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Impacts of surgical interventions on the long-term outcomes in individuals with trisomy 18

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ABSTRACT

Objective: We aim to clarify whether surgical interventions can contribute to improve the long-term outcomes among individuals with trisomy 18.
Methods: We retrospectively studied 69 individuals with trisomy 18 admitted to 4 tertiary neonatal centers between 2003 and 2017. A cohort was divided into two groups: subjects with surgical interventions and conservative treatments. We compared the rates of survival and achieving homecare between the groups.
Results: Gestational age and birth weight were 37 (27–43) weeks and 1,700 (822–2,546) g, respectively. There were 68 patients with congenital heart disease and 20 patients with digestive disease. Surgical interventions including cardiac and digestive surgery were provided in 41% of individuals. There was no difference in gestational age ($p = 0.30$), birth weight ($p = 0.07$), gender ($p = 0.30$), and fetal diagnosis ($p = 0.87$) between the groups. During the median follow up duration of 51 (2–178) months, overall survival rates in 6, 12 and 60 months were 57%, 43% and 12%, respectively. Survival to hospital discharge occurred in 23 patients, and the rates of achieving homecare in 1, 6, and 12 months are 1%, 18% and 30%, respectively. There was no significant difference in survival rate ($p = 0.26$) but in the rate of achieving home care ($p = 0.02$) between the groups. Cox hazard analysis revealed that prenatal diagnosis (hazard ratio 0.30, 95%CI: 0.13–0.75), cardiac surgery (hazard ratio 2.40, 95% CI:,1.03–5.55), and digestive surgery (hazard ratio 1.20, 95%CI: 1.25–3.90) were related to the rate of achieving homecare.
Conclusion: Aggressive surgical interventions contribute not to the long-term survival but to achieve homecare among individuals with trisomy 18.
Evidence Level: Level 3 (Prognostic study, Case-Control study)

Trisomy 18 is the second most common aneuploidy in live births, and the prevalence is 1.5 per 10,000, or about 1 in 6,670 live births [1]. Median survival time for trisomy 18 is around 14 days that is extremely shorter than that for trisomy 21 (the most common aneuploidy) of 58 years [2,3,4,5]. Therefore, the majority of care providers considered trisomy 18 as lethal and advocated providing palliative care [6]. However, recent advances in neonatal intensive care have altered this perception. Neonatologists have intended to resuscitate individuals with trisomy 18 after birth [3,7,8]. Patient-centered care is advocated from the aspects that an individual's specific health needs, and desired health outcomes are the driving force behind all health care decisions and quality measurements. Patient-centered care is also important in the management of individuals with trisomy 18, and patient- and family-centered care encourages the active collaboration and decision-making to design an individualized care plan [9,10].

In the managements of individuals with trisomy 18, there are problems associated with major organ complications. Approximately 80% of individuals with trisomy 18 have congenital heart disease including ventricular septal defect (50%), atrial septal defect (15%), double outlet right ventricle (10%) and polyvalvular disease (75%) [11,12]. Complex cardiac anomalies such as hypoplastic left heart syndrome can occur.

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Digestive disease also occurs and potentially become hazardous to discharge. The most common digestive disease is esophageal atresia with/without trachea-esophageal fistula (10%), following diaphragmatic hernia and omphalocele [13]. Recent reports have shown the trend of more aggressive surgical interventions including cardiac and digestive surgery among them [12,13,14]. However, it remains unclear whether surgical interventions contribute to improve the long-term outcome in individuals with trisomy 18. Actually, they require numerous therapeutic procedures, and a number of in-patient hospital stays increased over time [3]. We therefore study the impact of aggressive surgical interventions on long-term outcomes among them.

1. Patients and methods

1.1. Patients

This study was approved in the Institutional Review Board of Kyushu Hospital, Japan Community Healthcare Organization (approval number 531). We studied 69 individual with trisomy 18 (26 males) who were admitted to 4 tertiary neonatal medical center in Kitakyushu City, Japan: Kitakyushu Municipal Medical Center (N = 11), Kokura Medical Center (N = 12), University of Occupational and Environmental Health (N = 3) and Kyushu Hospital (N = 44) between 2003 and 2017. As there are 8,000 live births per year in Kitakyushu City, the prevalence of trisomy 18 in Kitakyushu City was estimated as 5.57 per 10,000 live births. Therefore, these 4 centers cover almost all of individuals with trisomy 18 in Kitakyushu City during the period.

