



# Weight gain velocity and adequate amount of nutrition for infants with congenital diaphragmatic hernia

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## Abstract

**Purpose** Growth retardation is a severe morbidity in infants with congenital diaphragmatic hernia (CDH). This study aimed to determine when catch-up growth starts in infants with CDH and to determine the adequate amount of nutrition required during catch-up growth.

**Methods** This was a multicenter retrospective cohort study involving neonates with isolated CDH (born 2006–2010;  $n=98$ ). Weight gain velocity (WGV) was calculated using body weight Z-scores. The minimum required weight gain was defined as  $WGV \geq 0$ . Patients were dichotomized into severe and non-severe cases according to diaphragmatic defects.

**Results** Average monthly WGV changed from  $<0$  to  $\geq 0$  at 2 months of age. Total caloric intake at 2 months of age was lower when the WGV between 1 and 3 months was  $<0$  in both severe cases [122 (95% confidence interval (CI) 116–128) vs. 97 (95% CI 84–110) kcal/kg/day,  $p=0.02$ ] and non-severe cases [115 (95% CI 110–120) vs. 99 (95% CI 87–111) kcal/kg/day,  $p<0.001$ ].

**Conclusion** Catch-up growth started at approximately 2 months of age. During this period, total caloric intake of  $>122$  kcal/kg/day was needed to avoid decreases in the body weight Z-score in severe cases.

**Keywords** Body weight · Parenteral nutrition · Enteral nutrition · Neonatal intensive care · neonatal care

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## Introduction

Congenital diaphragmatic hernia (CDH) remains a challenging condition encountered by neonatologists and pediatric surgeons. Not only in the acute phase but also in later life, survivors often suffer from various morbidities. Growth retardation was observed in 21–69% of CDH survivors showing Z-scores of  $<-2.0$  for body weight-for-age at 1 year of age [1–3]. Growth retardation has been linked to poor neurodevelopment in both preterm [4] and term infants [5].

We previously reported that the independent risk factors for growth retardation in CDH survivors were not only low birth weight, but also the need for home oxygen treatment (HOT) [1]. This result supports the idea that infants with CDH consume more calories than normal infants due to respiratory distress, and they need more energy to gain enough body weight [6]. It follows that infants with severe respiratory condition need more energy to grow adequately. Nevertheless, the amount of nutrition for adequate growth has not been elucidated.

Weight growth velocity (WGV) is one of the useful indices for assessing infantile growth. WGV is a commonly used measure in growth and nutrition research in very-low-birth-weight infants, and it is also useful for the non-constant change in body weight [7]. Gien et al. calculated the overall WGV from birth to discharge among CDH infants and reported that WGV during hospitalization was evidently lower in CDH infants than in normal infants. The slope of WGV, however, was not constant; there were often periods of negative WGV in the acute phase, followed by periods of positive WGV [8]. Leeuwen et al. performed anthropometric measurements among infants with CDH at 3, 6, and 12 months of age and reported that catch-up growth occurred during infancy [2]. These findings suggest that early adequate nutritional support would be crucial during catch-up growth. Nevertheless, it remains unknown when catch-up growth begins and how we should manage it.

Therefore, the purposes of this study were (1) to determine when catch-up growth starts in infants with CDH and (2) to assess the adequate amount of nutrition required during the catch-up growth.

## Methods

### Patient sample

A nationwide multicenter retrospective observational study of neonatal CDH was conducted by the Japanese Congenital Diaphragmatic Hernia Study Group in 2011 [9]. Data from 614 patients with CDH in 72 institutions were collected between January 2006 and December 2010. Subsequently, an additional survey focusing on nutritional management was conducted by five high-volume centers that declared their intention to participate in the study. This study included patients who survived to discharge in the five participating institutions between 2006 and 2010. Patients who had chromosome abnormalities, severe cardiac malformation, or very low birth weights were excluded.

