) is the most common anomaly in children born with trisomy 21, reported to be in the range of 40-60%.[6,7] Similarly, Hoe TS and Boo NY observed 50% of the DS babies born at Maternity Hospital Kuala Lumpur had CHD.[8] Data from Thailand showed 49.8% of Down syndrome patients with CHD[9,10] while data from Singapore showed higher, with 65% DS had CHD.[11] Congenital heart defect, being the most common congenital anomaly, has huge impact on the outcome of DS patients. Recent studies from the West support the approach of providing early surgical or interventional therapy to all patients with DS providing better outcome and longer life-expectancy.[12,13,14]

However, up to date, there is limited local data on the incidence and types of CHD in DS children and the subsequent intervention as well as their outcome. This study hopes

to shed some light on local data that would be helpful in providing information for genetic counselling as well as to improve the management of CHD in children with DS in the future. This study focused on congenital heart defect as a major congenital defect in DS and includes types of CHD, and their outcome.

Genetics of Down Syndrome

DS occurs in individuals with extra copy of chromosome 21. The cytogenetic analysis of metaphase karyotype remains as confirmatory test for trisomy 21. In approximately 95% of cases, DS is due to non-disjunction during meiosis. DS due to translocation that involves chromosome 21 present in 4% with majority involves fusions at the centromere known as Robertsonian translocation. In about 1% of DS are mosaics.

Risk factor associated with DS

DS is associated with advanced maternal age, with highest risk in women who conceived at the age of more than 35 years old. Twenty-one population-based EUROCAT registries involving 6.1 million births in Europe between 1990 and 2009 showed the proportion of births in the population to mothers aged more than 35 years has increased from 13% in 1990 to 19% in 2009. There was also an increase in prevalence of trisomy 21, in parallel to the increasing maternal age.[10]

With the advancement of care in prenatal period, the growth in imaging technology and tests, these allows earlier detection and high suspicion of fetus with DS. Advanced detail antenatal scans identifying soft markers such as small or no nasal bone, large ventricles and nuchal fold thickness, allow recognition for DS risk as early as 14 to 24 weeks gestation. The quadruple test measuring the levels of four pregnancy hormones which includes alpha-fetoprotein, human chorionic gonadotrophin, unconjugated estriol

and inhibin A, which has sensitivity of 85%, is also used to identify the risk. Prenatal diagnostic testing via amniocentesis and chorionic villous sampling are offered to high risk pregnancies as these are reliable test with small risk of miscarriage up to 1%.

Clinical characteristics

One of the hallmarks of DS is the variability in the clinical features and associated congenital abnormality. DS has distinct dysmorphic features that is fairly consistent, allowing recognition of trisomy 21 based on their clinical features. The clinical features are apparent since birth e.g craniofacial features, excessive skin at the nape of neck, central hypotonia, short and stubby fingers, clinodactyly, single transverse palmar crease and wide spacing groove between the first and second toes. DS are associated with many congenital abnormalities that are present in the first year of life such as congenital heart defect, gastrointestinal atresia, congenital hypothyroidism, otitis media and transient myeloproliferative disorder. Other complications like obstructive sleep apnoea, atlanto-axial subluxation, leukaemia and Alzheimer disease, may develop later in life.

Congenital heart defect

CHD is the most common defect associated with DS, reported between 40-60% compared to 1% in general population.[15] American Academy of Paediatrician recommended for Paediatric Cardiology referral of all newborn with DS for screening echocardiogram.[14]

In general, endocardial cushion defect is the commonest cardiac defect in DS; reported approximately 30-40%.[6,15] However, recent regional studies from different countries especially Asian countries have reported differently.

Hoe et al observed 34 babies with DS, born at the Maternity Hospital Kuala Lumpur in 1989. 50% (17/34) had CHD, consisted of 7 patients with VSD followed by 3 with PDA, 2 AVSD, 2 VSD with PDA, 1 hypertrophic cardiomyopathy, 1 hypertrophic obstructive cardiomyopathy and 1 complex cyanotic heart .[8] Tan et al reported that their prevalence of CHD among DS was higher in Singapore; 65% from the 588 trisomy 21 patients studied from 1996 to 2010. This is probably because the study was conducted at the 2-main paediatric cardiology tertiary centres in Singapore. Hence, the trisomy 21 without CHD may not have been referred. Their distribution showed 39% DS with CHD had VSD followed by PDA (34.3%), secundum ASD (23.4%) and AVSD (15.6%).[11]

Similarly, Layangool et al reported from their study conducted in Thailand, ventricular septal defect (VSD) is the most common lesion followed by patent ductus arteriosus (PDA).[9] Data from Mexico City reported higher incidence of CHD among DS; 58% (160/275) with 3 most common lesions were ASD, VSD and PDA (90%). Only 14 patients (8%) had AVSD. Similarly, in Oman, with a high consanguineous marriage population, Venugopalan P and Agarwal AK reported that CHD was detected in 60% of 90 DS patients. ASD is the most common (18/54), followed by AVSD (15/54) and VSD (14/54). [16,17]

Although more recent studies have showed that endocardial cushion defect is no longer the most common cardiac lesion among children with Down syndrome, trisomy 21 constitutes as majority of children with endocardial cushion defect, in which more than half AVSD patients were DS.[18] This defect only occurs in about 7% of CHD among the non-DS cases. However, the prognosis seems better in DS compared to non-syndromic

populations. For DS, extensive bridging of both superior and inferior bridging leaflets is more common while associated cardiac lesions such as left ventricular hypoplasia and left heart obstructive lesions are less common. The AVSD anatomy in DS seems to be more favourable for surgical repair compared to the non-Down with AVSD. [19] The survival was also better in Down compared to non-Down AVSD whereby the actuarial survival after 12 years of follow up was reported at 94% among DS versus 86% for normal karyotype.

Life-expectancy

Down syndrome has significant medical morbidity leading to shorter life expectancy. The main morbidity leading to mortality are respiratory diseases, heart failure, pneumonia and epilepsy.[20] However, the survival has much improved past few decades. This is partly due to better antenatal care allowing prenatal detection of cardiac anomalies and other co-morbidities, and also advancement in surgical techniques and better neonatal ICU and post-operative ICU care allowing earlier intervention in these patients.

Data from the United States showed that life expectancy of people with DS has increased dramatically between 1960 and 2007, from average life span of 10 years to 47 years. [18]

Congenital heart disease is one of the biggest factor that determine the outcome of DS. [21] DS children with congenital heart defect (CHD) were five times more likely to die in the first year of life compared to DS without CHD with AVSD being the commonest cardiac lesion leading to death.[21] Most of the deceased DS with CHD died from heart failure and respiratory infections, mainly pneumonia. [22]

Their difference in the mortality rate persists and substantially larger in adults compared to children as shown in Table 1.[20]

Table 1: Comparison of mortality rates for persons with Down syndrome with and without congenital heart defects (CHD). Adapted from Day SM et al, 2005.[20]

Age (y)	No CHD			CHD			CHD vs No CHD		p
	Exposure[a]	Deaths[b]	Mortality rate[c]	Exposure[a]	Deaths[b]	Mortality rate[c]	RR	EDR[e]	
2–4	11728	36	0.0031	3160	18	0.0057	1.9	0.0026	<0.05
5–9	16621	27	0.0016	3612	12	0.0033	2.0	0.0017	<0.05
10–19	18553	31	0.0017	1781	10	0.0056	3.4	0.0039	<0.001
20–29	15842	47	0.0030	909	12	0.0132	4.5	0.0102	<0.001
30–39	11673	57	0.0049	630	18	0.0286	5.8	0.0237	<0.001
40–49	7069	112	0.0158	280	12	0.0429	2.7	0.0270	<0.001
50+	3336	198	0.0593	108	10	0.0930	1.6	0.0336	*ns*
All	84822	508	0.0060	10479	92	0.0088	1.5	0.0028	<0.001

p values are based on a χ^2 variable with 1 degree of freedom and a null hypothesis that a CHD has no effect on mortality. RR, relative risk, equal to ratio of mortality rates for CHD and no CHD. EDR, excess death rate; *ns*, not significant. [a]Number of person-years, rounded to nearest year. [b]Observed number of deaths. [c]Mortality rate, equal to observed deaths divided by exposure. [e]Excess death rate, equal to difference between mortality rates for CHD and no CHD.

Treatment and outcome

For most congenital heart defect, surgical is the definitive treatment. In the past, cardiac surgery in children with Down syndrome has been a dilemma due to the poor surgical outcome and the natural history of Down syndrome with shorter life span compared to normal population. However, it has been shown that Down syndrome had no increase in postoperative mortality compared to non-DS. [13,23]

Without early surgical intervention, pulmonary hypertension is a major concern in Down syndrome children by the end of their first year of life. Children with DS has 10-fold increase risk to develop pulmonary hypertension regardless of presence or absence of congenital heart disease. This is possibly due to the pre-existing pulmonary vascular obstructive disease and intrinsic factors such as abnormal production of nitric oxide and low pulmonary vasodilation response, or related to other conditions such as recurrent chest infections, alveolar hypoventilation or chronic upper airway obstruction.[24]

In CHD patients, pulmonary arterial hypertension may develop due to the presence of systemic-to-pulmonary shunt with unprotected pulmonary blood flow. Pulmonary vascular resistance may progressively increase in uncorrected cardiac defect and ultimately lead to reversal of the systemic-to-pulmonary shunt leading to Eisenmenger syndrome.[25] The presence of Eisenmenger syndrome is an ultimate contra-indication for corrective repair surgery as the right ventricle will not be able to cope with the increase in afterload and subsequently the ventricular function will fail. [26]

Over the years, more patients with DS are referred for definitive surgery at earlier age, within the first year of life. The first 6 months of life is considered as the best time for definitive repair before the patients progress to develop pulmonary vascular disease and atrio-ventricular valve regurgitation.[27]