Definitive diagnosis of trisomy 18 was based on chromosomal analysis from peripheral blood or amniotic fluid by G-banding or fluorescence *in situ* hybridization with written informed consents from their guardians. We retrospectively collected data including demographic data, the presence of fetal diagnosis, and cardiac and digestive complications from clinical charts. Diagnosis of cardiac disease was determined by echocardiography. Cardiac surgery is carried out when patients survived beyond 14 days of age, symptoms related to cardiac disease are hazardous in achieving homecare, and their parents preferred aggressive managements. Digestive disease was diagnosed by X-ray, computed tomography or fluoroscopic gastrointestinal series. Digestive surgery is carried out when patients need to establish enteral nutrition. When parents did not wish aggressive treatments, or when we considered that a patient possessed a great risk for surgical intervention, we provided conservative treatments including intravenous administration of drugs or tube feeding. Achieving homecare is defined as a discharge alive and receiving care at home. In the current study, requirements to be discharge were following; when patients' circulatory and respiratory status are stable without invasive treatments such as intravenous administration of drug or mechanical ventilator support, and when enteral nutrition including oral bottle feeding, tube feeding or gastrostomy is established. All patients were followed up at each center. We retrospectively reviewed clinical data and divide our cohorts into two groups: patients who underwent cardiac or digestive surgery and those who were received conservative treatment. We compared the survival rate between patients with and without surgical intervention including cardiac and digestive surgery.

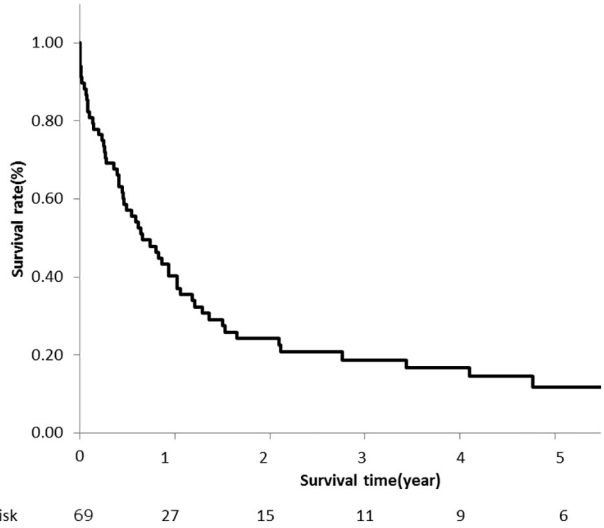

Fig. 1. The cummurative overall survival among 67 patients with trisomy 18.

1.2. Statistical analysis

Results are expressed as median values following an interquartile range. Comparisons between patients with surgical interventions and conservative treatments were made using the chi square test or Mann–Whitney *U*-test, as appropriate. We performed Kaplan-Meier survival analyses to estimate the rates of survival and achieving

Table 1
Patients' characteristic data and comparison between patients with and without surgical interventsions.

	Total N = 69	With surgical intervention N = 28	Without surgical intervention N = 41	p
Sex, male	26	9	17	0.3
Gestational age, weeks	37 (27–43)	38 (31–43)	37 (27–41)	0.3
Birth weight, g	1700 (822–2546)	1714 (994–2546)	1690 (822–2260)	0.07
Fetal diagnosis	48 (70%)	21 (75%)	27 (66%)	0.87
Cardiac disease	68 (99%)	28 (100%)	40 (98%)	1
Ventricular septal defect	38	17	21	
Double outlet right ventricle	21	9	12	
Atrioventricular septal defect	4	0	4	
Cardiac surgery (+)	18 (26%)	18 (64%)		
Pulmonary arterial banding	9			
Aortoplumonary shunt	2			
Intracardiac repair	4			
Digestive disease (+)	20 (29%)	14 (50%)	6 (15%)	<0.01
Esophageal atresia	10	8	2	
Omphalocele	2	1	0	
Digestive surgery (+)	14 (20%)	14 (50%)		
Esophageal banding + gastrostomy	8			
Gastrostomy	2			
Others	4			
Dead				
In-hospital death	46	14 (50%)	32 (76%)	0.03
Achieve home care	23	14 (50%)	9 (22%)	<0.01

homecare and compared them using log-rank test between the groups. In addition, Cox proportional hazard regression analyses were carried out to determine factors influencing the rates. $p < 0.05$ is considered statistically significant. Variables with $p<0.05$ in the univariable analysis were selected for inclusion in the multivariable model.

