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ORIGINAL ARTICLE

Risk factors for pneumothorax associated with isolated congenital diaphragmatic hernia: results of a Japanese multicenter study

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Abstract

Purpose This study aimed to elucidate the clinical characteristics of neonates with congenital diaphragmatic hernia (CDH) associated with pneumothorax and evaluate the risk factors for the development of pneumothorax.

Methods A retrospective cohort study was conducted in the 15 institutions participating in the Japanese CDH Study Group. A total of 495 neonates with isolated CDH who were born between 2011 and 2018 were analyzed in this study.

Results Among the 495 neonates with isolated CDH, 52 (10.5%) developed pneumothorax. Eighteen (34.6%) patients developed pneumothorax before surgery, while 34 (65.4%) developed pneumothorax after surgery. The log-rank test showed that the cumulative survival rate was significantly lower in patients with pneumothorax than in those without pneumothorax. Univariate analysis revealed significant differences between patients with pneumothorax and those without pneumothorax with regard to the best oxygenation index within 24 h after birth, mean airway pressure (MAP) higher than 16 cmH_2O, diaphragmatic defect size, and need for patch closure. Multiple logistic regression analysis indicated that only the MAP was associated with an increased risk of pneumothorax.

Conclusions The cumulative survival rate was significantly lower in isolated CDH patients with pneumothorax than in those without pneumothorax. A higher MAP was a risk factor for pneumothorax in CDH patients.

Keywords Congenital diaphragmatic hernia · Pneumothorax · Ventilator-induced lung injury · Gentle ventilation · Pulmonary hypoplasia

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Introduction

Congenital diaphragmatic hernia (CDH) is a disease in which the abdominal organs are herniated into the thoracic cavity through a congenital defect in the diaphragm. The severity of CDH varies widely from mild cases, which are completely asymptomatic at birth, to the most severe cases, in which death occurs immediately after birth. The severity of CDH depends on the presence of pulmonary hypoplasia and pulmonary hypertension. Advanced treatments including extracorporeal membrane oxygenation (ECMO), inhaled nitric oxide (iNO), high-frequency oscillation ventilation (HFOV), and fetal interventions have been used in these patients. Improvements in protocol-based neonatal management strategies such as gentle ventilation including permissive hypercapnia to prevent the negative effects of hyperventilation have led to improvement in survival rates [1–3]. Despite these advances, the incidence of pneumothorax, which is a life-threatening perioperative complication due to ventilator-induced lung injury, ranges from 13.5 to 30% in CDH patients [4–7]. Pneumothorax was more likely to develop in neonates with CDH associated with larger diaphragmatic defects and was reported to be associated with a fatal outcome in neonates with CDH, especially those with large defects of the diaphragm [7]. Although the survival rate decreased as the severity of the disease worsened, the risk factors related to the development of pneumothorax, except for the severity of the disease itself, have not been clearly identified. This study aimed to elucidate the clinical characteristics of neonates with CDH associated with pneumothorax and evaluate the risk factors for the development of pneumothorax.

Materials and methods

Patient selection

This retrospective observational cohort study was conducted among neonates with CDH who were born between January in 2011 and December in 2018 in the 15 institutions participating in the Japanese CDH Study Group. A total of 600 neonates with CDH were registered in this study. Ninety-eight non-isolated CDH patients with serious associated anomalies, such as major cardiac malformations or chromosomal abnormalities, were excluded. Two bilateral CDH patients and five patients who received palliative care without proactive treatments were also excluded. Therefore, only 495 neonates with isolated CDH were included in the following analysis. Patients were classified based on the presence or absence of pneumothorax (Fig. 1). This study was approved by the institutional review board of Osaka Women's and Children's Hospital (Approval number #952).