### Variables

Data on body weight and nutrition were extracted from medical records. Body weights, measured at 1, 2, and 3 months and at 1.5 and 3 years of age, were used to indicate growth. The daily doses and types of nutrition at 1, 2, and 3 months of age were also retrieved from the medical records. Daily caloric intakes of enteral nutrition (EN) were calculated, using 0.66 kcal/mL and 0.67 kcal/mL when mother's milk or formula milk was given, respectively. When patients were fed on demand, the daily

dose of EN was estimated to be 180 mL/kg/day. The daily amounts of glucose and protein in parenteral nutrition (PN) were retrieved from the prescription. The total amount of nutrition was defined to be simply the addition of PN to EN.

Data of other clinical variables were extracted from the database that was previously constructed by the Japanese Congenital Diaphragmatic Hernia Study Group [1, 9]. The variables included sex, gestational age, birth weight, international classification of the diaphragmatic defect [10], Terui's risk stratification of CDH severity using Apgar score at 1 min, best oxygenation index (calculated using the highest PaO<sub>2</sub> from the preductal artery within 24 h after birth and ventilator settings) [11], total caloric intake at 1, 2, and 3 months of age, WGV, amount of PN at 1, 2, and 3 months of age, rate of PN use, rates of gastroesophageal reflux (GER) and chylothorax during hospitalization, tracheal intubation duration of  $\geq 30$  days (including tracheotomy), and need for HOT. A "large diaphragmatic defect" was defined as a diaphragmatic defect of  $> 50\%$  of the portion of the chest wall devoid of the diaphragm tissue; this corresponds to the C + D international classification [10]. The patients were dichotomized into the following groups depending on the size of the diaphragmatic defect: severe cases with a large diaphragmatic defect and non-severe cases with a small diaphragmatic defect.

### Weight gain velocity

The Z-scores for body weights were calculated according to the patients' sex, using the average values and the standard deviations for weight at each month/year of age. These values were obtained from the national databases from 12,426 infants and 695,600 school children, respectively [12, 13]. WGV of each period was calculated by dividing changes in the Z-score for body weight by the number of month(s). WGV was used as an indicator of growth and comprised the primary outcome of this study. For instance, when WGV is zero, the patient grows along the line of the standard growth curve; when WGV is positive, the patient may be in catching-up process. The time when WGV changes from negative ( $< 0$ ) to positive ( $\geq 0$ ) was taken as the start of catch-up growth.

An exploratory analysis was conducted. WGV during the period of catch-up growth was calculated, and the patients were divided into two groups according to the presence of positive and negative WGV. To assess the risk of negative WGV, the variables were compared between the positive and negative WGV groups. To elucidate the adequate amount of nutrition during catch-up growth, the amount of nutrition between the positive and negative WGV groups was compared.

## Statistical analysis

Summary statistics were expressed as frequencies and proportions for categorical data and a means  $\pm$  standard deviations or 95% confidence intervals (CIs) for continuous variables. Statistical comparison between the two groups was tested using the unpaired *t* test or Mann–Whitney *U* test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. A mixed effects model for repeated measures was used to determine between-group differences in mean changes in Z-scores for body weight, WGV and total calorie.

$p < 0.05$  was defined as indicating statistical significance. All statistical analyses were performed using the JMP software program, version 12.01 (SAS Institute, Inc., Cary, NC, USA).

## Ethical approval

The study design was approved by the Research Ethics Committee of the Graduate School of Medicine, Chiba University (no. 509), and the independent ethics committees of the four other participating institutions (no. 11017 in Osaka University, no. 25–222 in Kyusyu University, no. 2016–0416 in Nagoya University, and no. 468 in Osaka Women's and Children's Hospital). Written informed consent was not required, as this was a retrospective study with de-identified data. The details of the study were published on the institutional website, and individuals were guaranteed the right to decline participation in the study. The study was performed in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Japanese government.

## Results

### Patient data

A total of 141 infants who were born with CDH and received treatment for the disease at the five participating institutions were included. Of them, 109 (77%) survived to discharge. Patients with chromosome abnormalities ( $n=3$ ), severe cardiac anomaly ( $n=5$ ), and very low birth weights ( $n=3$ ) were excluded. The remaining 98 patients were included in the present study.