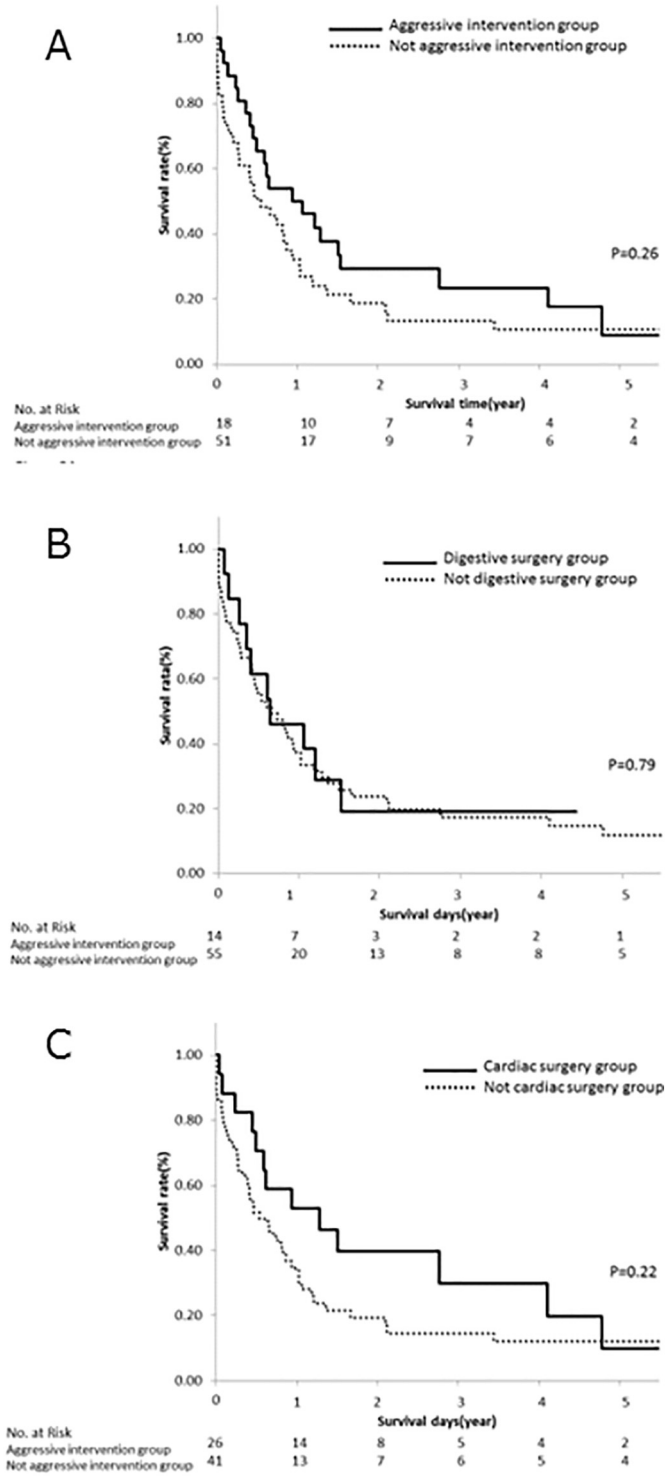

Fig. 2. A, The cummurative overall survival between patients with surgical interventions (solid line) and with the conservative treatment (dot line). B and C, The cummurative overall survival between patients who did and did not undergo digestive and cardiac surgery, respectively.

2. Results

Median gestational age and birth weight were 37 (27–43) weeks and 1,700 (822–2,546) g, respectively. Fetal diagnosis was made in 48 individuals (69%). There were 68 patients with congenital heart disease and 20 patients with digestive disease. Cardiac malformations included ventricular and/or atrial septal defects in 38, double outlet right ventricle in 21, patent ductus arteriosus in 3, tetralogy of Fallot in 1, and hypoplastic left heart in one. Polyvalvular mxyomatous thickening and regurgitation were observed in the majority of them. The most common digestive malformation was esophageal atresia in 10, following idiopathic gastrointestinal perforation in 2, umbilical hernia in 2, atresia in 2, diaphragmatic hernia in 1, and intestinal malrotation in one patient. Surgical interventions were provided in 28 patients (41%). Cardiac surgeries were performed in 18 patients (26%), including palliative in 14 and corrective surgery in 4. Digestive surgeries were performed in 14 patients (20%), including correction of esophageal atresia in 8 and gastrostomy in 8. The duration of follow up was 51 (2–178) months.