Data collection

The primary outcome measure was the occurrence of pneumothorax in neonates with isolated CDH. The secondary outcome measures were patient demographics,

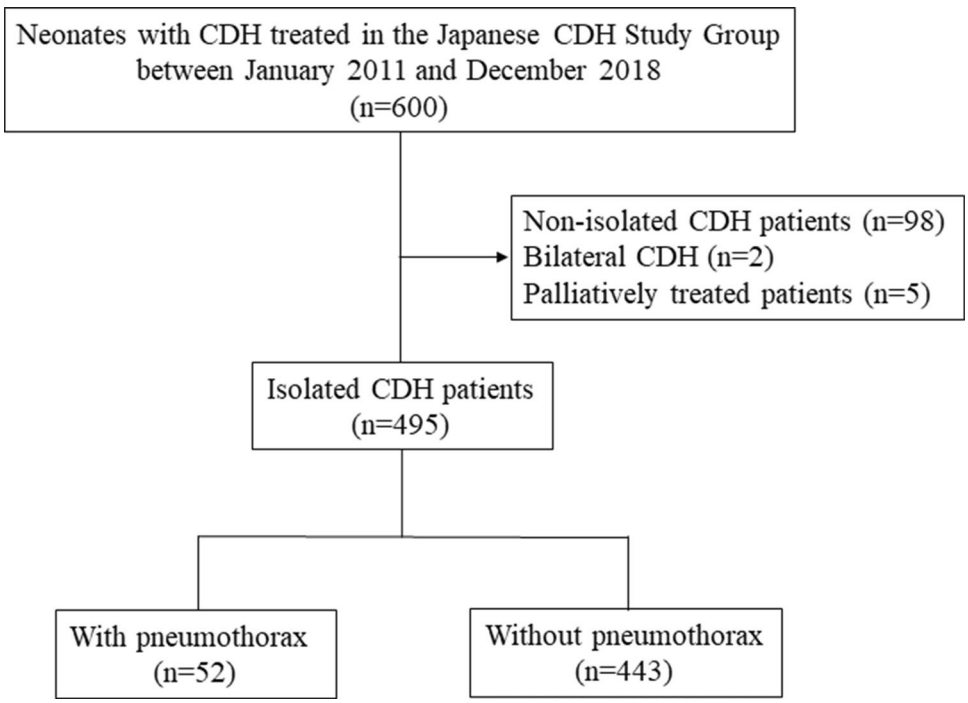

Fig. 1 The patients included for analysis. *CDH* congenital diaphragmatic hernia

including sex; gestational age at birth; birth weight; mode of delivery; side of hernia; presence of prenatal diagnosis; intrathoracic liver herniation (liver-up); lung-to-thorax transverse area ratio (L/T ratio); observed to expected lung-to-head ratio (o/e LHR); Apgar score at 1 min; administration of surfactant; shunt directions at the ductus within 24 h after birth; best oxygenation index (OI), which was calculated using the highest PaO_2 within 24 h after birth; use of HFOV when the best OI was obtained; mean airway pressure (MAP) at the highest PaO_2 of preductal arterial blood gas data within 24 h after birth; operability; defect size of the diaphragm; need for patch closure; need for iNO; need for ECMO; survival time; and survival at 90 days. In CDH patients with pneumothorax, we also obtained the following data: side with pneumothorax; timing of pneumothorax development; treatment used for pneumothorax; primary cause of death; and whether the pneumothorax was presumed to be the primary cause of death.

We defined pneumothorax as an air leakage from the lungs, which was recognized in the pleural cavity by chest plain radiography, regardless of whether or not the patients required a chest tube replacement. Among the patients who underwent surgery for a diaphragmatic hernia, the defect size of the diaphragm was reviewed according to the operative record and classified into the four scales from A to D as described by Lally et al. [8]. We defined A and B defects as "small" diaphragmatic defects, and C and D defects as "large" diaphragmatic defects.

