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Clinical outcomes and protocol for the management of isolated congenital diaphragmatic hernia based on our prenatal risk stratification system☆

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ABSTRACT

Background/Purpose: The aim of this study was to evaluate our prenatal risk stratification system for risk-adjusted management in fetuses with isolated congenital diaphragmatic hernia (CDH).
Methods: Ninety-four infants prenatally diagnosed with isolated CDH treated between 1998 and 2017 at our institution were included in this retrospective single-center cohort study.
Results: The patients were prenatally classified into four risk groups: Group A (n = 54), which consisted of infants with neither liver-up nor a contralateral lung-to-thorax transverse area (L/T) ratio <0.08. The infants in group A were divided into two subgroups: Group A-1 (n = 24) consisted of mild conditions; and Group A-2 (n = 30) consisted of severe conditions; Group B (n = 23), which consisted of infants with either liver-up or L/T ratio <0.08; and Group C (n = 17), which consisted of infants with both liver-up and L/T ratio <0.08. The rates of survival to discharge in Groups A-1, A-2, B, and C were 100.0%, 100.0%, 87.0%, and 58.8%, respectively. The rates of intact discharge were 91.7%, 90.0%, 52.1%, and 23.5%, respectively.
Conclusions: Our prenatal risk stratification system demonstrated a significant difference in the severity of postnatal status and clinical outcomes between the groups.
Study type: Case Series, Retrospective Review.
Levels of Evidence: LEVEL IV.

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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. However, advancements in prenatal diagnostic imaging and perioperative respiratory and circulatory management have recently improved patients' prognoses. An accurate prenatal assessment of severity including pulmonary hypoplasia is essential for the standardization of prenatal and postnatal care. Prenatal prognostic classification of CDH would provide the infant's family with more precise information about the prospective course of treatment and allow for the establishment of a management protocol based on prospective.

We used a prenatal risk stratification system in which some fetal ultrasonographic findings are added to the prenatal risk prediction, as reported by Usui et al. [1]. Using this system, we classified severity using a combination of the presence of liver herniation (liver-up) and the lung-to-thorax transverse area ratio (L/T ratio). We currently utilize this system to select treatment strategies according to prenatally predicted severity. The purpose of the present study was to investigate the usefulness of our prenatal risk stratification system by analyzing outcomes of patients with CDH treated at our institution over the

Abbreviations: CDH, congenital diaphragmatic hernia; GA, gestational age; L/T ratio, the lung-to-thorax transverse area ratio; ECMO, extracorporeal membrane oxygenation; iNO, nitric oxide inhalation; PPHN, persistent pulmonary hypertension of the newborn; CMV, conventional mechanical ventilation; HFOV, high-frequency oscillation ventilation; FiO_2, fraction of inspiratory oxygen; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; PGE_1, prostaglandin E1; LHR, The lung area to head circumference ratio; o/e LHR, the observed-to-expected LHR.

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past 20 years. Herein, we also describe the treatment protocols for prenatal, perinatal and perioperative management, including surgical treatment based on stratified risk, which we have used at our institution since 2017.

1. Materials and methods

1.1. Study design and data collection

We conducted a retrospective review of the medical records of 138 patients with CDH treated at Osaka Women's and Children's Hospital between January 1998 and December 2017. Patients with serious associated anomalies, such as major cardiac malformations and chromosomal abnormalities, were excluded. Another patient with bilateral diaphragmatic hernia was also excluded. Medical records were reviewed to obtain demographic information on the patients. The neonatal data we collected included gestational age at birth, birth weight, need for circulatory support [e.g., extracorporeal membrane oxygenation (ECMO) and nitric oxide inhalation (iNO)], need for patch closure, duration of respiratory support [e.g., mechanical ventilation and oxygen administration], duration of hospitalization, rate of survival to discharge and rate of intact discharge. Intact discharge was defined as discharge from the hospital without any need for home treatments, such as ventilatory support, oxygen administration, tube feeding, parenteral nutrition, or administration of pulmonary vasodilator. The primary outcome measure was the rate of survival to discharge, and the secondary outcome measure was the rate of intact discharge. This study was approved by the institutional review board of Osaka Women's and Children's Hospital (approval number 1199).