Comparison between patients with and without surgical interventions is shown in Table 1. There was no difference in gender, gestational age, birth weight, fetal diagnosis between the groups. During the follow-up period, there were 14 in-hospital deaths (50%) and 14 discharges alive (50%) among patients with surgical intervention, whereas there were 32 in-hospital deaths (76%) and 9 discharges alive (22%) among patients without surgical intervention. There were significant differences in in-hospital death and discharges alive ($p=0.02$) between the groups. The patients without surgical intervention had poor mortality and could not achieve home-care compared to those with surgical intervention.

In Kaplan-Meier analysis of 69 patients, overall survival rates at 6 months, 1 year and 5 years are 57%, 43% and 12%, respectively (Fig. 1). The cumulative survival rates at 6 months, 1 year and 5 years in the group with surgical interventions were 65%, 50% and 11%, respectively, compared with 51%, 30% and 13% in the group without surgical interventions. There was no significant difference in the survival rates between the groups ($p=0.26$). When our cohort was divided into patients who underwent digestive or cardiac surgery, there was no significance between the groups (Fig. 2). These findings suggest that surgical intervention contributes to decrease in-hospital death but not overall survival rate in individuals with trisomy 18.

There were a total of 23 patients achieving homecare. The overall rates of achieving homecare at 6 months, 1 year and 2 years are 18%, 30% and 33%, respectively (Fig. 3). The rates of achieving homecare at 6 months, 1 year and 2 years in patients with surgical interventions were 29%, 41% and 49%, respectively, whereas 13%, 18% and 21% in

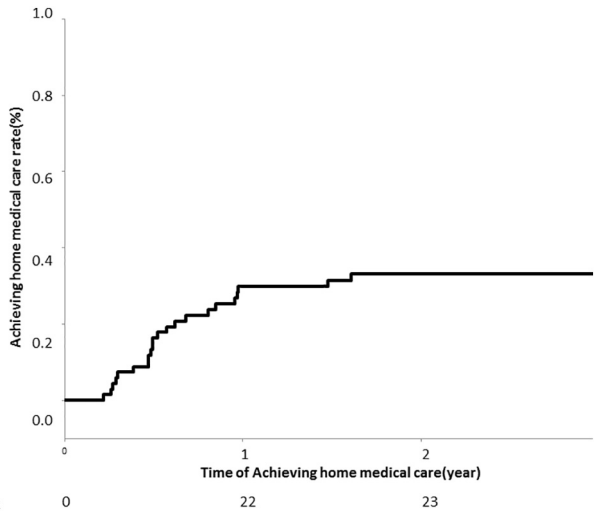

Fig. 3. The rate of achieving home medical care among 24 patients with trisomy 18.

those without it, respectively (Fig. 4). There was a significant difference in the rates of achieving homecare between the groups (p = 0.02). Cox proportional hazard regressions analysis revealed that fetal diagnosis (adjusted hazard risk: 0.3, 95% confidential interval: 0.13-0.74, p = 0.009) and cardiac surgery (adjusted hazard ratio; 2.4, 95% CI 1.02-5.55, p = 0.04) were significantly related to increase the rate of achieving homecare. Birth weight and digestive surgery were not related to the rate of achieving homecare (Fig. 5).

