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Congenital heart disease, gastrointestinal defect, and low birth weight as the contributing factors for three-year survival rates among Down syndrome children in Indonesia

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ABSTRACT

Background: Down syndrome is the most common congenital chromosomal anomaly and occurs in about 1-10:1.000 live births globally. Various reports stated an increasing survival rate because of advanced medical and surgical care. The highest mortality in Down syndrome children takes place in the first three years of life with its comorbidities being congenital heart disease and gastrointestinal defect. Low birth weight was also more common in Down syndrome children compared to normal children and was one of the contributing factors to higher mortality. This study aims to examine three-year survival rates among children with Down syndrome.

Methods: We included all medical records with Down syndrome children in Dr. Sardjito Hospital, Yogyakarta, Indonesia during 2013 to 2016. We excluded all medical records with inadequate data. Three-year survival rates were analyzed using Kaplan-Meier and hazard ratio was analyzed using Cox regression.

Results: The 1-year, 2-years and 3-year survival rates in Down syndrome children were 80.1%, 72.4%, and 70.8% respectively. Overall, 45% of births with Down syndrome had congenital heart disease, 11% had a gastrointestinal defect, and 9% had both congenital heart disease and gastrointestinal defect. Three-year survival rates in Down syndrome children with congenital heart disease was 61.4% (78/127) and 81.7% (89/109) (p=0.001). Three-year survival with gastrointestinal defect was 47.8% (22/46) and without was 76.3% (145/190) (p<0.001). Furthermore, three-year survival with low birth-weight was 64.6% (42/65) and without was 71.6% (111/155) (p=0.328).

Conclusion: Congenital heart disease and gastrointestinal defect lower the survival rate in Down syndrome children.

Keywords: Down syndrome, children, survival rate, comorbid.
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INTRODUCTION

Down syndrome is the most common congenital chromosomal anomaly. World Health Organization (WHO) predicts the incidence of Down syndrome was 1-10:1,000 live birth globally and 1.24:1,000 live births in Indonesia.[1] Down syndrome contributed to lower life expectancy with 17 to 23 years lower compared to general population.[2] Research conducted in Australia in 2002, showed that the Down syndrome population had a 17 until 23 years lower survival rates than the general population.[2] The highest mortality rate for Down syndrome occurs in the first year of life. Down syndrome survival in the first year was 94.9% in Norway in 1994-2009. In another study, O'Leary *et al*., 2018 stated the mortality rate in the first year was 74 out of 1,000 live births with Down syndrome, which was 8.3 times higher than the general population.[3]

Congenital heart disease (CHD) and gastrointestinal defect were two major comorbid in Down syndrome.[3] Congenital heart disease occurs in 40-50% Down syndrome children and contribute to increasing mortality with 3.4 times higher hazard ratio compared to Down syndrome population without CHD.[3,4,5] Gastrointestinal defect occurs in 6-12% Down syndrome children, but the survival rates in their group were still unknown.[3] Down syndrome babies who weighed less than 2,500 grams had a lower survival rates compared with those weight at least 2,500 grams at birth and rising the risk of death. Relative to those who weighed at least 2,500 grams, the hazard ratio for those who weighed less than 2,500 grams was 1.8.[6]

Technological advances in medicine in the last decade have increased survival in children with Down syndrome.[2,3,4] Early detection during pregnancy and neonates hastens intervention in cardiac and other comorbidities.[2] Many studies in developed countries already discussed the survival rates in Down syndrome children but the survival in Indonesia is still unknown. Therefore, from the

background mentioned above, this study aims to estimate survival rates in Down syndrome children particularly those with CHD, gastrointestinal defect, and low birth weight.

METHODS

This was a survival analysis study with cohort retrospective design in Down syndrome children using medical records in tertiary level hospital (Dr. Sardjito Hospital, Yogyakarta, Indonesia) during January 2013 to December 2017. Dr. Sardjito Hospital is the only one tertiary level referral with teaching hospital in Yogyakarta Province. All Down syndrome patients from 0-3 years old who came to children outpatient clinics and inpatient clinics were included into this study. We excluded all subjects with incomplete medical records. Data was collected using a questionnaire taken from the medical records. We contacted the parents using short text messages to know the last condition of the study subjects.

