Mortality among Children with Down Syndrome in Hong Kong: a Population-based Cohort Study from Birth

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None to declare

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ABSTRACT

OBJECTIVES:

Using hospitalisation data, this study aimed to describe the mortality patterns, comorbidities, and attendance at Accident & Emergency Department (AED) among children with Down Syndrome (DS) in Hong Kong.

METHODS:

This is a population-based, retrospective cohort study of DS live births delivered between 1995 and 2014, as identified from territory-wide hospitalisation data in Hong Kong. Kaplan-Meier product-limit method was adopted to estimate the survival probabilities of children with DS by selected demographic and clinical characteristics. Cox regression analyses were conducted to examine associations of comorbidities and AED attendances with mortality patterns.

RESULTS:

There were 1010 DS live births in Hong Kong within the study period and the average rate of live births with DS was 8.0 per 10,000 live births [95% confidence interval (CI): 6.8, 9.3]. 83 DS patients died in this period. The overall half-, one-, and five-year survival probabilities were 95.8%, 94.4%, and 92.6%, respectively. There was significant reduction in the mortality rates over the study period, particularly among those born between 2000 - 2004 and 2005 - 2009 compared to those born between 1995 and 1999 ($p < 0.05$). DS patients without congenital cardiovascular anomalies and not born with low birth weight had lower mortality rates than those with these diagnoses.

CONCLUSIONS:

Over the past two decades, the early-life mortality of DS children in Hong Kong has significantly improved along with a reduction in DS live births.

MAIN TEXT

INTRODUCTION

Down syndrome (DS), characterised by the presence of or part of a third copy of chromosome 21, is the most common genetic cause of intellectual disability.(1) Live birth prevalence of Down syndrome varies between 1 and 3 per 1,000, with the exact rate depending on the maternal age distribution in the general population, and the rates of DS-related elective terminations.(2, 3) DS is known to cause multiple serious medical and surgical abnormalities, as well as health-related problems. Earlier studies showed that children with DS are at risk of congenital heart defects,(4) respiratory infections,(5) gastrointestinal malfunction,(4) ear and hearing impairments,(4, 6) childhood leukaemia,(7) and endocrine and immunological diseases.(8, 9) In particular, cardiac defects and respiratory infections have been shown to be the most common complications(10) that increase the risk of hospitalisation and early mortality. Nevertheless, with an improved general medical care and advancement in cardiac surgery,(11) health outcomes and the survival rate of individuals with DS have improved dramatically over the past decades, with the first-year survival rate increasing from 50% in 1940 to around 90% in 1990, and above 95% from 2000 onwards.(12)

Due to its medical complexity, individuals with DS require extra healthcare resources. Recent studies focused on their health problems from infancy by tracking their hospitalisation data to facilitate the development of appropriate healthcare services to address their special needs.(5, 13) Accident and Emergency Department (AED) records are a good reflection of the health impacts and associated comorbidities that affect children with DS.(14) These data could provide comprehensive and detailed descriptions on the number, the reasons and the timing of hospital attendance in patients with DS. Several different studies have demonstrated

the usefulness of assessing patterns of health care service usage. Studies have revealed that people with DS usually have early and frequent need of inpatient care, with almost 90% being hospitalised or admitted to AED in their first year of life.(15, 16) Frequent AED attendances and hospital admissions might represent higher incidence of DS-related comorbidities, and on-going or recurrent health issues. These data provide comprehensive and detailed descriptions on the mortality and morbidity patterns of new-borns with DS. These risk factors could vary across populations. Hence it is important to conduct context-specific, population-based research so that locally relevant policies and services could be implemented for people with DS in different populations.

Given that most of the studies on DS have been conducted in western contexts, and there might be substantial differences in health outcomes across ethnic groups, (17) findings from western studies might not be applicable to the Chinese population. Hence, this study utilised population-based hospital data on new-borns with DS in Hong Kong to examine the patterns of AED attendances and hospitalisation, including the number visits and reasons, and the associated mortality patterns in early-life.