Analysis of the patients' characteristics and risk factors for pneumothorax development

We analyzed the patients' demographic data and clinical outcomes. The clinical characteristics were compared between the CDH patients with pneumothorax and those without pneumothorax. The clinical features of the patients with pneumothorax were also analyzed. Subsequently, we evaluated the risk factors for the development of pneumothorax among CDH patients by univariate and multivariate analyses. Variables that had previous relevance to pneumothorax development in neonates (such as birth weight, Apgar score at 1 min, and administration of surfactant) were considered to be potential risk factors [9–12]. Birth weight, Apgar score at 1 min, best OI within 24 h after birth, and MAP were converted into binary variables using cutoff values. The optimal cutoff value of birth weight and Apgar score at 1 min were determined according to the previous report [9, 10, 12]. The optimal cutoff value of best OI within 24 h after birth and MAP was determined as the value that maximized predictive ability for development of pneumothorax based on a receiver operating characteristic (ROC) curve analysis.

Subgroup analysis of clinical features according to the size of the diaphragmatic defect

We classified patients into three categories: patients with small defect (A or B), patients with large defect (C or D), and patients who could not undergo surgery due to a severe respiratory/circulatory condition. According to these categories, we analyzed the risk factors for the development of pneumothorax and clinical outcomes of the patients with and without pneumothorax. We compared the mortality of patients with pneumothorax in each category and evaluated whether the development of pneumothorax was the primary cause of death. Twenty-seven patients who underwent surgery but whose diaphragmatic defect size was not recorded in their operative note were eliminated from this subgroup analysis.

Statistical analysis

Statistical analyses were performed using the JMP software program (version 13.0; SAS Institute, Inc., Japan). Data were reported as the median and interquartile range or as frequencies and percentages. The Wilcoxon rank-sum test was used to compare continuous variables; the Chi-square test or Fisher's exact test was used for the analysis of categorical variables. The log-rank test and Kaplan–Meier method were used to compare survival times. After performing a univariate analysis of the risk factors for the development of pneumothorax, we subsequently conducted a series of multiple logistic regression analyses of the variables that were significant with P values of less than 0.05 in the univariate analysis and had low correlations with other factors ($r < 0.7$), to determine the independent risk factors for the development of pneumothorax. P values < 0.05 were considered statistically significant.

Results

Comparison of the demographics and clinical parameters between the two groups

Of the 495 neonates with isolated CDH, 426 (86.1%) were diagnosed prenatally and 462 (93.3%) underwent surgical repair of diaphragmatic hernia after birth. A total of 436 (87.8%) patients survived for 90 days. Pneumothorax was prevalent in 52 (10.5%) patients. There were no significant differences in the prenatal factors (liver-up, L/T ratio < 0.08, and o/e LHR $< 25\%$) and postnatal factors (Apgar score at 1 min, right-to-left shunting at ductus within 24 h after birth, and use of HFOV) that may indicate CDH severity. There were significant differences between the two groups in terms of the best OI within 24 h after birth, MAP, diaphragmatic

defect size, need for patch closure, use of iNO, and use of ECMO (Table 1). Although there was no significant difference in survival at 90 days, the log-rank test showed that cumulative survival rate was significantly lower in patients with pneumothorax than in those without pneumothorax (Fig. 2).

The median age of the development of pneumothorax was 5.5 days. Eighteen (34.6%) patients developed pneumothorax before surgery, while 34 (65.4%) developed this condition after surgery. Of 18 patients who developed pneumothorax preoperatively, 70% developed pneumothorax in the contralateral lung with diaphragmatic hernia. Meanwhile, of the 34 patients who developed pneumothorax postoperatively, 70% developed pneumothorax in the ipsilateral lung with diaphragmatic hernia. Fifteen (28.8%) patients did not require treatment or required thoracentesis only, while continuous drainage was performed in 37 (71.2%) patients and four of them required ECMO for lung rest. There was no significant difference in the survival rate at 90 days between patients with preoperative development and those with postoperative development as well as among patients