Congenital heart disease was confirmed based on echocardiography performed by child cardiologists. Gastrointestinal defect was confirmed based on surgical notes or radiology examination. Low birth weight was defined as those who were born weighing less than 2,500 grams. Data was collected using SPSS for Windows 25. Overall survival rates and survival rates in Down syndrome children with CHD, gastrointestinal defect and low birth weight were presented using Kaplan-Meier analysis. Hazard ratios were presented using univariate and multivariate Cox regression.

RESULTS

All Down syndrome patients during March 2013 and June 2016 were 260 subjects. We excluded 24 subjects with incomplete medical records. There were 69 subjects who died before their three years old birthday, while 10 of them died outside the hospital confirmed by their parents. Sixty-seven subjects completed the observation until three years old; 18 of the subjects did not come to the hospital but were confirmed by their parents that they are still alive after three years old and 49 of the subjects still came to the hospital more than three years later. One hundred subjects were lost to follow-up, among them 43 subjects did not have phone numbers and 52 subjects did not respond when contacted. Lost to follow-up subjects were considered alive and called as uninformative censoring.

Figure 1 shows the survival rates of Down syndrome children from 0 to 3 years old. Thirteen subjects (18.8%) died

Table 1. Baseline characteristics of subjects.

Characteristic	n=236 (100%)
Sex	
Male	118 (50.0)
Female	118 (50.0)
Gestational age (weeks)	
<37	39 (16.5)
37-42	175 (74.2)
>42	1 (0.4)
No data	21 (8.9)
Mothers age (years)	
<20	3 (1.3)
20-34	79 (33.5)
≥35	129 (54.7)
No data	25 (10,5)
Karyotype	
Classic trisomy 21	16 (6.8)
Robertsonian translocation	2 (0.8)
Not performed	218 (92.4)
Birth weight (grams)	
<2,500	65 (27.5)
≥2,500	155 (65.7)
No data	16 (6.8)
Heart defect	127 (53.8)
Atrial septal defect (ASD)	41 (32.3)
Patent ductus arteriosus (PDA)	40 (31.5)
Ventricular septal defect (VSD)	22 (17.3)
Atrioventricular septal defect (AVSD)	18 (14.2)
Tetralogy of Fallot (TOF)	3 (2.4)
Ebstein anomaly	1 (0.8)
Pulmonary atresia	1 (0.8)
Pulmonary stenosis	1 (0.8)
Gastrointestinal defect	46 (19.5)
Anal atresia	19 (41.3)
Hirschsprung disease	13 (28.3)
Duodenal atresia/stenosis	8 (17.4)
Biliary atresia	3 (6.5)
Annular pancreas	2 (4.3)
Pyloric stenosis	1 (2.2)

Table 2. Multivariate analysis using Cox regression.

Variable	n	Multivariate		
		p	HR	CI 95%
Congenital heart disease				
No	109			
Yes	127	0.001	2.52	1.49 – 4.24
Gastrointestinal defect				
No	190			
Yes	46	<0.001	3.42	2.08 – 5.64

*HR: hazard ratio

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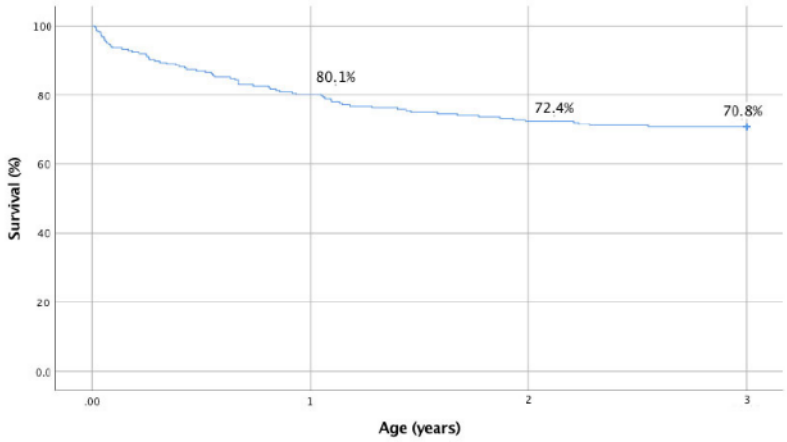

Figure 1. Down syndrome children survival rates.