Korten et al looked at 1549 patients with DS and CHD identified from the German National Register. Majority (84%) of the patients had corrective surgery or interventional procedure, with 57% of them had the intervention in the first year of life. The likelihood of being treated before the age of 1 has significantly increased from 0% in 1950s/1960s, 2.1% in 1970s to 85.6% for those born after the year 2000. In contrast, the likelihood to develop Eisenmenger syndrome decreased from 53.3% in the 1950s/1960s to only 0.5% for the post-2000 birth cohort. Patients who did not undergo surgical correction or intervention has significantly increased risk to develop Eisenmenger syndrome. DS patients with Eisenmenger syndrome has 40-fold increase mortality compared with general population as compared to 4-fold increase mortality rate in DS without Eisenmenger syndrome.[28] Most patients died due to progressive cardiovascular disease and heart failure, or from intrapulmonary hemorrhage due to rupture of major vessels. [29]

Tumanyan et al showed early surgical correction of DS patients with AVSD, prior to increasing pulmonary vascular resistance and deforming AV valve reduces the rate of early mortality. The characteristics of AVSD defect with favourable morphology of the left side of the common atrioventricular valve in children with DS lead to good surgical repair outcome. [23] Lange et al who looked at the outcome post AVSD repair, reported that among the patients who had repair of atrioventricular septal defect, patients who are not Down syndrome are more likely to develop complications of recurrent subaortic stenosis as well as requiring re-intervention on the left atrioventricular valve (LAVV) presumably because of the associated LAVV anomalies; double orifice mitral valve and single papillary muscle.[30]

Figueroa et al studied 102 patients with DS and CHD subjected to treatment; corrective or palliative surgery, or therapeutic catheterisation. The main cardiac complications were rhythm dysfunction and low cardiac output syndrome while the most frequent non-cardiac complications were infection. The 30-day mortality rate reported was low; 2.9% (3/102 cases). [31]

Successful surgical management of congenital heart defects provides the same life expectancy for these patients as compared to Downs patients without cardiac defects. The results of current studies support the current approach of providing early treatment either surgical or interventional to all DS patients.[28] In Thailand, DS with CHD that received surgical treatment, the overall survival at 1 and 5 years of age were 96% and 86% respectively. Layangool et al also reported that from the 98 cases that undergone surgery, 10 cases died immediate post cardiac surgery AVSD in 9, VSD in 1) while 37 cases died from non-surgical related cause, with congestive heart failure in 8,

pneumonia in 7, leukaemia in 4, airway disease in 3, others in 7 and unknown in 8 cases.[9]

Furthermore, Jin et al reported the decline in the mortality rate among Danish with DS, appears to occur in patients with CHD indicating the improvement is an effect of treatment of the CHD.[32]

CHAPTER 2: OBJECTIVES

1 PRIMARY OBJECTIVE

The general objective is to study the outcome of Down syndrome children with congenital heart defect

2 SECONDARY OBJECTIVES

1. To identify the distribution of CHD types in DS.
2. To identify the risk factors associated with poor outcome among patients with CHD

CHAPTER 3: METHODOLOGY

Study design:

This is a retrospective, observational, cohort study conducted at two centres; University Malaya Medical Centre (UMMC) and Hospital Sultanah Aminah Johor Bahru (HSAJB).

Place:

4.1.a University Malaya Medical Centre (UMMC) is a government-funded medical institution located at the capital city of Malaysia, Kuala Lumpur. UMMC is affiliated to the University of Malaya (UM), Malaysia's premier institution of higher learning. It provides educational and training needs of undergraduate and postgraduate students of UM. UMMC has well-established paediatric services offering both cardiology and genetic services among many other services. UMMC has annual delivery rate around 5000 per year. Apart from providing healthcare for the Klang Valley region, UMMC also receives referral from other government and private hospitals from all over Malaysia.

4.1.b Hospital Sultanah Aminah Johor Bahru (HSAJB), a government hospital is located in the southern region of Malaysia. Johor has a population of 3.554 million with birth rate around 55,000 per year. HSAJB which alone has annual birth rate around 12,000 per year, is the only hospital in the southern Malaysia with Paediatric Cardiology services, receiving referral for cardiac cases from all over Johor. Majority of DS patients born in Johor are referred to HSAJB for their cardiac assessment.

Study population:

All clinically diagnosed DS with or without chromosomal results. Among the features of DS are; craniofacial features such as epicanthic folds, upslanting palpebral fissures, brachycephaly and excessive skin at the nape of neck, central hypotonia, short and stubby fingers, clinodactyly, single transverse palmar crease and wide spacing groove between the first and second toes.

Duration of study:

This study observing data for 10 years duration, from 1st January 2006 -31st December 2015.

Inclusion Criteria:

All phenotypically confirmed DS born between 1st January 2006 -31st December 2015

Diagnosis

Congenital Heart Defect (CHD) is defined as a gross structural abnormality of the heart or intrathoracic great vessels that are actually or potentially of functional significance, that is present at birth.

The diagnosis of CHD was made after thorough cardiac assessment including cross-sectional, Doppler and colour imaging echocardiography with finding confirmed by paediatric cardiologist or paediatric cardiology trainee. Conditions with no functional significance were categorised as non-CHD, including patent foramen ovale (PFO), mild branch pulmonary stenosis, isolated dextrocardia, isolated bilateral superior vena cava (SVC) and right arch without symptoms or other lesions. Patent ductus arteriosus that closes spontaneously within first 6 months in premature and 3 months in term infant were excluded from CHD.

Patients with multiple lesions had their lesions classified hierarchically and the main lesion which required first intervention or hemodynamically significant was considered as the CHD lesion. The CHD was divided into 3 groups; mild, moderate and severe as described by Hoffman. [33]

Table 2. Categories of congenital heart defect. Adapted from Hoffman et al, 2002.

Categories	Lesions
Mild	Patients are asymptomatic. Often undergo early spontaneous resolution of the lesions. Includes small VSD, small PDA, small ASD, mild PS
Moderate	Require expert care but less intensive than severe lesions. Includes; mild or moderate aortic stenosis or aortic incompetence, moderate pulmonary stenosis or incompetence, non-critical coarctation of aorta, large ASD, complex forms of VSD
Severe	Present as severely ill in the newborn or early infancy. Includes: A. All cyanotic heart disease; transposition of the great arteries (TGA), Tetralogy of Fallot (TOF), hypoplastic left heart, tricuspid atresia (TA), pulmonary atresia with intact ventricular septum (PAIVS), Double outlet right ventricle (DORV), total anomalous pulmonary venous drainage (TAPVD), critical pulmonary stenosis B. Acyanotic lesions; AVSD, large VSD, large PDA, severe PS, critical coarctation

Outcome

1. Overall mortality rate of all DS children
2. Survival

Exclusion criteria

Patients whose medical records were untraceable were excluded from the study.

4.4 Data collection

4.4.i. UMMC

Cases were identified from the lists of patients attending Paediatric Cardiology and Genetic Cardiology UMMC from the respective unit database. DS patients that were born between 1st January 2006 to 31st December 2015 were selected. Electronic medical records of these patients were traced and reviewed. Echocardiography data obtained from Xcelera software which contain echocardiography data on images and official reports. Mortality data was obtained from department of paediatric mortality lists and record book in UMMC mortuary. Data were recorded in a data collection form (Appendix 2)

4.4.ii HSAJB

DS patients were selected from the Pediatric Cardiology Clinical Information System (PCCIS). PCCIS was developed in 2004 and has been used for past 12 years, since beginning of 2006. It contains demographic, clinical and 2D-echocardiographic data of all patients that were referred to the Paediatric Cardiology clinic.

To negate the possibility of transfer error during the data were captured, patients' clinic records were traced and reviewed. Records were also traced from the General Pediatric Clinic and neighbouring Hospital Sultan Ismail Johor Bahru which is also a referral centre for Oncology cases in Johor. Parents were also contacted via phone call to gather missing information. To validate the patients alive and death status, the names of the patients were submitted to Jabatan Pendaftaran Negeri Johor. Data were recorded in a data collection form. (Appendix 3)

4.6 Statistical methods

Data entry and statistical analysis were done using the Statistical Package for Social Science (SPSS) version 23. Comparisons of groups were performed using student t-test for continuous data and Chi square test for categorical variables. Survival analysis was done using Kaplan-Meier analysis. The relation between parameters and mortality was assessed using the univariate and logistic regression analysis. p-value <0.05 was considered as statistically significant.

4.7 Ethics approval

This study was approved by the UMMC Ethics Committee (MREC ID NO: 201723-4886) and Medical Research and Ethics Committee Ministry of Health (NMRR-17-957-35260(IIR)).