Twenty-five and 73 patients had severe and non-severe CDH, respectively. Demographic data of patients with severe and non-severe cases are presented in Table 1. Patients' background (sex, gestational week, and birth weight) did not significantly differ between the two groups. Body weight

Z-score at 2 months ( $-2.897 \pm 0.718$  vs.  $-2.218 \pm 1.121$ ,  $p < 0.01$ ) and 3 months ( $-2.852 \pm 0.792$  vs.  $-1.789 \pm 1.240$ ,  $p < 0.001$ ) was lower in the severe group than in the non-severe group. The potential risk factors for malnutrition did not significantly differ between the severe and non-severe groups. The rate of tracheal intubation for  $\geq 30$  days [13/25 (52%) vs. 13/73 (18%),  $p < 0.01$ ] and the need for HOT [5/25 (20%) vs. 2/73 (3%),  $p = 0.01$ ] significantly differed between the two groups.

### Weight gain velocity

Table 1 shows that WGV between 1 and 2 months was lower in the severe group than in the non-severe group ( $-0.45 \pm 0.60$  vs.  $0.00 \pm 0.09$ ,  $p < 0.01$ ). WGV between birth and 3 months was significantly different between the severe and non-severe group ( $-0.72 \pm 0.41$  vs.  $-0.42 \pm 0.43$ ,  $p < 0.01$ ); however, there was no difference in WGV between birth and 1.5 years ( $-0.03 \pm 0.08$  vs.  $0.00 \pm 0.07$ ,  $p = 0.13$ ).

Change in the body weight Z-score is shown in Fig. 1a. The average WGV changed from negative ( $< 0$ ) to positive ( $\geq 0$ ) at 2 months of age (WGV between 0 and 1 month,  $-1.53$ /month; WGV between 1 and 2 months,  $-0.20$ /month; WGV between 2 and 3 months,  $+0.34$ /month; WGV between 3 months and 1.5 years,  $+1.32$ /month; WGV between 1.5 and 3 years,  $+0.03$ /month). Figure 1b shows the changes in the body weight Z-score in the dichotomized cohort of severe and non-severe cases. In the severe cases, the bottom of the Z-score was at least after 3 months of age, whereas the bottom of the Z-score in non-severe cases was after 2 months of age.

### Risk of negative WGV

Changes in WGV from negative to positive were observed at 2 months of age. Thus, the risk of negative WGV between 1 and 3 months was assessed in severe and non-severe cases (Table 2). In severe cases, positive and negative WGV values between 1 and 3 months were 0.33 (95% CI  $-0.03$  to 0.66) and  $-0.42$  (95% CI  $-0.57$  to  $-0.30$ ), respectively ( $p < 0.001$ ). In non-severe cases, positive and negative WGV values between 1 and 3 months were 0.39 (95% CI 0.30–0.48) and  $-0.27$  (95% CI  $-0.36$  to  $-0.18$ ), respectively ( $p < 0.001$ ). Total caloric intake at 2 months of age was lower in the negative WGV group than in the positive WGV group in both severe [122 (95% CI 116–128) vs. 97 (95% CI 84–110) kcal/kg/day,  $p = 0.02$ ] and non-severe cases [115 (95% CI 110–120) vs. 99 (95% CI 87–111) kcal/kg/day,  $p < 0.001$ ] (Fig. 2). In non-severe cases, the rate of chylothorax was higher in the negative WGV group than in the positive WGV group [8/46 (17%) vs. 12/24 (50%),  $p < 0.001$ ].