METHODS

Data

We extracted data relating to individuals born with DS in Hong Kong from the Clinical Data Analysis and Reporting System (CDARS) developed by the Hospital Authority (HA). The HA is a statutory body in Hong Kong that manages all public hospitals (inpatient) and ambulatory clinics (outpatient), providing public-funded health service to all Hong Kong residents. The CDARS contains health records of all local residents including all attendances at inpatient, outpatient, and AED of public clinics and hospitals since 1995.(18) All records in CDARS are anonymous to protect patients' confidentiality. Previous local studies have demonstrated CDARS to be a reliable data source for clinical research.(19-22)

All individuals born with DS in any public hospital in Hong Kong between 1 January 1995 and 31 December 2014 were identified by using the diagnosis code of 758.0 from CDARS, which accounts for over 70% of all local live births. Most of the new-borns diagnosed with DS, however, are referred to the public health system due to its complexity necessitating regular and comprehensive medical care, which make them identifiable in our database of CDARS. Identified individuals were followed from birth until the age of five years, up to 30 June 2017, or the date of registered death, whichever was earliest. Using the unique ID generated from CDARS, their health records including diagnostic, procedural, and discharge information of all attendances at public hospital in Hong Kong were extracted from CDARS.

Ethics approval for this study was obtained from the Institutional Review Board of Hospital Authority, Hong Kong West Cluster (Reference: UW 16 – 487). Informed consent was not required from participants as all the data extracted from CDARS was de-identified and replaced by a random unique ID generated by the CDARS.

Measurements

The study dataset contained de-identified profiles of AED attendances of all infants born with DS between 1 January 1995 and 31 December 2014. Each patient had a unique profile with demographic and hospitalisation-related variables. Demographic variables included sex and date of birth; and hospitalisation-related variables included the main outcomes (i.e. the proportion of children with DS who survived and died during the follow-up period), total number of AED attendances and the reasons, and types of comorbidities. We adopted the International Classification of Diseases – 9 (ICD-9) categories to investigate the reasons for hospitalisation for each attendance.

Statistical methods

Overall survival probabilities of children with DS in the first half-year, first year, and first five years, or end of the follow-up period were estimated by the Kaplan-Meier product-limit method. The primary analysis in this study was the pattern of survival rates of new-borns with DS within their first five years of life. The first year survival of the children with DS born in each year was estimated using yearly-stratified data by the Kaplan-Meier product-limit method. The effects of sex, birth cohort, pattern of AED attendance and different congenital conditions were assessed using a Cox regression model. A two-tailed *p*-value less than 0.05 was considered statistically significant. Microsoft Excel and Statistical Package for Social Science (SPSS, version 24.0) were used for data manipulation and analysis.

RESULTS

Participant characteristics

Figure 1 shows the trend in the rate of live births with DS by year with a total of 1010 live births diagnosed with DS in Hong Kong in the period from 1 January 1995 to 31 December 2014.(23) The average rate of live births with DS was 8.0 per 10,000 live births (95% CIs: 6.8, 9.2). There was a decreasing trend in the rate of live births with DS over the past two decades, from 11.8 per 10,000 live births in 1995 to 3.4 per 10,000 in 2014. The characteristics of all identified individuals are shown in Table 1. Among the 1010 identified individuals, 593 (58.7 %) were male; and 346 (34.3%) were born in 1995-1999, 201 (19.9%) in 2000-2004, 260 (25.7%) in 2005-2009, and 203 (20.1%) in 2010-2014. Individual follow-up periods ranged from a minimum of 0.01 years to a maximum of 22.0 years. 83 (8.2%) of them died during the observation period, of which 45 has never been discharged from the hospital since birth till death.

AED attendance and its associated diagnoses

Of all the 965 individuals that were not fully admitted to hospital, 779 (80.7%) had at least one AED attendance during the follow-up period. There were 4,531 attendances in total, with a median of two AED attendances per patient. Among those with AED attendance history, 478 (61.3%) were admitted in their first half-year of life, whereas 592 (over 75%) were admitted in their first year of life. 186 (19.3%) of them have never been admitted to the AED.