FLOW CHART SHOWING OVERVIEW OF STUDY

Figure 1:

Flow Chart: Overview of Study Design-UMMC

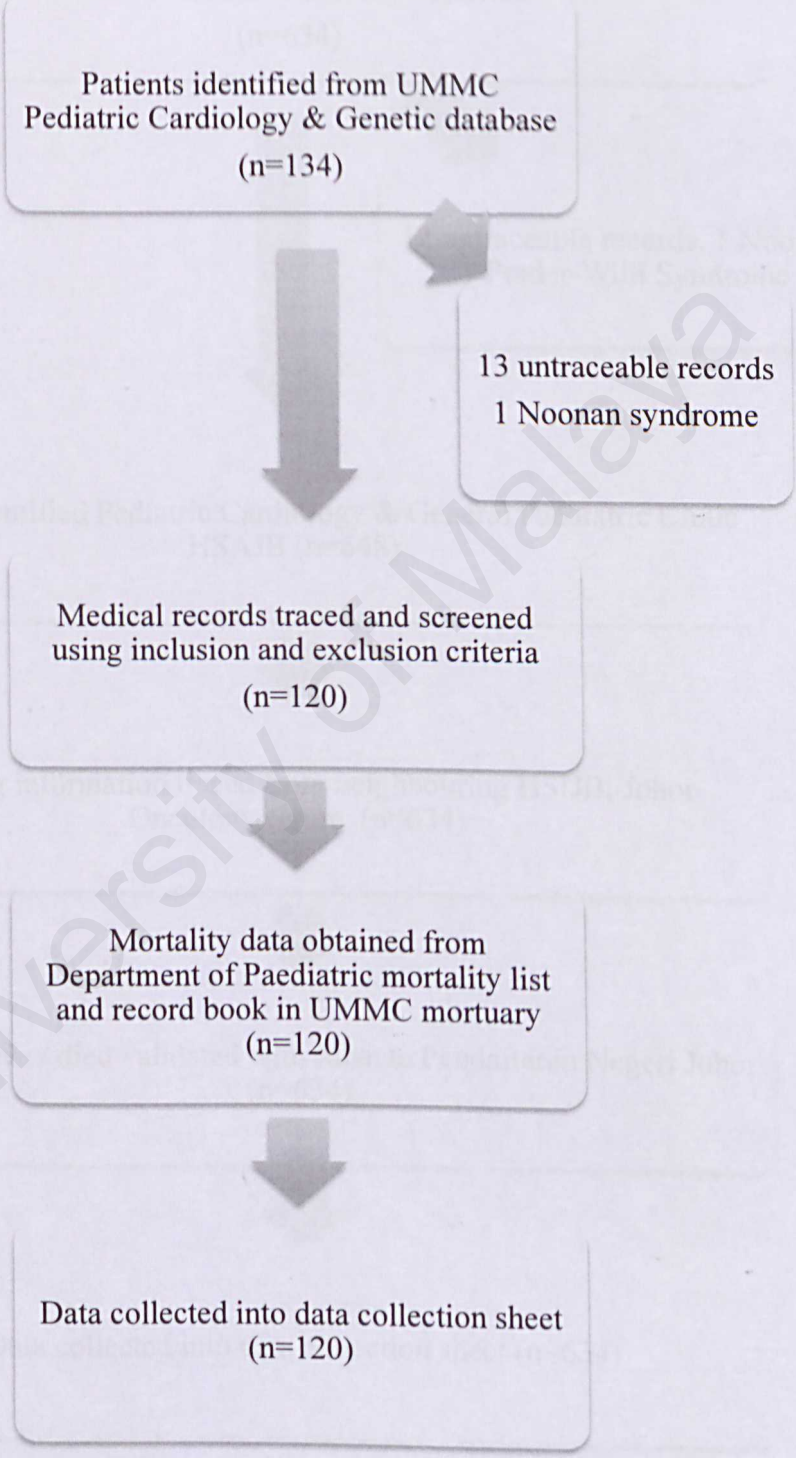
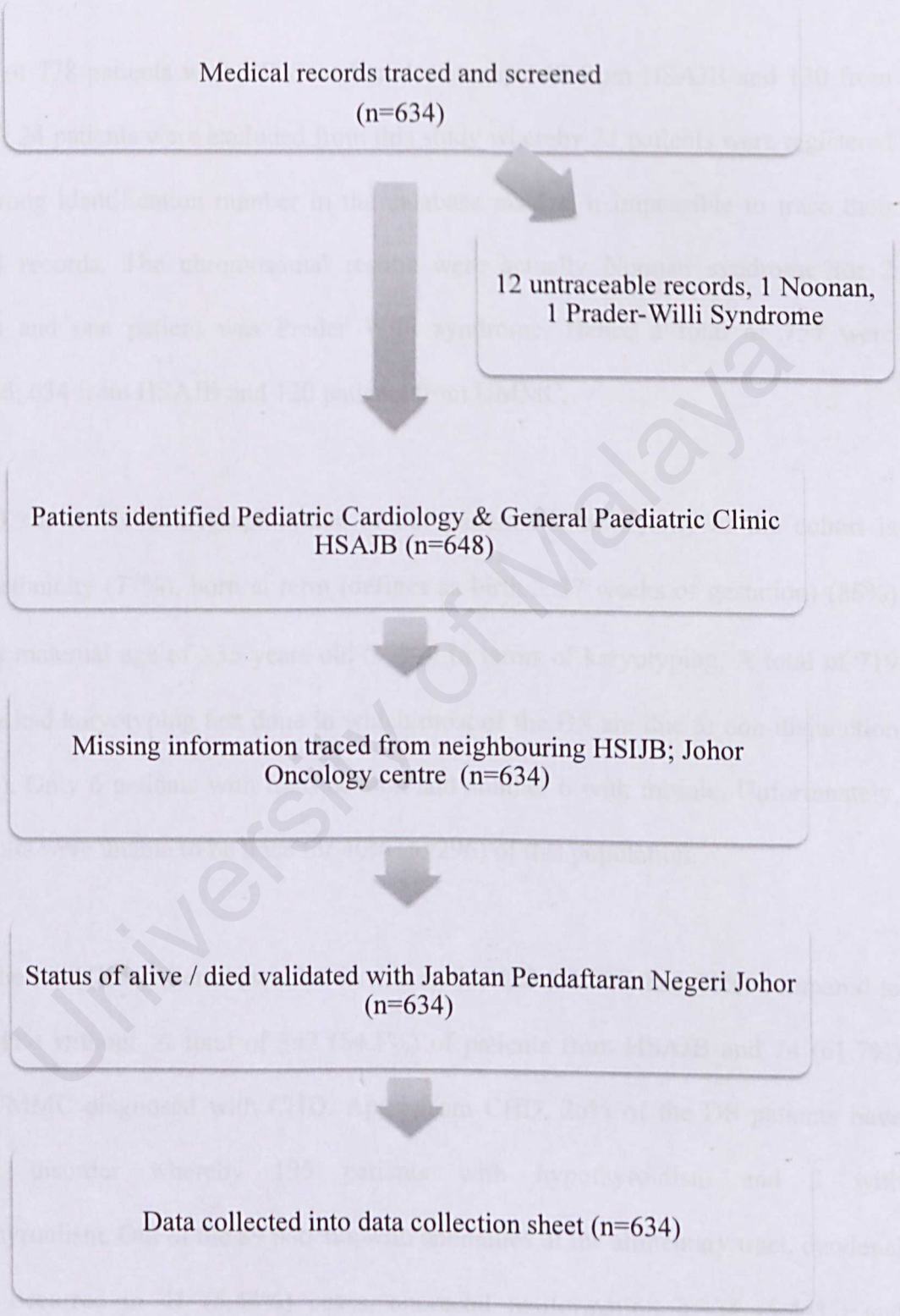


Figure 2:

Flow Chart: Overview of Study Design-HSAJB



RESULTS

Patient Characteristics

A total of 778 patients with DS were found whereby 648 from HSAJB and 130 from UMMC. 24 patients were excluded from this study whereby 21 patients were registered with wrong identification number in the database making it impossible to trace their medical records. The chromosomal results were actually Noonan syndrome for 2 patients and one patient was Prader Willi syndrome. Hence a total of 754 were analysed; 634 from HSAJB and 120 patients from UMMC.

Table 3 shows the demographic data of our patients. The majority of the cohort is Malay ethnicity (77%), born at term (defines as birth ≥ 37 weeks of gestation) (86%) and has maternal age of ≥35 years old (57%). In terms of karyotyping, A total of 719 patients had karyotyping test done in which most of the DS are due to non-disjunction (n=411). Only 6 patients with translocation and another 6 with mosaic. Unfortunately, the results were unable to be trace for 40% (n=296) of this population.

From the total 754 patients included in this study, 420 (55.7%) has CHD compared to 334 (44%) without. A total of 347 (54.7%) of patients from HSAJB and 74 (61.7%) from UMMC diagnosed with CHD. Apart from CHD, 26% of the DS patients have thyroid disorder whereby 195 patients with hypothyroidism and 2 with hyperthyroidism. Out of the 89 patients with anomalies of the alimentary tract, duodenal atresia occurred in 41 (5.44%) cases, anorectal malformation in 34 (5.44%) and Hirschsprung disease in 14 (1.9%).

A total of 101 (13.4%) patients with primary persistent pulmonary hypertension (PPHN) where by 71 (70.3%) have CHD and 30 (29.7%) are without CHD. PPHN is defined based on combination of clinical finding of different in preductal and postductal transcutaneous oxygen saturation of 10% or greater associated with echocardiographical finding of bidirectional shunting through PDA.[34]

Pulmonary hypertension which is diagnosed by presence of mean pulmonary artery pressure of more than 25mmHg on echocardiogram[35], occurred in 103 (13.7%) patients. Most of the patients (n=90, 88.3%) with pulmonary hypertension were among the patients with CHD.

More than 90% (n=702) of the patients had their first cardiac screening in their first year of life with more than half was seen in the neonatal period. Almost all of patients from UMMC had their first cardiac screening in the neonatal period (n=119, 99.2%).