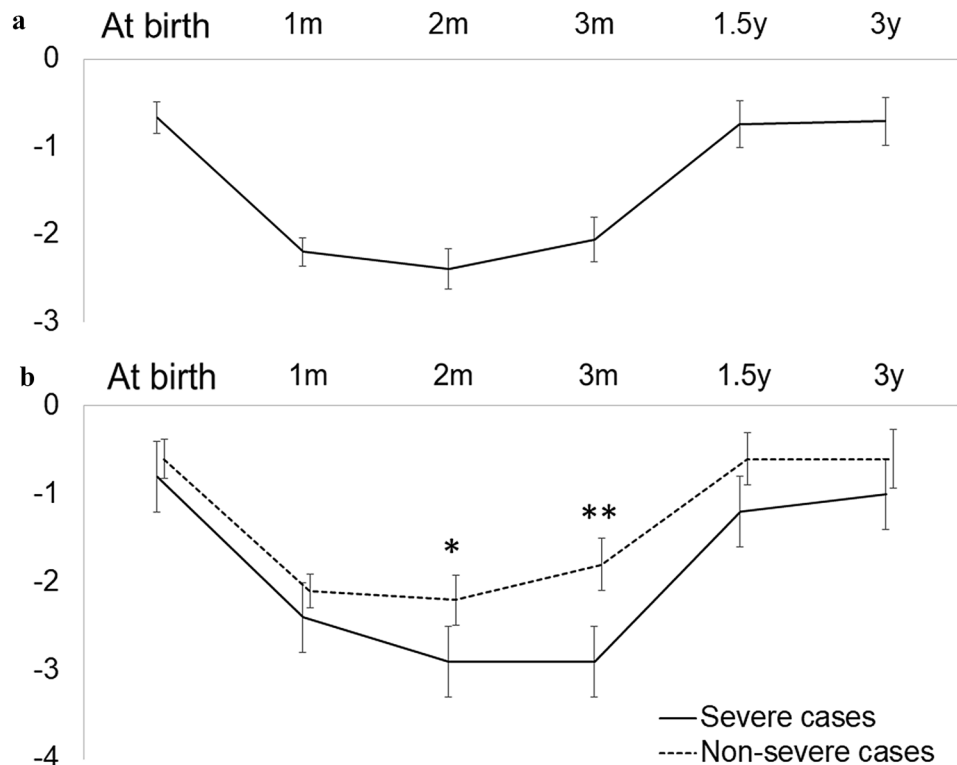
**Table 1** Anthropometric measurements and the potential risk factors for malnutrition of severe and non-severe cases

Variables	Severe cases (n = 25)	Non-severe cases (n = 73)	p
Male sex	13/25 (52%)	42/73 (58%)	0.65
Gestational week	37.6 ± 1.3	37.9 ± 0.2	0.29
Liver-up	13/23 (57%)	5/59 (8%)	<b>&lt; 0.0001</b>
Thoracic stomach	21/23 (91%)	39/58 (67%)	<b>0.03</b>
Terui's category, C + D	10/23 (43%)	11/69 (16%)	<b>0.01</b>
Birth weight (g)	2656 ± 290	2756 ± 373	0.22
Birth weight Z-score	- 0.799 ± 0.760	- 0.627 ± 0.970	0.5
Body weight Z-score at 1 month	- 2.423 ± 0.762	- 2.130 ± 0.806	0.27
Body weight Z-score at 2 months	- 2.897 ± 0.718	- 2.218 ± 1.121	<b>&lt; 0.01</b>
Body weight Z-score at 3 months	- 2.852 ± 0.792	- 1.789 ± 1.240	<b>&lt; 0.001</b>
Body weight Z-score at 1.5 years	- 1.210 ± 1.118	- 0.613 ± 1.147	<b>0.046</b>
WGV between birth and 1 month	- 1.59 ± 0.48	- 1.50 ± 0.66	0.53
WGV between 1 and 2 months	- 0.45 ± 0.60	0.00 ± 0.09	<b>&lt; 0.01</b>
WGV between 2 and 3 months	0.06 ± 0.51	0.30 ± 0.54	0.09
WGV between birth and 3 months	- 0.72 ± 0.41	- 0.42 ± 0.43	<b>&lt; 0.01</b>
WGV between birth and 1.5 years	- 0.03 ± 0.08	0.00 ± 0.07	0.13
Total calorie at 2 months (kcal/kg/day)	103 ± 24	108 ± 26	0.34
Parenteral nutrition at 2 months	4/25 (16%)	5/73 (7%)	0.23
Rate of gastroesophageal reflux	8/25 (32%)	22/73 (30%)	1
Rate for chylothorax	9/25 (36%)	20/73 (27%)	0.45
Tracheal intubation ≥ 30 days	13/25 (52%)	13/73 (18%)	<b>&lt; 0.01</b>
Need for HOT	5/25 (20%)	2/73 (3%)	<b>0.01</b>