1.2. Prenatal risk stratification system

Prenatal ultrasonographic findings, including fetal liver position and the contralateral L/T ratio, were assessed. Liver-up was defined as the liver occupying more than one-third of the height of the thoracic space, as determined using fetal ultrasonography. Fetuses with slight liver herniation or those with liver herniation that was first recognized during surgery were not considered to have liver-up. The L/T ratio was measured using ultrasonography in the transverse section containing the four-chamber view of the heart [2]. Briefly, the L/T ratio was calculated by dividing the area of the contralateral lung determined by tracing the outline of the contralateral lung by the area of the thorax defined as the space surrounded by the inner border of the bilateral ribs, the sternum, and the vertebra [3]. Prenatal ultrasonographic findings, including fetal liver and stomach position, and the L/T ratio, were collected at least 3 times, according to the gestational age at diagnosis: before 30 weeks and between 30 and 35 weeks of gestation, and after 35 weeks of gestation. As the parameters were measured several times and were judged based on the worst value among the representative data.

The severity of CDH was assessed via fetal ultrasonography, and risk was stratified using a combination of liver-up and the L/T ratio. The cutoff value for the L/T ratio was set to 0.08, based on our previous studies [4–6]. The patients were classified into three risk groups: a low-risk group (Group A), which consisted of patients with neither liver-up nor an L/T ratio <0.08; an intermediate-risk group (Group B), which consisted of patients exhibiting either liver-up or an L/T ratio <0.08; and a high-risk group (Group C), which consisted of patients exhibiting both liver-up and an L/T ratio <0.08 [1]. Group A was further classified into two subgroups: a low-risk mild group (Group A-1) and a low-risk severe group (Group A-2). Group A-1 included patients exhibiting any of the following: an L/T ratio ≥0.18, staying of the whole stomach within the abdominal cavity, or observable ipsilateral lung at the level of four-chamber cross-section. Patients in Group A-2 did not exhibit any of the abovementioned characteristics (Table 1).

1.3. Statistical analysis

Data were reported as medians and ranges, or frequencies and percentages. The Kruskal-Wallis test was used to compare continuous variables; the χ^2 test and Fisher's exact test were used for the analysis of categorical variables. The log-rank test and Kaplan–Meier method were used to compare treatment durations and survival times, respectively. p Values <0.05 were considered statistically significant. A Bonferroni test was used multiple comparison tests in this statistical analysis.

2. Results

2.1. Patient characteristics

Of the 138 patients with CDH who were treated at our institution during the study period, 20 were diagnosed after birth and were therefore excluded; thus, 118 patients had a prenatal diagnosis. Twenty-three non-isolated patients with associated chromosomal abnormalities or severe associated anomalies and one patient with bilateral CDH were further excluded; therefore, 94 patients were included in this analysis. According to our prenatal risk stratification system, 24 patients were classified into

Table 1
Prenatal risk stratification for congenital diaphragmatic hernia.

Prenatal risk groups	Findings of the fetal ultrasonography
Group A (Low-risk group)	Neither Liver-up nor L/T ratio < 0.08 *
Group A-1 (mild)	Apply when one of the following criteria is met in the Group A. 1. L/T ratio ≥ 0.18 ** 2. Whole stomach is staying in the abdominal cavity 3. Ipsilateral lung is observable at the level of four-chamber view of the heart
Group A-2 (severe)	Apply when none of the above findings is detected in the Group A.
Group B (Intermediate- risk group)	Either Liver-up or L/T ratio < 0.08 *
Group C (High-risk group)	Both Liver-up and L/T ratio < 0.08 *

L/T ratio; the contralateral lung-to-thorax transverse area ratio; o/e LHR; observed-to-expected fetal lung area to head circumference ratio
* L/T ratio < 0.08 is equivalent to o/e LHR < 25%,
** L/T ratio ≥ 0.18 is equivalent to o/e LHR ≥ 70% [14].