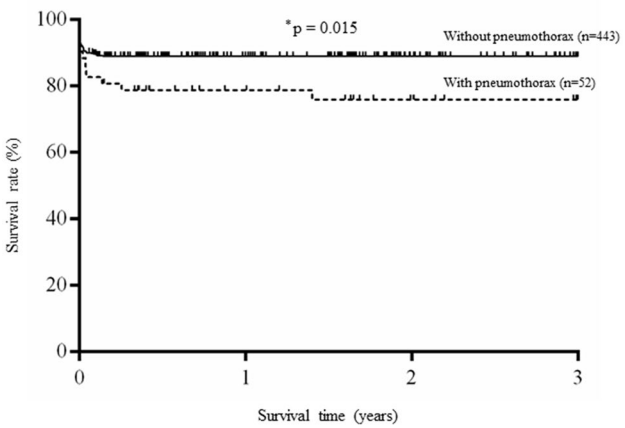

Fig. 2 Comparison of the survival curves between the CDH patients with and without pneumothorax. *CDH* congenital diaphragmatic hernia. *$P < 0.05$

Table 1 Comparison of the demographics and clinical parameters between patients with and without pneumothorax

	Total ($n = 495$)	With PTX ($n = 52$)	Without PTX ($n = 443$)	P value
Sex; male, *n/N* (%)	266/495 (53.7)	32/52 (61.5)	234/443 (52.8)	0.243
Gestational age at birth (weeks)[a]	37.8 [37.2–38.6]	38.0 [37.3–38.7]	37.8 [37.1–38.6]	0.329
Birth weight (g)[a]	2744 [2479–3019]	2867 [2555–3084]	2740 [2474–3018]	0.183
Caesarean section at delivery, *n/N* (%)	328/494 (66.4)	31/52 (59.6)	297/442 (67.2)	0.281
Side of hernia; left, *n/N* (%)	455/495 (91.9)	46/52 (94.1)	409/443 (92.3)	0.293
Presence of prenatal diagnosis, *n/N* (%)	426/495 (86.1)	48/52 (92.3)	378/443 (85.3)	0.207
Liver-up, *n/N* (%)	147/419 (35.1)	21/48 (43.7)	126/371 (34.0)	0.200
L/T ratio < 0.08, *n/N* (%)	42/251 (16.7)	4/31 (12.9)	38/220 (17.3)	0.797
o/e LHR < 25%, *n/N* (%)	35/303 (11.5)	4/42 (9.5)	31/261 (11.9)	1.000
Apgar score at 1 min[a]	5 [3–7]	5 [4–7]	5 [3–7]	0.349
Administration of surfactant, *n/N* (%)	111/495 (22.4)	14/52 (26.9)	97/443 (21.9)	0.386
Right-to-left shunting at ductus within 24 h after birth, *n/N* (%)	183/430 (42.5)	27/51 (52.9)	156/379 (41.2)	0.131
Best OI within 24 h after birth[a]	4.3 [3.1–10.3]	5.3 [3.6–19.6]	4.1 [3.1–9.3]	0.013*
Use of HFOV, *n/N* (%)	341/495 (68.9)	40/52 (76.9)	301/443 (68.0)	0.208
MAP (cmH_2O)[a]	14 [12–15]	15.0 [13.0–16.0]	14.0 [12.0–15.0]	0.002*
Surgery performed for diaphragmatic hernia, *n/N* (%)	462/495 (93.3)	48/52 (92.3)	414/443 (93.4)	0.767
Diaphragmatic defect size; large, *n/N* (%)	161/435 (37.0)	24/47 (51.0)	137/388 (35.3)	0.038*
Need for patch closure, *n/N* (%)	175/461 (38.0)	26/48 (54.1)	149/413 (36.1)	0.018*
Minimal access surgery for repair CDH, *n/N* (%)	73/462 (15.8%)	9/48 (18.7)	64/414 (15.4)	0.533
Use of iNO, *n/N* (%)	354/495 (71.5)	44/52 (84.6)	310/443 (70.0)	0.033*
Use of ECMO, *n/N* (%)	31/495 (6.3)	10/52 (19.2)	21/443 (4.7)	< 0.001*
Survival at 90 days, *n/N* (%)	436/495 (88.1)	42/52 (80.7)	394/443 (88.9)	0.109