Bold text indicates  $P < 0.05$

WGV weight gain velocity (changes of weight Z-score per month), HOT home oxygen therapy

**Fig. 1** Change in the body weight Z-score in the whole cohort (a) and dichotomized cohort (b). Plots represent mean. Whiskers represent 95% confidence intervals. \* $p < 0.01$ , \*\* $p < 0.001$



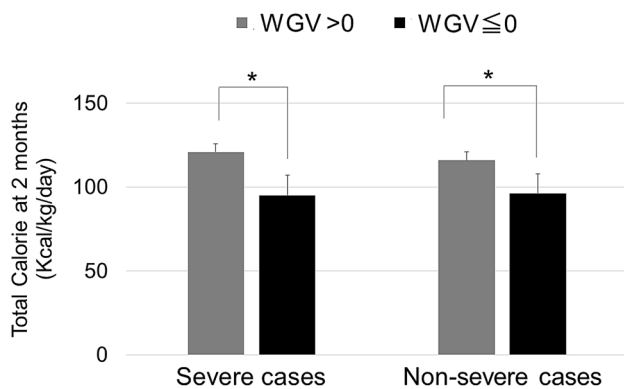
**Table 2** The risk for malnutrition of positive and negative WGV in severe and non-severe cases

WGV between 1 and 3 months	Severe cases (n=25)			Non-severe cases (n=73)		
	Positive (n=7)	Negative (n=18)	p	Positive (n=47)	Negative (n=26)	p
Birth weight (g)	2506 (2245–2766)	2748 (2603–2893)	0.07	2718 (2603–2832)	2806 (2651–2962)	0.35
WGV between 1 and 3 months	0.33 (– 0.03 to 0.66)	– 0.42 (– 0.57 to – 0.30)	<b>&lt; 0.001</b>	0.39 (0.30–0.48)	– 0.27 (– 0.36 to – 0.18)	<b>&lt; 0.001</b>
WGV between birth and 1.5 years	0 (– 0.09 to 0.09)	– 0.06 (– 0.09 to 0.00)	0.14	0.03 (0.00–0.03)	– 0.03 (– 0.06 to 0.00)	<b>&lt; 0.01</b>
Total calorie at 1 month (kcal/kg/day)	98 (73–124)	73 (54–92)	<b>0.02</b>	105 (97–114)	95 (79–112)	0.09
Total calorie at 2 months (kcal/kg/day)	122 (116–128)	97 (84–110)	<b>0.03</b>	115 (110–120)	99 (87–111)	<b>&lt; 0.01</b>
Total calorie at 3 months (kcal/kg/day)	127 (109–145)	110 (103–118)	0.15	118 (116–121)	108 (101–115)	0.08
Parenteral nutrition at 2 months	0/7 (0%)	4/18 (22%)	0.29	2/47 (4%)	3/26 (12%)	0.34
Rate of GER	2/7 (29%)	6/18 (33%)	1	12/47 (26%)	10/26 (38%)	0.29
Rate of chylothorax	2/7 (29%)	7/18 (39%)	1	8/47 (17%)	12/26 (46%)	<b>0.01</b>
Tracheal intubation ≥ 30 days	2/7 (29%)	11/18 (61%)	0.2	6/47 (13%)	7/26 (27%)	0.2
Need of HOT	0/7 (0%)	5/18 (28%)	0.27	1/47 (2%)	1/26 (0%)	1