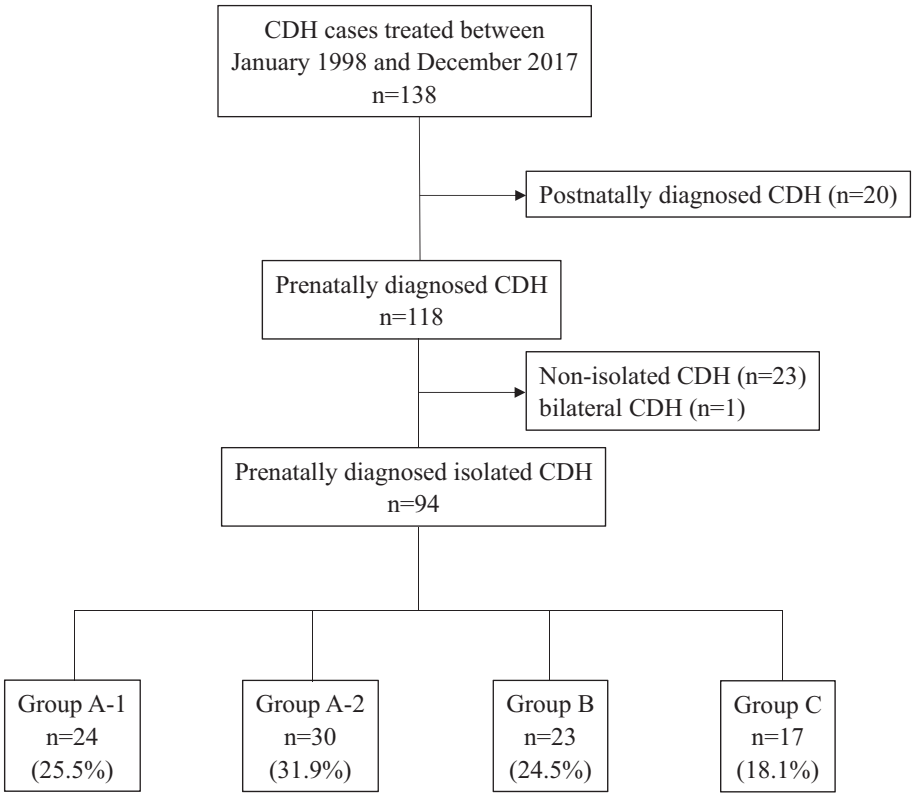

Fig. 1. Patients included in this analysis.

Group A-1 (25.5%), 30 patients into Group A-2 (31.9%), 23 patients into Group B (24.5%), and 17 patients into Group C (18.1%) (Fig. 1).

Median gestational age was 37.6 weeks, and median birth weight was 2669 g. Surgery for diaphragmatic hernia was performed in 90 patients, of whom 46 underwent patch closure. Eighty patients underwent iNO therapy for the treatment of persistent pulmonary hypertension of the newborn (PPHN), seven of whom required the use of ECMO. The overall rate of survival to discharge was 88.3%, and the overall rate of intact discharge was 69.1% (Table 2).

2.2. Infant outcomes

The four prenatal risk groups were compared in terms of clinical characteristics, including treatment methods and outcomes (Table 3).

Table 2
Demographics of patients prenatally diagnosed with isolated CDH.

Number of patients	94
Gender (male)	55 (58.5%)
Gestational age (weeks) [a]	37.6 (32.1–41.6)
Birth weight (g) [a]	2669 (1162–3994)
Side of hernia (left)	88 (93.6%)
Surgery performed for diaphragmatic hernia	90 (95.7%)
Age of surgery (day after birth) [a]	1 (0–14)
Presence of hernia sac	10 (10.6%)
Need for patch closure	46 (48.9%)
Need for iNO	80 (85.1%)
Need for ECMO	7 (7.4%)
Survival to discharge	83 (88.3%)
Intact discharge	65 (69.1%)

CDH: congenital diaphragmatic hernia, iNO: inhaled nitric oxide, ECMO: extracorporeal membrane oxygenation.
[a] Median (range).