PTX pneumothorax, *CDH* congenital diaphragmatic hernia, *Liver-up* intrathoracic liver herniation, *L/T ratio* lung-to-thorax transverse area ratio, *o/e LHR* observed to expected lung-to-head circumference ratio, *OI* oxygenation index, *HFOV* high-frequency oscillatory ventilation, *MAP* mean airway pressure, *iNO* inhaled nitric oxide, *ECMO* extracorporeal membrane oxygenation

*$P < 0.05$

[a]Median [interquartile range]

Table 2 Clinical features of patients with isolated CDH who developed pneumothorax

Number of patients	52	
Age at the PTX development (day)[a]	5.5 [1–11]	
Timing of pneumothorax development (before surgery/after surgery), *n* (%)	18 (34.6%)/34 (65.4%)	
Side of PTX development (ipsilateral/contralateral/bilateral), *n* (%)	27 (51.9%)/20 (38.5%)/5 (9.6%)	
Side of preoperative PTX development (ipsilateral/contralateral), *n* (%)[b]	6 (30.0%)/14 (70.0%)	$P=0.005$*
Side of postoperative PTX development (ipsilateral/contralateral), *n* (%)[c]	26 (70.3%)/11 (29.7%)	
Treatment for PTX		
None, *n* (%)	12 (23.1%)	
Thoracentesis only, *n* (%)	3 (5.8%)	
Continuous drainage, *n* (%)	33 (63.5%)	
Lung rest under ECMO with continuous drainage, *n* (%)[d]	4 (7.7%)	
Preoperative development, *n*/*N* (%)	14/18 (73.7%)	$P=1.000$
Postoperative development, *n*/*N* (%)	27/34 (79.4%)	
Survival at 90 days		
Preoperative development, *n*/*N* (%)	14/18 (73.7%)	$P=0.484$
Postoperative development, *n*/*N* (%)	30/34 (83.3%)	
Survival at 90 days		
PTX in ipsilateral lung, *n*/*N* (%)	24/27 (88.9%)	$P=0.063$
PTX in contralateral lung, *n*/*N* (%)	13/20 (65.0%)	
PTX in bilateral lung, *n*/*N* (%)	5/5 (100.0%)	

CDH congenital diaphragmatic hernia, *PTX* pneumothorax, *ECMO* extracorporeal membrane oxygenation

*$P<0.05$

[a]Median [interquartile range]

[b]Two patients developed in both side

[c]Three patients developed in both side

[d]ECMO was required in four patients underwent continuous drainage

with ipsilateral development, contralateral development, and bilateral development (Table 2).

Risk factors for the development of pneumothorax in patients with isolated CDH

The crude ORs for factors that were significantly associated with the development of pneumothorax were the best OI within 24 h after birth, MAP, size of the diaphragmatic defect, and need for patch closure. Among them, we eliminated patch closure as a factor due to the high correlations with the defect size ($r=0.714$) in the subsequent analysis. Because the need to use a patch was at the discretion of each surgeon in different institutions, while the defect size was evaluated based on an unbiased international classification. Eventually, the following factors were included in the multivariate analysis: best OI within 24 h after birth, MAP, and size of the diaphragmatic defect. Subsequent multiple logistic regression analysis demonstrated that only the MAP was a significant risk factor for pneumothorax in neonates with isolated CDH (Table 3). According to the ROC curve analysis, the cutoff value of the MAP was 16 cmH_2O [AUC, 0.631; $P=0.0005$] (Fig. 3).

Subgroup analysis of the clinical features according to the size of the diaphragmatic defect

The survival at 90 days and the mortality rate of the patients with pneumothorax were significantly different among the three categories. Although pneumothorax was not the primary cause of death in patients with small defects, pneumothorax was presumed to be the primary cause of death in three of six (50.0%) patients with a larger defect. The primary causes of death of the three patients with large defect were respiratory failure with pulmonary hypoplasia. Of the 33 patients who could not undergo surgery due to an unstable respiratory/circulatory condition, four patients developed pneumothorax. Pneumothorax was presumed to be the primary cause of death in one patient, and respiratory failure with pulmonary hypoplasia was the primary cause of death in the other three patients (Table 4). In patients with a small defect, no significant differences were observed in the best OI within 24 h after birth, MAP higher than 16 cmH_2O, need for patch closure, use of ECMO, and survival at 90 days between patients with pneumothorax and those without pneumothorax. In patients with a large defect, there were significant differences in the MAP higher than 16 cmH_2O,