Table 3. Demographic data of all patients with Down syndrome

Characteristic	Total n (%)	HSAJB			UMMC		
		CHD	Non-CHD	Total	CHD	Non-CHD	Total
		347 (54.7)	287 (45.3)	634	74 (61.7)	46 (38.3)	120
Sex							
Female	368 (48.8)	201	123	324	27	17	44
Male	386 (51.2)	146	164	310	47	29	76
Ethnicity							
Malay	581 (77.1)	272	233	505	45	31	76
Chinese	108 (14.3)	48	28	76	22	10	32
Indian	40 (5.3)	14	14	28	7	5	12
Others	25 (3.3)	13	12	25	0	0	0
Gestation							
Premature	105 (13.9)	50	31	81	12	12	24
Term	647 (85.8)	297	257	554	61	32	93
Maternal age[a]							
< 35yr	245 (43.5)	127	77	204	25	16	41
≥35	306 (56.5)	138	96	234	44	28	72
Maternal DM							
Yes	57 (7.6)	32	0	32	13	12	25
No	697 (92.4)	314	288	602	61	34	95
Age at cardiac screening							
Neonate	437 (58)	204	114	318	73	46	119
≥1- 3months	137 (18.2)	69	67	136	1	0	1
≥3-6 months	60 (8.0)	32	28	60	0	0	0
≥6 months- 1year	68 (9.0)	23	45	68	0	0	0
1-5 years	46 (6.1)	17	29	46	0	0	0
≥5 years	6 (0.8)	2	4	6	0	0	0

Table 3, continued

Characteristic	Total n (%)	HSAJB			UMMC		
		CHD	Non-CHD	Total	CHD	Non-CHD	Total
		347 (54.7)	287 (45.3)	634	74 (61.7)	46 (38.3)	120
Karyotyping[b]							
Non-disjunction	411 (97.2)	164	146	310	65	36	101
Translocation	6 (1.4)	3	2	5	0	1	1
Mosaic	6 (1.4)	0	1	1	3	2	5
Additional medical problems							
Thyroid dysfunction	197 (26.1)	89	65	154	28	15	43
Alimentary tract:							
Duodenal atresia	41(5.44)	15	11	26	10	5	15
Anorectal malformation	34 (4.51)	14	13	27	6	1	7
Hirschsprung disease	14 (1.90)	8	6	14	0	0	0
Transient abnormal myelopoiesis	26 (3.5)	10	8	18	4	4	8
Acute myeloid leukaemia	11 (1.5)	4	3	7	4	0	4
Persistent pulmonary hypertension of newborn	101 (13.4)	71	30	101	0	0	0
Pulmonary hypertension	103 (13.7)	86	13	99	4	1	5

[a] 203, [b] 296 missing data

Distribution of CHD among children with DS

Table 4 shows the distribution of CHD according to severity. Majority of the patients have shunt lesion CHD. VSD has the highest occurrence with 32.9% from the 420 patients, followed by PDA (29.8%) and AVSD (18.4%). In terms of severity, 176 (42%) are severe, 43% mild and 15% moderate CHD.

Table 4. Distribution of severity of the congenital heart defect

Specific CHD	Total		Severity of CHD					
			Mild		Moderate		Severe	
	n	%	n	%[a]	n	%[a]	n	%[a]
Shunt lesion								
VSD	138	32.9	62	44.9	29	21.0	47	34.1
PDA	125	29.8	77	61.6	24	19.2	24	19.2
AVSD	77	18.4	0	0	0	0	77	100
ASD	44	10.5	35	79.5	9	20.5	-	-
RVOT obstruction	17	4.0	0	0	0	0	17	100
TOF	8	1.9	7	87.5	0	0	1	12.5
PS	2	0.5	0	0	0	0	2	100
PAVSD	1	0.2	0	0	0	0	1	100
PAIVS								
LVOT obstruction	1	0.2	0	0	1	100	-	-
Aortic stenosis								
Ebstein Anomaly	2	0.5	0	0	0	0	2	100
DORV	2	0.5	0	0	0	0	2	100
TGA	1	0.2	0	0	0	0	1	100
TAPVD	1	0.2	0	0	0	0	1	100
Tricuspid atresia	1	0.2	0	0	0	0	1	100
Total	420	100	181		63		176	

[a] % of specific CHD

Management option of the CHD

As shown in Table 5, 207 (49.3%) of the patients with DS and CHD required surgical treatment whereby 145 patients had the surgery and 62 are waiting for surgery. In 171 (40.7%) patients, surgery was not offered due to small shunt defect and high likelihood that the shunt will close spontaneously with majority were diagnosed with PDA (n=73). A total of 42 (10%) patients were decided for conservative treatment, of which 28 of them diagnosed with AVSD.

Table 5. The management option of congenital heart defect among Down Syndrome

Specific CHD	Total	Surgery		No surgery		Conservative	
		n	%	n	%	n	%
Shunt lesion							
VSD	138	73	52.9	59	42.8	6	4.3
PDA	125	50	40.0	73	58.4	2	1.6
AVSD	77	49	63.6	-	-	28	36.4
ASD	44	9	20.5	31	70.5	4	9.0
TOF	17	17	100				
RVOT obstruction							
PS	8	1	12.5	7	87.5		
PAVSD	2	2	100				
PAIVS	1	1	100				
LVOT obstruction							
AS	1			1	100		
Ebsteins anomaly	2	1	50			1	50
DORV	2	1	50			1	50
TGA	1	1	100				
TAPVD	1	1	100				
Tricuspid atresia	1	1	100				
Total	420	207		171		42	

[a]145 from the 207 had corrective surgery done, 62 awaiting surgery
% of specific CHD

Mortality among the patients with Down Syndrome

Table 6 shows the demographic features among the patients that died. There were total of 131 deaths with the majority of them are female and of Malay ethnicity. From the total of 420 patients with CHD, 95 (29%) died, compared to 36 (10.8%) died among the 334 patients without CHD.

Among the patients with other medical conditions, 11 (26.8%) with duodenal atresia and 4 (36.4%) with hematological malignancies died. A large number of patients with primary persistent pulmonary hypertension and pulmonary hypertension died with, 40 (30.9%) and 42 (40.4%) respectively.

Table 6. Outcome of patients with Down syndrome

Characteristic	Total n=754	Outcome			
		Alive		Died	
		n= 623	%	n= 131	%
Sex					
Female	368	294	79.9	74	20.1
Male	386	329	85.2	57	14.8
Race					
Malay	581	474	81.6	107	18.4
Chinese	108	91	84.3	17	15.7
Indian	40	36	90.0	4	10.0
Others	25	22	88.0	3	12.0
Gestation					
Premature	105	82	78.1	23	21.9
Term	647	541	83.6	106	16.4
Maternal age					
< 35yr	245	199	81.2	46	18.8
≥35	306	248	81.0	58	19.0
Maternal DM					
Yes	58	46	79.3	12	20.7
No	696	577	82.9	119	17.1
CHD					
Yes	420	325	70.8	95	29.2
No	334	298	89.2	36	10.8
Weight at diagnosis					
<2.5kg	178	133	74.7	45	25.3
≥2.5kg	515	441	85.6	74	14.4

Table 6, continued

Characteristic	Total n=754	Outcome			
		Alive		Died	
		n= 623	%	n= 131	%
Additional medical conditions					
Thyroid dysfunction	197	174	88.3	23	11.7
Alimentary tract:					
Duodenal atresia	41	30	73.2	11	26.8
Anorectal malformation	34	31	91.2	3	8.8
Hirschsprung disease	14	12	85.7	2	14.3
Transient abnormal myelopoiesis	26	20	76.9	6	23.1
Acute myeloid leukaemia	11	7	63.6	4	36.4
Persistent pulmonary hypertension of newborn	101	61	60.4	40	30.9
Pulmonary hypertension	103	62	59.6	42	40.4

Mortality among children with DS and CHD

Table 7 shows the mortality rate according to the CHD diagnosis. AVSD has high mortality rate with 44% (n=34) in which 20 of them were treated conservatively. Almost 18% (n=24) of the patients with VSD died. Among the 17 patients diagnosed with tetralogy of Fallot (TOF), 6 (35.3%) patients died, all died prior to surgery. None of the patients with pulmonary stenosis died.

Meanwhile, a total of 38 (40%) patients died prior to surgery. Almost 16% (n=15) died after had surgery and almost a third of the patients died are among the patients treated conservatively.

Table 7. Diagnosis specific mortality rate of congenital heart defect among patients with Down Syndrome

Specific CHD	Total	Mortality Rate (%)	Death							
			Prior surgery		After surgery		No surgery		Conservative	
			n	%	n	%	n	%	n	%
Shunt lesion										
VSD	138	17.4	9	6.5	3	2.2	7	5.1	5	3.6
PDA	125	13.6	6	4.8	9	7.2	2	1.6	0	0
AVSD	77	44.2	12	15.6	2	2.6	0	0	20	26.0
ASD	44	15.9	1	2.3	0	0	4	9.1	2	4.5
TOF	17	35.3	6	35.3	0	0	0	0	0	0
RVOT obstruction										
PS	8	0	-		-	-	-	-	-	-
PAVSD	2	100	1	50.0	1	50.0	0	0	0	0
PAIVS	1	0	-		-		-	-	-	-
LVOT obstruction										
AS	1	0	-	-	-	-	-	-	-	-
Ebstein's anomaly	2	50.0	0	0	0	0	0	0	1	100
DORV	2	100	1	50.0	0	0	0	0	1	50.0
TGA	1	100	1	100	0	0	0	0	0	0
TAPVD	1	0	-	-	-	-	-	-	-	-
Tricuspid atresia	1	100	1	100	0	0	0	0	0	0
Total	420	22.6	38		15		13		29	

% of specific CHD

Death per year according to management option

The lowest number of patients with DS diagnosed with CHD was in 2007 with only 36 patients per year as shown in Table 8. The highest number of patients was born in 2012 which also had highest number of death with 18 from the 51 DS with CHD. Unfortunately, there is a high number of patients that died while waiting for surgery especially for those born in 2011-2012 with 50% died prior surgery. However, from 2013 to 2015, the number of deaths reduced with only 2 died before surgery in 2015. The number of patients who died after surgery was relatively low with less than 5 patients each year.

Table 8. Total death according to treatment categories per year

Outcome	Total n (%)	Birth Year									
		2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Total DS With CHD	420	41	36	39	37	42	39	51	47	46	43
Patients requiring surgery	207	15	19	16	20	14	15	29	27	25	27
Surgery	38	2	1	4	4	2	5	8	5	5	2
-Died before surgery	15	0	0	1	0	1	1	4	2	3	3
-Died after surgery											
Patients not requiring surgery	171	21	11	20	15	22	20	17	16	16	14
-Died	13	2	0	1	1	3	2	1	2	1	0
Conservative	42	5	6	3	2	6	4	5	4	5	2
-Died	29	3	4	3	1	5	1	5	3	3	1
Total death	95	7	5	9	6	11	9	18	12	12	6

Risk factors of death among patients with DS and CHD

Table 9 shows univariate analysis looking at the factors associated with death for the patients with DS and CHD. Age at the diagnosis less than 3 months old, severe CHD, AVSD and presence of PPHN were significantly associated with poor outcome.