There were no significant differences in background information, such as gestational age or birth weight, between the four groups. All patients in Groups A-1, A-2, and B were stabilized and underwent surgery; however, only 76.5% of the patients in Group C could undergo surgery after stabilization. Patch closure was required in all patients who received surgery in Group C. In contrast, 8.3% and 40.0% required patch closure in Groups A-1 and A-2, respectively, indicating that the rate at which patch closure was needed differed between mild and severe cases within the low-risk group (Group A). The higher the severity of CDH, the higher the rate at which patients required iNO therapy and ECMO support. Significant differences were also observed between the groups in terms of the durations of artificial ventilation, oxygen administration, and hospitalization. The rate of intact discharge was 91.7% in Group A-1 and 90.0% in Group A-2, but only 23.5% in Group C. All patients survived to discharge in Groups A-1 and A-2; however, the rate of survival to discharge was 87.0% in Group B and 58.8% in Group C (Table 3).

Combination group analysis demonstrated that time-to-event analysis of the necessity of artificial ventilation and oxygen administration revealed significant differences between the 4 prenatal risk-stratified groups (Fig. 2), and the cumulative survival rate also significantly differed between the 3 risk-stratified groups (Fig. 3).

2.3. Protocols for the management of CDH

Based on the results of this analysis, we designed protocols for the prenatal, perinatal and perioperative management of CDH, including resuscitation at birth and surgical treatment according to the prenatally stratified risk in patients with isolated CDH (Table 4). We began to follow these risk-adjusted protocols for the treatment of prenatally diagnosed isolated CDH in 2017. In a joint conference, an obstetrician, neonatologist, pediatric surgeon, pediatric cardiologist, intensivist and

Table 3
Comparison of clinical characteristics between the four prenatal risk groups.

	Group A-1 (n = 24)	Group A-2 (n = 30)	Group B (n = 23)	Group C (n = 17)	p Values
Gestational age (weeks)[a]	38.6 (32.1–41.6)	37.6 (35.6–40.1)	37.7 (33.6–41.4)	37.3 (36.1–38.3)	0.076
Birth weight (g) [a]	2884 (1162–3994)	2760 (1834–3830)	2628 (1888–3678)	2627 (1978–3460)	0.399
Number of patients performed surgery for CDH (%)	24 (100%)	30 (100%)	23 (100%)	13 (76.5%)	p < 0.001*
Need for patch closure (%)	2 (8.3%)	12 (40.0%)	18 (78.3%)	13 (100%)	p < 0.001*
Need for iNO (%)	15 (62.5%)	26 (86.7%)	21 (91.3%)	17 (100%)	0.0056 *
Need for ECMO (%)	0 (0%)	1 (3.3%)	2 (8.7%)	4 (23.5%)	0.028 *
Duration of artificial ventilation (d) [a]	6 (2–15)	10 (3–34)	13.5 (4–81)	26 (9–1824)	p < 0.001*
Duration of O_2 administration (d) [a]	12 (4–36)	20 (5–215)	43 (11–378)	60 (37–1824)	p < 0.001*
Length of hospitalization (d) [a]	38 (21–84)	59 (22–233)	73 (25–476)	158 (60–1075)	p < 0.001*
Intact discharge (%)	22 (91.7%)	27 (90.0%)	12 (52.1%)	4 (23.5%)	p < 0.001*
Survival to discharge (%)	24 (100%)	30 (100%)	20 (87.0%)	10 (58.8%)	p < 0.001*

CDH: congenital diaphragmatic hernia, iNO: inhaled nitric oxide, ECMO: extracorporeal membrane oxygenation.
[a] Median (range),
* $p < 0.05$

anesthesiologist collectively assess the risk of each patient. Treatment is then performed using the protocols described below, based on prenatally stratified risk.

2.3.1. Mode of delivery

In principle, spontaneous onset of labor is expected in Group A and planned delivery is expected in Group C. In Group B, the decision to wait for spontaneous labor or to have a planned delivery corresponds to the maturity of the cervical canal and the presence of relevant clinicians required for resuscitation at birth. The method for planned delivery is vaginal delivery; cesarean section is only selected if indicated obstetrically.

2.3.2. Resuscitation

In Groups A-2, B, and C, birth is followed immediately by tracheal intubation and artificial ventilation. In Group A-1, the respiratory condition is observed after birth, rather than performing immediate intubation; tracheal intubation is only performed when specific respiratory symptoms are observed. To prevent distention of the stomach, ventilation using a mask and bag should be avoided before tracheal intubation. An electrocardiography monitor and oxygen saturation monitors should be placed immediately; the oxygen saturation monitors should be placed on the right hand and on one leg to determine the presence or absence of PPHN.