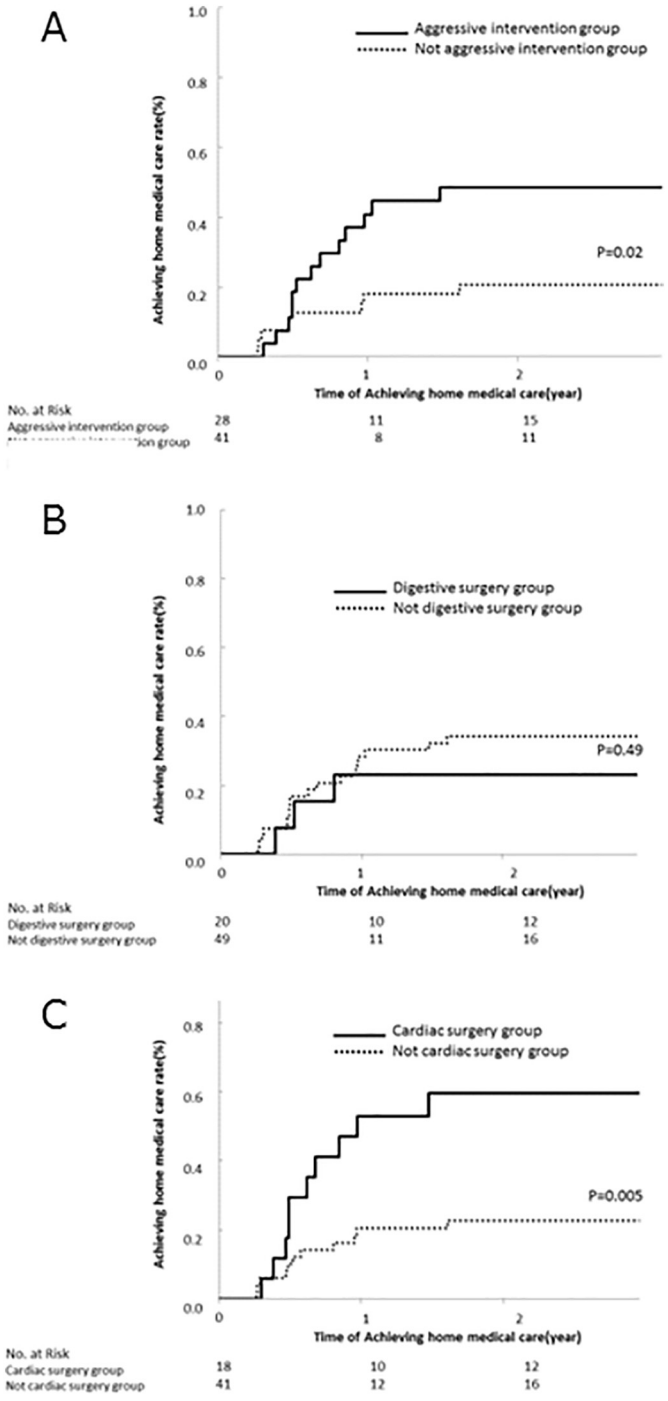

Fig. 4. A, The rate of achieving home medical care between patients with surgical interventions (solid line) and with the conservative treatment (dot line). B and C, The rate of achieving home medical care between patients who did and did not undergo digestive and cardiac surgery, respectively.

3. Discussion

The major finding of our study is that surgical interventions contribute to improve the rate of in-hospital survival and achieving homecare, but not long-term survival rate, in patients with trisomy 18. We also find that fetal diagnosis and cardiac surgery are independent factors related to achieving homecare. We have provided patient- and family-centered care among patients with trisomy 18. The concept of patient- and family-centered care is based on dignity and respect, information sharing, participation, and collaboration, aligned with clinical ethics principles and associated with enhanced patients' satisfaction, which allows healthcare providers to treat patients with trisomy 18 not only from a clinical perspective, but also from an emotional, mental, spiritual, social, and financial perspective and share decision-making between families and healthcare providers to design an individualized and comprehensive care plan. The indications of surgical interventions should be individualized according to profound communications between patient's family and care providers.

Recent reports have shown that a 5-year survival is 12.3% in individuals with trisomy 18 [5]. According to a large cohort of 254 individuals with trisomy 18 in the United States, individuals surviving beyond 6 months lived 10 years or longer, and 10-year survival was 9.8%. Male gender, higher birth weight and mosaic- or translocation- type trisomy are correlated with longer survival, but neither cardiac nor neurological complication was associated with survival rate [2,3,5]. Previous reports have shown that cardiac surgery also contributes to improve the early survival rate among trisomy 18 individuals. Muneuchi et al. described that the survival rate at 1 month was 83% in trisomy 18 individuals with cardiac surgery, compared to 37% in those without surgical intervention [14]. Peterson et al. described that median survival was 16.2 years for individuals with trisomy 18 after cardiac surgery and post-discharge survival was 56% after 15 years [15]. However, trisomy 18 individuals after aggressive treatments require numerous therapeutic procedures, and a number of in-patient hospital stays increased over time. The Kids' Inpatient Database from the United States reported that the number of hospitalizations and procedures for trisomy 18 had increased between 1997 and 2009. Pneumonia and seizure still remains major causes of death after discharge in addition to cardiac failure and pulmonary hypertension among them [3]. In our present study, the causes of death were not available unfortunately. In a Japanese cohort of 134 individuals with trisomy 18, only 17% of patients after cardiac surgery were alive [12]. A Japanese nationwide administrative database showed that surgical interventions were performed for 20% of trisomy18 individuals, while home discharge rates were 39% for trisomy 18 individuals [11]. Given the result of our present study and standing from the view of patient- and family-centered care, it is possible that aggressive surgical interventions can achieve early discharge and home care management in individuals with trisomy 18.