During the study period, subjects admitted to the AED received various treatments and were several diagnostic outcomes. Table 2 shows the distribution of diagnostic outcomes during their AED attendance or hospital admission. There were more DS individuals (67.9%) being admitted to the AED and hospitalised for respiratory conditions than any other diagnostic categories. Other conditions, such as infectious diseases (54.3%), perinatal period (49.5%), digestive system (40.1%), nervous system and sense organs (39.1%) problems, affected a high proportion of DS individuals in their early stage of lives. DS individuals with circulatory system problems had their first attendances at the youngest age (mean age = 1.14 years), whereas those with other conditions had their first attendances between 1.21 and 1.69 years (mean age = 1.37 years).

The comorbidity patterns among the death cases were further investigated. As shown in Table 3, six out of the ten common diagnostic codes were related to the cardiovascular system including patent ductus arteriosus (PDA), atrial septal defect, ventricular septal defect, heart failure or congestive heart failure, and endocardial cushion defects. The remaining four diagnoses were pneumonia, respiratory failure, fetal/neonatal jaundice, and sepsis. Although PDA was the most common cardiac co-morbidity, only eight of them were prematurely born infants and 76% (31/41) DS individuals had more than one congenital heart defects being diagnosed.

Survival rate and its associated factors

The overall half-, one-, and five-year (or end of follow-up) survival probabilities were 95.8%, 94.4%, and 92.6%, respectively, with the highest mortality rate observed in the first half-year of life. There were no gender differences in terms of mortality throughout the whole study period. Neonatal mortality fell across the four birth cohort periods and significant reductions were observed among those born from 2000 to 2004 (adjusted hazard ratio (aHR) = 0.39, 95% CI: 0.20 – 0.76) and from 2005 to 2009 (aHR = 0.54, 95% CI: 0.30 – 0.96) compared to those born from 1995 to 1999 ($p < 0.05$). In addition, the mortality rates varied according to different types of perinatal conditions. As shown in Table 1, DS individuals diagnosed with low birth weight (aHR = 2.38, 95% CI: 1.18 – 4.83), congenital heart defects (aHR = 1.85, 95% CI: 1.15 – 2.98), and congenital anomalies of the circulatory system (aHR = 2.24, 95% CI: 1.34 – 3.75) had higher mortality ($p < 0.05$). Moreover, those with four or more complications during the first 3 months of life also had higher mortality (aHR = 1.90, 95% CI: 1.17 – 3.08). There were no significant associations between the pattern of AED attendances and mortality rate.

DISCUSSION

This study comprehensively described the pattern of AED attendances and mortality rates of new-borns with DS in Hong Kong in the past two decades. During the follow-up period, 83 mortalities were recorded, with an average lifespan of less than 0.5 years. 45 of them were never discharged from hospital since birth till death. DS individuals who died had an average of five disease categories, implying that they are medically more complex. Analysis of their comorbidity patterns revealed that over 85% of these death cases were diagnosed with cardiac defects, including PDA, atrial septal defect, ventricular septal defect, heart failure or congestive heart failure, and endocardial cushion defects. Cardiac defects are

commonly reported as the cause of mortality in DS individuals.(24) Our results concur with a recent population-based cohort study in Denmark, reporting that early DS mortality was most likely associated with congenital heart defects.(25)

Nonetheless, this study demonstrated our Hong Kong DS patients' early-life survival has improved over the past two decades. In particular, the first-year survival rate of those born in the 2000s increased to around 95% and reached 100% for the first time in 2014, which is comparable to the US data. (12) Given that the universal, government-funded medical services have been accessible to all Hong Kong citizens for decades, such improvement is likely to be attributed by factors other than a change in the health care system accessibility.