2.3.3. Respiratory management

The initial mode for artificial ventilation is conventional mechanical ventilation (CMV). In Group A, the artificial ventilation conditions are started from the lowest settings [$FiO_2 = 0.6$, PEEP = 5 cm H_2O, PIP = 20 cm H_2O, 40/min], and then oxygen saturation and blood gas data are measured; the ventilation conditions are increased as necessary. In Groups B and C, the conditions are started from the maximum allowed settings [$FiO_2 = 1.0$, PEEP = 8 cm H_2O, PIP = 28 cm H_2O, 50/min] and are decreased rapidly when good oxygen saturation or blood gas data are obtained. The artificial ventilation mode is switched to high-frequency oscillation ventilation (HFOV), when artificial ventilation by CMV at maximum conditions is not found to maintain the required respiratory state. A certain level of hypercapnia and hypoxemia [e.g., $PaCO_2$ <70 mmHg, SaO_2 >85%] is permitted with artificial ventilation by both CMV and HOFV, based on the concept of gentle ventilation,

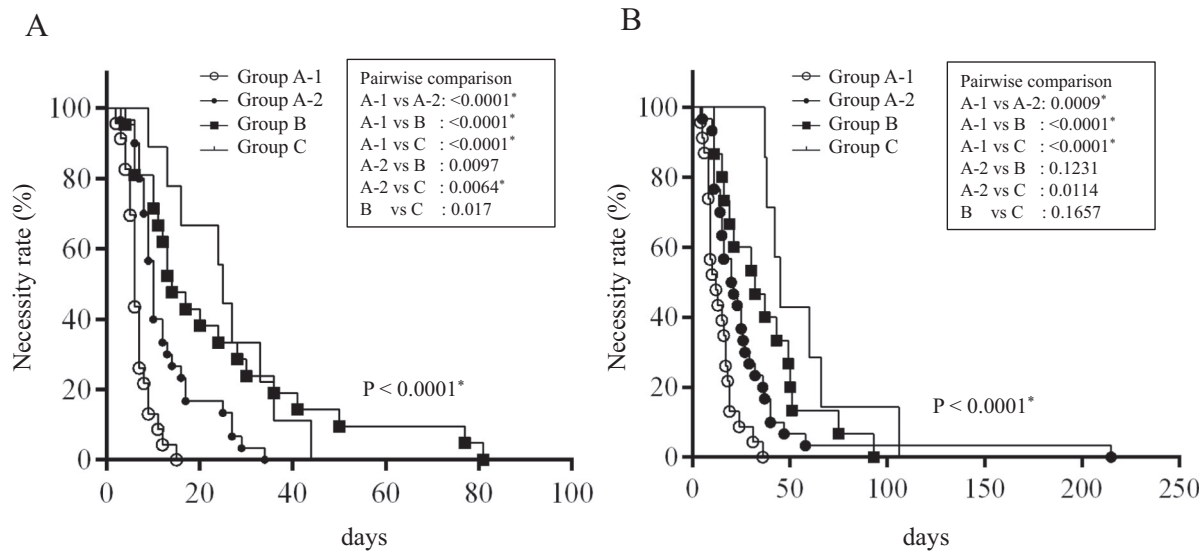

Fig. 2. Time-to-event analysis of the necessity for respiratory support in the patients with isolated CDH, compared between the four prenatally risk-stratified groups. (A) Necessity for artificial ventilation, (B) Necessity for oxygen administration. CDH: congenital diaphragmatic hernia. Adjusted significance level for multiple comparison of each curves by Bonferroni method, $p < 0.0083^*$.