However, after multivariate analysis, only 2 factors remain significant. As shown in Table 10, severe CHD (OR: 3.117, 95% CI 1.741- 5.581, $p<0.001$) and presence of PPHN (OR:2.606, 95% CI 1.452-4.667, $p=0.001$) significantly associated with higher risk for death.

Table 9. Univariate analysis of factors for high mortality among patients with DS and CHD

Characteristic	Total n=420	Outcome		p-Value
		Alive	Died	
Sex				
Female	228	173	55	0.4888
Male	192	152	40	
Race				
Malay	316	242	74	0.557
Chinese	70	56	14	0.632
Indian	21	17	4	0.689
Gestation				
Premature	62	44	18	0.143
Term	357	281	76	
Maternal Age[a]				
< 35yr	152	115	37	0.668
≥35	181	140	41	
Maternal DM				
Yes	45	33	12	0.099
No	375	292	83	
Weight at diagnosis				
<2.5kg	111	78	33	0.105
≥2.5kg	275	219	56	
Age at diagnosis				
<3 months	346	259	87	0.008
≥3 months	74	66	8	
CHD				
AVSD	77	43	34	<0.001
Other CHDs	343	282	61	
Severity				
Severe	176	111	65	<0.001
Moderate	63	49	14	
Mild	181	167	14	
Persistent Pulmonary Hypertension of Newborn				
Yes	71	43	28	<0.001
No	349	282	67	

Table 10. Multivariate analysis of risk factors of mortality among patients with Down syndrome with congenital heart defect

Risk factors	OR (95% ci for odds ratio)	p-value
Severe CHD	3.117 (1.741- 5.581)	**<0.001**
Presence of PPHN	2.606 (1.452-4.677)	**0.001**
AVSD	1.832 (0.976-3.440)	0.060
Age at diagnosis <3 months	1.944 (0.854-4.426)	0.113

Multicollinearity were checked and not found
Hosemer-Lemeshow test p= 0.998, Pearson Chi-square & Sig. p=0.000

Classification table (overall correctly classified percentage=78.5)

Survival probabilities

Survival analysis was done with Kaplan Meir analysis as shown in Figure 3. The survival probabilities for all DS in this study for patients up to 1 year of age was 82% while it was 79% for patients up to 5 years. 77% of patients survived at 10 years. The majority of the death (24%) occurred in the first 2 years of life.

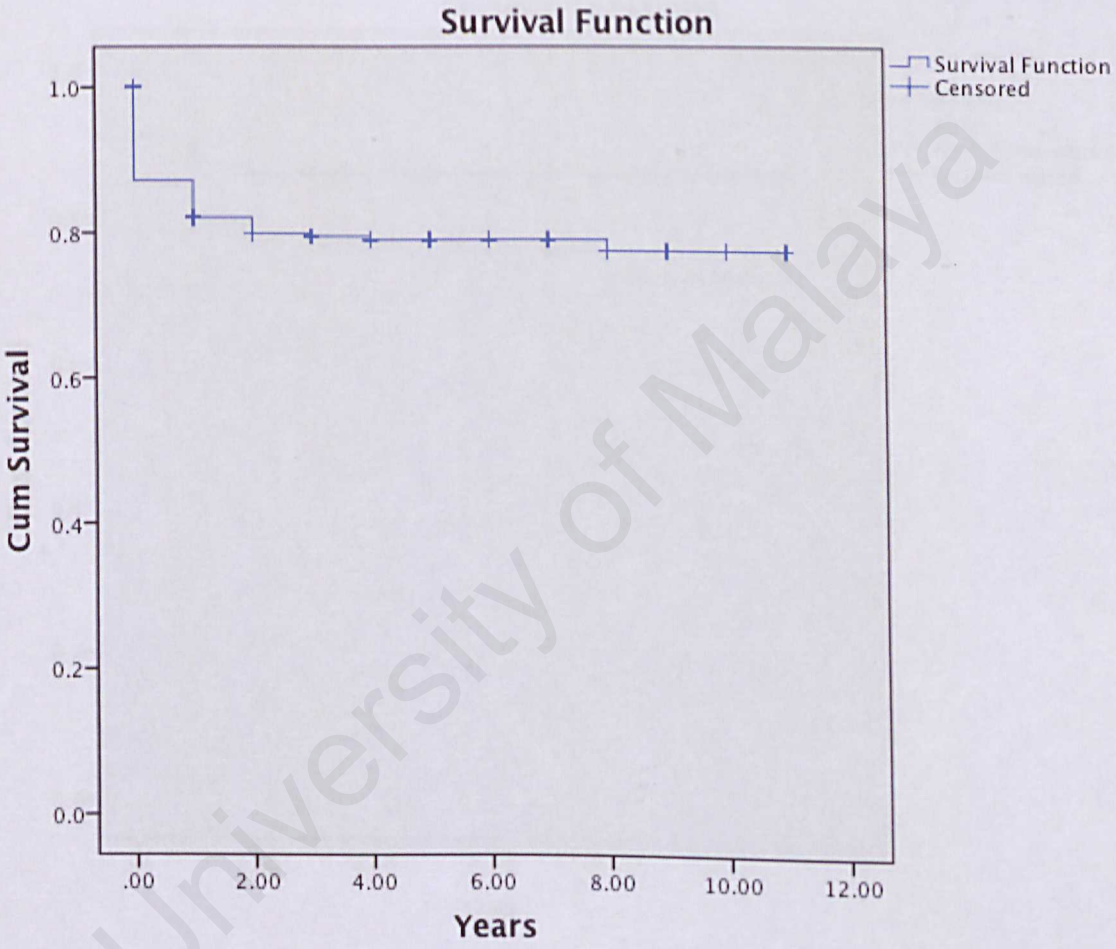


Figure 3. 10- year survival curve of all DS patients

Figure 4 shows the difference in survival probabilities between the patients with CHD and without CHD. At 1 year, 84% patients without CHD survives and 79% patients with CHD survives. The difference in survival probabilities widened at 10 years with 82%for patients without CHD and 75% for patients with CHD.

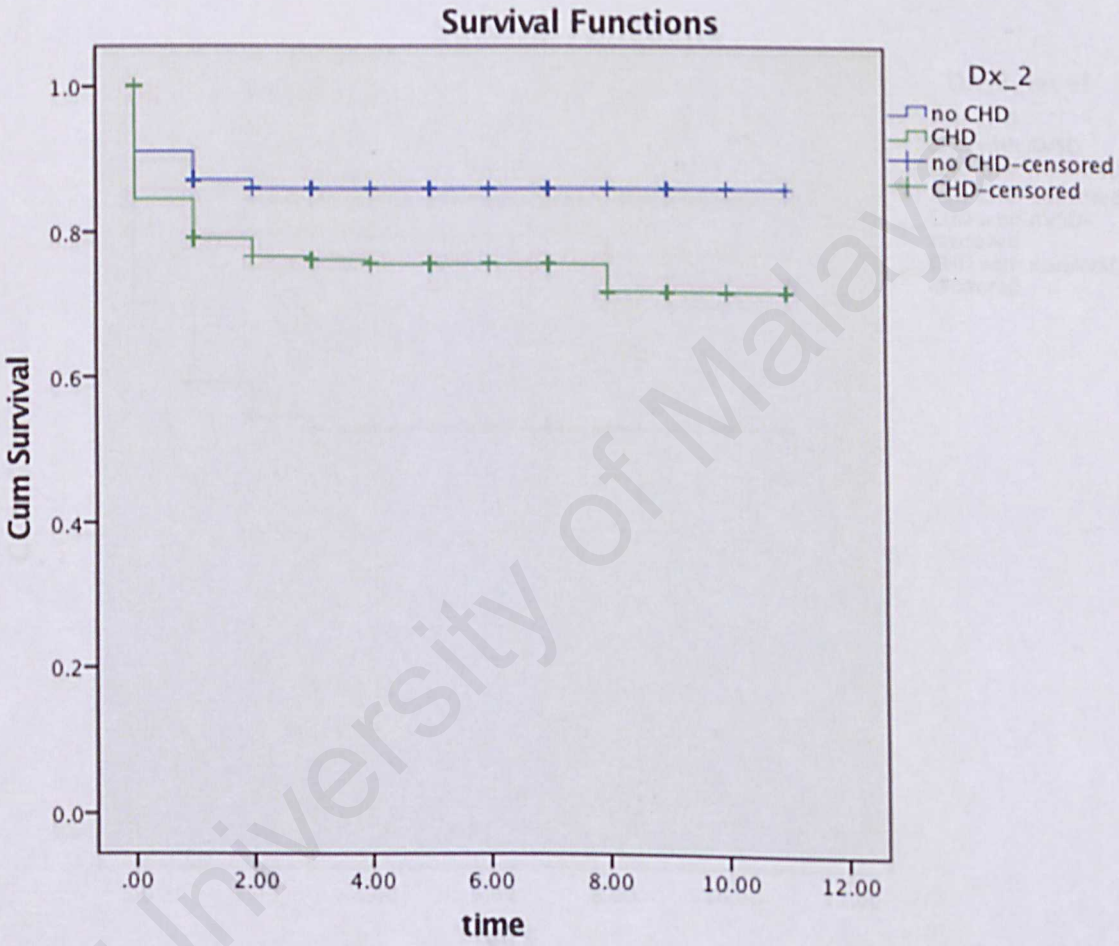


Figure 4. Survival curve comparing between patients with DS with and without CHD

Figure 5 shows the survival analysis when comparing between the 3 groups; non-CHD, CHD-AVSD and CHD other than AVSD as the diagnosis (CHD-non-AVSD). Patients with CHD other than AVSD has survival probability of 83% to 1 year and 78% to 10 years, close to the non-CHD group. AVSD has poorest survival outcome with only 60% to 1 year and 54% to 10 years.