Table 3 Risk factors for the development of pneumothorax in patients with isolated CDH

Variable	Univariate analysis		Multivariate analysis	
	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Birth weight ≥ 2500 g (ref.: < 2500 g)	1.259 (0.639–2.479)	0.498		
Apgar score at 1 min: 0–7 (ref.: 8–10)	1.167 (0.578–2.353)	0.663		
Administration of surfactant: yes (ref.: No)	1.322 (0.688–2.539)	0.410		
Best OI within 24 h after birth (per 1.0)	1.021 (1.007–1.036)	0.002*	1.004 (0.979–1.029)	0.819
MAP (per 1.0 cmH_2O)	1.206 (1.084–1.343)	< 0.001*	1.172 (1.022–1.345)	0.018*
Defect size: large (ref.: Small)	1.904 (1.036–3.500)	0.039*	1.544 (0.788–3.027)	0.205
Patch closure: yes (ref.: No)	2.078 (1.137–3.780)	0.017*		

Multiple logistic regression analyses were subsequently conducted for the variables that were significant at *P* values of less than 0.05 in the univariate analysis, and had low correlations with other factors ($r < 0.7$). We eliminated the patch closure as a factor due to the high correlations with the defect size ($r = 0.714$) in the subsequent analyzes

CDH congenital diaphragmatic hernia, *OR* odds ratio, *OI* oxygenation index, *MAP* mean airway pressure

*$P < 0.05$

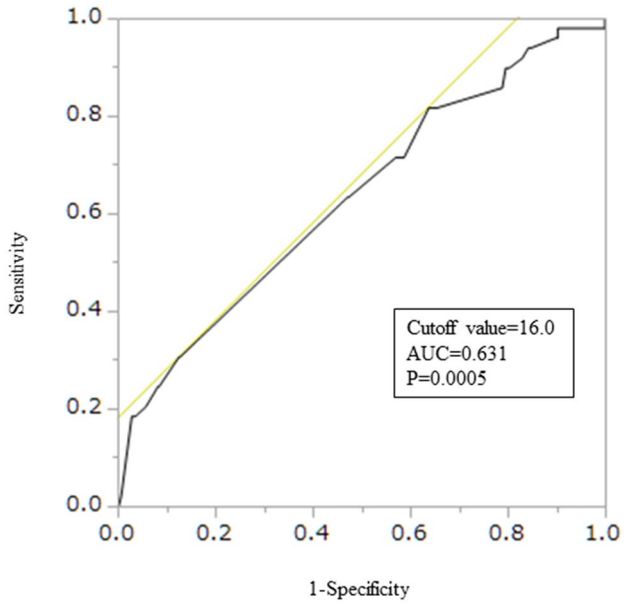

Fig. 3 The ROC curve analysis revealed the optimal cutoff MAP for identifying the patients with CDH. *ROC* receiver operating characteristic, *MAP* mean airway pressure, *CDH* congenital diaphragmatic hernia. *$P < 0.05$

use of ECMO, and survival at 90 days between patients with pneumothorax and those without pneumothorax (Table 5).

Discussion

To the best of our knowledge, this is the first study to determine the risk factors contributing to the development of pneumothorax in patients with isolated CDH. Our study demonstrated for the first time that a higher MAP is a risk factor for the development of pneumothorax in CDH patients.