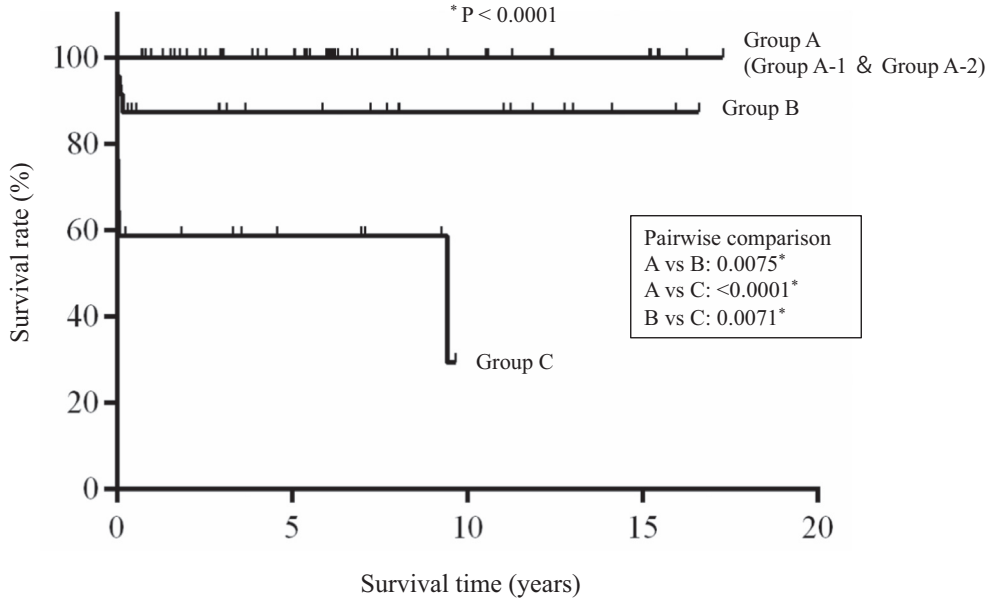

Fig. 3. Survival curves for the patients with isolated CDH, compared between the three prenatal risk groups. CDH: congenital diaphragmatic hernia. Adjusted significance level for multiple comparison of each curves by Bonferroni method, $p < 0.0167^{*}$.

in an effort to avoid pulmonary barotrauma as much as possible. Pulmonary surfactant is not routinely administered, but may be provided if it is found to be indicated by the microbubble test at a gestational age of less than 36 weeks.

2.3.4. Circulatory management

After the initial resuscitation, echocardiography should be promptly performed to assess the presence of a congenital cardiac anomaly, as well as the state of pulmonary hypertension and cardiac function. Any patient found to have PPHN is immediately started on iNO therapy. Pre- and postductal arterial lines are placed to monitor PPHN. When the direction of blood flow in the ductus arteriosus is predominantly a right-to-left shunt, prostaglandin E1 (PGE_1) should be preferably administered to maintain patency of ductus arteriosus, as well as to reduce right ventricular afterload and maintain systemic circulation by the cardiac output from the left ventricle. When echocardiography shows recovery from PPHN and that the blood flow of the ductus arteriosus is predominantly a left-to-right shunt, administration of PGE_1 should be shortly reduced/suspended.

2.3.5. Preoperative preparation

A gastric tube is placed to prevent distention of the stomach, and deep sedation is induced by intravenous injection via peripheral venous or peripherally inserted central catheter. The use of muscle relaxants should be minimized as much as possible; however, in cases where patients are fighting against the ventilator, a muscle relaxant may be proactively administered to avoid barotrauma. During iNO therapy, sputum suction can be performed proactively to prevent atelectasis, along with an enema use to promote bowel decompression. Systemic administration of steroids may also be considered in cases of severe edema.

2.3.6. Surgical treatment

Surgery should be performed after stabilization of respiratory and circulatory status is confirmed. In term infants, systolic blood

Table 4
Our protocol for the treatment strategies in the four prenatally stratified risk groups.

	Group A-1	Group A-2	Group B	Group C
Delivery	Spontaneous labor		Spontaneous labor or planned delivery	Planned delivery
Resuscitation at birth	Endotracheal intubation, if necessary,	Immediate endotracheal intubation		
Initial setting for artificial ventilator	Start from minimum setting		Start from maximum setting	
Circulatory management	Frequent echocardiography, iNO for PPHN, Catecholamine and volume load based on the cardiac function, Prostaglandin E1 to maintain PDA when dominant of right to left shunting			
Preparation for surgery	Insertion of nasogastric tube, Insertion of peripherally inserted central catheter, Deep sedation, Minimal use of muscle relaxant, Proactive enema and sputum suction			
Surgical treatment	Thoracoscopic surgery	Open surgery		