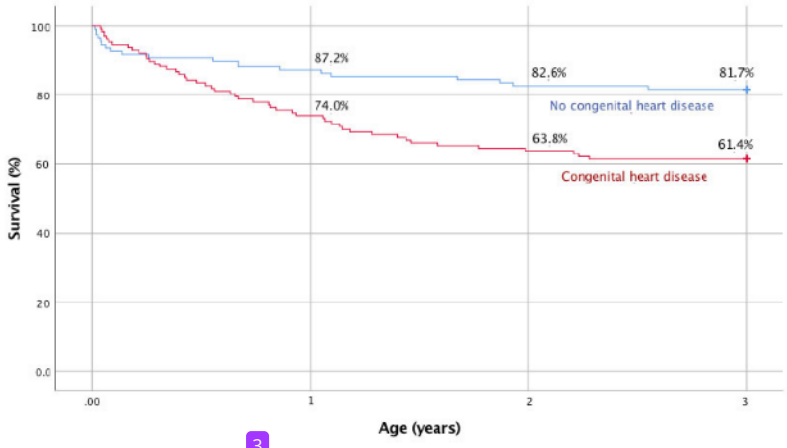

Figure 2. Survival rates in Down syndrome children with congenital heart disease.

during the neonatal period.

There was a statistically significant decrease in Down syndrome survival rates between those with and without CHD (Figure 2) (p=0.001). Relative to those without CHD, the hazard ratio for those with CHD was 2.52 (95% CI 1.38-3.91, p=0.002). The most common type of CHD was atrial septal defect (ASD) (32.2%).

Meanwhile there were also statistically significant survival rates between those with and without gastrointestinal defect (Figure 3) (p<0.001). Relative to those without gastrointestinal defect, the hazard ratio for those with gastrointestinal defect was 3.42 (95% CI 1.93-5.2, p<0.001). The most common gastrointestinal defects were anal atresia (41.3%) and Hirschsprung's disease (28.3%).

Furthermore, the three-year survival rates in Down syndrome children with low birth weight was 64.6% and without 71.6%, but the survival rates were not statistically significant (Figure 4) (p=0.328).

Multivariate analysis was carried out on the variables of heart disease and gastrointestinal defect, while the birth weight variable was not analyzed because it had p>0.25. The multivariate analysis using the Cox regression method was presented in Table 2. After multivariate analysis, the presence of gastrointestinal defects most affected Down syndrome survival rates compared to congenital heart disease.

In this study, there were 9% of subjects who had both gastrointestinal defect and congenital heart disease, 45% of subjects who only had congenital heart disease, 11% of subjects who had gastrointestinal defect, and 35% who did not have both defects. The survival rates in Down syndrome children with congenital heart disease and gastrointestinal defect was depicted in Figure 5. The lowest survival rates belonged to the group of subjects with both congenital heart disease and gastrointestinal defect.

The number of subjects who died in this study was 69 subjects. There were 10 subjects who died outside the hospital, while 59 subjects died in Dr. Sardjito Hospital. The most direct causes of death in children with congenital heart disease were sepsis 75% (18/41), acute respiratory distress syndrome (ARDS) (14.6%), pneumonia (9.8%) and disseminated intravascular coagulation (DIC) (9.8%). Meanwhile, the most direct causes of death in children with gastrointestinal defects were sepsis (54.2%), pneumonia (16.7%), DIC (12.5%), and pulmonary hemorrhage (8.3%).