The development of a more comprehensive prenatal screening program has played a significant role to the reduction of mortality in new-borns with DS. In the past two decades, this program has expanded by the introduction of the nuchal translucency scan in 2001, first-trimester serum markers in 2005, and the establishment of a universal screening program, which have markedly impacted on the local prenatal screening for DS.(26, 27) The integrated prenatal screening program is efficient with a high detection rate and low false positive rate.(28, 29) Furthermore, the number of pregnant women participating in any DS screening programs in Hong Kong has increased by 34% in the 2000s and the trend is anticipated to continue, which could be due to the inclusion of non-invasive screening methods with enhanced safety profile. (26) Our study demonstrated a decrease in the prevalence of DS among live births in Hong Kong from 11.8 per 10,000 live births in 1995 to 3.4 per 10,000 in 2014. This is supported by evidence that more than 90% of the Hong Kong pregnant women would choose to terminate their pregnancy after a confirmed diagnosis of DS.(30) Although there were more male with DS than female in this study, a skewed sex ratio, with more males than females, is quite common in DS. In a meta-analysis of studies, Kovaleva et al. found a

sex ratio (number of males divided by number of females) of 1.21 on average in children with DS born in the 1990s.(31) However, in our Hong Kong study, the distribution is even more skewed, with a sex ratio of 1.42. Leung et al showed that the majority of Hong Kong mothers do not support termination of pregnancy on basis of gender preferences. On the contrary, Hong Kong mothers felt that they should be given the right to terminate their pregnancy for lethal congenital malformations.(30) This concurs with Swedish data that complex cyanotic heart diseases have become less common in DS babies, because of an increased selective abortion of DS foetuses with antenatal diagnoses of complex cyanotic heart diseases.(32). A meta-analysis by Diogenes et al. shows that congenital heart diseases, especially the severe condition of AVSD, is more common in females than in males with DS.(33) So, in our Hong Kong study, selective termination of children with more severe congenital heart problems, being more often female, might explain the high number of males. This could also explain a lack of gender disparity in the early-life mortality rate among people with DS in our cohort, which is contrary to findings from previous studies. (10, 34) Further studies will be needed to look into the gender and cardiac diagnoses of these aborted DS foetuses.

Our Cox regression model examined the effects of congenital and early-life factors on the mortality of people with DS. It was found that low birth weight and a diagnosis of congenital heart defect or anomaly of the circulatory system increased the risk of early mortality. These conditions are known to be the most prevalent co-morbidities among new-borns with DS,(10) and were also found to be risk factors for early mortality in infants with DS. Similar findings were also observed in other large-scale studies conducted in western countries.(25, 35, 36) However, compared to the findings in these western studies, our study found only a small effect of congenital heart defects on the early mortality of infants with DS (aHR = 1.85 vs. aHR = 4.67 in the study by Zhu et al.(25)). Probably, this is the result of our study covering a more recent birth cohort than the study by Zhu et al.(25) and the study by

Glasson et al.(35), which both cover a long series of years of birth, dating back to 1968 and 1980, respectively. In both these studies, it was found that the effect of congenital heart defects on early mortality was much smaller in children born in more recent years. With a similar to higher prevalence of congenital heart disease nationally and regionally,(37-39) enhanced clinical management and surgical techniques should be accounting for the lower rate of mortality due to heart defects in this Hong Kong DS cohort. Advancement in non-invasive cardiac imaging allows more accurate antenatal and postnatal assessment of congenital heart diseases,(40) while early correction of congenital cardiovascular and gastrointestinal defects improved early-life mortality among DS patients.(41-43) Versacci et al. reviewed how a better understanding of various congenital heart defects and an improvement in their surgical management could reduce early-life mortality among DS patients. Newborn physical examination alone may not be sufficient to detect congenital heart defects as persistently elevated pulmonary vascular resistance could mask important clinical signs.(44) Data has shown that early screening by neonatal cardiac echocardiogram enabled the detection of congenital heart defects in DS newborns significantly earlier.(45) Persistent pulmonary arterial hypertension is common in DS due to congenital heart defects, therefore warranting early surgical corrections, especially for large left-to-right shunt lesions.(46) Repair of partial or complete atrioventricular septal defect, tetralogy of Fallot, or the combination of both in DS patients during their early childhood was also reported to carry low operative risk.(44) Recent cohort studies in the USA and Japan also showed that there were no significant mortality rate differences in major congenital heart operations between patients with or without DS.(47, 48) Therefore, the advancement in medical technologies in detecting and treating comorbidities, along with an effective of prenatal screening program, and option of selective abortion of DS foetuses with more severe congenital abnormalities attributes to an overall reduction of mortality amongst live-born DS babies.