Range represents 95% confidence interval

Bold text indicates  $P < 0.05$

WGV weight gain velocity (changes of weight Z-score per month), GER gastroesophageal reflux, HOT home oxygen therapy



**Fig. 2** Comparison of total caloric intake at 2 months of age between positive and negative weight gain velocity (WGV) groups in both severe and non-severe cases. WGV was calculated by dividing the changes in body weight Z-score between 1 and 3 months by 2 months. Whiskers represent 95% confidence intervals. \* $p < 0.01$

## Discussion

The principal findings of this study, in which the WGV of 98 infants with CDH was analyzed retrospectively, were as follows: (1) catch-up growth of infants with CDH started at approximately 2 months of age according to the body

weight trajectory, (2) the risk of negative WGV between 1 and 3 months was lower total caloric intake at 2 months of age in both severe and non-severe cases, and (3) 122 kcal/kg/day of total caloric intake was needed at least to achieve positive WGV in severe cases.

Growth retardation is one of the serious morbidities of infants with CDH. In our cohort, growth retardation was observed in 23% of the CDH survivors [1]. Various factors may be associated with poor growth during infancy, including the fact that patients with CDH are sometimes intolerant to EN due to cardiorespiratory instability, deep sedation, or restrictions in volume loading. GER, oral aversion, and allergies can also contribute to difficulties in enteral feeding [14, 15]. We previously reported that EN and supportive PN in the acute phase were essential for weight gain during infancy [16]. Furthermore, increase in the energy requirement may be an underestimated factor [17]. Haliburton et al. reported that 59% of patients with CDH were hypermetabolic with a high resting energy expenditure, and 30% more energy was needed for ideal body weight gain [6]. We previously reported that the need for HOT was an independent risk factor for growth retardation in CDH survivors [1]. These findings indicated that increased energy requirement in infants with CDH was a considerable risk factor of growth retardation. However,

minimal evidence has been available mainly because a precise measurement of resting energy expenditure is difficult in infants. It is also difficult to define “adequate growth” in each individual. Haliburton et al. used different approaches to this issue. They showed that body mass index correlated with lung function in CDH survivors. This finding supports the hypothesis that increased respiratory effort results in slow growth. The hypothesis has not been proved completely because the correlation between lung function and resting energy expenditure was not observed in their study [18].

Catch-up growth is defined as an accelerated compensatory growth of an organism following a period of slowed development, particularly as a result of nutrient deprivation [19]. Catch-up growth during infancy can be directly related to improved neurodevelopment [4, 5]. Evidence, therefore, has been accumulated in preterm infants [20]. Furthermore, nutrient deprivation during the neonatal period is seen not only in preterm infants, but also in term infants requiring surgery and/or intensive care. Correia Martins et al. reported that earlier surgical closure of ventricular septal defects resulted in better acceleration of postoperative growth than later surgery [21]. However, there has been scarce evidence on catch-up growth in term infants who underwent other types of surgeries. To the best of our knowledge, this is the first report to provide new insights into catch-up growth in infants with CDH.

To assess the catch-up growth of infants with CDH, WGV based on the Z-score was used in the present study. This method has the following advantages: (1) the growth of each infant can be rigorously assessed through standardization rather than through the absolute value of body weight; (2) growth can be evaluated dynamically, rather than the value at one point, using the concept of velocity; and (3) the value of WGV calculated based on the Z-score can be easily interpreted, with 0 indicating growth along the line of the standard growth curve and the positive value indicating accelerated growth over the line of the standard growth curve.

We identified that catch-up growth starts at approximately 2 months of age in infants with CDH. Then, the risk of negative WGV around this period was assessed. To eliminate the bias of severity of CDH, the cohort was divided into two groups (severe and non-severe cases). We found that the lower amount of nutrition at 1 and 2 month(s) of age was the significant risk factor both in severe and non-severe groups. We also found that negative WGV between 1 and 3 months resulted in negative WGV between birth and 1.5 years of age in non-severe groups. These data indicated that the less amount of nutrition during infancy subsequently leads to less catch-up growth at least in non-severe cases. The reason why WGV between birth and 1.5 years in severe cases had no difference between cases with positive and negative WGV between 1 and 3 months was unclear. Various factors such

as recurrence of CDH, severe GER or respiratory distress may affect the outcome.