DISCUSSION

The incidence of congenital heart disease in this study was 53.8%. This was similar to study by Bull, 2011 estimated the incidence to be 40-50%.[4] As in other studies, congenital heart disease is the most common disorder in Down syndrome.[7-10] In study of Irving *et al.*, 2012, the most common types of congenital heart defect were atrial septal defect (ASD) (32.2%), patent ductus arteriosus (PDA) (31.5%), ventricular septal defect (VSD) (17.3%) and atrioventricular septal defect (AVSD) (14.2%).[7] Meanwhile, Morris *et al.*, 2014 and Stoll *et al.*, 2015 stated that AVSD was the most common type of disorder.[8,9] However, similar to this study, Cleves *et al.*, 2007 stated that ASD was the most common defect found.[10] Three-year survival rates in Down syndrome children with congenital heart disease were 61.4% compared with 81.7% without congenital heart disease. More recent survival studies did not compare survival at three years of age, but five-year survival rates in the most recent study were much higher at 92% vs 97.4% (CHD vs non-CHD), 87% vs 97%

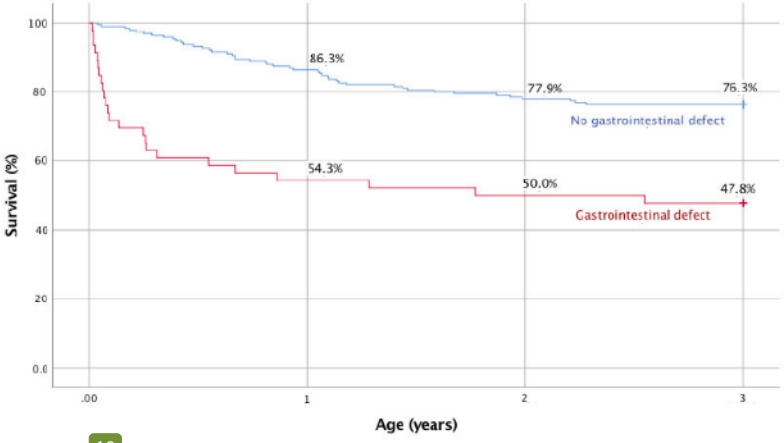

Figure 3. Survival rates in Down syndrome children with gastrointestinal defect.

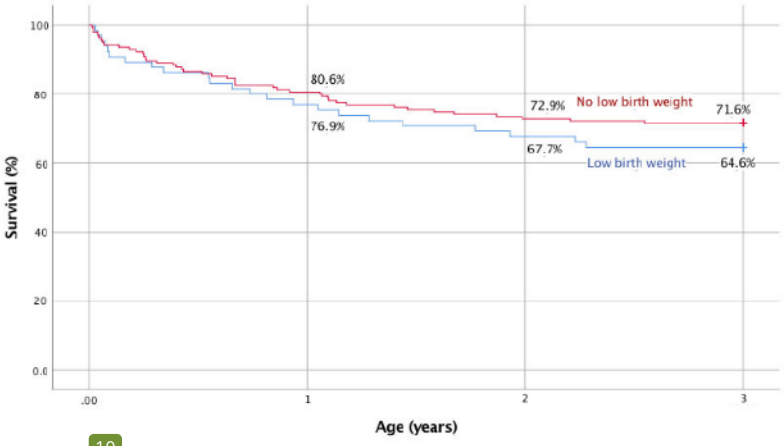

Figure 4. Survival rates in Down syndrome children with low birth weight.

and 78% vs 93%.[5,6,11]

The one-year and three-year age survival rates in this study were still equivalent to those conducted in the past three decades, and were still far behind compared to studies conducted by developed countries in this decade.[12,13] This may be due to differences in data sources, where all previous studies used national/population registers, while this study used data from tertiary referral hospitals, so that only subjects with severe conditions would be referred to the hospital. In other studies, the improvement in survival rates in the last decade can also be due to an earlier diagnosis of congenital heart disease and more aggressive intervention.[5,12,13]

The hazard ratio of Down syndrome children with congenital heart disease was 2.52 times higher than that of those without congenital heart disease (95% CI 1.49-4.24; p=0.001). In other studies, congenital heart disease had a higher hazard ratio, as in Glasson *et al.*, 2002 by 3.1 times and Leonard *et al.*, 2005 by 3.4 times.[2,5] The incidence of gastrointestinal defect in this study was 19.5%. The incidence in this study was higher than in previous studies which stated that it was 6-13%.[3,9,10] Types of gastrointestinal disorders in Down syndrome varied over passing years. In this study, the most common types were anal atresia (41.3%), Hirschsprung's disease (28.3%), and duodenal atresia/stenosis (17.4%). Based on Stoll *et al.*, 2015 the most common types of abnormalities were duodenal atresia (67%), Hirschsprung's disease (14%), and trachea-oesophageal atresia (10%).[9] While in the study of Cleves *et al.*, 2007 the most common types of abnormalities were duodenal atresia (57%), Hirschsprung's disease (21%), and anal atresia (13%).[10] Three-year survival in Down syndrome children with gastrointestinal defect was 47.8% compared to 76.3% without gastrointestinal disorders. Survival rates in Down syndrome children with gastrointestinal defects have not been studied. The hazard ratio of patients with Down's syndrome with gastrointestinal defect was 3.42 times (95% CI 2.08-5.64; p<0.001).