Despite a reduction in mortality, new-borns with DS experience early onset of health complications. In our study, DS patients who died had on average five categories of medical diagnoses, particularly those related to the endocrine, haematological, respiratory, and neurological systems. DS new-borns with four or more complications in the first 3 months of life also had higher mortality. These findings suggest that healthcare professions should provide timely and appropriate counselling for their associated complications, starting from prenatal visits to help families decide whether they should continue with their pregnancies, financial planning and psychological preparation for the long-term care of their children with DS; as well as health supervision and anticipatory guidance from birth to various stages of lives till adulthood.(49) Moreover, our findings can also provide evidence to policymakers and healthcare professionals in planning and allocating resources to DS individuals who have multiple complications.

This study has several limitations. First, we included all live births with DS born after 1 January 1995 and we focused on assessing the early-life mortality pattern of people with DS. Later life mortality and life expectancy was not assessed. Second, the CDARS electronic health record system only captures live births and AED admissions in public hospitals, but not in private hospitals, which might lead to a slight under-estimation of the actual prevalence. However, over 70% of the live births in Hong Kong and 90% of AED admissions were estimated to take place in the public sector. Our cohort remained to be a representative sample of people with DS in Hong Kong. Third, because of the limited accessibility of antenatal care data from the CDARS, we were unable to determine whether all the DS babies in our study were diagnosed antenatally. However, only a minority of pregnant women in Hong Kong did not receive any antenatal care or only receive antenatal care elsewhere where antenatal screening may not be comprehensive. Therefore we could predict the majority of the DS babies were identified antenatally in Hong Kong and their mothers decided to

continue with their pregnancies. Fourth, the use of ICD-9 diagnostic codes carries the risk of misclassifying patients. Although we were unable to confirm whether all patients in our cohort were diagnosed cytogenetically, genetic tests were performed in most circumstances in Hong Kong either antenatally for high-risk foetuses or postnatally if clinical features of DS were recognized. It is also uncommon in our local practice that a patient with DS is labelled without a genetic diagnosis. Therefore the chance of misclassifying a patient with DS is low.

Despite these limitations, our Hong Kong population-based DS study provides compelling evidence on the pattern of AED attendance, hospitalisation, and mortality rate in new-borns with DS during the neonatal and early childhood period. Advancements in treating comorbidities, along with an effect of a prenatal screening program, and the option of selective abortion of DS foetuses, especially those with more severe congenital abnormalities, may explain the overall reduction of mortality amongst live-born DS babies. Nevertheless, people with DS remain to be a significant population requiring careful long-term health care planning.

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Table 1. Adjusted mortality HR for covariates among children with Down Syndrome in Hong Kong

Covariate	Number of persons	Number of deaths	Adjusted HR#	95% CI
Sex				
Male	593	47	0.96	0.62 - 1.48
Female	417	36	1.00	Reference
Birth cohort				
1995 - 1999	346	45	1.00	Reference
2000 - 2004	201	10	0.39	0.20 - 0.76
2005 - 2009	260	16	0.54	0.30 - 0.96
2010 - 2014	203	12	0.53	0.28 -1.01
Number of complications in the first 3 months				
>= 4	263	27	1.90	1.17 - 3.08
< 4	747	56	1.00	Reference
Low birth weight				
Presence	64	9	2.38	1.18 - 4.83
Absence	946	74	1.00	Reference
Congenital heart defects				
Presence	235	26	1.85	1.15 - 2.98
Absence	775	57	1.00	Reference
Congenital anomalies of the circulatory system				
Presence	153	20	2.24	1.34 - 3.75
Absence	857	63	1.00	Reference
Congenital disorders of the endocrine/metabolic system				
Presence	42	5	1.74	0.70 - 4.31
Absence	968	78	1.00	Reference
Age at first AED visit				
< 0.5 year	478	28	3.17	0.96 - 10.47
0.5 - 1 year	114	5	2.36	0.56 - 9.91
>1 year	187	2	0.52	0.09 - 3.14
Never	186	48	1.00	Reference