In the past, hyperventilation was used as the mainstay of respiratory management for the treatment of persistent pulmonary hypertension of newborns with CDH [13]. However, some studies demonstrated that ventilator-induced lung injury caused by hyperventilation could have a significant impact on the survival outcome and the long-term pulmonary function in patients with CDH [14, 15]. Sakurai et al. suggested that the degree of lung injury was related to a high peak inspiratory pressure and that ventilator-induced lung injury plays an important role in the mortality of patients

Table 4 Comparison of the clinical outcome among the patients with tree categories

	Small defect (A or B) ($n = 274$)	Large defect (C or D) ($n = 161$)	Inoperable cases ($n = 33$)	*P* value
Survival at 90 days, *n*/*N* (%)	269/274 (98.2)	142/161 (88.2)	0/33 (0.0)	< 0.001*
Incidence of PTX, *n*/*N* (%)	23/274 (8.4)	24/161 (14.9)	4/33 (12.1)	0.106
Mortality rate of the patients with PTX, *n*/*N* (%)	0/23 (0.0)	6/24 (25.0)	4/4 (100.0)	< 0.001*
Death due to PTX, *n*/*N* (%)	0/0 (0.0)	3/6 (50.0)	1/4 (25.0)	0.571

PTX pneumothorax

*$P < 0.05$

Table 5 Comparison of the clinical features between patients with and without pneumothorax according to the size of the diaphragmatic defect

	Small defect (A or B) ($n=274$)			Large defect (C or D) ($n=161$)		
	With PTX ($n=23$)	Without PTX ($n=251$)	*P* value	With PTX ($n=24$)	Without PTX ($n=137$)	*P* value
Best OI within 24 h after birth[a]	3.5 [3.0–4.8]	3.5 [2.7–4.9]	0.908	10.4 [5.1–21.6]	6.2 [4.0—15.8]	0.119
MAP > 16 cmH_2O, *n*/*N* (%)	2/20 (10.0)	10/228 (4.4)	0.251	16/24 (66.7)	14/133 (10.5)	0.007*
Need for patch closure, *n*/*N* (%)	3/23 (13.0)	32/251 (12.7)	1.000	22/24 (91.6)	114/137 (83.2)	0.375
Use of ECMO, *n*/*N* (%)	0/23 (0.0)	2/251 (0.8)	1.000	9/24 (37.5)	18/137 (13.1)	0.007*
Survival at 90 days, *n*/*N* (%)	23/23 (100.0)	246/251 (98.0)	1.000	18/24 (75.0)	124/137 (90.5)	0.041*

PTX pneumothorax, *OI* oxygenation index, *MAP* mean airway pressure, *ECMO* extracorporeal membrane oxygenation

*$P < 0.05$

[a]Median [interquartile range]

with CDH [14]. Therefore, gentle ventilation strategies based on the concept of permissive hypercapnia and permissive hypoxia became the mainstay of respiratory management for neonates with CDH in the 1990s, and have led to the improvement in survival rates [16, 17]. However, pneumothorax remains a life-threatening complication that occurs in patient with CDH, even in those under respiratory management with gentle ventilation [7].

Pneumothorax is characterized by the collection of air in the pleural space, which can lead to clinically serious complications such as acute respiratory deterioration and hemodynamic instability, and is associated with increased morbidity and mortality [9, 18]. It is generally considered a complication of resuscitation, positive pressure ventilation or mechanical ventilation, and barotrauma or volume trauma [19]. The incidence of neonatal pneumothorax reportedly ranges from 0.14 to 6.7% [9, 20]. Most of the patients who developed pneumothorax on mechanical ventilation have an underlying lung disease such as acute respiratory distress syndrome or pulmonary hypoplasia, in which the lung has a physiologically small volume and consequently a low compliance [21, 22]. In infants with persistent pulmonary hypertension, development of pneumothorax was significantly associated with high prevalence and mortality rate [12].

In terms of the clinical features of patients with CDH associated with pneumothorax, our data demonstrated that pneumothorax is likely to occur in the contralateral lung before surgery and likely to occur in the ipsilateral lung after surgery. This difference can be due to several factors. Before surgery, the ipsilateral lung was surrounded by the abdominal organs, that were herniated into the thoracic cavity through the diaphragmatic defect and collapsed without expanding with ventilated air. On the contrary, after surgery, a large free space is made around the ipsilateral lung and allows the lung to expand easily without pressure. Therefore, ventilator-induced lung injury caused by hyperinflation with mechanical ventilation is likely to occur in the ipsilateral lung, which was hypoplastic and had low compliance after surgery. In general, the occurrence of a pneumothorax after surgery for CDH is a physiological phenomenon that normally does not require any treatment. However, 79.4% of the patients with postoperative pneumothorax required treatment in our study.