The incidence of low birth weight in Down syndrome children in this study was 27.5%. This incidence was higher than the incidence of low birth weight in Indonesia, which was 6.2%.[13] This was similar to the study conducted by Glasson *et al.*, 2002 that showed incidence of low birth weight in Down syndrome children compared to without Down syndrome was 20.4% versus 6.1%.[2] Three-year survival in Down syndrome children with low birth weight compared to moderate birth weight is 64.6% versus 71.6%. However, the hazard ratio from univariate analysis of Down syndrome children with low birth weight was not statistically significant (hazard ratio=0.78; 95% CI 0.47-1.29; p=0.330) and had p>0.25, so it was discontinued with multivariate analysis. In another study, hazard ratio at low birth weight was 1.8 times and 2.1 times.[5,6]

Even though other studies using retrospective data and medical records or national register data, in this study, some medical record data were incomplete, such as not mentioning Down syndrome scoring and supporting physical examination in Down syndrome. The majority of Down syndrome diagnoses in this study still used clinical criteria, while it is better to make a diagnosis of Down syndrome using karyotyping. In this study, there were 42.4% of data lost to follow-up, subjects who had lost to follow-up were subjected to uninformative censoring. Uninformative censoring is the standard method used in survival analysis, in

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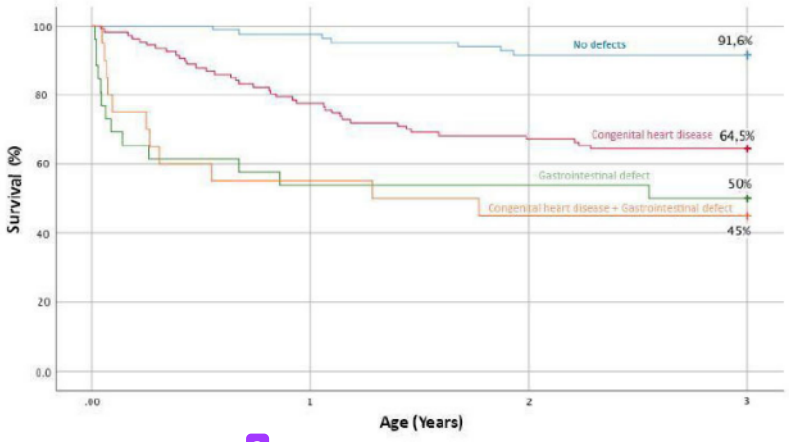

Figure 5. Survival rates in Down syndrome children with congenital heart disease and gastrointestinal defect.

which subjects who experience censoring (incomplete observations) are treated the same as individuals who remain in the study.[13,14]

CONCLUSION

The 1-year, 2-years and 3-year survival rates in Down syndrome children were 80.1%, 72.4%, and 70.8% respectively. Overall, 45% of live births with Down syndrome had congenital heart disease, 11% had gastrointestinal defect, and 9% had both congenital disease and gastrointestinal defect. Three-year survival with congenital heart disease was 61.4% (78/127) and without was 81.7% (89/109) (p=0.001). Three-year survival in Down syndrome children with gastrointestinal defect was 47.8% (22/46) and without was 76.3% (145/190) (p<0.001). Furthermore, three-year survival in Down syndrome children with low birth-weight was 64.6% (42/65) and without was 71.6% (111/155) (p=0.328).

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

ETHICAL STATEMENT

Ethical clearance was obtained from the ethical committee in the Faculty of Medicine, Universitas Gadjah Mada.

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All authors were responsible for funding in this study.

AUTHOR CONTRIBUTION

All authors contributed equally for publication of this study.

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