iNO: inhaled nitric oxide, PPHN: persistent pulmonary hypertension of newborn, PDA: patent ductus arteriosus

pressure ≥ 50 mmHg and urine output ≥ 1 ml/kg/h, along with an absence of significant acidosis, indicate stabilization. Except in cases of uncontrollable acidosis or extreme hypoxia, surgery should not be postponed due to a PPHN or a hypercapnia. Surgery is usually performed at the age of 1 to 2 days, but not on the day of birth. However, it may be necessary for infants in Group C to wait several days more before surgery to reach stabilization. In non-isolated patients, the timing of surgery should be decided on a case-by-case basis, depending on the presence of chromosomal abnormalities or severe associated anomalies that have a serious impact on prognosis. Groups A-2, B, and C undergo open surgery with an incision created in the upper abdomen of the ipsilateral side. When the defect of the diaphragm is small, the diaphragm is closed with direct suture; when it is large, the diaphragm is closed with patch closure using a sheet made of Gore-Tex. Patch closure is preferably selected to avoid excessive tension on the diaphragm caused by direct closure for large defects. In patch closure, the sheet is sutured to form a dome like shape to avoid excessive tension at the suture site. A chest drainage tube is not routinely inserted. An enteral feeding tube should be placed at the proximal site of the jejunum during surgery in order to start feeding early after surgery.

2.3.7. Thoracoscopic surgery

Thoracoscopic repair of the diaphragmatic hernia is indicated in Group A-1 as well as when onset occurs over 24 h after birth. For thoracoscopic surgery, carbon dioxide gas is used for artificial pneumothorax at 4 to 6 mmHg; once the organs herniated into the thoracic cavity have been repositioned to the abdominal cavity, the diaphragm should be closed with the pledgeted horizontal mattress suture technique using a non-absorbable thread.

3. Discussion

In the present study, infants prenatally diagnosed with isolated CDH who were treated at our institution over the past 20 years were stratified into four risk groups based on prenatal fetal ultrasonographic findings, and outcomes were compared between risk groups. One advantage of prenatal diagnosis is that mothers whose fetuses have been diagnosed with CDH can be referred to an advanced medical institution experienced in perinatal management of CDH. Another advantage of an accurate prenatal assessment of the severity of CDH is that peri- and postnatal treatment strategies can be planned in advance. The present study showed that our risk stratification system makes it possible to predict not only the patient's prognosis, but also the severity of the infant's respiratory and circulatory status.

The fetal lung area to head circumference ratio (LHR) was previously used internationally to predict the severity of CDH [6–8]. However, given that the LHR increases over the course of pregnancy in normal fetuses, a ratio of the observed-to-expected LHR (o/e LHR), which is not influenced by gestational age, is more informative in cases of CDH [3, 4, 9–13]. However, calculating the o/e LHR is complex and requires a healthy reference value for the LHR, which may vary depending on nationality and ethnicity. In contrast, the L/T ratio appears to be a reliable predictive parameter as it is reportedly not influenced by gestational age in fetuses with CDH [2–4]. The L/T ratio is linearly correlated with the o/e LHR; thus, the two can be interconverted. Specifically, an L/T ratio of 0.08 is equivalent to an o/e LHR of 25%, and an L/T ratio of 0.18 is equivalent to an o/e LHR of 70% [14].

Several prenatal prognostic parameters for fetal CDH have previously been proposed by other investigators [2, 6, 7, 9, 15–22]. The presence of liver-up has been previously identified as a powerful indicator of the severity of CDH [9, 15–19]. Therefore, we used the classification system proposed by Usui et al., which combines liver-up with an L/T ratio < 0.08 [1]. The patient population of the present study was partly overlapped with the population of previous multi-institutional study. However, the L/T ratio was measured only in 58% of the patients in the multi-institutional study and some institutions did not evaluate the severity of CDH as intimately as we did in our institution. Moreover, in the present study, Group A was further divided into two subgroups based on the several additional findings. Thus, there were a total of four groups in the present study. However, the two subgroups could not be determined in a previous multi-institutional study due to the absence of precise ultrasonographic data of patients with CDH.