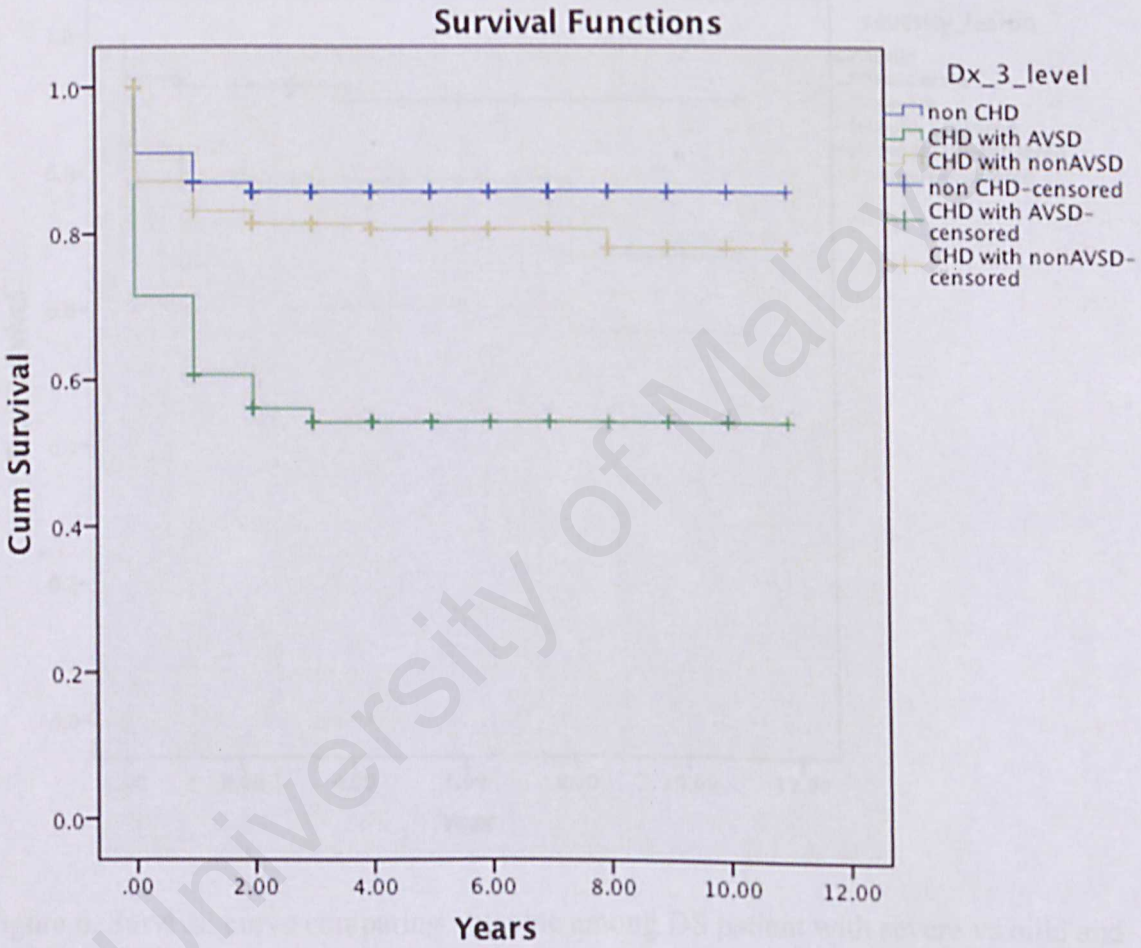


Figure 5. Survival analysis comparing between non-CHD, CHD-AVSD and CHD-non-AVSD patients

Figures 6 to 8 showed the survival curve according to the risks that were associated with poorer outcome for children with DS and CHD. From Figure 6, only 66.3% patients with severe CHD are alive at 1 years compared to 78.7% for moderate and 92.4% for the mild group. ($p<0.001$)

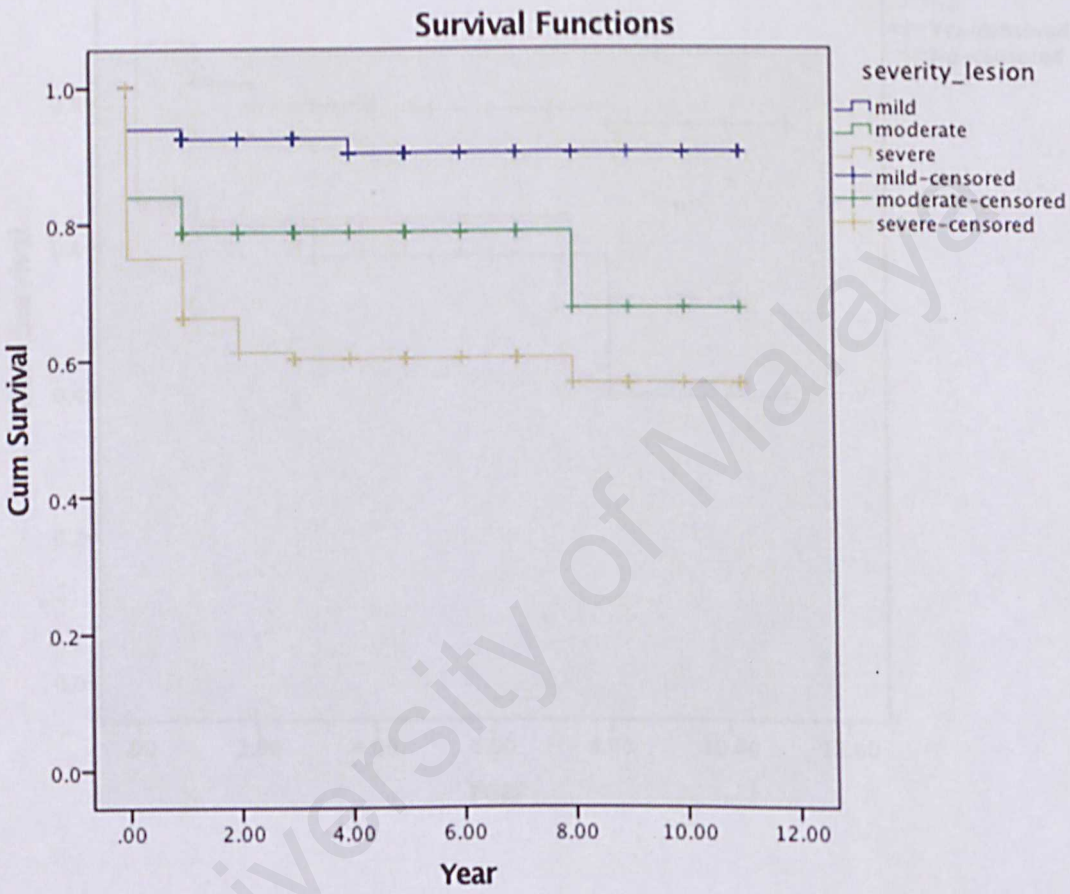


Figure 6. Survival curve comparing outcome among DS patient with severe vs mild and moderate CHD

From figure 7, only 62.4% patients that had PPHN survives to 1 year of age compared to 82.8% for those without. At 10 years, only 38% with PPHN survived.

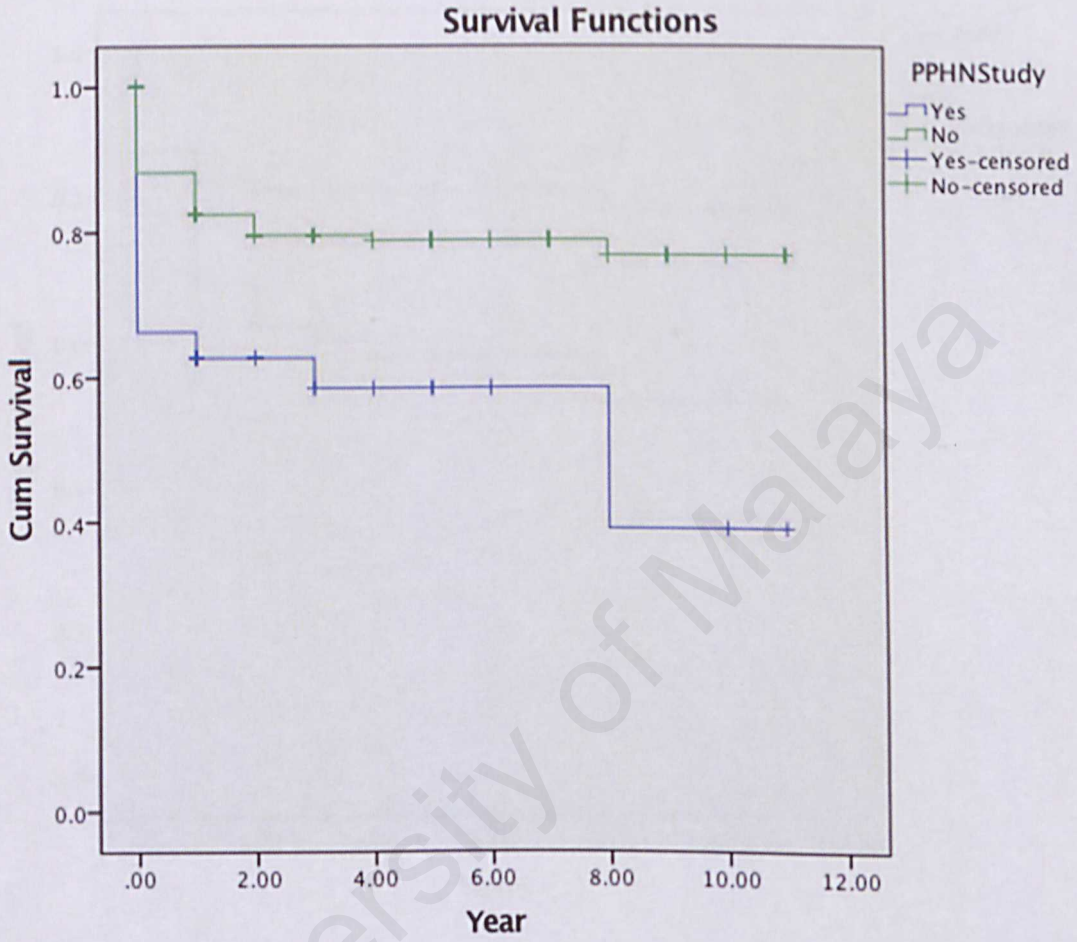


Figure 7. Survival curve comparing outcome among DS patient with and without PPHN