By comparing the positive and negative WGV groups, finally, we found that 122 kcal/kg/day of total caloric intake was needed at least to achieve positive WGV in severe cases. However, the target amount of nutrition for adequate catch-up growth remains unclear. Haliburton et al. reported that a caloric intake of 125 kcal/kg/day at discharge from the hospital was required to achieve an adequate weight gain (25–35 g/day) [6]. Although it is unclear whether or not additional 3 kcal/kg/day is enough for adequate catch-up growth, 125 kcal/kg/day might be a potential target amount of nutrition. We have now established a nutritional support program involving a high concentration of milk; we are currently applying the program in the clinical setting. A key point is to evaluate the nutritional status of the individual repeatedly and increase the amount of nutrition until an adequate body weight gain can be ensured.

In the present study, we had originally expected that severe cases would require more calories for positive WGV than non-severe cases; however, the obtained result was different, as there was no significant difference between severe and non-severe cases. This finding may be due to the fact that we assessed only the minimum amount of nutrition to prevent a further decrease in the body-weight Z-score. The adequate caloric intake for an adequate WGV possibly differed between these groups. Further studies are needed to validate this finding.

Interestingly, chylothorax was the risk factor for negative WGV only in the non-severe cases. Chylothorax is a significant postoperative complication that occurs in 5–6% of patients with CDH [22–24]; the rate of chylothorax was higher in more severe cases [24]. More than 80% of patients with CDH experiencing chylothorax were effectively treated by non-surgical management, including fasting and medication [24]. This fasting management may have a potential risk for malnutrition if the PN is not appropriately applied. Our data suggest that, even in non-severe cases, chylothorax is a considerable risk factor for growth retardation.

Our study had several limitations. First, because of the multicenter retrospective study design, the therapeutic strategies employed in the five participating institutions were not uniform, and they totally depended on the policies of the facility and decisions of the attending physicians. The strategies included treatment of CDH, nutritional management strategy, and follow-up programs. These may have resulted in a bias in the findings. Second, neither respiratory function nor resting energy expenditure was measured. The relationship between respiratory effort and growth, therefore, could not be discussed. Further prospective studies with more detailed data are warranted to validate our findings. Third, we only assessed the force feeding, and the daily dose of EN on demand was tentatively assigned as 180 mL/kg/day.

These may have resulted in incorrectness of analysis. The present study will need to be supported by further prospective studies that assess the nutrition in more detail.

In conclusion, catch-up growth started at approximately 2 months of age. Insufficient WGV during this period resulted in inadequate catch-up growth. Total caloric intake of 122 kcal/kg/day was needed to avoid a decrease in the body weight Z-score in severe cases. Given that the ideal nutritional management for adequate catch-up growth in infants with CDH remains unclear, further studies are needed to clarify this.

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**Author contributions** K.T. designed the study and wrote the initial draft of the manuscript. Y.T., K.N., M.I., H.O., M.H., T.T., Y.S., and H.Y. contributed to the analysis and interpretation of data and assisted in the preparation of the manuscript. All other authors have contributed to the data collection and interpretation as well as the critical review of the manuscript. The final version of the manuscript was approved by all authors.

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**Code availability** The datasets during the current study are available from the corresponding author on reasonable request.

## Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no conflicts of interest.

**Ethics approval** The study design was approved by the Research Ethics Committee of the Graduate School of Medicine, Chiba University (no. 509), and the independent ethics committees of the four other participating institutions. The study was performed in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects.

**Consent to participate** Signed informed consent was not required, as this was a retrospective study with de-identified data. The details of the study have been published on the institutional website and individuals have been guaranteed the right to decline participation in the study.

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