Adjusted by age and sex of the individuals

Table 2. Health complications in children with Down Syndrome

Health complications	No of children (%)				Mean age at first admission
	Total	Age of first admission			
		<0.5 year	0.5 to 1 year	1 - 5 years	
Respiratory system	686 (71.09%)	318 (66.53%)	86 (75.44%)	131 (70.05%)	1.38
Other diagnoses	631 (65.39%)	295 (61.72%)	75 (65.79%)	111 (59.36%)	1.19
Infectious & parasitic	548 (56.79%)	252 (52.72%)	60 (52.63%)	106 (56.68%)	1.48
Perinatal period	500 (51.81%)	236 (49.37%)	51 (44.74%)	91 (48.66%)	1.21
Digestive system	405 (41.97%)	202 (42.26%)	44 (38.6%)	75 (40.11%)	1.29
Nervous system & sense organs	395 (40.93%)	187 (39.12%)	49 (42.98%)	78 (41.71%)	1.37
Circulatory system	312 (32.33%)	144 (30.13%)	36 (31.58%)	53 (28.34%)	1.14
Endocrine, nutritional and metabolic diseases, and immunity disorders	304 (31.5%)	140 (29.29%)	35 (30.7%)	50 (26.74%)	1.29
Mental disorders	261 (27.05%)	130 (27.2%)	32 (28.07%)	54 (28.88%)	1.49
Injury & poisoning	258 (26.74%)	119 (24.9%)	37 (32.46%)	44 (23.53%)	1.34
External causes	230 (23.83%)	100 (20.92%)	30 (26.32%)	45 (24.06%)	1.5
Genitourinary	181 (18.76%)	81 (16.95%)	22 (19.3%)	34 (18.18%)	1.69
Blood & blood forming organs	167 (17.31%)	75 (15.69%)	24 (21.05%)	27 (14.44%)	1.25
Skin & subcutaneous tissue	143 (14.82%)	74 (15.48%)	15 (13.16%)	27 (14.44%)	1.52
Neoplasms	70 (7.25%)	27 (5.65%)	12 (10.53%)	16 (8.56%)	1.53
Musculoskeletal & connective tissue	67 (6.94%)	32 (6.69%)	12 (10.53%)	13 (6.95%)	1.25

Table 3. Health complications in death cases of children with Down Syndrome

Health complication	No of children (%)			
	Total	Age of death		
		<0.5 year	0.5 to 1 year	1 - 5 years
Patent Ductus Arteriosus	41 (49.40%)	19 (45.24%)	7 (46.67%)	15 (57.69%)
Pneumonia	36 (43.37%)	13 (30.95%)	7 (46.67%)	16 (61.54%)
Heart Failure	35 (42.17%)	13 (30.95%)	10 (66.67%)	12 (46.15%)
Atrial Septal Defect	30 (36.14%)	11 (26.19%)	7 (46.67%)	12 (46.15%)
Ventricular Septal Defect	28 (33.73%)	11 (26.19%)	5 (33.33%)	12 (46.15%)
Fetal/Neonatal Jaundice	24 (28.92%)	13 (30.95%)	4 (26.67%)	7 (26.92%)
Sepsis	22 (26.51%)	11 (26.19%)	3 (20.00%)	8 (30.77%)
Endocardial Cushion Defects	20 (24.10%)	11 (26.19%)	3 (20.00%)	6 (23.08%)
Respiratory Failure	16 (19.28%)	4 (9.52%)	3 (20.00%)	9 (34.62%)

Figure 1. First-year survival probabilities and the live birth rates of Down Syndrome (DS) in Hong Kong. Between 1 January 1995 and 31 December 2014, the average rate of live births with DS was 8.0 per 10,000 live births (95% CIs: 6.8, 9.2), with a decreasing trend from 11.8 per 10,000 live births in 1995 to 3.4 per 10,000 in 2014. The first-year survival rate of DS children born in 1995 was 86%, which increases to around 95% in the 2000s and reached 100% in 2014.