When the survival of patients with PHT were analysed, 67.9% survived at 1 year and 51.4% survived at 10 years of age. ($p<0.001$). (Figure 8)

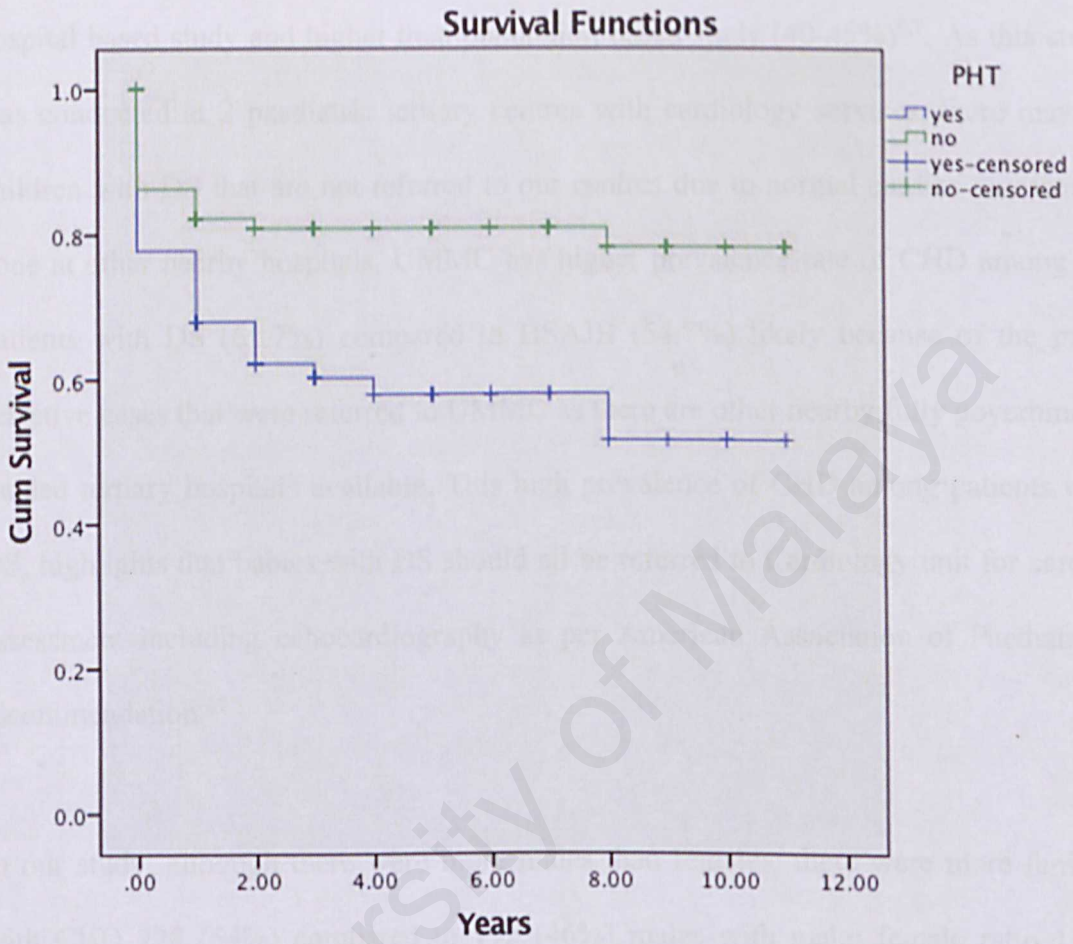


Figure 8. Survival curve comparing outcome among DS patient with PHT

DISCUSSION

CHD is one of the most common congenital anomaly associated with DS. 56% of the DS patients in this study has CHD, within the range 50-60%[9,11] described in previous hospital based study and higher than population based study (40-45%)[6,7]. As this study was conducted at 2 paediatric tertiary centres with cardiology services, there may be children with DS that are not referred to our centres due to normal cardiac assessment done at other nearby hospitals. UMMC has higher prevalence rate of CHD among the patients with DS (61.7%) compared to HSAJB (54.7%) likely because of the more selective cases that were referred to UMMC as there are other nearby fully government-funded tertiary hospitals available. This high prevalence of CHD among patients with DS, highlights that babies with DS should all be referred to Cardiology unit for cardiac assessment including echocardiography as per American Association of Paediatrics' recommendation.[27]

In our study, although there were more males than females, there were more females with CHD 228 (54%) compared to 192 (46%) males with male: female ratio 1:1.2, similar as reported in other studies. [7,11] Malay was the largest ethnicity in this cohort, followed by Chinese and Indian, reflecting the racial distribution in Malaysia. There were 105 patients that born prematurely (13.9%), defined by delivery before 37 weeks' gestation. This is similar to the nation premature percentage which was reported at 12.3% in 2014. From the 423 available karyotyping results, non-disjunction was the cause of the trisomy 21 in 97% of the patients, similar as the report by Parker et al.[1]

The majority of the patients are born to mothers aged more than 35 years which correlate with the higher incidence of Down syndrome with advanced maternal age. CHD occurred in 44 (77%) infants of diabetic mother higher than the 5% risk of CHD

among non-syndromic infant of diabetic mother.[36] Overall, 95% of patients with DS was referred in their first year of life, with 65% in the neonatal period. Almost all patients from UMMC had their first cardiac screening in the neonatal period due to easily accessible cardiac services compared to HSAJB. There were 6 patients with DS that had the cardiac assessment after 5 years old. They missed the cardiac assessment due to logistic reasons and had been well. They were picked up when referred for developmental delay. The diagnosis was small VSD in 2 patients and normal heart for the other 4 patients.

Thyroid dysfunction was reported in 197 (26%) of our patients, higher than the reported incidence of 4-18% of patients with DS[27]. Transient abnormal myelopoiesis occurred in only 26 (3.5%), lower than the 10% reported but acute myeloid leukaemia occurred in 11 (1.5%) patients, similar as the incidence rate reported in the American Academy of Paediatrics' report[27]. However, it is beyond the scope of this study to look in depth the criteria used by the clinicians for the diagnosis of the associated medical illness reported. The number of patients with anomaly of the gastrointestinal tract in this study was also higher than reported in previous studies. Freeman et al reported among 1892 children of Down syndrome in 6 states in United States of America, duodenal atresia present in 3.9%, anorectal malformation in 1%, and Hirschsprung disease in 0.8%. [37] In this study duodenal atresia present in 5.4%, anorectal malformation in 4.5% and Hirschsprung disease in 1.9%. However, this could reflect the fact that this study was done at the tertiary referral centre for paediatric surgical cases.

Recent studies from Asian countries including our neighbouring Singapore and Thailand had shown that VSD was the most common cardiac defect in their DS patients. This was different from vast studies conducted in Caucasian communities that reported

AVSD as the number one CHD among their patient with DS. Our study had similar finding with our Asian counterparts whereby VSD is the commonest CHD with 32.9% followed by PDA (29.8%), as shown in Table 11. AVSD falls to number three with 18.4%. Another difference of CHD distribution between Asian and Caucasian is that there were none or very small number of coarctation of aorta among Asian DS in comparison to Caucasian that has higher prevalence of left heart lesions. We did not found any coarctation of aorta in our patients. This highlights genetic predisposition to different types of CHD or possibility that termination of pregnancy in Caucasian societies resulting in different distribution of the cardiac defects.

Table 11. Comparison with other studies on prevalence and types of CHD

	Current study	Hoe[8] (Malaysia)	Tan[11] (Singapore)	Layangool[9] (Thailand)	Freeman[7] (Atlanta)	Stoll[6] (France)
Number of cases	754	34	588	400	218	139
Percentage with CHD	56	50	65.5	49.8	44	44.6
Types of CHD among DS (% of DS+CHD)						
VSD	*32.9	*43.6	*39.2	*24.6	35	22
PDA	29.8	8.8	34.3	22.6	20	5
AVSD	18.4	15.5	15.6	17.1	*45	*30
ASD	10.5	13.4	23.4	17.1	26	25
CoA	0	0	0.3	1.0	1	5

*Most common CHD reported.

In general, the presence of CHD has huge impact for the survival of the DS patients. To the best of our knowledge, this is the first study looking at the outcome of DS patients with CHD in Malaysia. The mortality rate among the children with DS and CHD in this study was 22.6%, similar to report by Frid et al.[22] The mortality was highest in the first year of life with majority of the patients died due to heart failure or associated with pneumonia or sepsis.

The survival probabilities for patients with CHD were 79% and 75% up to one and 10 years, lower than the survival probabilities for patients without CHD; 84% and 82% up to one and 10 years. Our survival rate among the patients with CHD was also lower than the rate reported from United Kingdom (94% in 1996-2006) and United States of America (93% in 1993-2003). This is likely because of the fact that they are more resourceful allowing prenatal diagnosis from fetal echocardiography, early surgery; as early as within the first 4 months of life and the advancement in technical surgical expertise and postoperative care.