The rate of survival to discharge of patients with isolated CDH over this study period at our institution (88.3%) was better than previous reports from other countries [23]. There were significant between group differences in the rate of patch closure, rate of iNO therapy for PPHN, need for ECMO support, duration of artificial ventilation, duration of oxygen administration, duration of artificial ventilation, rate of intact discharge, and rate of survival to discharge.

In our series, iNO therapy and ECMO support were performed in 80 (85.1%) and 7 (7.4%) patients, respectively. These results demonstrated the less frequent use of ECMO support and high use of iNO therapy for pulmonary hypertension. In Japan, the use of ECMO has decreased in recent years, as was described by the CDH study groups [24]. Recent reports showed no difference in survival rate between patients born in ECMO centers and those born in non-ECMO centers [25]. Therefore, we suggest that some infants with extremely severe pulmonary hypoplasia or irreversible respiratory failure have been considered not to be indicated for ECMO support.

Compared with Group A, there was a significant decrease in the survival and intact discharge rates in Groups B and C. Therefore, we believe that the risk-adjusted treatment protocols that we describe herein are practical and useful in patients with CDH. We designed these protocols based on the results of the analysis presented in this study. The basic concepts underlying these protocols include: starting from the maximum treatment level at birth in cases that have been predicted to be severe; and avoiding excessive treatment beyond requirements in cases that have been predicted to be mild.

The rate of patch closure was approximately five times higher in Group A-2 than Group A-1, representing a significant difference even within this low-risk group, Group A. Although both Group A-1 and Group A-2 had identical survival and intact discharge rates, a higher proportion of patients in Group A-2 underwent patch closure or received iNO therapy, and had a longer duration of oxygen administration and hospitalization compared with Group A-1. Thus, further stratifying Group A into Group A-1 and Group A-2 made it possible to isolate cases with the mildest conditions as having the smallest diaphragmatic defect.

Previous studies focusing on minimal access surgery repair reported recurrence rates ranging from 8.4–26.5% [26–29]. In our institution, of the 3 postnatally diagnosed stable patients with CDH underwent thoracoscopic surgery, no patients had postoperative recurrence. Therefore, we decided to perform thoracoscopic surgery only on patients in Group A-1, in which respiratory and circulatory status are stable and patch closure might not be required because of relatively small diaphragmatic defects as there is a reportedly higher rate of recurrence in patients who require patch closure due to large diaphragmatic defects [26–30]. We found that isolating the mildest group from the larger low-risk Group A enabled the prenatal selection of cases in whom endoscopic surgery was indicated.

A significant number of CDH patients have growth retardation of 21–69% for body weight at 1 year of age [31–34]. The amount of enteral nutrition received has been shown to be an independent risk factor for growth retardation [35]. Terui et al. reported that the amount of enteral nutrition in the acute phase of CDH management is essential for weight gain during infancy [34]. Therefore, we suggest that an enteral feeding tube should be placed at the proximal site of the jejunum during surgery in order to start enteral feeding as early as possible after surgery.

If it was possible to isolate the most severe patients associated with fatal pulmonary hypoplasia from the high-risk Group C, these fetuses would be considered for fetal treatment or palliative care. Although fetoscopic tracheal occlusion has been tested in many countries as a

fetal treatment [36], its exact clinical therapeutic effects remain unclear. Fetal treatment with sufficient consideration of the mothers' safety may hopefully improve a patient's prognosis and respiratory function for the most severe fetuses in the high-risk Group C.

There are several limitations in this study. A major limitation is that liver-up and the L/T ratios were determined by various investigators even at a single institution. A prospective study in which those factors are determined by a limited number of investigators who understand the prenatal risk stratification system may be required to verify the accuracy of this system. The other limitation of this study is that the therapeutic strategies practiced at our institution have changed over the long-term study period. Further, this was a retrospective study, and the sample size was small. Therefore, our new prenatal risk stratification system must be verified in a multicenter prospective study in future.

4. Conclusion

Our prenatal risk stratification system demonstrated a significant between group differences in postnatal status and clinical outcomes. The combination of liver-up and the L/T ratio with several additional fetal ultrasonographic findings was useful in the prenatal risk stratification of patients with CDH.

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