We attempted to identify the risk factors for the development of pneumothorax. In the present study, multiple logistic regression analysis demonstrated that a MAP was the only risk factor related to the development of pneumothorax in patients with isolated CDH. Boloker et al. advocated that the use of high positive inspiratory pressure should be reduced in CDH patients because of the risks of iatrogenic pneumothorax to their vulnerable lungs [16]. From the results of our study, we concluded that the effects of high airway pressures on lung hyperinflation should be minimized to avoid ventilator-induced lung injury including pneumothorax. Previous studies reported that several risk factors such as birth weight, administration of surfactant, and low Apgar scores at 1 min were significantly associated with the development of pneumothorax in neonates [9–12]. However, there was no significant difference in those factors between the patients with pneumothorax and those without pneumothorax in our study. A higher MAP and severity of CDH, including pulmonary hypoplasia, were considered to be the most important factors in the development of pneumothorax, particularly in patients with CDH.

We stratified the severity of CDH patients into three categories according to the operability due to unstable conditions and the diaphragmatic defect size, which was determined when a surgery was performed. In several inoperable patients and several patients with a large diaphragmatic defect, the primary cause of death was pneumothorax. On the contrary, none of the patients in the group with small diaphragmatic defect died of pneumothorax. The size of diaphragmatic defect correlates with the degree of pulmonary hypoplasia, and the high prevalence and mortality of pneumothorax are dependent on the severity of pulmonary hypoplasia [7, 8].

In the present study, we demonstrated that ECMO was more frequently applied in patients with pneumothorax

than in those without pneumothorax, especially in patients with a large diaphragmatic defect. Nine of 24 patients who developed pneumothorax underwent ECMO, and ECMO was initiated in four patients as a treatment for pneumothorax. Although none of the patients in the small diaphragmatic defect group who developed pneumothorax underwent ECMO, ECMO might be required in CDH patients with large diaphragmatic defect whose condition is deteriorating due to pneumothorax to allow the lungs to rest, subsequently improving the mortality rate. These results showed that pneumothorax can be a life-threatening complication if it occurs in patients with severe CDH who have a large defect and that it should be recognized and treated promptly, even in those receiving respiratory management with gentle ventilation.

There are several limitations in this study. First, this was a retrospective study of CDH cases that were registered in the institutions participating in the Japanese CDH study group, and the standard protocol for the management of CDH was only established in 2017. Therefore, the timing of surgery depended only on the policies of the facility and the decisions of the attending physicians. Consequently, there was a possibility of bias in the timing of pneumothorax development. Second, the institutions had no standardized therapeutic strategies for CDH patients who developed pneumothorax, and the indication for ECMO as a treatment for pneumothorax might be different in each institution. Third, we analyzed the effects of the MAP obtained while recording the best OI, but we could not do the same at the development of pneumothorax owing to the lack of data. Fourth, we did not consider the difference of ventilatory mode in the analysis. Although 70% of the patients used HFOV and 30% used conventional mechanical ventilation in both groups, pneumothorax development may be affected by the ventilatory settings of each ventilatory mode. Further study is warranted to determine the correlation of ventilatory settings in each ventilatory mode with the development of pneumothorax. Fifth, 27 patients were eliminated from subgroup analysis due to the lack of information regarding the defect size of the diaphragm.

Conclusions

The cumulative survival rate was significantly lower in isolated CDH patients with pneumothorax than in those without pneumothorax. Pneumothorax in CDH is more likely to occur in the contralateral lung before surgery and is likely to occur in the ipsilateral lung after surgery. A higher MAP was a risk factor for pneumothorax in isolated CDH patients.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study. We would like to thank Editage (http://www.editage.com) for English editing.

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