The types of CHD would definitely determine the outcome. We observed significantly poorer outcome among the patients with AVSD. The survival probabilities to 1 year was only 60% for AVSD compared to 83% for others CHD and 87% for those without CHD. Even though AVSD may affect the survival of children with DS, it is usually amenable to curative surgical intervention. Only 2 of the 34 patients with AVSD died after surgery. Both patients died from sepsis, non-related to the cardiac surgery. The patients that went for AVSD repair were strictly selected. Patients with AVSD were treated conservatively because of the presence of severe atrio-ventricular valve regurgitation, pulmonary hypertension or unbalanced AVSD morphology. Single ventricle palliative surgery is not an option in DS children due to their pre-existing

vascular obstructive disease which may contribute to elevated pulmonary arterial pressure.[38]

Studies have shown that early surgical treatment is beneficial. Surgery within the first 6 months of life is considered as the optimal time for definitive repair before the patients progress to develop pulmonary vascular disease.[28] In this study, patients were strictly selected for surgery, with 42 (17%) of the patients that required surgery were decided for conservative management. Apart from that, with small number of surgically treated patients, analysis of the age at surgery was not feasible. However, this study was not designed to look at the impact of early in comparison to late surgery.

The gestational age is not a risk factor for poor prognosis in the patients with DS and CHD. Only the severity of the CHD and the presence of PPHN were significantly associated with the poor prognosis. From our survival analysis, the severity of CHD has the highest impact on the survival for the first 2 years of life. This emphasis on pre-operative management in terms of providing adequate nutrition to gain sufficient weight, avoidance of infection and vaccination including influenza and RSV vaccine, and optimisation of medical therapy to control heart failure.

The presence of persistent pulmonary hypertension in newborn affects the survival probabilities from early age with further declining by 10 years of age. Thus, close monitoring of pulmonary pressure from estimated right ventricle systolic pressure from echocardiography is necessary in DS newborn with PPHN. Medical treatment options such as oral pulmonary vasodilator can be offered to patients with PPHN to prevent progression while waiting for surgery.

From the survival analysis, presence of PHT declines further the survival probabilities at 10 years consistent to the finding reported by Boris et. al that reported PHT increased the mortality rate by 2-fold in adults with CHD.[34] The further declining is seen because of the progression of the disease causing reducing functional status and subsequent right heart failure. This leads to premature death mostly related to recurrent chest infections.[39]

CONCLUSIONS

CHD is the commonest congenital anomaly associated with DS. The prevalence was 56% in this study, highlighting the importance of early cardiac screening including echocardiography for children with DS. Types of CHD is different compared to the Caucasian. VSD is the commonest CHD; similar to findings from other Asian studies. The survival of DS with CHD to 1 and 10 years are 79% and 75%, respectively. The severity of the CHD and the presence of PPHN carries poor prognosis for the survival of the children with DS. It is important to refer for early surgery before pulmonary hypertension occurs.

Limitations

There are several limitations in this retrospective study. Data obtained rely heavily on good documentation. Some important data were lost or not properly documented. There were also missing medical records and karyotyping results. There is possibility of selection bias as this study was done at centres with cardiology services.

Recommendations

It is recommended that a nation-wide DS registry to be available. Findings from such registry would aid clinicians in making decisions as well as enable better family counselling. There is a need further prospective studies to explore children with DS and PHT as well as the quality of life of children with DS and CHD.

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APPENDIX

Appendix 1: Ethical Committee Approval: HSAJB

UNIVERSITY OF MALAYA MEDICAL CENTRE

MEDICAL RESEARCH ETHICS COMMITTEE
(Formerly known as Medical Ethics Committee)
UNIVERSITY OF MALAYA MEDICAL CENTRE
ADDRESS : LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEPHONE : 03-79493209/2251 FAXIMILE : 03-79492030

NAME OF ETHICS COMMITTEE/IRB Medical Research Ethics Committee, University Malaya Medical Centre	**MREC ID NO**: 201723-4886
ADDRESS : LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA	
PROTOCOL NO(if applicable) :	
TITLE: OUTCOME OF DOWN SYNDROME PATIENTS WITH CONGENITAL HEART DEFECT	
PRINCIPAL INVESTIGATOR : Dr Norazah Bt Zahari	**SPONSOR**

The following item [✓] have been received and reviewed in connection with the above study to conducted by the above investigator.

[✓] Application to Conduct Research Project(form)	Ver.No :	Ver.Date : 08-02-2017
[✓] Study Protocol	Ver.No : 1	Ver.Date : 16-02-2017
[ ] Patient Information Sheet	Ver.No :	Ver.Date :
[ ] Consent Form	Ver.No :	Ver.Date :
[ ] Questionnaire	Ver.No :	Ver.Date :
[✓] Investigator's CV / GCP (Dr Norazah Bt Zahari,Hasliza A Razak, Premala Muthukumarasamy,)	Ver.No :	Ver.Date :
[ ] Insurance certificate	Ver.No :	Ver.Date :
[✓] Other documents		

and the decision is [✓]

[ ] Approved (Full Board)
[✓] Approved (Expedited)
[ ] Rejected(reasons specified below or in accompanying letter)

Comments:

Retrospective study

The Investigators are required to:

1) *follow instructions, guidelines and requirements of the Medical Research Ethics Committee.*
2) *report any protocol deviations/violations to Medical Research Ethics Committee.*
3) *provide annual and closure report to the Medical Research Ethics Committee.*
4) *comply with International Conference on Harmonization – Guidelines for Good Clinical Practice (ICH-GCP) and Declaration of Helsinki.*
5) *obtain a permission from the Director of UMMC to start research that involves recruitment of UMMC patient.*
6) *ensure that if the research is sponsored, the usage of consumable items and laboratory tests from UMMC services are not charged in the patient's hospital bills but are borne by research grant.*
7) *note that he/she can appeal to the Chairman of Medical Research Ethics Committee for studies that are rejected.*
8) *note that Medical Research Ethics Committee may audit the approved study.*
9) *ensure that the study does not take precedence over the safety of subjects.*

Date of expedited approval : 20-03-2017

This is a computer generated letter. No signature required.

Appendix 2: Ethical Committee Approval: HSAJB

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Institut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur

Tel.: 03-2287 4032/2282 0491/2282 9085
03-2282 9082/2282 1402/2282 1449
Faks: 03-2282 0015

Ruj.Kami:(5)KKM/NIHSEC/ P17-1121
Tarikh: 17-July-2017

Dr Hasliza A Razak
Hospital Sultanah Aminah

Dato'/ Tuan/ Puan,

SURAT KELULUSAN ETIKA:

NMRR-17-957-35260 (IIR)
No Protokol : NA
Outcome Of Down Syndrome Patients With Congenital Heart Defect

Lokasi Kajian:
HOSPITAL SULTANAH AMINAH

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) tiada halangan, dari segi etika, ke atas pelaksanaan kajian tersebut. JEPP mengambil maklum bahawa kajian tersebut hanya melibatkan pengumpulan data melalui:

i. **Data Sekunder**

3. Segala rekod dan data subjek adalah **SULIT** dan hanya digunakan untuk tujuan kajian ini dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi.

4. Kebenaran daripada Pegawai Kesihatan Daerah / Pengarah Hospital dan Ketua-Ketua Jabatan atau pegawai yang bertanggungjawab disetiap lokasi kajian di mana kajian akan dijalankan mesti diperolehi sebelum kajian dijalankan. Dato'/ Dr / Tuan / Puan perlu akur dan mematuhi keputusan tersebut. Sila rujuk kepada garis panduan Institut Kesihatan Negara mengenai penyelidikan di Institusi dan fasiliti Kementerian Kesihatan Malaysia (Pindaan 01/2015) serta lampiran *Appendix 5* untuk templet surat memohon kebenaran tersebut.

5. Adalah dimaklumkan bahawa kelulusan ini adalah sah sehingga **16-July-2018**. Tuan / Puan perlu menghantar dokumen-dokumen seperti berikut selepas mendapat kelulusan etika. Borang-borang berkaitan boleh dimuat turun daripada laman web Jawatakuasa Etika & Penyelidikan Perubatan (JEPP) (http://www.nih.gov.my/mrec).

i. ***Continuing Review Form*** selewat-lewatnya dalam tempoh 1 bulan (30 hari) sebelum tamat tempoh kelulusan ini bagi memperbaharui kelulusan etika.
ii. ***Study Final Report*** pada penghujung kajian.

iii. Mendapat kelulusan etika sekiranya terdapat pindaan ke atas sebarang dokumen kajian/ lokasi kajian/ penyelidik.

6. Sila ambil maklum bahawa sebarang urusan surat-menyurat berkaitan dengan penyelidikan ini haruslah dinyatakan nombor rujukan surat ini untuk melicinkan urusan yang berkaitan.

Sekian terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menurut perintah,

.....

DATO' DR CHANG KIAN MENG
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia

s.k:
HRRC Hospital Sultanah Aminah, Johor

Appendix 3: Data Collection Form

Study No:

☐Inborn
☐Outborn; _____

Antenatal History
Maternal age (years): ☐<20 ☐20-30 ☐ 30-40 ☐ >40
Gestational Diabetes: ☐ Yes ☐ No If yes, treatment:_____
Gestation : ☐ Premature ☐Term

Family h/o CHD ☐ Yes; _____ ☐No

Chromosome study result:

Age at 1st cardiac screening:
Diagnosis: ☐ DS with CHD ☐DS without CHD
CHD Diagnosis:
☐ AVSD
☐ ASD
☐ VSD
☐ TOF
☐ PDA
☐ Others:_____
PPHN ☐Yes. If yes, age resolves _____
☐No
PHT ☐Yes. If yes, age at PHT develop: _____
☐No
Other non-cardiac defect:
☐Endocrine : _____
☐Gastrointestinal : _____
☐Hematological : _____
☐Respiratory : _____
☐Musculoskeletal : _____
☐Eye : _____
☐ENT : _____
☐Others : _____
Cardiac management:
☐Surgery required
Type of surgery required: _____
Surgery ☐Done; Date of surgery: _____
☐Awaiting surgery
☐Surgery not required
☐Conservative, reason: _____
Complication of surgery
☐Yes: _____
☐No

Outcome:
☐ Survive. Date last seen : _____
☐ Died. Date of death : _____
Cause of death: _____
Death ☐Cardiac related
☐Not cardiac related