With an increase in women delaying childbearing and prenatal screening test such as cell-free fetal DNA technologies, there is an increase in the number of fetuses with trisomy 18 diagnosed prenatally [10]. A prenatal diagnosis of trisomy 18 often leads to the termination of a pregnancy, spontaneous loss, or the shortened life of a child [16,17]. Our present study also suggested that fetal diagnosis was hazardous to achieve homecare management. We assumed the following two reasons: First, fetal diagnosis is associated with more complex anomalies. Medical providers tend to hesitate surgical intervention in trisomy 18 patients concomitant with cardiac and digestive anomalies, although they choose surgical treatment for trisomy 18 patients with relatively simple congenital anomaly, i.e. ventricular septal defect or patent ductus arteriosus. In our cohort, there were 48 patients concomitant with cardiac and digestive anomaly who were prenatally diagnosed. Secondly, despite an increase in the number of fetuses with trisomy 18 diagnosed prenatally, it is likely that most parents choose to continue pregnancy because of moral beliefs, either personal or religious, followed by child-centered reasons involving the value of life

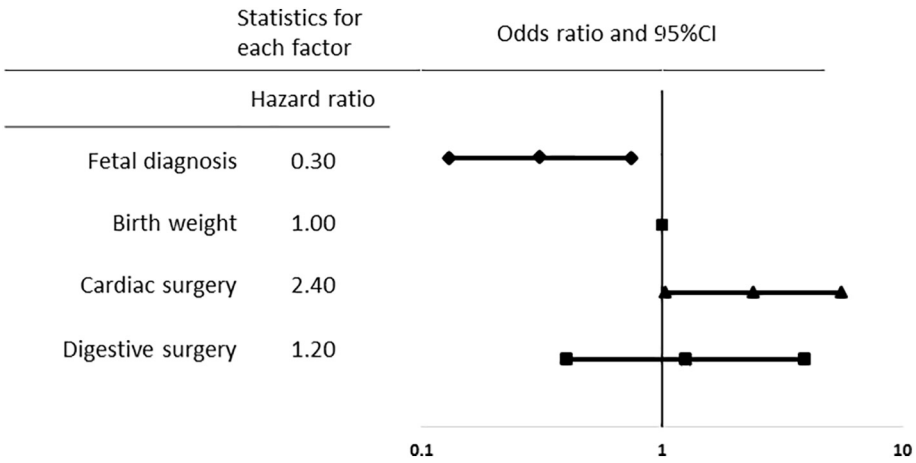

Fig. 5. Forest plot for cox proportional hazard analysis regarding with achieving home-care. Fetal diagnosis and cardiac surgery are significantly related to achieving home-care.

and love for their child. Moreover, there may be a bias that parents who are more motivated and accept a surgical intervention are more capable for providing home-care.

There is limited information about the outcomes of surgical intervention to digestive disease. Nelson et al. described that 35 individual with trisomy 18 underwent 92 surgeries including 10 cardiac surgeries and 8 digestive surgeries. More than 10% of children with trisomy 18 underwent 1 or more interventions, raging from minor procedures (e.g. myringtomy) to major cardiac repairs (e.g. hemi-Fontan). Another prior population-based study reported none for 67 children trisomy 18 underwent 2 surgeries. Infants with omphalocele had lower survival than their counterparts without omphalocele. In our present study, esophageal atresia was the most common digestive disease and there was no patient with omphalocele. Fig. 4B shows that surgical interventions for digestive disease, or esophageal atresia, could not contribute to improve the rate of achieving home-care. However, we consider that surgical interventions for esophageal atresia are necessary for them to establish enteral feeding. Therefore, esophageal atresia is a hazardous factor for achieving home-care among individuals with trisomy 18.

4. Conclusions

The aggressive surgical interventions do not contribute to the improvement of the survival rate, but cardiac surgery, in particular, contribute to improving the rate of achieving home medical care. For trisomy 18 patients with limited life time, cardiac surgery can be a nice option to have more time to stay with their own families.

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